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driving innovation in oncology

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Japanese Society of Medical Oncology JSMO

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ANNALS OF ONCOLOGY

driving innovation in oncology

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Annals of Oncology, the journal of the European Society for Medical Oncology and the Japanese Society of Medical Oncology, provides rapid and efficient peer-review publications on innovative cancer treatments or translational work related to oncology and precision medicine.

Main focuses of interest include: systemic anticancer therapy (with specific interest on molecular targeted agents and new immune therapies), randomized trials (including negatives ones), top-level guidelines, and new fields currently emerging as key components of personalized medicine, such as molecular pathology, bioinformatics, modern statistics, and biotechnologies. Radiotherapy, surgery and pediatrics manuscripts can be considered if they display a clear interaction with one of the fields above or are paradigm-shifting.

With a large international editorial board of experts who are leaders in their fields, *Annals of Oncology* aims at delivering the best communication on the fast moving, and continually evolving, global oncology landscape.

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European Society for Medical Oncology (ESMO)

ESMO is the leading professional organisation for medical oncology. With more than 30,000 members representing oncology professionals from 168 countries worldwide, ESMO is the society of reference for oncology education and information. Driven by a shared determination to secure the best possible outcomes for patients, ESMO is committed to standing by those who care about cancer through addressing the diverse needs of #ONEoncologycommunity, offering #educationforLIFE, and advocating for #accessiblecancerCARE.

Drawing on more than 45 years of experience, ESMO serves its members and the oncology community by:

- providing networking and professional growth opportunities: through ESMO, oncologists can engage in projects, committees and working groups aiming to promote science and foster improvements in the oncology practice;
- providing training, resources and tools which enable oncologists to stay up-to-date with the latest scientific advances and continue to deliver the best possible care to cancer patients;
- representing and advocating for the oncology community at the highest political levels, ensuring that the needs of both patients and doctors are properly taken care of.

Cancer care becomes more integrated and more specialised every day; whether their field is research, diagnosis, treatment, care, or advocacy, oncology professionals need to both build their specialist knowledge and connect with the best practitioners in other disciplines worldwide. ESMO membership makes this possible.

www.esmo.org

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European Oncology Nursing Society (EONS)

The European Oncology Nursing Society (EONS) is a pan-European membership organisation for cancer nurses — the largest group of healthcare workers in the oncology workforce.

EONS provides leadership in all areas of cancer nursing: research, practice, continuing education, communications and advocacy for better recognition of cancer nursing across Europe.

Vision

Our vision is that cancer nursing will be recognised by the cancer community, national and European level policy makers, as a profession with specialised training and qualifications available across the continent. Working conditions for cancer nurses will be optimal, providing a commensurate financial income as well as protecting and promoting individual well-being. We anticipate that this will produce a relatable improvement in the health and clinical outcomes for people affected by cancer. Finally, we envisage that all our members will become confident and empowered cancer nurses operating as leaders in research, practice and education within multi-professional teams.

Strategic goals

All strategic goals are equal and assume no hierarchy. EONS aims to achieve the following:

1. Cancer nursing is recognised across Europe for its positive impact on the lives of people affected by cancer through C.A.R.E. — Communication, Advocacy, Research and Education.
2. All cancer nurses have access to specialised education that is aligned with the EONS Cancer Nursing Education Framework.
3. All cancer nurses gain official recognition, reward and respect as a result of the RECaN and advocacy campaigns.
4. All cancer nurses are connected in order to exchange and share information and support for their work.
5. EONS facilitates, leads and promotes collaborative cancer nursing research across Europe.
6. EONS leads EU-wide advocacy initiatives at EU policy level.
7. EONS provides evidence-based advice to people and organisations affected by cancer on healthy lifestyles and cancer prevention.

EONS has prepared an update strategy for 2024-2028.

Read more about this at https://cancernurse.eu/about-eons/strategy/

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BASIC SCIENCE

1O CircIGF1R_0001 mediates platinum resistance in ovarian cancer that sensitive to PARP inhibitors via promoting PARP1 binding to DNA damage sites

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Background: Clinical research indicated that some platinum-resistant ovarian cancer patients are sensitive to Poly (ADP-ribose) polymerase inhibitors(PARPi) and it is associated with high Poly(ADP-ribosyl)lation (PARylation) activity of PARP1. However, the specific mechanism remains unclear.

Methods: Key functional circRNAs that promote platinum resistance in epithelial ovarian cancer (EOC) were screened and identified through next-generation sequencing, quantitative real-time polymerase chain reaction (qRT-PCR), and comet assay methods. Experiments such as RNA immunoprecipitation (RIP), RNA pull-down, laser micro-irradiation, and fluorescence colonization were used to identify the proteins and domains that interact with target circRNA. The recruitment and trapping of PARP1 at DNA damage sites were detected through Chromatin extract isolation and Biotin-tagged Nicked DNA pulled down.

Results: The circIGF1R_0001 is highly expressed in some platinum-resistant tissues and cell lines, and its overexpression enhances DNA repair and platinum resistance in ovarian cancer cells. The circIGF1R_0001 binds to the DNA binding domain of PARP1 and can be recruited together to DNA damage sites. Silencing circIGF1R_0001 significantly reduces the PARylation of PARP1, weakens the recruitment of PARP1 at DNA damage sites, and inhibits the activation of downstream DNA liag3. Furthermore, EOC patients and cell lines with platinum resistance that overexpressing circIGF1R_0001 are more sensitive to PARP inhibitors; silencing circIGF1R_0001 increases the resistance to PARPi while weakening the DNA trapping effect of PARP1.

Conclusions: 1. Overexpression of circIGF1R_0001 promotes platinum resistance but also promotes sensitivity to PARPi in ovarian cancer. 2. The circIGF1R_ 0001 binds to and regulates the DBD domain of PARP1 to promote its PARylation and enhance its recruitment to DNA damage sites then enhanced the base excision repair pathway. Importantly, circIGF1R_ 0001 also enhances the DNA trapping of PARP1 by PARPi. 3. The circIGF1R_ 0001 acts as a potential biomarker for platinum resistance in ovarian cancer and a marker for screening patients who can benefit from PARPi after platinum resistance.

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2O PD-1 defines a distinct, functional, tissue-adapted state in V-delta-1+ T cells with implications for cancer immunotherapy

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Background: Checkpoint inhibition (CPI), particularly that targeting the inhibitory co-receptor, programmed cell death protein (PD-1), has transformed cancer care. Although CPI can de-repress cancer antigen-specific $\alpha\beta$ T cells that ordinarily show PD-1-dependent exhaustion, it can also be efficacious against cancers evading $\alpha\beta$ T cell recognition through loss of MHC or low mutational burdens. In such settings, tissue-associated Vδ1$^+$ $\gamma\delta$ T cells have been implicated as these cells are not classically peptide-MHC dependent. Despite some evidence for association of Vδ1$^+$ T cells to CPI response, the immunological significance of PD-1 expression by human Vδ1$^+$ T cells remains uncharacterised.

Methods: As Vδ1$^+$ T can operate independent of neoantigen load, we looked for a transcriptomic signature of Vδ1$^+$ T cells in a public dataset of patients with melanoma receiving anti-PD-1 therapy and correlated this signature to response in the context of neoantigen load. Alongside this, we developed a protocol which enabled the extraction of substantial numbers of human skin $\gamma\delta$ T cells to permit transcriptomic and functional studies of these rare cells. Skin-derived PD-1$^+$ and PD-1$^-$ Vδ1$^+$ T cells were sorted and analysed by NanoString using the nCounter Immune Exhaustion Panel. The cells were also activated *in vitro* both in the presence and absence of recombinant PD-L1 +/- atezolizumab and assayed for cytotoxic degranulation and production of effector cytokines.

Results: We found that a transcriptional signature of intratumoral Vδ1$^+$ T cells predicts response to anti-PD-1 in patients with melanoma, particularly in the context of low neoantigen load. Moreover, we found that skin-derived PD-1$^+$ Vδ1$^+$ T cells display a transcriptomic programme of tissue-residence, survival/self-renewal, and functional competence distinct from the canonical exhaustion programme of co-located PD-1$^+$ CD8$^+$ $\alpha\beta$ T cells. Indeed, PD-1$^+$ Vδ1$^+$ T cells retained effector responses to T cell receptor signalling that were inhibitable by PD-1 engagement and partially derepressed by CPI.

Conclusions: Our formal demonstration that Vδ1$^+$ T cells can be suppressed by PD-1 engagement and de-repressed by anti-PD-(L)1 CPI therapy supports their utility as a predictive biomarker for therapy.

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3O IGSF8 is an innate immune checkpoint and cancer immunotherapy target

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Background: Loss of MHC-I antigen presentation is often associated with T cell excluded tumors, and represents a common mechanism of both primary and acquired resistance to immune checkpoint blockade (ICB) treatment. MHC-I normally acts as a marker of "self" and cells that lack MHC-I are recognized and killed by innate immunity. A major puzzle in cancer immunology remains as to how T cell excluded tumors with MHC-I antigen presentation defects evade innate immune killing.

Methods: Integrating functional genomics, big data, and artificial intelligence, we discovered that IGSF8 expressed on cancer cells is a conserved innate immune checkpoint. IGSF8 is normally expressed in neuronal tissues and is not essential *in vitro* or *in vivo*. However, knockout of IGSF8 in B16-F10 melanoma cell line decreased tumor growth *in vivo*. For clinical relevance of IGSF8 in tumor immunity, we analyzed genomics, transcriptomics, and clinical data from The Cancer Genome Atlas (TCGA). We developed an antibody (GV20-0251) against IGSF8 and tested its function to induce immune cell killing of cancer cells *in vitro* and inhibit tumor growth *in vivo*.

Results: IGSF8 has receptors on both natural killer (NK) cells and dendritic cells (DC) to strongly suppress NK cytotoxicity and antigen presentation. In many cancer types across TCGA, IGSF8 is frequently DNA copy number amplified and overexpressed, and IGSF8 expression is associated with low antigen presentation, low immune infiltration, and worse overall survival in patients with low MHC class I expression. We developed a cross-species reactive antibody against IGSF8 (GV20-0251) which blocks IGSF8 interaction with NK and DC. This antibody enhances NK killing of cancer cells *in vitro* and increases antigen presentation, NK-mediated cytotoxicity, and T cell signaling *in vivo*. In multiple syngeneic tumor models (B16-F10, CT26, LLC and EMT6), anti-IGSF8 shows single-agent efficacy and is synergistic with anti-PD1 in controlling tumor growth.

Conclusions: IGSF8 is a novel innate immune checkpoint and cancer immunotherapy target. Given the ability for anti-IGSF8 to activate innate immunity, a phase 1 study has been initiated to explore the IGSF8 inhibitor GV20-0251 in patients with advanced or metastatic solid tumors (NCT05669430).

Legal entity responsible for the study: GV20 Therapeutics.

Funding: GV20 Therapeutics.

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Wu, B. Xie, R. Zheng, Q.Yu: Financial Interests, Personal, Full or part-time Employment: GV20 Therapeutics. Q. Ding: Financial Interests, Personal, Full or part-time Employment, Stock Ownership: GV20 Therapeutics. C. Sheng: Financial Interests, Personal, Financially compensated role, Stock options: GV20 Therapeutics; Financial Interests, Personal, Full or part-time Employment: Novartis. X. Hu: Financial Interests, Personal, Officer, Stock Options: GV20 Therapeutics. X.S. Liu, T.Xiao: Financial Interests, Personal, Officer, Director, Stock ownership: GV20 Therapeutics.

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4P Spatially resolved transcriptome elucidates bidirectional tertiary lymphoid structure interacts with tumor microenvironment of non-small cell lung cancer

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Background: The presence of tertiary lymphoid structure has a significant correlation with the lung cancer patient's response to immune checkpoint inhibitors. Nonetheless, the developmental characteristics of TLS and their surrounding tumor microenvironmental features in the primary tumor have not been elucidated comprehensively.

Methods: We utilized spatially resolved transcriptome and single-cell RNA sequencing to examine the molecular signatures and the essential cell types of TLS during its maturation process in the tumor microenvironment. Additionally, multiplex immunofluorescence staining and whole transcriptome sequencing were performed for validation.

Results: We categorized 406 potential TLSs into four states: pre-TLS, primary TLS, mature TLS, and aging TLS - based on their spatial molecular characteristics. The high expression of FDCSP in follicular DCs is a novel marker to promote TLS maturation by specifically binding to activated B cells. Three types of receptor-ligand interactions in mature and aging TLS could predict the prognosis in early-stage LUAD. Interestingly, aging TLS with significantly upregulated FOXP3 and TOX2 could limit anti-tumor immunity. Additionally, the molecular characteristics of aging TLS showed a lower expression of a group of CC chemokine ligands compared to mature TLS, which could potentially lead to a weaker anti-tumor response. We also observed an increase in tumor proliferation activity in the periphery of the aging TLS region. One approach to reverse the anti-tumor activity of aging TLS to that of mature TLS could be to increase the concentration of environmental chemokines while simultaneously blocking the upregulation of TIGIT in aging TLS.

Conclusions: Those results demonstrated that the condition of TLS was influenced by the neighboring tumor microenvironment in the early-stage LUAD. And the conventional mature TLS would eventually reach a biologically aged state in the same tumor microenvironment. By regulating chemokine signaling in the aging TLS's surrounding environment, it could potentially serve as an adjuvant therapy to enhance the anti-tumor activity of immune elements in resectable LUAD patients.

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5P Tertiary lymphoid structures (TLS) presence and stromal blood vessels heterogeneity differentially influence recurrence, lymphovascular, and perineural invasion in breast cancer molecular subtypes

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Background: Tertiary Lymphoid Structures (TLS) mediate local antitumor immunity. Since cancer immunotherapy, TLS interests grown considerably. We examined TLS and tumor stromal blood vessels for BC molecular subtypes associated with recurrence, lymphovascu-lar (LIV), and perineural invasion (PnI).

Methods: CD34/SMA double immunostaining revealed TLS high endothelial venules and BC tumor stromal immature and mature blood vessels. Statistical study linked microscopic data to recurrence, LIV, and PnI.

Results: TLS- subgroups have higher LIV, PnI, and recurrence ($p<0.001$), except for Luminal A type. LIV and PnI rise in HER2+/TLS- subgroups ($p<0.001$). TNBC/TLS- had the highest recurrence and invasion risks. TNBC/TLS- subgroup recurrence is related to tumor grade and LIV/PnI ($p<0.001$), unlike other TLS- subgroups. PnI but not LVI are related with TNBC/TLS+ subgroup recurrence ($p<0.001$).

Conclusions: TLS affect BC molecular subtype recurrence, LVI, and PnI differently. Its antitumor immunity mediator seems closely associated to tumor aggressiveness and stromal blood vessels.

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6P Combined single-cell and spatially resolved mapping of the human lymph node ecosystem reveals fundamental principles of lymphoma tissue organization

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Background: Lymph nodes (LN) act as central hubs for the orchestration of adaptive immune responses. A network of lymph node stromal cells (LNSC), including mesenchymal and endothelial cells, build a 3D network for immune cells to migrate and home to distinct niches in the LN. Within B cell non-Hodgkin lymphomas, indolent follicular lymphomas (FL) are characterized by subtle structural changes while the compartmentalization of the tissue remains present. In contrast, aggressive diffuse large B cell lymphomas (DLBCL) are defined by a complete loss of tissue organization indicating a potential role of LNSCs in tumorigenesis. While the morphological differences are well-known, the underlying molecular and cellular mechanisms remain poorly understood.

Methods: Here, we dissect the mechanisms underlying loss of structure in lymphomagenesis using combined single-cell transcriptome and spatially-resolved mapping approaches of LNSCs and immune cells.

Results: Using ultra-high plex immunofluorescence imaging, we characterized how lymph node cells organize into spatially distinct cellular neighborhoods, the disruption of which was congruent with lymphoma-induced remodeling. Using single-cell transcriptome data, we investigated the molecular programs driving this loss of organization. In DLBCL, chemokines relevant for immune cell organization were downregulated, while chemokines contributing to inflammation were upregulated, suggesting a phenotypic switch from a structural organized to an inflammatory and fibrotic state. *In silico* cell-cell interaction analysis indicated that besides the loss of mesenchyme-derived chemokine gradients, inflammatory immune cells outside of follicles turn into ectopic sources of these chemokines, an effect which likely contributes to the diffuse growth pattern of aggressive lymphomas. High expression of organizing chemokines was associated with better overall survival, this association being significant in FL and a trend in DLBCL.

Conclusions: Collectively, these data suggest that a reprogramming of the LN microenvironment triggers an imbalance in chemokine gradients, which underlies loss of tissue organization in aggressive lymphomas.

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7P Engineered salmonella blocks cancer metastasis by activating NK cells in an IFN-γ-dependent manner

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Background: Metastasis accounts for 90% of cancer related deaths and blocking of metastatic cascade has critical clinical impact. However, the clinical drug development for cancer treatment, including cancer immunotherapies, is evaluated largely depending on their ability to cause tumour shrinkage and ignores the effect on metastasis as it has proven challenging to target. Therefore, there is an urgent need for novel therapeutic strategies and agents targeting metastasis. Using an attenuated *Salmonella typhimurium* strain YB1 engineered by our lab, we have found a potent suppressive effect of attenuated *Salmonella* on cancer metastasis, regardless of cancer types and genetic background, by evoking strong anti-metastatic immune response.

Methods: Mutant mice and antibody-mediated cell depletion were used to identify the host genetic and cellular requirement for the bacterial supression of cancer cell metastasis. CyTOF (mass cytometry or cytometry by time of flight) was used to investigate the the innate immune responses after *Salmonella* treatment.

Results: Our studies showed that suppression of cancer metastasis by attenuated *Salmonella* only requires the innate immune response. Among the many induced cytokines, IFN-γ was identified as an indispensable factor for inhibiting cancer metastasis. CyTOF and antibody-mediated cell depletion analysis of the innate immune responses after *Salmonella* treatment, revealed that NK cells are the major factor involved in *Salmonella*-provoked metastasis suppression.

Conclusions: We found that IFN-γ was mainly produced by NK cells during early *Salmonella* infection, and in turn, IFN-γ promoted the accumulation, activation and cytotoxicity of NK cells. The IFN-γ-dependent NK cells directly eliminated newly accumulated cancer cells in the lung to block the cancer metastasis cascade in response to the *Salmonella* treatment.

Legal entity responsible for the study: The author.

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8P Modulating tumor microenvironment using a VEGF active immunotherapeutic approach in gastrointestinal tumors: Beyond angiogenesis modulation

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Background: Targeting of the vascular endothelial growth factor (VEGF) is known for going beyond mere modification of angiogenesis, and extends to the systemic and intratumoral regulation of immune cells activation state. In this study, we aim to explore the effect of a VEGF active immunotherapy based on a recombinant antigen named CIGB-247, in the systemic and tumor compartments in preclinical settings for mice, and in a subset of 22 patients with advanced gastrointestinal cancer (GIC) from phase I clinical trials (RPCEC00000102 and RPCEC00000155).

Methods: BALB/c mice were immunized with CIGB-247, and challenged with CT26 colon carcinoma cells subcutaneously. A week after the last immunization mice were euthanized and the tumor and the systemic compartment, were analyzed by ELISA, flow cytometry, and RT-QPCR assays. GIC patients' serum and leukocyte samples were evaluated for cytokines, specific VEGF antibody titers, and VEGFR2 neutralization using ELISA, while the cellular response was assessed by ELISPOT.

Results: The vaccine significantly boosted the infiltration of activated CD3+ cells and caused a decrease in the number of MDSCs and Tregs in analyzed compartments. The levels of VEGF, PLGF, and CXCL1 were significantly reduced in the tumor lysates, while the concentration of CD8 activation-related molecules like IFN-γ, and GRZ-B were induced. Finally, we analyzed GIC cases within the two phase I clinical trials after stratification between responders and non-responders. The evaluations indicate a significant increase in the VEGF-specific humoral and cellular response parallel to a reduction in VEGF that relates significantly to increased survival. Within this small cohort, reduction or stabilization of other proangiogenic factors was also detected.

Conclusions: CIGB-247 antigen-based vaccine increased tumor-infiltrating lymphocytes and reversed the immunosuppressive effect of the tumor microenvironment in the CT26 mouse model. Such results were corroborated in a GIC patient cohort indicating that the strategy might be a successful treatment option for such patients by modifying systemic and tumor microenvironment beyond angiogenesis modulation.

Clinical trial identification: RPCEC00000102, RPCEC00000155.

Legal entity responsible for the study: Center for Genetic Engineering and Biotechnology.

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9P Identification of a μCT-based radiomic signature of CD8+ tumour infiltrating lymphocytes in an orthotopic murine model

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Background: In the era of immunotherapy (IT), radiomics emerged as a non-invasive tool to decode tumor immune microenvironment (TIME) and predict IT response. Intrinsic patient and tumor variability challenging the explainability of radiomic readouts might be overcome in preclinical settings. Thus, we aimed to develop a μCT radiomic platform in a CD8 T cell functionally manipulated orthotopic murine model, closely mimicking human head and neck cancer, to validate the biological reality of radiomics in assessing tumor infiltrating lymphocytes (TILs).

Methods: Set-up, training and validation experiments (N Tot = 50 C57BL/6 mice) were conducted as follows: submucosal injection of 0.5 x 10^6 TC1-luc cells in the right inner lip and generation of an orthotopic model of head and neck cancer (day [D] -7); tailored treatment consisting of irradiation [D0] ± anti-CD8 antibody [D3] to selectively enrich or deplete CD8+ TILs; in vivo preclinical imaging through Quantum FX μCT technology [D3, D4]; mice euthanasia and tumor sampling [D4], followed by immunohistochemical staining for CD8; μCT image pre-processing (voxel resampling, image discretization and delineation of the volume of interest) and radiomic features (RFs) extraction (pyradiomics).

Results: We developed and optimized an efficient quantitative μCT imaging approach. Overall, 106 μCT RFs (shape, first- and second- order) were extracted and correlated with distinct TIME. Following redundant feature elimination (Spearman correlation, cut-off = 0.99) and Z-score standardization, we identified 12 μCT-RFs differentially regulated in T CD8 enriched *vs* depleted TIME ($P < 0.05$, Mann Whitney). The statistical performance of our CD8 signature, documented in both training and validation sets, was further implemented when pooled data were analysed ($P < 0.01$). Finally, by applying a reconstruction algorithm, we obtained a 3D map of CD8+ TILs, which enabled us to correlate the spatial distribution of immune cells with μCT textural parameters.

Conclusions: Our results document the feasibility and accuracy of radiomics to detect dramatic changes in T cells within the TIME, thus providing effective radio-immune signatures potentially translatable into clinical practice.

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10P Cancer cells induce intracellular gap formation in sinusoidal endothelial cells to produce liver metastasis through pro-inflammatory paracrine mechanisms

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Background: Engraftment of cancer cells to liver pre-metastatic niches requires complex interaction with liver sinusoidal endothelial cells (LSECs). Intracellular gap (iGap) formation in LSECs is caused by the destruction of fenestrae and appears under pathological conditions. Here, we aimed to explore the novel role of LSECs-iGap in liver metastasis of cancer cells.

Methods: Mouse models using acetaminophen (APAP) or thioacetamide (TAA) followed by intrasplenic injection of hepatocellular carcinoma (HCC) cell line, Hepa1-6 cells, to assess the LSECs-iGap formation. Functional effects of LSECs-iGap on cancer cells were analyzed using MMPs inducer, monocrotaline and inhibitor, doxycycline and MMP2/9 inhibitor. Morphological and molecular features of LSECs-iGap were examined using *in vivo* mouse models and *in vitro* co-culture system with electron microscopy, 3 dimensions tomographic reconstruction image (3D-TRI), RNA-sequencing, cytokine array and endothelial trans-endothelial migration assay. Biopsy specimens from 98 patients with HCC were statistically evaluated.

Results: APAP-induced liver injury and TAA-induced fibrotic liver resulted in LSECs-iGap formation, which positively correlated with increased numbers of metastatic foci after Hepa1-6 cells injection. In addition, Hepa1-6 cells induced IL-23-dependent TNF-α secretion by LSECs and triggered LSECs-iGap formation, toward which their processes protruded to transmigrate into the liver parenchyma. TNF-α caused depolymerization of F-actin and increased MMP9, ICAM1, and CXCLs expression in LSECs. Moreover, high expression of ICAM1 and MMP9 was significantly associated with intrahepatic metastasis and overall survival of patients with HCC. Blocking MMP9 activity by doxycycline or MMP-2/9 inhibitor eliminated LSECs-iGap formation and attenuated liver metastasis of Hepa1-6 cells.

Conclusions: This study revealed that cancer cells induced LSEC-iGap formation via pro-inflammatory paracrine mechanisms and proposed MMP9 as a novel target for blocking cancer cell metastasis to the liver.

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11P Targeting stromal cells to reverse immune suppression in triple-negative breast cancer

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Background: Although there have been some positive results, the success of immune checkpoint inhibition in triple-negative breast cancer (TNBC) to date remains rather limited. A better understanding of mechanisms of immune evasion other than via PD1/PD-L1 axes and how to overcome these is therefore much needed to improve the efficacy of immunotherapy in this poor prognosis disease. Recent studies of the tumour microenvironment (TME) have elucidated the heterogeneity of stromal cells and suggested that stromal subsets play an important role in regulating anti-tumour immunity. Here we investigate how stromal cells contribute to the immunosuppressive TME and as a potential therapeutic target to overcome this.

Methods: Using co-culture models of patient-derived TNBC cancer-associated fibroblasts (CAFs) and peripheral blood mononuclear cells (PBMCs) from healthy donors, we applied flow cytometry and single-cell RNA sequencing (scRNAseq) to assess stromal-immune interactions *in vitro*. A high throughput drug screen was performed to identify novel stromal-targeting drug candidates which could reverse stromal-induced immunosuppression in our coculture models.

Results: TNBC CAFs suppress the proliferative capability of both CD4 and CD8 T cells *in vitro*. scRNAseq of these co-culture models demonstrate that CAF-cocultured T cells are driven into LAG3+ exhausted state enriched for canonical pathways of immunosuppressive cytokine signalling. Drug screen identified Talabostat as a novel candidate which shifts stromal subtype composition from aSMA-positive to aSMA-negative phenotypes. Talabostat treatment in the co-culture models reverses CAF-induced suppression of T cell proliferation.

Conclusions: Talabostat reverses stromal-mediated T cell suppression and is a potential therapeutic strategy to elicit a more effective immune response.

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12P Immuno-suppressive role of tumour-derived GDF-15 on myeloid cells

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Background: Growth and differentiation factor 15 (GDF-15), a divergent member of the TGF-β superfamily, shows high expression during pregnancy. Beyond that, GDF-15 is induced in stressed and damaged tissues limiting inflammation. GDF-15 also functions as a prognostic marker in numerous cancers and was shown to be a key inhibitor of T-cell infiltration in solid tumors. However, the impact of GDF-15 on other immune cells in the tumor microenvironment (TME) is still poorly understood.

Methods: M1 and M2 macrophages were derived from either the human monocytic THP-1 cell line or monocytes from healthy donors by incubation with IFNγ and LPS (M1) or IL-4 and IL-13 (M2) in combination with or without GDF-15. Analysis was performed by Western Blot, flow cytometry and RT-qPCR. To investigate the role of GDF-15 *in vivo* we inoculated NOG mice subcutaneously with SK-Mel5 *GDF15*$^{-/-}$ cells. On day 35/36 tumors were assessed on myeloid immune cell subpopulations by flow cytometry.

Results: Our initial studies have shown that monocytes are sensitive to GDF-15 mediated inhibition of tumor infiltration. Now we wanted to understand how GDF-15 affects the myeloid compartment beyond infiltration. In primary cells, GDF-15 exposure of monocytes during IFNγ or LPS induced M1 polarization led to a reduction of activation marker expression such as HLA-DR, CD80 and CD86 and an altered cytokine secretion profile. M2 macrophages did not show differences in their activation pattern. This effect was transferable to THP-1 derived M1 macrophages. TGF-ß was not able to exert this biologic effect. Activation was restored by addition of a GDF-15 neutralizing antibody. *In vivo*, GDF-15 had no direct effect on tumor growth, yet we observed that loss of GDF-15 altered the TME and led to an increase of activated myeloid cells such as M1 macrophages and dendritic cells.

Conclusions: GDF-15 secretion helps tumors to generate a TME that is poorly infiltrated by anti-tumoral immune cells. GDF-15 counteracts myeloid activation in the TME, a hallmark of initiation of antitumoral immune responses. By inducing a more pro-inflammatory tumor phenotype, anti-GDF-15 antibodies may synergize with other immunotherapeutic agents. A clinical phase 2 trial combining anti-GDF-15 (CTL-002) with anti-PD-1 (NCT04725474) is ongoing.

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13P Disrupting the immunosuppressive tumor microenvironment using genetically engineered macrophages for triple-negative breast cancer therapy

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Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer and accounts for 40% of breast cancer deaths. Currently, surgery and chemotherapy are standard therapy in TNBC, whereas immunotherapies often fail due to a cold tumor microenvironment (TME), which is mainly generated by tumor associated macrophages (TAMs). Importantly, immunosuppressive M2-like TAMs are associated with worse outcome in TNBC patients. Cytokines like IL-10 and TGFβ induce M2-like TAMs, which inhibit the adaptive immune response and promote tumor growth, migration, and vascularization. In contrast, M1-like macrophages induce an anti-tumor immune response and tumor cell death. Thus, we aim to develop an adoptive cell therapy employing macrophages that are polarized towards a M1-like phenotype by the immunosuppressive cytokines, which will generate an inflamed TME.

Methods: To achieve M1 polarization in a M2-inducing TME, we genetically modified macrophages to express a chimeric cytokine receptor (ChCR), which will induce an M1 signaling upon stimulation with M2 inducing cytokines. Here, we evaluated two ChCR variants activated by IL-10 and TGFβ, respectively. We transduced monocytes to express the ChCR using lentiviruses. Upon differentiation to macrophages, we assessed M1 polarization by analyzing surface marker expression and the secretome. Moreover, we assessed their effect on TNBC cell line viability.

Results: We could successfully transduce macrophages at 80% and confirmed ChCR expression and M1 signaling. Furthermore, we could show that stimulation of ChCR macrophages by IL-10 or TGFβ switches them towards an M1-like phenotype, as analyzed by surface marker expression and IP-10 secretion. Moreover, we found that the viability of TNBC cell lines was reduced upon treatment with supernatants of TGFβ or IL-10 stimulated ChCR macrophages.

Conclusions: We could show that we can engineer macrophages to switch towards an M1-like phenotype in an M2-inducing environment. Thus, ChCR macrophages represent a promising strategy to disrupt the immunosuppressive TME. Currently, we are assessing the effect of ChCR macrophages on immune activation in vitro and their phenotype in TNBC co-cultures.

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14P Peripheral immune kinetics in survival prediction of small cell lung cancer patients treated with immune checkpoint blockade therapy

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Background: Small cell lung cancer (SCLC) is a lethal neoplasia. Chemotherapy (Ct) plus immune checkpoint blockade therapy (ICBt) is now the standard of care although limited survival benefit. Lack of biomarkers of response leads to suboptimal patient selection, distorting results of clinical trials. Deciphering the ICBt-driven peripheral immune events may recognize those patients who benefit the most. Here, we characterize early peripheral immune kinetics in SCLC patients treated with Ct + ICBt with improved survival.

Methods: SCLC patients from 8 centers were prospectively recruited into 3 cohorts. Cohort 1 include patients treated with Ct (n=24). Cohort 2 (n=37) comprise patients treated with Ct + anti-CTLA-4, and cohort 3 (n=20) patients treated with Ct + anti-PD-1/PD-L1. Peripheral blood mononuclear cells were obtained prior to treatment and after the first dose of ICBt. Variation in proliferation, senescence, adhesion, immunosuppression, and checkpoints markers was assessed by FACS. Kaplan−Meier and log-rank test were used for survival analysis. MaxStat was used to calculate cut points. A p-value <0.05 was considered statistically significant.

Results: We found 6 independent cellular subsets which modulation right after the start of ICBt identify patients with improved survival. An increase in CD8+CD103+Ki67+ cells identify survival benefit in cohorts 1 and 3 (p=0.043; 0.0033). An upregulation of Ki67 in total CD4+ (p=0.012; 0.0027) and CD4+PD-1+ T cells (p=0.026; 0.027), predicts long survival in ICBt cohorts 2 and 3, while a downregulation of CD4+ICOS+ T cells (p=0.025; 0.011) identified survival benefit in these ICBt cohorts. Expansion of Ki67+ and ICOS+ (p=0.0024; 0.0074) CD8+ T cells was also observed in CD8+ T cells from long survivors exclusively from cohort 2.

Conclusions: Expansion of CD8+CD103+Ki67+, CD4+Ki67+, and CD4+PD-1+Ki67+, or a reduction in CD4+ICOS+ circulating T cells subsets identify long survival patients treated with anti-CTLA-4 or anti-PD-1/PD-L1, while an increase in CD8+Ki67+ or CD8+ICOS+ cells predicts benefit only in patients treated with anti-CTLA-4. Assessment of the immune kinetics of these peripheral cellular subsets identify patients who benefit the most from ICBt in SCLC.

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15P CBL E3 ubiquitin ligases are key inhibitory regulators in PD-1/LAG-3 co-signaling in human cancers, targeted through bispecific co-blockade

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Background: A significant number of cancer patients do not benefit from PD-L1/PD-1 blockade immunotherapies. PD-1 and LAG-3 co-upregulation in T-cells is one of the major mechanisms of resistance by establishing a highly dysfunctional state in T-cells.

Methods: A high-throughput screening was performed of PD-1/LAG-3 multiomic expression profiles in public databases of human cancer biopsies, to establish relationships between infiltrating tumor-infiltrating PD-1/LAG-3 T cells with biomarkers both in T cells and within the tumour microenvironment. These results were validated in engineered T-cell lines with constitutively active PD-1, LAG-3 pathways, and their combination, analysed by high-throughput quantitative proteomics and validated by conventional molecular techniques on primary T cells from NSCLC patients.

Results: The high-throughput multiomic human cancers screening and the experimental proteomic T cell lines uncovered a strong PD-1/LAG-3 dysfunctionality signature that was found which regulated immune, proteomic, metabolic, genetic, and epigenetic pathways. These mainly relied on differential regulation of E3 ubiquitin ligases CBL-B and C-CBL. Notably, LAG-3 expression has never been associated to CBL ubiquitin ligases before.

Conclusions: PD-1/LAG-3 co-signaling profile uncovers a highly dysfunctional regulated programme. Co-blockade with a bispecific drug but not with a combination of anti-PD-1/anti-LAG-3 antibodies achieved both CBL-B and C-CBL inhibition, reverting T-cell dysfunctionality in lung cancer patients resistant to PD-L1/PD- 1 blockade. These results will help identifying the mechanisms of intrinsic resistance to PD-1 blockade mediated by LAG-3 co-signaling.

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16P Terminally exhausted CD8+ T cells and increased immunosuppressive soluble factors in malignant ascites of patients with gastric cancer with peritoneal metastasis

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Background: Peritoneal metastasis is a relatively common manifestation of poor prognosis and resistance to immune checkpoint blockades in patients with gastric cancer (GC). In the present study, we aimed to investigate the exhaustion status of $CD8^+$ T cells and immunosuppressive soluble factors in malignant ascites from patients with GC and peritoneal metastasis.

Methods: We obtained pathologically confirmed malignant ascites samples along with peripheral blood from 27 patients with GC peritoneal metastasis and examined the exhaustion status of $CD8^+$ T cells using multicolor flow cytometry. A multiplex enzyme-linked immunosorbent assay for immunosuppressive soluble factors, including matrix metalloproteinase-2 (MMP-2), MMP-7, transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), E-cadherin, and angiopoietin-2, was performed on 45 cell-free fluid samples (15 paired malignant ascites and plasma of patients with GC and 15 benign ascites of liver cirrhosis patients).

Results: $CD8^+$ T cells in the malignant ascites of GC showed significantly increased expression of PD-1, TIGIT, and TIM-3 compared with peripheral blood $CD8^+$ T cells. $CD8^+$ T-cells in malignant ascites had more terminally differentiated phenotypes (T-$bet^{low}Eomes^{high}$) and tumor antigen reactivity ($CD39^+$ $CD103^+$) than peripheral blood $CD8^+$ T cells. The expression levels of immunosuppressive soluble factors, including MMP-2, MMP-7, TGF-β, HGF, VEGF, E-cadherin, and angiopoietin-2, were significantly higher in the malignant ascites than in the plasma of patients with GC or in the benign ascites of liver cirrhosis patients.

Conclusions: We found that $CD8^+$ T cells in the malignant ascites of GC are terminally exhausted and tumor antigen-reactive T cells. Furthermore, immunosuppressive soluble factors were significantly increased in cell-free fluid of malignant ascites of GC. Thus, the present findings suggest that the co-blockade of immune checkpoints and immunosuppressive soluble factors may be a feasible therapeutic option for patients GC with peritoneal metastasis.

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17P Continued expansion of long-lived effect CD8+ T cells associates with durable response post-PD-1 blockade

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Background: Early $CD8^+$ T cell responses to PD-1 blockade are well-characterised. However, an understanding of the long-term clonal and transcriptomic signatures of complete response (CR) to Immune Checkpoint Blockade (ICB) is currently lacking. We aimed to identify and describe $CD8^+$ T cell clonal and transcriptomic changes post complete response to PD-1 blockade in metastatic melanoma (MM).

Methods: We performed single-cell RNA sequencing (scRNAseq) of both the T cell receptor (TCR) and transcriptomes of PBMCs and sorted peripheral $CD8^+$ T cells in patients with MM with a complete response to PD-1 blockade (n=10), patients with progressive disease (PD, n=6) and healthy donors (HD, n=2). Blood was sampled at multiple time points, including a median of 3.2 years following cessation of PD-1 blockade for CR.

Results: Following a CR and cessation of ICB, there is increased abundance of a subtype of $CD8^+$ T cell characterised by high expression of NK-associated genes, termed a killer-like subset. Using the top 25 genes upregulated by this subset to generate a 'Killer Score', we show that patients with CR to anti-PD-1 demonstrate a broad increase in killer gene expression over time absent in those with PD and HDs. By tracking key clones through TCR usage, we identify those which are stable/expanding from pre-treatment to post treatment, occupy >0.5% of the repertoire and are persistent post-cessation of ICB, terming these large expanding persistent clones. These clones have a predominantly cytotoxic, effector, gene expression profile and display surface markers consistent with a recently-described 'Long-lived Effector Cell' subtype.

Conclusions: CR to PD-1 blockade is associated with persistence of highly-cytotoxic effector $CD8^+$ T cells that circulate years after cessation of treatment. Whilst similar subsets have been implicated with chronic viral infection, these observations are novel in the cancer setting and have important implications for mechanisms of durable disease control.

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18P Exposure of calreticulin is required for vitamin C immunomediated cancer surveillance

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Background: Vitamin C (VitC) was shown to synergize with immune checkpoint blockade in tumor bearing immunocompetent mice, which provided the rationale for the ongoing ALFEO trial in colorectal cancer patients (Clinical Trial Registration Number 2022-502101-15-00). In this work, we aimed to elucidate the molecular mechanisms underlying these preclinical observations. We hypothesized that VitC could strain cancer cells, which react by emitting danger signal molecules, which in turn could stimulate an immune mediated anticancer response.

Methods: We assessed expression of the oxidative stress marker hydroxyguanosine (8-OHG) and danger signal molecules (calreticulin and HMGB1) in breast and colon murine tumors treated with VitC. A calreticulin blocking antibody was given in combination with VitC to functionally ascertain the role of this stress signal protein.

Results: Pharmacological doses of VitC were able to strongly induce oxidative stress as indicated by strong 8-OHG staining in tumor sections. VitC-stressed tumor cells mobilized the danger molecules calreticulin and HMGB1. Although the induction of these danger markers was seen in tumors grown both in immunocompromised and immunocompetent VitC treated mice, its anticancer activity was evident only in the presence of an intact immune system. In vivo, a calreticulin blocking antibody effectively prevented its translocation and inhibited HMGB1 release in murine tumors. Notably, preventing calreticulin exposure abrogated the immunomediated anticancer effect of VitC. VitC enhanced the infiltration of natural killers, activated CD8+ T lymphocytes, while it decreased the number of Tregs. Calreticulin blockade impaired the modulation of the immune tumor microenvironment induced by VitC.

Conclusions: We unveil that VitC is able to mobilize calreticulin and HMGB1, which are among the established markers of immunogenic cell death. These results, alongside the observation that VitC exerts its maximal antitumor activity only in immunocompetent mice are clues that VitC could act as immunogenic cell death inducer when given at pharmacological doses. Our findings have implications for cancer patients enrolled in clinical trials based on VitC containing regimens

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19P Preclinical and clinical significance of VEGF deprivation in ovarian cancer through a specific active immunotherapy

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Background: Vascular endothelial Growth factor (VEGF) has an important role in the physiology of normal ovaries and is a major player in the pathogenesis of OvCan. We have designed HEBERSaVax which is an active immunotherapy approach based on the use of a functionally deficient VEGF 121 isoform as antigen combined with an adjuvant. On immunocompetent mice, the ID8 model resembles the advanced stages of human OvCan and intervention results offer data potentially translatable to the clinical setting. Two sequential phase I clinical trials with single HEBERSaVax treatment have been concluded in patients with advanced solid tumors including subjects with advanced OvCan. A phase II clinical trial in this oncologic setting was recently finished. Herein we present data on HEBERSaVax effects on tumor development and reshaping of the microenvironment in OvCan.

Methods: C57BL/6 mouse tumor ID8 model was used to evaluate the vaccine effects in cancer growth control and tumor microenvironment remodeling. Immune response and cytokines concentrations were assessed by ELISA. Ascitic leukocytes were characterized by flow cytometry. Serum and leukocyte samples from selected OvCan patients (n=9) from the phase I clinical trials (RPCEC00000102 and RPCEC00000155) were also analyzed. Human anti-VEGF antibodies and cytokines were determined by ELISA. The cellular response was evaluated by IFN-γ ELISPOT.

Results: HEBERSaVax-based treatment increases the survival of ID8 tumor-bearing mice by reducing the ascites loads. An increase in VEGF-specific antibodies were detected in mice ascitic fluids, in parallel to a reduction of VEGF levels. The numbers of T lymphocytes and the expression of MHCII in macrophages were increased in the ascitic fluid. Data analyses from OvCan patients in clinical trials revealed that decreased or stabilized VEGF serum levels, positive anti-VEGF titers, and cellular responses, were related to an increase in survival. Processing of phase II clinical trial (RPCEC00000246) immune variables evaluations is ongoing (n=38, final data: ESMO).

Conclusions: Our findings indicate that HEBERSavax's impact on preclinical ID8 settings might be translatable to a positive outcome in advanced OvCan patients.

Clinical trial identification: RPCEC00000102, RPCEC00000155 and RPCEC00000246.

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20P The essential role of DNA repair in the pharmacological activities of AST-3424

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Background: AST-3424 is an AKR1C3-activated prodrug and releases a toxic bis-alkylating moiety after activation by tumor-specific AKR1C3. AST-3424 is currently being investigated in multiple phase I/II clinical trials for the treatment of various cancers. Wild-type p53 cells have checkpoint redundancy via G1/S checkpoint and G2/M checkpoint while p53-mutant tumor cells are solely dependent on G2/M checkpoint to arrest the cell cycle after DNA damage and allow DNA repair before progressing. Here, we have explored the essential role of DNA repair in AST-3424-mediated pharmacological activities *in vitro* and *in vivo*.

Methods: We employed *in vitro* cytotoxicity, DNA damage, apoptosis, cell cycle and cellular signaling assays in both p53-proficient H460 and p53-deficient HT29 cells as well as *in vivo* xenograft models to investigate the essential role of DNA repair in AST-3424-mediated pharmacological activities.

Results: AST-3424 induced cytotoxicity, DNA damage, apoptosis and cell cycle arrest at G2 phase in a dose- and AKR1C3-dependent manner in both p53-proficient H460 and p53-deficient HT29 cells. However, enhancement of AST-3424 cytotoxicity by G2 arrest inhibitors, including adavosertib, AZD7762 and ceralasertib was only observed in HT29 but not in H460 cells. Similarly, AST-3424-induced γH2AX and apoptosis were also enhanced in HT29 upon the addition of G2 arrest inhibitors. The enhanced activity of AST-3424 in HT29 cells by G2 arrest inhibitors was due to the attenuation of cell cycle G2 arrest, as evidenced by decreased phosphorylation of Cdc2-Y15 and increased phosphorylation of histone H3, as well as reduced expression of RAD51, resulting in impaired DNA repair capacity. To further examine the essential role of DNA repair in AST-3424 anti-tumor activity, we utilized two PDX models with BRCA deleterious mutations lacking capacity of double-strand DNA repair. The results showed that AST-3424 exhibited excellent anti-tumor activity in two pancreatic PDX models with BRCA deleterious mutations and high expression of AKR1C3.

Conclusions: DNA repair plays an essential role in AST-3424-mediated *in vitro* biological activities and *in vivo* anti-tumor activity. The preclinical data presented in this study support a new approach for cancer treatment.

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21P Implications of KMT2C knockdown for DNA damage repair in breast cancer

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Background: Pathogenic mutations in the epigenetic modulator histone-lysine N-methyltransferase 2C (KMT2C) occur in up to 1 in every 6 breast cancers and KMT2C likely functions as a tumour suppressor. Despite this high frequency, therapeutic implications of deleterious KMT2C mutations are poorly understood and detailed preclinical work is still needed. DNA damage repair pathways may be affected by KMT2C mutations according to published preclinical data. The aim of this study is to identify the effects of KMT2C knockdown in vitro in breast cancer cells as a basis for identifying potential synthetic lethality drug targets.

Methods: MCF-7 (ER+ breast cancer) cells were cultured and 500,000 cells per well were plated on 6-well plates. KMT2C siRNA was transfected via Lipofectamine as per protocol in three wells, with universal control siRNA in three wells. Total RNA was extracted and sent for sequencing. RNA expression was quantified by RT-qPCR.

Results: RNA-seq confirmed reduction in expression of KMT2C in KMT2C siRNA-treated cells vs controls. RT-qPCR showed a reduction in expression of DNA damage repair genes including BRCA1 (RQ = 0.36), BRCA2 (RQ = 0.37), RAD51 (RQ = 0.36), RAD54L (RQ = 0.28) and POLD3 (RQ = 0.47).

Conclusions: KMT2C loss-of-function in breast cancer may impact DNA damage response pathways including homologous recombination and therefore be implicated in response to established treatments such as PARP-inhibitors. Further study including mapping of co-dependencies by whole genome siRNA screens in KMT2C-mutant breast cancer cells to identify synthetic lethality targets, as well as cell toxicity assays, are being performed in light of these results.

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22P Clinical significance of DNA damage response mutations in early stage NSCLC

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Background: DNA damage response (DDR) pathways are essential to sustain genomic stability and play a critical role in cancer development and progression. Here, we investigated DDR genes mutations profile in early-stage non-small cell lung cancer (NSCLC) and their prognostic values.

Methods: We first examined 74 DDR genes involved in seven DDR pathways and then focused on six specific genes: *ATM, BRCA1/2, CHEK1, BARD1, BRIP1*. A total of 179 stage I and IIIa NSCLC patients who received curative resection in Peking Union Medical College Hospital and their corresponding samples were collected for DNA sequencing, immunohistochemistry and survival analysis.

Results: A total of 167 eligible patients were finally analyzed. Mutation frequencies were 82% and 26.3% for the selected 74 genes and 6 genes, respectively. No association was found between DDR gene status and PD-L1 expression, CD8 positive lymphocyte and tumor-associated macrophage (TAM) infiltration in tumor area. Numbers of gene mutations was significantly increased among patients with DDR alterations. Deleterious mutations in *ATM, BRCA1/2, CHEK1, BARD1* and *BRIP1* were independent prognostic indicators of significantly longer disease-free survival.

Conclusions: Deleterious mutations of these six genes were common in early-stage NSCLC and may serve as prognostic biomarkers.

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23P PMC-309: A highly selective anti-VISTA antibody reverses immunosuppressive TME to immune-supportive

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Background: PMC-309 is a novel human monoclonal IgG1 antibody (mAb). It binds with human VISTA, an immune checkpoint protein, with the effect of regulating the immunological activity of myeloid cells such as MDSC or myeloid-derived immune cells, thereby improving the antitumor activities of immune cells. In addition to being a novel drug substance, PMC309 will be the first IgG1 monoclonal antibody to act synergistically with other immunotherapies to improve treatment efficacy.

Methods: In vitro T cell activity: human PBMC was employed for the evaluation of T cell activity, and was stimulated with or w/o PMC-309 in the presence of anti-CD3/28 Antibody. In vivo study: MC38-bearing human VISTA knock-in (KI) mice were employed for the assessment of the anti-tumor activity of PMC-309. The tumor infiltrated immune cells: Immune cells in the TME were evaluated by immunohistochemistry (IHC) or flow cytometry (FACS) analysis.

Results: PMC-309 binding to VISTA-expressing cells is highly selective and the selectivity is maintained even in the low pH conditions that mimic TME. PMC-309 enhances the secretion of IFN-gamma, TNF-alpha, and IL-2 in Mixed Lymphocyte Reaction (MLR) settings. In addition, PMC-309 promoted monocyte differentiation into M1 macrophage which stimulates proinflammatory cytokine secretion of T cells. For the in vivo study, PMC-309 was intravenously administrated in VISTA-KI mice. The tumor growth rate was suppressed accompanied by a synergistic effect with an anti-PD1 antibody. The anti-tumor activity was associated with enhanced T cell activation, increased secretion of pro-inflammatory cytokines, and increased penetration of cytotoxic T cells, but lowing immune-suppressive MDSC cells into TME as demonstrated with IHC analysis.

Conclusions: PMC-309 enhanced both T-cell activation and monocyte activation. PMC-309 increased the number of T cell infiltration while a decrease of MDSCs in the TME. PMC-309 in combination with chemotherapy or other IO drugs could address the high medical unmet needs of patients with drug resistance to currently available IO treatment options.

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24P Single cell transcriptomics of the immune cells during chemotherapy in triple-negative breast cancer patients

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Background: Chemotherapy is the mainstay of systemic treatment for patients with triple-negative breast cancer (TNBC) due to the lack of targets for targeted therapy (HER2/neu; ER; PR). Components of the immune system are known to be involved in the response to chemotherapeutic treatment. Here we aimed to study the dynamics of changes in immune cell composition during neoadjuvant chemotherapy (NACT).

Methods: The immune cells were purified from peripheral blood and biopsy samples of 5 TNBC patients before NACT and 21st days of first course of NACT (AC regimen). Total cell concentration and viability (Calcein/DRAQ7) were assessed by flow cytometry (Cytoflex, Beckman Coulter). Single cells were sequenced on a Genolab M platform (GeneMind Biosciences) using 10x Genomics technology for fixed multiplexed samples. Data were analyzed using Seurat and SingleR.

Results: Sequencing revealed a variety of immune cell populations including: B cells, DC cells, NK cells, CD4+, CD8+ and T regulatory lymphocytes, classical and non-classical monocytes, granulocytes and others. In the blood, the pool of classical monocytes and NK cells were depleted up to day 21 after the first NACT cycle, while naive CD4+, CD8+ T cells and end effector CD8+ T cells, were increased by day 21. In the populations of monocytes and NK cells overexpression of *RGS2*, *ANXA1*, *FGL2*, *MX1*, *IFI6* genes were observed, involved in induction apoptosis. CD8+T-cells, as well as Th-1 and Th-2 CD4+ T-cells were characterized by increased expression of *NFKBIA*, *JUN*, *FOS*, involved in T cell differentiation. In the tumor microenvironment, depletion of CD4+ T cells, CD8+ T cells and memory B cells and an increase in T-regulatory cells and plasma cells were observed. *DUSP4*, *LCK, CXCR4*, *LTB*, *TNFRSF18*, *IL2RB* and *PTPN7* genes were overexpressed and involved in the regulation of cytokine secretion and inhibition of TCR signaling in CD4+ and CD8+ T cells; chemotaxis-mediated inflammation in memory B cells; T cells differentiation, and induction of invasion/migration of tumor cells in T-regulatory cells and plasma cells.

Conclusions: The first cycle of NACT induced renewal of the immune cells' composition in the blood and tumor microenvironment skewing towards to immune disfunction.

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25P Role of AXL activation on adaptive resistance to KRAS-G12C inhibitors in KRAS-G12C-mutated non-small cell lung cancer

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Background: KRAS is the most frequent targetable oncogene in non-small cell lung cancer (NSCLC). Recently, novel KRAS inhibitor have been clinically developed for treatment of KRAS G12C-mutated NSCLC patients. However, it is difficult to achieve complete remission of tumor. Therefore, the optimal combined therapeutic intervention with KRAS G12C inhibitors has a potentially crucial role in the clinical outcomes of patients. In this study, we focused on the mechanisms underlying adaptive resistance to KRAS G12C inhibitors and therapeutic strategies required to overcome them.

Methods: We used KRAS G12C-mutated NSCLC cell lines to evaluate the adaptive response to KRAS G12C inhibitors in vitro and in vivo. We also investigated the correlation between AXL expression in pre-treated tumors and clinical outcomes with sotorasib for KRAS G12C-mutated NSCLC patients.

Results: We reveal that AXL signaling was caused to the adaptive resistance to KRAS G12C inhibitors in KRAS-G12C mutated NSCLC, activation of which was induced by GAS6 production via transcriptional coactivator YAP. AXL inhibition reduced the viability of AXL-overexpressing KRAS G12C-mutated lung cancer cells by enhancing KRAS G12C inhibition-induced apoptosis. In xenograft models of AXL-overexpressing KRAS G12C-mutated lung cancer treated with KRAS G12C inhibitors, initial combination therapy with AXL inhibitor markedly regressed tumors and delayed tumor regrowth compared with KRAS G12C inhibitor alone or the combination after acquired resistance to KRAS G12C inhibitor. AXL was highly expressed in clinical specimens of KRAS G12C-mutated lung cancers and its high expression was associated with a low response rate to sotorasib.

Conclusions: These results indicated pivotal roles for AXL activation and its inhibition in the intrinsic resistance to KRAS G12C inhibitor.

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26P Pre-clinical modelling and treatment of BRAF mutated colorectal cancer

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Background: 10% of colorectal cancers (CRC) have a BRAF mutation (BM). This is a poor prognostic group with distinct clinical characteristics. Robust preclinical models that reflect this CRC subtype are currently lacking. We have developed a novel, aggressive, immune competent, genetically engineered mouse model (GEMM) that aligns well with human BM CRC.

Methods: 4 genes were targeted with the villinCre^{ER}: activating *Braf*$^{V600E/+}$ (B), deletion of *Trp53*$^{fl/fl}$(P), deletion of ALK5$^{fl/fl}$ and NOTCH1 intracellular domain expression *Rosa26*$^{N1icd/+}$ (N). This generated BPNA mice. Mice were induced and aged until clinical endpoint. Clinically relevant treatments were benchmarked, including BRAFi (Dabrafenib) combined with EGFRi (Erlotinib). Mouse tumour organoids were derived and high throughput drug screening was performed.

Results: BPNA mice developed endpoint tumours in the proximal colon in a short time period (37 DPI). Mice had high rates of T4 disease (57%) and, despite short latency, developed peritoneal metastasis in 5/27 mice (19%). Primary tumours had proficient mismatch repair (pMMR). Tumours classified as CMS4, aligned with the BM1 transcriptional subtype and displayed regenerative cancer stem cell markers. Therapeutic interventions based on the BEACON CRC (BRAFi+EGFRi) combinations were tested. Both BRAFi and EGFRi as monotherapies had no significant survival advantage (OS) *in vivo*. However in combination, mice lived twice as long with median OS of the combination group 66 DPI vs 32 DPI in the vehicle control (log-rank $p<0.001$). DUSP6 was only significantly suppressed in the BRAF/EGFRi arm suggesting effective MAPK targeting requires combination therapy. Through organoid drug screening, 28/166 compounds were identified as hits of which 3/5 top hits were proteasome inhibitors.

Conclusions: The BPNA GEMM aligns with human disease in terms of primary tumour characteristics and metastatic pattern. Mice also respond to standard of care therapeutics similarly to humans creating a good benchmark for further investigation. Organoid drug screens have highlighted a potentially novel drug class for BM CRC treatment. Future work will utilize these mice to test therapeutics enabling robust pre-clinical evidence to de-risk future novel early phase trials for BM CRC.

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27P Extending a classification system for atypical BRAF mutations to improve targeted therapies in colorectal cancer cells

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Background: Unlike other types of cancer that are sensitive to single-target agents, such as lung cancer and chronic myeloid leukemia, colorectal cancer (CRC) involves a complex network of interactions between activating oncogenes and is thus more likely to respond to multi-target therapy. Approximately 10% of CRC mutations are within the BRAF gene, the most frequent being BRAFV600E. While this mutation can be targeted with relatively high efficacy by single-target therapies, there exists a cohort of atypical BRAF mutations that confer higher resistance to currently available treatments. Furthermore, a large proportion of these atypical BRAF mutations are poorly understood.

Methods: We used principal component analysis and semi-supervised clustering learning methods to classify mutants unassigned by the previous BRAF classification system. By leveraging previously established protein-protein networks, we overlaid them with gene essentiality data to successfully classify 84 new BRAF mutations. We then evaluated the oncogenic potential of the newly classified atypical class-2 or -3 BRAF mutations compared to wild-type and class-1 BRAF mutations to validate that our extended system was consistent with the previously established BRAF classes. We also performed a network analysis to determine which genes were co-mutated for each BRAF class.

Results: Cell viability analysis of the BRAF-mutant Ba/F3 cells yielded no significant differences in the median AUC values between the new and old classification systems. Several key genes (including PIK3CA, EGFR, and MEK) were identified as potential drug targets (IC 50: 0.1 μM) for cell lines with class-2 and -3 atypical BRAF mutations. We found that atypical BRAF mutations have significantly more positive CERES scores than class-1 mutations and thus need to partner with other oncogenes to drive oncogenesis due to their lower oncogenic potential.

Conclusions: In conclusion, we extended the previous Yao classification system to establish a more comprehensive BRAF-mutant classification system, Yao Classification System Plus, that encompasses more atypical BRAF mutations. This allows for greater therapeutic options to target cells carrying these previously uncharacterized mutations.

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28P Xanthine oxidase as a prognostic factor in colorectal cancer metastatic disease

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Background: Obesity and related diseases, namely, diabetes and metabolic syndrome, are associated with chronic inflammation and colorectal cancer (CRC). In CRC liver metastases (mCRC) and adjacent liver tissue defects are formed in the mitochondrial electron transport chain that causes mitochondrial dysfunction, activation of redox-molecules (SR, NO) generation sources and MMP-2, -9 activity. Radical oxygen species take a part in the regulation of gelatinases (MMP-2 and -9) and the xanthine/xanthine oxidase reaction is widely used as a source of exogenous ROS in considering of MMPs. The aim of the study was to determine the state of XO, SR and MMPs in liver tissue and CRC liver metastases (MT) and set the clinical significance of obtained results.

Methods: The prospective study on 37 mCRC patients who underwent the liver resection due metastatic disease has been performed. The rate of SR generation of neutrophils and in the tissue samples, the rate of XO and the activity of matrix metalloproteinases in the tissue samples was measured accordingly study design.

Results: The highest level of XO in mCRC patients was detected in metastatic tissue (1.47 ± 0.18 a.u.). The level of XO enzyme in the adjacent tissue (AT) and distant tissue (DT) were 0.38 ± 0.10 a.u. ($p<0.05$) and 0.19 ± 0.008 a.u. ($p<0,05$) respectively. A correlation was found between the BMI and amount of XO in DT of the liver $r^2 = 0,64$. The total activity of gelatinases in subgroup of mCRC patients with BMI $\geq$ 25 was found to be significantly higher than in normal body weight patients withing the DT (1.52; $p<0.001$), as well as in the AT (1.28 times; $p<0.001$). High XO levels (HR (95% CI) = 0,002 (2,63 to 15.05) P = 0,002) and SR generation levels (HR (95% CI) = 0,01 (2,4 to 10,37) P = 0,01) in adjusted liver tissue to metastatic lesions had a negative impact on overall overall survival rates.

Conclusions: Xanthine oxidase and superoxide radicals can be a new metastatic disease prognostic factors for colorectal cancer patients, the latter requiring further randomized trials.

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29P The effect of cancer associated fibroblast-derived activin A on colorectal cancer progression

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Background: Colorectal cancer (CRC) is one of the most common cancers worldwide. In particular, the yearly mortality emphasizes the limited spectrum of treatment possibilities. The tumor microenvironment with its relevant influence on malignant tumor initiation, progression and chemoresistance represents a promising target for

cancer therapeutics. Especially cancer-associated fibroblasts (CAFs) are of importance in carcinogenesis as they are involved in tumorigenesis, metastasis, inflammatory responses, and extracellular matrix changes. Based on preliminary data, we found upregulated expression of *INHBA*, a gene encoding for the βA subunit of the TGFβ superfamily members Activin A, Activin AB and Inhibin A, in the stromal compartment of human CRC. Therefore, we wanted to investigate the autocrine and paracrine functional consequences of CAF-secreted Activin A in CRC.

Methods: We knocked down *INHBA* in primary patient-derived CAFs and used *in vitro* 3D collagen gel assays, flow cytometry, immunofluorescence, secretome analysis and Western blotting to check the autocrine effects of Activin A on CAFs. Regarding the paracrine impact on tumor cells and immune cells, we employed 3D co- and triple-culture collagen gel assays to determine the impact of CAF-derived Activin A. Here, we focused on proliferation, apoptosis and invasion levels of tumor cells as well as on monocyte differentiation, myeloid cell plasticity and T-cell activation.

Results: Our data demonstrate that CAFs expressing *INHBA* show a pro-proliferative, pro-motile and pro-contractile phenotype. Furthermore, the secretome and plasticity of CAFs were notably modified by the *INHBA* knockdown. Additionally, CAF-derived Activin A seems to influence various aspects of tumor progression and the plasticity of immune cells.

Conclusions: Together, our results indicate key functions of CAF-derived Activin A in CRC progression suggesting a potential novel therapeutic target.

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30P Prostaglandin signaling in tumour stroma interaction in colorectal cancer and its impact on the secretome and functional relevance

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Background: One of the risk factors to develop colorectal cancer (CRC), which is one of the deadliest types of cancer, is inflammation. Among the factors involved in the inflammatory response, prostaglandins (PGs) seem to play an important role. The tumor microenvironment (TME) influences the development of the tumor and within the TME, cancer associated fibroblasts (CAFs) represent the major compartment. Despite the importance of the TME, there is limited evidence on the secretome-dependent communication of CRC cells with CAFs and myeloid cells with respect to PG signaling. In this project we mainly focus on PGE2 and PGF2α, that we have previously found are secreted by CAFs.

Methods: By using *in vitro* 3D cocultures secreted molecules induced by increased or decreased PGE2 and PGF2α expression were identified. The levels of both PGs were measured by ELISA, whereas the expression of the production enzymes was analyzed by Western Blot. Phenotypic analysis and functional assays were carried out using siRNA or specific inhibitors to analyze the effect on angiogenesis and contractility of CAFs, their proliferation, motility, and apoptosis levels. Finally, preliminary *in vivo* experiments were performed and, additionally, paraffin tissue sections from patient-derived xenografts (PDX) models were stained to prove the stroma expression of the PGs specific synthases.

Results: We demonstrate that a combination of proinflammatory cytokines can increase the expression of COX-2 and mPGES-1 while IL-4 decreases it. Knocking down the specific synthases of PGE2 and PGF2α in the CAFs also leads to a decrease in their proliferation, contractiliy, motility and angiogenesis capacity, but did not induce apoptosis. *In vivo*, knocking down of the PGs specific synthases seems to lead to a worse survival capacity, and some of these enzymes seem to be only expressed in the stromal cells of PDX models.

Conclusions: More information about the link between cancer and its TME would help us to achieve a higher degree of accuracy in the development of potential future therapies. Here we have proved that the action of PGs, especially PGF2α and PGE2, is involved in tumor development in 2D and 3D suggesting a possible therapeutic target.

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31P Cell-free tumor microRNA as early biomarkers of high-grade cervical intraepithelial neoplasia using liquid biopsy

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Background: Cervical cancer (CC) is the fourth most common type of cancer among women worldwide. Considering that the early diagnosis of cervical intraepithelial neoplasia (CIN) is the main strategy to improve the prognosis of patients, new methodologies based on molecular analyzes performed on liquid biopsy samples, represent promising alternatives for minimally invasive biomarkers. miRNAs have been shown their role as non-invasive biomarkers, providing a wide perspective for personalized treatment and early diagnosis of cervical cancer through liquid-based cytology (LBC). However, more research is under way to identify miRNA signatures that can be implemented in clinical practice specially for early detection. In this study, we aimed to identify molecular signatures of miRNAs in cervical precursor lesions (CIN 2 and CIN 3) from LBC and their interaction with molecular pathways related to CC in a prospective study.

Methods: We analyzed 96 LBC cervical samples, that were divided into two groups: the case group was composed of women diagnosed with CIN 2 and CIN3 ($n = 48$); the control group corresponded to women without cervical precursor lesions ($n = 48$). We performed miRNA expression profiling using the nCounter® miRNA Expression Assay (NanoString Technology), which evaluated 800 targets. A functional analysis in silico was performed by mirDIP and enrichment were performed using Cytoscape with the Reactome plugin.

Results: We identified 54 miRNAs that were differentially expressed between case and control groups ($p \leq 0.05$). Using logistic regression analysis, we identified a signature composed of five miRNAs, with a fold change ≥ 1.5 and FDR-corrected p-value of ≤ 0.05, of which two were up-regulated and three were down-regulated. The signature had a predictive value with an AUC of 0.90. Furthermore, we found 26 miRNA target genes for four of the five identified miRNAs, mainly related to pathways in cancer, RNA Polymerase II Transcription, RhoA signaling pathway, and PI3K-Akt signaling pathway.

Conclusions: This study demonstrated that those miRNAs could be used as non-invasive biomarkers in LBC samples, once they were able to distinguish CIN 2 and CIN3 patients from healthy women and regulate important molecular pathways of onset carcinogenesis.

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32P Epigenetic reprogramming induced prostaglandin E2 accumulation via overactivated arachidonic acid metabolism during trastuzumab resistance formation of HER2-positive breast cancer

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Background: Secondary trastuzumab resistance seriously affects HER2-positive breast cancer treatment. However, we still lack knowledge about changes in tumor cells and their interaction with tumor microenvironment (TME) components during resistance formation. This study aimed to uncover metabolism pathway changes during trastuzumab resistance formation and potential epigenetic variations that are relevant to these processes.

Methods: Induced secondary trastuzumab-resistant SKBR3_HR cell line together with the original trastuzumab-sensitive SKBR3 cell line were applied in this study. Total RNA was collected for transcriptome analysis. Anti-H3K4me3, K27me3 and K27ac antibodies were chosen for CUT&Tag sequencing library preparation. Total genome DNA was prepared for Micro-C sequencing library preparation. Activity score of metabolism pathway was calculated as relative gene expression value averaged over all genes in this pathway in certain cell types. Extracellular prostaglandin E2 (PGE2) was measured by ELISA.

Results: SKBR3_HR cells showed higher trastuzumab tolerance than SKBR3 cells. Upregulation of arachidonic acid metabolism, which was characterized by two over-expressed genes, PTGS1 and PTGES, was observed in SKBR3_HR cells, resulting in PGE2 accumulation in culture medium. Variations of 1519 H3K27me3 peaks and 256 H3K4me3 peaks at promoters were observed during resistance formation. Little H3K27me3 but considerable raised H3K4me3 levels at PTGS1 and PTGES gene promoters may stimulate their transcription.692 altered active enhancers were measured

during resistance formation. Meanwhile, 2741 and 7007 DNA loops were lost and gained. New DNA loops formation between PTGS1 gene promoter and enhancers nearby, indicating a positive synergy regulatory on PTGS1 gene expression together with promoter modifications.

Conclusions: During trastuzumab resistance formation, promoter H3K4me3, active enhancers and DNA loops together regulate PTGS1 and PTGES expression, activate arachidonic acid metabolism, and eventually stimulate PGE2 accumulation.

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33P Visualizing trastuzumab-deruxtecan action in HER2+ breast cancer cells at nanoscale

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Background: Breast cancers that test positive for the human epidermal growth factor receptor 2 (HER2+) are known to be highly aggressive and hold poor survival rates. However, advances in therapies targeting HER2 have led to anti-HER2 antibodies like Trastuzumab and tyrosine kinase inhibitors. Trastuzumab-deruxtecan (Tz-Dxd) is an antibody-drug conjugate that has shown remarkable results in both HER2+ and HER2-low BCa. By promoting its internalization and trafficking to lysosomes through HER2 binding, Tz-Dxd has great potential to revolutionize cancer treatment.

Methods: This study aimed to investigate the effects of Tz-Dxd on HER2+ breast cancer cell lines at the nanoscale level using high-resolution light and electron microscopy techniques, biochemistry and flow cytometry analysis.

Results: We found that after 2 hours, Tz-Dxd induced ERBB2 phosphorylation and downstream signaling activation without significant internalization of the receptor. However, the receptor was internalized towards lysosomes at later stages (72 hours), but only in a limited fraction of cells. Nonetheless, Tz-Dxd induced apoptosis in more than 50% of cells after 72 hours of treatment, even in cells where ERBB2/Tz-Dxd was not internalized. This suggests that deruxtecan was efficiently released from Tz in lysosomes reaching by diffusion surrounding cells. In addition to apoptotic cells, we observed a consistent fraction of cells displaying suggestive hallmarks of senescence. In particular, we detected dramatic cell flattening, increased nuclear size, chromatin reorganization, nuclear envelope ruptures and expansion of the lysosomal compartment. Cells also displayed alterations of the mitochondrial network dynamics and induction of autophagy; indicative of an elevated energy demand to sustain autophagy and senescence.

Conclusions: These results suggest that Tz-Dxd has potent anti-tumor activity in vitro but might also induce cellular senescence, which would merit further investigation due to its uncertain role in cancer progression in the long run.

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35P SAT-122: A potential first-in-class, potent, small-molecule disruptor of RAD51-BRCA2, attenuates RAD51 foci formation and tumor progression in preclinical models

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Background: The DNA damage repair pathway plays a crucial role in signalling for effective DNA repair and cell cycle progression. DNA double-strand breaks (DSBs) are primarily repaired by homologous recombination. Acting downstream of ATR, ATM and PARP, RAD51 is a central recombinase in HR-mediated DDR pathway that participates in DSB repair *via* interaction with BRCA2, followed by its nuclear translocation. RAD51:BRCA2 interaction disruptors represent a first-in-class anticancer target with therapeutic potential in refractory solid tumors.

Methods: Binding of SAT-122 to RAD51 and its interaction with BRC4 was determined using Surface Plasmon Resonance (SPR) and pull-down of the RAD51:BRC4 complex, respectively. Downstream modulation of RAD51 and gamma H2AX foci, along with effect on cell cycle was studied. Antiproliferative effects of SAT-122 was evaluated in a panel of multiple solid tumor cell lines. Selectivity was evaluated in a kinase panel. Nanostring based evaluation of pathway-related genes following incubation of cells with SAT-122 was conducted. *In Vivo* efficacy was evaluated in NCI-H358 and MDA-MB-231 xenograft models.

Results: SAT-122 binds to RAD51 and disrupts RAD51:BRCA2 interaction with an IC_{50} of 20 nM. Fluorescent microscopy studies indicated a dose dependent reduction of RAD51 foci, and an increase in g-H2AX foci at 500 nM. FACS analysis demonstrated arrest at late S and G2 phase with subsequent apoptosis. SAT-122 inhibited proliferation of over 30 different cancer cell lines at IC_{50}ranging from 150-800 nM. Biochemical selectivity was established against a 345-kinase panel. RNA seq studies suggested modulation of multiple genes in the homologous recombination repair (HRR) pathway in line with the mechanism. *In vivo* translation was confirmed in NCI-H358 and MDA-MB-231 xenograft models with TGI of $>$70% and 50%, respectively. Pharmacokinetic studies and tolerability studies in rodents, revealed sufficient exposures, along with a wide therapeutic window.

Conclusions: SAT-122 is a novel and potent disruptor of RAD51:BRCA2 with potential to be used in the DDR context, in solid tumors. IND-enabling studies are ongoing with clinical trials planned in H1 2024.

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36P Molecular assessment of clinical antitumour therapeutics utilising established pancreatic ductal adenocarcinoma patient-derived models

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Background: Our proteogenomic analysis using pancreatic ductal adenocarcinoma (PDAC) tissues provides significantly mutated genes/biomarkers, cell signaling pathways and cell types as potential therapeutic targets to improve stratification of PDAC patients (Nat. Can., 2023). The current study aimed to evaluate clinical chemotherapeutics to validate targeting molecules and signaling pathways based on previous results, using patient-derived primary cells and tumor organoids.

Methods: The sensitivity on drugs was also evaluated on established primary PDAC cells and tumor organoids. To explore the mechanistic molecular changes for the development of drug resistance, we established resistant-cells on gemcitabine combined with radiation through long term treatment of the combination and selection procedure. Signaling pathways, EMT and cancer were explored at protein as well as RNA levels, and metabolomics were performed

Results: PDAC cells and organoids showed growth inhibition when treated with inhibitors against RhoA phosphorylation, HIF1A, or gemcitabine combined with radiation, respectively. Each chemotherapeutics showed reduced tumor growth through cell cycle arrest, apoptosis or autophagy. Biochemical analyses showed that drug-treated cells showed reduced expressions of phosphorylated ERK, phosphorylated Akt, or phosphorylated RhoA. HIF1A together with HK2 genes was overexpressed in resistant cells. Metabolomics showed differential glycolysis patterns among parental and resistant primary PDAC cells.

Conclusions: The results suggest that the targeting molecules associated with squamous PDAC malignancy discovered in our previous study would provide significant therapeutic advantage. Additionally, hypoxic tumor microenvironment (TME) plays a critical role for chemotherapeutics sensitivity, according to the metabolomics analysis. Importantly, the study implicates the critical role of patient-derived models, especially tumor organoids, for precise evaluation of drug sensitivity, and to validate functional mechanism of drug resistance on individual PDAC patients.

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37P Nischarin can be a target for stromal normalisation in pancreatic ductal adenocarcinoma

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Background: Nischarin (NISCH) is a scaffolding protein involved in the control of cytoskeletal dynamics. Its tumor suppressive role has been demonstrated in breast cancer; and high expression in tumor tissue was reported as a positive prognostic marker in breast and ovarian cancers. Of interest, there are several approved nischarin agonists used in treatment of hypertension. We have previously found that NISCH is expressed in both tumor cells and cancer-associated fibroblasts (CAFs) in pancreatic ductal adenocarcinoma (PDAC) and that nischarin agonist rilmenidine can limit cancer cell invasion. As the dense tumor stroma makes up to 80% of the bulk tumor tissue in PDAC, and is one of the causes of current treatment failure, the aim of this study was to examine the effects of nischarin agonists on the phenotype of cancer-associated stroma in PDAC.

Methods: NISCH expression and co-localization with CAF markers were examined by immunohistochemistry in PDAC tissue microarray. CAFs were isolated from fresh tumor tissue by the outgrowth method. MTT test was used to evaluate cytotoxicity of nischarin agonist rilmenidine on patient-derived CAFs. Immunoblotting, immunocytochemistry, ELISA and qRT-PCR were used to examine the effects of rilmenidine treatment on the extracellular matrix deposition and cytokine and growth factor production in CAFs and *ex vivo* cultures of PDAC tumor tissue.

Results: Nischarin was expressed in both aSMA$^+$ and FAP$^+$ cells in the tumor tissue. Patient-derived CAFs were a heterogeneous population, positive for aSMA$^+$ FAP$^+$, collagen I and fibronectin. Rilmenidine treatment of patient-derived CAFs *in vitro* was not cytotoxic at concentrations achievable in the human plasma. Nevertheless, rilmenidine treatment decreased fractions of both aSMA$^+$ and FAP$^+$ cells *in vitro* and decreased the production of pro-inflammatory cytokines IL-6, IL-8 and CCL-2. Treatment of *ex vivo* PDAC tumor cultures for 72h remodeled the extracellular matrix.

Conclusions: Our results imply that rilmenidine treatment *in vitro* and *ex vivo* shows a potential for normalizing PDAC tumor-derived CAFs and may be a good candidate for drug repurposing.

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38P Effects of antiemetics on zolbetuximab-induced gastric injury and emesis frequency in ferrets

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Background: Claudin 18.2 (CLDN18.2) is expressed in normal gastric tissue and gastric cancers. Zolbetuximab is a chimeric IgG1 monoclonal antibody that selectively targets CLDN18.2, inducing antibody- and complement-dependent cytotoxicity and cancer cell lysis. In phase 3 studies of zolbetuximab for HER2-negative, advanced gastric/gastroesophageal junction adenocarcinomas (SPOTLIGHT, GLOW), the most frequent adverse events were nausea and vomiting (N/V). We investigated the mechanism of zolbetuximab-induced N/V and effects of antiemetic agents on gastric injury and emesis frequency in ferrets.

Methods: Ferrets were administered zolbetuximab with/without single or combination antiemetic treatment (Table). Retching/vomiting were monitored for 6 hours, after which gastric tissues were sampled for histopathologic assessment. The study was conducted twice.

Results: Zolbetuximab induced emesis within 30 minutes of administration. Singly, dexamethasone (DEX), ondansetron (OND), and fosaprepitant (FOS) significantly reduced emesis vs control (no antiemetic) in Study 1; olanzapine (OLA) did not. In Study 2, FOS alone (but not DEX, OND, or OLA) almost completely suppressed emesis. Further, both combination regimens containing FOS reduced emesis. Histopathologic analysis indicated that zolbetuximab induced gastric injury, evidenced by submucosal inflammation in the corpus and pylorus. DEX alone and the DEX-based combination regimen showed a tendency to alleviate submucosal inflammation in the corpus and pylorus, although the other antiemetics did not show any clear suppression of gastric mucosal damage. The combination of OND+FOS also tended to alleviate gastric mucosal abnormalities.

Table: 38P Study groups

Group (n=4, each study)	Emesis Agent	Antiemetic Agent(s) Study 1	Antiemetic Agent(s) Study 2
1 — Normal	Saline IV	—	
2 — Control	Zolbetuximab 1 mg/kg IV	—	
3 — DEX		DEX 20 mg/kg IV	
4 — OND		OND 3 mg/kg IV	
5 — FOS		FOS 3 mg/kg IV	
6 — OLA		OLA 0.03 mg/kg IM	
7 — Combination		DEX+OND+FOS+OLA	OND+FOS

DEX, dexamethasone; FOS, fosaprepitant; IM, intramuscular; IV, intravenous; OLA, olanzapine; OND, ondansetron.

Conclusions: These findings in ferrets demonstrate that zolbetuximab-induced emesis may be associated with gastric mucosal damage. Further, antiemetics may have the potential to mitigate N/V in patients treated with zolbetuximab.

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39P Casein kinase 2 modulates epithelial—mesenchymal transition through helicobacter pylori CagA-dependent pathway in gastric cancer cells

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Background: *Helicobacter pylori* is the most important carcinogen in human gastric cancer. However, the pathogenic molecular mechanism which underlies the carcinogenesis in gastric cancer by *H. pylori* remains largely unknown. In this study, we understand that molecular biological mechanism related to gastric carcinogenesis by investigating the role of CK2 in EMT. Casein kinase 2 is a serine/threonine protein kinase and consists of two catalytic subunits (α or α') and regulatory subunits (β). CK2 regulates many substrates and its involved in cell growth, proliferation, invasion. EMT is involved in many signaling pathways, but the key regulatory kinases in this process have not been clearly identified. Although the role of CK2 catalytic subunits has remained largely uncharacterized, several studies have recently focused on regulator subunits in EMT.

Methods: AGS and MKN74 cells as human gastric epithelial cells and *H. pylori* strains, *H. pylori* 60190 (CagA+) and *H. pylori* ΔCagA (CagA-) were used. Protein and mRNA levels of CK2 were tested by Western blot and RT-PCR in AGS cells infected with *H. pylori* 60190. We also examined *in vivo* assay through tumor weight and size by xenograft mouse model. Expression levels of CK2 were analyzed in 54 gastric tissues from patients with gastric carcinoma by immunohistochemistry.

Results: Although CK2α protein expression remained unchanged during *H. pylori* infection, we found that CK2α kinase activity was increased in gastric epithelial cells. We also found that the CK2β protein level decreased in *H. pylori*-infected gastric cancer cells in CagA-dependent manner and demonstrated that CagA induced CK2β degradation via HDM2. We observed that CagA induced HDM2 protein phosphorylation and that p53 levels were decreased in *H. pylori*-infected gastric cancer cells. We also found that the downregulation of CK2β triggered the upregulation of Snail levels in gastric cancer cells. Furthermore, our *in vivo* experiments and functional assays of migration suggest that CK2β downregulation is a major factor responsible for the EMT in gastric cancer.

Conclusions: In summary, we have shown that the downregulation of CK2β in *H. pylori*-infected gastric cancer cells promotes the EMT in CagA-dependent manner.

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Disclosure: All authors have declared no conflicts of interest.

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40P Bioinformatic evaluation of the transcriptomic and immunologic profile of prostate tumors with high expression of kallikrein-2

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Background: Identification of tumor associated antigens (TAAs) expressed on the cell membrane of tumoral cells is a main goal in cancer research. T cell engagers (TCE) are bi-specific antibodies that engage a TAA with an effector T cell receptor mainly CD3. Kallikrein-2 (KLK2) is a surface protein for which TCE are currently in clinical development. In our study we explore genomic correlates and the transcriptomic and immunologic profile of tumors with high expression of KLK2.

Methods: Primary prostate cancer data was downloaded from TCGA to study transcripts up or down regulated when high expression of KLK2 was present. Tumor Estimation Resource (TIMER) platform was employed to investigate the association between high expression of KLK2 and immune cell populations. Correlations between transcripts were performed using Spearman's correlation test.

Results: KLK2 was specifically upregulated in prostate cancer compared with other solid tumors and normal tissue (tumor 5956.5 TPM versus normal 4175.26 TPM). KLK2 expression did not associate with the presence of any immune cell population either innate or adaptive cells including CD8+ (Rho = 0.339, p = 1.03E-12), CD4+ (Rho = -0.244, p = 4.56E-07), B cells (Rho = 0.047, p = 0.332), neutrophils (Rho = -0.139, p =0.004), dendritic cells (Rho =-0.152, p = 0.001), or macrophages (Rho= 0.074, p =0.128). No clear association was observed for any biomarker of T cell activation including CD8A, CD8B, GZMA, GZMb or PRF1, or an additional battery including more than 40 additional genes linked with T cell cytotoxic. A mild correlation was observed between high expression of KLK2 and TMPRSS2 (Rho = 0.481, p = 1,68E-11). Protein protein interaction analysis showed interactions with AR, KLK3, IGF1, IGFBP3 (PPI enrichment p-value: 4.51e-07), among others. Co- upregulated surface proteins include TMEFF2, OR51E2, CD320 and FAM17AB; and nonsurface proteins: RDH11, FX4D3, SSR4 and NDUFA13. None of them were specifically expressed in tumoral cells or associated with biochemical (PSA) relapse.

Conclusions: KLK2 is highly and exclusively expressed in prostate cancer mainly in inmune desert tumors. Future studies should be performed in other clinical scenarios like in androgen resistant prostate tumors.

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41P Evaluation of ARX517: A next-generation anti-PSMA antibody drug conjugate for prostate cancer treatment, in preclinical enzalutamide-resistant and enzalutamide-sensitive pharmacology models and in toxicology models

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Background: Prostate cancer is the second leading cause of cancer death among men in the United States. Metastatic castration-resistant prostate cancer (mCRPC) is an advanced disease stage in which patients ultimately fail androgen-deprivation therapies and exhibit a poor survival rate. Recently, prostate-specific membrane antigen (PSMA) has been validated as a mCRPC tumor antigen with its over-expression in tumors and low expression in healthy tissues. Using an expanded genetic code to create Engineered Precision Biologics, Ambrx has developed ARX517, a PSMA-targeted antibody drug conjugate (ADC), which is composed of a humanized anti-PSMA antibody site-specifically conjugated to a tubulin inhibitor drug-linker at a drug-to-antibody ratio of 2. After binding to PSMA, ARX517 is internalized and catabolized, leading to cytotoxic payload delivery and cellular apoptosis. To minimize premature payload release and maximize delivery to tumor microenvironments, ARX517 employs a non-cleavable PEG linker and stable oxime conjugation chemistry, enhancing systemic stability.

Methods: ARX517 was evaluated in multiple pre-clinical pharmacology and toxicology models using standard methodology.

Results: In vitro studies demonstrate that ARX517 selectively induces cytotoxicity of PSMA-expressing tumor lines. ARX517 exhibited a long terminal half-life and high serum exposure in mice, and dose-dependent anti-tumor activity in both enzalutamide-sensitive and -resistant CDX and PDX prostate cancer models. Repeat dose toxicokinetic studies in non-human primates demonstrated ARX517 was tolerated at exposures well above therapeutic exposures in mouse pharmacology studies, indicating a wide therapeutic index.

Conclusions: In summary, ARX517 inhibited tumor growth in diverse mCRPC models, demonstrated a tolerable safety profile in monkeys, and had a wide therapeutic index based on preclinical exposure data. Based on strong preclinical data and recent clinical validation of PSMA targeting, ARX517 is being evaluated in a phase 1/2 clinical trial (NCT04662580).

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42P Developing a photodynamic therapy strategy targeted to endometrial cancer stem cells

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Background: Cancer stem cells (CSC) motivate the investigation of novel anticancer-targeted therapies. In endometrial cancer (EC), overexpression of aldehyde dehydrogenase (ALDH) was associated with endometrial CSC, highlighting its therapeutic target potential. Photodynamic therapy (PDT), a minimally invasive anticancer approach, emerges as a promising targeted therapy for endometrial CSC, through a structural modulation of optimized photosensitisers with aldehyde moieties. Thus, the aim is to investigate PDT based on the 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorins (PX), modulated to target endometrial CSC by incorporation of aldehyde substituents.

Methods: A solution of a mono-esther/mono-alcohol derivative chlorin was added to Dess-Martin periodinane in dichloromethane solution and stirred to synthesise a mono-aldehyde derivative of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorin (A-PX). The presence of the aldehyde group was confirmed by proton nuclear magnetic resonance (^{1}H-NMR). The ALDH1A1-promoted oxidation of A-PX was followed through reverse-phase high-performance liquid chromatography (HPLC). This was done by reacting 50nM ALDH1A1 with 1mM A-PX in a 2% DMSO, Tris pH 7.5, KCl, DTT and β-NAD solution at 37 °C. The reaction was stopped every 30' with acetonitrile. To evaluate A-PX-based PDT (7.5mW/cm2, 10J) the resazurin assay was performed on endometrial CSC.

Results: The A-PX ^{1}H-NMR revealed a peak at 10.28ppm corresponding to the aldehyde. The kinetics of the enzymatic reaction, followed by HPLC, showed the decreasing relative area of the aldehyde peak (retention = 2'13'') in parallel with the increase of the carboxylic acid (retention = 3'04'') formed by ALDH1A1-promoted oxidation, reaching complete conversion at 120'. Preliminary results of the A-PX-PDT cytotoxicity on the endometrial CSC pointed to decreased proliferation, while A-PX *per se* did not show toxicity.

Conclusions: It was possible to develop chlorins able to interact with ALDH1A1, allowing the *in situ* modification of the hydrophilicity of the photosensitizer. A-PX seem to be effective PDT agents against endometrial CSC. The promising results encourage further studies to confirm this rationale for endometrial CSC-targeted PDT.

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43P Looking for therapeutic targets on the proteome profile of endometrial cancer stem cells

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Background: Endometrial cancer (EC) is one of the most frequent gynaecological malignant diseases whose incidence presents an increasing trend. Cancer stem cells (CSC), a subpopulation of undifferentiated tumour cells identified in EC, are the main actors in the resistance mechanisms to conventional therapies. Thus, the main aim of this study is to identify novel molecular targets in endometrial CSC for the future development of innovative targeted therapies for EC.

Methods: Two EC cell lines, ECC-1 and RL95-2, were cultured, and endometrial CSC were obtained through an optimized 5-day sphere formation assay. A proteomic profile of cell lines and endometrial CSC was determined through mass spectrometry-based proteomics. The analysis was performed through the comparison of CSC *vs.* cell line proteins significantly up-regulated by a 40-fold change and their cellular localization. R package was used for statistical analysis.

Results: The proteomic analysis of ECC-1 samples allowed the identification of 477 up-regulated ECC-1-CSC-specific proteins, 108 ECC-1-specific proteins, and 2306 common proteins. Regarding RL95-2 samples, the analysis identified 76 up-regulated RL95-2-CSC-specific, 994 cell line-specific, and 1420 common proteins. The cellular localization of up-regulated proteins identified from CSC populations was mainly the cytoplasm (25-31%), nucleus (19-23%), and membrane (21-22%). Regarding the functional analysis, the more regulated subcategories were the intracellular ferritin complex, poly(A) RNA binding, (acetyl-CoA carboxylase) kinase activity, (hydroxymethylglutaryl-CoA reductase (NADPH)) kinase activity, and ubiquitinyl hydrolase activity for ECC-1-CSC *vs.* ECC-1; the proteasome, cytosol, extracellular vesicular exosome, poly(A) RNA binding, glutamate dehydrogenase (NAD+) activity, and glutamate dehydrogenase (NADP+) activity for RL95-2-CSC *vs.* RL95-2; and poly(A) RNA binding, (acetyl-CoA carboxylase) kinase activity, NADPH kinase activity, and ubiquitinyl hydrolase activity for both.

Conclusions: CSC population-specific proteins were identified, as well as their cellular localization and functional enrichment. This information allows for the future development of endometrial CSC targeted therapies.

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44P PAUF as a target for treatment of high PAUF-expressing ovarian cancer

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Background: Pancreatic adenocarcinoma up-regulated factor (PAUF) plays an important role in tumor growth, metastasis, and immune evasion in the pancreatic tumor microenvironment, and recent studies suggest an association between PAUF expression and poor prognosis in ovarian cancer patients. However, the role of PAUF in ovarian cancer development has not been clearly understood at the molecular level, and whether PAUF can be used as a therapeutic target of ovarian cancer awaits more scientific evidence.

Methods: The current study characterized the functions of PAUF in ovarian cancer using cell-based assays and mouse xenograft experiments, and further evaluated whether an anti-PAUF antibody can become a potential ovarian cancer treatment in human ovarian cancer models.

Results: Recombinant PAUF significantly increased tumor metastatic capacity (migration, invasion, and adhesion) in all the ovarian cancer cell lines tested, except for the OVCAR-5 cell line which expresses PAUF at a much higher level than the other cells. PAUF-knockout in the OVCAR-5 cell line led to apparently delayed tumor growth *in vitro* and *in vivo*. Furthermore, the administration of an anti-PAUF antibody exhibited notable sensitizing and synchronizing effects on docetaxel in mice bearing the OVCAR-5 xenograft tumors, the docetaxel + anti-PAUF antibody combination group showed the most potent anti-tumor efficacy demonstrated as a nearly 5-fold improved survival in this group (HR: 0.22, 95% CI: 0.09 to 0.54), compared to the control group (Table).

Table: 44P Survival data in OVCAR-5 xenograft human ovarian cancer mouse model. Treatments (started from day 0): Human IgG (control), Anti-PAUF antibody (10 mg/kg, twice/week, ×4 weeks), Docetaxel (10 mg/kg, once, on day 0), or Anti-PAUF antibody + Docetaxel (via the same regimens of the two drugs)

Time elapsed (Day)	Human IgG (n = 15)	Anti-PAUF (n = 15)	Docetaxel (n = 15)	Anti-PAUF + Docetaxel (n = 15)
0	15	15	15	15
20	15	15	15	15
23	13	15	15	15
26	10	15	15	15
31	3	11	13	15
34	2	5	10	14
37	0	4	7	9
40	0	2	2	6
HR (95% CI)	**1**	**0.42 (0.19-0.93)**	**0.32 (0.14-0.74)**	**0.22 (0.09-0.54)**

Conclusions: Taken together, this study shows that the expression level of PAUF is an independent factor determining malignant behaviors of ovarian cancer and, for the first time, it suggests that PAUF may be a promising therapeutic target for high PAUF-expressing ovarian cancer. The anti-PAUF antibody used in this study, PBP1510, has gained orphan drug designation from the EMA, FDA, and MFDS (Korea), and entered phase I clinical trials.

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45P Therapeutic potential of ISM8207: A novel QPCTL inhibitor, in triple-negative breast cancer and B-cell non-Hodgkin lymphoma

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Background: Glutaminyl-peptide cyclotransferase-like protein (QPCTL), mediates the trafficking of monocytes as well as the CD47/SIRPa interaction which blocks macrophage phagocytosis. Genetic deletion of QPCTL in tumor or host immune cells promotes anti-tumor activity. We evaluated ISM8207, a novel QPCTL inhibitor, in preclinical triple-negative breast cancer (TNBC) and B-cell Non-Hodgkin Lymphoma (B-NHL) models.

Methods: Gene expression datasets, METABRIC (TNBC), and GSE4475 and GSE10846 (diffuse large B cell lymphoma [DLBCL]), were analyzed for association between QPCTL expression and overall survival (OS). *In vitro* SIRPα binding to the human cell lines (MDA-MB-231, TNBC; and Raji, B-NHL) was evaluated after pre-treatment with ISM8207. *In vivo* antitumor efficacy was assessed in the murine 4T1 TNBC model and in human B-NHL OCI-Ly10 or Raji xenografts in CB17 SCID mice treated with ISM8207.

Results: Patient tumor dataset analyses revealed QPCTL was overexpressed in TNBC and DLBCL, and that a higher expression correlated with a shorter OS. ISM8207 treatment (IC50 $<$ 0.5 nM in enzymatic assay) phenocopied the genetic deletion of QPCTL and reduced the binding of SIRPα to CD47 in TNBC cells, without affecting cell viability. In the murine 4T1 TNBC model, ISM8207 (30 mg/kg BID) demonstrated modest but significant anti-tumor activity. Circulating monocytes and the binding affinity of SIRPα to peripheral white blood cells were reduced. ISM8207 combined with an anti-PD-1 antibody potently and synergistically inhibited tumor growth, with Tumor Growth Inhibition (TGI) of $\sim$50%. The bulk RNA-seq profiling for combined ISM8207 and anti-PD-1-treated tumors showed a higher infiltrating potential of $CD8^+$ T-cells in the tumor microenvironment vs anti-PD-1 alone. ISM8207 (10 mg/kg BID) combined with rituximab resulted in synergistic effects in the B-NHL xenografts. In the Raji model, TGI with the combination was 86% vs 41% with rituximab alone. In the OCI-Ly10 model, 7/8 mice achieved complete remission with the combination vs 1/8 with rituximab alone. ISM8207 was well-tolerated with favorable ADME and PK properties.

Conclusions: These data strongly support the clinical evaluation of ISM8207 as a novel cancer immunotherapy in TNBC and B-NHL.

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46P Effect of coadministration of antioxidant chlorophyllin with docetaxel on invasion and metastasis in triple-negative breast cancer in vivo/in vitro

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Background: The drug resistance against chemotherapy and high metastasis rate in triple-negative breast cancer reduce the success of breast cancer treatment. Glutathione S-transferase P1 enzyme (GSTP1) expression increases in cancer cell lines and leads to the development of drug resistance against chemotherapy. The antioxidant chlorophyllin is shown to have an inhibitory effect on GSTP1. The purpose of this study is to investigate the effects of GSTP1 inhibitor chlorophyllin and/or its coadministration with anticancer drug docetaxel on metastatic processes in vitro/in vivo in the 4T1 triple-negative breast cancer cell line and animal model.

Methods: Cell viability, cell cycle, and cell migration were investigated by MTT test, flow cytometry, and wound closure assay, respectively. Matrix metalloproteinase 9 (MMP-9) expression, causing invasion, was determined by Western Blot in the 4T1 cell line and tissue samples. Further, total gelatinase enzyme activity was also detected by gelatin degradation assay. Total GST enzyme activity and glutathione levels of tissue were investigated by colorimetric methods. Micrometastatic foci in liver tissue sections were evaluated by histochemistry.

Results: As a result, coadministration of chlorophyllin and docetaxel significantly inhibited cell migration in vitro. Chlorophyllin significantly reduced the expression of MMP-9 in the tissue samples, and this effect was higher when it is coadministered with docetaxel. In coadministration, a significant decrease was observed in the total gelatinase activity in vivo. It was also determined that chlorophyllin increased in vivo total glutathione levels and decreased GST enzyme activity. Finally, the micrometastases in the liver were reduced by coadministration.

Conclusions: Our results suggest that the coadministration of chlorophyllin and docetaxel may have a potential role in the control of metastatic processes by suppressing cell migration and invasion which is mainly characterized by gelatinase enzyme expression & activity.

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47P An ozone delivery system by cisplatin prodrug self-assembling micelles combining microwave to sensitizing immune checkpoint inhibitor in triple-negative breast cancer

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Background: Immunotherapy based on T cells has gained great success and is now in its infancy. Despite a high mutation load, triple-negative breast cancer (TNBC) remains a poor response to the immune checkpoint blockades (ICBs) due to an infertile tumor microenvironment (TME). Chemotherapy shows an outstanding synergizing effect with ICB in TNBC due to its cell lysis effect. However, limited bioavailability, significant systematic toxicity, and immunosuppressive metastatic niche induced by chemotherapy restrict its systematic application.

Methods: We constructed self-assembled micelles consisting of fluorocarbon chain-modified cisplatin prodrugs, which loaded ozone-saturated perfluorodecalin (PFD) emulsion as a cargo. Cisplatin is controllably released from the prodrug by ROS triggered by the microwave excitation of ozone. The appearance of the ozone carried prodrug was visualized by Transmission electron microscope and the hydrodynamic sizes and stability were measured with nanoparticle tracking analysis. Cell function experiments were performed to assess the biological effect of the ozone-delivery prodrug in vitro. The biodistribution and biological effect of the ozone-loaded prodrug were also verified in 4T1 tumor-bearing mice model.

Results: The hydrodynamic sizes were about 130.5 nm of PtF and 174.7 nm of PFD@PtF, and both of the two showed good stability in weak acidic (pH $=$ 6.0), neutral (pH $=$ 7.0), and weak alkaline (pH $=$ 8.0) environment at 4°C, room temperature, and 37°C. Ozone was well stabilized by the PFD@PtF as the ROS donor which in turn boosts the intracellular GSH concentration, and decomposed rapidly upon the excitation of microwave. Once endocytosed by TNBC cells, Pt(IV) can be reduced and released from the prodrug upon the triggering of reducing substance (e.g. GSH). The released cisplatin crosses cell membranes to form cross-links with DNA, resulting in cell cycle arrest, apoptosis, and immunogenic cell death. A significant inhibiting effect of tumor proliferation and TME reediting effect were observed in mice model.

Conclusions: We successfully constructed an ozone-delivery cisplatin prodrug with enhanced anti-tumor activity and attenuated toxicity.

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48P Non-steroid anti-inflammatory treatment enhances the efficacy of modulated electro hyperthermia on triple-negative breast cancer and melanoma cancer models in vivo

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Background: Modulated electro-hyperthermia (mEHT) is an advanced option in the hyperthermia field, applying a 13.56 MHz radiofrequency electromagnetic current to induce tumor-specific damage. This study investigates the mEHT-induced molecular effect and the potential of combination non-steroid anti-inflammatory drugs (NSAIDs) to enhance its anti-tumor effects in 4T1 triple-negative breast cancer (TNBC) and B16F10 melanoma mouse models.

Methods: 4T1 TNBC and B16F10 melanoma cell lines were injected into Balb/C and C57BL/6 mice, respectively. They have been treated according to the protocol with only mEHT or mEHT combined with non-selective COX-inhibitors (Aspirin) or selective COX2 inhibitors (SC236). Tumor volume was monitored by ultrasound and a digital caliper. At the end of the experiments, mice were euthanized and tumors excised for molecular studies.

Results: Here we report that mEHT monotherapy stimulates local IL1-beta and IL6, and consequently cyclooxygenase 2 (COX 2) production. These effects could be considered as part of a self-defensive, wound-healing reaction of the tumor to protect itself from the mEHT-induced stress. In the present study, we combined mEHT with non-steroid anti-inflmmatory drugs (NSAIDs), the non-selective (Aspirin), or the selective COX2 inhibitor (SC236) in vivo. Here we demonstrate that NSAID treatment synergistically increased the effect of mEHT in 4T1 TNBC. Tumor weight and tumor volume (measured by ultrasound and a digital caliper) were lowest, and the tumor destruction ratio (TDR) was the highest in the combination treated (NSAID + mEHT) groups. Tumor damage was accompanied by a significant increase in cleaved caspase-3 (cC3), suggesting an important role for apoptosis. Similarly, in the B16F10 melanoma model, lung nodules were significantly less in mice treated with mEHT + Aspirin.

Conclusions: NSAIDs effectively enhance the mEHT anti-tumor effect in TNBC and melanoma cancer models; they increase tumor destruction, where apoptosis may play a role. Disecting the exact molecular mechanisms further is under our current investigation.

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49P Circulating miRNA signatures to predict recurrence in patients with pathological complete response of triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) is characterized by aggressive clinicopathological features and is associated with a poor prognosis. Identifying patients who respond to chemotherapy and yet relapse early remains the subject of many studies and a critical goal for effective personalized therapies. In the present study, we investigated the role of miRNAs in TNBC that responded to neoadjuvant chemotherapy (NAC). Circulating miRNAs were isolated from TNBC patients who underwent NAC and who had a pathologic complete response (pCR).

Methods: The miRNA expression analysis was conducted by nCounter® Human v3 miRNA assay (NanoString Technologies, Seattle, USA) on plasma samples. Sample collected from patients participating in a phase II prospective clinical trial. About 800 human miRNAs were screened, and the resulting data were normalized using the normalization method based on the low coefficient of variation (low CV). Further analysis was carried out using parameters such as fold change and area under the curve (AUC).

Results: A total of 33 differentially expressed miRNAs were identified between relapsed and non-relapsed patients who achieved pCR. Of the 33 miRNAs, only one was downregulated. Of these, we identified 7 miRNAs (hsa-miR-654-5p, hsa-miR-433-5p, hsa-miR-520c-3p, hsa-miR-376a-2-5p, has-miR-4741, has-miR- 513c-3p, hsa-miR-506-5p) which showed better accuracy to discriminate patients with pCR with a higher probability of relapse, with the area under the curve value ranging from 0.80 to 0.93. In network analysis, "TGF-beta signaling pathway", "cancer transcriptional dysregulation" and "JAK-STAT signaling pathway" were identified as the crucial pathways in breast cancer patients who also developed recurrence.

Conclusions: In conclusion, our study hypothesizes that circulating miRNAs may be useful non-invasive biomarkers to identify patients who are more likely to develop recurrence even after achieving pCR in TNBC patients.

Clinical trial identification: NACATRINE trial (NCT02978495).

Legal entity responsible for the study: Barretos Cancer Hospital.

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50P Application and mechanism of tarloxotinib in HER2-positive breast cancer

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Background: HER2 (Human epidermal growth factor receptor-2)-positive breast cancer occupies about 15%—20% of all breast cancer, the current treatment of which is still based on surgery and adjuvant targeted therapy with monoclonal antibody. Problems of drug resistance and cardiotoxicity hinder the use of monoclonal antibodies. And, TKIs (Tyrosine Kinase Inhibitors) have the advantages of multi-target, reduced drug resistance and lower cardiotoxicity. Tarloxotinib is a prodrug that harnesses tumor hypoxia to generate high levels of a potent, covalent pan-HER TKI, Tarloxotinib-effector (Tarloxotinib-E), within tumor microenvironment. This tumor-selective delivery mechanism was designed to minimize the dose-limiting toxicities.

Methods: HER2-positive breast cancer BT-474, SK-BR-3, HCC-1954 and JIMT-1 cells were treated with different concentrations of Tarloxotinib-E, Lapatinib and Tucatinib. The IC50 values were determined by CCK-8 assay. Then, we used Western Blot to detect the changes in the phosphorylation of EGFR, HER2, HER3, HER4, AKT and ERK and the protein expression of Cleaved Caspase-3, Caspase-7 and Parp1. Flow cytometry was used to determine the apoptosis rates and mitochondrial membrane potentials, and the mitochondrial superoxide was detected by the Immunofluorescence. Importantly, we used HPLC-TQ-MS to determine the ratio of Tarloxotinib-E released by Tarloxotinib. Finally, the subcutaneous xenograft mice were used to evaluate the antitumor effect and toxicity of Tarloxotinib in vivo.

Results: Tarloxotinib could be transformed into Tarloxotinib-E by breast cancer cells under hypoxia. Meanwhile, Tarloxotinib-E could effectively inhibit the level of HER family phosphorylation and downstream signaling in HER2-positive breast cancer cells, and superior to Lapatinib and Tucatinib. Mechanistically, Tarloxotinib-E induced apoptosis in HER2-positive breast cancer cells through a ROS-dependent manner, with significant decrease in the potential of mitochondrial membrane and increase in mitochondrial superoxide. During the in vivo experiment, Tarloxotinib significantly inhibited tumor growth in nude mice compared with Lapatinib.

Conclusions: Tarloxotinib released Tarloxotinib-E under hypoxic microenvironment of breast tumors, and inhibited the phosphorylation of HER2 dimers and downstream pathways to induce apoptosis in HER2-positive cells through a ROS-dependent manner. This lays a foundation for the further development of Tarloxotinib in HER2-positive breast cancer.

Legal entity responsible for the study: The authors.

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51P Nanoengineered sonosensitive platelets for synergistically augmented sonodynamic breast tumour therapy by glutamine deprivation and cascading thrombosis

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Background: Ultrasound (US)-activated sonodynamic therapy (SDT) stands for a distinct antitumor modality because of its attractive characteristics including intriguing noninvasiveness, desirable safety, and high tissue penetration depth, which, unfortunately, suffers from compromised therapeutic efficacy due to cancer cell-inherent adaptive mechanisms, such as glutathione (GSH) neutralization response to reactive oxygen species (ROS), and glutamine addictive properties of tumors.

Methods: In this work, we developed a biological sonosensitive platelet (PLT) pharmacytes for favoring US/GSH-responsive combinational therapeutic of glutamine deprivation and augmented SDT. The amino acid transporter SLC6A14 blockade agent α-methyl-DL-tryptophan (α-MT)-loaded and MnO2-coated por- phyrinic metal-organic framework (MOF) nanoparticles were encapsulated in the PLTs through the physical adsorption of electrostatic attraction and the intrinsic endocytosis of PLTs.

Results: When the sonosensitive PLT phar- macytes reached tumor sites through their natural tendencies to TME, US stimulated the PLTs-loaded porphyrinic MOF to generate ROS, resulting in morphological changes of the PLTs and the release of nanoparticles. Subse- quently, intracellular high concentration of GSH and extracellular spatio-temporal controlled US irradiation programmatically triggered the release of α-MT, which enabled the synergistically amplified SDT by inducing amino acid starvation, inhibiting mTOR, and mediating ferroptosis. In addition, US stimulation achieved the targeted activation of PLTs at tumor vascular site, which evolved from circulating PLTs to dendritic PLTs, effectively blocking the blood supply of tumors through thrombus formation, and revealing the encouraging potential to facilitate tumor therapeutics.

Conclusions: It offers a bioinspired design strategy to improve SDT efficiency, and rends an innovative paradigm for cooperatively ablating refractory tumor.

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53P Treatment of cancer cells based on circulating tumor cell's expression profile using off-label drugs

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Background: Circulating tumor cells (CTCs) constitute a cell subpopulation with great prognostic value in oncology. They detach from the primary tumor, and through the blood stream can initiate metastatic spread to other organs. Their gene and protein expression profile, provides useful information about their resistance to specific therapeutic agents, including chemotherapeutic drugs, targeted therapies (monoclonal antibodies (MoAbs) or small molecular weight molecules (SMW)), or their sensitivity to other treatment options, such as hyperthermia or radiation. The present study aimed to identify whether the expression profile could contribute to success treatment using off-label drugs.

Methods: Blood samples were collected from more than 500 patients, suffering from different types of cancer. CTCs detected and isolated with Fluorescence Activated Cell Sorting (FACS), evaluated with specific biomarkers for each cancer type, and then used for gene and protein expression assays, with qPCR and Flow Cytometry respectively. In parallel, literature research was performed for these proteins, and the approved drugs against them. Based on the expression profile, off-label drugs for the specific targets used and viability/chemosensitivity assays followed on patients' isolated CTCs.

Results: Expression profile of CTCs revealed overexpression in a wide variety of biomarkers, for whom there are already approved drugs, but only in specific types of cancer. The highest percentages observed for ALOX5, DHFR, DPYD, KIT, PDGFA, RET and others. The use of approved drugs against these targets, such us Zileuton, Pemetrexed, Capecitabine, Dasatinib, Imatinib and Cabozantinib respectively, led to decrease in CTCs' viability independent the type of cancer up in approximately 25% of the cases. Among them, there were included also refractory cases (5%).

Conclusions: In this study, we demonstrated that CTCs' expression profile, could be an indicator of treatment response, using off-label drugs. It is noteworthy that efficient data observed also in refractory cases, representing different types of cancer. Drug repositioning might be beneficial for cancer patients, and it should be taken into consideration, mainly in cases where no other options are available.

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54P Enhanced oxidative phosphorylation of metastasis-initiating cells facilitates esophageal tumor cell seeding in lymph nodes

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Background: Lymph nodes (LN) are the most frequent metastasis sites in oesophageal squamous cell carcinoma (ESCC), but the associated mechanisms are poorly understood. Tumor cells seed and survive at LN during the early adaptation step, which is the bottleneck for successful metastasis. However, the phenotypic and molecular characteristics of heterogeneous metastatic cells that contribute to such a challenging process remain elusive.

Methods: We established a human xenograft spontaneous LN metastasis model to capture tumor cell dissemination behaviors. We conducted single-cell RNA sequencing on tumor cells collected from primary tumors and metastatic LN to profile the dynamic cellular and molecular changes in tumor cells associated with LN metastasis. We further identified and characterized the early metastasis tumor cells in LN through *in vitro* and *in vivo* functional assays.

Results: We revealed that LN metastasis is initiated by rare ESCC subpopulations with stemness and mesenchymal regulatory gene expression signatures. These tumor cell subpopulations are critical to driving metastasis in distant organs through the blood circulation in mice, supporting the metastasis-initiating cells (MICs) properties. Importantly, these key driver cells were observed to convert the metabolic strategy to mitochondrial oxidative phosphorylation (OXPHOS) during cell seeding in the LN. Enhanced OXPHOS in LN metastatic cells is induced by fatty acids and regulated by NRF2 signaling. Pharmacological inhibition of OXPHOS with IACS-010759 markedly attenuated metastasis in mice.

Conclusions: Our results demonstrate the important role of mitochondrial OXPHOS in promoting ESCC metastasis and suggest the clinical therapeutic potential of OXPHOS inhibitors for preventing metastatic spread in ESCC patients.

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55P Transcriptional profiles of engineered T cells stimulated with different receptor structures and co-stimulatory domains

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Background: T cells engineered with chimeric antigen receptor (CAR-T) have shown success in treating hematological malignancies. However, the limited efficacy and potential side effects hinder the use of CAR-T in solid tumors. Research on this heterogeneous cell therapeutics at single-cell level can advance the current understanding and strategy of CAR-T therapy.

Methods: We used single-cell transcriptome analysis to characterize the transcriptional profile of stimulated CAR-T. T cells engineered with second-generation CAR constructs (with 4-1BB or CD28 co-stimulation domains) were stimulated with anti-CD3/CD28-coated beads and Nalm6 and subjected to microwell-based single-cell transcriptome analysis.

Results: A broad spectrum of transcripts was differentially expressed in T cells under various conditions. The sequence derived from the 3'-untranslated region of the CAR transcript distinguished CAR-T from non-transduced T cells within the analyzed cell population. CAR-T stimulation, mediated by either CD3/CD28 or CAR, significantly changed the gene-expression landscape compared to unstimulated CAR-Ts. Notably, CAR stimulation triggered higher expression of immune-related genes compared to CD3/CD28 stimulation. Additionally, comparing 4-1BB and CD28 co-stimulatory domains showed distinct transcriptional profiles contingent upon each co-stimulation signal.

Conclusions: This study revealed characteristic features of CAR-T signals affected by receptor structure (CD3/CD28 vs. CAR) and co-stimulation domain (4-1BB vs. CD28).

These findings provide insights into a deeper understanding of CAR-T therapy, ultimately leading to the development of more effective CAR-T therapy.

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56P SLC34A2-ROS1 L2026M+G2032R confers resistance to ROS1 tyrosine kinase inhibitors in Ba/F3 cells through a reduced ATP binding pocket volume

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Background: The ROS1 G2032R mutation is the most common on-target resistance mutation in crizotinib treated ROS1-positive lung cancer patients. The aim of our study was to investigate resistance mechanisms in SCL34A2-ROS1^{G2032R} positive Ba/F3 cells against second line treatment with lorlatinib.

Methods: Ba/F3 SLC34A2-ROS1^{G2032R} cells were subjected to N-ethyl-N-nitrosourea (ENU) mutagenesis and clones were selected upon treatment with 1000 nM lorlatinib for 4 weeks. Resistant clones were analyzed for presence of on-target resistant mutations using Sanger sequencing. In addition, we generated subclones expressing SLC34A2-ROS1$^{L2026M+G2032R}$ and SLC34A2-ROS1^{L2026M} in Ba/F3 cells. Sensitivity to ROS1 TKIs was determined by measuring cell viability and ROS1 phosphorylation. Molecular Dynamic simulations of the ATP binding pocket were performed for all ROS1 variants.

Results: The ENU-screen of 41 lorlatinib resistant clones revealed one with a mutation in the kinase domain: L2026M. Cell viability assays of the ENU-induced resistant cell line and the Ba/F3 cells transfected with the mutant SCL34A2-ROS1 fusion gene constructs revealed a decreased sensitivity of SLC34A2-ROS1$^{L2026M+G2032R}$ cells for lorlatinib, crizotinib, entrectinib and repotrectinib compared to the single mutants. Consistent with these findings, we observed phosphorylation of ROS1 fusion protein in the double mutant cells which was not inhibited upon treatment with ROS1 TKIs. The single mutant cells showed as expected a clear reduction in phosphorylated ROS1 fusion protein . Molecular modeling to unravel the effect of the mutations demonstrated that the volume of the ATP-binding pocket was reduced in single and double mutants compared to wild type. The double L2026M+G2032R mutant displayed the smallest pocket.

Conclusions: We identified a novel on-target mutation after inducing lorlatinib resistance in SLC34A2-ROS1^{G2032R} Ba/F3 cells. This SLC34A2-ROS1$^{L2026M+G2032R}$ cell line was also resistant to crizotinib, entrectinib and repotrectinib. The resistance can be explained by a smaller ATP binding pocket in the mutated ROS1 fusion protein preventing effective binding of the investigated TKIs.

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57P Metastasis organotropism: Unveiling associated proteins using network biology

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Background: The formation of distant metastases is the deadliest phase of cancer progression. Nevertheless, it is a very inefficient process. Chances of a tumor cell surviving the metastatic process depend on its ability to communicate with the surrounding environment. We hypothesize that metastasis organotropism can be partially explained by the intercellular communication established between cancer cells and other cells in the organ microenvironment.

Methods: Network biology tools are well suited for studying complex diseases such as cancer. Using this computational approach we looked at the complex interplay between proteins and pathways affected in metastasis and identified new metastasis-associated proteins. We built networks of tissue-specific intercellular protein-protein interactions between pairs of primary tumor location and metastasis tissues. Using these networks we identified interactions significantly more frequent in organotropism tissue pairs (primary tumor and metastasis organ) that potentially influence the success of metastasis in specific organs.

Results: Overall, we identified 607 proteins involved in 1095 metastasis-associated interactions. Of these, 881 interactions were positively associated with metastasis, meaning that these interactions occur more frequently in organotropism tissue-pairs than in other tissue pairs. Of the 607 proteins found, 222 are already targeted by known drugs and 53 are targeted by drugs that are not used in cancer treatment.

Conclusions: Cell-cell communication is of paramount importance for the development of metastasis. Experimental studies of the non-oncological drugs targeting the 53 identified proteins are needed to select the most promising candidates to test in drug repurposing clinical trials.

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59P Correlation of tumor microenvironment signature in advanced stage non-small cell lung cancer with EGFR mutation who received EGFR-TKIs

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Background: The impact of tumor microenvironment in advanced non-small cell lung cancer (NSCLC) who had epidermal growth factor receptor (EGFR) mutation remained debated. We investigated the correlation of tumor microenvironment (PD-L1, CD8 and FOXP3) and the association of EGFR TKI treatment outcome.

Methods: A prospective study was conducted to recruit 100 participants who were diagnosed advanced NSCLC with EGFR mutation. All patients were received treatment with EGFR-tyrosine kinase inhibitors (TKIs). Tumor microenvironment composed of programmed cell death ligand-1 (PD-L1) expression, CD8+ tumor infiltrating lymphocyte (TILs) and forkhead box P3 (FOXP3+) TILs density were evaluated by immunohistochemistry. The primary endpoint was the correlation between PD-L1, CD8+, and FOXP3+ TILs density. The Correlations among TILs and clinicopathological characteristics/outcome of treatment were analyzed.

Results: Eighty-five patients with adequate tumor material were evaluated. Twelve (14%) patients expressed high PD-L1 ($\geq$15%) or intratumoral CD8+ TILs ($>$10%). The correlation of PD-L1 and intratumoral CD8+ TILs was significantly ($r = 0.3034$, $p=0.005$). Multivariate analysis revealed that Inflamed tumor was correlated with shorten PFS with the HR of 2.110, 95%CI: 0.968-4.599, p-value 0.06.

Conclusions: Among advanced stage NSCLC with EGFR mutation, tumor microenvironment PD-L1 and intratumoral CD8+ TILs expression was correlated with outcome of treatment.

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60P Establishment and characterization of a novel lung adenocarcinoma cell line HX-JCJ harboring MET ex14 skipping mutation

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Background: MET exon14 skipping mutations are considered an important driver of oncogenesis and are observed in approximately 3-4% of patients diagnosed with non-small cell lung cancer (NSCLC). Various MET tyrosine kinase inhibitors (TKIs) are currently being developed for clinical use in the treatment of NSCLC patients with

MET exon14 skipping mutation. However, preclinical research in this area has been restricted due to the rarity of MET exon14 mutant cases. Almost all the studies conducted have been on patients or patent-derived xenografts (PDX). To address this issue, there is a need for a NSCLC cell line with MET exon14 skipping mutation. In this study, we have established a novel lung adenocarcinoma cell line that harbors MET exon14 skipping mutation. This new cell line represents a valuable tool for the research of MET targeted therapy.

Methods: The cell line was established using the primary tumor tissue from a 67-year-old male patient with NSCLC, and named as HX-JCJ. The cell line has been growing well for more than 10 months and has been passaged over 50 times. Phenotypes of the cell line, such as proliferation, invasion, protein expression, and xenografting were characterized in vitro and in vivo. MET ex14 skipping mutation of this cell line was validated by RT-PCR and Sanger sequencing.

Results: Drug screen showed that this cell line was extremely sensitive to KC1036 (IC50=4.8nm), which is a home-made small molecule inhibitor with strong anti-MET and anti-angiogensis activity.

Conclusions: In conclusion, we successfully established a novel NSCLC cell line (HX-JCJ) harboring MET ex14 skipping mutation from the primary tumor tissue, which may provide a promising cell model for further MET relevant research.

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61P Next generation sequencing and its clinical utility in advanced cancer: Single institute experience from low-middle income country

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Background: Advances in DNA sequencing over the past decade have made it possible to systematically study the genetic changes responsible for cancer development, and we now have a better understanding of the commonly involved processes and signaling pathways. As more genetic alterations become targetable by specific drugs, DNA sequencing is becoming part of routine clinical care but its clinical utility is not well known in low and middle income country.

Methods: This was a single center, retrospective cohort study, which include adult advanced metastatic solid tumor patient who underwent next generation sequencing (NGS) either on tissue block or liquid biopsy (Illumina NGS 560 genes 1000X coverage). Primary end point was to assess the clinical utility of NGS in advanced stage. Secondary end point was to assess the progression free survival (PFS) in patients who received treatment based on NGS.

Results: Over the period of 18 months (from 1st January 2021 to 30th 2022), a total of 93 patients were enrolled in the study, and their baseline characteristics are presented in the table. Patients received a median of 2 lines (range:0-4) of prior systemic therapy and genomic alteration were identified in 45% (n=42) of them. Of the patients with genomic alterations, 33% (n=31) had a targeted therapy option available either in the form of an approved drug or a clinical trial. However, only 19% (n=18) of the patients received treatment based on the results of NGS testing. Among these patients, 9%(n=8) had a progression-free survival of 6 months or more following NGS-guided treatment

Table: 61P Baseline characteristics of study population(n=93)

	Percentage (number of patients)
Gender	
Male	**60%(n=56)**
Female	**40%(n=37)**
Type of Biopsy	
Tissue	**71%(n=66)**
Liquid	**29%(n=27)**
Genetic alteration present	**45%(n=42)**
Targetable approved treatment or clinical trial available	**33% (n=31)**
Patient received treatment as per Molecular alteration	**19%(n=18)**
PFS ≥ 6 months in molecular alteration guided	**9% (n=8)**

Conclusions: Advances in DNA sequencing over the past decade have made it possible to discover new genetic changes, and more genetic alterations are now targetable by specific drugs . However, in routine practice, the results are not very promising, especially in low- and middle-income countries where cost is a major constraint.

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62P Prebiotics modulate gut microbiota-mediated T cell immunity to enhance sintilimab inhibition of lung cancer

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Background: Sintilimab (Sin) helps the body to restore the anti-tumor response of T lymphocytes. However, in clinical use, the treatment process is more complicated due to adverse effects and different dosing regimens. It is not clear whether prebiotics (PREB) have a potentiating effect on Sin for lung adenocarcinoma, and this study intends to investigate the inhibitory effect, safety and possible mechanism of Sin combined with PREB on lung adenocarcinoma from animal experiments.

Methods: Lewis lung adenocarcinoma cells were inoculated into the right axilla of mice subcutaneously to prepare the Lewis lung cancer mouse model and treated in groups. The volume of transplanted tumors was measured, the histopathology of the liver and kidney of mice was observed by H&E staining, the levels of ALT, AST, UREA, CREA, WBC, RBC, and HGB in blood were analyzed biochemically; the ratio of T-cell subpopulations in blood, spleen, and bone marrow was detected by flow cytometry, the expression of PD-L1 in tumor tissue was detected by immunofluorescence staining, and 16S rRNA to analyze the diversity of fecal flora.

Results: Sin inhibited tumor growth and regulated immune cell homeostasis in lung adenocarcinoma mice, but liver and kidney histopathology showed different degrees of damage after Sin treatment, while the addition of PREB reduced liver and kidney damage in lung adenocarcinoma mice and promoted Sin's regulation of immune cells. In addition, the beneficial effects of Sin were associated with changes in intestinal flora diversity.

Conclusions: The mechanism by which Sintilimab combined with prebiotics inhibits tumor volume and regulates immune cell subpopulation balance in lung adenocarcinoma mice may be related to gut microbes.

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63P Addition of human chorionic gonadotropin to the current standard mobilization approach with granulocyte-colony stimulating factor increases overall survival in a murine model of peripheral blood stem cell transplantation: Are we far enough for therapy?

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Background: One important limitation of the current standard approach of mobilizing hematopoietic stem cells (HSCs) in the peripheral blood (PB) using granulocyte-colony stimulating factor (G-CSF) for the prophylaxis of chemotherapy induced febrile neutropenia or in donors for PB stem cell transplantation (PBSCT) is insufficient mobilization. Based on our preliminary results on the effect of human chorionic gonadotropin (HCG) on stimulating the peripheral mobilization of HSCs *in vivo,* the aim of the current study was to assess the effect of the addition of HCG to mobilization with G-CSF on the overall survival (OS) as the primary endpoint in a mouse model of PBSCT.

Methods: Male donor mice (n=20) were pretreated with a single dose of either peg-G-CSF alone (group A, n=10) or HCG + peg-G-CSF (group B, n=10), 5 days prior to PBMC harvest. PBMCs were immediately transplanted to the equivalent number of Busulfan mieloablated female mice by intravenous tail injection and OS was assessed in both recipient groups.

Results: The median OS in the group of recipients transplanted with peg-G-CSF mobilized PBMCs (group A`) was 81 days. In the recipients transplanted with HCG+ peg-G-CSF mobilized PBMCs (group B`} the median OS is not reached at 154 days with 90% of the recipients still being alive.

Conclusions: Addition of HCG to the current standard mobilization approach with G-CSF in donors has almost doubled the survival rate in the recipients of a murine model of PBSCT with the median OS not yet reached after 154 days. This prompts for the translation of the preclinical study`s approach in a human proof-of-principle/feasibility clinical trial.

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64P Developing novel therapeutics for bladder cancer leveraging drosophila models

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Background: The prevalence of bladder cancer (BC) has been increasing worldwide. Particularly, patients carrying the Basal/Squamous BC (BSBC) have poor prognosis. Mammalian models such as cultured human BSBC cells and their xenografts have provided critical insights into its mechanisms, but effective therapeutics for BSBC is still lacking. Recently, the fruit fly *Drosophila* has made significant contributions to cancer research. Here, we employed *Drosophila* to generate the first fly model reproducing the BSBC genotypes and to discover novel therapeutic candidates for BSBC treatment.

Methods: BSBC often harbors mutations in genes '*A*', '*B*' and/or '*C*'. To model various alteration patterns in *Drosophila*, we employed the binary GAL4/UAS system, which targets expression of exogenous transgenes to a desired fly tissue. We prepared GAL4 driver strains expressing a transcription factor GAL4 specifically in the eye cells and wing cells (*GMR-GAL4* and *nub-GAL4*, respectively, for validating transgene functions), or the Malpighian tubule which corresponds to human bladder (for modeling BSBC genotypes). We also generated UAS transgenic strains which carry mutated cDNA and/or shRNA sequences as transgenes downstream of the GAL4 target UAS sequence.

Results: Previous studies have reported that induction of wild-type *A* in fly eyes causes 'rough eye' phenotype by promoting apoptosis, which we confirmed using the eye-specific *GMR-GAL4* driver. We found that additional expression of missense-mutated *A* or knockdown of *A* by shRNA rescued the phenotype as expected. Furthermore, we confirmed that overexpression of *B* using the same driver increased the fly eye size as previously reported. Using the wing-specific *nub-GAL4* driver, we validated that knockdown of *C* by shRNA reduced the fly wing area, verifying its reported function to control tissue growth.

Conclusions: The eye and wing phenotypes induced by transgenes were consistent with their reported functions and our expectation, proving our strategy effective in validating functions of the transgenes and in modeling the BSBC genotypes in flies. We will next perform whole-body assays such as comprehensive genetic and drug screenings using these flies to demonstrate the mechanisms of BSBC pathogenesis and to develop novel BSBC treatments.

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65P Ionizing radiation induces vascular smooth muscle cell senescence through activating NF-κB-CTCF-p16 pathway

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Background: Radiation injury of blood vessels (RIBV) is a serious long-term complication of radiotherapy, and the main pathophysiological change of which is atherosclerosis. Senescence of vascular smooth muscle cells (VSMCs) is implicated in the pathogenesis of radiation-induced atherosclerosis. The mechanisms underlying VSMCs senescence, however, remain poorly understood.

Methods: Using cultured human aortic smooth cells (HASMC) and SD male explored whether IR could induce transformation of senescent phenotype of VSMCs. ChIP assay explored whether SICC bind to p16 gene in irradiated cells. SA-β-gal staining indicate radiation-induced senescence.

Results: Using cultured human aortic smooth cells (HASMC) and SD male rats showed that IR could induce transformation of senescent phenotype of VSMCs with significant positive dose and time dependence in vitro and in vivo. IR activated DDR/NF-κB pathway and induced the nuclear loss of HMGB2 and thus spatial aggregation of CTCF, known as senescence-induced CTCF clusters (SICC), but had no significant effect on the expression level of CTCF. And ChIP assay showed that SICC exhibited stronger binding ability to p16 gene in irradiated cells. Overexpressing HMGB2 and silencing CTCF abrogated radiation-stimulated p16 upregulation with less SICC formation. Suppression of the activation of NF-κB by PDTC (a common inhibitor of NF-κB) attenuated radiation-induced senescence, indicated by less SA-β-gal staining, downregulation of p16. We also found that PDTC reduced radiation-induced nuclear loss of HMGB2 and formation of SICC.

Conclusions: In summary, we demonstrated here, for the first time, that IR induced transformation of senescent phenotype of VSMCs in vivo and in vitro, and activated NF-κB pathway to initiate HMGB2 nuclear loss and thus promote the formation of SICC, which further strengthen the binding ability of CTCF and p16 gene, and resulted in the occurrence of radiation-induced senescence in VSMCs. These findings may have a significant impact on the research of radiation-induced atherosclerosis and open a new prospective in the prevention and therapeutic intervention in RIBV.

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66P Exploring the radiobiology and dosimetry of targeted alpha therapy as a tool to optimize its clinical application: A preclinical study

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Background: The use of molecular radionuclide therapy (MRT), such as targeted alpha therapy, is an emerging option for cancer treatment. The first alpha-emitter approved for therapeutic use was radium-223 (Ra-223), indicated for metastatic castration-resistant prostate cancer (mCRPC), with exclusive bone metastasis. However, treatment outcomes are below expectations. There are some limitations, such as precise dosimetry, that could be addressed to improve clinical outcomes. In fact, there is no inclusion of radiobiology and molecular dosimetry data obtained in preclinical studies into MRT planning as occur for radiotherapy. Moreover, there is a lack of these data for MRT. Thus, the aim of this study was to develop preclinical studies to access radiobiology and dosimetry for MRT, namely for Ra-223.

Methods: Preclinical studies were conducted using metastatic PCa cells or spheroids, to better mimic tumor architecture, as cellular models of mCRPC. Radiobiological endpoints, such as viability, survival and death, were measured 7days post-irradiation of cellular models with increasing activities of Ra-223 (0-7040 Bq/mL) for 24h. The size, geometry and cell distribution of each cellular model were analyzed by confocal microscopy and values were used in combination with radiobiological and kinetics endpoints to perform cell dosimetry using MIRDcell V3.

Results: The exposure to increasing activities of Ra-223 induces a decrease in viability, survival with increasing of cell death for both cellular models, with biological effects depending on the cell model characteristics. These effects are less evident when evaluated in spheroids, when exposed to the same activities of Ra-223. These biological data were validated with dosimetric calculations that confirm differences in absorbed doses depending not only on initial activity but also on cellular model characteristics.

Conclusions: The radiobiological and dosimetric studies showed that radiation effects for Ra-223 are dependent on molecular and structural characteristics of the cellular model, being the spheroids more representative of tumor architecture and better to conduct translational preclinical studies for MRT, as well as to obtain precise dosimetry.

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67P The effect of non-viral gene-immune therapy via OX40L or 4-1BBL on murine subcutaneous CT26 colon cancer model

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Background: One way to significantly reduce the incidence of systemic side effects of antitumoral immunotherapeutics is intratumoral gene-immune therapy. The use of non-viral systems is attractive for gene therapy due to low immunogenicity of the carrier, low production costs, and relatively high capacity. Thus, non-viral intratumoral gene-immune therapy is a promising area for development of antitumor drugs. OX40 and 4-1BB T cell co-stimulators are popular targets in immunotherapeutic drug development, but currently there are no approved drugs targeting these receptors. We suppose that the natural ligands of these receptors, OX40L and 4-1BBL, would be effective in non-viral gene-immune therapeutics.

Methods: The antitumor effect of stable OX40L or 4-1BBL expression by inoculated cancer cells on CT26 tumor growth was studied. CT26 cell lines stably expressing OX40L or 4-1BBL were obtained, tumor graftability and growth in BALB/c mice were evaluated. Next, antitumor effect of non-viral gene-immune therapy with OX40L or 4-1BBL was studied, complexes of polymeric carrier with plasmid DNA encoding OX40L or 4-1BBL were prepared and injected three times into CT26wt subcutaneous tumors in BALB/c mice, starting when tumors reached 50±15 mm^3 .

Results: Stable expression of OX40L and 4-1BBL significantly suppressed CT26 tumor growth, delayed tumor resorption was observed in the experimental groups. The use of OX40L and 4-1BBL in the context of gene-immune therapy had a significant effect on CT26 tumor growth — median animal survival compared to the control group was increased by 26.5% (OX40L) and 41.2% (4-1BBL), life expectancy was increased by 24% (OX40L) and 24.5% (4-1BBL), tumor growth inhibition 10 days after treatment was 70% (OX40L) and 71.3% (4-1BBL). No visible immune-related adverse events (irAEs) were observed.

Conclusions: OX40L and 4-1BBL have a comparable potent antitumoral effect on CT26 tumor growth in the context of non-viral gene-immune therapy, and such therapeutic approach does not yield visible systemic irAEs.

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68P Dendritic polylysine with paclitaxel and triptolide codelivery for enhanced NSCLC ferroptosis through the accumulation of ROS

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Background: The clinical application of Paclitaxel (PTX), a first-line chemotherapeutic for NSCLC, is severely limited because of its developed resistance and insolubility. It is reported by our previous studies that the resistance to PTX is closely related to intracellular redox balance in cancer cells. Moreover, our preliminary data demonstrated that Triptolide (TPL) could improve the cytotoxicity of PTX through inducing ROS production. Most importantly, the synergistic anticancer effect between PTX and TPL is mainly through the induction of ferroptosis in NSCLC cell lines. To improve the delivery efficiency of both drugs, we constructed a novel nano-drug delivery system NDDS chemosynthesis by PEGylated generation 3 (G3) dendritic polylysine co-loaded with PTX and TPL (PTX-TPL-PEG-PLL, PTPP), which was endowed with the ability of tumor targeting and favorable solubility. this is the first report on the dendritic polylysine loaded with PTX and TPL for NSCLC treatment. In addition, the enhanced ferroptosis-inducing effect of PTPP was mediated through ROS level, which illustrated the possible mechanism underlying the synergistic effect of PTX and TPL.

Methods: First, the PTPP was characterized by 1H NMR analysis, mass spectra, and HPLC. the in vitro synergetic effect and mechanism of PTX and TPL were explored by MTT assay and western blot. In vivo evaluation was performed in a xenograft mice model of NSCLC cell lines.

Results: The PTPP was synthesized successfully through covalent bonding and the MTT assay indicated the synergetic effect of PTX and TPL. Besides, regarding the mechanism, the TPL could promote the generation of ROS by inhibiting the NF-κB signaling pathway, which synergistically increased ROS level with PTX, inducing NSCLC cells ferroptosis. In the end, in vivo experiments suggested the outstanding tumor-inhibiting ability of PTPP.

Conclusions: Overall, the current study suggested that PTPP exerted an excellent antitumor effect than PTX, TPL, or PTX combined with TPL through ferroptosis induction. PTPP may be a potential treatment system for NSCLC treatment.

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69P Novel monoclonal antibodies can distinguish Cripto-1 from Cripto-3 proteins: Clinical implications and potential new biomarkers

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Background: Cripto-1 (CR1) is an oncofetal protein required for implantation and expressed in the adult during wound repair, inflammation, and tumorigenesis. A second gene codes for a very homologous protein, Cripto-3 (CR3). Both proteins contain 188 amino acids and differ only in 6 residues. Heretofore, all available antibodies cannot discriminate between these two proteins, preventing any investigation on their differential contributions to cancer biology. Here, we present the generation, characterization, and clinical implications of highly specific monoclonal antibodies (MoAbs) for these two proteins.

Methods: Different peptide fragments of either protein were used as antigens to generate mouse MoAbs (233 clones for CR1, 319 clones for CR3) that were selected by their target protein specificity through SPR and ELISA assays. Selected MoAbs were used for immunohistochemistry on tissue arrays including normal tissues as well as cancers of the lung, breast, colon, ovary, and prostate. MoAbs were also used for Western blotting and ELISA characterization of human serum (breast cancer vs healthy controls).

Results: MoAbs NCI 5G1-1 and NCI 5G11-2 were highly specific for CR1 and CR3, respectively. No crossreactivity was observed with the other protein. Immunohistochemical analysis of cancer specimens showed differential staining patterns, where some tumor cells expressed both proteins, others expressed only CR3, and still others show vascular endothelial cells stained for CR1 while tumor cells express CR3. In prostate, colon, and breast cancer, CR1 and/or CR3 protein expression correlates with clinical parameters, such as TMN_N, TMN_M, tumor stage, tumor grade, or PR expression. Lastly, both CR1 and CR3 interact with established binding proteins Nodal, GRP78 and Alk4 and competitively interfere with one another for targeted binding.

Conclusions: We describe for the first time the development of MoAbs that discriminate human CR1 from CR3, confirming that CR3 is translated into a protein in human cells, thus removing its pseudogene status. We also confirm CR1, and propose CR3, as cancer prognosis and severity markers.

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70P The human intratumor mycobiome is significantly influenced by an individual's race

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Background: Recently, the intratumor mycobiome has been characterized in 17,401 cancer patients, covering 35 cancer types from The Cancer Genome Atlas (Narunsky-Haziza et al., 2022), revealing a previously overlooked aspect of cancer research. Moreover, Recent study showed that race is a key determinant of the human intratumor microbiome. We aimed to better understand the effects of patients' demographic factors (age, sex, and race) on the intratumor mycobiome composition.

Methods: We analyzed the Narunsky-Haziza et al. de-contaminated and normalized intratumor fungal abundance data for 11 cancer types and 224 fungal species. We performed a systematic characterization of the tumor mycobiome across different cancer types using a propensity score algorithm, adjusting for the potential confounding factors of histological type and tumor stage.

Results: Fungus species abundances differed significantly between races in all cancer types. For example, in breast cancer, we identified 42 significantly differentially

abundant fungal species in European vs. Asian, 45 species in European vs. African, and 56 in Asian vs. African. Notably, 19 fungal species *Talaromyces marneffei, Scheffersomyces stipites, Debaryomyces fabryi, Lachancea lanzarotensis, Ogataea polymorpha, Tetrapisispora blattae, Fusarium proliferatum, Kazachstania Africana, Torulaspora delbrueckii, Naumovozyma castellii, Wickerhamomyces anomalus, Yamadazyma tenuis, Naumovozyma dairenensis, Sugiyamaella lignohabitans, Clavispora lusitaniae, Candida tropicalis, Vanderwaltozyma polyspora, Meyerozyma guilliermondii, Lachancea thermotolerans* — had significantly different abundances in all three race comparisons. Moreover, regarding age (>65) and sex, only 5 fungal species abundance in stomach adenocarcinoma varied significantly for age and *Malassezia sympodialis* differed significantly with respect to sex. In thyroid carcinoma, 3 species varied by age and *Cordyceps militaris* for sex.

Conclusions: Our research reveals that the composition of the fungal community within tumors varies significantly across races, underscoring the importance of accounting for this demographic factor when conducting fungal-related analysis and clinical trials involving microbiota modulation.

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71P Preclinical characterization of ARX305: A next-generation anti-CD70 antibody drug conjugate for the treatment of CD70-expressing cancers

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Background: CD70 is an attractive tumor target due to its over-expression in numerous solid and hematological cancers and limited expression in healthy cells. In the last decade, multiple anti-CD70 antibody drug conjugates (ADCs) have been developed, but most have been discontinued due to unacceptable toxicity or a narrow therapeutic index. Using an expanded genetic code to create Engineered Precision Biologics, Ambrx has developed ARX305, a CD70-targeted next-generation ADC to potentially overcome the challenges associated with earlier ADCs. ARX305 is comprised of a proprietary, high-affinity, humanized anti-CD70 antibody stably and site-specifically conjugated to AS269, a potent microtubule inhibitor. After binding to CD70 expressed on tumor cells, ARX305 is internalized and catabolized, releasing the cytotoxic payload pAF-AS269 which inhibits cellular proliferation. ARX305 utilizes stable oxime conjugation chemistry, a non-cleavable PEG linker, and a membrane-impermeable payload to minimize premature payload release in circulation and associated off-target toxicity.

Methods: ARX305 was evaluated in multiple pre-clinical pharmacology and toxicology models using standard methodology.

Results: In vitro studies demonstrate that ARX305 selectively induces cytotoxicity of CD70-expressing tumor lines. In multiple *in vivo* xenograft or disseminated models, ARX305 induced significant tumor growth inhibition or regression whereas unconjugated antibody exhibited poor activity. The stable conjugation and cell-impermeable payload of ARX305 led to high serum stability, a long terminal half-life, and a similar exposure profile as unconjugated antibody in rodent pharmacokinetic studies. Repeat dose studies in cynomolgus monkeys demonstrated ARX305 was tolerated at exposures well above therapeutic exposures in mouse pharmacology studies, indicating a wide therapeutic index.

Conclusions: In summary, the highly selective and potent anti-tumor activity in multiple tumor types and wide pre-clinical therapeutic index of ARX305 support clinical evaluation of this next generation anti-CD70 ADC. ARX305 is currently in a phase 1 dose-escalation study in China.

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72P Impact of extended panel of genes for germline cancer testing

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Background: Traditional genetic screening was based previously on the analysis of classical high penetrance genes such as BRCA1 and BRCA2. In the context of our clinical practice in Dubai, individuals fulfilling the criteria are tested for germline mutations to subsequently establish the clinical management. Our current standard diagnostic approach focuses on sequencing 110 genes through NGS leading to increase the chance of finding the causal mutation and to the widespread clinical use of genes for germline cancer testing.

Methods: A total of 111 cases were tested in UAE with a traditional panel (BRCA1, BRCA2 and CHEK2) from October 2013 till September 2016. Then we have integrated extended panels (36 then 110 genes) from October 2016 till March 2023 and tested 509 cases. Median age was 47 years. Cases were referred for genetic testing mainly due to personal history of breast and ovarian cancer.

Results: Mutations in traditionally screened cases represent 8.1% for BRCA1, BRCA2 and 1% for CHEK2 for all types of panels. However extended panel analysis had a higher detection rate of pathogenic mutations compared to traditional analysis with an average increase of 7% in several genes mainly MUTYH, TP53, MLH1, RAD51D, PALB2 (respectively 2.6%, 0.8%, 0.8%, 0.6%, 0.6%). The heterogeneity of the newly detected mutations identified reinforces the value of using an extended hereditary panel. Further analysis will correlate the characteristics of germline mutations and their correlation with the tumor type and with the age group.

Conclusions: To our knowledge this is the first abstract from the MEA focusing on the impact of the analysis of extended panel of genes to patients with suspicion of hereditary cancer. Our findings reinforce the utility of extended panels involved in hereditary cancer predisposition in the diagnostic routine which may impact their clinical management. The use of this approach facilitates the detection of pathogenic mutations in non-BRCA1/2 genes and aided management. This will allow opportunities for enhanced surveillance and intervention in a range of tumors.

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73P Preclinical and clinical presentation of the nerve-driven tumor spread

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Background: Tumor infiltration by nerves and axial bone metastases often occur in prostate cancer (PCa) patients, however the mechanisms and the link between these processes are not well understood. Here, we report a PCa mouse model, which recapitulates this cancer route of spreading and correlates with radiological images from PCa patients.

Methods: The human androgen-independent PC3-ML cell line with reported bone metastasis potential was orthotopically injected into the prostate of SCID/Bg mice to observe the natural history of cancer spread instead of commonly used intratibial or intracardiac injections. The process of primary and secondary tumor development was monitored by magnetic resonance imaging (MRI). The tissues were collected and immunostained for neuronal markers, neurofilament (NF), and tyrosine hydroxylase (TH), as well as prostate cancer cell marker, pan-cytokeratin, and a vascular marker, CD31. Additionally, clinical cases of patients with representative MRI images of bone metastases and PNI were selected.

Results: The mice MRI revealed the presence of primary prostate tumor with secondary tumors located mostly along the lumbar spinal cord and pelvis, which led to secondary bone infiltration. The histopathological analysis confirmed the presence of PCa cells along the spine with its infiltration. The PCa cells created clusters, which spread along the small, NF-positive nerve fibers that were directed into the bone area. We ruled out the retrograde vessel infiltration by CD31 immunostaining. The clinical relevance of our model was confirmed by the radiological presentation of human PCa cases: 1) a patient with castration-sensitive PCa, with oligometastatic disease (one sacrum metastasis) and infiltration of neurovascular bundle; 2) a patient with castration-resistant PCa with PNI and a relapse in the ilium, who subsequently developed perispinal metastases along the lumbar plexus and spine.

Conclusions: Altogether, the results of our study suggest that PNI may be responsible for the initial PCa dissemination to bone. MRI imaging has adequate sensitivity to detect the nerve infiltration, however it is not commonly used in disseminated PCa patients. Consequently, the number of cases with spine infiltration and bone metastases may be underreported.

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74P Characterization of ERBB2 variation and their association with immune response in solid tumours

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Background: *ERBB2*, a receptor tyrosine kinase, is commonly affected by mutations, amplifications, and overexpression in various types of cancers. Drugs targeting ERBB2 are gradually being promoted to various types of cancer. However, the variation of ERBB2 in Chinese population and the relationship between *ERBB2* high expression abnormalities and the tumor immune microenvironment remains unclear.

Methods: We utilized genomic data from over 10,000 pan-cancer Chinese populations in CbioPortal to detect somatic mutations and copy number variations. We also performed RNA sequencing date in TCGA (pan-cancer Atlas studies) to determine *ERBB2* expression in diverse cancer types and evaluate the immune gene characteristics and content of tumor-infiltrating immune cell populations.

Results: A total of 309 *ERBB2* amplifications, 169 *ERBB2* substitution or insertion deletions, and 28 *ERBB2* fusions or rearrangements were detected in 10,194 patients. The *ERBB2* amplification rate of breast cancer (23.84%), gallbladder cancer (13.75%) and urothelium cancer (8.33%) ranked the top three among all cancer types. Among the co-mutated genes with *ERBB2* mutations, TP53 (68.8%), CDK12 (34.7%), and RARA (18.7%) have the highest proportion of mutations. Furthermore, among 10,967 RNA datasets in TCGA, breast cancer, esophageal squamous cell carcinoma, and gastric adenocarcinoma displayed the highest average expression levels of *ERBB2*. Patients with high *ERBB2* expression exhibited similar TMB values to those with low *ERBB2* expression. However, in breast cancer, colon cancer, lung adenocarcinoma and lung squamous carcinoma, *ERBB2* high expression was significantly associated with a higher proportion of activated mast cells, monocytes, and regulatory T cells, while the percentage of resting mast cells and M1 macrophages was notably lower.

Conclusions: Our study identified *ERBB2* variation patterns among a cohort of Chinese solid tumor patients and demonstrated that *ERBB2* abnormality high expression is associated with an activated immune system and a stronger inflammatory response. Our findings offer insights into the potential benefits of using immune checkpoint inhibitors for this type of patient.

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75P Double-stranded RNA transfection induced anti-tumour effect mediated by dual RIG-I and TLR-3 immune pathways

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Background: Cancer immunotherapy is dependent on immunostimulation to reorganise the tumour microenvironment (TME) and to increase anti-tumour effects of immune cells. There are currently many immunostimulants applicable to cancer therapy, such as antibodies, molecular drugs and PAMP activators. Choice of immunostimulant may be key, but method of delivery of treatment is equally as important as different routes may stimulate different immune pathways. Despite of the rapid development of nucleic acid drugs in recent years, the effect of nucleic acid on tumor immunity needs to be further investigated. Polyinosinic:polycytidylic acid (poly I:C) is a synthetic double-stranded RNA analog that shows promise as an adjuvant in cancer vaccines or immunotherapies. Poly I:C is known to interact with Toll-like receptor 3 (TLR3) when taken up by endocytosis, but when directly transfected into cells, poly I:C stimulates retinoic acid-inducible gene I (RIG-I) instead.

Methods: Poly I:C was used to mimic anti-tumour response after nucleic acid administration. Murine 4T1 mammary tumour-bearing BALB/c mice were treated with poly I:C by electroporation (EP) or syringe injection (SI) and monitored for tumour growth. To determine whether poly I:C-activated immune pathways differed between delivery modes, RIG-I and TLR3 pathway inhibitors were used to inhibit poly I:C-induced anti-tumour effect in 4T1 tumour model.

Results: Our results showed that poly I:C EP treatment induced stronger tumour suppression effect and tumour-specific adaptive immune response than via SI. And that this EP-treated anti-tumour effect could be suppressed by both RIG-I and TLR3 pathway inhibitors, but not in SI, suggesting that treatment of poly I:C via different delivery modes do activate different immune pathways.

Conclusions: We have demonstrated that poly I:C could induce different anti-tumour effects dependent on treatment delivery method. Our results suggest that the effects of nucleic acid drugs may vary depending on how they are administered.

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76P Improvement of whole-cell cancer vaccine anti-tumor effect by different injection methods

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Background: It is common for cancer to recur even after successful treatment of the primary tumor. Recurrent or metastatic cancers are less responsive to existing therapies and often have high mortality rate. Whole-cell cancer vaccine, which utilizes patient-derived primary tumor tissue may be a promising approach in preventing recurrence. A major advantage is the provision of a plethora of patient-specific tumor antigens, but overall whole-cell vaccine efficacy is still limited and insufficient. To improve on the efficacy of whole-cell cancer vaccine, we explored the use of different injection methods. It has been previously shown that injection method and location of injection may vary vaccine efficacy and effects. Therefore, we investigated different injection methods to improve the effectiveness of the whole-cell cancer vaccine.

Methods: We compared the efficacy of needle-syringe injection and needle-free (pyro-drive jet injector) injection to evaluate the differences in effectiveness of whole-cell cancer vaccines using murine MC38 colon adenocarcinoma or 4T1 mammary tumor cell lines, by analyzing tumor challenge and the inhibition of cancer metastasis using the C57BL/6 and BALB/c mouse models. We also analyzed the *in vitro* activation of APCs and innate immune cells using the expelled whole-cell vaccine following each injection method by flow cytometry, cytokine array and quantitative real-time PCR.

Results: Our results showed that whole-cell vaccine administered via needle-free injection induced higher tumor suppression effect and stronger tumor-specific immunity than traditional needle-syringe injection in both MC38 and 4T1 tumor models. *In vitro*, the whole-cell cancer vaccine preparation discharged through the needle-free injection device induced a stronger immune stimulation on immune cells than from the syringe method.

Conclusions: In contrast to needle injection, needle-free injection of whole-cell cancer vaccine resulted in more pulverized cancer cell fragments, which potentiates APC phagocytosis and adaptive immune activation, thereby improving anti-tumor effect of the vaccine. Therefore, needle-free injection or pre-pulverized formulations should be considered to improve anti-tumor effects of whole-cell cancer vaccines.

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77P Normative data on the sexual health questionnaires - QLQ-SHQ22, and the sexual domains of the QLQ-BR23/BR45 - for Norwegian general population with and without cancer

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Background: Sexual dysfunction is of the most common late effects after cancer. Normative general population data on sexual health is essential for supporting the interpretation of patient-reported outcomes (PROMs) in cancer studies and clinical practice and can contribute to improve survivorship care. This study aims to provides age-, sex- and morbidity specific Norwegian normative values for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires; the Sexual Health Questionnaire QLQ-SHQ22, and the sexual domains of the breast modules QLQ-BR23/QLQ-BR45 inindividuals with and without history of cancer.

Methods: A nationwide general population sample stratified by sex and age (18—29, 30—39, 40—49, 50—59, 60—69, 70-79 years) was drawn from the Norwegian Population Register. Participants were notified through National online health services and postal mail. The survey included sociodemographic background, morbidity assessed bythe Self-Administered Comorbidity Questionnaire and sexual health assessed by the sexual health EORTC questionnaires.

Results: Of the 15,627 eligible individuals, 5,135 (33%) responded. Among these, 453 persons reported being diagnosed one or several times with cancer, and 4669 persons had no former history of cancer (breast, prostate, gynecological and others). Individuals with cancer scored significantly lower ($p<0.01$) on several functional scales: *libido* (scores 54 vs. 70), *sexual functioning* (45 vs 58), *sexual enjoyment* (67 vs 76), and for women *femininity (*65 vs. 84). The most prominent differences in symptoms were *fatigue* (32 vs 20) and *worry of incontinence* (27 vs. 9). Women and individuals with comorbidities had in general poorer sexual health, and differences were most pronounced in the youngest age groups.

Conclusions: The present study is the first to use normative EORTC data to compare sexual health in individuals with- and without cancer. Sexual health was in general significantly poorer in individuals with history of cancer compared to individuals without cancer.

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78P Peroxiredoxin-1 knockout negatively affects the viability of ph+ B-cell acute lymphoblastic leukemia cells and sensitizes them to tyrosine kinase inhibitors

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Background: Breakpoint cluster region-Abelson (*BCR:ABL1*) gene fusion is an essential oncogene in both chronic myeloid leukemia (CML) and Philadelphia-positive (Ph^+) B-cell acute lymphoblastic leukemia (B-ALL). While tyrosine kinase inhibitors (TKIs) are effective in up to 95% of CML patients, 50% of Ph^+ B-ALL cases do not respond to treatment or relapse. This calls for new therapeutic approaches for Ph^+ B-ALL. Dysregulation of redox homeostasis and reliance on the thioredoxin (TXN) antioxidant system has been previously shown in B-ALL. Herein, we investigated the role of peroxiredoxin-1 (PRDX1), an enzyme responsible for the scavenging of hydrogen peroxide, in Ph^+ myeloid and lymphoid leukemia.

Methods: PRDX1 knockout and apoptotic proteins were assessed by immunoblotting. The numbers of viable BV173 (lymphoid) and K562 (myeloid) cells were evaluated by light microscope counting after discriminating dead cells with Trypan Blue staining. Cell cycle and proliferation were assessed with MUSE and Click-iT EdU tests, respectively. The viability of K562 and BV173 knockouts treated with TKIs was assessed with propidium iodide staining and flow cytometry.

Results: PRDX1 knockout reduced the numbers of viable BV173 cells grown in vitro, but did not affect the numbers of K562 cells. The addition of hydrogen peroxide scavenges to the culture medium restored the viability of BV173 cells. We observed no significant differences in cell proliferation or in cell cycle fractions in BV173sgPRDX1 cells. Notably, in contrast to the myeloid K562 cell line, lymphoid B-ALL cells lacking PRDX1 were much more sensitive to three tested TKIs: imatinib, dasatinib, and ponatinib.

Conclusions: The results reveal that the important role of PRDX1 for Ph^+ leukemic cell viability and sensitivity to TKIs is restricted to lymphoid leukemias. The observed reduced numbers of PRDX1 knockout cells were not the effect of an altered cell cycle or proliferation but most likely due to increased apoptosis. These findings are part of a larger ongoing in vitro and in vivo study examining the sensitization of Ph^+ lymphoid leukemia to TKIs through inhibition of the thioredoxin system and PRDX1.

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79P Co-delivered crizotinib and gefitinib based on nanoparticle for synergically overcoming resistance lung adenocarcinoma treatment

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Background: Gefitinib has been employed as a first-line treatment for patients with NSCLC with EGFR mutation, but rapid drug resistance in tumors induces disease progression. Overactivation of PI3K/AKT is associated with gefitinib resistance (GR) in lung adenocarcinoma. Clinically, crizotinib inhibits AKT and extracellular regulated protein kinases (ERK) signal activation in various tumor cells.

Methods: Gefitinib and crizotinib were loaded into a hydrophobic core, which was formed by the amphiphilic block poly (ethylene glycol)—poly (hexyl ethylene phosphate) (GC@NP) through nano self-assembly method. And the anti-tumor effect and mechanism of GC@NP were verified in vivo and in vitro.

Results: According to particle characterization results, GC@NP had a homogeneous and stable nanoscale, which was 40.1±1.1 nm. Especially, GC@NP had a good drug loading efficiency, the values are 6.52 ± 0.21% and 7.09 ± 0.39% for gefitinib and crizotinib respectively. At the cellular level, GC@NP can be effectively ingested by PC9GR cells within 2 hours. When the concentration of gefitinib was set to 2 μM, the cell viability of the free gefitinib group was 90%, while GC@NP group was only about 50%. At the same time, GC@NP exhibited higher proliferative inhibition and apoptotic induction effects compared to free gefitinib group, the apoptosis rates were 25% and 5% respectively. At the animal level, GC@NP significantly inhibited the growth and metastasis of PC9GR tumors, and also inhibited the brain metastasis associated with GR. Meanwhile, we validated GC@NP has good biosafety in the transgenic zebrafish model. In the nude mouse tumor model, our results indicate that GC@NP can significantly inhibit the growth of PC9GR tumors, while the combination of free gefitinib and crizotinib didn't show significant therapeutic effects. Mechanistically and importantly, GC@NP synergism promoted the dephosphorylation of the overactivated AKT signal and inhibited the feedback activation of ERK signal, which inducing apoptosis in PC9GR cells.

Conclusions: The co-delivery nanoparticle GC@NP we have constructed provides a potential therapeutic approach for advanced lung adenocarcinoma patients with targeting-drug resistance and brain metastasis.

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80P Steroidal oximes: A new potential therapeutic approach for cancer treatment

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Background: Cancer still remains one of the life-threatening diseases worldwide despite the large number of therapeutic approaches currently available. Steroidal compounds possess numerous biological activities being antitumor one of them. Oximes have also been associated with antitumor activity. Moreover, previous studies by our group demonstrated that steroidal oximes were also very potent against several types of cancer. Thus, we embarked in the design and synthesis of new steroidal oximes and evaluated their potential antitumor activity against lung, prostate, and triple-negative breast cancer cells, with the aim of finding alternative cytotoxic compounds for cancer treatment.

Methods: Compounds **OX1**, **OX2, ExeOx and Formox** and their parent compounds **P1**, **OL2**, **Exe** and **Form** were synthesized, and their cytotoxicity evaluated in H1299, PC3 and HCC1806 cell lines through SRB assay after the treatment of the cells with the compounds (1-75 μM). Cell viability, cell death profile, alterations on cell cycle and mitochondrial membrane potential were assessed by flow cytometry.

Results: All compounds decreased H1299, PC3 and HCC1806 cancer cell proliferation in a dose-dependent manner, with the exception of **OX2**. Overall, the parent compounds decreased cancer cell proliferation in a less pronounced way, proving that the introduction of an oxime group was beneficial for the cytotoxicity displayed. Moreover, the best compound was **OX1** in all cell lines with IC_{50} values of 18.69, 22.90 and 29.95 μM in H1299, HCC1806 and PC3, respectively. Flow cytometry studies with **OX1** showed that this compound was able to decrease cell viability in all cell lines by causing cell death mainly by apoptosis, which was accompanied by a blockage at phases G2/M and S, depending on the cell line. Considering the mitochondrial membrane potential, **OX1** induced mitochondrial dysfunction, which might also be related to apoptosis.

Conclusions: Our results show that **OX1** possesses a beneficial antitumor effect from the introduction of the oxime group, which is mediated by apoptosis. This effect encourages further studies on its mechanism of action and selectivity in order to discover new molecules for cancer treatment.

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81P miR-23b and -133a role on TRAIL-induced apoptosis pathway components expression and TRAIL sensitization in lung adenocarcinoma cells

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Background: TRAIL-induced apoptosis pathway is a potential therapeutic target, but the majority of tumors are TRAIL-resistant. TRAIL receptors translocation is associated to TRAIL resistance. Besides TRAIL receptors, DR4 and DR5, other potentially TRAIL-induced apoptosis pathway regulatory proteins are: Apaf-1, CUL3, CLTA (clathrin chain A , involved in TRAIL receptors nuclear translocation) and KPNA-1 (involved in TRAIL receptors internalization). Overcome TRAIL resistance is essential to therapeutic strategies development.

Methods: A549 cell line was used. Expression of miR-23b, miR-133a, DR4, DR5, Apaf-1, CUL3, CLTA/CLTC and KPNA-1 were estimated by RT-qPCR. Transfection effects of miR-23b inhibitor and Mimic-133a on TRAIL apoptosis pathway components expression. Western Blotting to TRAIL receptors compartmentalization after Mimic-133a and TRAIL stimulus. MTT cell viability assay to evaluate TRAIL-induced cytotoxicity of miR-23b inhibition and Mimic-133a transfection.

Results: A549 was TRAIL resistant. miR-23b was superexpressed and miR-23b inhibition upregulated Apaf-1 and CUL3 expression. miR-133a was undetectable. Mimic-133a transfection downregulated CLTA and DR5 expression. miR-23b inhibition and Mimic-133a transfection promoted TRAIL sensitization.TRAIL receptors were predominantly located in nuclear compartment. Mimic-133a downregulated CLTA expression but did not alter receptors compartmentalization. Mimic-133a and TRAIL associated stimulus leaded to predominant nuclear TRAIL receptors localization in comparison to control cells.

Conclusions: Both miR-23b and -133a are involved in TRAIL cells resistance. Apaf-1 and CUL3 expression downregulation by miR-23b can contribute to resistance. miR-133a role on TRAIL sensitization mechanisms must be further investigated. Mimic-133a downregulated CLTA expression but did not alter TRAIL receptors compartmentalization, suggesting that receptors translocation is clathrin independent.CLTA expression control by miR-133a, however, can contribute to drug-resistance research. Although more research is needed to fully clarify miRs roles on TRAIL-induced apoptosis, our findings deepen TRAIL resistance understanding.

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83P Impact of VHL-associated tumor treatment on mental health: An international patient survey

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Background: Treatment (tx) options for patients (pts) with Von Hippel-Lindau syndrome (VHL) were previously limited to surgeries between regular scans, observation and txs that preserve organ function. Little data exists on the burden of VHL-associated tumor tx on the mental health of pts.

Methods: International, cross-sectional survey comprising pts in the United States, Canada, UK, France, and Germany. Pts recruited via the VHL Alliance. Pts must have renal cell carcinoma (RCC), pancreatic neuroendocrine tumors (pNET), and/or central nervous system hemangioblastoma (CNS Hb). Data collected included demographics, impact of most recent surgery on aspects of their condition (1-7 scale 1: greatly worsened and 7: greatly improved), feelings before/after their most recent surgery (1-5 scale, 1: completely disagree, 5: completely agree with presented statements), and treatment preference questions.

Results: Data collected from 220 pts (68% female, median age 40 years, median disease duration 16 years) in US (n=108), CA (n=37), UK (n=21), FR (n=3), and DE (n=51). 146 pts reported RCC (66%), 122 pNET (56%), and 190 CNS-Hb (86%). 205 (93%) pts had experienced surgery; 171 (78%) had experienced multiple surgeries (median = 4). Top three concomitant self-reported conditions were anxiety (36%), depression (29%) and high blood pressure (28%). 24% of pts consulted a mental health specialist. 51% of pts indicated that their most recent surgery worsened their mental health (rated 1-3), 84% of pts agreed they felt anxious before their most recent surgery (rated 4-5). After their most recent surgery 50% of pts agreed they felt anxious. 33% of pts indicated improving quality of life was in their top 3 treatment goals; 17% indicated improving mental wellbeing was in their top 3 treatment goals. 73% of patients indicated they would prefer to take a pill which would possibly delay time until surgery, rather than watch and wait to see if the tumor would grow.

Conclusions: Pts with VHL-associated disease report anxiety and depression as the most common mental health conditions, and agree that upcoming surgery worsens their anxiety. Over half of pts reported that their most recent surgery worsened their mental health. Despite this, less than a quarter of pts consulted a mental health specialist.

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84P Microenvironment immune differences between sexes in multiple myeloma

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Background: Several studies showed that sex is a biological variable that influence immune response in several types of solid tumors; however, there is scarce information in hematological malignancies. In this work, we evaluate differences in immune cells compositions and immune response of multiple myeloma between sexes.

Methods: We conducted a computational biology study using transcriptomic data obtained from bone marrow aspiration collected from untreated multiple myeloma patients under the MMRF-COMMPASS protocol (study accession phs000748). Data was pre-processed and the expression levels were normalized to TPM (transcript per million). To evaluate differences in immune cells compositions, we quantified the immune cell in the tumor microenvironment with the analytic platform CIBERSORT. Differences in activated immune pathways was evaluated with the gene set enrichment analysis (GSEA). Pre-processed counts were normalized to TMM (trimmed mean of M-values) and GSEA was performed using the GSEA java desktop application (v4.3.2). In both analysis, patterns of immune gene sets and the immune cell composition were compared between tumors from female vs. male patients. A $p<0.05$ and a FDR<25% were considered statistically significant for GSEA analysis, while a $p<0.05$ and a FDR<0.05 6.1x10-5 was considered statistically significant for CIBERSORT analysis.

Results: Overall, 451 males and 313 female patients were included. We detected in samples from female patients an enrichment of dendritic cells activated (p=0.0023, FDR=0,0257) and NK cells activated (p=0.0059, FDR=0,0326). In contrast, we observed in male patients an enrichment of monocytes (p=6.10x 10^{-5}, FDR=0,0013) and macrophages M1(p=0,0050, FDR=0,0326). The GSEA analysis revealed an overregulation of natural killer cell degranulation (p=0.007, FDR=0.21624), positive regulation of type I interferon mediated signaling pathway (p<0.0001, FDR=0.23946), and regulation of natural killer cell proliferation (p=0.01, FDR=0.2495).

Conclusions: The computational analysis showed some differences in the immune microenvironment, between sexes in multiple myeloma. Studies about the influence of these differences in the clinical outcomes of patients should be evaluated.

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85P In silico evaluation of the transcriptomic and immunologic profile of lung adenocarcinomas with deletions or disruptive mutations of SMARCA4

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Background: Characterization of the immune microenvironment is key. In tumors with wide presence of genomic alterations like non-small cell lung cancer (NSCLC) the evaluation of the immune profile can help to better select treatment options. In this study we explored the transcriptomic landscape of lung adenocarcinoma tumors (LUAD) with genomic alterations at SMARCA4.

Methods: Data from TCGA was downloaded to evaluate the expression of transcripts up or down regulated when deletions or disruptive mutations of SMARCA4 were present in LUAD. Median values were used and genes with fold change (FC) > than 2.5 were selected. Gene set enrichment analysis was performed with Enricher. TIMER platform was employed to investigate the association with immune cell populations.

Results: Of the 507 evaluated patients, disruptive mutations were present in 43 and gene deletions in 5. Molecular/biological functions enriched within the upregulated genes in tumors with SMACA4 deletions included: ncRNA 3'-end processing (GO:0043628) or ketosteroid monooxygenase activity (GO:0047086), among others; involving representative genes like CT45A10; SAGE1; CT45A3; CT45A5; CT45A1, AKR1C1; AKR1C2, CBR1 or CBR3. In tumors with no deletion the most represented molecular/biological functions included the antigen processing and presentation of lipid antigen via MHC class Ib (GO:0048003) with relevant genes as: CD1E; CD1C; CD1B; CD1A; CX3CR1; P2RY12, among others. Presence of CD1A, CD1B, CD1C, CD1E in tumors with no SMARCA4 genomic alterations strongly associated with the presence of dendritic cells (DC) (Corr Rho 0.41, 0.48, 0.44 and 0.45, respectively) and dendritic resting cells (DRC) (Corr Rho 0.75, 0.70, 0.71 and 0.72, respectively). A direct comparison between SMARC4 deletions and DC and DRC, showed a clear negative correlation (Corr Rho -0.5, -4,3, respectively). Similar findings were observed with SMARC4 mutations (DC Corr -0.69, DRC Corr -0.91).

Conclusions: SMARCA4 deletions in LUAD tumors associated with loss of antigen presenting genes including CD1E; CD1C; CD1B; CD1A that are present in myeloid dendritic cells. We hypothesized that loss of antigen presentation functions can be present in LUAD with genomic alterations of SMARCA4.

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86P Effect of chemotherapy-induced autophagic secretome on natural killer cell activity

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Background: Autophagy achieves a tumor-suppressing function in the initial stages of cancer by eliminating protein aggregates and damaged organelles that might promote genomic instability and lead to tumor formation. Autophagy induced by hypoxia or metabolic stress also plays an important role in the regulation of inflammatory pathways. In cancer cells, this may lead to secretion of pro- and/ or anti-inflammatory cytokines and chemokines which may help the immune escape of the tumor. However, the underlying mechanism of autophagy-mediated modulation of anti-tumor immune response is not yet fully understood. Our aim is to investigate whether chemotherapy-induced autophagy-associated secretome has the potential to modulate the NK cell-mediated anti-tumor immune responses.

Methods: Initially, western blot and immunostaining analyses were performed for autophagy markers (LC3I/II and p62) to demonstrate that Etoposide (Eto) induces autophagy in MCF-7 cells. LC/MS-MS analysis was performed to determine the content of chemotherapy-induced autophagic secretome in supernatants of autophagy-induced MCF-7 cell cultures. Finally, how the chemotherapy-induced autophagic secretome effects the capacity of DNAM1-NK-92 cells to target MCF-7 cells was determined by degranulation assays.

Results: We demonstrated Etoposide (Eto) induces autophagy in MCF-7 cells as confirmed by detection of autophagy markers including LC3I/II and p62 by WB and by immunostaining analysis. LC/MS-MS results revealed that, metabolic enzymes, tumor antigens, chaperones and metastasis-related proteins were secreted during etoposide induced autophagy which could be reduced by use of Chloroquin. When wildtype or DNAM1 overexpressing NK-92 cells were treated with autophagic secretomes, it was observed that there were differences in the capacity of targeting MCF-7 cells.

Conclusions: This study provides new insights in the field of chemo-immunotherapy by characterizing the chemotherapy-induced autophagic secretome and determining its possible effect on NK cells.

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87P WIP1 phosphatase promotes etoposide induced autophagy in medulloblastoma and neuroblastoma

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Background: Wip1/PPM1D is a serin/threonine phosphatase which is involved in timely termination of DNA damage response. Overexpression of Wip1 is commonly seen in human solid cancers including neuroblastoma and medulloblastoma that displays oncogenic features. Oncogenic Wip1 negatively regulates tumor suppressor responses such as apoptosis or senescence. Autophagy plays a tumor suppressor role by removing damaged organelles/proteins and limiting cell growth and genomic instability in cancer cells. The molecular mechanisms underlying autophagy's tumor-promoting activities are largely unknown Here, we investigated the role of oncogenic

Wip1 phospahates in regulation of autophagy in neuroblastoma and medulloblastoma.

Methods: D283-med and IMR32 cells are grown according to ATTC protocol. Autophagy was stimulated with etoposide and inhibited with chloroquine. GSK2830371 is used to target Wip1. Autophagy markers are tested with WB analysis and with confocal microscopy analysis of LC3 I/II puncta formation. Vacuolazion was measured by quinacrine staining. Wip1-Ulk1 interaction was investigated via co-IP and co-localization analysis. BrDU/PI and Annexin V/7AAD assays were used to examine the cell cycle and apoptosis, respectively.

Results: In neuroblastoma and medulloblastoma cells, oncogenic Wip1 promotes etoposid induced autophagy and improves cancer cell survival. Wip1 phosphatase interacts with and dephosphorylates Ulk1 during etoposide induced autophagy which is associated with elevated p53 levels. Suppression of Wip1 and/or autophagy prevents degredation of pro-apoptotic proteins thus results in promotion of apoptosis. Furthermore, inhibition of Wip1 and autophagy reduce cancer cells ability to colonize in vitro.

Conclusions: Oncogenic Wip1 play a key role in enhancing etoposide induced autophagy by dephosphorylating ULK1 and contributes to cancer cell survival. Wip1 mediated autophagy may be a promising therapeutic target for improvment of chemotherapy response.

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88P PPM1D/WIP1 phosphatase mediates basal and genotoxic stress-induced autophagy via ULK-1 de-phosphorylation

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Background: PPM1D/WIP1 is a Ser/Thr phosphatase activated upon genotoxic stress in a p53 dependent manner and involved in regulation of DNA damage response (DDR) . Wip1 is amplified and over expressed in common human cancers and thus exerts oncogenic functions. Oncogenic Wip1 negatively regulates cellular responses to chemotherpy such as apoptosis and senescence. Here, we aimed to investigate the role of oncogenic Wip1 in induction of basal autophagy and chemotherpy mediated autophagy in breast cancer cells.

Methods: Etoposide was used to induce autophagy and Chloroquin (CQ) for inhibition. GSK2830371 was used to inhibit Wip1. LC3I/II conversion P62 degradation, total and phosphorylated (Ulk1 p-Ser757) levels were by analysed WB. Wip1-Ulk1 interaction was demonstrated by co-IP analysis. LC3 puncta formation was analysed by and immunofluorescence staining. Apoptosis, cell cycle, and senescence were measured by AnnexinV/7AAD, BrdU/PI analysis and SAβ-gal staining, respectively Colony formation assay was used to assess cells ability to colonize.

Results: Utilizing Wip1 over expressing MCF-7 cells, here we showed that oncogenic Wip1 increased basal autophagy and mediated etoposide-induced autophagy as confirmed by accumulation of LC3-II, degradation of p62, and formation of LC3II puncta. Inhibition of Wip1 increased phosphorylation of Ulk1 from Ser757 both in basal and etoposide induced autophagy. Further, endogenous Wip1 co-precipitated with Wip1 during basal and etoposide induced autophagy. Inhibition of autophagy or Wip1 enhanced apoptosis in response to etoposide but not senescence.

Conclusions: In conclusion our data suggest that oncogenic Wip1 may increase basal autophagy to support the survival of cancer cells. In addition Wip1 dependent autophagy in response to chemotherpy agents may cause resistance to chemotherapy. Thus targeting of Wip1-Ulk1 may lead enhancement of the chemotherapy response as a promising therapetic strategy.

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89P Cold atmospheric plasma-activated fluids as a potential new intravesical agent for the treatment of bladder cancer

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Background: Cold atmospheric plasma (CAP) has been studied for cancer treatment. One of its forms, CAP activated liquids (CAPAL), may be an alternative to intravesical agents to treat bladder cancer (BC). The surgical bipolar resectoscope, when in use, is a source of thermal plasma (TP), which exerts effects on the surrounding sodium chloride solution for irrigation (NaCl 0.9%), transforming it into a TP activated liquid (TPAL), which is produced in very close contact with the bladder wall. To accelerate a possible introduction of plasma-activated liquid in the treatment of BC, we decided to compare the properties and biological effects of CAPAL and TPAL.

Methods: An electronic device was designed by our group to create CAP. TP was produced by a resectoscope. NaCl 0.9% was exposed to CAP or TP during short periods of time (30, 60, 120, 180 seconds) creating CAPAL or TPAL. The reactive oxygen and nitrogen species (RONS) activity was evaluated using the OxiSelect™ RONS Assay Kit in each activated liquid. BC cell lines, TCCSUP (grade IV) and HT-1376 (grade III), were incubated with CAPAL or TPAL. Metabolic activity was evaluated by MTT assay and protein content by SRB assay, 24h post-incubation.

Results: In comparison to non irradiated NaCl 0.9%, both CAPAL and TPAL, in all exposure times resulted in a significant rise in the activity of RONS. Regarding the biological activity of the activated liquids in the BC cell lines, both CAPAL and TPAL induced a decrease in cell metabolic activity and protein content in an exposure-time dependent manner. CAPAL induced a higher antitumor effect on the high-grade cell line (TCCSUP), while TPAL had a similar effect on both cell lines. Comparing the two activated liquids, CAPAL required longer exposure times to achieve the same effects observed with TPAL at lower exposure times.

Conclusions: This study shows that PAL can be a therapeutic agent for BC. Both TPAL and CAPAL showed similar biologics in BC cells. Currently, in clinical practice, TPAL is already in close contact with the bladder wall during surgery, however only briefly and diluted by irrigation. This work intends to get one step closer to demonstrate that CAPAL can be a safe and effective BC treatment.

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90P Discovery of CMPD1 as a tumor-specific cytotoxic microtubule inhibitor

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Background: Microtubule-targeting agents (MTAs) have been widely used as first- and second-line agents in various cancers for several decades. Furthermore, the value of MTAs is currently increasing due to their usefulness as combination drugs with immune checkpoint inhibitors. However, many development resources have been devoted to molecular-targeted agents, and the development of new MTAs has not progressed, leaving many patients struggling with the toxicity of existing MTAs. In other words, there is an urgent need to develop new microtubule inhibitors with high cancer-specificity.

Methods: Time-lapse images were taken every 2-3 minutes for 24-72 hours. Microtubules nucleated from GMPCPP-stabilized seeds were prepared and imaged using total internal reflection fluorescence (TIRF) microscopy (Ecklund KH et al. Nature Comm 2017). Tubulin polymerization activity, Trans-well migration assay were measured using the HTS-Tubulin Polymerization Assay Biochem Kit (Denver, CO, USA), CytoSelect 24-well cell invasion assay kits (Cell Biolabs). Orthotopic breast cancer model (MDA MB 231) and treatment - CMPD1 (i.p., 15 µg/mouse/inj, 10 times for 3 wks), Taxol (i.p., 5 mg/kg/inj, 10 times for 3 wks) were performed. Vascular invasion was identified by tumor cells within vessels in HE staining. RNAs Sequencing libraries

were prepared with the TruSeq stranded mRNA kit and sequenced on NovaSeq6000 at Macrogen Japan.

Results: CMPD1, a known inhibitor of MAP kinase-activated protein kinase 2(MK2), rapidly induces microtubule depolymerization in several cancer cell-lines, resulting in robust prometaphase arrest. CMPD1 levels alter the fate of cancer cells, either inducing mitotic slippage or resulting in mitotic defects. CMPD1 inhibits microtubule polymerization and specifically induces microtubule depolymerization at the plus end in in vitro assays; resulting in significant inhibition of tumor growth, cancer cell migration, and invasion in both in vitro and in vivo. Furthermore, clinically relevant low doses of CMPD1 induced severe and prolonged mitotic failure specifically in cancer cells, but not in non-transformed cells, with only modest effects on microtubules in vitro.

Conclusions: CMPD1 has the potential to serve as a cancer cell-selective MTA chemotherapeutic agent.

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91P Erythroid precursor-differentiated myeloid cells promote pulmonary metastasis in hepatocellular carcinoma

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Background: Pulmonary metastasis is the most frequently occurring distant metastases of hepatocellular carcinoma (HCC). However, the indicated mechanism of pulmonary metastasis in HCC remains unclarified. Erythroid progenitor-differentiated myeloid cells (EDMCs) were reported to mediate immunosuppression and curtail anti-PD-1/PD-L1 treatment efficacy. The role of EDMCs in the metastasis of HCC and the development of pulmonary metastasis was investigated here.

Methods: The existence of EDMCs in the circulation and spleen of HCC mouse model were validated through Flow Cytometry. EDMCs were sorted using fluorescence-activated cell sorting. CFSE stained EDMCs transfer experiment were conducted to evaluated the Pulmonary metastasis promoting role in HCC mouse model. The transwell migration and invasion experiment of hepa1-6 cells (HCC cell line) cocultured with EDMCs were performed.

Results: Mouse with Pulmonary metastasis of HCC showed higher level of EDMCs in the circulation and spleen than those without Pulmonary metastasis. CFSE EDMCs stained with 5 , 6- carboxyfluorescein diacetate, succinimidyl ester (CFSE) were detected in the lung of HCC mouse after infusion though caudal vein and those infused mice developed more frequency of pulmonary metastasis than those without EDMCs infusion. IN the coculture experiment EDMCs promoted the migration and invasion of hepa1-6 cells.

Conclusions: EDMCs existed in the circulation of HCC mouse model. EDMCs could migrated from the circulation to the lung of HCC mice. EDMCs could facilitate migration and invasion of hepa1-6 cells migrate and invade. Thus, EDMCs can promote Pulmonary metastasis in Hepatocellular Carcinoma.

Legal entity responsible for the study: Wei-hang Zhu.

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92P Discovery of novel AXL and MER inhibitors as potential anticancer and immune modulator drugs

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Background: In cancer progression, abnormal expression of AXL could lead to tumor growth and metastasis and resistance to chemotherapy, while MER could identify apoptotic cancer cells and induce immune suppression in the tumor microenvironment. Combination of AXL and MER inhibitors could generate a synergistic effect, enhancing antitumor responses, and further suppressing resistance formed by monotherapy with AXL selective or MER selective inhibitors. According to the explicit function of AXL and MER, the development of dual AXL and MER inhibitors may provide tremendous advantages to cancer patients.

Methods: Based on our experience in the discovery of an anti-EGFR and anti-HER2 clinical candidate, we introduced several AXL-active and MER-active pharmacophores into DBPR112. We also modified the scaffold and the solubilizing groups to improve the drug-like properties. We have constructed a comprehensive SAR study to discover promising AXL and MER inhibitors.

Results: Upon synthesizing about 200 compounds, we identified several potent dual AXL and MER inhibitors. These compounds were evaluated for their anti-AXL and anti-MER activities, as well as their anti-tumor abilities. Our candidate 5K230 exhibited satisfied oral bioavailability (F% = 55%) and promising in vivo antitumor effects in several mouse xenograft models, including MDA-MB-231, 4T1, MC-38 tumors. Our compound also overcome erlotinib-acquired resistance via the combination with erlotinib in the PC9 xenograft model.

Conclusions: We have described the discovery of potential AXL and MER inhibitors, in which we identified potential candidate 5K230 which showed potent anti-AXL and anti-MER activities. Moreover, 5K230 displayed anti-tumor efficacy in several mouse xenograft models. Further preclinical evaluation of 5K230 is underway to develop it as a promising anticancer and immune modulator drug.

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93P Transcriptome changes of immune cells across chemotherapy of triple-negative breast cancer

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Background: Immune system plays an important role in the development, treatment response, and progression of triple-negative breast cancer. Here, we aimed to assess the dynamics of cell populations and their transcriptome changes during neoadjuvant chemotherapy (NACT) in triple-negative breast cancer patients.

Methods: Mononuclear cells were purified from peripheral venous blood before NACT, after 3rd and 21st days of NACT using a ficoll density gradient. Total cell concentration and viability (Calcein/DRAQ7) were assessed by flow cytometry (Cytoflex, Beckman Coulter). Single cells were sequenced on a NextSeq 2000 (Illumina) using targeted panel Immune Response from Rhapsody Express (Becton Dickinson). Data were analyzed using Seurat and SingleR.

Results: According to single cell sequencing data we revealed 10 main populations of mononuclear leukocytes: B cells (*CD79+*), NK cells (*KIR2DL+*), classical (*CD14+*) and non-classical (*CD16+*) monocytes, T-cytotoxic cells (*CD8+*), T-helpers (*CD4+*), T-regs (*FOXP3+*), CD4 memory cells (*CD4+*, *IL32+*, *KLRB+*, *RGS1+*), CD8 naïve (*CD8+*, *LEF1+*, *CCR7+*, *PIK3IP1+*), CD4 naïve (*CD4+*, *LEF1+*, *CCR7+*, *PIK3IP1+*). 3 days after NACT overexpression of *BAX*, *FOSb*, *JUN*, *CXCR4*, *CD69* genes were observed, that mediating apoptosis of CD4 memory/naïve and CD8 naïve lymphocytes, T regs and monocytes; chemotaxis and proliferation of NK and T-cytotoxic lymphocytes. The population of blood monocytes was selectively depleted (up to 3%). 21 days after NACT overexpression of *CCR2*, *S100A9*, *ITGAM*, *CXCL8*, *CCL4*, *CCL5* genes were observed, mediating migration of monocytes to tissue, chemotaxis of immune cells and inflammation. The population of monocytes increased by up to 20%.

Conclusions: Chemotherapy affects the quantitative and qualitative composition of mononuclear leukocytes and changes their transcriptomic profile towards proinflammatory activation. This study was funded by the Russian Science Foundation (grant #22-75-10128).

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

BILIARY TRACT CANCER, INCL. CHOLANGIOCARCINOMA

94MO Advanced extrahepatic cholangiocarcinoma: Post-hoc analysis of the ABC-01, -02 and -03 clinical trials

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Background: Prior data suggest that patients with iCCA have a better prognosis compared to other biliary tract tumours (BTC) (Lamarca et al, JNCI 2019). However, the outcome for eCCA is not well described and some of the current studies focused on this patient population may be challenging to contextualise.

Methods: The aim of this post-hoc analysis is to provide reference survival data for patients with advanced eCCA treated with first-line cisplatin-gemcitabine (CisGem) chemotherapy within the prospective, randomised Advanced Biliary tract Cancer (ABC)-01, -02 and -03 studies. Individual level data from patients with eCCA recruited to these studies were retrieved.Survival analysis was performed using univariate and multivariable Cox Regression. All statistical tests were two-sided.

Results: Of 534 patients recruited into the ABC-01, -02 and -03 studies,179 (33.5%) had eCCA (107 distal (dCCA), 72 hilar (hCCA)). Of these, 117 were treated with CisGem and eligible for analysis. Most patients (n=82; 70.1%) had metastatic disease at the time of recruitment. Objective radiological response was achieved in 28 (23.9%) of eCCA: 19 dCCA (27.9%) and 9 (18.4%) hCCA. The median progression-free survival (PFS) for eCCA, dCCA and hCCA were 8.4 (95% CI 7.36-9.33), 8.3 (95% CI 6.3-9.4) and 8.4 months (6.5-10.6), respectively; median overall survival (OS): 12.8 months (95%CI 10.4-16.1), 14.3 (95% CI 8.8-17.4) and 12.2 (95% CI 8.3-16.1), respectively. eCCA with locally advanced disease had longer median PFS (13.1 (95% CI 8.8-16.6) and OS (17.4 (95% CI 14.3-21.1) . Multivariable survival analysis for OS confirmed worse OS for eCCA with performance status of 2 (vs 0; HR 45.877 (95% CI 9.55-219.45)) and high baseline CA125 (HR 1.0007 (95% CI 1.0001-1.001; p-value 0.017) when adjusted for other prognostic factors identified in the univariate analysis (stage, Ca 19.9). These remained significant when adjusted for site of eCCA (data not shown).

Conclusions: Patient outcomes were similar regardless of location of eCCA but worse than those reported historically for iCCA (specifically OS). Performance status and baseline tumour markers (CA125) were strongly associated with survival in eCCA. Outcomes with first-line CisGem + immunotherapy should also be explored.

Clinical trial identification: NCT00262769; NCT00939848.

Legal entity responsible for the study: University College London (UCL).

Funding: This post-hoc analysis did not receive any external funding.The ABC-1, -02 and -03 clinical trials received funding from Cancer Research United Kingdom (CRUK) and unrestricted educational grants from Lilly Oncology and AstraZeneca Pharmaceuticals.

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95MO Tinengotinib in patients with advanced, fibroblast growth factor receptor (FGFR) inhibitor refractory/relapsed cholangiocarcinoma

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Background: FGFR inhibitors (FGFRi) have a proven role for the management of FGFR-altered cholangiocarcinoma (CCA) after chemotherapy. However, disease progression occurs in 6-8 months. Secondary polyclonal mutations in the FGFR2 kinase domain represent a prominent acquired resistance mechanism. Tinengotinib was identified as a novel FGFRi with high potency to a variety of FGFR2 kinase domain mutations and has shown promising clinical results in CCA pts who have progressed on prior FGFRi. Here, we present pooled data from three trials.

Methods: Pts received tinengotinib orally once daily for 28 days per cycle. Pooled analyses of treatment-related adverse events (TRAEs), overall response rate (ORR), disease control rate (DCR), and median progression-free survival (mPFS) in the stratified CCA population were performed.

Results: A total of 73 advanced CCA pts were enrolled between Dec 2019 - Mar 2023. Median age was 60 years (24-81), 60% were female, 100% pts had $\geq$ 1 prior therapy including 47% pts with prior FGFRi, 97% had stage IV disease at screening. TRAEs were reported in 63 (86.3%) pts. 28 (38.4%) were Grade (G) 1-2, 32 (43.8%) were G3, 3 (4.1%) were G4, no G5 was observed. The most common TRAEs ($\geq$20%) were hypertension (43.8%, G3 19.2%), stomatitis (32.9%, G3 4.1%), diarrhea (30.1%, G3 4.1%) and palmar-plantar erythrodysesthesia (24.7%, G3 2.7%). Among 58 evaluable pts, the ORR and DCR were 20.7% and 75.9%, respectively. In 29 pts with FGFR2 alteration who received prior FGFRi, the ORR and DCR were 34% and 89.7%, respectively. 21 pts who acquired resistance to prior FGFRi had ORR of 38.1%, DCR of 95.2% and mPFS of 6.90 months (95%CI, 4.90-9.20). 10 pts who developed FGFR2 kinase domain mutations (N549D/H/K/T, V564F/I/L, E565A/G/K) detected by liquid biopsy at baseline had ORR of 50%, DCR of 90% and mPFS of 7.03 months (95%CI, 0.95-11.86).

Conclusions: These pooled results suggest that tinengotinib has a manageable toxicity profile in CCA pts. Notable clinical benefit was noted with tinengotinib in FGFR-altered CCA pts with acquired resistance to prior FGFRi. A global phase III clinical trial is planned to further evaluate the efficacy and safety of tinengotinib for CCA with FGFRi resistance.

Clinical trial identification: NCT03654547, NCT04742959, NCT04919642.

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96P Comparing the outcome of doublet therapy (gemcitabine and cisplatin) with triplet therapy (gemcitabine and cisplatin, nab paclitaxel) in locally advanced or metastatic gall bladder cancer patients an open label randomised control trial

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Background: To compare the doublet gemcitabine and cisplatin which is a standard of care in locally advanced or metastatic gall bladder cancer to a triplet gemcitabine, cisplatin and nab paclitaxel regime which has shown promising results in a single arm phase II study.

Methods: A total of 60 patients with locally advanced or metastatic gall bladder cancer were randomized 30 in each arm after imaging [contrast enhanced CT scan of chest, abdomen, and pelvis / MRI abdomen and pelvis with CECT chest /whole-body PET CT scan] and biopsy. Arm A received two drugs gemcitabine 1000mg/m2 i.v and cisplatin 25mg/m2 i.v on Day1 and Day8 of 21-day cycle and arm B received three drugs gemcitabine, 1000 mg/m2 , cisplatin, 25 mg/m2 , and nab-paclitaxel, 125 mg/m2 , on days 1 and 8 of 21-day cycle. Evaluation was done post 3 and 6 cycles of chemotherapy. Then patients were followed up every 6 months for 2 years period for assessment of primary and secondary endpoints of the study.

Results: The combination of gemcitabine and cisplatin (arm A) showed an overall radiological response rate (complete response and partial response) of 13.3% while it was 61.9 % in patients who received gemcitabine, cisplatin, and nab-paclitaxel. This difference was statistically significant with a p-value of 0.004. The median progression-free survival for the patients who received gemcitabine and cisplatin was 4.5 months (95% CI, 4.0-4.9) vs 7.6 months (95% CI, 3.9-11.2) for the patients who were treated with gemcitabine, cisplatin, and nab-paclitaxel. This difference was statistically significant with a p-value of ≤ 0.05. The median overall survival for the doublet was 9.2 months (95% CI 2.6-15.7) vs not reached for the patients who were treated with gemcitabine, cisplatin, and nab-paclitaxel. There was no increase in grade 3 adverse events with the addition of nab-paclitaxel.

Conclusions: To conclude, our study showed that the triplet chemotherapy with gemcitabine and cisplatin and nab-paclitaxel was significantly better in terms of overall response rate, and median progression-free survival with a longer follow up needed to comment on median overall survival.

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97P Neoadjuvant durvalumab plus gemcitabine and cisplatin (D+GemCis) versus gemcis alone for localized biliary tract cancer (BTC): Results of a randomized, multicenter, open-label, phase II trial (DEBATE)

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Background: D+GemCis demonstrated significantly improved efficacy in patients (pts) with advanced/metastatic BTC compared to GemCis alone. However, the efficacy of D+GemCis in the neoadjuvant setting has not been studied.

Methods: This was a multicenter, open-label, non-comparative, randomized phase 2 trial including treatment-naïve pts with histologically or cytologically confirmed localized BTC. Pts were randomly assigned (2:1) to receive either 4 cycles of neoadjuvant D+GemCis or GemCis alone. Postoperative 6 cycles of D were given if pts underwent surgery regardless of assigned neoadjuvant therapy. The primary endpoint was R0 resection rate. ctDNA analysis was performed using GuardantOmni platform.

Results: A total of 45 pts were enrolled (n=31 in the D+GemCis arm and 14 in the GemCis arm). Intrahepatic cholangiocarcinoma (n=18, 40%) was the most common primary tumor site and 69% (n=31) had clinical stage III. Response rates were 36% (n=11) in the D+GemCis arm and 7% (n=1) in the GemCis alone arm. In the D+GemCis and GemCis arms, surgical exploration was performed in 68% (n=21) vs 36% (n=5), curative-intent resection (R0+R1) in 61% (n=19) vs 36% (n=5), and R0 resection in 48% (n=15) vs 36% (n=5), respectively. Median PFS were 15.1 mo (95% CI, 4.5-25.8) in the D+GemCis arm and 3.6 mo (0-13.0) in the GemCis alone arm. Pts able to receive curative-intent surgery after study treatment had significantly better overall survival ($p<0.001$). No new safety signal for D+GemCis were identified. ctDNA analysis revealed that 5 pts (11%) had actionable genetic alterations including 4 with IDH1 R132C and 1 with ERBB2 amplification, and 2 pts (4%) were MSI-H.

Conclusions: Neoadjuvant D+GemCis resulted in a higher surgical resection rate in pts with localized BTC, and surgical resection was associated with better survival. ctDNA analysis was shown to be a feasible method for assessing actionable target gene alterations in early BTC.

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98P Efficacy and safety of durvalumab plus gemcitabine and cisplatin in Chinese participants with advanced biliary tract cancer: Extension cohort of the phase III, randomised, double-blind, placebo-controlled, global TOPAZ-1 study

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Background: At the TOPAZ-1 (NCT03875235) primary analysis, first-line treatment with durvalumab (D) + gemcitabine and cisplatin (GC) significantly improved overall survival (OS) and progression-free survival (PFS) v placebo (P) + GC; the regimen has been approved by multiple health authorities globally for advanced biliary tract

cancer (BTC).[1] Here, we present prespecified exploratory analyses in an extended cohort of TOPAZ-1 enrolled in China.

Methods: Participants (pts) with BTC were randomised 1:1 to D (1500 mg) or P every 3 weeks (Q3W) + GC (G 1000 mg/m^2 and C 25 mg/m^2 on Days 1 and 8 Q3W) for $\leq$8 cycles, followed by D (1500 mg) or P Q4W until disease progression, unacceptable toxicity or other discontinuation criteria. The primary endpoint was OS. Secondary endpoints included PFS, objective response rate (ORR) and safety. Results from the China cohort (data cut-off [DCO] 14 Oct 2022, 72.3% OS maturity) are compared with the global cohort (primary analysis; DCO 11 Aug 2021, 61.9% OS maturity)[1] and a pooled global + China cohort (China and pooled cohort analyses are exploratory).

Results: In the China cohort, 130 pts were randomised (65 to D + GC, 65 to P + GC; 5/130 were recruited to the global cohort and 125/130 to the extension). OS and PFS benefit with D + GC v P + GC in the China cohort (hazard ratio [HR], 0.78 and 0.79) were consistent with the global[1] and pooled cohorts (Table). OS rates at 12 and 18 months and ORR in the China cohort were numerically higher for D + GC v P + GC. D + GC was tolerable across cohorts.

Table: 98P

	China		Global[1]		Pooled, global + China	
	D + GC n=65	P + GC n=65	D + GC n=341	P + GC n=344	D + GC n=405	P + GC n=405
Median OS; 95% CI, months	9.1; 6.3 −13.7	9.2; 7.1 −10.2	12.8; 11.1 −14.0	11.5; 10.1 −12.5	12.6; 11.0 −13.6	10.9; 9.7 −11.9
OS HR; 95% CI	0.78; 0.51−1.18		0.80; 0.66−0.97		0.79; 0.67−0.94	
Median PFS; 95% CI, months	4.7; 3.1 −6.4	4.4; 3.1 −5.4	7.2; 6.7 −7.4	5.7; 5.6 −6.7	7.2; 6.4 −7.4	5.7; 5.4 −5.9
PFS HR; 95% CI	0.79; 0.52−1.19		0.75; 0.63−0.89		0.76; 0.65−0.89	
12-month OS, %	40.3	27.4	54.1	48.0	52.0	44.6
18-month OS, %	30.5	12.5	35.1	25.6	34.3	23.9
ORR, %	12.3	9.2	26.7	18.7[†]	24.4	17.1[‡]
Grade 3/4 TRAEs, %*	67.7	63.1	62.7	64.9	63.4	64.3
TRAEs leading to discontinuation, %*	16.9	7.7	8.9	11.4	10.2	10.7

*In safety analysis set. [†]Total n=343. [‡]Total n=404. AE, adverse event; TRAE, treatment-related AE

Conclusions: Consistent with the global cohort, D + GC demonstrated a clinically meaningful OS and PFS benefit compared with PBO + GC in pts enrolled in China. D + GC was tolerable and represents a potential new first-line standard of care regimen in China. References 1. Oh et al. *NEJM Evid* 2022.

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99P Bevacizumab plus erlotinib maintenance versus observation in advanced biliary tract cancers: Results from the phase II component of a prospective integrated phase II-phase III parallel design superiority clinical trial (BEER-BTC study)

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Background: Patients with chemotherapy-responsive advanced biliary tract cancer (BTC) are usually observed post 6 months of gemcitabine-based therapy, though most progress within a short time-span and there is limited prospective evidence for maintenance strategies.

Methods: The study is an integrated phase II — III randomised clinical trial (Clinical Trial Registry of India number: CTRI/2017/10/010112) conducted at 2 centres in India. Eligible patients with advanced BTC who had responsive or stable disease status post 6 months of gemcitabine — based chemotherapy were randomly assigned (1:1) to either observation arm (O) or intervention arm (BEER), which was a combination of Bevacizumab 5 mg/m2 IV every 21 days plus erlotinib 100 mg once daily, . Both arms were continued till disease progression, significant toxicity or patients choice. The primary endpoint of the phase II component was progression free survival, measured from randomization into the trial.

Results: Between May 2021 and November 2022, 98 patients (O: 48; BEER: 50) comprising 78 patients with gallbladder cancer (GBC) and 20 patients with cholangiocarcinoma (CC) were randomised with all 98 patients included in the final analysis. With a median follow up of 11.2 months, patients in the BEER cohort showed an improved PFS compared to the observation cohort [5.2 months (95% CI: 3.4-6.9) vs. 3 months (95% CI: 2.5 - 3.5); p=0.004]. The CC cohort tended to derive greater benefit from BEER (6.7 months vs. 2.2 months) than the GBC cohort (4.3 months vs. 3 months). There were no grade 3 or grade 4 adverse events noted, though temporary cessation of erlotinib was required due to grade 2 skin rash in 7 patients (14%), and grade 2 oral stomatitis in 1 patient (2%).

Conclusions: The combination of bevacizumab and erlotinib improves progression free survival in patients with chemotherapy responsive advanced BTC in this phase 2 clinical trial. The ongoing phase III component of the study will evaluate whether the significant benefit in PFS translates to improvement in overall survival.

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100P Hepatitis B virus (HBV)-related outcomes in patients (pts) with baseline HBV infection in the KEYNOTE-966 study of pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) for advanced biliary tract cancer (BTC)

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Background: Pembro + gem/cis significantly improved OS versus placebo (pbo) + gem/cis as 1L therapy for unresectable or metastatic BTC in KEYNOTE-966 (NCT04003636). Pembro monotherapy had limited impact on underlying HBV infection in advanced HCC. The effect of chemoimmunotherapy on underlying HBV in pts with cancer is unknown. We characterized HBV-related outcomes in pts with HBV enrolled in KEYNOTE-966.

Methods: Pts were randomized 1:1 to pembro 200 mg or pbo Q3W for $\leq$35 cycles plus gem/cis. Pts with clinically resolved HBV infection (ie, HBsAg negative, anti-HBc positive, and HBV DNA $<$20 IU/mL) were eligible. Pts with chronic HBV infection (ie, HBsAg positive or HBV DNA $\geq$20 IU/mL) were eligible if antiviral therapy was started $\geq$4 wk before study therapy if HBV DNA was $>$100 IU/mL. HBV DNA and HBsAg were assessed every 6 wk in pts with undetectable HBV DNA at baseline (BL) not taking HBV therapy and every 12 wk in pts taking HBV therapy. Pts with HBV DNA $>$100 IU/mL were to start HBV treatment. Pts on HBV therapy at BL were to stay on same therapy throughout the study. HBV reactivation and HBV-associated hepatitis were defined per AASLD criteria.

Results: 164 (30.8%) of 533 pts in the pembro arm and 165 (30.8%) of 536 in the pbo arm had BL HBV infection, including 150 (28.1%) and 149 (27.8%) with clinically resolved and 14 (2.6%) and 16 (3.0%) with chronic HBV. In the pembro and pbo arms, 6.0% and 5.4% with clinically resolved and 100% and 93.8% with chronic HBV received antiviral drugs during the study. Among evaluable pts with clinically resolved HBV, 4 (3.1%) of 127 in the pembro arm and 1 (0.8%) of 128 in the pbo arm had HBV reactivation. Among evaluable pts with chronic HBV, 1 (11.1%) of 9 in the pembro arm and 2 (15.4%) of 13 in the pbo arm had HBV reactivation. All reactivation was detected by HBV DNA increase. No pts developed HBV-associated hepatitis.

Conclusions: The low incidence of HBV reactivation and lack of HBV-associated hepatitis in pts with clinically resolved or controlled chronic HBV on antiviral therapy suggest that with careful monitoring, pembro plus gem/cis is unlikely to affect underlying HBV in advanced BTC.

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101P Quality of life (QoL) outcomes in patients (pts) with zanidatamab (zani)-treated HER2-positive (HER2+) biliary tract cancer (BTC) in the phase IIb HERIZON-BTC-01 study

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Background: In the pivotal HERIZON-BTC-01 study, the HER2 bispecific antibody zani demonstrated rapid, durable responses (confirmed objective response rate, 41% by independent central review; median duration of response, 12.9 mo; data cut-off: Oct 2022) and manageable safety in pts with HER2+ BTC. Here we report QoL outcomes for those pts with HER2+ BTC.

Methods: HERIZON-BTC-01 (NCT04466891), an ongoing open-label, global phase 2b study, evaluated zani (20 mg/kg IV every 2 wks) in pts with HER2+ (gene amplification with immunohistochemistry of 2+ or 3+), locally advanced, unresectable or metastatic BTC (gallbladder cancer, intra-/extra-hepatic cholangiocarcinoma) who received prior gemcitabine-containing treatment (tx). QoL, an exploratory endpoint, was assessed using the EQ-5D-5L descriptive system and visual analogue scale (VAS) at baseline (BL) and every 8 wks; best on-treatment score (BONT) was the lowest descriptive or highest VAS value observed post-BL.

Results: A total of 80 pts with HER2+ BTC were evaluated for primary efficacy analyses (median age, 64 years; 56% female). Of these, 1 (1%) had complete response (CR), 32 (40%) had partial response (PR), 22 (28%) had stable disease (SD) and 24 (30%) had progressive disease (PD); 1 pt was not evaluable. Pts with CR or PR reported the greatest improvement in QoL followed by those with SD, while pts with PD generally reported worsening QoL (Table). Median VAS scores improved by ≥10 points from BL to time of BONT for pts with CR and PR, by 5 points for pts with SD and worsened by 10 points for pts with PD. In each dimension, the proportion of pts reporting 'no problem' increased more from BL to BONT for pts with PR than for pts with SD or PD.

Table: 101P EQ-5D-5L QoL outcomes in pts with HER2+ BTC by tumour response

	Confirmed Best Overall Tumour Response							
	CR		PR		SD		PD	
	BL n=1	BONT n=1	BL n=31	BONT n=32	BL n=21	BONT n=22	BL n=24	BONT n=19
Median VAS score	40	80	80	95	80	88	80	70
Median VAS change from BL[a]		40		10		5		-10
Least severe response level (no problem), n (%)								
Mobility	0	0	23 (74)	30 (94)	16 (76)	19 (86)	15 (63)	12 (63)
Self-care	0	0	28 (90)	31 (97)	18 (86)	19 (86)	23 (96)	16 (84)
Usual activities	0	0	23 (74)	29 (91)	11 (52)	15 (68)	16 (67)	10 (53)
Pain/discomfort	0	1 (100)	15 (48)	28 (88)	10 (48)	13 (59)	10 (42)	7 (37)
Anxitey/ depression	0	0	18 (58)	28 (88)	12 (57)	14 (64)	13 (54)	14 (74)

[a]Out of pts with a BL and ≥1 post-BL score

Conclusions: In HERIZON-BTC-01, pts with HER2+ BTC who responded to zani reported improved QoL compared with BL, while those with PD reported worsening QoL compared with BL. These results support the continuing development of zani as a HER2+ BTC tx option.

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102P Potentially prognostic factors of overall survival in advanced biliary tract cancer in the randomised phase III TOPAZ-1 study

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Background: In TOPAZ-1 (NCT03875235), durvalumab (D) + gemcitabine and cisplatin (GC) improved overall survival (OS) vs placebo (PBO) + GC in participants with advanced biliary tract cancer (aBTC; primary analysis: hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.66–0.97, p=0.021 [significance threshold p=0.03]) and after a further 6.5 months of follow-up (HR 0.76, 95% CI 0.64–0.91). This exploratory analysis assessed baseline clinical factors for potential prognostic (associated with OS) or predictive (of OS benefit with D + GC) value in TOPAZ-1.

Methods: Potentially prognostic factors were evaluated using Cox proportional hazards models with treatment and each factor. An exploratory adjusted HR for D + GC vs PBO + GC was estimated with a model adjusting for prognostic factors identified by stepwise selection. Unstratified Cox proportional hazards models and interaction tests were performed to assess potential predictive factors. Data cut-off was 25 February 2022.

Results: Potentially prognostic clinical factors are shown (Table). The HR for D + GC vs PBO + GC, adjusted for disease status, primary tumour location, sex, PD-L1, neutrophil to lymphocyte ratio (NLR), cancer antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), liver metastasis, liver involvement (locally advanced or metastatic site in liver/gallbladder), body weight, LDH, albumin and total bilirubin, was 0.70 (95% CI 0.59–0.84). OS HRs for D + GC vs PBO + GC were <1 across assessed clinical (Table) and laboratory factors; no predictive factors for D + GC were found.

Table: 102P

		Predictive		Prognostic	
Factor	**Subgroup**	**HR (95% CI), D + GC v PBO + GC**	**Interaction p**	**HR (95% CI), top v bottom subgroup**	**p**
Disease status	IU	.79 (.65–.95)	.93	2.14 (1.69–2.76)	<.01
	R	.76 (.49–1.20)			
ECOG PS	0	.87 (.68–1.12)	.14	1.29 (1.09–1.53)	<.01
	1	.70 (.55–.89)			
Disease classification	LA	.54 (.32–.88)	.13	1.35 (1.05–1.76)	.02
	M	.80 (.67–.97)			
NLR	<3	.75 (.56–1.01)	.83	2.14 (1.79–2.58)	<.01
	≥3	.76 (.61–.94)			
CA19-9	<500 U/mL	.72 (.57–.92)	.53	2.08 (1.73–2.50)	<.01
	≥500 U/mL	.82 (.62–1.08)			
CEA	<5 ng/mL	.75 (.58–.97)	.75	1.78 (1.49–2.14)	<.01
	≥5 ng/mL	.81 (.63–1.05)			
Liver metastasis	Y	.83 (.66–1.06)	.32	1.37 (1.56–1.63)	<.01
	N	.69 (.54–.88)			
Liver involvement	Y	.76 (.63–.91)	.76	1.67 (1.32–2.14)	<.01
	N	.77 (.49–1.20)			

IU, initially unresectable; LA, locally advanced; M, metastatic; R, recurrent

Conclusions: Benefit with D + GC was consistent across assessed factors and stable after adjusting for potentially prognostic factors, supporting D + GC as first-line treatment for aBTC.

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103P Individual patient data (IPD) meta-analysis of randomised trials to compare efficacy of second-line fluoropyrimidine-based chemotherapy in advanced biliary tract cancer (BTC)

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Background: For patients (pts) with advanced BTC with progression on gemcitabine plus cisplatin (GemCis), fluoropyrimidine-based chemotherapy, including liposomal irinotecan (nal-IRI) plus fluorouracil and leucovorin (5-FU/LV) and 5-FU/LV plus oxaliplatin (FOLFOX) showed clinical benefit in prior randomized trials (NIFTY and ABC-06). However, there is no trial for head-to-head comparison among these agents.

Methods: We performed IPD meta-analysis of two multicenter, randomized trials performed in South Korea, which compared efficacy of second-line chemotherapy for advanced BTC after progression on GemCis, including the phase 2b NIFTY trial (nal-IRI plus 5-FU/LV vs. 5-FU/LV, NCT03524508) and the phase 2 FIReFOX trial (modified FOLFOX [mFOLFOX] vs. modified 5-FU/LV plus irinotecan [mFOLFIRI], NCT03464968). ITT population of the two trials were included and survival outcomes were compared between the 4 treatment groups by pairwise log-rank test. Hazards ratio (HR) adjusted by potential prognostic variables was estimated by Cox proportional hazards modeling with shared frailty to account for the trials effect.

Results: A total of 278 pts were included in this analysis (178 pts from the NIFTY trial and 99 pts from the FIReFOX trial). The nal-IRI plus 5-FU/LV group (n=88) showed

significantly better overall survival compared to the mFOLFOX group (n=49, p = 0.02), mFOLFIRI group (n=50, p = 0.03), and 5-FU/LV group (n=90, p = 0.008). Multivariable analysis showed consistent trends with adjusted HR of 1.44 (95% CI 0.93-2.07, p = 0.11), 1.36 (95% CI 0.92-2.03, p = 0.13), and 1.52 (95% CI 1.37-1.09-2.10, p = 0.01), respectively. Also, nal-IRI plus 5-FU/LV group showed trends toward better progression-free survival compared to the other 3 groups with adjusted HR of 1.44 (95% CI 0.98-2.11, p = 0.06), 1.29 (95% CI 0.87-1.89, p = 0.20), and 1.88 (1.38-2.55, p < 0.001), respectively.

Conclusions: Nal-IRI plus 5-FU/LV showed better survival outcomes when compared to mFOLFOX, mFOLFIRI, or 5-FU/LV alone. Nal-IRI plus 5-FU/LV may be a preferable second-line regimen for advanced BTC pts without targetable genetic alterations.

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104P Final analysis of the prospective, randomized phase II STAMP trial: Adjuvant gemcitabine plus cisplatin (GemCis) versus capecitabine (CAP) in node-positive extrahepatic cholangiocarcinoma (CCA)

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Background: The primary analysis of the STAMP trial demonstrated that adjuvant GemCis did not improve disease-free survival (DFS) compared to CAP in patients (pts) with resected, lymph node (LN)-positive extrahepatic CCA. As overall survival (OS) data were not matured at primary analysis, we report the updated analysis with an additional 19 months (mo) of follow-up.

Methods: Pts with adenocarcinoma of perihilar/distal bile duct with regional LN metastasis who underwent curative-intent surgery was randomized to receive GemCis (Gem 1000 mg/m2, Cis 25 mg/m2 on days 1, 8) or CAP (1250 mg/m2 twice daily on days 1—14) every 3 weeks for 8 cycles. Primary endpoint was DFS. Secondary endpoints were OS and safety. All P values were one-sided and considered significant if < 0.1.

Results: A total of 101 pts (50 in the GemCis and 51 in the CAP group) were included in the intention-to-treat population. The median follow-up duration was 52.8 mo (one-sided 90% CI, 50.1-58.2). In the GemCis and CAP groups, the median DFS was 14.6 mo (10.7-16.5) and 11.1 mo (8.4-12.7), respectively, and the 4-year DFS rates were 15.9% (9.4-24.0) and 19.4% (12.4-27.5) respectively (HR = 1.02 [0.76-1.37], P = 0.47). Median OS was 35.0 mo (29.5-42.7) and 32.3 mo (28.3-45.6), respectively, and the 4-year OS rates were 35.7% (26.5-45.1) and 38.4% (29.2-47.5), respectively (HR = 1.04 [0.75-1.44], P = 0.43). Subgroup analyses showed consistent results without significant interactions in the DFS and OS between groups, except that pts with R1 resection favored CAP in DFS and OS, and females favored GemCis in OS.

Table: 104P

	GemCis	CAP	HR (CI) and P-value
DFS events/pts	40/50	41/51	
Median DFS (months) (CI)	14.6 (10.7-16.5)	11.1 (8.4-12.7)	1.02 (0.76-1.37) P = 0.47
4Y DFS rates (%) (CI)	15.9 (9.4-24.0)	19.4 (12.4-27.5)	
Deaths/pts	33/50	33/51	
Median OS (months) (CI)	35.0 (29.5-42.7)	32.3 (28.3-45.6)	1.04 (0.75-1.44) P = 0.43
4Y OS rates (%) (CI)	35.7 (26.5-45.1)	38.4 (29.2-47.5)	

Conclusions: In this final analysis of the STAMP trial, adjuvant GemCis did not improve OS compared with CAP in LN-positive extrahepatic CCA. Biomarker analyses, including ctDNA-guided minimal residual disease (MRD), are currently underway.

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Legal entity responsible for the study: The authors.

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105P A phase II study of SHR-1316 plus IBI310 in patients with advanced intrahepatic cholangiocarcinoma after failure of first-line therapy

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Background: Advanced intrahepatic cholangiocarcinoma (iCCA) is highly invasive and holds high mortality due to limited therapeutic strategies after failure of first-line therapy. This study aimed to evaluate the efficacy and safety of anti-PD-L1 antibody SHR-1316 in combination with anti-CTLA-4 antibody IBI310 for patients (pts) with previously treated advanced iCCA.

Methods: The study was an ongoing open-label, single-arm, phase 2 trial. Unresectable, locally advanced or metastatic iCCA pts who had failed first or subsequent-line therapy were enrolled. A combination of SHR-1316 (IV 20mg/kg q3w) and IBI310 (IV 3mg/kg q3w) were administered for 4 cycles, followed by SHR-1316 monotherapy until disease progression, unacceptable toxicity, or a maximum of 2 years after enrollment. The primary endpoint was objective response rate (ORR). Secondary objectives included safety, overall survival (OS), progression-free survival (PFS), and disease control rate (DCR). Response was evaluated according to RECIST1.1. Adverse effects (AEs) were assessed according to CTCAE V5.0.

Results: Up to May 1, 2023, 39 pathologically confirmed advanced iCCA pts were enrolled. Median age was 59 years (range 28 to 74). Previous treatments included systemic chemotherapy (39 pts), anti-PD-1 antibody (21 pts), and tyrosine kinase inhibitors (26 pts). At date cut-off, the median follow-up was 6.1 months (95%CI, 0.2-18.7), 28 pts were alive, 18 pts remained on treatment. Of 25 evaluable pts, 2 pts achieved complete response and 3 had partial response. The confirmed ORR and DCR were 20.0% and 60.0%, respectively. Notably, the ORR for pts previously treated with anti-PD-1 antibody was 16.7% (2/13). Median PFS and OS was not reached yet. Grade 3 or higher AEs occurred in 16 pts (41.0%), most commonly jaundice (15.4%), rash (10.3%), ALT elevation (7.7%), anaphylaxis (7.7%), AST elevation (5.1%), diarrhea (5.1%) and dyspnea (5.1%).

Conclusions: The treatment of SHR-1316 combined with IBI310 was tolerable and showed promising antitumor activity in iCCA refractory to standard therapy. Further studies are required to identify predictive/prognostic biomarkers to improve selection of pts most likely to benefit from this treatment strategy.

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106P The impact of alterations in cancer driver genes and other potentially targetable mutations on progression and overall survival in patients with biliary tract cancer treated on the randomised phase III multicentre BILCAP clinical trial

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Background: The BILCAP clinical trial established adjuvant capecitabine as the current standard of care treatment after biliary tract cancer resection.

Methods: Translational work from this clinical trial involved collecting archived fixed formalin tissue from consented BILCAP patients and carrying out low-pass whole genome (lp-WGS), targeted gene (TGS) and RNA sequencing (RNAseq) for copy number (CN), mutation and gene-fusion analysis. In total, 98 patients underwent RNAseq, 95 of 98 underwent lp-WGS and 39 of 98 underwent TGS.

Results: 47 patients had intrahepatic cholangiocarcinoma, 47 patients had gallbladder cancer, 2 patients had perihilar cholangiocarcinoma, and 2 patients had distal cholangiocarcinoma. 62 (63.3%) patients were female, and 48 (49.0%) received adjuvant capecitabine. FGFR2 gene fusions were present in 24 patients (24.5%), as were fusions in NTRK1 (n=4, 4.1%), FGFR1 (n=4, 4.1%), FGFR3 (n=2, 2.0%) and FGFR4 (n=2, 2.0%). Known pathogenic mutations were seen in IDH1(n=4, 10.3%, total number of mutations=8, 20.5%), IDH2 (n=1, 2.6%, total n=6, 15.4%), and FGFR2 (n=1, 2.6%, total n=7, 17.9%). Commonly amplified (CN $\geq$ 4) genes included NTRK1 (n=28, 29.5%), ERBB2 (n=27, 28.4%) and MDM2 (n=20, 21.1%) with MYC (n=19, 20.0%), EGFR (n=16, 16.8%) and MET (n=15, 15.8%) also amplified. Nearly all the alterations investigated did not significantly affect recurrence risk (PFS) or overall survival (OS), including FGFR2 fusions (OS hazard ratio (HR) 1.11 p=0.762, PFS HR 1.10 p=0.763). However, the presence of amplified EGFR (CN $\geq$ 4) significantly decreased both OS (HR 5.40 p=0.01) and PFS (HR 3.44 p=0.04).

Conclusions: The BILCAP cohort shows a wide variety of driver and potentially targetable mutations in unselected biliary tract cancer patients, comparable to similar datasets. Of note, patients with EGFR amplification had significantly reduced OS and PFS. This indicates that EGFR amplification may be an important indicator in determining prognosis and could provide an attractive target for future targeted anti-cancer therapy in biliary tract cancer.

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107P Comprehensive genomic profiling of "The German-registry of incidental gallbladder carcinoma" cases

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Background: Gallbladder cancer (GBC) is a biliary tract cancer with an aggressive progression and poor prognosis. Although high throughput sequencing revealed some driver variations in genes like *EGFR, TP53, SMAD4, ARID1A, PIK3CA, and CDKN2A/B,* there is no specific biomarker for GBC. Due to the low incidence rate, the studies are limited and generally covered under all biliary tract cancer (BTC) types. Here we present the clinical, histopathological, and molecular spectrum of a large series of patients from the German Registry of Incidental GBC.

Methods: A total of 1040 (793 female and 247 male) completely documented cases with a median age of diagnosis 70.79 (min:30-max:98) were enrolled in the study. The majority of tumors were diagnosed at pathological stage pT2 (60.6%), and distant metastasis was detected in 15.2% of cases. The patients presented a tumor grade of G2 or G3 with a ratio of 53% and 36%, respectively. Among the cohort, 116 cases were already analyzed by a targeted panel (FMI Heme Panel) which combines more than 400 DNA and 250 RNA-sequenced genes.

Results: In 91 of the cases, at least one pathogenic gene variation was detected. The median TMB was 4.67 (0—52.95) mutations/Mb, and in 6.5% of the cases, the total TMB was $\geq$ 10 mutations/Mb ("TMB-intermediate/high"). The tumor with the highest TMB (52.95 mutations/Mb) presented 12 pathogenic variants. *TP53* was the most commonly altered gene (59.34%), followed by *CDKN2A* (20.6%) amplifications. In 11.2% of the cases, likely functional fusions/rearrangements were also detected.

Conclusions: This study presents one of the largest isolated GBC cohorts, analyzed by a comprehensive targeted NGS panel with a precision oncology approach. These findings will provide insights into a rare but severe type of upper GI cancer. The analysis is currently ongoing, and a further 84 patients will be molecularly characterized till the meeting to be able to present complete molecular data of 200 patients.

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108P FGFR2 fusions and their impact on efficacy of standard chemotherapy in patients with biliary tract cancer

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Background: The incidence of biliary tract cancer (BTC) is increasing globally, while its survival remains dismal. *FGFR2* fusions offer a potential therapeutic option with oral inhibitors, although the optimal treatment sequence for these patients remains unclear.

Methods: We included patients from all three Mayo Clinic sites diagnosed with *FGFR2* fusion-positive (F2P) BTC and used patients with *FGFR2* fusion-negative (F2FN) BTC as historical controls. We estimated overall survival (OS) and progression-free survival (PFS) using Kaplan-Meier techniques.

Results: We identified 43 F2P and 155 F2FN patients with BTC. The most common gene fusion partner was *BICC1* (28%). *FGFR2* fusion was associated with age $\leq$65 years (74% vs 44%), female gender (72% vs 45%), intrahepatic BTC (95% vs 71%), and advanced stage at diagnosis (60% vs 11%). In advanced disease, 25 patients in the F2P group received first-line (1L) chemo of which 14 (56%) received gemcitabine/cisplatin (GC). In the F2FN group, 37 had 1L chemo, 16 (43%) with GC. The F2P group had significantly lower PFS compared to F2FN patients, respective median PFS were 5.4 (95% CI 3.8-9) vs 7.6 months (95% CI 4.6-13.3) (p=0.038). In the F2P group who received second-line (2L) therapy, PFS was longer with an FGFR inhibitor (8.2 months, 95% CI 7.2-NE) vs. chemo (5.5 months, 95% CI 4.8-19.3) (Table). The median OS was significantly higher in the F2P patient who never received an FGFR inhibitor (14.8 months, 95% CI 13.2-NE) vs F2FN group (9.6 months, 95% CI 5.52-22.9) (p=0.04).

Table: 108P Median PFS in F2FN and F2P groups based on 1L and 2L therapies

	FGFR2 Fusion Negative		*FGFR2* Fusion Positive	
	N	PFS, months (95% CI)	N	PFS, months (95% CI)
1L chemo	37	7.6 (4.6-13.3)	21	5.4 (3.8-9)
1L FGFR inhibitor	0	na	4	7.7 (2.1-NE)
1L Overall	37	7.6 (4.6-13.3)	25	5.9 (3.8-8.5)
2L chemo	20	10 (4.6-13.8)	9	5.5 (4.8-19.3)
2L FGFR inhibitor	0	na	16	8.2 (7.2-NE)
2L Overall	20	10 (4.6-13.8)	25	8.4 (7.2-13.8)

Conclusions: Our study highlights the distinct features of *FGFR2* fusion-positive BTC, which is associated with a significantly longer OS despite a shorter PFS on standard 1L chemo. These findings underscore the need for trials to evaluate the efficacy of 1L FGFR inhibitors in these patients.

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109P DNA damage repair pathways in biliary tract cancer: A new target for precision medicine?

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Background: Biliary tract cancers (BTC) show a high mortality quote and heterogeneity in terms of clinical and molecular profile. Aim of this work is the molecular characterisation of a BTC cohort focusing on genomic alterations of DNA damage repair (DDR) genes.

Methods: A retrospective analysis of the clinical course and mutation status of patients with locally advanced or metastatic BTC treated at the West German Tumour Centre of the University.113 (96%) patients received the MAPK-TRON DNA-based NGS panel (47 included genes), 81 (72%) patients the AmoyDx HRD Focus panel (32 genes), which focuses on DDR genes. DNA mismatch repair (MMR) status was determined in 59 patients by immunohistochemistry and DNA sequencing. 33 patients received an RNA fusion assay (FusionPlex CTL panel [Archer]) too. The primary endpoints of the study were the time in first palliative regime till disease progression (Time on Treatment=TTE) and the overall survival (OS). To form a clear defined DDR cohort, the annotation of DDR gene alterations was not only performed by the local Institute of Pathology but also by quering the databases ClinVar and COSMIC.

Results: The cohort of the present study was divided in 7 molecular subgroups: TP53 (34/118, 29%), KRAS (25/118, 21%), IDH1/2 (18/118, 15.2%), PIK3CA (8/118, 7%) and BRAF (6/118, 5%) and FGFR2 (5/33, 15%, with different fusion partners). BRAF- und PIK3CA-mutated BTC showed a slight benefit in primary endpoints, whereas KRAS- and TP53- mutated showed worse prognosis. 13 DDR-mutated BTC were identified (13.5%). The patients with DDR mutations showed a weak but coherent benefit in all primary endpoints (OS, TTE, TTE under platinum-based therapy). Comparison of our data with BTC data of The Cancer Genome Atlas (TCGA) in cbioportal showed a similar trend in OS (19,1 months in TCGA data vs 22,7 months in the studied cohort).

Conclusions: Pathogenic alterations in DDR pathway genes were seen in 13.5% of the cases studied. DDR-deficient BTC patients showed a trend for better OS and TTE representing a potential subgroup that could benefit from targeted treatment strategies, like PARP-inhibitors. Moreover the slight benefit of DDR-mutated BTC under platinum-based therapy supports the hypothesis of better response of DDR-mutated tumours to platinum.

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110P Detection of HER2 overexpression in biliary tract cancers: Comparison of AmoyDx® HER-2 (29D8) assay with ventana PATHWAY anti-HER-2/neu (4B5) assay

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Background: The human epidermal growth factor receptor 2 (HER2/neu), a member of epidermal growth factor receptor protein family, play a role as predictive and prognostic biomarkers in various tumor types, particularly biliary tract cancers (BTCs), a heterogeneous group of poor-prognosis solid tumors with limited treatment options. Accurate evaluating of HER2 overexpression is essential for selection and determination of eligible patients for HER2-directed therapy. Herein, we report the results of an immunohistochemistry (IHC) concordance study comparing the AmoyDx® HER-2(29D8) assay and the well-established Ventana PATHWAY anti-HER-2/neu (4B5) assay using a BTC cohort of 432 samples.

Methods: Performance of the AmoyDx® HER-2 (29D8) assay was compared against the Ventana PATHWAY anti-HER-2/neu (4B5) assay using 432 pre-selected BTC samples. Further ISH testing was successfully performed in 134 of the samples to identify HER2-positive and HER2-negative samples according to standard criteria.

Results: There was a high concordance between results from the AmoyDx 29D8 and PATHWAY 4B5 assays for HER2-negative (IHC 0, 1 +) and HER2-positive (IHC 2 + , 3 +) BTCs (98.38%, 425/432). When combined with the ISH results, the aggrement was even increased to 99.29% (422/425) (Table). In addition, the low concordance (34.63%, 9/26) between the two assays for IHC 1+ samples, indicating that the detecton criteria for HER2 IHC 0 and 1+ still need further clarification, which reminds researchers to carefully select appropriate assays if they focus on BTC with HER2-low expression types.

Table: 110P Comparison of HER2 scorings derived from the indicated assays

		Ventana PATHWAY anti-HER-2/neu (4B5)		
		+	-	Total
AmoyDx® HER-2 (29D8)	**+**	19	2	21
	-	1	403	404
	Total	20	405	**425**
Positive percent agreement		95.00% (95%CI: 75.13%, 99.87%)		
Negative percent agreement		99.51% (95%CI: 98.23%, 99.94%)		
Overall percent agreement		99.29% (95%CI: 97.95%, 99.85%)		

Conclusions: Our data demonstrate that AmoyDx 29D8 exhibited high concordance with PATHWAY 4B5, and could provide critical information for the selection of HER2-targeted therapy for BTC patients.

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111P The concordance between circulating tumor DNA and tissue genomic profiling in patients with advanced biliary tract cancer

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Background: Recent advances in molecular profiling have revealed potential therapeutic targets for biliary tract cancer (BTC). However, difficulties in obtaining an adequate sample could hamper molecular evaluations in patients with BTC. Circulating tumor DNA (ctDNA) can thus help address any challenges associated with the

limited use of tissue-based analysis in BTC. In this study, we aimed to evaluate the concordance between ctDNA and tissue genomic profiling in patients with advanced BTC and evaluate the feasibility of liquid biopsy in the treatment of patients with BTC.

Methods: Patients who underwent tissue-based next-generation sequencing (NGS) before systemic chemotherapy for advanced BTC at CHA Bundang Medical Center from January 2019 to December 2022 and for whom sufficient plasma samples were available for ctDNA analysis (AlphaLiquid®100 from IMB Dx) were included. Clinically important (tier 1 or 2) variants detected in tissues with a variant allele frequency (VAF) of >0.05 were considered as true positive for concordance.

Results: Of one hundred two patients, 49.0%, 26.5%, and 24.5% had intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gall bladder cancer, respectively. The concordance between intra-patient ctDNA and tumor tissue for mutations indicated 84.8% sensitivity and 79.4% positive predictive value. In ctDNA, targetable alterations were detected in 34.3% of patients, such as *IDH1* mutation (7.8%), *FGFR2* fusion (2.0%), microsatellite instability (MSI)-high (2.0%), *ERBB2* amplification (4.9%), *PIK3CA* hotspot mutations (6.9%), *BRCA1/2* mutations (9.8%), and *MET* amplification (2.9%). Among the two *FGFR2* fusions, one FGFR2-TNS1 fusion was novel, because it was not targeted in tissue NGS panel. Lastly, patients with high ctDNA VAF showed poor prognosis in gemcitabine-cisplatin based chemotherapy in both overall survival and progression-free survival ($p = 6.9 \times 10^{-6}$ and $p = 9.8 \times 10^{-10}$), respectively.

Conclusions: ctDNA-based genotyping demonstrated acceptable concordance with tissue genomic profiling in patients with advanced BTC. Thus, liquid biopsy using ctDNA could complement the limitation of tissue-based genomic analysis in BTC.

Legal entity responsible for the study: Hong Jae Chon.

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112P Clinical, genomic and transcriptomic characteristics of young-onset biliary tract cancers

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Background: Biliary tract cancers (BTC), including cholangiocarcinomas (CCA) are rare but aggressive cancers primarily affecting patients (pts) >70 years (median age at diagnosis : 72-78 years). However, there has been a rise in the incidence of CCA among younger individuals (<50 years). This study aimed to investigate clinical, genomic and transcriptomic characteristics and outcomes of young-onset BTC/CCA (YOC) pts.

Methods: We identified all consecutive patients with histologically confirmed CCA treated at Gustave Roussy (France) between 2015 and 2021 as part of the ACABI-PRONOBIL multicenter cohort study. Clinical data were extracted from medical records. Genomic data were obtained through in-house or Foundation Medicine® panels. Transcriptomic analyses were performed for 58 pts (13 YOC) at metastatic diagnosis.

Results: Of the 546 pts with CCA, 92 (16.8%) had YOC (median age, 42 years; range, 27-50). Median overall survival (mOS) from 1st line therapy was 22.7 months (mo) (95%CI: 18.3-27.6) for YOC patients vs 19.2 mo (95%CI: 18.0-22.0) for non-YOC patients (p=0.14). Molecular profiling was more often performed for YOC pts (68% vs 55%, p<0.05). Rates of actionable molecular alterations (*IDH1/2*, *BRAF*, *FGFR2*, *NTRK*, *HER2*, MSI) and targeted therapies administration did not differ between YOC and non-YOC pts. *CDKN2A* alterations were less frequent in YOC than in non-YOC pts (12.6% vs 25.2%, p<0.05). Differentially expressed genes between YOC and non-YOC pts with *Gene Set Enrichment Analysis* were mostly genes involved in immunity and WNT signaling pathways.

Table:112P

Genomic characteristics		Age <=50 n=92		age>50 n=454 [BA1]	
		n	%	n	%
Molecular profile available	No	29	32%	204	45%
	Yes	63	68%	250	55%
Actionable alteration	No	41	65%	141	56%
	Yes	22	35%	109	44%
Main actionable alterations	No alteration	11	17%	43	17%
	Mutation IDH1/2	8	13%	40	16%
	Fusion FGFR 1-4	8	13%	21	8%
	Amplification HER2	3	5%	15	6%
	Mutation BRAF V600E	0	0%	10	4%
	EGFR	2	3%	7	3%
	Fusion NTRK	6	10%	11	4%
	Mutation KRAS G12C	1	2%	3	1%
Other relevant alterations	KRAS	16	25%	40	16%
	TP53	25	40%	91	36%
	CDKN2A/B	8	13%	63	25%
MMR status (n=199)	dMMR/MSI	0	0%	11	7%
	pMMR/MSS	47	100%	141	93%
Targeted therapies administration	No	41	65%	141	56%
	Yes	22	35%	109	44%

Conclusions: Although tending to have a more advanced disease at diagnosis, YOC patients had OS similar to that of non-YOC pts, and no more actionable molecular alterations. Our findings suggest that the biological mechanisms driving CCA in YOC patients may be different from those in older patients and warrant further investigation.

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113P Molecular profiling of biliary tract cancers in patients of African and European ancestries

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Background: Molecular differences between genetic ancestries in patients (pts) with bilary tract cancers (BTCs) and how they affect prognosis and treatment response are largely unknown. Compounding this problem is clinical trial enrollment for racial minorities with BTCs have been historically low, making it difficult to assess differences in treatment response between genetic ancestries. Our prior data indicated significant variation in somatic cancer genes between Caucasian and Asian pts. However, variations in African ancestry (AA) pts have not been described.

Methods: 12,932 cases of BTCs of AA and European ancestries (EA) were reviewed from 3 databases (Foundation Medicine (n=10,849), MD Anderson Cancer Center (n=167) and AACR Genie (n=1,916). BTCs were divided into intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinomas and gallbladder cancers (GBC). Prevalence of alterations in 30 genes between genetic ancestries were compared using Fischer's exact test on the Foundation Medicine database. P-values were corrected for false discovery rate using the Benjamini/Hochberg adjustment.

Results: We identified key clinical and genomic differences between AA and EA BTC cases in all 3 databases. The mean age of AA pts at diagnosis was earlier (62.3 years) compared to EA pts (65.1 years) (p<0.05). There was a higher percent of female AA BTC cases (63.2%) compared to female EA BTC cases (52.4%) (p<0.05). AA BTC cases had a statistically significant higher prevalence of *TP53* (55.1% vs 39.7%) and *TERT* (10.0% vs 5.4%) alterations (p<0.001) compared to EA BTC cases. AA BTC cases also had a statistically significant higher prevalence of *STK11, CCNE, ERBB2,* and *ARID2* alterations (p<0.05), and lower prevalence of *IDH1*, *ARID1A*, *BAP1*, *BRAF*, and *PBRM1* alterations (p<0.05) compared to EA BTC cases. AA ICC cases had a statistically significant higher prevalence of *FGFR2* (16.8% vs 11.7%) alterations (p<0.001) compared to EA ICC cases.

Conclusions: Our results highlight significant differences in genomic profiles among BTC cases of different genetic ancestries and support further research in how these differences contribute to prognosis and treatment response to targeted therapies.

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114P Prospective longitudinal tumor-informed ctDNA in resectable biliary tract cancers

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Background: Circulating tumor DNA (ctDNA) is an emerging strategy to define minimal residual disease (MRD) in resected cancers. Data in biliary tract cancers (BTC) is limited. We describe a prospective evaluation of ctDNA as part of a feasibility study of multi-platform profiling of resected BTC (NCT04561453).

Methods: We conducted a prospective multi-platform profiling study for resectable BTC from 2020 to 2023, which included tumor-informed ctDNA testing (Signatera™, Natera USA) obtained pre-operatively, within 6 weeks post-operatively prior to adjuvant therapy (MRD detection) and longitudinally every 3 months thereafter until death or last follow-up.

Results: 12 patients were included, median age 70 years (range 61-83), 6 female. BTC subtypes: intrahepatic (9) and perihilar (1) cholangiocarcinoma, and gallbladder carcinoma (2). Median follow up was 20.5 months (range 6-33 months). Median tumor size was 5.2cm (range 2.1-8.3 cm), stage II-III disease 67%, R1 resection 33%. All patients received post-operative therapy: adjuvant capecitabine (9), chemoradiation (2), gemcitabine and cisplatin (1). Two patients received neoadjuvant gemcitabine and cisplatin. Pre-operatively, all 12 patients (100%) had detectable ctDNA, while only 4 pts (33%) had elevated CA 19-9. For post-operative MRD detection, 2/12 patients had a detectable ctDNA level, while none had an abnormal CA 19-9. Among 10 patients with undetectable ctDNA MRD postoperatively, 5 patients have remained ctDNA negative without evidence of recurrence, 4 of which are ctDNA negative for $\geq$18 months (range 20-33 months). During adjuvant therapy, 2 patients converted from ctDNA positive to negative, neither have recurred. During longitudinal follow up, 4/12 patients have confirmed recurrence: 1 patient was ctDNA MRD positive while the others converted from negative to positive during adjuvant therapy or surveillance. Rise in ctDNA preceded radiographic recurrence in all patients with recurrence.

Conclusions: Baseline ctDNA had higher detection rate compared to CA 19-9 prior to resection. Longitudinally negative ctDNA was associated with improved recurrence free survival. Assessing ctDNA levels may have potential utility in evaluating response in the absence of radiographically visible disease.

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115P Inhibition of KLF5 reduces tumor growth and sensitizes to chemotherapy-induced cell death in experimental models of cholangiocarcinoma

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Background: Cholangiocarcinoma (CCA) comprises a heterogeneous group of cancers with bad prognosis. Krüppel-like factors (KLF) are a family of transcription factors involved in organogenesis, differentiation and cellular homeostasis. Here, we studied the role of KLF5 in CCA development and evaluated the therapeutic potential of its inhibition.

Methods: *KLF5* expression was measured in human CCA tissues [Copenhagen (n=210), TCGA (n=36), Job (n=78), TIGER-LC (n=90) and San Sebastian cohorts (n=12)] and cell lines. *KLF5*$^{-/-}$ CCA cells were created by CRISPR/Cas9. The functional effects of KLF5 genetic silencing with CRISPR technology, or chemical inhibition with ML264, were evaluated *in vitro* and *in vivo*.

Results: *KLF5* expression was upregulated in human CCA tissues from 5 different patient cohorts compared to surrounding normal liver tissue. High *KLF5* levels correlated with lymph node invasion and worse overall survival. *In vitro*, KLF5 protein and mRNA levels were overexpressed in human CCA cells compared to normal human cholangiocytes. Functionally, *KLF5*$^{-/-}$ CCA cells displayed decreased cell proliferation, migration, invasion and colony formation while promoting cell cycle arrest at G1/S and apoptosis *in vitro*, when compared to control cells. In agreement, *KLF5*$^{-/-}$ CCA cells did not develop any tumor after subcutaneous or orthotopic injection in a xenograft animal model of CCA. Likewise, chemical inhibition of KLF5 with ML264 hampered CCA cells proliferation and migration *in vitro* and blocked tumor growth *in vivo*. Lastly, both genetic and chemical inhibition of KLF5 sensitized CCA cells to chemotherapy-induced apoptosis *in vitro*, and the combination of gemcitabine + cisplatin and ML264 completely halted CCA tumor growth in mice. Accordingly, *KLF5*$^{-/-}$ CCA display altered levels of several proteins related to chemoresistance when compared to control cells, that were shown to significantly correlate with *KLF5* expression in human CCA tissues.

Conclusions: Increased KLF5 is a general event in CCA, contributing to cancer progression and chemoresistance. KLF5 inhibition with ML264 may represent a potential therapeutic strategy for CCA.

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116P Circulating tumour DNA- based minimal residual disease detection for biliary tract cancer

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Background: Although circulating tumor DNA-based minimal residual disease (MRD) is useful for prediction of prognosis, but clinical value of MRD for BTCs are remain clear.

Methods: The OriMIRACLE S™ MRD assay (OrigiMed, Shanghai, China) uses whole exome sequencing (WES) for detecting patient-specific somatic alterations from tumor tissues and for blood a personalized panel designed to target up to 45 variants.

Results: A total of 26 biliary tract cancer (BTC) patients including 13 gallbladder carcinoma and 13 extrahepatic cholangiocarcinoma patients were enrolled. Among the patients, 53.85% (14/26) were male and 46.15% (12/26) were female, and the median age was 61 years, ranging from 49 to 73 years old. Fifteen patients underwent radical surgery, 4 patients underwent local tumor resection and 7 patients could not undergo radical surgery. Based on WES, we found that 58.33% (4005/6866) of the mutated genes were unique to each patient and100% (26/26) of patients successfully constructed MRD panels, suggesting that tumor-informed MRD is superior to panel-based MRD in BTC. For each patient, we selected up to 45 clonal somatic mutations for a personalized ctDNA assay design. MRD detection was performed on 26 cases and revealed a positive rate of 42.31% (11/26). Among the 11 patients with positive MRD at postoperative or, 71% (5/7) of patients who could not undergo radical surgery, 100% (4/4) of the patients underwent local tumor resection and 13.3% (2/15) of patients underwent radical surgery. MRD detection was performed 4 times on one female GBC patient with stage IV throughout the treatment course. we found that

MRD at baseline was positively detected by tumor-informed assay with a higher variant allele fraction (VAF), and decreased after neoadjuvant therapy. CT image also showed local control of the tumor, but CA199 and CEA levels were elevated in patients with obstruction, suggesting the limits of tumor markers in BTC patients with obstruction.

Conclusions: Up to 58% of mutated genes of BTC are unique individually, and 100% of patients successfully constructed MRD panels, which may be more suitable for monitoring with tumor-informed MRD panel. The VAF of ctDNA could be used to predict the efficacy of neoadjuvant therapy and tumor progression in BTC patients.

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117P Genomic landscape of biliary tract cancers from India show distinct geographic variation

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Background: Biliary tract cancers (BTC) are a group of heterogeneous tumors that include intrahepatic, perihilar, and distal cholangiocarcinoma and gall bladder cancers (1). India has a high burden of biliary tract tumors, particularly gallbladder cancers. It contributes to 10% of global burden of gall bladder cancers. Within India, the Indo-Gangetic doab has a higher incidence of BTCs of 21/100,000 individuals affected (2). Cholangiocarcinoma and gall bladder cancers have distinct genomic diversity (3). Genomic profiling of BTCs from India are scarce. Understanding of genomic diversity of BTCs in India shall help in strategizing therapy and prevention. **Aim** The main objectives of the study are: 1. Retrospective analysis of genomic profile of biliary tract cancers from India 2. Pathway analysis of BTCs based on genomic profiling.

Methods: 46 BTC cases from India were recruited for the study spanning 10 centers across India. All the cases were tested using comprehensive genomic profiling under Foundation One CDx or Foundation One Liquid CDx assay. Only the genomic results were used for retrospective analysis.

Results: 33 cases of cholangiocarcinoma and 13 cases of gallbladder cancers were analyzed. The most commonly altered genes in cholangiocarcinoma were TP53 (45%), CDKN2A/B (33%), ARID1A (21%), KRAS (21%). The most commonly altered genes in gallbladder were TP53 (77%), CDKN2A/B (31%), RB1 (23%) and SMAD4 (23%). Pathway analysis showed a distinct difference between cholangiocarcinoma and gallbladder tumors. Transcriptional factors and Immune-modifier pathways were enriched in gallbladder tumors compared to cholangiocarcinoma, while the cell cycle pathway was more commonly altered in cholangiocarcinoma. When the cholangiocarcinoma cases were stratified by demographic origin within India, we found cell cycle pathway genes to be significantly less among North Indian samples, while RAS-RAF pathway was significantly more among North Indian samples.

Conclusions: The genomic landscape of BTCs in India showed distinct variation compared to the rest of the world. A trend of variation in the genomic landscape of BTCs between North & South India was observed. Further study with higher sample size is warranted.

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118P Artificial intelligence (AI)-powered spatial analysis of tumor-infiltrating lymphocytes (TILs) as a predictive biomarker for anti-PD-1 in advanced biliary tract cancer (BTC)

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Background: Recently, anti-PD-1/L1 plus gemcitabine and cisplatin (GemCis) has demonstrated significant survival benefits in randomized phase 3 trials for advanced BTC. However, no biomarker has been established for anti-PD-1 in BTC. Here, we assessed TILs using artificial intelligence (AI)-powered spatial analysis in advanced BTC treated with anti-PD-1.

Methods: An AI-powered whole-slide image (WSI) analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) was used to segment tumor epithelium and stroma, and identification of intratumor TIL (iTIL) and stromal TIL (sTIL). H&E-stained WSI from pre-treatment samples was acquired from Asan Medical Center and Yonsei Cancer Center (n = 354), and a total of 337 samples (95.2%) after quality control were used for the final analysis. Immune phenotypes (IP) were defined as follows: inamed as high iTIL and sTIL; immune-excluded as low iTIL and high sTIL; immune-desert as low TIL overall. Among them, 29 patients (pts) were available for multi-color flow cytometry analysis (FACS) using peripheral blood mononuclear cells (PBMC), collected at baseline and C1D8.

Results: All patients were treated with anti-PD-1 monotherapy, and 188 pts (55.8%) were treated as 2nd line. In overall pts, anti-PD-1 showed median overall survival (OS) of 5.7 months (mo), median progression-free survival (PFS) of 2.0 mo, and objective response rates (ORR) of 10.1%. IP were classified as inflamed in 40 pts (11.9%), immune-excluded in 167 (49.6%), and immune-desert in 130 (38.6%). The inflamed group showed better OS (12.5 vs. 5.1 mo, $P<0.001$), PFS (5.0 vs. 2.0 mo, $P=0.001$), and ORR (27.5% vs. 7.7%, $P<0.001$) than non-inflamed groups. In the FACS, the inflamed group showed significantly higher proportion of baseline CD8+Tem and lower baseline CD8+Tnaive than non-inflamed groups. At C1D8 of anti-PD-1, CD69+CD8+T, GZMB+CD8+T, and PRF1+CD8+T cells were increased, while PD1+CD8+T cells was decreased in PBMC of the inflamed group.

Conclusions: Immune phenotype classified by AI-powered spatial TIL analysis was effective to predict the efficacy outcomes of advanced BTC pts treated with anti-PD-1 therapy. Further evaluation is required in the setting of anti-PD-1/L1 plus GemCis.

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119P Management of biliary tract cancers in older patients: A French multicenter cohort study

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Background: Biliary tract cancers (BTC) including cholangiocarcinomas (CCA) and gallbladder cancer (GBC) are uncommon tumors with poor prognosis, often diagnosed after age of 70, where comorbidities and altered performance status (PS) are more

frequent. We aimed to compare clinical characteristics, molecular profile, and outcomes of patients (pts) with BTC < and ≥ 70 years old.

Methods: A retrospective chart review was performed in treated BTC pts in 16 French centers from 2003 to 2021. Data on demographics, therapeutic management, molecular profile, progression-free survival (PFS) and overall survival (OS) were collected.

Results: Overall, 1256 pts with BTC were included (male, 52%; median age, 64.5 years), including 384 pts (31%) over 70. Older pts had poorer PS (PS ≥2, 17% vs 8%; p<0.0001) and more comorbidities (≥1 comorbidity, 89% vs. 78%; p<0.0001). They were diagnosed more frequently with extrahepatic CCA and GBC (respectively, 18% vs.12% and 16% vs. 13%, p=0.0073) and less advanced disease stage at diagnosis (bilobar liver involvement, 29% vs 37%; p=0.008). They were offered less frequently first-line systemic therapy (87% vs 97%, p<0.0001)(gemcitabine 3% vs 0.3%; gemcis 31% vs 35%; gemox 54% in 2 groups; p=0.007) and molecular profiling (43% vs 65%, p<0.0001) than pts <70. Proportions of actionable alterations were significantly different, with more HER2 amplifications and less IDH1 mutations and FGFR2 fusions in older patients (p=0.0419). MSI status were similar between groups. OS after resection was similar in older and younger pts (median OS, 47.0 months (mo) [95%CI: 37.8-71.9] vs 48.8 mo [95%CI 41.4-57.3]), but shorter in older pts at advanced stage (14.6 [95%CI 12.7-16.5] vs. 17.4 mo [95%CI 16.1-18.9), p<0.0001). First-line PFS did not differ (median, 6.6 mo [95%CI 5.5-7.2] vs 5.8 mo [95%CI, 5.3-6.2), p=0.61).

Conclusions: Older BTC pts presented more frequently eCCA and GBC and a less advanced disease at diagnosis. At advanced stages, older pts had poorer OS and received less often first-line chemotherapy. If treated, PFS of older pts was similar to younger pts. Molecular profiling was less often performed in older pts.

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120P Management of biliary tract cancers in early onset patients: A French multicenter real-life study from the ACABI-PRONOBIL cohort

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Background: Biliary tract cancers (BTC) including cholangiocarcinoma (CC) and gallbladder cancer (GBC) are rare cancers with poor prognosis. Few data are available on early-onset BTC (EOBTC) defined as patients (pts) under age of 50.

Methods: A retrospective chart review was performed in pts treated for BTC in 14 French centers between 2003 and 2021. Data on demographic characteristics, therapeutic management, and molecular profile were collected. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan Meier method. Prognostic factors were assessed by univariate and multivariate analyses by Cox regression.

Results: Overall, 1256 pts with BTC were included. Patients with EOBTC (n=188, 15%) had less comorbidities according to Charlson score (63.5% vs 84.4%, p<0.0001), higher tumor stage (cT3-4: 49.9% vs 32.17%, p=0.0126), bilobar liver involvement (47.7% vs 32.1%, p=0.0002) and metastatic disease (67.5% vs 57.49%, p=0.0097) compared to older pts, but did not differ regarding primary tumor location (intrahepatic vs extrahepatic CC vs GBC), WHO performance status (PS 0-1: 94.4% vs 85.5%, p=0.15), and sex-ratio (50.8% vs 53.4% of males). First-line systemic therapy for advanced BTC (n=818, 65.2%) was mostly a doublet by GEMCIS (45.5% vs 32.1%, p=0.0091) or GEMOX (43.3% vs 56.5%, p=0.0091) in EOBTC vs non-EOBTC respectively. EOBTC pts received more frequently a 2nd line therapy (89.5% vs 80.9%, p=0.02). For advanced BTC pts, median (m)OS was 17.0 mo vs 16.2 mo (p=0.08) and mPFS was 5.8 mo vs 6.0 mo (p=0.89), in EOBTC vs older pts respectively. Molecular profiling was performed in 72.6% of EOBTC pts vs 52.4% in older pts (p=0.0019), and less actionable alterations were found (e.g. IDH1 mutations, 7.8% vs 16.6%; p=0.029; FGFR2-fusion, 11.7% vs 8.9%; p=0.029). We did not find any usual prognostic factors in BTC (CEA, CA19-9, PS, neutrophile-lymphocyte ratio, number of extra-hepatic metastases) associated with EOBTC survival.

Conclusions: Pts with EOBTC have a more advanced disease at diagnosis, are treated more heavily at an advanced stage, and have similar PFS and OS in comparison to older BTC pts. Molecular profiling was more often performed in EOBTC pts but less actionable alterations were found.

Legal entity responsible for the study: GERCOR.

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121P PemiBil: Efficacy and safety of pemigatinib in advanced cholangiocarcinoma with FGFR2 fusions/rearrangements in real-world, results of multicentric French cohort from ACABI consortium

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Background: Fibroblast growth factor receptor 2 (FGFR2) fusions or rearrangements (f/r) occur in up to 14% of patients with intrahepatic cholangiocarcinoma (iCCA). PEMIGATINIB, an oral FGFR 1-3 inhibitor, demonstrated significant efficacy in the phase II FIGHT-202 study with a response rate of 37% in heavily pretreated patients. Neither phase III nor phase IV data are currently available but due to the reported efficacy, PEMIGATINIB was FDA and EMA approved and is available in France since July 2020. Our study aimed to evaluate the efficacy and safety of pemigatinib and the disease profile of iCCA with FGFR2 fusions/rearrangements in an unselected population.

Methods: This national multicenter retrospective cohort collected data on demographics, therapeutic management, toxicity profile, objective response rate, progression-free survival and overall survival from French patients with advanced cholangiocarcinoma with FGFR2 f/r who received PEMIGATINIB since July 2020.

Results: From July 2020 to September 2022, 50 patients were included. At diagnosis the mean age was 57 years with 74% female, mainly ECOG 0-1 (82%). 58% had received two or more previous systemic therapies. The objective response rate was 45.3% (3 complete responses and 21 partial responses, n = 24). The median progression-free survival was 9 months (IIQ 6-14) and the median overall survival was 18 months (IIQ 12-NA). Neither clinical nor molecular characteristics were predictive factors for treatment response. The most common toxicities were hyperphosphatemia (58%), nail toxicity (58%) and fatigue (58%). 35% of patients developed grade 3 toxicity at the 13.5 mg daily dose. 57.5% (n = 19) of patients with progression were able to receive at least one subsequent line of treatment, mostly a new FGFR inhibitor (58%). The median overall survival from the locally advanced or metastatic stage was 37 months.

Conclusions: Our study confirms the efficacy of pemigatinib in an unselected population with high response rates and survivals similar to the FIGHT-202 data. It also confirms the good tolerability of pemigatinib and the better prognosis of iCCA with FGFR2 f/r.

Legal entity responsible for the study: Dr Nadim Fares, MD PhD, Digestive Oncology Department, Centre Hospitalier Universitaire de Toulouse - Hopital Rangueil, Toulouse, France.

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122P Largest examination of cholangiocarcinoma (CCA) patients (pts) treated with novel targeted therapies after extended molecular profiling on liquid biopsies

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Background: CCA is associated with poor outcomes with limited treatment options. Targeted therapies have recently gained traction in CCA but data remains sparse in this domain. Here, we present the largest multi-institutional review to date evaluating outcomes following targeted agents in this pt population.

Methods: All consecutive CCA pts receiving systemic therapy between 2010 - 2022 at UCLH were included. Treatment response, survival outcomes and predictors of clinical benefit were evaluated. Pt demographic factors, disease characteristics and survival outcomes were evaluated using the Kaplan-Meier method and Cox proportional-hazards models.

Results: Of the 147 screened pts, 119 (81%) underwent molecular profiling. We identified 48 (40%) eligible CCA pts where 47 received molecularly guided targeted treatment. Most pts received targeted agents in a 2nd treatment line setting (N = 26). Frequently observed genomic alterations occurred in *FGFR* (N = 21), *BRCA* (N = 8), *KRAS* (N = 7), *IDH* (N = 5) and *PIK3* (N = 3) genes. The median progression-free survival (PFS) following 1st, 2nd and 3rd line systemic therapy and overall survival (OS) were: 8.38 (5.45 - 13.50), 5.52 (3.22 - 7.85), 8.15 (2.79 - not reached) and 27.07 (24.21 - 36.63) months, respectively. Median duration of clinical benefit (DoCB) (complete response, partial response and stable disease) in 2nd line treatment setting was 3.10 (2.31 - 4.20) and 5.32 (2.89 - 8.41) months in the chemotherapy and targeted agent (with or without chemotherapy) cohorts, respectively. In a 3rd line setting, the median DoCB was 5.03 (2.63 - 5.42) and 8.34 (2.87 - 14.09) months in the chemotherapy and targeted agent (with or without immunotherapy) cohorts, respectively. This duration extended to 9.66 (3.06 - 14.06) months among futibatinib recipients. Duration of 2nd line targeted treatment was associated with PFS ($P < 0.0001$) and OS ($P < 0.0001$). Duration of 3rd line targeted treatment was associated with PFS ($P = 0.001$) but not OS ($P = 0.14$).

Conclusions: Our study demonstrated the efficacy of novel therapeutic agents in CCA. Liquid biopsies can reliably provide information on extended molecular profiling to aid pt selection for personalised therapeutics.

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123P Artificial intelligence (AI)-powered analysis of human epidermal growth factor receptor-2 (HER2) and tumor-infiltrating lymphocytes (TILs) in advanced biliary tract cancer (BTC)

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Background: HER2 is overexpressed in a subset of BTC patients, and recent developments in HER2-targeted agents are expanding therapeutic options. However, accurately assessing HER2 expression is challenging in BTC, especially at a low-expression level. We evaluated HER2 expression as well as TILs density through AI models in BTC.

Methods: Whole-slide images (WSI) of pre-treatment HER2 immunohistochemistry (IHC) slides, matched H&E-stained slides and clinicopathological data were obtained from advanced or metastatic BTC patients at CHA Bundang Medical Center in South Korea, between 2019 and 2022. An AI-powered HER2 analyzer classifies tumor cells by HER2 staining intensity (H0, H1, H2, or H3) and quantifies the cells in each staining category. Then, it calculates HER2 categories (0/1+/2+/3+) following the latest ASCO/CAP HER2 IHC guidelines. For evaluating immune landscape, a separate WSI analyzer identified and quantified. TILs within the cancer epithelium or stroma from H&E-stained slides.

Results: In a total of 328 patients, the AI-scored HER2 categories were 0 in 92 (28.9%), 1+ in 137 (43.1%), 2+ in 68 (21.4%), and 3+ in 21 (6.6%). The overall concordance of HER2 categories between the AI and pathologists' readings was 75.3%. HER2 3+ rates by AI in intrahepatic, extrahepatic, gallbladder, and Ampulla of Vater are estimated to be 3.1%, 3.4%, 21.4%, and 5.9%, respectively. HER2-expressing tumors (1+, 2+, and 3+) have significantly higher densities of stromal TILs (983.2 $\pm$ 1347.5 / mm2) than HER2-negative tumors (683.5 $\pm$ 739.7 / mm2, p=0.012) and there were no significant TIL density differences between HER2-high expressing (3+) and low expressing tumors (1+, 2+), which were consistent with either by the AI or pathologists.

Conclusions: AI-powered HER2 scoring showed good agreement with pathologists' scoring, and HER2-expressing tumors harbored high stromal TIL in BTC. Objective expression analysis and the associated differences in immunogenicity will be important for future treatment strategies.

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124P Clinicopathological nomogram for predicting fibroblast growth factor receptor 2 (FGFR2) gene fusion/rearrangement (F/R) in intrahepatic cholangiocarcinoma (iCCA)

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Background: FGFR2 gene F/R is present in 10-15% of iCCA and FGFR2 inhibitors have demonstrated significant antitumor activity in this population. However, specific clinicopathological features of iCCA patients (pts) harboring FGFR 2 gene F/R have not yet been well clarified. So far, limited literature data seem suggest a correlation between FGFR2 gene F/R and young age and female gender. The aim of this study is to construct a nomogram predicting FGFR2 gene status.

Methods: iCCA pts from four Italian Institutions were retrospectively collected. The following clinicopathological variables were selected: gender; age ($<$ 55 vs $\geq$ 55 years); synchronous vs metachronous metastases (mts); number of metastatic sites (1 vs $>$1), lung/distant lymph-node/peritoneal/bone mts (present vs absent). A multivariate logistic regression model was used to screen out independent predictive factors with a cut-off of 0.10 and a nomogram was established.

Results: Among 464 iCCA pts retrospectively evaluated, 63 (14%) had FGFR2 gene F/R. Univariate and multivariate analysis suggested that age $<$ 55 years [odds ratio (OR): 2.06, 95% confidence interval (CI) 1.15-3.9], bone mts (OR: 2.58, 95% CI 1.28-5.20) and female gender (OR: 1.53, 95% CI 0.88–2.67) were independent predictive factors of FGFR2 gene F/R. A predictive nomogram was established: pts with the highest score (age $<$ 55 years, bone mts, female gender) had a 60% chance to bear FGFR2 gene F/R iCCA [AUC 0.64 (95% CI: 0.57 -0.72)] in comparison to pts with low score (age $\geq$ 55 years, no bone mts, male gender) which had a 7% chance to have FGFR2 positive iCCA.

Conclusions: In the era of molecular characterization, we have developed a simple nomogram for predicting FGFR2 gene status in iCCA. This nomogram might help clinicians to identify pts more likely to harbour FGFR2 gene F/R and increase their therapeutic opportunities. An external validation-set will be analyzed to improve predictive performance.

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125P Real-world treatment patterns in patients with biliary tract cancer (BTC): Retrospective chart review survey in Europe (GARNET-2)

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Background: BTC is a diverse group of hepatic and perihepatic malignancies with a 5-year survival rate of $<$20%. This study described real-world treatment patterns and outcomes among patients with advanced and/or unresectable (aBTC) in France, Germany, Italy, Spain, and the United Kingdom (UK).

Methods: In this retrospective, web-based chart review survey, physicians reported anonymized patient-level data for adult patients diagnosed with aBTC between May 2018 and October 2021 who received first-line (1L) systemic therapy (index date). Patients were followed from index date until death or last available date at abstraction. Patient characteristics, treatment patterns, and clinical outcomes were summarized descriptively.

Results: A total of 196 physicians extracted data for 792 aBTC patients who initiated 1L systemic therapy. More patients had intrahepatic cholangiocarcinoma (CCA; 34.8%), than extrahepatic CCA (29.9%), gallbladder (23.5%), and ampullary cancer (10.2%) whereas 1.5% patients had missing information. During follow-up (median=12.4 months), less than half of patients were prescribed gemcitabine + cisplatin (GemCis; 47.9%) as 1L. Median 1L treatment duration was 5.3 months with disease progression (49.2%) being the most common reason for treatment discontinuation. Only 33.1% received 2L and 4.1% received 3L+ of treatment. Median real-world overall survival (rwOS) from index date was 13.4 months, with regional variation (Table).

Table: 125P Key results by country*

	France (N = 167)	Germany (N = 150)	Italy (N = 153)	Spain (N = 167)	UK (N = 155)
Male, %	67.1	66.7	55.6	65.9	57.4
Age ≥60, %	73.1	60.7	76.5	76.0	85.2
Site of primary BTC tumor, %					
Intrahepatic CCA	31.1	35.3	51.0	28.7	29.0
Extrahepatic CCA	30.5	28.0	26.8	29.3	34.8
Gallbladder	23.4	29.3	11.1	28.7	24.5
Ampulla of Vater	13.8	6.0	9.8	13.2	7.7
Unknown	1.2	1.3	1.3	0	3.9
ECOG at diagnosis, %					
0	20.4	14.7	27.5	18.6	32.9
1	52.1	48.0	64.1	67.7	52.3
2+	22.2	22.0	8.5	11.4	11.6
Unknown	5.4	15.3	0	2.4	3.2
GemCis 1L regimen, %	28.7	30.0	69.9	44.3	67.7
Median rwOS (months)	17.8	18.3	14.7	13.1	8.8

*All decimals have been rounded to the nearest tenth, thus the overall % may result in getting a value slightly higher than 100%.

Conclusions: This study demonstrated the unmet needs of patients with aBTC, with less than half of the patients receiving standard-of-care – GemCis (ESMO recommendation) and a median rwOS of just over one year suggesting the need for new

treatments that extend survival. With the recent approval of immunotherapy for aBTC patients, exploration of the benefits in real-world is needed. Additional efforts in the earlier detection of BTC are essential to improve survival.

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126P Biliary tract cancer (BTC) characterization on a cohort of patients (pt) from the Spanish RETUD Registry

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Background: BTC constitutes a heterogeneous group of invasive tumors, including intrahepatic, perihilar, and extrahepatic cholangiocarcinoma, and gallbladder carcinoma (GC). We aimed to characterize the epidemiology, clinical management, and survival outcomes of BTC pt in our environment.

Methods: We evaluated a large real-world cohort of pt diagnosed with BTC from 1st January 2017 to 31st December 2022 from the Spanish RETUD registry. We described the demographic and clinical features, therapies received and outcomes. We assessed progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier method in different settings.

Results: A total of 1,285 evaluable pt were included in 28 Spanish sites. The median age was 69.2 years, and 56.2% were men. At primary diagnosis, tumors were mostly intrahepatic (54.8%), followed by extrahepatic (28.5%), and GC (14.6%). Overall, 48.7%, 22.6%, and 28.6% pt were diagnosed with metastatic, locally advanced, and resectable disease, respectively. Only 29.5% of pt underwent surgical resection and 9.6% locoregional procedures. Most pt (74.8%) received systemic treatment as a first-line strategy (86.2%), mainly gemcitabine-based combinations (90%), with 62.7% of pt receiving cisplatin plus gemcitabine (CISGEM). At the database cut-off, 945 pt had died because of disease progression. The median OS at the advanced setting was 9.2 months (m) (95% confidence interval [95CI]: 8.3-10.3). The median PFS in pt with advanced BTC exposed to first-line CISGEM was 5.5 m (95CI 5.0-6.0) with a median OS of 11.6 m (95IC 10.8-12.5). For pt with resectable BTC, OS was analyzed based on whether they received adjuvant treatment (ADJ) and developed metastases (met) during follow-up (see table)

Table: 126P

Group of pt		Median OS (m)	95% CI
No ADJ	No met	36.6	22.8-57.3
	met	21.6	17.8-29.0
ADJ	No met	45.7	33.7-not reached
	met	25.4	21.4-32.6

Conclusions: This study provides insights into the clinical characteristics and management of BTC in the real-world framework in Spain. Our results are consistent with the literature, nevertheless, they must be considered in the context of a currently evolving scenario.

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127P Prognostic significance of intratumoral and peritumoral budding in distal extrahepatic bile duct carcinoma

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Background: Although tumor budding (TB) has been recognized as a representative adverse prognosticator in gastrointestinal malignancies, it is not well elucidated in distal-extrahepatic bile duct carcinoma (DBDC).

Methods: Herein, we investigated the prognostic significance of peritumoral (PTB) and intratumoral (ITB) budding according to the modified DBDC staging of the 8th edition of the American Joint Committee on Cancer. PTB and ITB were independently evaluated in a cohort of DBDC patients (n=410) based on the 2016 International Tumor Budding Consensus Conference (ITBCC).

Results: High levels of PTB (PTB^{High}, $\geq$ grade 2) and ITB (ITB^{High}, $\geq$ grade 3) were identified in 316 (77%) and 238 (58%) cases, respectively. In univariate analysis, PTB^{High} and ITB^{High} (both P=0.001); larger size and sclerosing tumor growth pattern (both P<0.001); higher histologic grade (P=0.006); extrapancreatic location (P=0.015); adenocarcinomas unrelated to intraductal papillary neoplasm of the bile duct (IPNB) (P=0.008); pancreatic, duodenal, and lymphovascular invasion (all P<0.001); perineural invasion (P=0.003); cancer involvement of the bile duct resection margin, nodal metastasis, and higher T and N categories and disease stages (all P<0.001) were associated with shorter patient overall survival (OS) times. In

multivariate analysis, PTB^{High} and ITB^{High} remained poor independent prognostic indicators of OS in DBDC patients. Specifically, ITB^{High} could predict poor prognosis (P=0.025) in patients with stage I (T1N0) DBDC.

Conclusions: Both PTB^{High} and ITB^{High} were strong prognostic indicators in patients with DBDC. Thus, ITB could be used to predict worse prognoses in patients with DBDC, in which PTB is difficult to assess, especially for patients with stage I (T1N0) DBDC.

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128P Biliary tract cancers: Epidemiological and prognosis trends of Latin American population

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Background: Biliary tract cancers are heterogeneous tumors defined by the anatomical location, intrahepatic, cholangiocarcinoma (ICC), extrahepatic (ECC), gallbladder and ampulla of Vater cancer (AVC).The outcome of treatment by location remains unclear in Latin American population, resulting in inconsistently data to enhance treatment decisions and outcome. The aim of this study is to describe the epidemiological features and prognosis of overall survival of Latin American population with biliary tract cancers.

Methods: Retrospective, observational study. Included patients treated at the National Cancer Institute between 2008 and 2022. Statistical analysis required: X^2 *and t* test, Kaplan Meier, Log Rank and Cox Regression. Statistical significance differences were assessed when p was bilaterally <0.05.

Results: A total 786 of patients diagnosed with biliary tract cancer were included in the analysis. Patients had a median age of 61 years (24-96). Alcohol consumption and smoking were observed in 22% and 29% respectively. Regarding comorbidities, 22% had Type2DM, 27% HAS, and obesity & overweight was present in 13% and 32% respectively. Anatomical location included ICC (19%;n=151), ECC (22%;n=172), gallbladder (33%;n=259) and AVC (26%;n=204). Female were more prevalent in gallbladder and ICC (79% & 71%) ($p<0.001$). Median time to diagnosis was 3 months (0–120); extent of disease was observed as localized (18%;n=144), local-advanced (20%;n=158), and metastatic (60%;n=472). In metastatic patients, mean number of metastasis was 1 (1-7), being liver (66%), retroperitoneum (7%), and lung (6%) the most frequent sites. Comparing Chemotherapy and extent of disesase, 35%, 53%, and 55% patients received treatment for localized, unresectable, and metastatic **(p =0.001).** An OS analysis was conducted considering location, ICC patients showed a median-OS of 9months, ECC a median-OS of 12months, gallbladder a median-OS of 1months and AVC did not reach median-OS **(p<0.001).**

Conclusions: Prognosis and outcome for patients with biliary tract cancer differ depending on the anatomical subsite. This is one of the main studies describing epidemiological features, and outcome in Latin American patients with biliary tract.

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129P Prognostic factors associated with survival in resected biliary tract cancers: A multicentre Italian experience

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Background: Biliary tract cancers (BTC) are classified as gallbladder tumours (GBC) and intrahepatic (iCCA) or perihilar and distal extrahepatic cholangiocarcinomas (eCCA). BTC's 3-year recurrence rate is up to 80%. Capecitabine (CAP) is the standard for adjuvant (adj) chemotherapy (CT). We collected a retrospective multicentre Italian series of resected BTC and analysed the impact of adj CT on survival.

Methods: Main variables were ECOG performance status (PS), pre-surgical (SUR) Ca 19.9 value, type of SUR, site, histology, invasion (T), nodal status (N), vascular invasion (V) resection margins (R), grade (G). Median follow-up (FU) was estimated with reverse Kaplan-Meier (KM) approach; median RFS (RFS) and median overall survival (OS) were estimated by KM method.

Results: We included 142 all-stages BTC resected from 2005 to 2022, adj CT was given to 69 BTC. With median FU of 89 months (mo), overall RFS and OS were 17 and 30 mo. Lower ECOG PS was associated with longer RFS and OS ($p<0.001$). A pre-SUR Ca19.9 $\leq$ 29 was associated with longer RFS in iCCA ($p=0.001$) and OS both in iCCA ($p=0.010$) and GBC ($p=0.019$). Lower T was associated with longer RFS ($p=0.002$) and OS ($p<0.001$) in iCCA and GBC but not in eCCA. N0 status correlated with longer RFS in iCCA ($p<0.001$) and OS both in iCCA and GBC ($p<0.006$). R0 status was associated with longer RFS in eCCA ($p=0.043$) and GBC ($p<0.001$), showing longer OS only in GBC only ($p<0.001$). V0 status was associated with longer RFS ($p=0.017$) and OS ($p=0.009$) in iCCA . Adj CT didn't impact both on RFS ($p=0.539$) and OS ($p=0.978$) in the whole cohort. After stratification by site, eCCA showed an advantage given by adj CT on mRFS ($p=0.047$). Comparing all adj CT, CAP performed better in iCCA, with a mRFS of 19 mo. Multivariate Cox regression analysis for RFS and OS was stratified for iCCA, eCCA and GBC: ECOG PS, R and N status retained significant correlation with RFS ($p<0.001$, $p<0.001$ and $p=0.034$, respectively) and OS ($p<0.001$, $p<0.001$, $p=0.013$, respectively). Pre-SUR Ca19.9 value correlated with OS ($p=0.001$).

Conclusions: In our series, adj CT didn't impact on survival except for eCCA. Evaluation of multiple prognostic variables (including T, N, R and V status and pre-SUR Ca19.9) is necessary to identify a subgroup of BTC that can benefit more from adj CT.

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130P Phase I study evaluating KIN-3248, a next-generation, irreversible pan-FGFR inhibitor, in patients with advanced cholangiocarcinoma, urothelial carcinoma and other solid tumors harboring FGFR2 and/or FGFR3 gene alterations

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Background: Preclinical and clinical evidence indicates that activating FGFR1-4 gene alterations drives oncogenesis and tumor growth. Pharmacological inhibition of FGFR1-4 leads to tumor shrinkage and disease control, supporting development of FGFR inhibitors. A critical limitation of currently approved, clinical-stage FGFRi is the

emergence of secondary, on-target resistance mutations (mutn) that reduce duration of response. About 70% of cholangiocarcinoma (CCA) patients treated with FGFRi exhibit secondary FGFR2 kinase domain resistance mutn at the time of relapse. KIN-3248 is a next-generation, selective, irreversible, small molecule pan-FGFRi, designed to inhibit primary FGFR oncogenic alterations as well as secondary kinase domain mutn associated with disease progression. Preclinically, KIN-3248 has favorable pharmaceutical properties, is well-tolerated with continuous, daily oral administration in GLP toxicology studies and is efficacious against primary FGFR2 and FGFR3 oncogenic driver alterations as well as secondary FGFR2 resistance mutn (eg, gatekeeper and molecular brake) in human cancer cells and PDX models.

Trial design: KN-4802 (NCT05242822) is a first in human, multicenter, Ph1 study of KIN-3248 in pts with advanced and metastatic solid tumors (AMST) harboring FGFR2 and/or FGFR3 gene alterations. KIN-3248 is given continuously in 28-day cycles until drug intolerance or disease progression. The study is conducted in 2 parts: Part A is a dose escalation of KIN-3248 to MTD/RP2D. Part B evaluates a selected dose of KIN-3248 in previously treated intrahepatic cholangiocarcinoma (ICC) or urothelial carcinoma (UC), treatment naïve ICC or UC, or other AMST. Enrollment criteria include ECOG PS 0-1 and prior standard treatment with clinical benefit, if appropriate. Primary endpoints are safety and preliminary antitumor activity. Secondary objectives include pharmacokinetic and pharmacodynamic assessments including measures of FGFR pathway modulation. Planned sample size is 140 pts and the study is enrolling patients in the US, EU and globally.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

BIOMARKERS (AGNOSTIC)

131O A composite biomarker for evaluation of homologous recombination repair deficiency in a pan-cancer cohort

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Background: Assessing the functional state of homologous recombination repair (HRR) is crucial to predict an effective response to *PARP* inhibitor (PARPi) treatment or platinum-based chemotherapy in cancer patients. Drug approvals are currently mostly based on mutations in *BRCA1* and *BRCA2* or genomic scarring alone. Composite biomarkers may extend the discriminative power and make targeted treatment approaches available to a wider range of patients and entities.

Methods: Whole-genome or -exome sequencing (WGS or WES) data from 739 patients including various rare cancers were evaluated for germline and somatic alterations in one of 183 genes related to HRR as well as for genomic patterns of HRR deficiency (HRD), i.e. exposure to single-base substitution signature 3, quantification of HRD-derived loss of heterozygosity (LOH-HRD), and the number of large-scale state transitions (LST). The individual markers were integrated into a composite biomarker, the TOP-ART score, with a scoring system (0-7) and compared to the other published HRR biomarkers. Currently, this biomarker is used to determine eligibility for the TOP-ART trial (ClinicalTrials.gov identifier: NCT03127215, olaparib/trabectedin vs. physician's choice, estimated study completion: December 2023).

Results: The occurrence and severity of HRD predicted by the TOP-ART score varies between entities. Strong associations were found between genomic patterns of HRD and mutations affecting several genes, including but not limited to *BRCA1* and *BRCA2*. The phenotypic susceptibility to *BRCA1* and *BRCA2* impairment varies between entities and depends on zygosity. TOP-ART score positivity (score $\geq$3; 312 cases) overlaps with but is more inclusive than HRDetect (55 cases) and CHORD (26 cases). In particular, we identify patients who were biomarker-negative for HRDetect and CHORD, but positive in the TOP-ART score, and achieved long-lasting disease control upon treatment with olaparib/trabectedin.

Conclusions: The TOP-ART score is a novel composite HRR biomarker developed and validated in an observational precision oncology cohort. It has the potential to broaden access to targeted treatments and is prospectively used to determine eligibility for the TOP-ART trial.

Clinical trial identification: NCT03127215 Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors (NCT-PMO-1603) Estimated Primary Completion Date: December 2023 Estimated Study Completion Date: December 2023.

Legal entity responsible for the study: The authors.

Funding: German Cancer Consortium (DKTK).

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132MO Molecular profiling of 991 prospectively recruited rare cancers patients in EUROPE: First results of ARCAGEN – an EORTC-SPECTA and EURACAN study

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Background: Within the EORTC-SPECTA platform, the ARCAGEN collaborative study between EORTC and EURACAN was initiated in June 2019 and aimed to assess the prevalence of genomic alterations, high tumor mutational burden (TMB) and microsatellite instability (MSI), as well as actionability in patients diagnosed with advanced rare cancers (defined with an incidence$<6/10^5$/y).

Methods: Patients with a rare adult solid tumor of one of the 10 domains or EURACAN in advanced phase were proposed for the ARACAGEN study as part of the SPECTA program.

Results: Within 3.5 years, 991 patients were enrolled within 14 countries in Europe, 918 were evaluable, receiving a molecular profile (92.60% success rate), with a median turn-around time of 13.25 days [range 11.5-17]. Molecular profiling was preferentially performed on FFPE material (FoundationOne, 73.5%), if not feasible, liquid biopsy was used as a rescue (FoundationOne Liquid, 26.5%). The 3 most common histotypes were cancer of unknown primary (CUP, 103, 11.2%), mesothelioma (80, 8.7%), cholangiocarcinoma (72, 7.8%). Clinically relevant molecular alterations were identified in 606 patients (66%), with top alterations seen in *TP53* (28.5% of all enrolled patients), *CDKN2A/B* (16.8%), *KRAS* (9.2%). The TMB was above 10 for 53 patients (5.3%) and 9 MSI-high patients were identified. A differential profile was seen between FFPE and blood analysis due to CHIP identification (DNMT3A, MLL2, TET2 for example). Altogether, 456 patients (46%) received a therapy recommendation based on the molecular analysis: 63 (6.8%) patients for an already approved treatment (ESCAT 1A); 232 (25.3%) for an off-label use of an approved treatment in another indication with similar molecular alteration (ESCAT IC, II or III); and 161 (17.5%) for a clinical trial. Response rate, duration of response and survival will be presented.

Conclusions: Close to 50% of patients with rare cancers received a therapeutic recommendation based on molecular characterization, a majority within clinical trials. Molecular characterization should be recommended routinely for rare cancers in advanced phase.

Clinical trial identification: SPECTA NCT02834884.

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All other authors have declared no conflicts of interest.

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133MO Differentiation of malignant and benign lung nodules using epigenetically modified nucleosomes in plasma

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Background: Recent lung cancer screening trials indicate that low-dose computed tomography (LDCT) has been successful in reducing mortality in high-risk patients. Nonetheless, the high frequency of false-positives leads to expense and possible harm, emphasizing the necessity for complementary biomarkers. To address this, we aimed to enhance the accuracy of lung cancer screening by utilizing a lung cancer-specific immunoassay panel for epigenetically modified nucleosomes in plasma to help differentiate between benign and malignant nodules.

Methods: During the years 2021 and 2022, a total of 806 individuals who had a positive result from LDCT screening and underwent surgery or biopsy were included in the study. Plasma samples from these participants were analyzed for nucleosomes containing histone modifications including H3K27Me3, H3K36Me3, or the H3.1 histone isoform by quantitative immunoassay (Nu.Q®, Belgian Volition SRL). Among these individuals, 648 were diagnosed with either lung cancer or a pre-cancerous lesion, while 158 were diagnosed with a benign lesion based on pathological reports. Logistic regression was used to analyze the assay data, and a simple algorithm was developed to predict whether a nodule was benign or malignant. The algorithm was created using samples collected in 2021 (n=561) as a training set and validated using samples collected in 2022 (n=245).

Results: The plasma epigenetic nucleosome assay for detecting lung cancer showed a diagnostic sensitivity of 92% and a specificity of 82% using a simple regression algorithm, trained on data from the 2021 group. The AUC for differentiating between cancerous and benign nodules was 88%. When the assay was applied to data from 2022, it achieved an AUC of 77% for distinguishing between cancer and benign nodules, with a sensitivity of 60% and a specificity of 84%. The validation test revealed that the algorithm correctly identified patients with stage I cancer and carcinoma in situ in 58% and 61% of cases, respectively.

Conclusions: This large validation study indicates that the epigenetic nucleosome assay has predictive, diagnostic, and prognostic value and could reduce the false-positive rate of LDCT.

Legal entity responsible for the study: The authors.

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134P TERT-associated DNA polymerases genes link CAF and CD8+ T cells to improve immunotherapy response rate across multiple cancers

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Background: Cancer cells exhibit heightened basal levels of responses to DNA breaks, accumulating DNA polymerases family (DNA-pol) as repair protein, thereby increasing DNA mutation and neoantigens. Based on this, we investigated the potential of DNA-pol as an immunotherapy biomarker and its underlying mechanism.

Methods: We conducted a pan-cancer analysis of DNA-pol gene dysregulation in 6366 samples. Normal fibroblast, cancer-associated fibroblast, and CD8+ T cells were cultured from cancer patients (3 esophagus, 5 lung, 5 renal, and 3 liver cancer), then treated them with PD-L1 inhibitor or overexpressing TERT for RNA-seq and proteomics. 996 multiple cancer cases with ICIs were collected to test biomarker efficiency. A phase II clinical trial is evaluating our biomarker prospectively.

Results: We defined a distinct signature score of DNA-pol genes upregulated in cancer (DNA-pol-up) and linked to worse prognosis (HR=1.2). DNA-pol-up program dysregulation led to immune processes alteration and was related to upstream activation of TERT signaling (z-score=3.6) in ingenuity pathway analysis and linked to immunologically active tumors by recruiting CD8+ T cell and downregulating CAF. DNA-pol-up score was elevated in PD-L1-treated CAF and TERT-overexpressed CD8+ T cell, in MSI-H cancer, also related to more neoepitope peptides, TMB (Rho=0.54), cancer stemness (Rho=0.78), and tumor purity (Rho=0.29). Cancers that activate this program carried distinct genomic profiles with PIK3CA, KRAS, and TP53 mutations. This signature was an independent predictor for ICIs response (OR=2.52), even outperforming cytolytic activity, MSI, TMB (OR=0.9). In 12 clinical trial datasets, this signature could stratify the responding patients (maxAUC=0.762). In our phase II clinical trial, 34 liver cancer were enrolled with 3-year follow-up, it also has a satisfactory performance in predicting the ORR (AUC=0.699) and classifies mortality rate (HR=2.3).

Conclusions: Our findings identify a distinct transcriptional pattern of DNA-pol genes across cancers, which highlighted the role of DNA-pol family genes in predicting the immunotherapy response for the first time, and TERT could be a novel vaccine candidate for improving immunotherapy response.

Legal entity responsible for the study: X. Bi, H. Zhao, Z. Luo.

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135P The lymphocyte stability index (LSI) forms a pan-cancer peripheral biomarker for overall survival post initiation of immune checkpoint blockade (ICB)

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Background: Robust, pan-cancer peripheral blood biomarkers for response to immune checkpoint blockade (ICB) are lacking. We have previously shown that a single nucleotide polymorphism at rs16906115 (intronic to *IL7*) associates with increased risk of ICB toxicity, but promotes increased lymphocyte count stability post-initiation of treatment. Individuals with a stable lymphocyte count had improved progression-free (PFS) and overall survival (OS) in metastatic melanoma (MM). We hypothesise that the Lymphocyte Stability Index (LSI) can predict outcome to ICB across a range of cancers.

Methods: We retrospectively collected treatment, blood count and survival data on all individuals treated with ICB since 2014 at Oxford University Hospitals NHS Foundation Trust (n=706). We performed survival analysis based on lymphocyte stability. The LSI was calculated by dividing the post-treatment lymphocyte count by the pre-treatment count.

Results: Using a replication cohort, we validated our previous finding that patients with stable LSI (>0.8) had significantly improved overall survival in MM. This was also the case for those with stable LSI and a diagnosis of non-small cell lung cancer (NSCLC) or metastatic renal cell carcinoma (mRCC) with previous pre-treatment. Using a Cox proportional hazards model to control for a range of covariates including age and number of prior treatments, a stable LSI was associated with a hazard ratio for death of 0.38 (95% CI: 0.26-0.56, p<0.0001) for MM (combined cohorts), 0.49 (95% CI: 0.33-0.77, p<0.001) for NSCLC and 0.33 (95% CI: 0.14-0.89, p=0.013) for pre-treated mRCC. Patients with MM and stable LSI treated with single-agent PD-1 blockade had equivalent survival to those treated with combination ICB.

Conclusions: The LSI is an extremely simple dynamic peripheral biomarker for survival following ICB treatment across multiple cancers with an underlying molecular and genetic association. Application of LSI in MM permits effective patient stratification, delineating those who single-agent ICB provides equivalent benefit to combination anti-PD1 and anti-CTLA-4 treatment, potentially sparing them of the associated toxicity burden.

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136P Pembrolizumab in patients of Chinese descent with microsatellite instability-high/mismatch repair deficient advanced solid tumors: KEYNOTE-158

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Background: The multicohort KEYNOTE-158 (NCT02628067) trial supported the US FDA and EMA approval of pembrolizumab across multiple microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) advanced solid tumors. The incidence of MSI-H/dMMR advanced cancer in patients (pts) of Chinese descent is similar to that reported in Western populations (Liu et al 2019, Cancer Research 79:616). In cohort L of KEYNOTE-158, we evaluated the efficacy and safety of pembrolizumab in pts of Chinese descent with MSI-H/dMMR solid tumors.

Methods: In this nonrandomized, phase 2, open-label trial, pts aged ≥ 18 years of Chinese descent were enrolled. These pts had to have confirmed MSI-H/dMMR unresectable or metastatic cancers who had ≥1 prior lines of therapy. Eligible pts received 200 mg pembrolizumab Q3W for up to 35 cycles, until progression, unacceptable toxicity, or pt/investigator withdrawal. MSI-H/dMMR status was assessed centrally by PCR or ICH. The primary endpoint was ORR per RECIST 1.1 by independent central review. Secondary endpoints were DOR, PFS, OS and safety. The database cut-off date was July 26, 2022.

Results: At data cut-off, a total of 24 pts were enrolled of which 20 pts were for efficacy evaluation having at least 6 months (mo) of follow-up. The overall ORR was 70.0% (95% CI: 45.7%- 88.1%) for the 20 pts. The median DOR was not reached (NR) (range, 2.1+ - 19.3+) with a 12-mo DOR rate of 85.7%. Median PFS was NR (95% CI: 15.8-NR) with an 18-mo PFS rate of 68.0%. The median OS was NR (95% CI: 9.5, NR) with an 18-mo OS rate of 80.2%. Treatment-related adverse events (AE) were reported in 19 (79%) of the 24 pts enrolled. Grade ≥3 treatment-related AEs occurred in 4 (17%) pts with no grade 5 AEs. Immune-mediated AEs occurred in 8 pts (33%). Of these pts, 2 (8%) had grade 3 AEs (myositis or rash in 1 pt each). No grade 4 or 5 immune-mediated AEs occurred.

Conclusions: Pembrolizumab provided clinically meaningful antitumor activity and durable responses in pts of Chinese descent with MSI-H/dMMR tumors, with a manageable safety profile. No new safety signals were identified. These results are consistent with those reported for patients in the global population.

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137P VEGFR-3 expression profiling by histology and mRNA signature to classify patient population for the selective VEGFR-3 inhibitor EVT801

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Background: EVT801 is a highly selective small molecule inhibitor of VEGFR-3 and acts by inhibiting tumor lymphangiogenesis and angiogenesis. A phase I clinical study (NCT05114668) has started to characterize safety, tolerability, pharmacokinetics of EVT801. Clinical samples from these patients will be used to explore preliminary signals of clinical efficacy and investigate the biological activity of the drug using several biomarkers. Among them, we have investigated VEGFR3 expression profiling by histology.

Methods: We validated a highly specific protocol for VEGFR-3 immunohistochemistry labelling and a VEGFR-3 mRNA signature, readily transferable to clinical centers.

Results: Initially, VEGFR-3 expression was assessed in 29 primary kidney cancer samples and 23 metastatic kidney cancer samples with CD34 to stain vessels and D2-40 to track lymphatics. We detected VEGFR-3 expression in the endothelial cells within the kidney tumor but not in the tumor cells. Remarkably, we observed a very distinct delineation between the kidney tumor vasculature, which showed high VEGFR-3 expression, and the normal adjacent tissue, which was devoid of VEGFR-3 expression. In addition, we found that VEGFR-3 expression in metastases from kidney tumors matched the expression pattern of the primary tumor. Then, We have demonstrated that it exists a strong correlation between VEGFR-3 expression by histology and VEGFR-3 mRNA signature. We applied both VEGFR-3 signatures in different indications of interest like soft tissue sarcomas and lung cancers.

Conclusions: We were able to quantify VEGFR-3 expression by histology and mRNA signature in the kidney and soft tissue sarcoma cohorts plus several others, such as

hepatocarcinoma and non-small cell lung cancer. This enables us to select indications that might benefit from EVT801 as a monotherapy (e.g., clear cell renal cell carcinoma and soft tissue sarcomas) or in combination with standard of care. Accordingly, VEGFR-3 expression is retrospectively quantified during the EVT801 phase 1 clinical trial and may be used to stratify patients in the future.

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138P Precision medicine phase II study evaluating the efficacy of olaparib in patients with progressive solid cancers and carriers of homologous recombination repair genes alterations

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Background: The improved understanding of the biological mechanisms of the homologous recombination repair and the emergence of PARP inhibitors has opened new therapeutic options for patients with progressive cancers on standard treatments. The MOST study was designed to treat patients with metastatic solid tumors according to specific molecular alterations. We present here the results of the olaparib cohort.

Methods: The MOST trial is an ongoing multicenter, prospective, randomized study conducted in six French university hospitals. Patients known to have germline or somatic alterations in the homologous recombination genes received olaparib (300mg, BID) outside standard recommendations, until disease progression, unacceptable toxicity, patient's or investigator's decision. Disease response was evaluated at 12 weeks of treatment per RECIST criteria.

Results: Amongst the 213 included patients (63.4% female, median age: 58 years [26-85], median number of prior lines of treatment: 3 [1-16]) e.g. platinium 63%), the main initial tumor sites were breast (25.8%), pancreas (19.2%), colorectal (7.5%), sarcoma (6.1%) and brain (5.2%). Tumor response after 12 weeks (W12) according to main HRD genes altered (>5%) are presented in table. Patients with PALB2 mutations showed the best disease control rate. Grade 3 or higher adverse events were reported in 81 patients (38%).

Table: 138P Tumor status at week 12 for the main molecular alterations (>5%)

Tumor status	CR or PR	SD	PD	Treatment discontinuation
All patients (n=213)	n=14 (6%)	n =34 (16%)	n=161 (76%)	n=4 (2%)
Gene altered, N (% of population)				
BRCA1, N = 26 (12.2%)	0 (0.0%)	3 (11.5%)	23 (88.5%)	0 (0.0%)
BRCA2 N= 49 (23%)	8 (16.3%)	5 (10.2%)	36 (73.5%)	0 (0.0%)
PALB2 N= 15 (7%)	4 (26.6%)	2 (13.3%)	8 (53.3%)	1 (6.6%)
ATM N= 49 (23%)	1 (2%)	11 (22.4%)	37 (75.5%)	0 (0.0%)
BAP1 N= 14 (6.6%)	1 (7.1%)	3 (21.4%)	10 (71.4%)	0 (0.0%)

CR/PR/SD/PD according to RECIST. Treatment discontinuation before W12 was due to toxicity or patient decision.

Conclusions: Overall, only a minority of patients benefit from olaparib treatment after 12 weeks of treatment even though their tumor harbor HRD gene alterations, with a 3-month PFS rate of 23% (48/213). Translational research is ongoing to explore which genomic signature is associated with olaparib response.

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139P The characteristics in Chinese NSCLC patients with different BRAF mutation classes

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Background: Compared with *BRAF* Class II and Class III mutations in non-small cell lung cancer (NSCLC), *BRAF* Class I mutations can be effectively targeted by inhibitors. However, the characteristics of Chinese NSCLC with different *BRAF* mutation types are still unclear. Thus, the more comprehensive exploration of *BRAF* mutation profile in Chinese NSCLC was investigated to guide the development of personalized treatment strategies.

Methods: Data was collected on a total of 2,030 cases of NSCLC throughout China between October 2018 and October 2021. Next Generation Sequencing (NGS) is based on the sequencing of tissue samples on the YUANSU™ panel (OrigiMed, Shanghai, China) with 706 cancer-related genes. Wilcoxon Rank Sum Test were applied to significance statistics.

Results: Among the samples, *BRAF* mutations were detected in 82 cases (4.0%, 82/2030), including 19 Class I (0.9%, 19/2030, V600E), 13 Class II (0.6%, 13/2030, K601E, L597R/Q, G464V, G469A/V), and 11 cases Class III (0.5%, 11/2030, G466A/E, N581I, D594G/N). In addition, 39 cases (1.9%, 39/2030) remained unclassified: 22 (1.0%, 22/2030) with potential significance. The *BRAF* mutations were more commonly observed in primary tumors (p=0.066) and the Class I mutations were more prevalent in female patients (63.2%, 12/19, p=0.005). In addition, the median TMB (7.21 mut/Mb) of Class I mutations tumor was significantly lower than that of Class II mutations (median TMB =12.69 mut/Mb), III mutations (median TMB =22.32 mut/Mb) and unclassified BRAF mutations (median TMB =10.33 mut/Mb)(p = 0.033), implying that the patients with Class I mutations may not be suitable for immunotherapy compared with patients with Class II and III mutations. Furthermore, *TP53*, *LRP1B*, *STK11*, *SPTA1*and *MAGI2* were significantly over-mutated in Class II and III ($p<0.06$) and *SETD2* is over-mutated in Class I ($p<0.001$), might suggesting relatively poor prognosis in NSCLC patients.

Conclusions: The characteristics of Chinese NSCLC were further explored, including BRAF mutation types, the incidence of related co-mutations and TMB value, which is helpful to formulate targeted therapy strategies to adapt to different types of *BRAF* mutation functions according to their genomic and clinical characteristics.

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140P Colorectal adenoma subtypes exhibit distinct molecular profiles- implications to early detection

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Background: Colorectal adenomas (AA) are pre-cursors for 85% of the cancers. Methylation and copy-number alterations are well described in colorectal cancer (CRC) context. We aimed to investigate these signals on AA sub-types.

Methods: Whole-genome Enzymatic Sequencing was performed on advanced adenoma (AA) and adjacent control (CNT) tissues of serrated (14), tubular (26), tubulovillous (24) and villous (10) patient samples, alongside colorectal cancer (CRC) stage I samples (23). Differential methylation analysis pipeline was applied, first to identify regions that are significantly altered between all AA subgroups and CNT tissue and then further investigated for sub-type and CRC I level differences. Additionally, mutation and copy-number alteration (CNA) detection were performed, alongside pathway enrichment.

Results: Initial differential methylation analysis revealed 7725 regions significantly altered between AA and CNT tissue. 137 and 2093 and 91 of those were

hypermethylated between serrated vs tubular, serrated vs tubulovillous, tubular vs tubulovillous sub-types respectively. Main pathways, differentiating serrated adenomas from the rest, belong to cAMP signalling, regulation of pluripotency of stem cells, while regions separating tubular and tubulovillous were enriched for WNT signalling. These differential signals could not be seen in stage I CRC samples, which presented CNT-like methylation. The CNA signals were mostly present in tubular or tubulovillous samples. The most frequent signals could be seen in chr7, 12, 19 and 20. Majority of CRC I exhibited CNA in chr 7, 8 and 20, indicating difference processes to be in place between AA and CRC I progression. Differences could also be observed on sub-type level, when looking at tumour mutational burden and specific mutations in APC and KRAS genes.

Conclusions: Colorectal adenoma histological subtypes show distinctly different methylation, CNA and mutational signals, between groups and compared CRC I. These findings are especially important when developing early detection or cancer prevention tests trying to capture adenoma (sub-type level) signatures. These results have been followed by plasma-based biomarker detection studies for pre-cancer screening intent.

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141P Microsatellite instability and its relationship with systemic inflammation as prognostic factors in localised colorectal cancer

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Background: Microsatellite instability-high (MSI-H) is a well-known favorable prognostic marker in localized colorectal cancer (CRC) patients, mainly due to local anti-tumor immunity of cytotoxic T cells. The tumor-induced systemic inflammation is also proven to be responsible for pro-tumor immunity. Despite the importance of tumor microenvironment, the relationships between MSI status, systemic inflammation, and their prognostic effects in CRC patients have not been widely studied.

Methods: We retrospectively analyzed a total of 1130 patients who had diagnosed as stage I to III CRC and had surgical resection from Jan 2007 to Oct 2016 at Gil Medical Center in South Korea. MSI status was evaluated by polymerase-chain reaction (PCR) of mononucleotide repeats. Neutrophil-lymphocyte ratio (NLR), from the blood cell count drawn before any treatment, was used to represent systemic inflammation. Univariable and multivariable analysis were performed with Cox's proportional hazard model to identify prognostic factors in localized CRC patients.

Results: Among 1130 patients of stage I to III CRC, 84 (7.4%) patients had MSI-H CRC, and the majority of MSI-H CRCs were found in stage II patients (12.2%, n=46/378). MSI-H was significantly associated with high NLR (20.2% vs 7.4%, $p<0.001$) as well as right-sided (67.4% vs 20.9%, $p<0.001$), poorly differentiated (17.4% vs 2.8%, $p<0.001$), less perineural invasion (11.6% vs 22.4%, p=0.020), and low BMI (5.8% vs 14.3%, p=0.028). Combining MSI and NLR, MSS/NLR$\geq$5 group showed worst PFS and OS consistently throughout stage I to III (p=0.017). Interestingly, MSI-H/NLR$\geq$5 group showed worse PFS and OS than MSS/NLR$<$5 group in stage II patients (p=0.006). In multivariable analysis, MSS/NLR$\geq$5 group was related significantly with poor PFS (HR 4.19, 95% CI 1.37-12.83, p=0.012), and showed a trend toward poor OS (HR 4.42, 95% CI 0.84-23.11, p=0.079).

Conclusions: MSI-H was significantly associated with high NLR, and its prognostic effect outweighed that of MSI-H, especially in stage II CRC. Therefore, we should consider more about factors of tumor microenvironment such as high NLR, as one of criteria to classify high-risk stage II CRC, which needs adjuvant chemotherapy.

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142P Correlating total tumor volume on CT-Scan and liquid biopsy ctDNA in 1017 patients with metastatic cancer: A novel study

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Background: Liquid biopsy is an emerging technology capable of detecting cancer, while CT-imaging is the gold standard. We aim to correlate imaging features from CT-scans to liquid biopsy ctDNA tumor fraction (TF) and blood Tumor Mutational Burden (bTMB).

Methods: This retrospective multicentric study included 1017 patients with metastatic cancer who underwent a variety of treatments. Liquid biopsy and contemporaneous CT-scans were collected. TF and bTMB values were computed using FoundationOne Liquid CDX solution by Roche, with high tumor fraction being over 10%. Two expert radiologists outlined all cancerous lesions in the largest axial diameter. Total tumor volume (TTV) was defined as the sum of estimated lesion volumes. Training set consisted of data from several imaging centers, while the validation set was single-center. Continuous value distributions by category were tested using the Mann-Whitney U-test, and a threshold was set with ROC curve analysis using Youden's Index. This cutoff defined high and low groups, and a X^2 test of independence was used to examine the correlation. Sensitivity and specificity were reported with imaging features taken as the gold standard. Subanalyses were run on patients with liver lesions.

Results: Overall, 55294 lesions were annotated, most commonly located in the lung (n=20074), liver (n=11297) and lymph nodes (n=10222). The train and validation sets included 599 and 418 patients. Preliminary analyses were performed on the train set. Patients with low TF had significantly less TTV than those with high TF ($p<0.001$). ROC analysis yielded an AUC of 0.63 with a threshold of 106 cm3. Correlation was significant between TTV and TF categories (X^2 test: $p<0.001$). The sensitivity and specificity were 76% and 42%. For patients with liver lesions (n=253) , TTV threshold was 108 cm3 with an AUC of 0.66. Correlation was significant between TTV and TF categories (X^2 test: $p<0.001$). The sensitivity and specificity were 82% and 42%.

Conclusions: Analysis showed significant correlation between TTV and ctDNA TF. Sensitivity was higher for patients with liver lesions, suggesting that some organs shed tumoral DNA more than others. The study of tumor heterogeneity on imaging and its correlation to bTMB is in progress.

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143P Is liquid biopsy a good tool for microsatellite instability (MSI) assessment in solid tumors?

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Background: Within the last decade, immunotherapy revolutionized cancer treatment and patients (pts) prognosis. MSI is a validated biomarker of response to immune checkpoint blockers (ICB). In daily practice, Immunohistochemistry (IHC) and polymerase chain reaction (PCR) are the most recommended techniques for MSI detection. Lately, next generation sequencing (NGS) performed on liquid biopsy emerged as a new tool for MSI detection and can be used as an alternative to IHC/PCR analysis on tissue. We aim to describe the characteristics of a cohort of pts with MSI solid tumors detected by liquid biopsy and to evaluate the concordance with IHC and NGS testing.

Methods: Data was collected from medical records and molecular profile reports (Foundation One Liquid CDx Assay — 324 genes) performed within the STING trial (NCT04932525) between June 2021 and April 2023.

Results: Among 4535 pts who underwent liquid biopsies, we found 1.5% (n=70) pts with a MSI positive status. The main characteristics were: 51% (n=36) were male with a median age of 68 years [32-89]. 24% of pts (n=17) had a known Lynch Syndrome. Most common tumor locations were colorectal (23%) and endometrial (16%). Median tumor fraction was 26% [10%-73%] and median tumor mutational burden (TMB) 113

mut/Mb [4-1450]. 40% (n=28) of pts had MSI positive tumor assessed by IHC and 55% (n=39) by NGS, with a concordance of 41%. A proportion of 58% (n=41) received ICB for advanced disease; pembrolizumab was the most frequent ICB administered and 66% (n=27) had received a median of 3 [1-8] prior lines of cytotoxic drugs. Median progression free survival (PFS) for concordant MSI status was 25 months (m) vs 9 m for non-concordant MSI (p=0.03), respectively.

Conclusions: MSI concordance on liquid biopsy with MSI on tumor were considerably lower than reported in the literature. However, PFS was better in pts with a concordant status than those with either MSI/IHC or MSI/NGS alone or in tissue.

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144P Artificial intelligence supported treatment decisions for precision oncology

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Background: Clinical interpretation of complex biomarkers for personalized treatment decisions requires extensive manual investigations of literature and databases. Recent progress in artificial intelligence (AI) and conversational large language models (LLM) suggests that these might be useful for assisting with automated screening and integration of large biomedical datasets. To better define their role in this application, we investigated several recent LLM as a support tool for precision oncology.

Methods: We generated ten fictional cases of patients with advanced cancers and genetic alterations. Each of the cases was submitted to four LLM (ChatGPT, Galactica, Perplexity, BioMedLM) and one physician as expert human annotator to identify personalized treatment options (TO). TO were blinded and presented to a molecular tumor board (MTB) if they were a) identified by a human, b) identified by more than one LLM or c) identified by a LLM and associated with clinical evidence. MTB members were asked to rate the likelihood of TO to come from an AI on a scale from 0 to 10 (0 extremely unlikely, 10 extremely likely) and to rate their usefulness.

Results: A median number of 4 and 3, 7.5, 11.5, and 13 TO per patient were identified by the human expert and four LLM, respectively. When considering the expert as gold standard, the four LLM reached median F1 scores of 0.04, 0.17, 0.14, and 0.19 over all patients combined. Combined TO by LLM reached a precision of 0.29 and a recall of 0.29 for a F1 score of 0.29 over all patients. When rated for recognizability as AI-generated, LLM-generated TO achieved a median of 8 (range 1 to 10) in contrast to 2 points (range 0 to 6) for manually annotated cases. At least one LLM-generated TO per patient was generally considered useful by MTB members. Two unique useful TO (including one unique treatment strategy) were identified only by a LLM.

Conclusions: Treatment recommendations of LLM in PO cases do not yet reach the quality and credibility of human experts. However, they can already generate useful ideas. Considering the speed of technological progress, LLM could increasingly assist with the screening and selection of relevant biomedical literature to support evidence-based, personalized treatment decisions.

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145P Identification of biomarkers of survival across multiple cancer types using eXplainable artificial intelligence

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Background: In this study, we use KEM® (Knowledge Extraction and Management) explainable Artificial Intelligence (xAI) platform to systematically explore association rules in a heterogeneous patient database accounting for above 30 cancer types and thus identify biomarkers characterizing patients with higher chances of survival. The list of candidates' biomarkers included drug scores generated by OncoKEM®, an AI-transcriptional-based therapeutic recommendation-tool that computes scores for up to 205 drugs based on the drug's transcriptional signatures and the tumor transcriptional profile. The goal was to demonstrate the biological relevance of OncoKEM® by confronting its results with the findings obtained through a standard pathway analysis.

Methods: Data was retrieved from the PROFILER study (NCT01774409), a molecular screening program, and aggregated into a consolidated database totaling 247 patients and 215,670 variables that included survival, baseline descriptors, gene expression, derived REACTOME pathway dysregulations, and OncoKEM® scores. KEM® xAI platform extracted 55,335 relations associating candidate biomarkers and survival. These results were then filtered based on Support (number of examples), Lift (relative probability) and statistical significance. The remaining relations were finally split into 2 sets to study the associations between survival and respectively pathways dysregulations or OncoKEM® scores.

Results: Our analysis first identified 4 pathway dysregulations that were associated with the overall survival (hazard ratio ranged from 2.36 to 2.80). 3 of these pathways were related to tubulin. Consistently, 4 OncoKEM® scores were then identified as associated with survival (hazard ratio ranged from 2.20 to 2.52) and all 4 corresponded to microtubule inhibitor drugs: ixabepilone, cabazitaxel, vinflunine and brentuximab vedotin.

Conclusions: Our analysis enabled the identification of biomarkers of survival across cancer types. The consistency of the findings both demonstrated the biological relevance of OncoKEM® for microtubule inhibitor drugs and paved the way for the use of this tool as a prognostic marker for refractory cancers.

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147P Non-small cell lung cancer: Artificial intelligence enables the identification of survival signatures complementary to an Immunologically active gene expression signature involving previous therapies

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Background: Non-small cell lung cancer (NSCLC) is one of the most prevalent cancers worldwide. Centre Léon Bérard, Lyon, France has developed a 27-gene expression-based HOT score that predicts outcome in patients with advanced stage treated with immunotherapy. Yet, this signature could be complemented with additional models involving a smaller set of genes. In this study, we used KEM® (Knowledge Extraction and Management) explainable Artificial Intelligence platform, a tool that systematically extracts relations within the variables of a database, to refine the HOT score, shortening the signature and improving performances.

Methods: Starting from GEO warehouse (GSE161537), 2,568 variables were aggregated into a consolidated database with 82 NSCLC patients. Analysis focused on the associations between combinations of genes, previous treatment lines and overall survival (OS): KEM® extracted 194,349 relations that were filtered on the number of involved genes, statistical significance and specificity.

Results: We identified 5 genes, DKC1, HPGD, MLPH, ABCC4 and MVP, combined into two 4-gene signatures with similar performances that predicted survival with a significant interaction between previous treatment lines and gene expression: patients who carry these signatures and that had undergone at least two treatment lines before immunotherapy showed an improved OS in both models (hazard ratio = 0.45 and 0.36). Compared to the HOT score, the number of genes retained was reduced from 27 to 4, and performances improved: balanced accuracy increases from 0.62 (HOT score) to 0.78.

Conclusions: Our analysis enabled the preliminary identification of signatures that complement the HOT score: the impact of previous lines of therapy was included into the model, the number of markers was reduced and performances increased. These findings are currently being confirmed using Cancer Research Institute iAtlas, a database that contains gene expression for over 1,100 cancer patients across five different tissue types. Specific adjustments may be required to account for differences in gene expression measurements between the training and testing tests.

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148P DESTINY-PanTumor02 study of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Exploratory biomarker analyses of HER2 expression and gene amplification in tissue and plasma

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Background: HER2 expression is prevalent in a range of solid tumors. Testing for HER2 is not routine outside breast and gastric cancers, and no HER2 assays are currently validated in all cancers. We evaluated the concordance between local and central HER2 immunohistochemistry (IHC) and between *HER2* amplification in tissue and in baseline plasma circulating tumor DNA (ctDNA).

Methods: In this open-label, multicenter, multicohort, phase 2 study (NCT04482309), T-DXd (5.4 mg/kg q3w) was evaluated in pts with HER2-expressing (IHC 2+/3+ by local or central testing) locally advanced or metastatic disease after ≥1 systemic Tx or without Tx options. HER2 IHC status was assessed centrally using HER2 HercepTest™ (DAKO) and scored according to gastric-specific criteria. *HER2* amplification was evaluated centrally using Ventana dual in situ hybridization (ISH) on archival tissue and detected in baseline plasma ctDNA using Guardant Health OMNI assay.

Results: Agreement between local and central HER2 IHC score was 59% for IHC 3+ and 55% for IHC 2+. *HER2* amplification was 35% by ISH and 18% by ctDNA. The table shows concordance between HER2 status by ISH or IHC and ctDNA; agreement with *HER2* focal amplification detected in plasma was 42% and 39%, respectively.

Table: 148P

Plasma *HER2amp*	Central ISH: HER2 ISH+	HER2 ISH-	N/A	Total
Detected	32	7	9	48
Not detected	44	136	32	212
N/A	2	2	3	7
Total	78	145	44	267
	PPA (95% CI): 42% (31–54%)	**NPA (95% CI): 95% (90–98%)**		

Plasma *HER2amp*	Central HER2* status: HER2+	HER2-	N/A	Total
Detected	35	7	6	48
Not detected	54	140	18	212
N/A	3	2	2	7
Total	92	149	26	267
	PPA (95% CI): 39% (29–50%)	**NPA (95% CI): 95% (90–98%)**		

*HER2+: IHC3+ and IHC2+/ISH+
HER2-: IHC2+/ISH- and IHC1+/0
PPA and NPA were calculated excluding N/A samples (failed/unprofiled/undetectable ctDNA); CI calculated using Clopper-Pearson method CI, confidence interval; *HER2*-amp, focal *HER2* amplification; N/A, not available; NPA, negative percent agreement; PPA, positive percentage agreement

Conclusions: The moderate concordance between local and central HER2 IHC results can be ascribed to multiple factors, including different assays/algorithms, tumor heterogeneity, and inter-pathologist variability, highlighting the need for a standardized method to score HER2 across indications. Detection of *HER2* amplification in plasma was accurate, as indicated by the low rate of false positives; however, sensitivity was poor. This suggests that ctDNA testing may help identify pts with *HER2* amplification but is not yet a substitute for tissue-based HER2 ISH and IHC testing.

Clinical trial identification: NCT04482309.

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149P Assessing the effect of single dose trastuzumab and pertuzumab (HP) on biological changes and pathological complete response (pCR) in ERBB2+ Breast Cancer: Results from the neoadjuvant BionHER study

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Background: HER2 blockade in ERBB2+ BC can boost the immune system and inhibit cell proliferation and survival. Here, we aimed to identify early molecular changes following a single dose of HP and its association with subsequent pCR following neoadjuvant HP-based chemotherapy.

Methods: Patients (pts) with stage I-III ERBB2+BC were treated with neoadjuvant pertuzumab+trastuzumab+paclitaxel (THP)x16w. Paired tumor biopsies were obtained at baseline (D1) and at day 8 (D8) following a loading-dose of HP, prior to weekly paclitaxel addition. HER2DX gene expression signatures and the expression of 185 genes were evaluated in both timepoints. Paired SAM analyses (FDR<5%) and t-tests determined significant changes between D1-D8. Logistic regression analyses identified associations with pCR (ypT0/isN0).

Results: Gene expression was evaluated in paired samples in 49 out of 52 pts (94%). cT1-2 disease represented 85% of cases, cN0 59%, and 67% were HR+. The overall pCR rate was 45.6% and 55.3% when ypT1miN0 was considered. In all pts, HP induced a significant decrease in HER2DX proliferation, HER2 amplicon, pCR, risk and *ERBB2* scores, and in 81 (43.8%) genes including *KRT18, SPDEF, MUCL1* or *FOXA1;* and a significant increase in the HER2DX IGG signature and 84 (45.4%) genes including *GPNMB, CD68, CD86* or *CD4*. At D8, the HER2DX IGG signature (p=0.002) and 61 (33.0%) genes including *LY9* (p<0.001), *CD8A* (p<0.001), *CD27* (p<0.001) or *GZMA* (p<0.001) were significantly associated with pCR. At D1, pCR rates in HER2DX IGG-high, medium and low were 71.4%, 22.2% and 25.0%, respectively. At D8, pCR rates in HER2DX IGG-high, medium and low were 81.0%, 33.3% and 6.3%, respectively. The ratio between D8 and D1 of HER2DX pCR (p=0.006) and risk (p=0.026) scores and 38 (20.5%) genes including *S100A9* (p=0.006), *TRPV6* (p=0.008), *GPNMB* (p=0.013) or *LY9* (p=0.016) were significantly associated with pCR.

Conclusions: In early-stage ERBB2+ BC, a single dose of HP induces significant biological changes that may better predict pCR. At day 8, pts with high expression of HER2DX immune signature and immune-related genes have a higher probability of achieving a pCR following THP.

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150P Validation of a genomic assay in early-stage HER2+ breast cancer (BC) treated with trastuzumab and pertuzumab (HP): A correlative analysis from PHERGain phase II trial

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Background: HER2DX is a prognostic (risk-score) and predictive (pathological complete response [pCR]-score) genomic assay in early-stage HER2+ BC. Here, we evaluated the ability of HER2DX following (neo)adjuvant HP-based therapy.

Methods: HER2DX was evaluated on baseline FFPE tumors from PHERGain (NCT03161353). Patients (pts) with newly diagnosed stage I-IIIA HER2+ BC and PET evaluable lesions were randomized (1:4) to receive either docetaxel (T), carboplatin (C), and HP (group A) or HP ± endocrine therapy (ET) (group B). PET was performed prior to randomization and after 2 cycles. Group A received TCHPx6 regardless of on treatment PET response. Group B received HP ± ETx2 and PET-responder (RX) pts continued with HP ± ETx6, while PET-non-RX pts received TCHPx6. After surgery, PET-RX without a pCR received TCHPx6. All pts completed HPx18. Primary objective was the association of HER2DX with pCR (ypT0/is ypN0). Secondary objective was the association of HER2DX risk-score with invasive disease-free survival (iDFS).

Results: HER2DX was evaluated in 292 (82.0%) pts. Clinical T2-4 and node-negative disease represented 84.6% and 49.3%, respectively, and 66.4% of tumors were hormone receptor (HR) positive. The overall pCR rate was 38.0% (56.4% in group A and 33.8% in group B). In the multivariable analysis, HER2DX pCR-score (as a continuous variable) was significantly associated with pCR (odds ratio [OR] per 10-unit increase=1.29 (1.5-1.8), p<0.001), after adjusting for treatment and clinicopathological factors such as HR status, treatment group, or PET response. In the overall population, the pCR rates in HER2DX pCR-high, med, and low groups were 50.4%, 35.8%, and 23.2% (pCR-high vs pCR-low OR=3.37, p<0.001), respectively. HER2DX low-risk showed a numerically better 3-year iDFS than HER2DX high-risk pts (100% vs 93.5%; hazard ratio= 0.37 [0.1-1.7]) after adjusting by pCR status. Eight out of 9 pts with metastatic progression had HER2DX high-risk prognostic score.

Conclusions: HER2DX predicts pCR following neoadjuvant HP-based therapy (with or without chemotherapy) and identifies pts with a higher risk of recurrence. This assay might help individualize HP-based therapy in early HER2+ BC.

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151P Baseline circulating tumor DNA (ctDNA) biomarker analysis of patients with human epidermal growth factor receptor 2 (HER2)-overexpressing metastatic non−small cell lung cancer (NSCLC) treated with trastuzumab deruxtecan (T-DXd)

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Background: DESTINY-Lung01 (NCT03505710) showed encouraging and consistent antitumor activity for T-DXd in heavily pretreated patients with HER2-overexpressing (immunohistochemistry [IHC] 3+/2+) NSCLC. We investigated associations between baseline gene mutations using ctDNA and clinical outcomes in these patients (data cutoff, May 2021).

Methods: Among 90 patients in the DESTINY-Lung01 HER2-overexpressing cohorts, 85 had baseline ctDNA samples analyzed at Guardant Health OMNI. Activating mutations in key oncogenes (*EGFR*, *RAS*, *BRAF*) and other genes of interest at baseline were assessed for their association with clinical efficacy (objective response rate [ORR] and progression-free survival [PFS]) with T-DXd treatment (cohort 1, 6.4 mg/kg [N = 49]; cohort 1a, 5.4 mg/kg [N = 41] every 3 weeks); analyses were not adjusted for baseline characteristics.

Results: The 85 evaluable patients had an ORR of 27.1% (95% CI, 18.0-37.8) and a median PFS (mPFS) of 5.9 months (95% CI, 4.5-7.4). Activating mutations were identified in *EGFR* (15 patients [17.6%]: 7 T790M, 7 L858R, 1 S768I, 4 E746_A750del, 2 G719A), *KRAS* (20 patients [23.5%]), *NRAS* (1 patient [1.2%]), and *BRAF* (1 patient [1.2%]). 13 of the 15 patients with *EGFR*-activating mutations had prior *EGFR* tyrosine kinase inhibitor treatment. No clear effects of *EGFR*- and *RAS*-activating mutations on ORR and mPFS were observed; however, mutations in *STK11* and *KEAP1* were associated with significantly shorter mPFS (Table).

Conclusions: Baseline ctDNA analysis showed that the presence of activating mutations in *EGFR*, *KRAS*, or *NRAS* did not impact the clinical efficacy of T-DXd in patients with HER2-overexpressing NSCLC whereas mutations in *STK11* and *KEAP1* were associated with shorter mPFS. Updated results will be presented (data cutoff, December 2021).

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Table: 151P Efficacy according to mutation status

N = 85	Mut n	ORR WT % (95% CI)	ORR Mut % (95% CI)	mPFS WT Months (95% CI)	mPFS Mut Months (95% CI)
Key oncogenes					
EGFR	15	27.1 (17.2-39.1)	26.7 (7.8-55.1)	6.7 (4.5-7.5)	4.6 (1.3-NA)
RAS[a]	21	26.6 (16.3-39.1)	28.6 (11.3-52.2)	6.7 (4.2-7.5)	4.6 (1.4-NA)
Other selected genes[b]					
STK11	11	29.7 (19.7-41.5)	9.1 (0.2-41.3)	7.0 (5.4-8.3)	1.2 (0.5-2.8)
KEAP1	11	29.7 (19.7-41.5)	9.1 (0.2-41.3)	6.7 (5.4-8.3)	1.4 (0.6-2.4)
ARID2	11	29.7 (19.7-41.5)	18.2 (2.3-51.8)	6.7 (5.4-10.5)	3.1 (1.2-6.7)
LRP1B	32	26.4 (15.3-40.3)	28.1 (13.7-46.7)	7.2 (5.4-15.5)	4.2 (1.5-6.7)

Mut, mutant; WT, wild-type. [a]*KRAS*/*NRAS*. [b]Top 4 genes based on log rank test significance for PFS.

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152P Efficacy of olaparib in advanced cancers with germline or somatic tumor mutations in BRCA1, BRCA2, CHEK2 and ATM: A Belgian precision tumor-agnostic phase II study

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Background: The Belgian Precision initiative aims to maximize the implementation of tumor-agnostic NGS in patients with advanced cancer and enhance access to molecularly-guided treatment options (MGTOs). Academic tumor-agnostic basket phase 2 studies are part of this initiative. The current investigator-driven trial aimed to investigate olaparib efficacy in advanced cancers with a pathogenic or likely pathogenic mutation (germline or somatic) in a gene that plays a role in homologous recombination (HR).

Methods: Open-label multi-cohort phase 2 study that examines the efficacy of olaparib in patients with an HR gene mutation in their tumor and failed SoC. Patients with a somatic or germline mutation in the same gene define a cohort. For each cohort, a Simon minimax two-stage design was used. If a response was observed in the first 13 patients, 14 additional patients were included (type I error rate of 5% and a power of 80% when the true response rate is 20%). Here, we report the results on four completed cohorts: patients with a *BRCA1*, *BRCA2*, *CHEK2* or *ATM* mutation.

Results: The overall objective response rate across different tumor types was 11% in the *BRCA1* (N=27) and 21% in the *BRCA2* (N=27) mutated cohorts. Partial responses were seen in pancreatic cancer, gallbladder cancer, endocrine carcinoma of the pancreas and parathyroid cancer. One patient with a *BRCA2* germline mutated colon cancer has an ongoing CR with 19+ months on treatment. mPFS in responding patients is 14+ months (5-34+ months). The clinical benefit rate was 63% in the *BRCA1* and 46% in the *BRCA2* mutated cohorts. No clinical activity was observed in the ATM (N=13) and CHEK2 (N=14) cohorts. Safety data were consistent with the known profile of olaparib.

Conclusions: Olaparib showed efficacy in different cancer types harboring somatic or germline mutations in the *BRCA1/2* genes but not in *ATM* and *CHEK2*. Patients with any cancer type harboring *BRCA1/2* mutations should have access to olaparib with real-world documentation of efficacy in a retrospective register.

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153P Descriptive analysis of the location of point mutations in BRCA and the risk of breast or ovarian cancer diagnosis

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Background: Within BRCA carriers, there are data suggesting that not all alterations confer the same risk of breast or ovarian cancer. In addition, the localization of the mutation as a biomarker of response to targeted therapies such as iPARP is in the process of being validated. The distribution of mutations according to the functional domain in which they are located may be a good method for establish their role in cancer risk.

Methods: We included all carriers from the registry of the Hereditary Cancer Unit. Functional domains (dom) of BRCA1 were defined as: Really Interesting New Gene (RING) from aa 8-96; DNA-binding dom (DBD) from aa 452-1092; and BRCA1 C terminal (BRCT) from aa 1650-1863 Functional doms of BRCA2 were defined as: PALB2-BD dom from aa 21-39, RAD51-binding dom (RAD51-BD) from aa 900-2000, and DBD from aa 2459-3190.

Results: 284 carriers were located. 66% women, 55% BRCA1 mutation carriers (mc). Of these, 63% healthy carriers (hc), half of whom were women. Among the BRCA1 muts, 55% of breast cancer (bc) were associated with BRCT muts compared with 5.5% in DBD. In the BRCT dom, the mean age at diagnosis (dx) of bc was 44 years, with 35% of luminal tumors. Among hc, only 33% were older than the mean age at dx. Among the BRCA2 muts, 61% of the cases with bc were associated with the RAD51-BD dom compared to 10% in the DBD dom. In the RAD51-BD dom, the mean age at dx of bc was 51 years, with 11% of cases being Her-2 positive and 29% triple negative. Among hc, only 40% were older than the median age at dx. As for ovarian cancer, a more heterogeneous pattern was observed, although again, the doms with the most cases were BRCT and RAD51-BD.

Conclusions: The characterization of the mut population can provide data for the personalization of follow-up. In our population, the age of hc is shown as a bias for the definition of risk, so more follow-up and multicenter studies are needed to validate the results.

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Table: 153P

	BRCA 1					BRCA 2					TOTAL
	RING	DBD	BRCT	Others	Total	PALB2-BD	RAD51	DBD	Others	Total	
Healthy carrier	**3**	**21**	**41**	**38**	**103**	**2**	**55**	**5**	**19**	**81**	**184**
Breast	**1**	**2**	**20**	**13**	**36**	**1**	**17**	**3**	**7**	**28**	**64**
Ovarian	**1**	**2**	**7**	**8**	**18**	**0**	**6**	**2**	**4**	**12**	**30**
Pancreas	**0**	**0**	**1**	0	**1**	**0**	**1**	**0**	**2**	**3**	**4**
Other tumors*	**0**	**1**	**0**	0	**1**	**0**	**6**	**0**	**1**	**7**	**8**
Total	**5 (3.1%)**	**26 (16.4%)**	**69 (43.4%)**	**59 (37.1%)**	**159**	**3 (2.3%)**	**85 (64.9%)**	**10 (7.6%)**	**33 (25.2%)**	**131**	**290**
Mean age at diagnosis	**53**	**63**	**44**	**43.9**	**46**	**51**	**51**	**43**	**49**	**49**	**47**

*Other tumors: cholangiocarcinoma, medulloblastoma, urotelial, astrocitoma, cervical and melanoma, all with 1 case reported.

154P Highly sensitive serum volatolomic biomarkers for pancreatic cancer diagnosis and prognosis

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Background: Pancreatic adenocarcinoma (PAC) is one of the most lethal kinds of cancer. PAC is usually diagnosed very late, thus limiting treatment options and leading to low survival rates. Volatile organic compounds (VOCs) are final metabolism products that can be detected in a number of fluids. Our goal was to identify and validate diagnostic and prognostic PAC biomarkers in serum samples.

Methods: Twenty PAC patients and a sex/age matched control group (n=19) were recruited. A second group of 5 patients and 5 healthy volunteers was used for validation. IRB approval was provided by "Comité de Ética de Investigación con Medicamentos de La Rioja (CEImLar)" and all subjects signed the informed consent. A Varian CP-3800 gas chromatographer coupled to a Saturn 2200 ion trap mass spectrometer was used for the non-targeted analysis of VOCs. Surrogate standards were added to all serum samples, that were heated at 50°C and VOCs were collected into a 50/30 µm CAR/PDMS/DVB fiber (Supelco). Desorption was done at 250°C for 30 seconds in the injection port. MassHunter software (Agilent) was used for chromatogram processing including deconvolution of the signals.

Results: The volatolomic profile identified 433 VOCs in serum. Of these, 40 were able to distinguish cases from controls (diagnostic biomarkers). Unsupervised PCA and heatmaps, as well as supervised PLS-DA, showed a clear separation of cases vs controls. ROC curves indicated that 19 VOCs showed excellent predictive potential, with AUC $>$ 0.90. The validation cohort confirmed the predictive value of 11 VOCs. Prognostic VOCs were identified by comparing patients that survived more than one year after diagnosis with those who did not. Sixteen VOCs showed prognostic discrimination and 3 of them had ROC with AUC $>$ 0.86. Furthermore, the chemical structure of 4 of the main VOCs was confirmed by comparison with standards.

Conclusions: We have identified a panel of VOCs that correctly classify patients from controls and predict patient survival with high specificity and sensitivity. Reliable biomarkers may open the door to new technologies and the early detection of PAC.

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155P Exploring the utility of serum anti-tNASP antibodies as a screening biomarker in prostate, pancreatic, and ovarian cancer

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Background: Nuclear auto-antigenic sperm protein (NASP) is a histone chaperone and a facilitator of chromatin assembly. One of two NASP splice variants, tNASP, is specific to the testis, where it is sequestered by the blood-testis barrier and also present in cancer cells. Exposure of tNASP from the cancer cells to the immune system induces a robust humoral immune response. We hypothesized that the autoantibodies produced against tNASP may be used as a supplementary diagnostic marker for prostate, pancreatic, and ovarian cancer.

Methods: Sera from patients with pancreatic cancer (74), prostate cancer (63), and ovarian cancer (19) were tested for the presence of antibodies against tNASP using enzyme-linked immunosorbent assay (ELISA) with a recombinant tNASP fragment as bait. Correlation analysis was used to determine correlations between anti-tNASP antibody level and the age, ethnicity, TMN staging, and diagnostic marker levels (PSA in the prostate cancer and CA19-9 in pancreatic cancer).

Results: Level of anti-tNASP antibody in prostate cancer patients ranged from 426 to 3810 µg/mL and was significantly higher compared to healthy individuals ($p<0.01$). The cutoff for anti-tNASP antibody thus was established at 400 µg/mL. Combined analysis of anti-tNASP and PSA tests demonstrated that 18% of PC patients with PSA higher than 4 ng/mL had a low level of anti-tNASP antibody (false positive PSA, supported by negative biopsy); 11.4% of PC patients with PSA lower than 4 ng/mL had high levels of anti-tNASP antibodies (false negative PSA, proved histologically). Level of anti-tNASP antibody in pancreatic cancer patients ranged from 564 to 2751 µg/mL and was significantly higher compared to healthy individuals ($p<0.01$). Correlations between expression of tNASP antibody and levels of CA19-9 are not conclusive. There is a significant difference in tNASP antibody concentrations between serum from patients with ovarian cancer and serum from the control group of patients.

Conclusions: Expression of serum anti-tNASP antibody is not a specific screening marker for prostate, pancreatic, or ovarian cancer. Combined use of PSA with anti-tNASP antibody analysis reveals significant elimination of false positive and false negative PSA test results.

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156P The association between fibrotic endotypes, determined by pre-treatment serum levels of collagen metabolites, and survival outcomes in patients with pancreatic cancer

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Background: Abnormal collagen fiber architectures in tumor fibrosis affect prognosis and treatment response in pancreatic cancer (PC) patients. Increased fibrotic activity releases collagen metabolites into the bloodstream. The aim was to explore these metabolites to cluster PC patients into tumor fibrosis endotypes and evaluate overall survival (OS).

Methods: Serum was collected from patients with PC prior to chemotherapy or resection and included in the BIOPAC Study (ID: NCT03311776) (stage I (n=15), Stage II (n=201), stage III (n=164) and stage 4 (n=434)). Principal component analysis was performed on the levels of five collagen metabolites (Table) measured by ELISAs. K-means clustering was used to discover clusters and Kaplan-Meier curves and the cox proportional hazards model used to dicover associations with OS.

Table: 156P

Biomarker name	collagen metabolite
C3M	Neo-epitope of MMP-9 mediated degradation of type III collagen
PRO-C3	Released N-terminal pro-peptide of type III collagen
PRO-C5	Released C-terminal pro-peptide of type V collagen
PRO-C6	C-terminal of released C5 domain of type VI collagen α3 chain (endotrophin)
PRO-C11	Released N-terminal pro-peptide of type XI collagen

Results: Three putative endotypes (cluster A, B, C) were identified. Patients in cluster B had higher C3M, PRO-C5 and PRO-C11 levels compared to cluster A, whereas patients in cluster C had higher PRO-C3 and PRO-C6 levels compared to cluster A. Patients with endotype A had a median OS of 332 days vs. 185 and 144 days for endotype B and C ($p<0.001$). Compared to endotype A, both endotype B (HR=1.56, 95% CI 1.28−1.91, $p<0.001$) and endotype C (HR=1.69, 95% CI 1.26−2.26, $p<0.001$) were predictors of poor OS when corrected for age, sex, performance status, body mass index, diabetes, cachexia, stage, number of metastatic sites, and CA19-9.

Conclusions: Clustering of patients with PC based on five collagen-derived metabolites measured in serum identifies 3 distinct endotypes that were associated with poor OS independent of other common risk factors. These findings indicate that non-invasive collagen biomarkers can be used to identify fibrotic endotypes in patients with PC and that such endotypes may inform on patient prognostication.

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157P CLDN18 fusions rather than expression is a biomarker related to the efficacy of paclitaxel in patients with ovarian metastasis of gastric cancer

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Background: Paclitaxel inhibits cellular microtubule depolymerisation and has anti-tumor effects in patients with ovarian metastases from gastric cancer. CLDN18 is aberrantly expressed in gastric cancer and plays an important role in tumor invasion and metastasis. However, the relationship between CLDN18 and the efficacy of paclitaxel is lacking in research.

Methods: A total of 74 GC patients with ovarian metastasis treated with paclitaxel were included in the study. 65 primary gastric and 73 ovarian metastatic tumor samples were collected from the enrolled patients, including 64 pairs of matched primary gastric and metastatic ovarian tumor samples. WES was performed with a mean coverage depth of 187x (range: 108-344x) for tumor samples. Immunohistochemistry (IHC) was performed on tissue samples to detect CLDN18 expression.

Results: Of 74 patients, 41 responded to paclitaxel (the "effective" group), while 33 did not respond (the "ineffective" group). Statistical analysis revealed that mutations in RHOA ($p = 0.037$), AFF2 ($p = 0.028$), PIK3CD ($p = 0.028$), and TAF1L ($p = 0.028$) were associated with the ineffectiveness of paclitaxel treatment, while mutations in SALL4 ($p = 0.036$), CCDC105 ($p = 0.018$), and CLDN18 ($p = 0.036$) were associated with a positive response to paclitaxel treatment. IHC was performed on six CLDN18 fusion patients and twelve patients with different responses to paclitaxel. Of CLDN18 fusion patients, four were CLDN18-positive and two were CLDN18-negative, indicating that CLDN18 fusion did not correlate with CLDN18 expression. CLDN18 expression was positive in nine patients who responded to paclitaxel treatment and four patients who did not, and negative in two patients who responded and three who did not. Statistical analysis indicated that there was no significant correlation between the effect of paclitaxel treatment and the expression of CLDN18 (9/11 vs. 4/7, $p = 0.17$).

Conclusions: We have identified potential biomarkers, including CLDN18, that could predict the efficacy of paclitaxel treatment based on the differential response to treatment. We have also confirmed that CLDN18 fusion is a potential predictive biomarker for paclitaxel treatment response, independent of CLDN18 expression.

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158P In silico analysis of HER2 enriched subtype and a HER2 index based on transcriptomic data of breast cancer compared to gastric and uterine serous carcinomas

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Background: In Breast cancer (BC) PAM50 platform has identified a HER2-enriched (HER2E) subgroup with predictive and prognosis implications. Our study aimed to perform an *in-silico* analysis to confirm the prognostic role and the association of two genomic signatures (HER2E and HER2index) with the HER2 expression in gastric (GC) and Uterine serous carcinoma (USC) in comparison to BC.

Methods: We extracted clinical, transcriptomic, and proteome data of primary tumors from 3 publicly available databases: 1) TCGA-BRCA of BC (n=1095), 2) TCGA-STAD of GC (n=412), and 3) TCGA-UCEC (serous subtype) of USC (n=138). Patients were classified according to the PAM50 definition of breast cancer. Moreover, we calculated the correlation of the tumor expression profiles with the HER2 index signature (Li et al 2020). The association of the HER2-related, expression-based biomarkers with overall survival was calculated with independent Cox Proportional Hazard models, separately for each TCGA cohort.

Results: In the BC dataset, HER2E subtype was positively correlated with HER2mRNA and HER2protein (HER2p) ($p<0.001$) with a trend towards a correlation with HER2phospoprotein (pp). HER2 index in BC was correlated with HER2pp ($p<0.001$) and non-signifcantly with HER2mRNA ($p=0.069$), and HER2p ($p=0.087$). Both HER2E and HER2index showed an impaired survival in BC ($p=0.032$ and $p=0.002$ respectively). In GC cohort, no correlation was found between HER2E and HER2mRNA. HER2 index was correlated only with HER2mRNA ($p<0.001$). HER2E and HER2 index were not associated with survival. For the USC cohort, HER2E and HER2index were not correlated with HER2mRNA, HER2p, or HER2p, although HER2E showed a trend towards a positive association with HER2mRNA and HER2p ($p=0.059$ and 0.053 respectively). These signatures were not prognostic in terms of PFS in the USC cohort (HER2E $p=0.284$ and HER2 index $p=0.771$).

Conclusions: HER2E subtype of PAM50 and HER2 index signatures showed significant correlations with HER2 expression and survival in BC, however when these signatures were applied to other HER2 tumors such as GC or USC the prognostic role and correlation with the HER2 protein expression is limited.

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159P Better performance of pan-claudin18 antibodies on claudin18.2 detection in gastric adenocarcinoma than claudin18.2 specific antibody

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Background: The claudin18 isoform 2 (CLDN18.2), a member of the tight junction protein family, is a highly selective target for development of novel therapies in various primary malignant tumors. Due to the interference of CLDN18.1, which is highly homologous to CLDN18.2, selection of appropriate antibodies still need to be further identified.

Methods: Expression of CLDN18.2 was evaluated in a total of 66 gastric adenocarcinoma samples by immunohistochemistry(IHC) using the pan-CLDN18 antibodies (clone 43-14A and clone MM02), which recognizes both CLDN18.2 and CLDN18.1, and the CLDN18.2-specific antibody (clone EPR19202-244). The results were further verified by qPCR and CLDN18.1-specific antibody respectively.

Results: The CLDN18.2 expression evaluated by 43-14A and MM02 showed highly consistentat in different eligibility criterions ($\geq$ 2+ membrane staining intensity in $\geq$ 40% or $\geq$ 75% of tumor cells) with 95.45% and 90.91% overall percent agreements(OPA) respectively. While EPR19202-244 showed low sensitivity (84.38%) compared with 43-14A, even after readjusting the optimal threshold according to the ROC curve and Youden index. *CLDN18*, *CLDN18.1* and *CLDN18.2* mRNAs were further measured via quantative real-time PCR and IHC for CLDN18.1 was applied. It was verified that all those samples determined to be negative for CLDN18.2 by EPR19202-244 but positive for CLDN18 by pan-CLDN18 antibodies should be identified as true positive for CLDN18.2.

Table: 159P Comparison of clone 43-14A, clone MM02, and clone EPR19202-244

		43-14A/MM02/EPR19202-244							
		+/+/+	+/+/-	+/-/-	-/+/-	-/-/+	-/+/+	**-/-/-**	**Total**
Samples		29	7	0	2	2	1	25	**66**
Samples were verified		20	5	/	2	1	0	9	**37**
qPCR	**pan-CLDN18**	19	4		2	0	/	1*	
	CLDN18.2	19	4		2	0		0	
	CLDN18.1	0	0		0	0		1*	
IHC	**CLDN18.1-specific**	0	0		0	0		0	

Note: $\geq$2+ intensity in $\geq$40% tumor cells defined as CLDN18.2-positive for 43-14A and MM02, and $\geq$2+ $\geq$25% for EPR19202-24. * : Possibly due to technical differences in qPCR and IHC

Conclusions: Our results clarify the differences between EPR19202-244, 43-14A and MM02, and suggesting a higher sensitivity and specificity of pan-claudin18 antibodies, which should be used for the dectction of CLDN18.2.

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160P Real-world practices and physician perspectives on biomarker testing and treatment patterns in patients with locally advanced unresectable or metastatic (La/m) gastric/gastroesophageal junction (G/GEJ) adenocarcinoma in the US

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Background: Human epidermal growth factor receptor 2 (HER2)-targeted therapy and immunotherapy have improved survival outcomes for patients with La/m G/GEJ adenocarcinoma. Biomarker testing for mismatch repair (MMR) or microsatellite instability (MSI), HER2, and programmed-death ligand 1 (PD-L1) is critical for determining appropriate therapy. We describe real-world data on testing and treatment patterns using the Adelphi Disease Specific Program (DSP).

Methods: Data was collected using the Adelphi's DSP, a cross-sectional survey of US physicians taken between Sept 2022 and Feb 2023. Patients included those diagnosed with La/m G/GEJ adenocarcinoma on or after Jan 2021. Current biomarker testing treatment patterns, and physician attitudes were analyzed descriptively.

Results: Of the 438 pt records received from 60 treating physicians, 338 pts (77%) had La/m G/GEJ adenocarcinoma. Most pts had de novo (85%) disease, 71% were on first-line (1L) therapy and 29% on second line. Fluorouracil-based regimens were most common in 1L. MSI/MMR testing increased over time. Regardless of disease stage, almost all physicians (97%) reported biomarker testing at initial diagnosis to be "important" to "extremely important". However, only a subset of patients had testing performed (Table): HER2 (69%), PD-L1 (51%), and MSI/MMR (44%); 18% had no biomarker testing.

Table: 160P Biomarker testing patterns

Biomarkers tested, patient n (%)	Total		Year of advanced diagnosis received					
			2021		2022		2023	
Overall	**338**		**44**		**207**		**17**	
HER2	234	(69)	24	(55)	157	(76)	11	(65)
PD-1	110	(33)	8	(18)	70	(34)	9	(53)
PD-L1	172	(51)	16	(36)	115	(56)	8	(47)
MSI/MMR IHC	148	(44)	11	(25)	103	(50)	9	(53)
VEGFR-2	54	(16)	4	(9)	34	(16)	5	(29)
CDH-1	35	(10)	3	(7)	18	(9)	5	(29)
CLDN 18.2	25	(7)	2	(5)	15	(7)	5	(29)
NTRK gene fusion	60	(18)	4	(9)	40	(19)	5	(29)
EBV	48	(14)	6	(14)	32	(15)	5	(29)
NTRK	58	(17)	4	(9)	39	(19)	5	(29)
FGFR2	61	(18)	3	(7)	40	(19)	5	(29)
FGFR2b	46	(14)	3	(7)	31	(15)	5	(29)
No biomarker/genetic tests conducted	60	(18)	9	(20)	31	(15)	5	(29)

Conclusions: This study describes potential gaps in biomarker testing in real-world practice for pts with La/m G/GEJ adenocarcinoma. Despite most physicians reporting biomarker testing to be important at the time of diagnosis, only a subset of patients had testing reported. This outcome highlights a need to understand barriers to testing in clinical practice and to establish routine testing as standard of care.

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Funding: This study, utilizing Adelphi Real World's DSPTM was sponsored by Astellas Pharma, Inc. Data collection was undertaken by Adelphi Real World as part of an independent survey, entitled the "Adelphi Real World Advanced Gastric Cancer DSP." The DSP is a wholly owned Adelphi Real World product. Astellas were one of multiple subscribers to the DSP.

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161P Biomarkers of neoadjuvant combinational therapy for locally advanced gastric or gastroesophageal junction adenocarcinoma

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Background: Gastric or gastroesophageal junction (G/GEJ) cancers is one of the most common lethal malignancies in the world. Nearly half of the G/GEJ cancers are locally advanced at diagnosis and with poor prognosis. Several clinical trials demonstrated that perioperative anti-PD-1 therapy in combination with concurrent chemoradiotherapy (cCRT) for locally advanced G/GEJ cancers could raise the pCR rate over 30%. However, the biomarkers for patients with pCR are nor clear.

Methods: 34 patients with locally advanced G/GEJ cancer received neoadjuvant sintilimab in combination with cCRT followed by gastrectomy and adjuvant sintilimab and chemotherapy in our center. Baseline tumor biopsies and post-treatment surgical tissues were collected for multiplex immunofluorescence (mIF), next-generation sequencing (NGS) and mass cytometry (CyTOF).

Results: Our results met the pre-specified primary endpoint, with a pCR rate of 38.2% and median DFS of 17.0 months. Biomarker analysis by mIF showed that patients with positive PD-L1 expression showed a numerically higher pCR rate. Also, higher levels of infiltrating $CD3^+$ T cells, $CD4^+$ T cells, and $CD56^+$ natural killers (NKs) were found in patients achieving pCR than those not achieving pCR (non-pCR). Moreover, the proportion of $CD127^+CD27^+$HLA-DR^-CD38^-CD4 TCM defined by CyTOF was significantly lower in pCR patients. Also, tumor mutation burden (TMB) analyzed by NGS was significantly higher in the pCR group. Clone evolution can explain the therapy efficacy, and could be deployed to overcame therapy resistance. Deletion of cytoband 7q35, where TPK1 locates, was significantly enriched in pCR groups while deletion of 11q14.3, which TRIM family sitting, was significantly enriched in non-pCR groups.

Conclusions: It is consistent with the acknowledged prognostic biomarker of immunotherapy that positive PD-L1 expression, higher T cell infiltration and TMB could be predictive biomarkers of perioperative anti-PD-1 therapy in combination with cCRT for locally advanced G/GEJ. Furthermore, we found a new TCM subtype defined with $CD127^+CD27^+$HLA-DR^-CD38^- and deletion of cytoband 7q35 or 11q14.3 could be novel biomarkers.

Clinical trial identification: The study protocol was published previously. Wei, J. *et al.* Efficacy and Safety of Sintilimab in Combination with Concurrent Chemoradiotherapy for Locally Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (SHARED): Study Protocol of a Prospective, Multi-Center, Single-Arm Phase 2 Trial. *Cancer Manag Res* **14**, 2007-2015, https://doi.org/10.2147/CMAR.S355687 (2022).

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162P MR imaging biomarkers profiles in patients with prostate cancer treated with androgen deprivation therapy

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Background: Radiomics has emerged as a potential tool to predict clinical outcomes in prostate cancer (Pca). MRI has a fundamental role in staging and radiotherapy planning, being affected in the case of receiving prior androgen deprivation treatment (ADT). The aim of this study was to determine imaging biomarker profiles that allow to identify patients with a worse prognosis and a higher risk of biochemical relapse (BQR).

Methods: A single-center, retrospective, observational study was designed. Baseline MRIs (T2w, DWI and/or DCE sequences) from PCa patients treated with ADT and radiotherapy were included. Using Quibim's QP-Prostate ® solution, subregions (Transition + Central Zone [TZ + CZ], Peripheral zone [PZ] and seminal vesicles [SV]) were automatically segmented. For each subregion and for the whole prostate (WP), computed using the weighted biomarkers averaging, 105 radiomic features (shape and textures) from T2w, apparent diffusion coefficient (ADC) variables from DWI and perfusion parameters from DCE were extracted.

Results: A total of 128 T2w, 107 DWI and 62 DCE MRIs from 128 PCa patients (32 [25%] low or favourable intermediate risk [group 1] and 96 (75%) high or unfavourable intermediate risk [group 2]) were included, of whom 20 (16%) experienced BQR (18 [19%] from group 2). According to risk stratification, patients from group 1 presented more homogeneous textures in PZ and WP than group 2. Regarding BQR, the ADC mean was higher in the TZ in those who did not relapse, while patients with greater major axis length in the PZ, WP and SV were more likely to relapse. In SV and WP heterogenicity-related feature values were significantly higher in BQR. In group 2, diffusion parameters and shape variables in the SV were significantly different in those experiencing BQR.

Conclusions: Imaging biomarker profiles in this PCa population may help to better stratify patients at risk based on baseline MRIs. High-risk patients may be identified by the heterogeneity of textures. Diffusion and texture parameters may determine a higher probability of relapse.

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163P Genomic alterations in circulating tumor DNA (ctDNA) and response to ABBV-400 treatment in patients with advanced solid tumors

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Background: Several solid tumors, including colorectal cancer (CRC), overexpress c-Met. The antibody-drug conjugate ABBV-400 comprises the c-Met—targeting antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor payload. ABBV-400 is being evaluated in a phase 1 trial (NCT05029882) in patients (pts) with advanced solid tumors. We analyzed correlations between genomic alterations and response of pts in this study.

Methods: Adults with advanced solid tumors and no validated treatment option were enrolled. Intravenous ABBV-400 was administered once every 3 weeks. ctDNA was isolated from plasma and analyzed using the GuardantINFINITY™ assay that evaluated various parameters including single-nucleotide variants and insertion-deletion mutations (753 genes), amplifications (415 genes), tumor mutational burden (TMB), and microsatellite instability (MSI) status. Molecular response (based on ctDNA variant allele frequencies) and radiographic response (RECIST v1.1) were assessed.

Results: As of 3 April 2023, 57 pts were efficacy evaluable, including 27 pts with CRC. The objective response rate was 25% (14/57; all confirmed partial responses [cPR]) in all pts and 22% in pts with CRC (6/27; all cPR). Most prevalent gene alterations were *TP53* (67%), *LRP1B* (43%), *APC* (41%), and *KRAS* (41%) mutations and *PTPRT* (45%) and *TOP1* (43%) amplifications. The table shows the correlation between response and select biomarkers (at baseline) in the 45 pts (22 CRC) who had both ctDNA and radiographic response data. A molecular response was observed in 48% (14/29) of all evaluated pts and 47% (8/17) of pts with CRC; median change from baseline tumor size was -22.5% and -20.3%, respectively.

Table: 163P Pts with molecular response and correlation between baseline biomarker status and radiographic response

	All pts		CRC pts			
N (pts with both ctDNA and radiographic response data)	45		22			
Pts with confirmed PR, n/N (%)	11/45 (24)		4/22 (18)			
Pts with molecular response, n/N (%)	14/29[a] (48)		8/17[b] (47)			
	High TMB	High MSI	High TMB	High MSI	*KRAS* mut	*BRAF* mut
Pts with confirmed PR with biomarker positivity, n/N (%)	3/20 (15)	0/3 (0)	3/13 (23)	0/1 (0)	2/16 (13)	1/3 (33)

[a]29 pts were evaluable for molecular response. [b]17 CRC pts were evaluable for molecular response. CRC, colorectal cancer; MSI, microsatellite instability; mut, mutations; PR, partial response; pts, patients; TMB, tumor mutational burden.

Conclusions: ABBV-400 showed promising preliminary efficacy, with molecular and radiographic responses in pts with advanced solid tumors with heterogeneous genomic profiles, including in pts with high TMB and *KRAS* mutations.

Clinical trial identification: NCT05029882.

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164P Early evaluation of effectiveness and cost-effectiveness of ctDNA-guided selection for adjuvant chemotherapy in stage II colon cancer

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Background: After curative surgery for stage II colon cancer (CC-II), only patients with high-risk features (pT4 tumor and MSS status) are offered adjuvant chemotherapy (ACT) in the Netherlands. Nevertheless, 15% of CC-II patients develop a recurrence. Post-operative circulating tumor DNA (ctDNA) is a prognostic biomarker that could improve selection of patients that may benefit from ACT. We performed an early evaluation of the effectiveness and cost-effectiveness of ctDNA-guided selection for ACT in CC-II in the Netherlands.

Methods: The validated PATTERN model, which simulates the course of disease from diagnosis till death in CC-II, was supplemented with data on the prognostic value of ctDNA from the Dutch PLCRC-MEDOCC study. Five strategies for selecting patients for ACT were evaluated: current guideline strategy (pT4 and MSS), ctDNA-only strategy, and three combination strategies of ctDNA in addition to pT4 and MSS status. For each strategy, we estimated costs, (quality-adjusted) life-years (QALYs), recurrences and CC deaths. The impact of uncertainty concerning strategy adherence, treatment effect of ACT, costs of ctDNA testing, and test performance on cost-effectiveness was assessed in sensitivity analyses.

Results: Model predictions showed that the ctDNA-only strategy was less effective (more recurrences, less QALYs) and that the combination strategies were more effective (less recurrences, more QALYs) than the current guideline strategy. From the viewpoint of cost-effectiveness, using a willingness-to-pay threshold of €50.000/QALY, the current guideline strategy was most favorable. Sensitivity analyses showed that the combination strategies could be cost-effective if the costs of ctDNA testing are lower than €1500, and/or if ACT is more effective in ctDNA+ than in ctDNA- patients. Improved ctDNA test had limited impact on the cost-effectiveness.

Conclusions: Selecting patients based on ctDNA status in addition to pT4 and MSS status for ACT can improve patient selection in terms of effectiveness, and can also potentially become a cost-effective strategy. However, more research is needed to investigate the prognostic and predictive value of ctDNA to accurately evaluate the (cost)effectiveness.

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165P Correlation between trophoblast cell-surface antigen-2 (Trop-2) expression and pathological complete response (pCR) in HER2-positive early breast cancer (EBC): A sub analysis of PHERGain trial

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Background: Trop-2 is a transmembrane calcium signal transducer widely expressed in multiple tumor types on the membrane surface of epithelial cells. Antibody-drug conjugates targeting Trop-2 are currently being developed for the treatment of breast cancer. However, there is little data regarding the therapeutic implications of Trop-2 expression in HER2-positive breast cancer.

Methods: Trop-2 expression, as determined by immunohistochemistry (IHC) and its relationship with clinicopathologic features and pCR, was retrospectively analyzed in patients (pts) with HER2-positive EBC treated with upfront neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab in the PHERGain study (Pérez-García et al, Lancet Oncol 2021). Trop-2 expression was classified into low, medium, and high groups according to a histochemical score (H-score) based on staining intensity and percentage of stained cells.

Results: A total of 41 pts were included. Of these, 31.7% (13/41) had node-positive disease and 63.4% (26/41) were estrogen receptor-positive. 68.3% (28/41) of the tumors showed Trop-2 expression (low [29.3%]; medium [17.1%]; and high [21.9%]). No relationship was found between Trop-2 expression and different clinicopathologic features, but there was a trend toward higher progesterone receptor negativity among Trop-2-expressing tumors ($p = 0.098$). pCR was achieved in 63.4% (26/41) of the pts. According to Trop-2 expression, pCR rates were 50.0% (14/28) and 92.3% (12/13) in pts with and without Trop-2 expression, respectively ($p=0.015$).

Conclusions: Trop-2 expression by IHC was identified in approximately two thirds of HER2-positive EBC pts. Trop-2 appears to be a potential mechanism of resistance in this patient population and may become a strategic target for future combinations.

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166P Metabolomic prediction of breast cancer treatment toxicities

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Background: Long term treatment related toxicity is a major issue for breast cancer patients in the adjuvant setting. Predicting toxicities may allow us to adapt the treatment strategy. We assessed whether the metabolomic profile of patients may predict long-term toxicities.

Methods: High-resolution untargeted metabolomics was performed at baseline for 857 ER-positive, HER2- breast cancer patients from the CANTO prospective cohort. Four metabolomic profiles per patient were produced: (i) shared and annotated metabolites (n=224), (ii) annotated but not always common metabolites (n=456), (iii) annotated but not always shared metabolites (n=766) and (iv) all metabolites (n=1693, *FullMet*). Samples were split into a discovery and validation set. We benchmarked algorithms adapted for high dimensional analysis (LASSO, Adaptive LASSO, machine learning, and deep learning) in order to select best models for prediction.

Results: 30.0% of patients were >65 years old, 24.4% <50 years old, 20.4% had BMI>30, 12.7% had previous history of neurological disorders, 6.1% had diabetes. 69.6% presented with pT1, 25.7% with pT2 and 3.4% with pT3; 11.1% had lymph node involvement. Among all benchmarked, adaptive LASSO was the most interesting statistical method with limited optimism bias. It also allows the selection of a subset of metabolites of particular interest. The addition of rare metabolites as well as non-annotated metabolites significantly increase the predictive power of models. Metabolic toxicity prediction mainly relied on endogenous metabolites while neurological toxicities were partly predicted using exogenous/environmental metabolites. In the validation set, compared to clinical data alone (AUC 0.50-0.54), addition of metabolomics data shows moderate (AUC = 0.55-0.60) but significant ($p<0.05$ adjusted for multiple comparison) predictive ability for neurological and metabolic toxicities.

Conclusions: Breast cancer patient metabolomic profile at baseline improves toxicity prediction after adjuvant chemotherapy, similar to what is reported for genomic fingerprints. Untargeted metabolomics allows the achievement of higher performance by taking into account environmental exposure, metabolites linked to microbiota as well as rare and uncommon metabolites.

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167P A tumor immune microenvironment-based model for prediction of everolimus efficacy in premenopausal women with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Preliminary results from MIRACLE trial

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Background: Everolimus (EVE), a mammalian target of rapamycin (mTOR) inhibitor, has been proven beneficial for patients with $HR^+/HER2^-$, advanced breast cancer (ABC) with endocrine resistance. Preclinical studies showed mTOR has close relationships with the tumor immune microenvironment (TME). Therefore, this study aimed to identify TME-related markers to predict efficacy of EVE in patients with $HR^+/HER2^-$ ABC.

Methods: Tumor tissues of patients from Miracle trial receiving EVE were collected for NanoString RNA expression analysis. TME cell type and TME signatures associated with efficacy were identified using the 289-immuno-gene panel of NanoString nCounter platform. Multiple statistical approaches were applied for enrichment analyses, survival estimation and validation.

Results: Mast cell scores significantly increased in patients who did not respond to EVE ($P = 0.031$) and those who had progression-free survival (PFS) < 6 months ($P = 0.029$). CD8 T cells were highly infiltrated in tumor tissue from patients with PFS < 1 year ($P = 0.035$). Patients with PFS > 1 year had lower scores of chemokines ($P = 0.032$) and Teff ($P = 0.028$) than those with PFS < 6 months did. Histidine decarboxylase (HDC), TNF receptor superfamily member 1A (TNFRSF1A), and RAD51 correlated with PFS and EVE response. Patients with HDC ($P = 0.013$) or TNFRSF1A ($P = 0.0031$) overexpression showed shorter PFS, whereas patients with RAD51 overexpression showed prolonged PFS ($P = 0.049$). A predictive model comprising HDC, TNFRSF1A, and RAD51 was established, and the receiver operating characteristic curve demonstrated its superiority (AUC = 0.96). The results also showed that patients whose tumors were non-responsive to EVE ($P = 0.00021$) or whose PFS was poor ($P = 0.0025$) were at a higher risk in the model.

Conclusions: The immune-related gene model consisting of HDC, TNFRSF1A, and RAD51 could potentially predict the efficacy of EVE in premenopausal patients with $HR^+/HER2^-$ ABC with endocrine resistance, which could help stratify responders to EVE and guide the choice of EVE in clinical practice.

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168P HUWE1 inhibition has tumor suppressive effect in triple-negative breast cancer cell lines by modulating glycolytic and immune modulatory markers

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Background: The E3 ligase HUWE1 is a key regulator of the DNA damage response, transcription, autophagy, apoptosis and metabolism in a variety of cancers. Due to its pivotal role in conferring substrate specificity, HUWE1 has attracted enormous attention as a promising anticancer drug target. In this study, we have studied the role of HUWE1 in triple-negative breast cancer (TNBC) cell lines and evaluated its role on aerobic glycolysis which is upregulated in cancer cells and immune modulatory markers for their roles in immunotherapy. TNBC subtype neither express hormone receptors nor Her2/neu. TNBC are highly aggressive, with poor prognosis and no well-defined treatment regimen. Therefore, considering HUWE1 as an oncogene its role has been explored on glucose metabolism and immune modulation in TNBC cell lines.

Methods: Two TNBC cell lines i.e. MDA-MB-231 and MDA-MB-468 were used in the present study. These cell lines were treated with HUWE1 inhibitor: BI8622 for 24 h and the effect of inhibition was seen on its substrate (c-myc), aerobic glycolytic (HK-2, GLUT-1) and immune checkpoint markers (PDL-1, CD-47) using western blotting approach. Wound healing assays and clonogenic assays were also performed in BI8622 treated cells to check the effects of HUWE1 inhibition on migration and colony forming ability of TNBC cells in both the cell lines.

Results: As expected, there was a decrease in the protein expression levels of c-myc after the HUWE1 inhibition. Furthermore, there was decrease in protein expression of glycolytic markers i.e. HK-2 and GLUT-1 as well as immuno modulatory markers i.e. PDL-1 and CD-47. Additionally, the HUWE1 inhibition in TNBC cells was positively associated with the inhibition of migration and clonogenic potential.

Conclusions: In this study for the first time, we have demonstrated that HUWE1 acts as a tumor suppressor in TNBC by regulating the glucose metabolism and immune

checkpoint inhibitors. HUWE1 inhibition could functionally suppress TNBC development possibly by regulating aerobic glycolysis and immune checkpoints through c-myc.

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169P Integration of metabolomics and transcriptomics to reveal potential biomarkers associated with treatment response of neoadjuvant therapy in HER2+ breast cancer

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Background: This study aimed to explore potential indicators associated with neoadjuvant efficacy of TCbHP regime (taxane, carboplatin, trastuzumab and pertuzumab) in HER2+ breast cancer.

Methods: LC-MS and GC-MS platform-based untargeted metabolomics were performed to determine the metabolic profiles of plasma samples from HER2+ breast cancer patients, who received and completed neoadjuvant therapy (NAT) with TCbHP regime and subsequent surgery at Chongqing University Cancer Hospital. Random forest (RF) was used to establish predictive models based on pre-therapeutic metabolic traits. Transcriptome analysis was performed in available samples to identify differentially expressed genes (DEGs) before treatment. Metabolic and transcriptomic data were integrated to uncover significantly perturbed pathways potentially involved in drug resistance.

Results: From July 20, 2020 to May 28, 2021, a total of 40 HER2+ breast cancer patients with 120 plasma samples were eligible and recruited for this study. Of whom 21 (52.5%) patients achieved pCR and 19 (47.5%) achieved non-pCR. There were significant differences in plasma metabolic profiles between non-pCR and pCR groups before and during treatment. A total of 100 differential metabolites were identified between pCR and non-pCR patients at pre-therapeutic period, which were significantly enriched in 40 metabolic pathways. Four key metabolites [sophorose, N-(2-acetamido)iminodiacetic acid, taurine and 6-hydroxy-2-aminohexanoic acid] were selected by RF analysis. The AUC value to discriminate pCR and non-PCR group to NAT of the single potential metabolite or combined panel of these metabolites were more than 0.910. 18 metabolites had potential value in monitoring effect. A total of 163 DEGs were identified between biopsy tissue samples from pCR and non-pCR patients. 39 altered pathways aberrantly expressed at both metabolic and transcriptional levels.

Conclusions: Metabolomics integrated with transcriptomics analysis could assist for gaining more insights into biochemical pathophysiology and facilitate the development of novel therapeutic targets for insensitive patients.

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170P Clinical significance and functional role of GPR56 (ADGRG1) in breast cancer

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Background: The clinical significance and functional role of adhesion G protein-coupled receptors (aGPCRs) in breast cancer remain largely unknown. We aimed to comprehensively analyze the prognostic potential of aGPCRs in breast cancer, identify the key prognostic GPCRs, and comprehend their functional roles.

Methods: A total of 1593 breast patients were analyzed using RNA-seq and clinical data from four independent public datasets, including 1064 patients from TCGA, 198 from GSE7390, 327 from GSE20685, and 104 from GSE42568. We also analyzed the mutated landscape based on exome and copy number alteration data from TCGA. In addition, single-cell RNA-seq (scRNA-seq) data from three breast cancer patients from GSE198745, and data on mammary gland tissue from the Tabula Muris, were used to measure the variation of the candidate GPCRs across diverse cell types. The CellMiner database was used to examine drug sensitivity.

Results: Among the 33 aGPCRs, GPR56 was the only significant prognostic factor in all four datasets. High GPR56 expression was significantly lined to worse relapse-free survival and overall survival. GPR56 expression was higher in younger, high-grade, and triple-negative breast cancers. GPR56-related genes were involved in several pathways, including cell division, DNA replication, cell cycle, protein binding, and others. GPR56 also participated in the activation of multiple cancer signaling pathways. High GPR56 expression was correlated with higher levels of several immune cells, immune checkpoints, and immune-related scores. scRNA-seq analysis revealed that GPR56 was mainly expressed in tumor cells, tumor stem cells and endothelial cells. In normal breast tissues, GPR56 expression was higher in basal cell subsets than in luminal epithelial cell subsets, suggesting that GPR56 may interact with breast stem cells. In addition, there were some differences in the mutant landscape between the high and low GPR56 expression groups. Furthermore, GPR56 was significantly associated with sensitivity to multiple antitumor drugs.

Conclusions: GPR56 was significantly linked to the molecular pathology and prognosis of breast cancer. GPR56 may serve as a promising novel therapeutic target in breast cancer.

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171P Combined expression of MKI67, FOXC1 and PDL1 is a pan-tumor tissue-agnostic predictor of PD1/PDL1 inhibitor efficacy in metastatic renal cell cancer: Validation in checkmate 009, 010 and 025 clinical trial cohorts

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Background: Accurate prediction of PD1/PDL1 inhibitor therapeutic efficacy (TE) as well as any resultant durable clinical benefit (improved progression-free survival (PFS), overall survival (OS)) is not consistently achieved with existing biomarkers like PDL1 or tumor mutational burden(TMB). We hypothesized that a multi-marker (MM) predictive biomarker strategy that tracks plasticity using FOXC1 expression, in parallel to tumor proliferation and immune evasion, using expression of MKI67 and PDL1, respectively, may demonstrate superior TR prediction, and also enable accurate prediction of risk for hyperprogressive disease (HPD).

Methods: Metastatic renal cell carcinoma (mRCC) patients enrolled in Checkmate (CM) 009, 010 and 025 clinical trials (n=35, 168, 803) with available pre-treatment tumor RNA-Seq data (n=16, 45, 250 respectively) were analysed for FOXC1, MKI67 and PDL1 expression, and correlated with overall response rate (ORR), PFS, OS and HPD, the latter defined as time-to-treatment-failure <=2 months post-treatment initiation. Optimized biomarker cut-off values based on model area-under-curve were leave-one-out cross validated and prediction algorithms derived to predict Predicted Responders (PR) and Non-Responders (NR). The unmodified strategy was then validated in independent datasets.

Results: In CM025 ORR prediction by MM was specific to the Nivolumab arm [ITT CR %=22.5%, PR CR%=41.8%, NR CR%-3.6% OR=19.4 (4.3- 87.8)95%CI, p<0.0001, n=111] and not the Everolimus arm [ITT CR%=4.6%, PR CR%=3.3%, NR CR%= 5.4%, n=109]. This was confirmed further in combined CM009+CM010 cohorts (OR=9.63 (0.98-94.54) 95%CI, p=0.03). MM-predicted PR consistently displayed superior PFS (p<0.0001) and OS (p=0.03) compared to predicted NR who displayed either Progressive Disease or Hyperprogressive Disease, and were superior to results with PDL1.

Conclusions: Tracking multiple dimensions of cancer biology using our MM approach again proved its superiority in predicting PD1/PDL1 inhibitor efficacy in advanced/metastatic tumors, this time in mRCC patients. This approach merits further testing in prospective clinical trials.

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172P T cell-derived circulating DNA and tumour inflammatory microenvironment in EGFR-mutant advanced non-small cell lung cancer: Correlation with the outcome of EGFR TKI treatment

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Background: We previously reported paradoxical impact of T-cell derived circulating DNA (T-cirDNA) in-term of prognosis marker in advanced non-small cell lung cancer (NSCLC). Longer durability of EGFR tyrosine kinase inhibitor (EGFRi) was correlated with undetectable T-cirDNA/cirDNA. This study aimed to confirm the finding in a larger cohort, correlated with tumor immune microenvironment (TIME).

Methods: Pretreatment plasma of patients with advanced *EGFR*-mutant NSCLCs who received EGFRi were collected. The semi-quantitative T-cirDNA /cirDNA was conducted by multiplex real-time polymerase chain reaction. Correlation with clinical outcome and TIME, including programmed cell death ligand-1 (PD-L1 clone 22C3), CD8 tumor infiltration lymphocyte (TIL), and Treg/FOXP3 were conducted.

Results: One-hundred and thirty-nine patients were divided according to T-cirDNA/cirDNA into undetectable (30%), low ($\leq$1% ratio; 38.1%), and high (>1% ratio; 31.6%). The median progression-free survival (PFS) was 13.1 [95% CI 8.8 − 17.4], 9.0 [95% CI 6.7 − 12.5], and 13.2 [95% CI 8.8 − 19.3] months respectively, which was longest in undetectable and high T-cirDNA/cirDNA. Sixty-eight available tissue blocks for TIME study revealed decremental proportion of high PD-L1 ($\geq$15% TPS) in high (21%), low (13%) and undetectable T-cirDNA/cirDNA (4%). While high intra-tumoral CD8 TIL ($\geq$1%) had lowest proportion in low T-cirDNA/cirDNA (17%) contrary to undetectable (36%) and high T-cirDNA/cirDNA (47%). Multivariate cox-regression analysis revealed that high PD-L1 and high intra-tumoral CD8 TIL were independent factors correlated with shortened PFS. Good ECOG performance status (0-1) and undetectable T-cirDNA/cirDNA were solely independent prognostic factor to overall survival.

Conclusions: Undetectable T-cirDNA/cirDNA represents inactivated naïve T-cell and indicated favorable prognosis in *EGFR*-mutant NSCLCs who received EGFRi. Inflammatory TIME including high PD-L1 and high intra-tumoral CD8 indicated shorted disease control with EGFRi. The interaction of active T-lymphocyte and TIME in *EGFR* alteration advanced NSCLC received EGFRi is warranted.

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173P Expression of programmed death-ligand 1 and EGFR on circulating tumour cells in advanced lung cancer patients

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Background: Targeted molecular therapy and immunotherapy have revolutionized the treatment of advanced lung cancer (ALC). Although therapeutically significant, the outcome of ICI or TKI is dependent on the presence of their respective targets in tumor cells. Evaluating targets based on solid biopsy may be often misleading, particularly in progressive patients despite therapy administration. Additionally, tissue biopsy provides a static signature of a target protein expression from the evolving tumor. The unmet need for dynamic detection and monitoring of actionable targets could be addressed by circulating tumor cells (CTCs). Here we report on the utility of CTCs to detect actionable targets from advanced lung cancer (ALCs) patients.

Methods: We retrospectively analyzed 193 ALC patients for Programmed Death - Ligand 1 (PD-L1) and EGFR expression on CTCs from. CTCs were isolated from Drug Controller General of India-approved OncoDiscover technology based on immunomagnetic targeting using anti EpCAM antibody, and immuno-staining with anti EGFR and PD-L1 antibodies. CTCs were detected based on the expression of CKs, absence of CD45, and prominent DAPI-stained nuclei. The presence or absence of EGFR and PD-L1 was determined with automated immunofluorescence microscopy.

Results: Among the evaluated cohort, 67 % patients showed the presence of CTCs with a mean value of 4.2 (Range: 1 to 62, SD =10.65). The absence of CTCs from the remaining 33 % of patients could be due to the therapy response of the clinically stable disease. From all patients showing the presence of CTCs, 66 % showed the detectable expression of PD-L1, while 42 % showed a strong expression of EGFR. The presence of PD-L1 was a significant association with CTCs. Similarly, the expression of EGFR among the detected CTCs showed high significance compared to the reported data on tissue biopsy from the literature.

Conclusions: Detection of therapeutic targets on CTCs obtained from ALC strongly indicate these patients qualify for anti-EGFR and PD-L1 therapies. Systematic studies with larger samples are required to strengthen the liquid biopsy-based detection of actionable targets. This could immensely help ALC patients showing progressive disease on chemo/radiotherapy.

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174P Frequency and prognostic value of circulating tumor cells in cancer of unknown primary

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Background: Cancer of unknown primary (CUP) is defined as a primary metastatic malignancy, where the primary tumor remains elusive in spite of a comprehensive diagnostic workup. Patients with CUP have a poor prognosis, making the need for the development of novel therapeutic and prognostic tools urgent. The frequency and prognostic value of circulating tumor cells (CTCs), which are considered to be the source of metastasis, has not yet been systematically evaluated in CUP.

Methods: 92 patients with a confirmed diagnosis of CUP according to the ESMO guidelines, who presented to our clinic between 07/2021 and 03/2023 provided blood samples for CTC enumeration using CellSearch® methodology. CTC counts were correlated with demographic, clinical and molecular data generated by comprehensive genomic profiling of tumor tissue.

Results: CTCs were detected in 35% of all patients. The highest CTC frequency was observed among patients with unfavorable CUP (18/53, 34%), while patients with single-site/oligometastatic CUP harbored the lowest CTC frequency (4/28, 14%). Disease burden and the number of affected organs had no significant effect on the CTC detection rate (P=0.251 and P=0.805). CDKN2A alterations were slightly more common in CTC-negative patients (P=0.086). High CTC levels (5 CTCs/7.5 ml) predicted for adverse overall survival (OS) compared to negative or low counts (median 74 vs. 19 months; Log-rank P=0.002; HR 3.73; 95% CI 1.54-9.00). Progression-free survival was also affected by CTC status, the effect did not, however, reach statistical significance (median 7.4 vs 3.6 months, Log-rank P=0.1). CTC dynamics over the course of the disease were prognostic for OS, with patients that were either consistently CTC-negative or turned negative during treatment demonstrating the best prognosis.

Conclusions: The number of CTCs is a predictor of survival in patients with CUP. Measurement of CTCs provides a useful prognostic tool in the management of these patients.

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175P Radiomic biomarker of vessel tortuosity for monitoring treatment change: Preliminary findings in prospective evaluation of ECOG-ACRIN EA5163

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Background: EA5163 is a phase 3 randomized trial investigating first-line mono immunotherapy (IO) or IO with chemotherapy in advanced non-small cell lung cancer (NSCLC). Previous work has retrospectively validated a CT based radiomic signature of tumor associated quantitative vessel tortuosity (QVT) for prognosticating outcomes in IO treated NSCLC (Alilou et al. Sci Adv 2022). In this study, we report initial results of evaluating QVT in assessing IO related treatment changes in EA5163, specifically associating changes in QVT (Δ-QVT) with changes in tumor volume (Δ-TV) between baseline (B) and 6 week post-treatment scans (TP1).

Methods: CT scans from 29 patients enrolled in EA5163 with measurable lung lesions at B and TP1 were included. Vasculature was automatically segmented in a 25mm region around manually annotated tumors in CT using MATLAB R2022b. 84 QVT features measuring tortuosity, curvature and angle statistics were extracted. No information on outcomes, survival, or treatment arm assignment was available due to the ongoing nature of the trial. Spearman correlation and false discovery rate corrected p-values were computed to associate Δ-QVT with Δ-TV in an unsupervised setting. A risk score (QRS) was generated as the output of a classifier previously trained on 5 Δ-QVT features prognostic of RECIST v1.1 response.

Results: 14 Δ-QVT features were significantly ($p<0.05$) correlated with Δ-TV with an absolute range of 0.45 and 0.76. 4 features in the QRS signature were significantly correlated with Δ-TV (Table). QRS based stratification showed net decrease in TV in low risk patients, whereas a net increase in high-risk patients at TP 1 ($p<0.001$). The Δ-QVT features were not associated with baseline tumor volume.

Table: 175P

Feature	Correlation	p-value
Vessel volume	0.71	<0.001
1st bin of tortuosity histogram	0.65	0.002
12th bin of angles histogram	0.61	0.004
2nd bin of curvature histogram	0.65	0.002
Vessel volume to tumor volume ratio	-0.48	0.053

Conclusions: This study demonstrated an association between CT derived radiomic biomarker Δ-QVT and Δ-TV in an ongoing prospective clinical trial. Validation of these results upon interim analyses or trial completion is warranted.

Clinical trial identification: NCT03793179.

Legal entity responsible for the study: The authors.

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176P Enhancing immunotherapy response prediction via multimodal integration of radiology and pathology deep learning models

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Background: The growing need for better predictive biomarkers in immunotherapy has driven the development of AI models across various fields. Despite this progress, most studies focus on single modalities, such as pathology or radiology. This study emphasizes the importance of multimodal biomarkers, combining radiology and pathology data, to optimize treatment outcomes and advance personalized medicine in immunotherapy.

Methods: We developed weakly-supervised deep learning (DL) models for CT and PDL1-stained immunohistochemistry (IHC) images. We trained a CT-based model to predict immunotherapy clinical benefit (PFS > 5 months) in a pan-cancer cohort from VHIO(n=369). Simultaneously, we trained a DL method to predict PD-L1 status from IHC images in an open source NSCLC cohort (n=233), validated in a pan-cancer cohort from VHIO (n=106). The model predictions of both modalities were aggregated and utilized for patient stratification in immunotherapy response. In the overlapping subset with both modalities' data (n=75), we explored the association between PFS and the combination of predicted clinical benefit by CT and predicted PDL1 status by IHC using Cox regression and log-rank test.

Results: The CT-based and IHC-based DL models exhibited effective performance in predicting PFS for immunotherapy response in the pan-cancer cohort, with hazard ratios (HR) of 0.62 [95% CI 0.5-0.78], $p<0.05$ and 0.66 [95% CI 0.44-1], $p<0.05$, respectively. In the multi-modal data subsets, patients classified as clinical benefit prediction by the CT-based model and PDL1 high by the IHC-based model ($n = 20$) exhibited better immunotherapy response (HR 0.44 [0.25-0.78], $p<0.05$) with longer PFS (median PFS 4.08 [2.70-10.91] months) compared to the rest (median PFS 1.81 [1.68-2.96] months).

Conclusions: Integrating radiology and pathology data improves response prediction compared to single modality models, emphasizing the potential of a multimodal approach for better patient stratification in immunotherapy.

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177P Revealing differences in radiosensitivity of advanced non-small cell lung cancer (NSCLC)through single-cell sequencing data

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Background: Radiotherapy resistance is a major therapeutic difficulty for advanced NSCLC patients because not all patients can benefit from radiation therapy. Identifying disparities in radiosensitivity of advanced lung cancer and antagonizing the radiotherapy resistance are the challenges for clinical oncologists.

Methods: We analyzed the scRNA-seq transcriptome data of 42 patients with advanced NSCLC, including lung adenocarcinoma and lung squamous cell carcinoma, used the radiosensitivity index (RSI) to calculate the radiosensitivity intensity (RSI ^{high} and RSI ^{low}) of each cell of 11 cell types, and drew the radiosensitivity difference map of different cell types in the system. The core role of malignant cells in radiosensitivity differences in advanced NSCLC was revealed using cell cycle inference, tumor cytoTRACE score, GO/KEGG enrichment, cell-cell interactions, cellular metabolic activity, and quasi temporal trajectory joint analysis, all in accordance with the "4R" principle of radiobiology (Repair, Reoxygenation, Redistribution, Regeneration).

Results: Malignant cells differ significantly from other types of radiosensitive cells in processes such as cell cycle, aging, apoptosis, chromosomal alterations, and cellular metabolic activity. RSI ^{high} cells make up the majority of cells in the G2/M and S phases, and the quantity and intensity of RSI ^{high} cell ligand receptors increases considerably. RSI ^{low} cells, as an exposure factor, tend to shift from epithelial to malignant cells, leading in alterations in ligand receptor input and output patterns. Furthermore, we discovered considerable changes in the metabolic activity of RSI ^{low} cells in lung squamous cell carcinoma.

Conclusions: Our findings show that radiosensitivity varies in advanced NSCLC. RSI ^{low} cells could be a subset of malignant cells with radiotherapy resistance, driving clinical researchers to delve deeper into the detailed mechanism of advanced NSCLC.

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178P Explainable radiomics, machine and deep learning models to predict immune-checkpoint inhibitor treatment efficacy in advanced non-small cell lung cancer patients

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Background: IO revolutionized NSCLC treatment paradigm, but only a relatively small proportion of pts shows benefits. Since available biomarkers demonstrated only limited predictive efficacy, novel models are urgently needed. Radiomics, through machine learning (ML) and deep learning (DL) techniques, allows to extract features from raw images to build predictive models. This study aimed to develop and test 2 type of radiomics models in predicting IO efficacy on advanced NSCLC, one ML-based, other through an end-to-end DL pipeline.

Methods: We collected CT scans and RWD from 295 consecutive pts with advanced NSCLC pts receiving any-line anti-PD(L)1 therapy either alone or in combination with CHT at our Institution from 23/04/2013 to 12/05/2022 within APOLLO 11 study. ML workflow consisted of image preprocessing, feature extraction, 3 step feature selection, correlation, algorithm training and evaluation of 6 ML classifiers. ML models were trained using radiomics +/- RWD. Models were evaluated on independent test set and SHAP values used to explain model predictions. We compared developed model with novel DL end-to-end model, a 3D convolutional neural network.

Results: 15 image features were selected to build radiomic model, achieving ACC of 0.61 and AUC of 0.58. Combining it with additional RWD features, accuracy and AUC of LR reached 0.71 and 0.76. SHAP analysis for best-performing models showed RW (ECOG PS, therapy line, concomitant CHT, PDL1) and radiomics features (tumor shape and intensity/distribution of gray-level values) that most influenced models. DL model achieved an ACC of 0.69 and a Loss value of 0.773. A high proportion of higher GLSZM and a high value of large area size zones were associated to a higher response to therapy.

Conclusions: The developed and validated ML-based model includes radiomic and RW features, demonstrating ability to predict IO efficacy and potential future applicability for treatment selection. We firstly demonstrated that a radiomics-based DL model outperform the all radiomics ML-based models highlighting the importance of this approach in image data. SHAP analysis provided valuable insights to explore features that most influenced the models' predictions

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179P Molecular tumor board directed treatment for patients with advanced stage solid tumors: A case-control study

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Background: Interpreting next-generation sequencing (NGS) results and directing treatment based on those results can be challenging. Molecular tumor boards (MTBs) can help by establishing collaborative frameworks to deliver patient care plans with the appropriate incorporation of genomic data.

Methods: This retrospective observational study evaluates the impact of MTB on the outcomes of adult patients diagnosed with advanced-stage cancer. Patients were grouped into those who received at least one treatment recommended by MTB or those who did not receive treatment recommended by MTB. Kaplan- Meier analysis was performed for overall survival (OS) and progression-free survival (PFS). Cox proportional hazard model was fit for PFS, OS, and time on treatment (ToT) with multivariate adjusting for age, stage, line of therapy, and primary site of diagnosis.

Results: Of 238 evaluable patients, 138 (58%) received at least one treatment recommended by MTB. Patient characteristics were well balanced between the cohorts except for a statistically significantly higher proportion of lung adenocarcinoma (33% v 14%, p=0.0009) & melanoma (9% v 2%, p=0.030) in the matched cohort and more glioblastoma in the unmatched cohort (8% v 1%, p=0.017) (Table). Median ToT was 4.3 months for patients on matched treatment versus 2.8 months for patients who received therapy of provider's choice (HR 0.58, 95% CI [0.41-0.83], p=0.0027). Median PFS was 9.7 months versus 4.3 months for MTB-matched treatment versus provider's choice of treatment (HR 0.64, 95% CI [0.42-0.97],p=0.035). Median OS was 18.5 months for patients on MTB-recommended therapy versus 9.1 months for patients who received therapy of provider's choice (HR 0.64, 95% CI [0.43-0.96],p=0.030).

Conclusions: MTB treatment recommendations improved survival outcomes for patients with cancer even after correcting for imbalances between the two cohorts. Our findings show that MTBs in community cancer centers are feasible and valuable in cancer care.

Table: 179P Histology

	Matched		Unmatched	
	No.	(%)	No.	(%)
	138		100	
Lung Adenocarcinoma	45	(33%)	14	(14%)
Colorectal Adenocarcinoma	10	(7%)	14	(14%)
Breast Carcinoma	8	(6%)	12	(12%)
Melanoma	12	(9%)	2	(2%)
Lung Squamous Cell Carcinoma	7	(5%)	7	(7%)
Prostatic Adenocarcinoma	5	(4%)	6	(6%)
Glioblastoma	2	(1%)	8	(8%)
Esophagogastric Adenocarcinoma	5	(4%)	5	(5%)
Pancreatic Adenocarcinoma	2	(1%)	6	(6%)
Cholangiocarcinoma	6	(4%)	1	(1%)
Non-cutaneous Squamous Cell Carcinoma	6	(4%)	1	(1%)
Lung Small Cell Carcinoma	2	(1%)	4	(4%)
Endometrial Carcinoma	3	(2%)	1	(1%)
Sarcoma	1	(1%)	3	(3%)
Urothelial Carcinoma	1	(1%)	2	(2%)
Appendiceal Adenocarcinoma	2	(1%)	1	(1%)
Other Histologies	21	(15%)	13	(13%)

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180P An HLA-diet-oriented system unveiling organ-specific occurrence of multiple primary cancers (MPC) with prevention strategy: A large cohort study of 47,550 cancer patients

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Background: Along with the prolonged survival of cancer patients in recent years comes another dilemma, multiple primary cancers (MPC), which rob cancer patients of their privilege to optimal treatments. Nonetheless, understanding the hereditary and postnatal predisposition of MPC is still in its infancy.

Methods: We included 47,550 cancer patients in UK Biobank. Hazardous and protective HLA alleles concerning MPC were recognized leveraging stepwise logistic regression, which was further validated by log-rank test and Cox proportional hazard model. Logistic regression was used to investigate the organ-specific association between HLA and MPC. Cox proportional hazard model was used to explore potential interventions.

Results: Two protective (DPA1*02:02 and DRB1*04:03) and four hazardous (A*26:01, A*24:03, DPB1*20:01 and DQB1*06:01) HLA alleles are significantly associated with MPC risk for male, whereas one protective (DRB5*01:01) and four hazardous (A*03:02, DRB1*08:03, DQB1*05:04, and DPB1*11:01) for female. Compared with patients without MPC-related HLA alleles, both male and female patients carrying protective HLA alleles have lower risk of MPC (HR, 0.67 [95% CI, 0.53-0.83] and HR, 0.84 [95% CI, 0.73-0.97], respectively), while those carrying hazardous HLA alleles have higher risk of MPC (HR, 1.31 [95% CI, 1.09-1.57] and HR, 1.55 [95% CI, 1.25-1.93], respectively). HLA alleles are associated with organ-specific MPC occurrence. Lower animal fat intake subsided (HR, 0.46 [95% CI, 0.26-0.82]) while unqualified vegetable fat intake increased MPC risk (HR, 2.23 [95% CI, 1.22-4.07]) for male cancer patients carrying hazardous HLA alleles. Lower free sugar intake subsided the risk of MPC for female patients carrying hazardous HLA alleles (HR, 0.34 [95% CI, 0.15-0.74]).

Conclusions: HLA alleles might help to understand the predisposition and organ-specific incidence of MPC. Intervention on diet could counteract the risk.

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181P GeNeo: Agnostic comprehensive genomic profiling versus limited panel organ-directed next-generation sequencing within the Belgian PRECISION initiative

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Background: Several targeted therapies are available through reimbursed organ-specific next-generation sequencing (NGS). Agnostic comprehensive genomic profiling (CGP) covering all classes of genomic alterations could improve access to molecularly-guided therapies (MGTs).

Methods: PRECISION is an initiative launched by the Belgian Society of Medical Oncology (ESMO Open. 2022 Aug;7(4):100524). In the prospective GeNeo trial, CGP (FoundationOne CDx or Heme) was centrally done on tumor samples for patients with advanced solid tumors (NCT04641676). In parallel, organ-directed NGS panel testing was mandatory if reimbursed. Patients with no tissue sample were enrolled with a liquid biopsy. Results were discussed at a national molecular tumor board (MTB). Reasons for non-initiation of the recommended treatment were recorded. Clinical and genomic data are stored in the PRECISION database, with prospective follow-up up to 2 years.

Results: From October 2020 to April 2022, 1000 patients were enrolled at 13 sites. CGP results were available for 937 (843 tissue and 94 liquid biopsies) patients, out of which 918 were discussed at the MTB. The largest cohorts were breast (n=137), colorectal (n=128) and rare cancers (n=100). Turnaround-time from sample received to MTB recommendation was $\leq$ 28 days for 45% of cases and $\leq$ 37 days for 80%. 576 patients (63%) received at least one recommendation for CGP-based therapy. Cohorts with most treatment recommendations (>75% of cases) were bladder, biliary tract, skin and thyroid cancers. 72% of 469 patients who also had an organ-directed NGS test received at least one additional treatment recommendation based on CGP testing. Among the patients who received at least one MTB recommendation, 123 (21%) were treated accordingly. Reasons for non-compliance include patient ineligibility (26%), physician decision (23%) and treatment unavailability (22%). Follow-up continues.

Conclusions: Tumor-agnostic CGP provides more treatment options to patients with advanced solid tumors when compared to organ-directed NGS panel testing. The national MTB provides recommendations within a clinically relevant timeframe and enhances the uptake of MGTs.

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Novartis, AstraZeneca; Non-Financial Interests, Member of Board of Directors: BSMO. A. Hebrant: Financial Interests, Personal, Full or part-time Employment: Sciensano. G. Raicevic: Financial Interests, Personal, Full or part-time Employment: Sciensano. E. Van Valckenborgh: Financial Interests, Personal, Full or part-time Employment: Sciensano. B. Maes: Financial Interests, Personal, Advisory Board: Servier, AstraZeneca, Illumina; Financial Interests, Personal, Invited Speaker: Pfizer, Illumina; Financial Interests, Institutional, Invited Speaker: Illumina, SeqOne; Non-Financial Interests, Principal Investigator: BSMO. J. Maetens: Financial Interests, Personal, Full or part-time Employment: Sciensano. J.J. Collignon: Financial Interests, Personal, Full or part-time Employment: Sciensano. S. Tejpar: Financial Interests, Institutional, Advisory Board: Roche, Boehringer Ingelheim, Bayer, Daiichi Sankyo; Financial Interests, Personal, Invited Speaker: Amgen, Merck Serono. J. Canon: Financial Interests, Institutional, Research Grant: Roche. S. Rottey: Financial Interests, Institutional, Advisory Board: Pfizer, Merck, Roche, Ipsen, BMS; Financial Interests, Institutional, Invited Speaker: Ipsen, BMS, Astellas; Financial Interests, Institutional, Research Grant: MSD, Roche, BMS; Non-Financial Interests, Principal Investigator, It is my main task in the hospital to attract and perform clinical trials in oncology phase I-III: all companies performing clinical trials in oncology in Europe. All other authors have declared no conflicts of interest.

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182P ALK fusion detection by RNA next-generation sequencing (NGS) compared to DNA in a large, real-world non-small cell lung cancer (NSCLC) dataset

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Background: While DNA NGS can detect clinically actionable fusions in tumors, technical and biological limitations may lead to false negatives, preventing patients from receiving approved therapies associated with outcome benefit. RNA NGS is recommended by ESMO guidelines to maximize fusion detection but is not widely used clinically. In a large, real-world dataset, we quantify the benefit of RNA concurrent with DNA NGS for ALK fusion detection in NSCLC.

Methods: We retrospectively analyzed de-identified stage IIIB-C and IV NSCLC samples sequenced with the Tempus xT assay (DNA and whole-exome capture RNA NGS). ALK fusion prevalence was compared to public DNA-seq-based data from Dana Farber Cancer Institute (DFCI, N=4,497) and Memorial Sloan Kettering Cancer Center (MSKCC, N=5,317) with one-sided proportion tests. ALK fusions were limited to known oncogenic partners detectable by FISH or IHC (EML4, KIF5B, KLC1, and PICALM). Therapeutic adoption was analyzed in cases with ≥90 days of first-line medication data.

Results: Among 7,428 NSCLC patients, 2.9% had ALK fusions (n=217), with 83% (n=180) detected by both DNA and RNA, 15% (n=33) from RNA alone, and 2% (n=4) from DNA alone. ALK fusion prevalence in the Tempus Database was higher than the combined MSKCC and DFCI rate (2.4%, n=236/9,814, P=0.036). To investigate RNA vs DNA discordance, we examined exonic EML4-ALK breakpoint locations (n=32). Most cases had canonical breakpoints in RNA (n=26), where 18 had no DNA support in these breakpoints, suggesting complex ALK rearrangements in DNA. The remaining 8 had limited DNA support but were below the clinical threshold for reporting. Of those with medication data (n=7), 6 patients with EML4-ALK fusions detected by RNA alone received targeted therapy post-testing and 5 remained on therapy for ≥100 days.

Conclusions: This large, real-world dataset demonstrates that RNA NGS increases ALK fusion detection by 18% over DNA alone for patients with advanced NSCLC. This increase is likely to translate to a larger number of patients matched to and receiving targeted therapy. Consequently, RNA NGS should be considered for more widespread adoption in the clinic.

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183P Frequency of actionable fusions in 7,735 patients with solid tumors

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Background: Identifying rare oncogenic gene fusions can be challenging. Comprehensive genomic profiling (CGP) approaches that include RNA sequencing can improve fusion detection versus exome or targeted DNA sequencing alone. Here, we characterize gene fusions in solid tumors detected with the OncoExTra™ tumor-normal, whole-exome (WES), whole-transcriptome (WTS) CGP assay.

Methods: The study included oncology patients with solid tumor samples tested with the OncoExTra assay between May 2018 and November 2022. We quantified the frequency of all potentially clinically-relevant fusions, including those with therapeutic, clinical trial eligibility, prognostic or diagnostic implications, and the subset of these with FDA-approved therapies at the time of testing.

Results: Overall, 7,735 patients and 33 tumor types were included. We identified 931 (12.0%) patients with clinically-relevant fusions, 224 (2.9%) of whom had a fusion associated with an FDA-approved therapy, with large variation in frequency across tumor types (Table). Sarcomas had one of the highest proportions (34.4%) of fusions identified, many of which are diagnostic or prognostic: *PAX3/7-FOXO1* (n=17), *SS18-SSX* (n=10), *CIC-DUX4* (n=8), and *MDM2* (n=6). We also detected fusions in 189 (9.5%) breast (including 43 with *ESR1*, 13 with *ERBB2*, 12 with *FGFR* family), 33 (3.4%) colorectal (including 5 *RSPO*, 3 *RET*), and 29 (9.9%) non-small cell lung (including 10 *ALK*, 5 *RET*, 3 *ERBB2*) cancer patients. Across all cancers, *ERG* (3.0%) was the most common fusion partner, found predominantly in prostate cancer patients. Other notable fusions involved *ESR1* (n=64); *RAF* family (n=30); *NTRK* family (n=27); and *RSPO* family (n=12).

Conclusions: Oncogenic gene fusions, including those with FDA-approved therapies, were identified with varying frequency across solid tumors. Sarcomas had a high proportion of fusions, including those with therapeutic, diagnostic and prognostic relevance.

Table: 183P Gene fusions in select tumor types

Tumor type	Patients, n (%)	Total fusions, n (% of patients)	Fusions with FDA-approved therapies, n (% of patients)
Breast	1989 (25.7%)	189 (9.5%)	65 (3.3%)
Colorectal	975 (12.6%)	33 (3.4%)	9 (0.9%)
Prostate	582 (7.5%)	277 (47.6%)	7 (1.2%)
Ovary	389 (5.0%)	21 (5.4%)	4 (1.0%)
Sarcoma	326 (4.2%)	112 (34.4%)	16 (4.9%)
NSCLC	293 (3.8%)	29 (9.9%)	18 (6.1%)
Brain	274 (3.5%)	41 (15.0%)	22 (8.0%)
Bladder	197 (2.5%)	14 (7.1%)	6 (3.0%)
Thyroid	132 (1.7%)	17 (12.9%)	15 (11.4%)
Biliary	93 (1.2%)	16 (17.2%)	11 (11.8%)
All Cancers	7735 (100.0%)	931 (12.0%)	224 (2.9%)

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184P Patient-specific HLA-I genotypes predict response to immune checkpoint blockade

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Background: Specific shared HLA Class 1 alleles have been linked to the response to immune checkpoint blockade (ICB). In this study, we aimed to identify the HLA-A subtypes associated with maximum benefit from ICB.

Methods: We compiled a prospectively maintained clinical dataset of patients who underwent CLIA-approved germline HLA status testing as part of various advanced immune and cell therapy trials undertaken at the Christie NHS Foundation Trust. The probability of overall survival (OS) or progression-free survival (PFS) was estimated by the Kaplan-Meier method, and their associations with the HLA-A alleles were tested with Cox regression analysis.

Results: A total of 285 patients from 11 immune and cell therapy clinical trials were eligible for final analysis. The median age at diagnosis was 57 years (range: 19 − 82). The tumor categories were NSCLC (n=93), melanoma (n=60), and other cancers (n=123). We identified 15 HLA-A subtypes, the most common alleles being HLA-A02 (42.2%), HLA-A01 (35.4%), and HLA-A03 (26.0%). A total of 145 patients received ICB either as first-line (56.5%) or as second or later-line (43.5%). Of these, 136 patients had evaluable clinical response status. 24.2% were positive for HLA-A02:01 and were eligible for screening for our HLA-specific trials. Patients with the HLA-A01 and HLA-A30 subtypes were significantly associated with a higher likelihood of clinical response to ICB (odds ratio = 2.58, 95%CI: 1.20 − 5.62, p = 0.017 and 1.80, 95% CI: 1.58-2.18, p= 0.011, respectively). In the NSCLC subgroup, patients with HLA-A01 subtypes were significantly associated with better OS (hazard ratio (HR): 0.42, 95%CI: 0.22-0.81, p= 0.010); meanwhile, HLA-A02 was associated with worse OS (HR: 1.95, 95%CI: 1.09-3.49, p= 0.024). In the other cancers subgroup, HLA-A11 and A24 were associated with better OS (HR: 0.20, 95%CI: 0.05-0.85, p= 0.030 and HR: 0.31, 95% CI: 0.10-0.89, p= 0.029, respectively).

Conclusions: HLA-A status predicted clinical outcomes of patients receiving ICB. HLA genotyping could be incorporated early into the diagnostic work-up of patients with solid cancers as a predictive and selective biomarker.

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185P Real-world data analysis of genomic profiling-matched targeted therapy outcomes in patients with fusion-positive NSCLC

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Background: While clinical oncology societies such as ESMO have recommended the use of Comprehensive Genomic Profiling (CGP) to identify patients eligible for targeted treatment, full utilization of the potential benefits of CGP has not yet occurred in routine clinical practice. Here we assess the compliance to ESMO targeted therapy recommendations and associated outcomes for CGP-based ALK, RET, ROS1, and NTRK fusions detected in a large real-world, observational dataset of advanced NSCLC patients.

Methods: We retrospectively analyzed de-identified stage IV or metastatic NSCLC records from the Tempus database which encompasses molecular and clinical data from hundreds of clinics across the United States sequenced with the Tempus xT assay (DNA and whole-exome capture RNA NGS) from 2018-2022. Therapeutic adoption was analyzed in cases with ≥30 days of medication data post-sequencing. Real-world overall survival (rwOS) was defined as the interval from start of medication prescribed after sequencing to date of death, censored on the last known physician encounter. A cox proportional hazards model was fit to evaluate the relationship between matched targeted therapy compliance and rwOS in fusion-positive patients.

Results: Among 1,950 patients that met study inclusion criteria, N= 65 (3.3%) had a fusion detected by CGP (N=38 ALK fusions, N=15 RET fusions, N=11 ROS1 fusions and N= 1 NTRK fusion). The overall compliance rate of targeted therapy was 82% (N=53). The median time from sequencing to start of targeted therapy was < 1 month. Fusion-positive patients receiving matched therapy had significantly longer rwOS than those that did not receive matched therapy (HR=0.13, p<0.001). ALK-positive patients receiving matched therapy had significantly longer rwOS than those that did not receive matched therapy, (HR=0.12, p<0.05).

Conclusions: This study demonstrates that in a real-world, retrospective cohort, most oncologists utilized CGP to timely treat patients with ESMO-recommended targeted therapy for fusion-positive advanced NSCLC. More importantly, CGP-matched guideline-recommended treatment is associated with improved rwOS. Future studies are needed to understand the gap in compliance with matched targeted therapy.

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186P Pooled efficacy and safety data of alectinib (A) vs. crizotinib (C) from the randomized phase III ALEX and J-ALEX trials

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Background: Among patients (pts) with *ALK*+ advanced non-small cell lung cancer (NSCLC) naïve to ALK-inhibitors, A significantly prolonged progression-free survival (PFS) over C. We present results of a post-hoc patient-level pooled analysis at interim data cut-off of the randomized phase III trials ALEX (NCT02075840) and J-ALEX (JapicCTI-132316), exploring new prognostic factors.

Methods: In both studies, the primary endpoint was PFS by RECIST v1.1. Treatment crossover was only allowed in the J-ALEX trial. Multivariate analysis was performed by Cox's model, the independence of the two trial data sets was managed by random effects models. Survival outcomes were correlated with baseline characteristics including high tumor burden (hTB, i.e. > median sum of diameter of target lesions) and body mass index (BMI).

Results: The pooled set included 500 pts (A=249, C=251) with data available for survival and safety analysis. There was no imbalance between A and C groups in age (median 58 *vs* 56), sex (female 58% *vs* 59%), brain metastases (29% *vs* 34%), BMI (<25 70% *vs* 67%). At a median follow-up of 17.1 months, A provided prolonged PFS over C (median not reached vs. 10.2 months, HR 0.41, 95% CI 0.31-0.55, p<0.001), with median OS not reached in any arm (HR 0.80, 95% 0.50-1.28, p=0.353). In the multivariate analysis with correction for ethnicity, hTB (>55mm) was linked to worse PFS regardless of the treatment received (HR 1.66, 95% CI 1.26-2.20, p<0.001), and BMI ≥25 was correlated with better OS compared to BMI <25 (HR 0.50, 95% 0.29-0.88, p=0.025). Treatment effectiveness in subgroups is shown in table. Significant interaction between treatment and TB (p=0.002) was found in subgroup PFS analysis.

Grade ≥3 adverse events occurred in 36% of pts with A *vs* 51% with C, 15% of pts discontinued A *vs* 20% C.

Table: 186P Subgroup analysis

	HR for PFS A vs C (95% CI)	p value for PFS	HR for OS A vs C (95% CI)	p value for OS
Ref. A vs C whole cohort	0.41 (0.31-0-55)	<0.001	0.80 (0.50-1.28)	0.353
Sum diam ≤55mm	0.25 (0.16-0.41)	<0.001	0.79 (0.35-1.80)	0.572
Sum diam >55mm	0.52 (0.36-0.76)	0.001	0.87 (0.49-1.55)	0.645
BMI <25	0.44 (0.32-0.62)	<0.001	0.99 (0.58-1.71)	0.976
BMI ≥25	0.35 (0.19-0.63)	0.001	0.39 (0.12-1.21)	0.103

Conclusions: hTB is a prognostic and predictive factor in patients with advanced *ALK*+ NSCLC under ALK-inhibitors, while a BMI ≥25 is linked to a reduced risk of death. Escalation strategies could be explored for hTB.

Clinical trial identification: This is a pooled analysis of ALEX (NCT02075840) and J-ALEX (JapicCTI-132316) trials. This abstract is based on research using data from data contributor F. Hoffmann—La Roche that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

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Remon Masip: Financial Interests, Personal, Invited Speaker: Roche, MSD, Boehringer Ingelheim; Financial Interests, Personal, Writing Engagement: Pfizer; Financial Interests, Personal, Advisory Board: AstraZeneca, OSE Immunotherapeutics, BMS, Jansse, Takeda, Sanofi; Financial Interests, Institutional, Invited Speaker: Merck Portugal; Non-Financial Interests, Principal Investigator, PI of PECATI trial in Thymic malignancies endorsed by a grant by MSD: MSD; Non-Financial Interests, Other, Co-PI of APPLE trial (EORTC-1525): AstraZeneca; Non-Financial Interests, Member, Secretary of the Lung Cancer Group at the EORTC: EORTC. L. 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187P Ipatasertib and atezolizumab in cancers with increased PI3K-AKT pathway activity: First results from the CRAFT trial

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Background: CRAFT (Continuous ReAssessment with Flexible ExTension in Rare Malignancies) is an open-label, 7-arm, cross-entity phase 2 trial investigating the efficacy of combinations of molecularly targeted agents and PD-L1 inhibition with atezolizumab in cancers with targetable molecular alterations (PMID: 34808524). We report the interim efficacy analysis of ipatasertib and atezolizumab in cancers with increased PI3K-AKT pathway activity.

Methods: Adult patients with locally advanced/metastatic cancer refractory to ≥1 medical treatment and selected molecular tumor characteristics (arm 1: BRAF V600E/K mutations; arm 2: ERBB2 amplification/overexpression, activating ERBB2 mutations; arm 3: ALK rearrangements/ALK mutations; arm 4: aberrations predicting increased PI3K-AKT pathway activity; arm 5: activating PIK3CA mutations; arm 6: aberrations predicting increased RAF-MEK-ERK pathway activity; arm 7: alterations predicting anti-PD-L1/anti PD-1 sensitivity) were eligible. Main exclusion criteria were hematologic/primary brain cancers. In arm 4, ipatasertib 400 mg q.d. was given in a 21-days-on/7-days-off schedule, and atezolizumab was administered every 3 weeks. Statistics are based for each arm on a Simon's optimal 2-stage design with 14 patients accrued in stage 1 and 11 additional patients if ≥4 patients achieve the primary endpoint, i.e., disease control (complete/partial remission [PR] or stable disease [SD]) at day 110.

Results: Until 04/2023, 51 patients were registered, and 28 were treated. Thirteen patients with various cancers and PI3K-AKT-activating alterations (PTEN deletion/loss-of-function mutation: n=8; activating PIK3CA mutation: n=2; activating AKT1 mutation: n=3) were enrolled in arm 4. One patient with breast cancer and a homozygous AKT1 E17K and one patient with prostate cancer and PTEN loss achieved a PR and SD, respectively. None of the remaining 11 patients reached the endpoint. Toxicity was mainly gastrointestinal and manageable.

Conclusions: Ipatasertib and atezolizumab were ineffective in this patient population with PI3K-AKT-altered tumors. More stringent molecular selection criteria and an addition trial arm were implemented (arm 5).

Clinical trial identification: NCT04551521, EudraCT 019-003192-18.

Legal entity responsible for the study: German Cancer Research Center, Heidelberg, Germany.

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188P The landscape of SMARCA2 genomic alterations in Chinese cancer patients

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Background: Alterations of the *SMARCA2* gene primarily promote cell proliferation and tumorigenesis by impacting the function of the SWI/SNF complex and activating multiple oncogenic signaling pathways. Previous studies have shown that selective inhibition of *SMARCA2* can induce death of tumor cells with *SMARCA4* mutations, providing a theoretical basis for *SMARCA2* as a therapeutic target for tumors. In addition, differences in mutation profiles in pan-cancer can help understand pathogenesis, identify targets for therapy and promote precision medicine.

Methods: We retrospectively analyzed genomic DNA alterations in tissue samples from 21206 patients by next-generation sequencing (NGS). The *SMARCA2* alterations were divided into functional or unfunctional mutations according to the OncoKB database.

Results: In total, 2.79% (592/21206) of pan-cancer patients carried *SMARCA2* mutations. A total of 710 *SMARCA2* alterations were identified in 592 patients, including missense mutations (60.56%), nonsense (4.51%), frameshifts (1.83%), splicing (21.83%), copy number variations (7.04%), non frameshift mutations (4.23%). Compared the genomic landscape among the *SMARCA2*-functional (S-F), *SMARCA2*-unfunctional (S-UNF) and *SMARCA2*-wide type (S-WT) patients. The results showed the S-F group have higher TMB (55.82 vs. 27.78 vs. 6.33, $p<0.05$) and higher proportion of MSI-H patients (31.15% vs. 22.48% vs. 1.72%, $p<0.05$). Additionally, 13.34% (n=79) of patients carried 2 (n=57) or more than 2 (n=22) *SMARCA2* mutations. Compared with carriers of single mutation, they presented significantly higher TMB (141.40 vs 27.18) and higher proportions of MSI-H (73.42% vs. 34.62%). It is worth noting that in the *SMARCA2* mutation cohort, 24.16% of patients also carried *SMARCA4* mutation, and patients with co-mutation have significantly higher TMB (105.52 vs. 21.78) and a higher proportion of MSI-H (59.44% vs. 22.80%). Based on our results, immunotherapy may be an alternative strategy, which needs more clinical explorations.

Conclusions: *SMARCA2* mutations are diverse, and patients with multiple *SMARCA2* mutations or both *SMARCA2*-*SMARCA4* mutations tumors had higher TMB and a higher proportion of MSI-H may more sensitive to immunotherapy, which may enable new therapeutic options in the future.

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189P Design and enrollment for a classifier development study for a blood-based multi-cancer early detection (MCED) test

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Background: The aim of the Ascertaining Serial Cancer patients to Enable New Diagnostic 2 (ASCEND 2) case-control study is to develop a classifier algorithm for a refined version of a multi-analyte blood-based MCED test. Here, we report the study design, enrollment, and sample selection from this large, multi-center, prospective, case-control study of clinically characterized participants.

Methods: The ASCEND 2 study engaged 151 sites within the US and Europe for subject enrollment. Samples consisted of blood collected using LBgard® tubes for plasma and buffy samples. The study population includes male and female subjects ≥50 years old with known cancer, suspicion of cancer, and controls without cancer. All subjects provided informed consent and were assessed for study participation eligibility.

Results: Over 11,000 subjects were enrolled in this study. A subset of 6361 samples was selected to develop and refine a multi-analyte cancer detection classifier. The subset includes 1440 cancer subjects, from more than 18 organ sites reflective of US cancer incidence by tumor type, and 4921 age-matched subjects without suspicion of cancer. Demographics are reported in in the table. Cancer cases include stage I (388), stage II (301), stage III (374), stage IV (317), stage unknown (60). The samples will be partitioned into training and independent test sets. The performance of one or more locked cancer detection models developed in the training phase will be tested.

Table: 189P Demographics

	Overall (6361)
Mean Age (SD)	65.5 (8.3)
Sex, n (%)	
Female	3579 (56.3%)
Male	2782 (43.7%)
Race, n (%)	
White	5198 (81.7%)
Black/African American	817 (12.8%)
American Indian/Alaska Native	29 (0.5%)
Asian	203 (3.2%)
Multiracial	13 (0.2%)
Native Hawaiian/Other Pacific Islander	6 (0.1%)
Unknown	95 (1.5%)
Ethnicity, n (%)	
Hispanic/Latino	828 (13.0%)
Not Hispanic/Latino	5452 (85.7%)
Unknown	81 (1.3%)
Region, n (%)	
Midwest	1184 (18.6%)
Northeast	833 (13.1%)
South	3059 (48.1%)
West	1069 (16.8%)
Outside US	93 (1.5%)
Unknown	123 (1.9%)
Cigarette Smoking Status, n (%)	
Current	801 (12.5%)
Former	1756 (27.6%)
Never	3787 (59.5%)
Unknown	17 (0.3%)

Conclusions: The ASCEND 2 study selected cancer types in an incidence-targeted manner, including rare and common cancers and evenly distributed stages. By enrolling a racially, ethnically, and geographically diverse cohort, the current study enables MCED test development with a representative cohort.

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190P Quantitative serum tumor markers (CEA, CA19-9, and CA-125) are independently predictive of survival in patients with appendiceal adenocarcinoma

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Background: Although grade is strongly predictive of survival, no other prognostic or predictive biomarkers have been validated to help guide therapeutic decision making in Appendiceal adenocarcinomas (AA). Here we investigated the clinical utility of the serum tumor markers CEA, CA19-9, and CA-125 by association with survival and tumor molecular features.

Methods: The MD Anderson patient database was queried to identify a total of 1,322 patients diagnosed with of AA between 1997 to 2022 with at least one TM measured. Elevation of TM defined as above laboratory ULN (CEA $>$ 3 ng/mL, CA 19-9 $>$ 37 U/mL, and CA-125 $>$ 37 U/mL, highly elevated defined as top 10th percentile (CEA $>$ 100.4 ng/mL, CA 19-9 $>$ 337.5 U/mL, and CA-125 $>$ 41.8 U/mL).

Results: CEA, CA19-9 and CA125 were elevated in 56%, 34%, and 37% of patients, respectively, 63.8% had at least one elevated. The proportion of patients with elevation of each TM did not differ in high- vs low-grade tumors or by histologic subtype (mucinous, colonic, goblet, signet ring). CEA stratified patients by survival with median not-yet-reached for patients with normal CEA vs 182 mo for those with elevated CEA vs 96 mo for those with highly elevated CEA (log-rank p $<$ 0.0001), 5-year OS was 95% vs 82% vs 61% for normal, elevated, and highly elevated, respectively. The prognostic effect of CEA was independent of grade, with 5-year OS (99%, 93%, 69%, log-rank p $<$ 0.0001) for low-grade and (91%, 73%, 55%, log-rank p $<$ 0.0001). Similar survival stratification was seen for CA19-9 (92%, 84%, 66%, log-rank p $<$ 0.0001) and CA-125 (93%, 70%, 60%, log-rank p $<$ 0.0001). CEA was more correlated with CA-19-9 (pearson r $=$ 0.62) than CA-125 (r $=$ 0.29). Elevation of multiple TM was associated with worse prognosis; HR relative to patients with no TM elevated was 4.9 (p $=$ 6.0e-6), 8.9 (p $=$ 6.5e-12), and 16.2 (p $=$ 8.0e-16), for 1, 2, or all 3 TM in multivariate cox model of survival including gender, race, age, grade, and histologic subtype.

Conclusions: Elevation of CEA, CA19-9 and CA125 are independently associated with poor prognosis in patients with appendiceal cancer, all three should be measured. Future efforts to evaluate incorporation of TM into clinical staging are warranted.

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191P Novel approach to proficiency testing demonstrates wide gaps in biomarker quality for colon cancer treatment

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Background: Biomarkers are fundamental to oncology, closely tying this practice to that of laboratory medicine. Results are required to be accurate, timely, comprehensive, and comprehendible. External proficiency testing is a key tool in maintaining quality. Traditional schemes test analytic accuracy. Here, we demonstrate the feasibility and utility of a novel end-to-end proficiency testing exercise examining the *entire* process of biomarker testing.

Methods: Challenge specimens were made using resected colon cancer tissue, each paired with a clinical vignette and distributed to participating labs. Participants were asked to provide all molecular testing required, which could include pre-analytic preparation, immunohistochemistry, gene sequencing, or other methodologies, and to draft and return a final report for each case upon completion. Reports were redistributed to an assessor team including oncologists, who chose therapy based on each lab's biomarker report. Finally, participants were graded based on their ability to guide oncologists to the most appropriate treatment. Gold standard treatments for each case were decided by assessors prior to the exercise, based on reference results and clinical vignettes.

Results: Eight laboratories participated. Three laboratories were found to have suboptimal results, two leading oncologists to incorrect therapeutic prescriptions (Table) and one withdrawn. Turnaround time ranged from 6-86 days (median 24).

Table: 191P Resulting number of medical oncologist assessors prescribing the optimal treatment choice based on reported results

	Lab ID							
Sample ID	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Gold Standard Treatment**
1	3	3	***0***	3	3	3	3	Immune Checkpoint Inhibitor
2	3	***0***	3	3	3	3	3	Anti-*EGFR* mAb
3	3	*2*	*2*	3	*2*	*2*	3	*BRAF* Inhibitor + Anti-*EGFR* mAb
Turnaround Time (Days)	24	***63***	***86***	20	29	21	6	14 Days

Conclusions: This is the first report of *end-to-end* proficiency testing, providing valuable insights into biomarker quality beyond analytic accuracy, including specimen management, communication, and turnaround time. Here, significant quality gaps were identified, generating opportunities for improvement. This paradigm shift in quality assurance to focus on the complete specimen journey is a promising tool in assessing and improving modern cancer care.

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192P Impact of oncogenic fibroblast growth factor receptor (FGFR) alterations in patients with advanced solid tumors in a real-world setting

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Background: Selective FGFR inhibitors are approved for treatment (tx) of FGFR+ advanced urothelial cancer (UC) and cholangiocarcinoma (CCA). The prognostic FGFR+ impact in solid tumors shows mixed results for select solid tumor types (TT). This study assessed the real-world (RW) prognostic impact of FGFR+ on overall survival (OS) of patients (pts) in a tumor agnostic (TA) setting.

Methods: This retrospective study used the Flatiron/Foundation Medicine, Inc Clinico-genomic database (FMI), including data from ∼280 US cancer centers. Pts (age ≥18 y) had advanced/metastatic (adv/met) disease (except UC), evidence of FGFR testing, and started first-line (1L) systemic tx in the adv/met setting. All pts had FMI's tissue-based genomic profiling. Pts with prior selective FGFR inhibitor tx were excluded. FGFR+ was defined as ≥1 of 81 prespecified FGFR oncogenic mutations or any FGFR fusion involving an intact kinase domain. Pts with wildtype FGFR (FGFR-) were matched 3:1 with pts with FGFR+ on TT, age, sex, date of adv/met disease diagnosis, and FMI test version. The statistically powered primary objective assessed differences in TA RW OS from 1L tx initiation in pts with FGFR+ vs FGFR- adv/met disease treated with standard of care systemic tx. Secondary objectives assessed differences in tumor specific RW OS and in time to tx discontinuation or to next tx. Delayed entry models and covariate-adjusted stratified Cox models were used to mitigate bias.

Results: Data from 253 FGFR+ and 759 FGFR- pts were analyzed. Demographics, baseline disease and clinical characteristics were balanced between groups. There were no significant differences in TA RW OS from 1L between groups (HR, 0.97 [FGFR+ vs FGFR-]; p=0.78). Median RW OS from initiation of 1L tx was 1.13 y (95% CI, 0.92-1.52) and 1.01 y (95% CI, 0.89-1.15) for FGFR+ and FGFR- pts, respectively. There were no significant differences in RW OS between groups in tumor-specific comparisons, including CCA, breast cancer, and NSCLC.

Conclusions: There was no statistically significant difference in RW OS between pts with FGFR+ or FGFRadv/ met solid tumors, with a median OS of ∼1 year in both groups. These results highlight the poor prognosis and high unmet need for novel, targeted tx.

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194P Early kinetics of C-reactive protein for cancer-agnostic prediction of therapy response and mortality in patients treated with immune checkpoint inhibitors: A multi-center cohort study

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Background: C-reactive protein (CRP) kinetics have recently been suggested as predictive biomarkers for the efficacy of immune checkpoint inhibitor (ICI) therapy in selected cancer types. The aim of this study was to characterize early CRP kinetics as a tumor-agnostic biomarker for ICI treatment outcomes.

Methods: In this multicenter retrospective cohort study, two independent cohorts of patients with various cancer types undergoing palliative ICI treatment at Austrian academic centers served as the discovery (n=562) and validation cohort (n=474). Four different patterns of CRP-kinetics in the first 3 months of ICI therapy were defined (CRP-flare responders, CRP-responders, CRP non-responders, patients with all-normal CRP). Objective response rate (ORR), progression-free- (PFS) and overall survival (OS) were defined as co-primary endpoints. Uni-and multivariable logistic regression, Landmark analysis and Cox-regression including CRP kinetics as time-dependent variable were performed.

Results: The ORR in patients with all-normal CRP, CRP responders, CRP flare-responders and CRP non-responders was 41%, 38%, 31% and 12%, respectively. The median OS and PFS estimates were 24.5 months (95%CI 18.5 – not reached) and 8.2 months (95%CI 5.9-12.0) in patients with all-normal CRP, 16.1 months (95%CI 12.6-19-8) and 6.1 months (95%CI 4.9-7.2) in CRP-responders, 14.0 months (95%CI 8.5-19.4) and 5.7 months (95%CI 4.1-8.5) in CRP flare-responders and 8.1 months (95%CI 5.8-9.9) and 2.3 months (95%CI 2.2-2.8) in CRP non-responders (log-rank p for PFS and OS <0.001). These findings prevailed in multivariable analysis and could be fully confirmed in our validation cohort. Pooled subgroup analysis suggested a consistent predictive significance of early CRP kinetics for treatment efficacy and outcome independent of cancer type.

Conclusions: Early CRP kinetics represent a tumor-agnostic predictor for treatment response, progression risk and mortality in patients with cancer undergoing ICI therapy.

Legal entity responsible for the study: The authors.

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195P Identification of biomarkers associated with checkpoint inhibitor pneumonitis based on serum proteomic approach and construction of an online interactive visual prediction model

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Background: Checkpoint inhibitor pneumonitis(CIP) is one of the most common fatal adverse events in the new era of immune checkpoint inhibitor(ICI). Screening the high risk group of CIP is a major clinical challenge to improve the safety of ICI therapy. However, there are lack of effective biomarkers to predict CIP. The practical difficulties of early screening highlight the need to explore new biomarkers. The aim of this study is to determine predictive biomarkers of CIP through proteomics methods, and then build a prediction model, so as to improve the safety of ICI therapy.

Methods: This study prospectively recruited 98 tumor patients. Fasting peripheral blood was collected from patients before ICI therapy for the first time. Patients were dynamically followed up and assessed for CIP. Serum protein spectrum was analyzed and identified by MALDI-TOF mass spectrometry(MALDI-TOF-MS) and LC-MS. Confirmatory studies were conducted by ELISA to quantitatively evaluate the expression of serum protein. R language is used to construct online interactive prediction model. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2021LSK-001).

Results: 31 patients with CIP constituted the case group. A total of 88 peptide peaks were detected by MALDI-TOF-MS. 15 protein polypeptides with the most significant differences were selected for further identification. After quantitative verification by ELISA analysis, it was found that plasma serine protease inhibitor (SERPINA5), A-kinase anchor protein 6 (AKAP6), tubulin alpha-4A chain (TUBA4A) were significantly highly expressed in CIP patients. Based on this, online interactive visual prediction model was constructed (https://mass-cip.shinyapps.io/DynNomapp/). Harrell's C-indices of the training set and validation set were 0.974 and 0.968, respectively. The calibration curve and clinical decision curve showed satisfactory predicted value.

Conclusions: SERPINA5, AKAP6 and TUBA4A are considered useful biomarkers for predicting CIP. The predictive model has the potential to be a convenient, intuitive, and personalized clinical tool for assessing the risk of CIP.

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196P Serum metabolomics to determine survival of immunotherapy for advanced non-small cell lung cancer: Metabolomic analysis based on two cohorts

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Background: Noninvasively collected samples are attracting significant interest as new areas of biomarker study in immune checkpoint inhibitors (ICIs) field, and metabolomics is one of these growing ones. We focused on the added value of the metabolomic profile as a means of distinguishing long-term survival from short-term survival in NSCLC patients treated with ICIs.

Methods: We prospectively recruited 97 patients with stage IV NSCLC who were treated with anti-PD-1 inhibitor, including patients treated with monoimmunotherapy as second-line treatment (Cohort 1), and patients treated with combination immunotherapy as first-line treatment (Cohort 2). Each cohort was divided into two groups, long-term survival and short-term survival. All blood samples were collected before beginning immunotherapy. Metabolomic profiling of serum was performed by UHPLC-Q-TOF MS analysis. Multivariate data analysis, including Pareto-scaled principal component analysis (PCA) and orthogonal partial least-squares discriminant analysis (OPLS-DA), was performed.

Results: A total of 41 differential metabolites in Cohort 1 and 47 in Cohort 2 were screened. Among them, 8 common metabolites in ESI^- mode and 11 in ESI^+ mode were significantly associated with both PFS and OS in cohort 1. In cohort 2, 3 metabolites in ESI^- mode and 6 in ESI^+ mode were significantly associated with both PFS and OS. In cohort 1, the top 3 enriched KEGG pathways, as determined through significant differential metabolic pathway analysis, were primary bile acid biosynthesis, african trypanosomiasis, and choline metabolism in cancer. In Cohort 2, the top 3 enriched KEGG pathways were the citrate cycle (TCA cycle), PPAR signaling pathway, and primary bile acid biosynthesis. The primary bile acid synthesis pathway had significant differences in the long-term survival and short-term survival groups in both Cohort 1 and Cohort 2.

Conclusions: Our study suggests that peripheral blood metabolomic analysis is critical for identifying metabolic biomarkers and metabolic pathways responsible for the NSCLC patients treated with ICIs, and the primary bile acid synthesis pathway may be the important one.

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197P Clinical benefit of HER2-targeted therapies versus prior chemotherapy in refractory HER2 expressing and mutant gastrointestinal malignancies

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Background: HER2-directed drugs are established therapies for patients with advanced HER2+ gastroesophageal (GEJ) cancers. However, while various anti-HER2 agents including antibodies, antibody-drug conjugates, and tyrosine kinase inhibitors are active in non-GEJ HER2+ GI tumors, the optimal integration/sequencing of these agents with conventional chemotherapy is unclear.

Methods: We assessed the outcomes of patients with metastatic HER2-expressing or mutated non-GEJ GI cancers who received anti-HER2 drugs at our institution from 2010 −2021. We measured the growth modulation index (GMI) − the ratio of progression-free survival (PFS) of the anti-HER2 drug to the time-to-progression on the immediately prior therapy − for each line of HER2 therapy. GMI $\geq$1.3 is considered meaningful clinical benefit, and we classified patients with GMI $\geq$2.6 as exceptional benefiters.

Results: Forty-one patients with adenocarcinomas (19 colorectal, 13 biliary tract, 3 intestinal, 3 pancreatic, 2 ampullary, and 1 appendiceal) were identified; 59% received $\geq$2 lines of therapy before their first anti-HER2 agent. Twenty-two patients who received $\geq$1 line of HER2-directed therapy were GMI evaluable. Fifty percent benefited from therapy and 36% derived exceptional benefit. The median PFS to the first anti-HER2 therapy was 5.5 (0.4 − 53.0) months. All HER2 benefiters were either *HER2*-amplified, 3+ by IHC, or 2+/ISH+; none (0/3) with *HER2* mutations derived benefit. Three patients had exceptional benefit to second-line HER2 drugs after deriving no benefit on their first HER2 therapy, with a median GMI of 4.9 (4.7 − 6.5) and a median PFS of 11.0 (4.3 − 13.7) months. One patient remains alive over 60 months since diagnosis and has received 5 lines of anti-HER2 therapy (median PFS of 8.8 months per agent).

Conclusions: Anti-HER2 drugs in later lines can provide durable benefit relative to earlier-line chemotherapy in a large proportion of patients with HER2+ non-GEJ GI malignancies. Patients not benefiting from initial anti-HER2 drugs may still achieve sustained benefit from subsequent HER2-directed regimens. Early and continued incorporation of anti-HER2 agents throughout a patient's treatment course may optimize clinical outcomes.

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198P Detection of ERBB2 (HER2) amplification by next-generation sequencing (NGS) in patients (pts) with gastrointestinal (GI) cancer

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Background: Recent advances have transformed care for HER2-positive gastrointestinal cancer. However, the clinical utility of NGS-based techniques for determining HER2 status in GI cancer has been limited. Here, we detail our experience regarding the assessment of HER2 alterations in GI cancer.

Methods: 626 colorectal cancer (CRC) samples, 80 esophageal cancer (ESCA) samples, 153 esophagogastric junction cancer (EGJC) samples, and 286 gastric cancer (GC) samples were collected from August 2021 to April 2023. Among them, there were 82 CRC plasma samples, 33 GC plasma samples, 7 ESCA plasma samples, and 22 EGJC plasma samples. All specimens were detected by OncoDrug-Seq 603-gene panel assay through NGS using Illumina NovaSeq 6000. For plasmas, HER2 amplification defined as HER2 copy number >2.22 was identified. For tissues, HER2 amplification defined as HER2 copy number >6.00 was identified.

Results: For tissue samples, ERBB2 amplification was detected in 0.74% of CRCs, 3.56% of GCs, 1.37% of ESCAs, and 3.05% of EGJCs. Only 2 GC cases (6.06%) were found to have ERBB2 amplification for plasma samples. No ERBB2-amplified CRCs showed mismatch-repair deficiency. ERBB2 amplification is anti-correlated with RAS/RAF mutations in CRCs (p=0.047). Interestingly, ERBB2 amplification was associated with microsatellite stability in GCs (p=0.00078). Other driver alterations were not present in the ERBB2-amplified cases that currently have targeted therapies approved by the FDA including NTRK fusion, RET fusion, and BRAF V600E mutation.

Conclusions: The proportions of ERBB2 amplification in GCs and EGJCs were relatively high. The high positive rate in GC plasma samples is worthy of attention. The mutational landscape of ERBB2-amplified cases provides novel insights that can help guide further patient-personalized therapy.

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199P Novel machine learning (ML) algorithm to predict immunotherapy response in small cell (SCLC) and non-small cell (NSCLC) lung cancer

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Background: Immune checkpoint inhibitors (ICI) are used to manage patients with SCLC and NSCLC lung cancer. Yet, response rates are often low and identifying patients that will benefit from ICIs can be challenging. Accurate and accessible tools that predict ICI responses could enable a precision medicine approach that improves patient outcomes. This study aimed to use ML to predict response to ICI therapies in patients with lung cancer based on clinically available data.

Methods: 334 eligible records were reprocessed using one hot encoding. 161 patients had complete datasets available. Differences in data distribution were handled using the Synthetic Minority Oversampling Technique. Six ML algorithms were trained, including Linear regression, Support Vector Classifier, XGBoost Classifier, Random Forest, Decision Tree and Gaussian Naïve Bayes Classifier. The algorithms used 80% of the training data, were tested on 20% of validation data and used the Grid Search Cross-Validation technique for hyperparameter optimization.

Results: Of the 161 patients, 9% had SCLC and 80% had NSCLC. Patients receiving Pembrolizumab, Nivolumab and Atezolizumab comprised 62%, 11% and 25% respectively. XGBoost Classifier predicted response with the most accuracy, 64%. The artificial intelligence (AI) algorithm predicted and stratified ICI response better than PD-L1 levels alone (Table). The model showed good performance status, female gender and adenocarcinoma sub-type predicted response to ICI. Conversely, M1, N2 staging, male gender, squamous cell carcinoma sub-type and receiving Atezolizumab were predictive of disease progression.

Table: 199P

		Response (R) %	Stable Disease (SD) %	Disease Progression (DP) %	AI-predicted validation cohort %		
					R	SD	DP
Total *N=161*		29	8	63	33	6	61
PD-L1 levels	**<1%** *N=23*	13	9	78	33.3	0	66.6
	1-50% *N=19*	42	0	58	66.6	0	33.3
	>50% *N=33*	33	11	56	50	14	36

Conclusions: Multiple novel ML models, developed using clinically available data, showed that ICI type, histopathology sub-type and TMN staging impact ICI response in lung cancer. Future studies will seek to include more SCLC cases and compare the prediction accuracy among the three ICIs.

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200P Precise tumor & patient selection for CDR404: A bispecific & bivalent MAGE-A4 T cell engager

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Background: A phase 1 trial of CDR404, an antibody-based T-cell engager (TCE) targeting MAGE-A4, is planned for 2024. CDR404 binds to a MAGE-A4 peptide presented on cancer cell surface HLA-A2. There are no validated assays to measure HLA peptide presentation. RNA sequencing or immunohistochemistry (IHC) for total MAGE-A4 can be used as surrogates. To identify tumors for trial inclusion and enable precise patient selection, we performed bioinformatic analyses and compared two IHC antibodies.

Methods: 32 solid tumors were selected from the TCGA dataset and ranked based on MAGE-A4 mRNA prevalence and expression (high to low). To assess protein expression, we compared specificity of two commercial MAGE-A4 antibodies for patient selection: an anti-rabbit E7O1U clone and an anti-mouse OTI1F9 clone. Cross reactivity to MAGE-A family members was confirmed using IHC of individually transfected HEK293 cells.

Results: In ranking order, we identified 6 (RNA^{HIGH}) tumors: squamous lung (LUSC), squamous head & neck (HNSC), bladder (BLCA), uterine carcinosarcoma (UCS), testicular germ cell (TGCT) and squamous cervical (CESC), which had both MAGE-A4 mRNA highest prevalence and median expression. Both parameters were positively correlated (R^2=0.64, p=0.00012). Mean RNA levels were different for the RNA^{HIGH} group compared to the remaining 26 tumors (RNA_{LOW} group), which consisted mainly of adenocarcinomas (p=$9.1e^{-120}$). Of interest, human papillomavirus (HPV) negative (-VE) HNSC had higher RNA levels vs. HPV-positive (+VE) tumors (p=0.0046). In vitro over-expression experiments demonstrated that E7O1U only bound to MAGE-A4 whereas OTI1F9 cross-reacted widely with MAGE-A3, -A6, -A8, -A10, -A11 and -A12.

Conclusions: Squamous cell carcinomas were enriched in the MAGE-A4 RNA^{HIGH} group. Trial screening efficiency can be optimized by enrolling RNA^{HIGH} tumors especially LUSC and HPV -VE HNSC, two cancers with high unmet medical need. Lack of response reported in another MAGE-A4 TCE trial (NCT03973333) where tumor screening in ovarian cancer was absent confirms that IHC selection will be essential for RNA_{LOW} tumors. In this regard, we have identified E7O1U as a highly specific MAGE-A4 antibody for precise IHC patient selection in the CDR404 trial.

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201P Afatinib for EGFR, HER2 or HER3 mutated solid tumors: A phase II Belgian precision study

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Background: The Belgian Precision initiative aims to implement tumor-agnostic NGS in advanced cancer patients (pts) and enhance access to genotype-matching drugs. The current study aimed to investigate the efficacy of afatinib in advanced pre-treated solid cancers with an EGFR (excluding non-small cell lung cancer (NSCLC)), HER2 or HER3 mutation.

Methods: Open-label phase 2 study including 3 cohorts for previously treated advanced cancers: EGFR, HER2 and HER3 mutated. The primary endpoint for each cohort was objective response rate (ORR). Response assessment was performed every 8 weeks. For each cohort, a Simon two-stage design was used. The null hypothesis that the true ORR is 10%, was tested against a one-sided alternative that the true ORR is 30%. If two or more ORR were observed in the first ten pts, 19 additional pts were included (type I error 5% and power 80%) Secondary endpoints were disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety.

Results: A total of 45 pts were included in the trial with median age 62 years. The EGFR cohort comprised 7 pts: 2 pancreas, 1 head and neck, 1 breast, 1 endocrine tumor, 1 cervix and 1 kidney. The HER2 cohort comprised 30 pts: 11 NSCLC, 8 breast, 3 cervix, 2 colorectal, 2 head and neck, 1 bladder, 1 kidney, 1 liver and 1 pancreas. The HER3 cohort comprised 8 pts: 2 breast, 2 pancreas, 1 colorectal, 1 head and neck, 1 esophagus and 1 stomach. ORR and DCR were respectively 28.6% and 42.9% in the EGFR cohort, 3% and 49% in the HER2 cohort and 0% and 62.5% in the HER3 cohort. Partial responses were observed in a HER2-mutated NSCLC (1/11) with a DOR of 8.5 months, an EGFR-mutated breast cancer (1/1) with a DOR of 6.6 months and an EGFR-mutated pancreas cancer (1/2) with a DOR of 15.4 months. PFS and OS data will be presented at the meeting Safety data were consistent with the known safety profile of afatinib.

Conclusions: Although three pts demonstrated a clinical meaningful benefit, afatinib did not result in a significant ORR improvement in the HER2 cohort, which completed accrual. Recruitment was hampered by a lack of systematic agnostic NGS sequencing and the COVID epidemic. Broader and more systematic agnostic NGS would enable further exploration of HER inhibition in solid tumors

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202P Participant perceptions and mammography adherence from DETECT-A: The first prospective interventional trial of a multi-cancer early detection (MCED) blood test

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Background: MCED tests may improve early cancer detection, but the impact of MCED testing on anxiety and standard of care (SOC) screening adherence is unknown. The DETECT-A trial evaluated the CancerSEEK MCED test in 9,911 women without a cancer history (Science, 359:6499, 2020). DETECT-A participants without a cancer diagnosis were invited to a follow-up observational study involving annual surveys. Here we report on participant satisfaction, anxiety, intent to adhere to SOC cancer screening, and adherence to breast cancer screening.

Methods: The survey, conducted approximately 3 years after DETECT-A enrollment, assessed: a) whether participants regretted DETECT-A participation or would participate again, b) how likely they were to adhere to routine cancer screenings, and c) how participation affected their anxiety. Adherence to biennial mammography screening was assessed at the month of survey completion for screening-eligible participants with evaluable medical records.

Results: Of the 7573 DETECT-A participants contacted, 3,870 (51%) completed a survey. Of the 3,788 respondents who answered all survey questions, 96.9% indicated no participation regret, 98.8% would participate again, 99.5% reported being equally or more likely to adhere to SOC screening, and 98.7% reported no change in or reduced anxiety. Of 1,053 participants eligible for mammography with available health records, 93.4% (n=984) were adherent with mammography screening. 94.3% of participants with false positive (FP) results who completed a survey ($n = 35$) reported no change or a reduction in anxiety; 5.7% (95%CI 1.6%-18.6%) reported an increase in anxiety compared to 1.3% (95% CI 0.9%-1.7%) of participants with true negative results ($p = 0.07$).

Conclusions: A follow-up study of MCED participant survey responses revealed high levels of participant satisfaction, intent to adhere to SOC screening, and mammography adherence. Most participants reported no change or a decrease in anxiety. This data suggest that MCED testing with imaging-based diagnostic resolution does not significantly increase anxiety or negatively impact mammography adherence for most participants, including those with FP results.

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Corporation; Financial Interests, Personal, Licencing Fees or royalty for IP, I receive royalties for intellectual property owned and managed by Johns Hopkins University: Johns Hopkins University. A. Klein: Financial Interests, Personal, Advisory Role, consulting: Merck; Financial Interests, Personal, Advisory Board, consulting: OptumInsight; Financial Interests, Personal, Funding: OptumLabs. Z. Salvati: Financial Interests, Institutional, Research Funding: Exact Sciences Corporation. C. Tomasetti: Financial Interests, Personal, Advisory Role: Haystack Oncology, PrognomIQ; Financial Interests, Personal, Stocks or ownership: Haystack Oncology, PrognomIQ; Financial Interests, Personal, Licencing Fees or royalty for IP, I receive royalties for intellectual property owned and managed by Johns Hopkins University: Johns Hopkins University. E. Wagner: Financial Interests, Institutional, Research Funding: Freenome Holdings, Inc, Exact Sciences Corporation. C. Walter: Financial Interests, Institutional, Research Funding: Freenome Holdings, Inc, Exact Sciences Corporation. E. Fishman: Financial Interests, Personal, Other, Honoraria: GE Healthcare, HipGraphics; Financial Interests, Institutional, Research Funding: GE Healthcare, HipGraphics, GE Healthcare; Financial Interests, Institutional, Other, Honoraria: Siemens Healthineers. K. Kinzler: Financial Interests, Personal, Advisory Role, I also own stock: Haystack Oncology, Exact Sciences Corporation, Cage Pharma, ManaT Bio, Neophore; Financial Interests, Personal, Advisory Board, I also own stock.: Personal Genome Diagnostics; Financial Interests, Personal, Licencing Fees or royalty for IP, I receive royalties for intellectual property owned and managed by Johns Hopkins University.: Johns Hopkins University. B. Vogelstein: Financial Interests, Personal, Advisory Role, I also own stock: Cage Pharma, Catalio Capital Management, NeoPhore; Financial Interests, Personal, Stocks or ownership: ManaT Bio, Haystack Oncology, Personal Genome Diagnostics, Exact Sciences Corporation; Financial Interests, Personal, Licencing Fees or royalty for IP, I receive royalties for intellectual property owned and managed by Johns Hopkins University: Johns Hopkins University. T.M. Beer: Financial Interests, Personal, Full or part-time Employment: Exact Sciences Corporation; Financial Interests, Personal, Stocks/Shares: Exact Sciences Corporation, Salarius Pharmaceuticals; Financial Interests, Personal, Advisory Role, I also own stock: Arvinas; Financial Interests, Personal, Advisory Role: AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Constellation Pharmaceuticals, Dantari Pharmaceuticals, GSK, GRAIL, Janssen, Pfizer, Sanofi, Sapience Therapeutics. A. Buchanan: Financial Interests, Personal, Full or part-time Employment: IMPACT Pharmaceuticals; Financial Interests, Institutional, Research Funding: Exact Sciences Corporation, Freenome Holdings, Inc; Financial Interests, Personal, Licencing Fees or royalty for IP: MeTree and You, Inc.

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203P Genomic characterization of sporadic MET amplified non-small cell lung cancer (NSCLC) and association with real-world outcomes

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Background: *MET* copy-number amplifications (CNAs) are implicated as a resistance mechanism in patients treated with EGFR-targeted tyrosine kinase inhibitors and are associated with poor outcomes. However, data are limited on associations of immune biomarker and clinical outcomes among patients with sporadic *MET* CNAs — defined as preceding first-line (1L) therapy. This is the first real-world dataset to assess the prevalence of sporadic *MET* amplifications and their association with real-world clinical outcomes.

Methods: We analyzed a de-identified, multimodal dataset of 3,998 NSCLC patients biopsied prior to or within 30 days after the start of 1L therapy. Samples underwent NGS testing with Tempus xT (DNA-seq of 595-648 genes, 500x coverage). *MET* CNAs were identified using a CN threshold of $\geq$ 4 copies and compared to patients that were copy-number neutral (CN-N); patients with *MET* exon14 skipping mutations were excluded.

Results: The prevalence of sporadic *MET* CNAs in NSCLC patients was 5.7% (n=227). Patients with *MET* CNAs were more likely to harbor EGFR mutations compared to CN-N patients (17.6% vs 12.3%; p=0.02). In the subset of *EGFR* mutation-negative patients with PD-L1 data (n=2,230), a higher proportion of patients with *MET* CNAs were PD-L1-H (tumor proportion score $\geq$ 50%) compared to *MET* CN-N patients (45% vs 25.9%; p<0.001). Amongst *EGFR* mutation-negative patients (n=3,494), *MET* CNA-H patients were significantly enriched for High Tumor Mutational Burden (TMB-H, $\geq$ 10 Mut/Mb) compared to CN-N patients (21.4% vs 13.5%, p=0.004). In the subset of *EGFR* mutation-negative patients treated with 1L immune checkpoint inhibitors (ICIs, n=1,464); there was no significant difference in rwOS for patients with *MET* CNAs (median OS 21.5 months) vs CN-N patients (median OS 16.5 months), (HR=0.81, CI=[0.57, 1.14], p=0.22).

Conclusions: The majority of treatment-naive patients with sporadic *MET* CNAs are *EGFR* mutation-negative and enriched with biomarkers that are predictive of immune therapy benefit (PD-L1-H and TMB-H). Future clinical trials evaluating *MET* targeted therapy should account for this genomic heterogeneity and immunogenic therapeutic potential.

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204P Performance assessment of a comprehensive genomic profiling (CGP) NGS kit across multiple study laboratories

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Background: Precision oncology is a rapidly evolving field. Reliable tools are required for comprehensive genomic profiling (CGP) in clinical and research settings. NGS provides capabilities to detect multiple alterations, but complex workflows may be difficult to implement. Roche Diagnostics and Foundation Medicine have developed the AVENIO Tumor Tissue CGP Kit, a streamlined and easy to implement Research-Use-Only CGP assay to enable translational research labs.

Methods: The AVENIO Tumor Tissue CGP Kit profiles 324 genes for cancer alterations, tumor mutation burden (TMB), microsatellite instability (MSI), and genomic loss of heterozygosity (gLOH)). The kit contains reagents to create libraries. A software provides access to Foundation Medicine's bioinformatics pipeline. Five laboratories tested 160 samples, consisting of cell line and formalin fixed paraffin embedded (FFPE) tumor specimens. To assess reproducibility, 144 samples were evaluated across operators, lots, and instruments. To evaluate diagnostic sensitivity and specificity, 314 FFPE samples were tested and positive and negative predictive agreements determined against an orthogonal NGS method.

Results: Across five labs, pass rate was 98.1%. Sequencing quality metrics were high, with most samples reaching 1500x-2500x median coverage. Sites had 99.7% agreement for short variants. In the 144 sample reproducibility study, samples were highly uniform across variables, achieving >90% on-target rate. In the 314 sample concordance study, pass rate was 99.06%, with most samples achieving 2000x-2500x median coverage. Out of 314 samples, PPA to an orthogonal NGS-based method were: 98.3% short variants, 90.5% rearrangements, 94.8% copy number, 100% MSI, 100% TMB, and 96.8% gLOH. NPA reached 99.97% across short variants. Detected alterations included EGFR T7090M, BRAF V600E, KRAS 12/13 mutations, and EML4-ALK fusions.

Conclusions: CGP tests are being utilized in precision oncology, but NGS workflows and bioinformatics pipelines can be difficult to implement. The AVENIO CGP Tumor Tissue Kit is highly reproducible across sites and operators, achieving high sequencing quality metrics and diagnostic sensitivity.

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205P A novel immunoprecipitation/PCR method for detection of plasma cfDNA fragments selectively occupied by CTCF in cancer

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Background: CTCF-binding site (BS) occupancy is plastic, tissue specific and altered in cancer. This principle underlies some fragmentomics methods. We hypothesized that ChIP-Seq of plasma CTCF-cfDNA might identify CTCF-BSs selectively occupied in cancer and that, having removed all nucleosomes or other non-CTCF bound cfDNA by CTCF immunoprecipitation (IP), the presence of cfDNA fragments corresponding to sites selectively CTCF occupied in cancer may be tested for by PCR. We now report a novel liquid biopsy method, and initial results, based on this principle.

Methods: (i) Identification of CTCF-BSs selectively occupied in cancer samples. Plasma samples were collected from healthy volunteers (n=5), and patients with inflammatory conditions (n=5) or cancer (n=5). IP was performed using anti-CTCF coated magnetic beads and immunoprecipitated cfDNA was extracted, amplified and sequenced on an Illumina platform. (ii) We developed specific qPCR assays for 10 CTCF-BS sequences that we observed to be preferentially bound in the plasma of cancer patients vs either inflammatory conditions or healthy subjects. The panel of qPCR assays was tested on CTCF associated cfDNA isolated from plasma samples (1ml) obtained from patients diagnosed with a variety of common solid cancer diseases (n=48).

Results: We observed that specific CTCF IP resulted in isolation of cfDNA fragments with a frequency peak in the 30-80bp range that was not present in negative controls (mouse-IgG). These short cfDNA fragments included previously described CTCF binding sites. Moreover, CTCF binding sites were not randomly distributed on cfDNA fragments but located at the centre of each fragment. Among the CTCF occupied binding sites observed, we identified 29 sites that were significantly differentially bound in cancer. We observed highly sensitive and specific qPCR test results for a number of common solid cancer diseases including high sensitivity at disease stage I and II.

Conclusions: This is the first demonstration of IP of plasma CTCF-cfDNA. IP followed by multiplex PCR may form the basis of a rapid, low cost liquid biopsy method that obviates expensive library preparation and NGS.

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206P WAYFIND-R: A global, real-world database of patients (pts) with a solid tumour profiled with next-generation sequencing (NGS)

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Background: WAYFIND-R is a global, multicentre, prospective pan-cancer registry collecting long-term data from pts diagnosed with a solid tumour profiled with NGS. The goal is to advance precision medicine by providing high-quality real-world data (RWD) to researchers internationally.

Methods: WAYFIND-R data are electronically collected into a centralised database with standardised forms and high quality data management procedures. To ensure reliability/accuracy and a fit-for-purpose data source, data are periodically evaluated. Enrolment began in Sep 2020. Sites submit baseline pt, tumour, biomarker, NGS and molecular tumour board (MTB) decision making at enrolment, and treatment and outcome data at routine follow up.

Results: As of 31 Mar 2023, 855 pts had complete baseline data collection and cancer-related information; 755 carried on to the next data collection, 119 had died and 18 had ended participation. Pts were enrolled at 61 sites across 23 countries, mostly at academic institutions/university hospitals. The median age was 65 years (range: 20—93), 50% were female, 49% were retired and 62% had government insurance. WAYFIND-R had 109 cancer types and 160 subtypes (most common: adenocarcinoma [n = 389]). The most commonly detected genes were *TP53*, *KRAS*, *EGFR*, *BRAF* and *APC*. The most commonly screened non-NGS biomarkers were cytokeratin 7 (CK7/KRT7), PD-L1, CA19-9, CEA and Ki67. Table shows data for the most common cancer types in the registry.Many pts (n [341; 40%) had not been evaluated by an MTB. The most frequent MTB recommendation after NGS testing (n [213; 25%) was to start other treatment (chemotherapy: 63%; immunotherapy: 19%; targeted therapies: 18%).

Conclusions: The WAYFIND-R registry captures precision oncology data using a standardised approach globally. WAYFIND-R can enable further insights into clinical decision making, the timeliness of NGS testing and access to therapy.

Clinical trial identification: NCT04529122, first posted 27 August, 2020.

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Table: 206P

	Lung (n = 280)	Colon (n = 92)	Pancreas (n = 81)	Breast (n = 54)	Ovarian (n = 30)
Median age, years (range)	66 (38—90)	59 (24—88)	65 (34—88)	48 (25—81)	60 (28—78)
Female, n (%)	129 (46.1)	43 (46.7)	40 (49.4)	54 (100)	30 (100)
Most frequently screened biomarker	TTF1 PD-L1 Cytokeratin 7 (CK7/KRT7) ALK Napsin A	CK20 CDX-2 MSH6 CEA MMR status	Cytokeratin 7 (CK7/KRT7) CA19-9 CEA CDX-2 Ki67	Ki67 ER GATA3 PR Cytokeratin 7 (CK7/KRT7)	Cytokeratin 7 (CK7/KRT7) PAX8/PPARγ Ki67 WT1 CA125
Most frequently detected genes	*EGFR KRAS BRAF MET ALK*	*TP53 APC KRAS PIK3CA BRAF*	*KRAS TP53 CDKN2A TET2 ATM*	*TP53 PIK3CA ESR1 DNMT3A ERBB2*	*TP53 BRCA2 PTEN BRCA1 DNMT3A*

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207P Palbociclib (P) in patients (pts) with solid tumors with CDK4 or CDK6 amplification (amp): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study

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Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alterations. Results from 2 cohorts of pts with solid tumors with *CDK4* or *CDK6* amp treated with P are reported.

Methods: Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function and no standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited labs. Amp cut-offs were defined per NGS providers. Recommended dosing was 125 mg P orally once daily for 21 days on followed by 7 days off, until disease progression. Low accruing histology-specific cohorts with *CDK4* or *CDK6* amp were collapsed into 2 histology-pooled cohorts for analysis. Primary endpoint was disease control (DC) defined as investigator assessment of complete or partial response (PR) or stable disease (SD) of at least 16+ weeks (wks) duration (SD16+) per RECIST v1.1. The hypothesized null DC rate of 15% was evaluated by a 1-sided exact binomial test ($\alpha = 0.10$; power 65% and 58%, respectively). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response (DOR) and SD, and safety.

Results: Pts with solid tumors with *CDK4* amp (N=16) or *CDK6* amp (N=15) were enrolled. 1 pt from each cohort was not evaluable for efficacy. Table shows demographics and outcomes. For the *CDK4* cohort, 2 pts had SD16+ for a DC rate of 13% (p=0.72); the null DC rate was not rejected. Of pts with SD16+, duration of SD was 28 (ovarian) and 52 (adrenal) wks. For the *CDK6* cohort, 1 pt had a PR (pancreatic, DOR = 8 wks) for a DC rate of 7% (p=0.897) and OR rate of 7%; the null DC rate was not rejected. 6/31 pts had ≥1 tx-related grade 3-4 adverse or serious adverse event of neutropenia or thrombocytopenia.

Conclusions: P did not show antitumor activity in heavily pretreated pts with advanced solid tumors with *CDK4* or *CDK6* amp.

Table: 207P Demographics and efficacy outcomes

	CDK4 (N=16)	*CDK6* (N=15)
Median (Med) age, years (range)	61 (32-77)	64 (45-74)
Female, No. (%)	9 (56)	9 (60)
ECOG PS, No. (%)		
0-1	13 (81)	14 (93)
2	3 (19)	1 (7)
Prior systemic regimens, No. (%)		
0	1 (6)	–
1-2	4 (25)	6 (40)
≥3	11 (69)	9 (60)
DC rate, % (OR or SD16+) (1-sided 90% CI)	13 (3, 100)	7 (1, 100)
OR rate, % (95% CI)	0 (0,21)	7 (<1, 34)
Med PFS, wks (95% CI)	8 (8, 12)	8 (5, 8)
Med OS, wks (95% CI)	36 (11, 71)	14 (7, 26)
Tumor type		
Adrenal	1	–
Biliary tract	2	4
Chordoma	1	–
Colorectal	–	3
Esophagus	1	3
Non-small cell lung	4	–
Ovarian	1	–
Pancreatic	1	4
Prostate	2	–
Small intestine	–	1
Uterine	3	–

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208P Identification of BCOR mutation as a novel predictor of immunotherapy efficacy in gastrointestinal tumors

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Background: Immune checkpoint inhibitors (ICIs) have become an important therapeutic option for gastrointestinal cancer (GC). *BCOR* (BCL6 Corepressor) is an epigenetic regulator, whose mutation has been found to be associated with the development of various tumors, while evidence in GC remains limited.

Methods: We analyze genomic data from 236 GC patients receiving immunotherapy from Memorial Sloan Kettering Cancer Center (MSKCC) to assess the relationship between *BCOR* mutation status and efficacy of immunotherapy. The prognostic value and RNA mechanism exploration of *BCOR* mutations are explored in 914 GC samples from The Cancer Genome Atlas (TCGA) database. CIBERSORT is used to evaluate the infiltration status of 22 immune cell types in TCGA GC cohort. Survival is estimated by Kaplan-Meiercurves, with the P-values are determined by log-ranktest.

Results: The TMB levels of *BCOR*-mutant (Mut) patients are higher than *BCOR*-wildtype (WT) patients in both TCGA (Median: 24.25 [0.55 - 245.56] *vs.* 2.78 [0.05 - 1296.91], $P < 0.001$) and MSKCC (Median: 54.65 [2.95 - 203.64] *vs.* 6.14 [0.00 - 93.04], $P < 0.001$) cohort. *BCOR*-Mut patients receiving ICIs achieve prolonged OS than *BCOR*-WT patients (median OS: 14 months *vs.* not reach; HR 95% CI: 0.28 (0.09-0.90); $P = 0.03$); moreover, a multivariable analysis using Cox proportional-hazards regression demonstrated that *BCOR*-Mut was associated with better OS (HR = 0.29; 95% CI: 0.092-0.93; $P = 0.036$), after adjusting for age, gender, metastasis and treatment. In TCGA cohort, there is no significance in OS between *BCOR*-wildtype and *BCOR*-mutant patients (median OS: 55.4 vs 61.8 months, $P = 0.94$). Based on the analysis of immune cell infiltration status, the mechanism of the predictive value of *BCOR* mutation to ICIs efficacy may be related to the greater abundance of activated CD4 memory T cell, CD8 T cell, follicular helper T cell and Macropghages M1, and lower abundance of Monocytes and CD4 memory resting cells in *BCOR*-mutant tumors.

Conclusions: Survival analysis of MSKCC shows *BCOR* mutation is an independent predictor of ICIs treatment in GC, rather than a prognostic factor, and may be associated with better immune cell infiltration.

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209P Molecular atlas of copy number variation(CNV) in lung cancer with brain metastases

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Background: Patients (pts) with lung cancer had high rates of brain metastasis (BM). Genetic alterations were associated with the metastatic spread of lung cancer cells in recent study, lung cancer driver genes, such as *EGFR*, *ALK*, and *RET* are risk factors for brain metastasis in advanced lung cancer pts. The number of CNV regions was markedly higher in the secondary metastatic tumor than the primary tumor in the lung. However, the precise mechanisms in BM were still unclear. In this study, we explored the clinical and molecular features of lung cancer with brain metastases in Chinese real word.

Methods: This study retrospectively analyzed the genomic alteration of Chinese lung cancer with brain metastases pts during 2019-2022. Next-generation sequencing (NGS) was performed to detect gene mutations in tumor. Lung cancer driver genes set, as *EGFR*, *ALK*, *ROS1*, *BRAF*, *ERBB2*, *MET*, *KRAS* and *RET* were evaluated in those pts.

Results: 193 lung cancer with brain metastases pts were enrolled. Male:Female ratio: 128:65. Median age 61 years(Min-Max: 38-78). 79% of pts had CNV, and tumors with CNV had higher TMB values than those without CNV (7.7 vs. 2.8, $p<0.001$). The top3 amplification genes were: *EGFR*(n=25), *MYC*(n=11), *ERBB2*(n=10), and the three most frequently deletion genes were: *CDKN2A* (n=69), *CDKN2B* (n=69), *PTEN* (n=15). Among pts with TMB≥10, the proportion of pts with CNV was higher than that of pts without CNV (24% vs. 5%, $\chi 2=7.22$, $p < 0.05$). The numbers of pts with driver gene mutation and pts without driver gene mutation were 145 and 48, respectively, and there was no significant difference in age between the two groups. Pts with CNV and no driver gene mutation had higher TMB values (average TMB=9.6). The proportion of pts that carrying CNV in driver gene mutation tumors was similar to those without driver gene mutation (82% vs. 68%).

Conclusions: 79% of pts with brain metastases had CNV. The top3 amplification genes were: *EGFR*, *MYC*, *ERBB2*, and the three most frequently deletion genes were: *CDKN2A*, *CDKN2B*, *PTEN*. The proportion of pts that carrying CNV in driver gene mutation tumors was similar to those without driver gene mutation. Pts with CNV and no driver gene mutation had higher TMB values, indicating the pts may have more clinical benefits from immunotherapy.

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210P Lung tumour vascularity is a risk factor for survival in NSCLC patients undergoing surgery

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Background: Vascularization is known to be linked to tumour growth. We explored the potential of automated lung tumour vascularity assessment as risk factor for landmark survival.

Methods: 131 CT scans from the NSCLC Radiogenomics dataset were evaluated. All patients underwent surgery, with or without other therapies. Primary lung tumour (PLT) is segmented by a radiologist. Vessels segmentation (arteries and veins) is performed by an in-house deep learning segmentation model. Vascularity features extracted for the PLT include: amount of blood vessel connections, % of the tumour surface connected to vessels (%area), and basic statistics on the surface area of the connections. A generalized linear model (GLM) to predict landmark survival was trained with these features, tumour volume, and clinical factors. Stepwise feature reduction was performed to arrive to the final model. We present the odds ratio (OR) as well as a combined risk score for the remaining independent predictors.

Results: Landmark survival was reached for 86/131 (66%) patients. GLM analysis showed 4 independent risk factors related to landmark survival: %area (OR= 1.69 for >2.5%), age (OR=1.57 for >70 years), gender (OR=2.10 for male) and radiation therapy (OR=1.51 for yes). Smoking status and tumor volume were not retained in the final model. We also showed that risk of dying before landmark survival increased with increased number risk factors (0%, 18%, 40%, 48% and 100% for 0, 1, 2, 3, 4 risk factors, respectively).

Conclusions: Lung tumour vascularity is an independent risk factor for landmark survival. We showed an approach were it can be used as additional prognostic factor to inform clinical decision making and therapy planning.

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211P Cost-efficient detection of NTRK1, NTRK2 and NTRK3 gene rearrangements using the test for 5′/3′-end unbalanced expression: The analysis of 8075 patients

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Background: The majority of NTRK1, NTRK2 and NTRK3 rearrangements result in the increased expression of the kinase portion of the gene due to its fusion to an actively transcribed gene partner. Consequently, the analysis of 5′-/3′-end expression imbalance is potentially capable of detecting the entire spectrum of NTRK gene fusions.

Methods: Formalin-fixed tissue specimens were subjected to manual dissection of tumor cells, followed by DNA/RNA isolation and cDNA synthesis. 5′-/3′-end expression imbalance in NTRK genes was analyzed by real-time PCR. Further identification of gene rearrangements was performed by variant-specific multiplexed PCR for 42 common NTRK fusions, and, whenever necessary, by RNA-based next-generation sequencing (NGS).

Results: The study initially included 8075 tissue specimens; 651 (8.1%) of these samples failed to pass the quality control. NTRK rearrangements were detected in 7/6436 (0.1%) lung carcinomas, 11/137 (8.0%) pediatric tumors, and 13/851 (1.5%) adult non-lung malignancies. The highest incidence of NTRK translocations was observed in pediatric sarcomas (7/39, 17.8%). Relatively high frequency of NTRK fusions was seen in microsatellite-unstable colorectal tumors (6/48, 12.5%) and salivary gland carcinomas (5/93, 5.4%). None of 1293 lung carcinomas with driver alterations in EGFR/ALK/ROS1/RET/MET oncogenes had NTRK 5′/3′-end expression imbalance. Variant-specific PCR was performed for 744 tumors with normal 5′/3′-end expression ratio: there were no rearrangements in 172 EGFR/ALK/ROS1/RET/MET-negative lung cancers and 125 pediatric tumors, while NTRK fusions were detected in 2/447 (0.4%) non-lung adult malignancies.

Conclusions: This study describes a robust pipeline for the detection of NTRK1, NTRK2 and NTRK3 gene fusions, which may be considered as a cost-efficient alternative to conventional methods of NTRK analysis.

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212P Extracellular vesicle miRNA as effective biomarkers for predicting antitumor efficacy in lung adenocarcinoma treated with chemotherapy and checkpoint blockade

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Background: Immune checkpoint inhibitors (ICIs) have improved the care of patients in metastatic lung adenocarcinoma (LUAD). However, PD-L1 status, high Tumor Mutational Burden (TMB), and mismatch repair deficiency are the only validated biomarkers of efficacy for ICIs. These markers remain imperfect, and new predictive markers represent an unmet medical need. MicroRNAs (miRNAs) encapsulated within plasma-derived extracellular vesicles (EVs) may be suitable for use as noninvasive diagnostic biomarkers for aggressive malignancies, including LUAD. Here, we assessed the possibility of plasma EVs derived miRNAs as potential biomarkers for predicting and identifying the beneficiaries of combined immunochemotherapy.

Methods: A total of 31 patients with metastatic LUAD who received pembrolizumab combined with pemetrexed and carboplatin were enrolled. After efficacy evaluation. 25 patients had durable clinical benefits from combined immunochemotherapy, and the rest patients showed disease progression. MiRNA profiles of plasma-derived EVs from these patients were investigated using unsupervised hierarchical clustering.

Results: 46 differentially expressed miRNAs (DEMs) were identified between responders and non-responders. Interestingly, we found that miR-6815-5p, miR-15a-5p, miR-92a-3p, and miR-107 were obviously down regulated in non-responder group. However, miR-769-5p, and miR-589-5p showed a trend of significantly increased expression. In addition, all these findings were further confirmed by clinical imaging assessment.

Conclusions: In conclusion, EVs miRNAs derived from patients with lung cancer showed promising application scenarios for effectively identifying true responders treated with combined immunochemotherapy.

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213P Unlocking cancer treatment opportunities by population-based advanced diagnostics in Norway

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Background: Targeted cancer treatment has been developed at a rapid pace, but implementation of precision cancer medicine (PCM) has met several challenges. Key challenges are: 1) lack of clinical evidence within and across tumor groups 2) lack of predictive biomarker 3) access to medication and 4) regulatory and economic factors. These are interconnected, and PCM trials are needed to address most of them. To meet the need for tailored diagnostics for PCM trials, we designed a national Infrastructure for Precision Diagnostics — InPreD-Norway.

Methods: In 2020, the CEOs of the four Norwegian health regions allocated funding to the six university hospitals to form a collaborative network, InPreD, with dedicated environments (nodes) at each site for implementing next-generation cancer diagnostics. The first task has been to build a complete program for Comprehensive Gene Profiling (CGP), including a national virtual tumorboard, for patients eligible for experimental cancer treatment and trial inclusion.

Results: The InPreD nodes were gradually built at the six university hospitals. The largest hospital, Oslo University Hospital, was initiated first, built a transdisciplinary environment and implemented a complete pipeline for CGP testing (TSO500). These solutions were used by the other nodes when they were initiated. In spring 2023, the InPreD nodes had completed CPG profiling of 1000 patient cases. A new treatment opportunity was found for 34% of the patients, where referral to the national PCM trial IMPRESS-Norway trial dominated (21%). The National molecular tumorboard meets virtually twice weekly to discuss the analysed cases with the InPreD nodes and the referring physicians, providing both an advisory but also and educational role. InPreD now plan novel diagnostics such as drug sensitivity screening and digital pathology biomarkers for planned trials.

Conclusions: The national Infrastructure, InPreD, secures competence building and standardised service in CGP testing nationwide, providing new treatment opportunities for cancer patients. Beyond strengthening the ability to identify patients to clinical trials, it serves as a united interaction partner for national stakeholders such as governmental bodies, health authorities and industry.

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214P PESSA: A shiny app for pathway enrichment score-based survival analysis in cancer

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Background: The activation levels of biologically significant gene sets are innovative molecular markers for tumours and play an irreplaceable role in the diagnosis, staging, prognosis evaluation and treatment of tumours; however, there is still a scarcity of web-based tools for prognosis analysis that use gene set activation levels as molecular markers for tumours. We have developed a web-based tool for survival analysis using gene set activation levels.

Methods: All data analysis within PESSA is implemented via R. Activation levels of MSigDB gene sets were assessed using the single-sample gene set enrichment analysis (ssGSEA) method based on microarray and high-throughput sequencing data from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA). PESSA was used to perform median and best cut-off dichotomous grouping of ssGSEA scores for each dataset, relying on the survival and survminer packages for survival-related analysis and visualisation. The web pages were built relying on Shiny.

Results: PESSA is an open-access online tool for visualising prognostic analysis based on the activation levels of biologically significant gene sets as molecular markers of tumour prognosis. A total of 214 datasets from the GEO and TCGA covering 51 different cancer types and 13 different survival status types were included; 13,434 tumour-related gene sets were obtained from the MSigDB for pre-grouping. For survival analyses, the gene set of interest was selected; Kaplan−Meier analyses and visualisation were conducted based on the median and best dichotomous cut-off, plus continuous variables were subjected to univariate Cox regression analyses.

Conclusions: PESSA (https://smuonco.shinyapps.io/PESSA/) is a large, interactive, easily accessible web-based analysis tool covering a large amount of data; it can creatively use predefined gene set activation levels as molecular markers of tumours and facilitate survival analysis for cancer patients.

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215P Identifying predictors of overall survival among TMB-low cancer patients treated with immune checkpoint inhibitors

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Background: Dichotomizing tumors into tumor mutational burden (TMB)-high and TMB-low is common practice but may not determine which patients will benefit from immune checkpoint inhibitors (ICI). This study examines the impact of somatic mutations on overall survival (OS) for TMB-low metastatic cancer patients (MCP) treated with ICI.

Methods: Genomic (MSK-IMPACT) and clinical data from 1,172 TMB-low (<10mut/Mb) MCP were collected. OS accordingly to single-genemutations was assessed by Kaplan-Meier (KM) method. For genes exhibiting a correlation with OS, we conducted a Cox multivariate analysis (CMA) stratified by TMB, sex, age, microsatellite instability (MSI), and histology. KM and CMA were also performed to investigate the relation between insertions and deletions (InDels) and OS. Linear regression (LR) investigated the relation between TMB and InDels burden. Decision tree modeling (DTM) aimed to predict whether patients that received ICI harbored OS shorter or longer than the median OS of 15 months. The discriminative features (DF) for DTM were TMB (continuous), gene mutations, sex, and histology.

Results: Mutations in 25 genes were related to OS. CMA confirmed 9 genes associated with superior (*VHL*) and inferior (*CTNNB1, DAXX, H3C2, HLA-A, IGF1R, KMT2D, SMARC4, TP53*) OS ($P < 0.05$). MSI, age, and gender did not affect OS. Melanoma, bladder, and RCC endowed patients with better OS ($P < 0.01$). TMB and InDels exhibited a R-squared of 0.38 - low (or absent) relation. The InDels burden was unrelated to OS ($P = 0.21$). *VHL* mutation was a predictor of better OS in uni- and multivariate levels for RCC (N=149; $P < 0.01$). At DTM, RCC histology was the first DF (gini 0.492). For RCC patients, VHL mutation was the second (gini 0.349). For non-RCC patients, melanoma histology was the second. At the third layer, a TMB threshold of 5.095 mut/Mb for *VHL* wild-type patients and *TP53* mutation for non-RCC and non-Melanoma patients were the following DF.

Conclusions: Tumor histology, mutated genes, and a better adjusted TMB cutoff (5.095 mut/Mb) are important for predicting ICI treatment outcomes in TMB-low patients. Among RCC patients, VHL mutations predict better OS. Individualized profiling is needed for a tailored ICI treatment strategy.

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216P PTCH1 mutation as a potential predictor of immune checkpoint inhibitors in gastrointestinal cancer

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Background: The association between genetic alterations and benefit of immunotherapy is well documented, but evidence for gastrointestinal cancer (GC) remains limited. Patched1 (PTCH1) mutation, a frequently altered gene in GC, lead to dysregulation of Hedgehog signaling. However, the efficacy of *PTCH1* mutations in immunotherapy in patients with GC remains unclear. Herein, we aimed to analyze the association between *PTCH1* mutations and immune checkpoint inhibitors (ICIs) efficacy in patients with GC.

Methods: We screened the following 3 cohorts: (1) MSKCC cohort (N=236) of GC (including esophageal, gastric and colorectal cancers) who received ICIs. (2) Peking University Cancer Hospital (PUCH) GC cohort (N=92) who received ICIs. (3) the TCGA cohort (N=914) of GC. The patients were divided into *PTCH1* mutant type (*PTCH1*-MT) group and *PTCH1* wild type (*PTCH1*-WT) group. We analyzed the differences in overall survival (OS) and TMB between the two groups. Tumor immune microenvironment (TIME) was evaluated by calculating the cell infiltration score as the arithmetic mean analysis of the constituent genes.

Results: In MSKCC cohort, *PTCH1*-MT group (9.3%) had significantly better OS ($p=0.017$, median OS, 34m vs. 13m) and higher TMB ($p<0.01$). The results of the multivariate analysis showed that *PTCH1* had a significant effect on OS, with the *PTCH1*-MT group had better OS ($p=0.035$; HR=0.37; 95%CI: 0.15-0.93). Furthermore, we consistently observed in the PUCH cohort that the *PTCH1*-MT group (7.6%) significantly prolonged OS ($p=0.036$). Additionally, in the TCGA cohort, we similarly observed a trend towards longer OS ($p=0.63$, mOS, 70.2m vs. 61.8m) and higher TMB ($p<0.01$) in *PTCH1*-MT group (5.8%). It shows that *PTCH1* is a predictor, but not a prognostic factor. Subsequently, we assessed the abundance of 22 predefined immune cells. The score of CD4 T cells, CD8 T cells, NK cells, mast cells, and M1 cells were all significantly higher in the *PTCH1*-MT group ($p<0.05$). It shows that the *PTCH1*-MT group has a higher activation TIME.

Conclusions: Our study demonstrated that *PTCH1* mutation could act as a potential predictor for ICIs therapy in GC. In the future, relevant prospective clinical trials need to be designed to verify this conclusion.

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217P Clinical and molecular features of PTCH1 mutant in solid tumors

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Background: *PTCH1*, a tumor suppressor and inhibitor of the hedgehog pathway. Hh signaling was reported to modulate the tumor microenvironment by increasing immune checkpoint expression and promoting an inflammatory environment. Mutations of *PTCH1* are potential therapeutic targets, Hh pathway inhibitor has been developed as a treatment for patients with advanced solid tumors. It is thus important to understand the genomic landscape of *PTCH1* mutation. Here, we explored *PTCH1* mutation profiles in Chinese solid tumors.

Methods: Next-generation sequencing of 551-gene profiling was performed to analyze postoperative tissues from 22312 Chinese solid tumors in 2019-2022. Somatic mutations and copy number variations were detected following the standard operating procedure.

Results: *PTCH1* mutations were present in 3.1% of patients with advanced solid tumors, a total of 791 *PTCH1* somatic mutations were detected in 684 tumor samples. The higher frequency cancer type contained lung cancer(n=239), colorectal cancer(n=137), and stomach cancer(n=60). Of 791 *PTCH1* mutations, missense mutations(65%,n=514) were more observed, and 25% were loss of function (LOF) mutations, including frameshift(n=124), nonsense(n=50), splicing(n=23) mutations. Exon 23, exon1 and exon22 of *PTCH1* were the main mutational hotspot regions found, with p.S1203Afs*52 (n=26), p.R1308Efs*64 (n=22), p.R602* (n=11), p.Y1316Tfs*56 (n=11) being the most frequent mutations in our study. There was a significant statistical difference in TMB values that the *PTCH1* mutant group was higher than the *PTCH1* wild-type group (39 vs. 5, $p < 0.001$), and patients who presented with two or more *PTCH1* mutations with higher compared with those patients carried only a single mutation (129 vs. 29, $p < 0.001$). TMB in *PTCH1* frameshift_variant tumors (53, 0−672) was significantly higher than TMB in *PTCH1* splice

variant tumors (15, 0—60; $P < 0.05$). The proportion of *PTCH1* alterations in MSI-H tumors was higher than those without mutations (22% vs. 1%, $p < 0.001$).

Conclusions: In our study, *PTCH1* mutations are present in 3.1% of solid tumors, and mostly occurred in exon 23, exon1, and exon22. *PTCH1* mutant tumors tended to be associated with higher TMB values (39 vs. 5), therefore, Hh pathway inhibitor combined immunotherapy may be considered in the future.

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218P Peripheral T cell activation phenotype is associated with clinical outcomes and immune-related adverse events of ipilimumab-nivolumab in advanced hepatocellular carcinoma

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Background: Although combination immunotherapies have become a mainstay of treatment for patients with advanced hepatocellular carcinoma (HCC), studies of circulating biomarkers for immunotherapy in HCC are still limited. Therefore, we aimed to evaluate the peripheral T-cell activation phenotype as a biomarker for clinical outcomes of immunotherapies for HCC.

Methods: Baseline blood samples from 86 patients with advanced HCC in three tertiary cancer centers in Korea (ipilimumab-nivolumab [Ipi/Nivo], n=55; nivolumab [Nivo], n=31) were prospectively collected and analyzed.

Results: In the discovery cohort of the Ipi/Nivo group, the peripheral T-cell activation phenotype (IFN-γ^+TNF-α^+) at baseline was significantly higher in patients with partial response or stable disease compared with those with progressive disease. The cut-off value for high-peripheral T-cell activation phenotype was set to 5.55% using maximally selected rank statistics for optimally predicting survival outcomes. In both the discovery and validation cohorts, the patients with high-peripheral T-cell activation phenotypes showed an increased ORR and more favorable PFS (discovery cohort: hazard ratio [HR], 0.35; 95% CI, 0.16—0.74; $P = 0.004$; validation cohort: HR, 0.22; 95% CI, 0.04—1.11; $P = 0.046$) and OS (discovery cohort: HR, 0.44; 95% CI, 0.20—0.99; $P = 0.042$; validation cohort: HR, 0.20; 95% CI, 0.04—1.02; $P = 0.036$) than those with low levels. These results were consistent in the Nivo cohort. Regarding immune-related adverse events (irAEs), patients with high-peripheral T-cell activation phenotype showed higher incidence of irAEs compared with those with low levels (14.3% vs. 37.0%). Of note, comparing baseline peripheral blood cytokine levels according to irAEs, the patients with irAEs had significantly lower serum levels of IL-6 at baseline.

Conclusions: Baseline peripheral T-cell activation phenotype was a predictor of clinical outcomes and irAEs in patients with advanced HCC receiving Ipi/Nivo immunotherapy. Patients with lower serum IL-6 levels at baseline might experience more frequent irAEs during Ipi/Nivo treatment in advanced HCC.

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219P Multicentric evaluation of amplicon-based next-generation sequencing solution for local comprehensive molecular tumor profiling

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Background: Molecular profiling of tumors is an essential step in the management of cancer patients, enabling personalized treatment decisions. Oncomine Comprehensive Assay Plus (OCA+) is an amplicon-based next-generation sequencing solution that can detect multiple biomarkers, including complex biomarkers, in a single assay. Here, we aimed to evaluate the sensitivity, specificity, and concordance of this comprehensive genomic profiling solution in detecting various types of biomarkers in a multicentric study using a cohort of 190 pre-characterized clinical tumor samples.

Methods: DNA and/or RNA were obtained from formalin-fixed paraffin-embedded (FFPE) tumor samples from patients with different cancer types from 5 different centers. Samples studied addressed the complete variety of genomic alterations targeted by the Oncomine Comprehensive Assay Plus. OCA+ was used to generate libraries that were sequenced using the Ion S5 Prime system and analyzed using Ion Reporter Oncomine Comprehensive Plus - w3.0 workflow. Single nucleotide variants (SNVs), insertions/deletions (indels), copy number alterations (CNAs), gene fusions, tumor mutation burden (TMB), microsatellite instability (MSI) and Genomic instability (GIN related to HRD) results were compared to orthogonal and gold standard methods.

Results: OCA+ demonstrated a total success rate of 97.2%. High sensitivity and specificity were obtained in detecting multiple biomarkers, including complex biomarkers. The assay detected >95% of SNVs and indels with a variant allele frequency (VAF) of ≥5%, and identified gene fusions, TMB, MSI and GIN with high concordance to orthogonal methods, 90%, 70%, 84% and 93% respectively.

Conclusions: OCA+ is a sensitive and specific platform for molecular tumor profiling, including the detection of complex biomarkers. The high concordance rate with orthogonal methods highlights the assay's potential in guiding clinical decision-making for personalized cancer care. OCA+ may provide comprehensive genomic information for cancer management and may be a valuable tool for further implementing precision medicine in oncology.

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220P Biomarker of blood age and inflammation in older cancer patients might predict outcome

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Background: Two-thirds of all cancers are diagnosed in patients above the age of 65 years, often associated with worse outcomes. The aim of this cohort study was to identify the predictive value of blood markers of inflammation, cell activity, and aging in older patients with solid malignant tumors.

Methods: Patients diagnosed with solid tumors were included at the Cancer Center Baselland, Switzerland. We investigated the predictive value on overall survival of blood markers sampled by clinical routine, including CRP (C-reactive protein), NLR (Neutrophil-to-lymphocyte ratio), LDH (Lactate dehydrogenase), Albumin, and Vitamin B12 (Cobalamin). The study analyzed the median value of each blood marker in all patients diagnosed after January 1, 2018, and calculated the survival curves and hazard ratios.

Results: From Jan 2018 to Feb 2022, a total of 510 patients were included with a median age at diagnosis of 72 years (57-91 years). Among these patients, 246 had localized disease, and 262 had advanced disease at primary diagnosis. The diagnoses included NSCLC (n=158, 31%), CRC (n=98, 19%), breast cancer (n=58, 11%), prostate cancer (n=82, 16%), pancreas cancer (n=42, 8%), urothelial cancer (n=42, 8%) and SCLC (n=30, 6%). Patients with abnormal median blood values had a significantly increased risk of poor outcomes. NLR>4 ($p<0.001$, HR=2.37), CRP >5mg/l ($p=0.021$, HR=1.6), CRP>10mg/l ($p<0.001$, HR=4.0-6.6), Albumin<35g/l ($p<0.001$, HR=3.05), LDH>250U/l ($p<0.001$. HR=2.24), and Vitamin B12>810pmol/l ($p<0.002$, HR=2.96) were associated with increased hazard ratios.

Conclusions: Older cancer patients with abnormal inflammation and aging markers had worse outcomes. This highlights the potential role of these blood markers in predicting outcomes in cancer patients with solid tumors. It is important to note that these blood markers are not cancer-specific, and their levels can be affected by other factors, such as infection, inflammation, and nutritional status. However, when used in conjunction with other clinical and pathological factors, they may provide additional information for risk stratification and treatment planning. Overall, our study adds to the growing body of evidence on the potential role of blood biomarkers in predicting outcomes in cancer patients.

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221P Peripheral T cell activation phenotype predicts clinical outcomes of atezolizumab-bevacizumab therapy in unresectable hepatocellular carcinoma

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Background: Atezolizumab plus bevacizumab (Ate/Bev) has demonstrated superior efficacy to sorafenib, thereby becoming the new standard first-line treatment in patients with unresectable hepatocellular carcinoma (HCC). However, there is a lack of reliable biomarkers that could predict clinical outcomes of Ate/Bev. In this study, we aimed to assess the clinical and immunological implications of peripheral T-cell activation phenotype as a biomarker in patients with HCC treated with Ate/Bev.

Methods: This study prospectively enrolled 106 patients with unresectable HCC treated with Ate/Bev (discovery cohort: 50 patients from one center; validation cohort: 56 patients) as the first-line systemic treatment in three tertiary cancer centers in Korea. Baseline blood samples were analyzed using multiplex flow cytometry.

Results: The optimal cut-off value for baseline peripheral T-cell activation phenotype (IFN-γ^+TNF-α^+), 2.50%, was determined using maximally selected rank statistics. In the discovery cohort, the patients with high-peripheral T-cell activation phenotype at baseline had an increased objective response rate (ORR) than those with low activation levels (15.4% vs. 35.1%). Moreover, progression-free survival (PFS) and overall survival (OS) were significantly longer in patients with high-peripheral T-cell activation phenotype than those with low levels (hazard ratio [HR], 0.37; 95% CI, 0.18−0.79; $P =$ 0.008 for PFS; HR, 0.18; 95% CI, 0.07−0.41; $P < 0.001$ for OS). In the validation cohort, these findings were consistently observed. The patients with high-peripheral T cell activation phenotype at baseline were associated with a higher ORR (15.0% vs. 38.9%) and longer PFS (HR, 0.43; 95% CI, 0.22−0.85; $P = 0.012$) and OS (HR, 0.41; 95% CI, 0.18−0.96; $P = 0.035$) compared with those with low activation levels.

Conclusions: Highly activated peripheral T-cell phenotype was associated with favorable clinical benefit in patients with unresectable HCC treated with Ate/Bev. Therefore, peripheral T-cell activation phenotypes could be used as a potential predictor of Ate/Bev treatment.

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222P Therapeutic opportunities for porcupine inhibition in gastrointestinal cancer

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Background: Gastrointestinal (GI) cancer (Upper/Lower GI and Hepatobiliary) causes more cancer deaths than any other body system. Wnt pathway activation promotes common GI cancers, but safely targeting this pathway is challenging. Inhibition of Porcupine, an enzyme essential for Wnt ligand activity, has clinical potential to suppress Wnt in a safe and tolerated manner. Preclinically, GI tumors with upstream Wnt pathway variants (RNF43 loss of function (LoF), RSPO gain of function (GoF)) are Wnt ligand dependent and exquisitely sensitive to RXC004, a small molecule Porcupine inhibitor. Using Caris data, 278,649 human tumor samples (across all 58 solid tumor lineages) were analysed for the prevalence of upstream Wnt pathway variants and associated features.

Methods: Human tumors were analysed by next-generation sequencing of DNA (592 genes, NextSeq; WES, NovaSeq) and RNA (WTS, NovaSeq) by Caris. Molecular profiles and prevalence of RNF43_LoF and RSPO2/3_GoF cases were compared with negative (WT) cases using Fisher-Exact analysis. Real world overall survival was obtained from insurance claims data and Kaplan-Meier estimates were calculated for defined cohorts from time of tissue collection to last contact.

Results: Prevalence of RNF43_LoF, RSPO2_GoF and RSPO3_GoF were 1.3%, 0.1% and 0.3% in all lineages; increasing to 3.6%, 0.2% and 0.9% in GI lineages. The top lineages by combined Wnt ligand dependent prevalence were GI: Small Bowel (9.6%), Colorectal (CRC; 5.9%), Pancreatic (5.4%) and Gastric (4.3%) cancers. Of 15,025 CRC cases, 13,886 (92%) were Microsatellite stable (MSS). Within MSS CRC cases, prevalence of RNF43_LoF was 2.6% and RSPO2/3_GoF was 1.6%; hence total prevalence was 4.2%. BRAF_V600E had high co-occurrence with Wnt ligand dependent (42%), compared to WT (3.4%), MSS CRC cases. In MSS CRC, upstream Wnt pathway variants were associated with poor prognosis in either all cases (HR 1.64; $p<0.0001$) or BRAF_WT cases (HR 1.52; $p<0.0001$) versus WT cases.

Conclusions: Upstream Wnt pathway variants are enriched in GI cancer, in particular Small Bowel cancer, a rare subtype of high unmet need. In MSS CRC cancer, the poor prognosis and high BRAF_V600E co-occurrence with upstream Wnt pathway variants suggests benefit of co-targeting Wnt and MAPK pathways in this population.

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223P Artificial intelligence-based pathomics biomarker predict primary resistance to first-line treatment in metastatic colorectal cancers

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Background: The backbone chemotherapy of first-line standard of care (SOC) for microsatellite stable (MSS) metastatic colorectal cancer (mCRC) combines 5-Fluorouracil to oxaliplatin and/or irinotecan. There are no biomarkers to predict response, which is complete or long-lasting (CR/LLR) in ∼25% of patients, while ∼15% are primary refractory. Our study aims at developing an accurate response predictor via a pathomics model based on Hematoxylin & Eosin (H&E)-stained digital slides (WSI).

Methods: We trained an unsupervised bag-of-words artificial intelligence (AI)-based model on 62 patients classified as response outliers as follow: i) *super-sensitive* if they achieved CR or LLR >10 months to any SOC (N=20); ii) *refractory* if progression occurred at first disease reassessment (N=42). WSIs of the resected primary tumors were tiled into patches of 224x224 pixel (0.5µm/pixel). First-order and texture features were subsequently extracted from all tumoral tiles, and grouped into homogenous clusters through a 3x3 self-organized map. For each patient, the percentage of tiles belonging to each tiles' cluster was computed and used by a dendrogram to create clusters of similar patients. Patients' survival was calculated by landmark analysis logrank test. Main clinicopathological features were matched to treatment response by Fisher's exact test.

Results: Primary resistant patients had significantly worse survival [logrank HR 4.2 95% CI (2.7-7.3)]. While outliers showed similar clinicopathological features (including stage, *RAS/BRAF* status, histotype and sidedness), pathomics signatures were significantly associated to primary resistance (p=.005). According to the unsupervised clustering, we classified as resistant patients belonging to four out of eight clusters obtaining an 88% (23/26) negative predictive value. We observed that patients classified as belonging to one of the four resistant clusters were predominantly characterized by a specific pattern of patches.

Conclusions: We demonstrated that a pathomics signature has the potential to predict resistance to SOC in MSS mCRC. Validation of these preliminary findings on a further cohort of 125 patients is ongoing.

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224P Germline HLA-I/II is not associated with clinical outcome but the absence of HLA-A01 or the presence of HLA-B27 supertypes were correlated with improved clinical outcome among patients with NSCLC treated with pembrolizumab in combination with chemotherapy

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Background: Maximal heterozygosity on the human leukocyte antigen (HLA) loci was found to be associated with improved survival among NSCLC patients treated with immune checkpoint inhibitors (ICI). Here we aimed to investigate the effect of germline HLA-I/-II zygosity on clinical outcomes among NSCLC patients treated with first-line pembrolizumab in combination with chemotherapy. We explored the correlation between different HLA-A/-B supertypes and clinical outcome among the same cohort.

Methods: We prospectively collected pre-treatment blood from patients with NSCLC treated with first-line pembrolizumab in combination with chemotherapy. DNA was extracted from white blood cells and used for high resolution HLA-I/II typing. Genomic HLA-I/II homozygosity was correlated with clinical benefit. We used Sidney et al to classify genomic HLA-A and -B into supertypes.

Results: Of 65 patients recruited, 53 complied with the inclusion criteria. Of those 76%(40/53) have PD-L1 expression of <50% of their cancer cells. Our analysis did not find any association between HLA-I/-II homozygosity and clinical outcome among patients with NSCLC treated with pembrolizumab in combination with chemotherapy. However, the absence of HLA-A01 was associated with favourable PFS (HR=2.09, 95% CI 1.03-4.27, P=0.22) and improved OS (HR=2.58, 95%CI 0.96-6.89, P=0.038). the presence of HLA-B27 was associated with improved PFS (HR=0.24, 95%CI 0.12, P=0.004) but not OS.

Conclusions: The absence of association between genomic HLA-I/-II homozygosity and clinical outcome among patients with advanced NSCLC treated with pembrolizumab in combination with chemotherapy might reflect a diminished role for HLA molecules among patients with low or no PD-L1. HLA-A01 and HLA-B27 might have a role in predicting clinical outcome among this cohort of patients. Further studies are needed to explore biomarkers for this group of patients.

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225P Utility of next-generation sequencing (NGS) in patients with advanced cancer in a low-middle income country

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Background: NGS use improve outcomes in cancer patients. However, approved drugs in differents countries is a concern. The impact in intermediate-low income populations is less studied. We report the results about the utility of NGS at a comprehensive cancer center in Cali, Colombia. Country with less approved drugs by the national regulator (INVIMA) compared to populations such as in Europe (EMA) or United States (FDA).

Methods: Retrospective study of patients with advanced cancer who underwent NGS either by tissue or liquid biopsy, between March 2019 and March 2023 at The Comprehensive Cancer Center Clinica de Occidente in Cali-Colombia. Relevant sociodemographic, clinical, and molecular variables were included. We performed descriptive, Kaplan Meier and cox regression analysis. The study was approved by the institutional ethics committee. The information was analyzed with Stata 16.

Results: 156 patients were identified. Median age was 66 years (20-89), 51% men. 18 different tumors types were included, with lung (39.1%), prostate (22.4%), breast (7.0%), colorectal (6.3), ovarian (5.1%), gastroesophageal (5.0%), between the principals. Actionable alterations (ESCAT I-V) were found in 49.6% of the patients, most were evidence I in 81% of them. 90% had FDA approval, 84% EMA, and 59% national approval by INVIMA. After the NGS result, clinical decision was modified in 46.4% of cases and match therapy was used in 57.5% of them. In those patients, there was better clinical benefit with OR 6 (95% CI 1.31-29.39, P=0.0059) and objective response OR 12 (95% CI 1.88-88.38, P=0.0012) There was significant improvement of PFS HR 0.27 (95% CI 0.13-0.56, P=0.000) and OS HR 0.34 (95% CI 0.15-0.73, P=0.002)

Conclusions: Genomic profiling through NGS had a significant impact on decision-making and patient prognosis, despite the fact that only 59% of the indicated matched drugs had national approval for their use.

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226P LongiBloodImmunoM: A multi-step analysis pipeline for longitudinal blood-based immunomonitoring for immunotherapy clinical trial

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Background: Yttrium-90 (Y90)-resin microspheres radioembolization followed by nivolumab (Nivo) has shown encouraging response rate in advanced hepatocellular carcinoma (HCC), but only a subset of patients benefit from it. Predictive biomarkers help to identify patients for the treatment.

Methods: Longitudinal plasma and peripheral blood mononuclear cells (PBMCs) collection from HCC patients who received sequential Y90-RE followed by nivolumab (CA209-678; NCT03033446) allowed assessment of dynamics changes. Predictor selection procedure includes individual timepoint comparison, average analysis, trajectory description, responsiveness prediction, and combined modalities validation. 65-plex Human ProcartaPlex Luminex panel was employed to examine the concentration of cytokines and chemokines in 187 plasma samples collected at eight timepoints (responder [R]=11, non-responder [NR]=22). Immunomonitoring of PBMCs (NR=12, R=5) was assessed with a 39-plex Cytek panel followed by dimension reduction analysis. CXCL9 was reported impacting the immune treatment response, thus we focused on CXCL9+ CD8 cluster. Mixed models were fitted for responsiveness represented by Luminex analytes and CD8 phenotypes. Logistic regression and Cox model were fitted for the association between analytes and treatment response and 3-year overall survival (OS). Biomarkers showed significant association ($P<0.05$) and AUC > 0.7 were selected as the potential predictors.

Results: All Luminex biomarkers showed difference between the R and NR groups 14 days after Y90 treatment ($P<0.05$). The higher increment of IL-18, IL-12p70, and CCL24 after Y90 treatment related to better treatment response and 3-year OS. CXCL9+ and CXCR3+ CD8 clusters differed between R and NR on the 21st and 35th day after Y90-RE, respectively. IL-18 and IL-12p70 were significantly associated with CXCL9+ and CXCR3+ CD8 clusters in the Rs, but not NRs.

Conclusions: IL-18, IL-12p70, and CCL24 were potential predictors for treatment response as well as 3-year OS for HCC patients treated by Y90-Nivo.

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227P Biomarkers for novel NK checkpoint inhibitor anti LLT1 antibody, ZM008: Patient transcriptome analysis

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Background: C-type lectin superfamily protein LLT1 interacts with CD161 on NK cells and facilitates tumor immune escape. Disruption of LLT1-CD161 with anti LLT1 antibody, ZM008 activates immune cells and kills cancer cells. This study aims to identify new biomarkers to classify specific patient population in ZM008 clinical studies.

Methods: TCGA transcriptome data was used to understand expression of LLT1 in 33 cancers. Correlation analysis was performed to compare LLT1 expression with immune gene signatures. Genomic cancer markers (TMB, MATH, MMR and MSI) status were determined using "Maftools" and "MSI sensor". Univariate Cox proportional hazard regression analysis (SURVIVAL) was used to measure patient survival.

Results: High expression of LLT1 was found in 11 different cancers. CIBERSORT analysis revealed significant immune cell infiltration (activated NK or CD8+ T) in TME. However, LLT1 expression in multiple cancers is negatively correlated with proinflammatory gene signatures (IL-2, IL-6, EOMES, and LAMP1 etc.), positively correlated with immune exhaustion markers PD1, LAG3, TIM3, TIGIT, ICOS and immune suppressive signals (high Treg cells and CD33+ MDSC; $p<0.05$). These data suggest immune suppressive "Cold tumor" phenotype associated with LLT1 expressing cancers. Further, immune check point predictors analysis in LLT1 positive tumors suggests positive correlation with high TMB score in COAD, UCEC and KICH; MSI score is elevated in PRAD and COAD; MMR genes expression is negatively correlated in COAD, KICH, BRCA, HNSC, KIRC, LUAD and PRAD; lastly, MATH score is correlated for GBM patients only ($p<0.05$). Subsequently, significant hazard ratios of 1.115, 2.114 and 1.067 were observed only for COAD, KICH and KIRC, respectively ($p<0.05$).

Conclusions: The transcriptome data analysis revealed LLT1 expression is associated with immune repressive TME in multiple cancers, suggesting therapeutic significance of ZM008. Multiple anti-inflammatory gene signatures could be useful in stratifying patients for ZM008 treatment. In addition, TMB & MSI scores and MMR gene expression could be monitored as potential biomarkers in phase I clinical trials with ZM008.

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228P Biomarker discovery via meta-analysis of immunotherapy clinical trials in cancer

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Background: Clinical profiling studies have shed light on molecular features and mechanisms that modulate response or resistance to immunotherapy but their predictive value remains largely unclear. We (Bareche et al., Annals of Oncology 2022) and others (Litchfield et al., Cell 2021) have recently curated a compendium of public datasets of DNA, RNA and clinical profiles of patients treated with immunotherapy.

Methods: Leveraging our compendium of immunotherapy clinical datasets, we developed, PredictIO, an open-source meta-analysis pipeline to assess the predictive value of molecular predictors. We first used PredictIO to compute the association between immunotherapy response and established biomarkers, such as tumor mutation burden (TNB) or CD8 gene expression, and a collection of 91 molecular signatures curated from the literature. Second, we used PredictIO for de novo RNA signature discovery pipeline to build a new predictor of immunotherapy response.

Results: Using molecular and clinical profiles of ∼3600 patients across 12 tumor types, our meta-analysis pipeline revealed thatTMB and ∼50% of the gene signatures were significantly predictive of immunotherapy response across tumor types, although their predictive value were strongly dependent on specific tumour types. We next developed a de novo gene expression signature from our pan-cancer analysis and demonstrated its superior predictive value over other biomarkers. To identify novel targets, we computed the T-cell dysfunction score for each gene within PredictIO and their ability to predict dual PD-1/CTLA-4 blockade in mice. Two genes, F2RL1 and RBFOX2, were concurrently associated with worse ICB clinical outcomes, T-cell dysfunction in ICB-naive patients and resistance to dual PD-1/CTLA-4 blockade in preclinical models.

Conclusions: Our study highlights the potential of large-scale meta-analyses in identifying novel biomarkers and potential therapeutic targets for cancer immunotherapy. These initial results, while promising, suffer from severe limitations in terms of data availability for specific cancer types and the lack of frameworks to develop and validate multi-omics predictors of immunotherapy response in a collaborative and scalable way.

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229P Leucine zipper 4 (LUZP4) IgG as a novel biomarker for testicular germ cell tumors

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Late withdrawal

230P Fibroblast growth factor receptor (FGFR) co-alteration (co-alt) landscape and its impact on erdafitinib (erda) response in the phase II open-label, single-arm RAGNAR trial

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Background: *FGFRalts* are present in 1%-20% of all cancers. Erda is an oral selective pan-FGFR inhibitor approved to treat locally advanced or metastatic (adv/met) urothelial carcinoma in adults with susceptible *FGFR3/2alt* who have progressed during or after ≥1 line of platinum-based chemotherapy. Interim results of RAGNAR showed tumor agnostic efficacy in patients (pts) with adv/met solid tumors with predefined *FGFRalt* after failure of standard therapies (Loriot et al, ASCO 2022). Here, we evaluated the *FGFR* co-alt landscape and its impact on response to erda treatment (tx) in RAGNAR.

Methods: Archival tumors from pts with adv/met solid tumors were prospectively screened for *FGFR1-4alts* using FoundationOne (FM) or, for those pts enrolled based on local results, retrospectively tested using FM. 217 pts received erda until progression or intolerable toxicity. The impact of co-alts on erda tx was evaluated with respect to objective response rate (ORR) (primary end point) using Fisher exact test, Kaplan-Meier analysis for duration of response (DOR), and Wilcoxon rank-sum test for maximum tumor shrinkage (MTS).

Results: Of 217 pts, 175 (81%) had tumors with pathogenic co-alts, most prevalent in *TP53* (27%), *PIK3CA* (18%), and *CDK2NA* (15%). Co-alts were histology dependent. *TP53* was altered in 75% of esophageal, 75% of ovarian, and 71% of colorectal; *TERT* mutations were seen in 55% of high-grade gliomas. ORR did not show an association between the presence or burden of co-alts (p=0.51). Of the 12 most prevalent co-alts and pathways, none were significantly associated with response vs non-response. Within each histology, individual co-alts were not associated with response. Among responders, *TP53* alt was associated with shorter DOR (HR=0.29 [95% CI, 0.15-0.58]; p=0.002). Further, RTK-RAS pathway co-alts were associated with less MTS (p=0.034).

Conclusions: High prevalence of *FGFR* co-alts reflects the complex genomic landscape of tx-refractory adv/met solid tumors. Despite most pts having histology-specific co-alts, erda showed clinical activity in these pts, supporting *FGFRalts* as oncogenic drivers in these tumors.

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Disclosure: Y. Loriot: Financial Interests, Institutional, Speaker, Consultant, Advisor, Consultancy Fees: Loxo/Lilly, Pfizer/EMD Serono, Roche, and Taiho Pharmaceutical, MSD Oncology, Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Immunomedics, Janssen; Financial Interests, Personal, Other, Travel Reimbursement: Astellas, AstraZeneca, Janssen Oncology, MSD Oncology, and Roche; Financial Interests, Institutional, Research Funding: Astellas Pharma, AstraZeneca, Basilea, Bristol Myers Squibb, Exelixis, Gilead Sciences, Incyte, Janssen Oncology, Merck KGaA, MSD Oncology, Nektar, Pfizer, Roche, Sanofi, and Taiho Pharmaceutical. S. 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231P Time to deterioration of quality of life as a surrogate of OS: A trial-level surrogacy analysis

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Background: Overall survival (OS) is the optimal marker of efficacy for evaluation of treatments in randomized clinical trials (RCTs) but can take a considerable amount of time to mature. Evaluation of changes in tumor size through objective response rate (ORR) and progression free survival (PFS) has served as an early surrogate of OS however they are imperfect. Time to deterioration (TTD) in quality of life (QoL) measures could act as an early alternative patient centered surrogate of OS.

Methods: We utilised published phase 3 RCTs in solid malignancies that reported OS, PFS, ORR, and time to deterioration (TTD) evaluations of overall QoL or physical function (PF) published between 1st of January 2010 and 30th of June 2022. Weighted regression analysis was utilised to assess the relationship between PFS, ORR ratio, TTD QoL and TTD PF with OS. The coefficient of determination (R^2) was used to quantify surrogacy.

Results: After identifying 9109 publications, 138 studies with 86199 patients were included for analysis. 47 RCT involved immunotherapy (IO) whilst 91 investigated non-IO agents. PFS (R^2= 0.19) and ORR (R^2= 0.05) were poor surrogates of OS. TTD QoL and TTD PF was available in 137 and 75 RCTs respectively. In the respected subset of studies, TTD QoL (TTD QoL R^2= 0.18 vs. PFS R^2= 0.19) and TTD PF (TTD PF R^2= 0.10 vs PFS R^2= 0.09) performed similarly to PFS as surrogates of OS. However, for IO agents, TTD PF (R^2= 0.38) had a higher surrogacy to OS compared to PFS (R^2= 0.19). Furthermore, combining PFS and TTD PF enabled improved prediction of OS (R^2= 0.57). Importantly, TTD PF and PFS were not correlated with each other (R^2= 0). TTD PF was not a surrogate endpoint of OS for non-IO trials.

Conclusions: Our trial level analysis identified TTD in PF as a potential marker of early OS in trials that utilized IO agents. It could potentially be used in conjunction with PFS to improve surrogacy in specific tumor types. Our results are based on published results and should be validated using patient-level data.

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232P Identification of 'secondary' germline cancer predisposition variants from somatic tumour testing: Should we evolve towards universal screening?

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Background: In recent years, the use of Next Generation Sequencing based gene panels for the management of solid tumours has become almost routine testing in many Cancer Genomics Laboratories. In most cases, the purpose of the analysis is to identify biomarkers with potential predictive value. However, the mutations identified in the tissue may also have a hereditary origin. The objective of this study was to analyse the pathogenic germline variants identified as a somatic secondary finding in genes that have not been established to confer an increased risk for this specific tumour ('off-tumour').

Methods: A retrospective analysis was carried out on 330 patients in whom a tumour genomic analysis (somatic testing) had been performed in our institution between February 2022 and 2023. The genomic analysis tool was *Oncomine™Comprehensive Assay* in all cases (500 gene panel). Germline-focused analysis was performed to variants with a variant allele frequency >30% (or >20% if small insertions/deletions) in genes consistent with hereditary predisposition to cancer.

Results: In the solid biopsies from 330 patients studied, 58 pathogenic variants of potential germline origin were identified in 54 patients (16.3%). In 23 of these patients (42.5%) the pathogenic variant was an 'off-tumour' finding. The median age at diagnosis of these 23 patients was 56 years-old, 21 patients (91.3%) had a metastatic or recurrent tumour and 11 (47.8%) did not meet any criteria of inherited predisposition to cancer. The results of the germline study are available in 10 of these 23 patients and the germline pathogenic variant was confirmed in 7 cases (70%): 4 *BRCA1*, 1 *ATM*, 1 *MUTYH* and 1 *PMS2*. The most frequent related tumour was lung cancer, in 3 cases.

Conclusions: In our series of 330 cases tested for tumour genomics, 23 patients harboured an "off-tumour" pathogenic variant with potential germline origin, that was confirmed in 7 out of 10 patients. Detected germline mutations included high penetrance cancer predisposing genes as *BRCA1*. This detection rate reflects the clinical utility, for patients and their families, of using the somatic genomic analysis as a source of information about a potential hereditary cancer predisposition syndrome.

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233P Germline genetic testing before formal counseling: Impact in cancer management in a Spanish university hospital

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Background: Performing rapid genetic testing before consultation in a Hereditary Cancer Unit (HCU) is becoming increasingly common due to its importance in the decision-making of cancer management. There are few studies analyzing this new genetic counseling approach.

Methods: We conducted a retrospective descriptive study in a cohort of patients (pts) who underwent germinal genetic testing during their treatment plan at Hospital Gregorio Marañon since April 2019 to November 2022. Tests were directly ordered by their oncologists with a brief pre-test counseling prior to the formal evaluation in the HCU. Primary objective was to analyze if having these results available prior to formal genetic counseling could impact in the management of the patient's cancer.

Results: 225 pts (32.9% men, 67.1% women) underwent genetic test. Cancer diagnoses were: pancreatic (49.3%), breast (40.4%), ovarian (5.8%), colorectal (2.6%), gastric (2.6%), prostate (1.3%), cholangiocarcinoma (1.3%), renal (1.3%) and endometrial 0.9%. A specific-syndrome genetic panel was performed in 55.1%, multigenetic in 44% and single gene in 0.9%. We found pathogenic/likely pathogenic variants (PV/LPV) in 31 pts (13.8%) and variants of unknown significance (VUS) in 53 (23.5%). 22.6% of the pts with PV/LPV (n=7) didn't meet the Spanish Society for Medical Oncology (SEOM) criteria for hereditary cancer. 40% of the pts (n=90) didnt receive post-test counseling in the HCU: 81.1% due to negative result and non-significant familial background, 10% due to patient's death, 4.4% did not attend the appointment (rest unknown). According to retrospective chart review in 32.3% with PV/LPV (n=10; 4.4% of the total) a change in cancer management was decided (Table).

Table: 233P

Pts with PV/LPV (n=31)		n (%)
Changes in cancer management*	Bilateral mastectomy	8 (25.8%)
	Avoid radiotherapy	1 (3.2%)
	PARP inhibitors	1 (3.2%)
	Platinum-based chemotherapy	2 (6.4%)
	None (due to death)	(22.6%)

*One patient could have more than one change

Conclusions: Genetic testing performance can modify the therapeutic plan of pts with cancer, especially for those with PV/LPV. Rapidity in obtaining the results is essential. The balance between this rapidity and a proper post-test genetic counseling needs to be warranted.

Legal entity responsible for the study: Hospital General Universitario Gregorio Marañon.

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234P Plasma cell free DNA hydroxymethylation profiling reveals anti-PD1 treatment response and resistance biology in non-small cell lung cancer

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Late withdrawal

235TiP Hamlet.rt Trans: Prospective single-centre translational study evaluating liquid biomarkers of radiation response

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Background: Hamlet.rt (Heuristics, Algorithms and Machine Learning: Evaluation & Testing in Radiation Therapy) is a multi-centre study exploring the role of machine learning in predicting response and toxicity in patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC), Head and Neck Cancer (H&N Cancer) and Prostate cancer. Hamlet.rt Trans is a translational sub-study that leverages the infrastructure of Cancer Research UK RadNet Cambridge to evaluate multiple liquid biomarkers of radiation response. This study aims to investigate biomarkers of treatment response in patients with lung and head and neck cancers and markers of treatment toxicity in patients with prostate cancer.

Trial design: HAMLET.trans is a translational biosampling study of patients undergoing radical radiotherapy for NSCLC, H&N cancer or prostate cancer. Venous samples for ctDNA analysis and senescence-related profiling are collected together with dried blood spot samples before chemotherapy and radiotherapy at multiple time points during radiotherapy and post-treatment. Urine is collected from patients with prostate cancer. Patients are completing toxicity questionnaires during and after radiotherapy. Delivery dose per fraction is assessed based on imaging just before radiotherapy delivery. The trial aims to recruit at least 20 patients per arm. Patient samples are analysed for tumor-specific mutation, methylation profiling of cfDNA as well as cytokine assays to establish markers or response and toxicity and identify optimal sample timings for future studies. Blood spots are analysed for ctDNA tumour content to establish a less invasive way of frequent sampling on therapy. The results of HAMLET.trans will inform ongoing translational work.

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Legal entity responsible for the study: Cambridge Cancer Trials Centre.

Funding: Cancer Research UK and the Medical Research Council UK.

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236TiP Large-scale prospective observational study to develop a liquid-based detection system of minimal residual disease (MRD): LC-SCRUM-MRD

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Background: MRD is a potential biomarker for predicting disease relapse or therapeutic response for lung cancer, and it is expected to establish a precise detection system by liquid biopsy. We have been conducting a prospective observational study to evaluate the clinical utility of MRD detection in lung cancer (LC-SCRUM-MRD) since August 2022, in parallel with a multicenter prospective genomic screening project in Japan (LC-SCRUM-Advantage).

Trial design: The main inclusion criteria are pathologically diagnosed treatment-naive lung cancer, 16 years of age or older, performance status 0-1, and normal organ function. A total of 10,680 patients in LC-SCRUM-Advantage/MRD will be enrolled over five years and assigned to one of six cohorts (A1 to B2) according to their histology, stage, and treatment (Table). In the MRD monitoring cohorts A2-B2 of 680 patients, we will analyze MRD every 1-6 months for up to 2 years, and computed tomography scans and serum tumor markers measurement will be performed at each time point. As for MRD analysis, we will perform tissue-based MRD detection systems that require sequencing of tumor tissue to create personalized plasma circulating tumor DNA (ctDNA) assay and liquid-based MRD detection systems that analyze plasma ctDNA by methylation profiling or urinary exosomal microRNA. The

performance of these liquid-based MRD detection systems will be compared with tissue-based MRD detection systems to establish the optimal MRD detection system for lung cancer. As of April 2023, a total of 154 patients have been enrolled in LC-SCRUM-MRD across 40 institutions, and preliminary results will be presented at this meeting.

Table: 236TiP LC-SCRUM-Advantage/MRD

Cohort	Histology	Stage	Treatment	Genomic screening	MRD monitoring	Sample size
A1	NSCLC	I-III	Surgery	○	-	9800
A2				○	○	200
A3		III	Chemoradiotherapy	-	○	100
A4		III/IV	Chemotherapy	-	○	150
B1	SCLC	LD	Chemoradiotherapy	-	○	30
B2		ED	Chemotherapy	-	○	200

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237TiP GUIDE.MRD: A Consortium guiding multi-modal therapies against minimal residual disease (MRD) by liquid biopsy to assess implementation of circulating tumor DNA (ctDNA) in clinical practice to improve patient outcomes

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Background: An integrated precision oncology approach that can guide the selection of personalized therapy is paramount to achieving improved outcomes in patients while maintaining responsible healthcare economics. Actionable precision oncology requires *in vitro* diagnostic tests that are sufficiently sensitive, accurate, reproducible, and reliable in the real-world setting with minimal risk of patient overtreatment or undertreatment. Liquid biopsies and specifically ctDNA based diagnostics provide a unique opportunity to optimize clinical decisions and thereby improve individual patient care. Such techniques could be particularly valuable in the adjuvant setting where multi-modal therapy (MMT) has curative potential. Multiple studies provide evidence that serial ctDNA monitoring can predict or detect recurrence earlier than conventional surveillance. However, as highlighted in the most recent ESMO ctDNA recommendations, the detection limit of current diagnostics to accurately report ctDNA fragments in peripheral blood remains a challenge. Importantly, it is currently unclear how to incorporate ctDNA as MRD biomarker or as a decision tool for treatment selection to improve cancer outcomes. GUIDE.MRD, a patient-centered precision oncology public-private partnership under the Innovative Health Initiative umbrella, is designed to improve the utility and clinical implementation of ctDNA as MRD biomarker and to evaluate the potential of novel decision tools to match patients to MMTs.

Trial design: Partners from academic, medical technology, pharmaceutical and patient advocacy sectors will join to (a) benchmark available ctDNA assays for sensitivity, specificity, and predictive value using reference material that closely mimic patient samples in the adjuvant setting, (b) to clinically validate the top performing ctDNA assay characteristics in patients with NSCLC, CRC and PDAC and develop patient-centric clinical implementation roadmaps, and (c) determine the utility of ctDNA assays as a prospective decision tool of clinical response and choice of MMT including novel combinations.

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BREAST CANCER, EARLY STAGE

238MO Long-term residential and workplace exposure to air pollution and breast cancer risk: A case-control study nested in the French E3N cohort from 1990 to 2011

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Background: Air pollution, classified as carcinogenic to humans, is a major public health concern. Studies on breast cancer are scarce and remain inconsistent. We studied the association between breast cancer risk and long-term exposure to particulate matters ($PM_{2.5}$, PM_{10}) and nitrogen dioxide (NO_2) estimated at the womens' residential and workplace addresses.

Methods: We conducted a case-control study of 2419 cases and 2984 individually matched controls nested in the French prospective E3N cohort, over the period 1990-2011. Controls were matched to cases on department of residence, age (±1 year); date (±3 months), and menopausal status at blood collection. Annual mean $PM_{2.5}$, PM_{10} and NO_2 concentration levels were estimated using a Land Use Regression (LUR) model (resolution 50m x 50m) and were assigned to women based on their geocoded residential and workplace addresses. The mean exposure was calculated for each woman from their inclusion into the E3N cohort to their index date (date of diagnosis of cases). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariate logistic regression models, for a 10 µg/m^3 increase in $PM_{2.5}$, PM_{10} and NO_2. Adjustment variables were selected from the literature, using a directed acyclic graph.

Results: The results showed a statistically significant linear increase in breast cancer risk related to mean exposure to $PM_{2.5}$ (adjusted OR 1.28; CI 1.00−1.63, for an increment of 10 µg/m^3). A numerically increased risk was observed for PM_{10} (adjusted OR1.09; CI 0.92−1.30) and NO_2 (adjusted OR 1.05; CI 0.97−1.13) for an increment of 10 µg/m^3. No effect modification by menopausal status was observed (p interaction 0.99, 0.90, and 0.86 respectively for $PM_{2.5}PM_{10}$ and NO_2). Analyses by hormone receptor status showed a positive but not significant association for $PM_{2.5}$ for oestrogen receptor positive (ER+) breast cancer cases (adjusted OR 1.32; CI 0.97−1.79).

Conclusions: To our knowledge, this study is the first to investigate breast cancer risk associated with long term air pollution exposure at both, the subjects' residence and workplace, estimated using a very fine spatial resolution LUR model. Future studies should consider exposure during commuting.

Legal entity responsible for the study: INSERM.

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239MO Impact of body mass index and its change on survival outcomes in patients with early breast cancer: A pooled analysis of individual-level data from BCIRG-001 and BCIRG-005 trials

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Background: The relationships between body mass index (BMI) and survival outcomes are complex, and have not been thoroughly investigated in breast cancer patients who received adjuvant chemotherapy.

Methods: We collected data on 2394 patients from two randomized, phase III clinical trials that investigated adjuvant chemotherapy in breast cancer identified in Project Data Sphere. The objective was to examine the effect of baseline BMI, BMI after adjuvant chemotherapy, and BMI change from baseline to post-adjuvant chemotherapy on disease-free survival (DFS) and overall survival (OS). Restricted cubic splines, adjusting for confounding factors, were used to examine potential non-linear associations between continuous BMI value and survival. Stratified analyses involved chemotherapy regimens used.

Results: On multivariate analysis, severe obesity (BMI≥40.0 kg/m^2) at baseline was independently associated with worse DFS (HR=1.48, 95%CI 1.02-2.16, *P*=0.04) and OS (HR=1.79, 95%CI 1.17-2.74, *P*=0.007) compared with underweight/normal weight (BMI≤24.9 kg/m^2). A BMI loss >10% was also an independent prognostic factor for adverse OS (HR=2.14, 95%CI 1.17-3.93, *P*=0.014). When stratified by chemotherapy regimens, the multivariate analysis revealed that severe obesity adversely affected DFS (HR=2.38, 95%CI 1.26-4.34, *P*=0.007) and OS (HR=2.90, 95%CI 1.46-5.76, *P*=0.002) in the docetaxel-based group, but not in the non-docetaxel-based group. Restricted cubic splines revealed a "J-shaped" association of baseline BMI with risk of recurrence (*P* for non-linearity=0.111) or all-cause death (*P* for non-linearity=0.008), and this relationship was more pronounced in the docetaxel-based group (DFS: *P* for non-linearity=0.011; OS: *P* for non-linearity <0.001).

Conclusions: In early breast cancer patients treated with adjuvant chemotherapy, baseline severe obesity was lined to worse DFS and OS, while a BMI loss over 10% from baseline to post-adjuvant chemotherapy also negatively affected OS. Moreover, the prognostic role of BMI might differ between docetaxel-based and non-docetaxel-based groups.

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240MO Prognostic and predictive impact of estrogen/progesterone receptor (ER/PR), and Ki-67 expression: An exploratory analysis from the monarchE trial in patients with high-risk, HR+, HER2-, early breast cancer (EBC)

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Background: The monarchE trial demonstrated that the addition of abemaciclib to endocrine therapy (ET) significantly improved invasive disease-free survival (IDFS) and distant relapse-free survival in node-positive, high-risk EBC patients (pts) with benefit deepening beyond the 2-year (yr) treatment (tx) period. Ki-67 ≥20% was prognostic of breast cancer outcomes but not predictive of abemaciclib benefit. Here, we evaluate expression of ER, PR and Ki-67 to determine their prognostic and predictive impact, including analyses as continuous variables.

Methods: ER/PR and Ki-67 expression was determined by immunohistochemistry (IHC). The graphical Subpopulation (subp) Tx Effect Pattern Plot (STEPP) analysis was conducted for each biomarker to robustly assess the tx effect ensuring a balance between subp sample size and enough number of overlapping subp. Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for ER/PR status subtypes (positive ≥1%).

Results: Each IHC cohort varied slightly in number of pts and the precise IDFS HR point estimate (abemacilib+ET vs ET), but STEPP analysis revealed consistent abemaciclib tx benefit regardless of ER, PR or Ki-67 expression (Table, A). The IDFS benefit of abemaciclib was also consistent in ER+/PR+ and ER+/PR- tumors (Table, B). The 3-yr IDFS rates of the control arm showed that pts with PR- tumors had a higher risk of recurrence. Pts with ER- tumors followed a similar trend, but the effect could not be robustly estimated due to small numbers..

Conclusions: Consistent IDFS benefit of adjuvant abemaciclib was observed regardless of the level of ER, PR or Ki-67 expression, as well as in ER+/PR+ and ER+/PR- tumors. Similar to Ki-67 ≥20%, PR- status was prognostic of worse outcomes with ET alone.

Table: 240MO Summary of STEPP and IDFS analysis

A. Summary statistics for the deviation of the STEPP Subp, HRs from the overall Tx effect

	Overall IDFS HR	Median of the STEPP HRs (IQR)
ER (n=4520)	0.74	0.75 (0.69 – 0.87)
PR (n=4012)	0.78	0.71 (0.64 – 0.78)
Ki-67 (n=4425)	0.65	0.65 (0.55 – 0.76)

B. IDFS in ER/PR Subtypes

	Abemaciclib+ET			ET			HR (95% CI)	Interaction p-value
	n	events	3-yr rate	n	events	3-yr rate		
ER+/PR+	2405	275	89.9%	2437	392	85.9%	0.698 (0.599, 0.815)	0.2531
ER+/PR-	298	50	83.2%	295	86	73.0%	0.560 (0.395, 0.794)	
ER-/PR+	16	5	NE*	17	8	NE*	NE*	NE*

IQR, Interquartile range. *Not estimated (NE) due to low numbers

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241MO Patient characteristics and real-world outcomes in HER2 negative/ ER zero and ER low patients treated as triple-negative breast cancer in Sweden 2008-2020

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Background: Estrogen receptor-low (ER-low) Her2-negative breast cancer has similar pathological and molecular characteristics as triple-negative breast cancer (TNBC), and it is questionable whether it should be considered a separate entity. When the international guidelines lowered the cutoffs for ER to ≥1% in 2010, the ≥10% threshold was kept in Sweden. ER-low breast cancer (ER 1-9%) has thus in Sweden been treated as TNBC, which is interesting now that the international community recognize limited data for benefit of endocrine therapy in the ER-low group The benefit of endocrine therapy in these tumors is under debate and discussion. We aimed to describe real-world patient and tumor characteristics, treatment patterns and overall survival in a Swedish population-based cohort of patients with HER2 negative/ ER zero and ER low breast cancer treated as TNBC.

Methods: TNBC cases diagnosed in Sweden 2008-2020 were included in a population-based cohort study. Patient, tumour and treatment characteristics were analysed by ER status (ER-negative 0% vs ER-low 1-9%), and associations between subgroups compared using χ^2 test. Endpoints were overall survival (OS) and distant disease-free survival (DDFS). Kaplan-Meier curves were used to describe time-to-event endpoints and Cox proportional hazards models to estimate adjusted hazard ratios.

Results: Of the 5657 tumors, 90.1% were ER-negative and 9.9% ER-low. In the unadjusted analysis of OS, ER-low disease was associated with a borderline significantly better OS than ER-negative disease (n=3893, HR 0.83 (0.70-1.001), p=0.051), but this was restricted to patients not given chemotherapy (n=1764, HR 0.65 (0.50-0.88), p=0.002). ER-status 0% vs 1-9% did not affect OS in the multivariable analysis (HR 1.09, 95% CI 0.89-1.34). DDFS did not differ by ER-status 0% vs 1-9% (n=1299, HR 0.97 for ER-negative vs ER-low (0.62-1.53)). After preoperative treatment, the importance of pCR for OS did not significantly differ between ER-negative or ER-low disease.

Conclusions: ER-low breast cancer has characteristics and prognosis similar to ER-negative breast cancer when treated as TNBC. The use of ≥10% as threshold for ER positivity is supported by this study.

Legal entity responsible for the study: Karolinska Institutet.

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242MO Association of tumor-infiltrating lymphocytes (TILs) with recurrence score (RS) in patients with hormone receptor-positive (HR+)/HER2-negative (HER2-) early breast cancer (BC): A translational analysis of four prospective multicentric studies

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Background: Oncotype DX represents one of the genomic assays associated with the highest quality of evidence driving a strong recommendation for its use to guide decisions on adjuvant therapy for HR+/HER2- early BC patients. The clinical value of TILs in HR+/HER2- BC may be unearthed by focusing on patients whose tumors exhibit features of higher biological aggressiveness. Here we deepen and describe the correlation between RS and TILs, proposing an immuno-genomic model for HR+/HER2- BC.

Methods: We enrolled T1-T3, N0-N1 BC patients with available RS and TILs in the context of four multicenter, prospective studies primarily aimed at assessing the impact of the Oncotype DX® test on adjuvant treatment decisions in a clinical practice scenario. RS was categorized into: 0-10 (low risk), 11-25 (intermediate risk) and 26-100 (high risk); TILs were categorized into: low (0-10%), intermediate (11-59%) and high (60-100%).

Results: 811 patients were included. RS distribution was (n=810): low risk 22.0%, intermediate risk 61.2%, high risk 16.8%. TIL distribution was (n=455): low TILs 84.6%, intermediate TILs 13.6% and high TILs 1.8%. A significant, weak positive, linear correlation was found between continuous TILs and RS (Pearson coefficient=0.223, $p<0.001$). When considering RS and TILs categories, tumors with intermediate/high TIL levels significantly enriched the high RS subgroup ($p=0.006$). This was confirmed both within Luminal A (Ki67<20% and PgR ≥20%) and Luminal B cohorts (ki67≥20% and/or PgR <20%). Among high-RS patients, 16.7% of Luminal A and 26.7% of Luminal B tumors had intermediate/high TILs.

Conclusions: We observed that RS and TILs capture only slightly overlapping information on the biology of HR+/HER2- tumor microenvironment. We demonstrated the feasibility of combining RS and TILs into a composite immuno-genomic model, which may identify patients simultaneously showing features of high biological/clinical risk and enhanced immunogenicity and may serve the purpose of guiding and focalizing patient selection in the further development of immunotherapy strategies for Luminal-like disease.

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243MO Omission of breast surgery after neoadjuvant systemic therapy for invasive cancer: Three-year preplanned primary-endpoint on a phase II multicentre prospective trial

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Background: Neoadjuvant systemic therapy (NST) for triple-negative breast cancer (TNBC) and HER2+ breast cancer (HER2+BC) yields a pathol-ogic complete response (pCR) in approximately 60% of patients. A pCR to NST predicts an excellent prognosis and can be accurately determined by percutaneous image-guided vacuum-assisted core biopsy (VACB). Radiotherapy alone, without breast surgery after NST among patients who had a VACB−determined pCR was evaluated in the feasibility phase (Johnson et al. *JACS* 2023), 2-year pre-planned primary outcome (Kuerer et al *Lancet Onc* 2022), the 32.4 mo patient reported outcomes (Johnson et al SSO 2023) and now at the preplanned 3-year primary endpoint.

Methods: This multicentre phase II clinical trial enrolled women aged ≥40 years with unicentric cT1-2N0-1M0 TNBC or HER2+BC and a residual breast lesion <2 cm on imaging after NST. One biopsy was obtained by 9G image-guided VACB containing a minimum of 12 cores from the tumour bed. If no invasive/in situ disease was identified, breast surgery was omitted, and patients underwent whole-breast radiotherapy/boost. Primary outcome was ipsilateral breast tumour recurrence (IBTR) rate and secondary outcomes included evaluation of baseline and longitudinal obtained circulating tumor cells (CTCs) in a total of 33 blood samples and patient-reported outcomes.

Results: During 2017-2021 50 total patients were enrolled and underwent VACB following NST. The mean age was 60·4 years (SD 7·8); 21 patients had TNBC and 29 had HER2+BC. Mean imaging final tumour size after NST was 0·90 cm (SD 0·81), and 17 patients (34%) had a complete radiologic response. VACB identified a pCR in 31 patients (62%). Among these 31 patients, median follow-up was 38.4 months (IQR: 22.4-49·5) the 3-year IBTR rate was 0% (primary endpoint) and 3-year DFS and OS rates were 100%. Two patients were CTC-positive at baseline, 2 were positive at 6-months, and 1 at 12-months. No patients had CTCs detected at more than one timepoint.

Conclusions: Eliminating breast surgery in highly selected patients with an image-guided VACB−determined pCR following NST shows promising 3-year results and additional time and clinical trials evaluating this approach are indicated.

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Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

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244MO A phase II trial targeting disseminated dormant tumor cells with hydroxychloroquine, everolimus or the combination to prevent recurrent breast cancer ("CLEVER")

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Background: Breast cancer (BC) recurrence may follow a dormant phase in which quiescent cells reside in niches such as bone marrow (BM). Dormant BM disseminated tumor cells (DTCs) are independently associated with BC recurrence/death. We investigated whether targeting dormancy through autophagy inhibition (hydroxychloroquine (HCQ), and/or mTOR signaling (everolimus (EVE) in DTC+ BC survivors was feasible, reduced DTCs and/or prevented recurrence.

Methods: The CLEVER trial (NCT03032406) is a randomized, phase II trial in patients (pts) diagnosed within 5 years, with positive nodes, triple-negative disease, high-risk Oncotype/Mammaprint, and/or residual disease post-neoadjuvant therapy who completed all treatment except endocrine therapy. DTCs were detected in BM aspirate (BMA) by IHC with pan-CK antibody AE1/AE3. DTC+ pts were randomized to six 28-day cycles (C) of HCQ (600 mg BID), EVE (10 mg daily) or both (+/- 3-month (m0) observation period). If DTC+ persisted after C6, pts received another 6C HCQ+EVE. DTC assessment was done after C3, C6, C12 (if applicable) and 6-mo after end of treatment. Adverse events (AE) were assessed by CTCAEv4. Primary endpoint was feasibility, defined as >75% completion of C6C without G3/G4 AE. Secondary endpoints were safety, DTC response rate (RR) and 3-year RFS. DTC RR was analyzed with Bayesian Poisson regression models.

Results: 184/197 eligible pts had baseline BMA, 55 (30%) were DTC+, 53 were randomized: HCQ (n=15), EVE (n=15), and HCQ+EVE (n=23). 13 patients had repeat after 3-mo observation. Feasibility endpoint was met. There were no G4/5 toxicities. At a median follow up of 42 mo (range 7-60), 1 pt recurred in lung (after 2 cycles EVE), 1 pt developed new contralateral breast cancer. The posterior probabilities that HCQ, EVE, and HCQ+EVE reduced DTCs by at least 80% after C3 vs observation alone are 99.1%, 98.2%, and 99.9%, respectively.

Conclusions: The CLEVER trial provides proof-of-principle that therapeutic targeting of dormant BC is feasible and active in eliminating DTCs by targeting dormancy-specific mechanisms. Follow up for recurrence and survival is ongoing.

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Legal entity responsible for the study: University of Pennsylvania.

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245P Neoadjuvant QL1209 (a pertuzumab biosimilar) compared with pertuzumab plus trastuzumab and docetaxel in early or locally advanced, HER2-positive, ER(-)/PR(-) breast cancer: A multicenter, randomized, double-blind, equivalence, phase III study

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Background: Dual HER2-blockade with trastuzumab (T) and pertuzumab (P) plus docetaxel as neoadjuvant therapy showed an improved pathological complete response (pCR) rate and was approved by the FDA and EMA for early HER2-positive breast cancer. QL1209 is a biosimilar of the originator P (Perjeta, Roche). Here we present the results of the phase 3 study comparing the efficacy, safety, immunogenicity of QL1209 with P in the neoadjuvant setting for early HER2-positive breast cancer.

Methods: Eligible patients (pts) had HER2-positive, early (T2-3, N0-1, M0) or locally advanced (T2—3, N2—3,M0 or T4, any N, M0), ER(-) and PR(-) breast cancer with primary tumor larger than 2cm in diameter, and had not received any previous anticancer therapy. Pts were randomly assigned (1:1, stratified by disease stage) to receive neoadjuvant treatment of QL1209 or P (loading dose 840 mg at cycle 1, followed by 420 mg from cycles 2 to 4) plus T and docetaxel once every 3 weeks for 4 cycles. The primary endpoint was tpCR by IRC. Secondary endpoints included tpCR by investigator (INV), bpCR by IRC, bpCR by INV, ORR, safety, immunogenicity etc.

Results: 517 pts were enrolled (52 sites in China) and 516 pts (QL1209/P: n=257/259) received neoadjuvant treatment, of whom 482 (93.2%) underwent surgery (QL1209: 238; P: 244). tpCR (by IRC) was observed in 109 (42.7%) pts with QL1209 and 117 (45.2%) pts with P; ratio of tpCR (QL1209:P) 0.946 (90% CI: 0.8-1.11), p=0.014. Incidences of TEAEs and Gr≥3 TEAEs: (QL1209 vs P) (94.6% vs 96.1%; Gr≥3, 31.9% vs 34.7%). TRAEs: 77.4% vs 78%. Incidences of ADA and Nab were similar between 2 groups (2.3% vs 3.1%; 0.8% vs 0.8%).

Table: 245P

	QL1209 (n=257)	P (n=259)
Overall, n (%)		
No of pts	255*	259
tpCR by INV	108 (42.4)	120 (46.3)
bpCR by IRC	128/256 (50.0)	134 (51.7)
bpCR by INV	124 (48.6)	133 (51.4)
ORR by INV, n (%)	211/257 (82.1)	212/259 (81.9)

*IRC didn't receive the complete specimens for 2 patients

Conclusions: QL1209 demonstrated equivalence to P in efficacy and showed comparable safety profile and immunogenicity in patients with early or locally advanced HER2-positive breast cancer.

Clinical trial identification: NCT04629846.

Legal entity responsible for the study: Qilu Pharmaceutical Co., Ltd.

Funding: Qilu Pharmaceutical Co., Ltd.

Disclosure: M. Zhao, B. Zhang, X. Kang: Other, Personal, Full or part-time Employment: Qilu Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

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246P Phase II study of anlotinib combined with taxanes and lobaplatin in the neoadjuvant treatment of triple-negative breast cancer: Efficacy, safety and biomarker analysis from the neoALTAL trial

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Background: Anlotinib, a novel multi-target tyrosine kinase inhibitor, has been proven effective in HER2-negative metastatic breast cancer, but its efficacy in early-stage TNBC is unknown. This phase 2 study aims to evaluate the efficacy and safety of adding anlotinib to neoadjuvant chemotherapy (NCT) in patients (pts) with TNBC.

Methods: Pts with clinical stage II/III TNBC were treated with 5 cycles of anlotinib (12mg, d1-14, q3w) plus 6 cycles of taxanes (docetaxel 75 mg/m^2 or nab-paclitaxel 125 mg/m^2, d1 and d8, q3w) and lobaplatin (30 mg/m^2, d1, q3w), followed by surgery. The primary endpoint was total pathological complete response (tpCR; ypT0/is ypN0) and the secondary endpoints include breast pCR (bpCR), axillary pCR (apCR), survival, and safety. Exploratory endpoints were efficacy biomarkers based on FUSCC classification (IHC-based) and NGS (425 gene panel).

Results: From Jan 2021 to Aug 2022, 48 pts were assessed and 45 were enrolled. All pts received at least one dose of study treatment and underwent surgery. The median age was 50 years (range, 26-65), 71% were nodal involved, and 20% had stage III. In the ITT population, 26 out of 45 pts achieved tpCR (57.8%; 95% CI, 42.2%—72.3%), and 39 achieved RCB 0-I (86.7%; 95% CI, 73.2%-94.9%). The bpCR and apCR rates were 64.4% (29/45) and 71.9% (23/32), respectively. No recurrence or metastasis occurred during the short-term follow-up. Based on the FUSCC IHC-based subtypes, the tpCR rates were 68.8% (11/16) for IM subtype, 58.3% (7/12) for BLIS subtype, and 33.3% (4/12) for LAR subtype, respectively. Next-generation sequencing revealed that the tpCR were 69.2% (9/13) and 53.6% (15/28) in MYC-amplified and wild-type pts, respectively, and 75.0% (9/12) and 51.7% (15/29) in BRCA1/2-mutated and wild-type pts, respectively. In the safety population (N=45), Grade 3 or 4 TEAEs occurred in 29 pts (64%), and the most common events were neutropenia (38%), leukopenia (27%), thrombocytopenia (25%), anemia (13%), and hypertension (13%), respectively. No treatment-related deaths occurred.

Conclusions: The addition of anlotinib to NCT showed manageable toxicity and promising antitumor activity for pts with early-stage TNBC.

Clinical trial identification: ChiCTR2100043027.

Legal entity responsible for the study: The authors.

Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. L.

Disclosure: All authors have declared no conflicts of interest.

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247P KN026 in combination with docetaxel as neoadjuvant treatment for HER2+ early or locally advanced breast cancer (BC): A single-arm, multicenter, phase II study

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Background: Trastuzumab (H) plus Pertuzumab (P) combined with cytotoxic agents has been the SOC for Her2+BC across perioperative to late stage. Even with high efficacy, optimized treatment strategy still needs to be explored. KN026 is a bispecific monoclonal antibody that targets domain II and IV of HER2. KN026 showed comparable or better efficacy with H+P in preclinical study. The superior efficacy had also been validated in a series of clinical trials in late line Her2+ solid tumors as well as the first-line Her2+ breast cancer and gastric cancer. Here we report the results of KN026 plus docetaxel as neoadjuvant treatment in HER2+ BC pts.

Methods: Treatment naive pts with HER2+ early or LABC were enrolled to receive 4 cycles of KN026 (30mg/kg, ivgtt d1, q3w) and docetaxel (75 mg/m^2, ivgtt d1, q3w) as neoadjuvant treatment. The primary endpoint was tpCR rate. Secondary endpoints were bpCR, ORR, safety, etc. This study is registered in ClinicalTrials.gov, number NCT04881929.

Results: From August 9th, 2021, to July 29th, 2022, a total of 30 pts were enrolled from 5 sites. 16 pts (53.3%) were stage II, and 14 pts (46.7%) were stage III; 26 (86.7%) pts with biopsy-confirmed lymph node metastases; 15 (50.0%) pts were hormone receptor positive. As of Nov 21st, 2022, the study completed the primary outcome. 28 pts completed the surgery followed by pathological evaluation, and 2 pts discontinued from the study earlier due to AEs. In FAS, tpCR rate was 56.7% (17/30, 95% CI: 37.43%-74.53%), bpCR rate was 60% (18/30, 95% CI:40.60%-77.34%), ORR was 90.0% (27/30, 95% CI: 73.47%-97.89%). The incidence of TEAEs and CTCAE Grade ≥3 TEAEs were 100% (30/30) and 53.3% (16/30), respectively. The most common (≥5%) Grade ≥3 TEAEs were neutrophil count decreased (50%, 15/30), white blood cell count decreased (40.0%, 12/30), and lymphocyte count decreased (10%, 3/30). 7 (23.3%) pts required docetaxel dose reduction due to AEs. KN026 and docetaxel related SAEs occurred in only one patient. No Grade 5 TEAEs occurred.

Conclusions: KN026 plus docetaxel as neoadjuvant treatment has shown promising clinical benefit and acceptable safety for pts with HER2+ early or LABC. Further validation in a large-scale randomized controlled trial is warranted.

Legal entity responsible for the study: Jiangsu Alphamab Biopharmaceuticals Co. Ltd.

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Disclosure: All authors have declared no conflicts of interest.

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248P Targeting triple-negative breast cancer metabolism with neoadjuvant chemotherapy plus fasting-mimicking diet plus/minus metformin: The BREAKFAST trial

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Background: Cyclic fasting or fasting-mimicking diets (FMDs) enhanced the antitumor activity of chemotherapy (CT) in TNBC mouse models, while the combination of fasting and metformin resulted in impressive antitumor activity in several preclinical tumor models. The BREAKFAST study was designed to investigate if cyclic FMD, plus/minus metformin, improves the antitumor activity of neoadjuvant CT in patients (pts) with localized TNBC.

Methods: BREAKFAST is a randomized, non-comparative, phase II trial originally designed to enrol 90 stage I-III (cT>1cm) TNBC pts candidate to receive neoadjuvant doxorubicin-cyclophosphamide q3w for 4 cycles, followed by weekly paclitaxel for 12 cycles. Pts were randomized 1:1 to receive: CT + triweekly 5-day FMD cycles (arm A), or CT + FMD + daily metformin (1700 mg) (arm B). The primary study objective was to investigate if one or both experimental treatments were able to increase pCR rates when compared to anthracycline-taxane CT alone according to historical data.

Results: We enrolled 30 pts between June 2020 and February 2022, when the study was prematurely interrupted after the introduction of chemo-immunotherapy (CT-IO) as a standard neoadjuvant therapy for early stage TNBC. Of these pts, 13 were randomized to arm A and 17 to arm B; 73.3% of enrolled pts completed the maximum of 8 FMD cycles, with an average number of 6.9 completed FMD cycles. The observed pCR rate was 56.6%, i.e., significantly higher than pCR rates previously reported with CT alone in phase II/III trials (26-39%), and with no significant differences among treatment arms (OR 1.67, 95% CI 0.39-7.43; p=0.49). RNA-seq analysis in tumor specimens revealed higher pCR probability in pts undergoing precocious enhancement of tumor infiltration by activated T and NK cells, as well as precocious downmodulation of glycolysis and oxidative mitochondrial metabolism pathways.

Conclusions: Preoperative CT plus cyclic FMD (plus/minus metformin) results in excellent pCR rates in early TNBC pts. Based on these findings, we recently initiated a phase II, randomized, multicentric trial, namely BREAKFAST-2, to investigate if adding cyclic FMD to neoadjuvant CT-IO increases pCR rates in stage II-III TNBC pts.

Clinical trial identification: NCT04248998.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori.

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BMS, Menarini, AstraZeneca, Pierre Fabre, Mattioli 1885 , MCCann Health, Taiho, IQVIA; Financial Interests, Personal, Speaker's Bureau: BMS, Healthcare Research & Parmacoepidemiology, Merck Group, MSD, Pfizer, Servier, Sanofi, Roche, AMGEN, Incyte, Dephaforum, Seagen, Nadirex, Ambrosetti, Itanet; Financial Interests, Personal and Institutional, Sponsor/Funding: Novartis, F.Hoffmann-LaRoche Ltd, BMS, Ignyta Operating INC, Merck Sharp & Dohme Spa, Kymab, Pfizer, Tesaro, MSD, MedImmune LCC, Exelixis Inc., LOXO Oncology Incorporated, Daiichi Sankyo, Basilea Pharmaceutica International AG, Janssen-Cilag Internationa NV, Merck KGAA. C. Vernieri: Financial Interests, Personal, Advisory Board: Novartis, Pfizer, Lilly, Daiichi Sankyo, Novartis, Lilly, Istituto Gentili; Financial Interests, Institutional, Research Grant: Roche. All other authors have declared no conflicts of interest.

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250P The impact of inter-cycle treatment delays on progression-free survival in early stage breast cancer

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Background: Up to 30% of systemic anti-cancer therapy (SACT) treatments are reported to be delayed within cycle, due to drug toxicity, hospital capacity issues and patient choice; however, the impact on survival is unknown. This study aimed to determine the association of delays on PFS.

Methods: This population-based observational study included stage II-III breast cancer patients in England for whom guidelines recommend SACT, and who received six cycles of treatment from 01/01/2014-31/12/2015 in adjuvant and neo-adjuvant settings. Data were collected by the National Health Service as part of routine care. Cox proportional hazards model was applied to evaluate risk of progression with respect to treatment delays, adjusting for age, stage, histology, Charlson comorbidity index, ethnicity, socioeconomic group, BMI, region of England, hospital type and surgical status. Overall survival at 5 years was assessed. Delays were defined as treatment >7 days after expected date. Progression was defined as time from completion of 1st line to start of 2nd line SACT.

Results: 8680 patients were included. 2211 (25.5%) experienced at least one delay of 7 days or more during a six-cycle drug regimen. PFS probability was significantly lower at 1, 2 and 5 years in delayed patients; 97% (CI 96.6-97.4) vs 95.8% (CI 94.9-96.6), 93.9% (CI 93.3-94.5) vs 91.6% (CI 90.5-92.8) and 86.6% (CI 85.8-87.5) vs 81.5% (CI 79.9-83.2) respectively at each timepoint in patients treated to schedule vs delayed. Cox proportional hazards analysis showed a positive association of delays >7 days with disease progression or death (HR 1.36, CI 1.19—1.55) compared to those treated to schedule. Covariates associated with reduced PFS were triple-negative histology (HR 1.63, CI 1.29-2.06) and BMI>40 (HR 1.55, CI 1.16-2.08). Non-significant associations were seen between treatment at local vs academic hospital (HR 1.15, CI 0.98-1.35), Asian (HR 0.73, CI 0.53-1.01) and Chinese (HR 0.54, CI 0.13-2.19) ethnicity compared to White ethnicity.

Conclusions: Treatment delays were significantly associated with reduced PFS and occur frequently in early-stage breast cancer patients in England. Hospitals must avoid centre-led treatment delays where possible to maximise treatment efficacy in this patient cohort.

Legal entity responsible for the study: University College London Hospital NHS Foundation Trust.

Funding: National Institute for Health and Care Research.

Disclosure: L. Steventon: Financial Interests, Institutional, Research Grant, Award ID: NIHR201481: UK National Institute for Health and Care Research. E. Kipps: Financial Interests, Personal, Advisory Board: Pfzier, Novartis, Roche, AstraZeneca. K. Man: Financial Interests, Personal, Research Grant: UK National Institute for Health and Care Research, Hong Kong Research Grant Council, CW Maplethorpe Fellowship, European Commission Framework Horizon 2020 , Innovation and Technology Commission of the Government of the Hong Kong Special Administrative Region; Financial Interests, Personal, Funding: IQVIA Ltd . M.D. Forster: Financial Interests, Personal, Advisory Board: Bayer, EQRx, Janssen, MSD, Roche, Takeda, Transgene; Financial Interests, Personal, Research Grant: Merck, MSD. I. Wong: Financial Interests, Personal, Research Grant, Award ID: NIHR201481: UK National Institute for Health and Care Research. R. Miller: Financial Interests, Personal, Advisory Board: GSK, AZD, Merck, Shionogi, Ellipses; Financial Interests, Personal, Invited Speaker: GSK, AZD, Clovis Oncology. S. Nicum: Financial Interests, Personal, Advisory Board: GSK, AstraZeneca; Financial Interests, Personal, Invited Speaker: GSK, AstraZeneca, Clovis; Financial Interests, Personal, Other, scientific committee: GSK; Financial Interests, Personal, Stocks/Shares: GSK; Financial Interests, Institutional, Funding: AstraZeneca. P. Chambers: Financial Interests, Personal, Research Grant, Award ID: NIHR201481: UK National Institute for Health and Care Research. All other authors have declared no conflicts of interest.

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251P Body mass index as a predictive factor for efficacy of taxane-based chemotherapy in early breast cancer patients

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Background: Adjuvant anthracyclines and taxanes reduce risk of recurrence and death in Early Breast Cancer (EBC) patients (pts) but the toxicity profile is a major concern. Several studies have shown conflicting results correlating Body Mass Index (BMI) and outcomes in these pts. There are limited data on the efficacy of adjuvant taxanes among BMI categories. The prognostic effect of BMI on disease recurrence between adjuvant Paclitaxel (P)-based Chemotherapy (CT) vs. Docetaxel (D)-based CT has not ever been reported.

Methods: Pt-level pooled analysis of 13,486 EBC pts treated with adjuvant anthracyclines +/- taxanes from 7 GEICAM & TRIO adjuvant randomized controlled trials (RCTs) carried out from 1996 to 2008. Pts were classified in 4 BMI (kg/m2) categories: normal (< 25.0), overweight (25.0 to 29.9), obese (30.0 to 34.9), and severely obese (≥ 35.0), to evaluate BMI as a predictive factor for efficacy and toxicity of adjuvant taxane-based CT. Hazard Ratios (HR) were calculated using a Cox proportional hazard model stratifying by RCT.

Results: Pts distribution based on BMI was: 44% normal, 33% overweight, 16% obese, and 8% severely obese. 79% were treated with taxane-based CT (83% with D and 17% with P). 10y iDFS was 71%, 70%, 68% and 64% in normal, overweight, obese, and severely obese pts who received CT, respectively, being statistically significant in obese (HR 1.15; 95% CI 1.05-1.26; p=0.002) and severely obese (HR 1.29; 95% CI 1.15-1.45; p<0.001). 10y iDFS by type of CT are describe in the table. Relevant toxicity was 5%, 5.5%, 5.9% and 9.3% in normal, overweight, obese, and severely obese pts who received D.

Table: 251P

	Normal	Overweight	Obese	Severely obese
D vs. non- D	70% vs. 62% HR 0.73 95% CI 0.59-0.89 ***p*=0.003**	67% vs. 66% HR 0.83 95% CI 0.66-1.05 *p*=0.124	66% vs. 62% HR 0.84 95% CI 0.61-1.16 *p*=0.285	64% vs. 67% HR 1.12 95% CI 0.70-1.78 *p*=0.646
P vs.non-P	79% vs. 77% HR 0.94 95% CI 0.75-1.17 *p*=0.554	77% vs. 74 HR 0.89 95% CI 0.71-1.13 *p*=0.347	78% vs. 72% HR 0.72 95% CI 0.52-0.98 ***p*=0.039**	71% vs. 65% HR 0.70 95% CI 0.45-1.09 *p*=0.113

Conclusions: Prognosis is worse in heavier vs. leaner EBC pts receiving adjuvant taxane-based CT. Leaner pts receiving D (compared to non-D) achieved a better outcome, while pts who benefited most from P were the obese subgroup (compared to non-P).

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Research Group.

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Gilead; Financial Interests, Personal, Advisory Role: Daiichi Sankyo, Gilead and Pierre Fabre. M. Martin Jimenez: Financial Interests, Personal, Advisory Board: AstraZeneca, Lilly, Roche/Genentech, Daiichi Sankyo, Menarini-Stemline; Financial Interests, Personal, Invited Speaker: Pfizer, AstraZeneca, Lilly, Novartis, Roche/Genentech; Financial Interests, Institutional, Research Grant: Novartis, Roche, Puma; Non-Financial Interests, Member of Board of Directors: TRIO; Non-Financial Interests, Leadership Role: GEICAM; Non-Financial Interests, Member: ASCO; Non-Financial Interests, Advisory Board: SEOM. A.L. Guerrero Zotano: Financial Interests, Personal, Advisory Role: Pfizer, AstraZeneca, Pierre Fabre, Novartis, Exact Science, Stemline; Financial Interests, Institutional, Funding: Pfizer; Financial Interests, Personal, Speaker, Consultant, Advisor: Roche, MSD, Novartis, Pfizer, AstraZeneca, Daiichi Sankyo, Pierre Fabre, Exact Science. A. Rodríguez-Lescure: Financial Interests, Personal, Speaker, Consultant, Advisor: Pfizer, Novartis, AstraZeneca, Daiichi Sankyo and Seagen ; Financial Interests, Personal, Advisory Role: Pfizer, Novartis, Roche, AstraZeneca, Daiichi Sankyo, Pierre Fabre and Seagen. All other authors have declared no conflicts of interest.

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252P Adjuvant chemotherapy in T1a/bN0 breast cancer patients with high oncotype DX recurrence scores (RS>25)

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Background: RS>25 is prognostic for distant recurrence and predictive for adjuvant chemotherapy (aChem) benefit in ER+HER2-negative early breast cancer (BC), independent of tumor size. For patients with tumors >0.5 cm and candidates for aChem, current NCCN guidelines recommend strongly considering OncotypeDX testing and aChem treatment for RS>25. Herein, we sought to evaluate the benefit of aChem in T1a/bN0 early BC patients with high RS>25 tested. We used the Clalit Health Services (CHS) dataset, the largest HMO in Israel, with more than 4.5 million insurers.

Methods: We identified all CHS patients tested between Feb-2006 and Dec-2019 with T1a/bN0 early breast cancer and a RS>25. Demographic, clinicopathological, and treatment data were extracted from the CHS centralized registry. A propensity score matching method based on nearest neighbor with replacements was used to balance differences. Kaplan-Meier analysis with log-rank test was used to test differences in clinicopathological characteristics. Freedom from recurrence of BC locally and at a distant site and freedom from second primary cancer and death also known as invasive disease-free survival (iDFS) between the treatment groups.

Results: 159 patients were identified of which 76 patients (47.7%) received aChem. Before applying the propensity- score matching aChem was more common among younger patients >50-years-old (25%) compared with patients ≤70-years-old (7.9)%, healthier patients with Charlson comorbidity score 0-1 (70%) compared with 30.2% for score ≥2, among Oncotype RS >30 72.5%. aChem was more often omitted in invasive lobular carcinoma (75%) and grade 1 tumors (72.7%). Propensity score matching balanced discrepancies among both treatment groups and Kaplan-Meier analysis demonstrated no iDFS improvement with aChem in T1a/bN0 early BC patients with high Oncotype DX recurrence scores (RS>25).

Conclusions: Utility of aChem in T1a-bN0 tumors and RS>25 is dependent on clinocopathologic variables beyond RS. After balancing between these variables no iDFS benefit for aChem was observed.

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Disclosure: All authors have declared no conflicts of interest.

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253P Is 6-weekly administration of pembrolizumab in combination with chemotherapy for early triple-negative breast cancer safe? A real-world early comparison of q6w versus q3w administration of pembrolizumab in two large cancer centres in the UK

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Background: The KEYNOTE 522 regimen is now established as the gold standard for patients with at least T2N0 or N+ early triple-negative breast cancer. In KEYNOTE 522, Pembrolizumab was administered every 3 weeks at 200mg. Following approval of 6-weekly administration by the FDA and EMA, hospitals could choose to implement q6w (400mg) or q3w (200mg) administration of Pembrolizumab. On implementation of q6w Pembrolizumab at St Bartholomew's Hospital (SBH), we observed a higher-than-expected rate of grade 3-4 hepatotoxicity. This led to this real-world retrospective study, comparing our rates of toxicity with those seen at Guys Cancer Centre using the q3w regime.

Methods: We identified 21 eligible patients treated at SBH, who received at least one of cycle of q6w Pembrolizumab and 17 patients who received it q3w at GSTT from November 2022 — March 2023. Epidemiological and clinical data were collected retrospectively.

Results: In KEYNOTE 522, grade 3-5 transaminitis was seen in 5.5% of patients receiving Pembrolizumab. Of the 21 patients receiving q6w Pembrolizumab at SBH, there was a higher frequency of grade 3 transaminitis (Table). All 4 patients (19%) with G3 transaminitis required hospitalisation for IV steroids, with 2 developing grade 4 hyperbilirubinaemia requiring additional immunosuppression. A liver biopsy was carried out with 1 of 2 patients demonstrating vanishing bile duct syndrome. Pembrolizumab was discontinued in all 4 patients and 1 patient had to discontinue chemotherapy. In comparison, patients who received q3w Pembrolizumab at GSTT experienced no grade 3 toxicities.

Table: 253P

Pembrolizumab frequency	Q6w	Q3w
Patient number	21	17
Mean age	49	50
T2	17 (80%)	10 (59%)
N+	10 (48%)	11 (65%)
HBcAb positive requiring prophylaxis	0	1
Transaminitis		
G1	0	3 (18%)
G2	3 (14%)	2 (12%)
G3	4 (19%)	0

Conclusions: Although this study is limited by short follow-up and small number of patients it suggests that administration of q6w Pembrolizumab may be associated with a higher risk of grade 3 immune related hepatotoxicity. Further studies are required to confirm these findings.

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254P Effects of delaying adjuvant chemotherapy initiation on clinical outcomes in early triple-negative breast cancer patients

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Background: TNBC is known for its aggressive nature, with early recurrence and limited treatment options beyond chemotherapy and recently immunotherapy. The optimal time to initiation of adjuvant chemotherapy (TTAC) for triple-negative breast cancer (TNBC) patients remains unclear. We aim to clarify, whether TTAC has an impact on survival in patients with early TNBC.

Methods: Data from a large population-based regional cancer registry covering over 2.2 million people was used for evaluation, including women with diagnoses of TNBC between 2010 and 2018. Data collected included demographics, pathology, treatment, recurrence, and survival. TTAC was defined as days from primary surgery to first dose of adjuvant chemotherapy. Kaplan-Meier and Cox regression methods were used to evaluate impact of TTAC on overall survival (OS).

Results: We identified 37 382 patients with malignant neoplasms of the mammary gland. The final study cohort included 732 patients with early TNBC, of whom 43.6% were treated with neoadjuvant chemotherapy and 40.3% with adjuvant chemotherapy. 245 patients with TNBC treated with adjuvant chemotherapy had a valid TTAC. Treatment given within 22-28 days led to the best outcome with a mean OS of 10.2 years, while later treatment (29-35, 36-42 days, or >6 weeks) had significant reduced survival rates of 8.3, 7.8, and 6.9 years. Patients who received therapy within 22-28 days had significantly better survival than those who received therapy between 29-35 days (p=0.043) or after more than 43 days (p=0.033).

Conclusions: The results in this large population-based study indicate that timing of adjuvant systemic therapy can influence OS in TNBC patients, with reduced OS if adjuvant chemotherapy is applied later than 42 days after surgery. To optimize patients' outcomes, we recommend avoiding a delay of more than 6 weeks when administering adjuvant chemotherapy for early TNBC patients.

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255P Prognostic stratification capacity of the CPS+EG scoring system in HER2-low and HER2-zero early breast cancer treated with neoadjuvant chemotherapy

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Background: CPS+EG scoring system properly defined prognosis subgroups of early breast cancer (eBC) patients (pts) treated with neoadjuvant chemotherapy (NACT) with a higher CPS+EG associated with worse outcomes. It remains unknown if CPS+EG similarly stratify prognostic in HER2-low and HER2-zero eBC patients after NACT.

Methods: This pluricenter french retrospective study included eBC pts treated with NACT from 2 cohorts, a monocenter local database at CGFL, Dijon and a pluricenter clinical trial PRIMUNEO (NCT01513408). Molecular features were determined on core biopsies. Threshold for HR positivity was ≥10%. HER2-low/zero status was defined by immunohistochemistry (IHC) HER2 staining. CPS+EG score was calculated for all pts with available data.

Results: 608 patients with HER2-negative eBC that have received NACT were included. Median age at diagnosis was 51.0 y-o. Nearly all pts (98.2%) received >3 NACT cycles. In the overall population, 288 pts (47.4%) were HER2-low. More pts were HR+ than TNBC with 367 (60.3%) and 241 pts (39.7%), respectively. The majority of pts harboring HR+ disease were HER2-low (61.0%) contrary to TNBC eBC pts (26.5%). In the HER2-low and HER2-zero population, CPS+EG was able to well categorized pts within prognosis subgroups (log-rank p <0.0001).

Table: 255P

Score	CPS+EG HER2-low (n =288) 5-year DFS rate (%) (95% CI)	CPS+EG HER2-zero (n =320) 5-year DFS rate (%) (95% CI)
0	100 (100-100)	100 (100-100)
1	92.9 (82.14-97.28)	86.11 (74.1-92.81)
2	71.95 (60.8-80.43)	86.8 (77.89-92.3)
3	69.78 (58.09-78.8)	72.5 (61.18-81.01)
4	48.03 (29.17-64.63)	55.48 (40.12-68.39)
5	38.1 (8.92-68.02)	30.77 (9.5-55.43)

In HR+/HER2-negative pts, CPS+EG still properly separated pts within prognosis subgroups between HER2-low and HER2-zero pts (log-rank p =0.0012 and p <0.0001, respectively). In TNBC population, CPS+EG appears to be less accurate. Within HR+ and TNBC molecular subtypes, there was no difference in 5-year DFS between HER2-low and HER2-zero pts harboring a similar CPS+EG score.

Conclusions: In this study, we show that the CPS+EG scoring system retains its interest for the prognostic stratification of pts treated with NACT for HER2-low and HER2-zero eBC. While it seems especially true for HR+ disease, CPS+EG appears to be less effective for TNBC in isolating different outcomes.

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256P Evolution and risk stratification of adjuvant treatment strategies for early breast cancer: A Chinese perspective based on a national cancer database

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Background: HR+, HER2- early breast cancer (EBC) patients (pts) with high-risk clinicopathologic features (CPF) are at increased risk of early recurrence. This is the first study aimed at investigating the evolving adjuvant therapy landscape.

Methods: The study cohort, based on the medical records from 50 major hospitals across China linked with China Vital Registration (death information), included pts with HR+, HER2- stage I-III EBC who received surgery and adjuvant endocrine therapy (AET) from Jan 1, 2013, to Mar 31, 2021. CPF were used to identify a 'high-risk group' (HiR) (including ≥ 4 positive axillary lymph nodes (LN), or LN1-3 with ≥ 1 of the following high-risk CPF: Grade 3, tumor size ≥ 5 cm or Ki-67 ≥ 20%) and 'low-risk group' (LoR) (do not meet above criteria). Survival analysis was performed on invasive disease-free survival (iDFS), distant relapse-free survival (DRFS), and overall survival (OS) with cutoff date of Sep 30, 2021.

Results: Of the 4088 eligible pts (median age: 50 years), 1310 were identified in HiR (46.6% had LN≥ 4 and 53.4% had LN1-3 with high-risk CPF), and 2778 in LoR (90.8% N0 pts). Pts in HiR were more likely to receive adjuvant chemotherapy (74.9% vs 63.7%) and radiotherapy (72.1% vs 45.6%) than LoR. From 2013 to 2021, the use of aromatase inhibitors and ovarian function suppression in AET gradually increased while the use of selective estrogen receptor modulators (tamoxifen/toremifene) decreased. The 5-year iDFS was 75.3% in HiR and 89.9% in LoR, respectively. Pts in HiR had a higher risk of recurrence or death than pts in LoR (Hazard Ratio: 2.38, 95% CI: 1.82-3.12). Similar results were observed for DRFS and OS (Table).

Table: 256P Risk of recurrence and death in HR+, HER2- early breast cancer[1]

Risk groups	HR_{iDFS} (95% CI)	HR_{DRFS} (95% CI)	HR_{OS} (95% CI)
N0, or LN1-3 without risk feature	Ref.	Ref.	Ref.
LN≥4, or LN1-3 with ≥1 risk feature	2.38(1.82,3.12) **	3.20(2.31,4.43) **	3.81(2.34,6.21) **
LN≥4	3.44(2.55,4.65) **	4.86(3.40,6.94) **	6.47(3.84,10.92) **
LN1-3 with ≥1 risk feature	1.50(1.05,2.14) *	1.82(1.19,2.80) **	1.68(0.85,3.30)

*P < 0.05; **P<0.01

CI: Confidence interval; HR: hazards ratio; LN: positive axillary lymph nodes.

[1] HR and 95%CI were estimated from Cox proportional hazards regression models with adjustments for age, menopausal status, neoadjuvant therapy, adjuvant chemotherapy and radiotherapy.

Conclusions: Nearly 25% EBC pts with high-risk CPF experienced recurrence or death within 5 years of initiating AET. Novel treatments are needed to prevent recurrence and death in these pts.

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257P The characteristics of HER2-positive microinvasive breast cancer and the necessity of chemotherapy and anti-HER2 therapy in these patients: A real-world study

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Background: The prognosis of microinvasive breast cancer (MIBC) is between ductal carcinoma in situ and T1aN0 stage tumors. We conducted this real-world study to explore the prognosis of human epidermal factor receptor 2 (HER2)-positive MIBC, as well as to find out whether chemotherapy and anti-HER2 therapy could improve outcome in this population.

Methods: Patients who received radical surgery and were diagnosed with lymph node-negative HER2-positive MIBC at the National Cancer Center in China from January 2010 to December 2019 were consecutively enrolled. The invasive components were confirmed HER2-positive by pathologists from our center. The exclusion criteria included: 1) distant metastasis before surgery; 2) HER2 status of the invasive components was unknown. Clinicopathologic characteristics and follow-up outcome data were collected.

Results: A total of 121 patients were included. The median age was 51 years old, and the median follow-up time was 68.3 months. Twenty-four patients (19.8%) received adjuvant chemotherapy (CT), of which 7 patients received CT combined with trastuzumab. Among these 24 patients, 17 patients were aged $\leq$ 50, and 20 patients were estrogen receptor (ER) negative. In total, 5 patients experienced recurrence (2 in situ breast recurrence, 3 distant metastasis), all within 3 years after surgery. The 3-year disease free survival (DFS) rate and 5-year DFS rate were all 95.9%. Univariate analysis showed that patients aged $\leq$ 50 might have worse outcomes than those aged $>$ 50 (5-year DFS rate 92.5% versus 98.5%, p=0.098). Using propensity score matching, patients who received CT with or without trastuzumab were matched with those who did not receive CT in a 1:2 ratio based on age and ER status. Patients who received CT with or without trastuzumab showed a trend of increase in 5-year DFS rate compared to those who did not receive CT (100% vs 89.6%, p=0.106).

Conclusions: HER2-positive MIBC had a relatively good prognosis. For patients with risk factors of relapse, CT and trastuzumab might decrease recurrence, so adjuvant CT and anti-HER2 therapy could be considered in this population.

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258P Cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab for high-risk early-stage triple-negative breast cancer in Colombia

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Background: In Colombia, 15,509 new cases of breast cancer (BC) were diagnosed in 2020. Furthermore, BC was the leading cause of cancer deaths. Triple-negative breast cancer (TNBC) is an aggressive subtype that represents 15-20% of BC. The KEYNOTE-522 (KN522) trial showed that neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab significantly improved pathological complete response and event-free survival when compared to neoadjuvant placebo + chemotherapy followed by adjuvant placebo in patients with high-risk early stage TNBC (eTNBC). This study evaluated the cost-effectiveness of neoadjuvant pembrolizumab + chemotherapy [paclitaxel + carboplatin followed by anthracycline + cyclophosphamide] plus adjuvant pembrolizumab versus neoadjuvant chemotherapy in high-risk eTNBC, from a third payer perspective in Colombia.

Methods: A Markov cohort model was developed with four mutually exclusive health states: event-free, locoregional recurrence, distant metastasis, and death, to simulate patients' lifetime disease course based on the efficacy and safety data from KN522. Outcomes and costs were discounted at 3% annually. Time on treatment was estimated using observed Kaplan-Meier curves from KN522. Utility inputs were derived from EuroQoL-five-dimension questionnaire in KN522. Costs for initial and subsequent therapies, disease and adverse events management, and terminal care were estimated using drug and healthcare public lists prices of Colombia.

Results: Over a 51-year time horizon, patients receiving pembrolizumab + chemotherapy accrued an additional 2.39 life-years (LYs) and 2.19 quality-adjusted life-years (QALYs) compared to neoadjuvant chemotherapy. The resulting incremental cost-effectiveness ratios (ICER) were COP 65,159,259/LY and COP 71,172,546/QALY, which were lower than the willingness-to-pay threshold of COP 85,093,272 in Colombia (based on 3-GDP per capita).

Conclusions: Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab is a cost-effective treatment versus neoadjuvant chemotherapy for high-risk eTNBC in Colombia, constituting a novel and key therapy option for those patients.

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259P Adjuvant doxorubicin-cyclophosphamide in early-stage breast cancer provides long-term cardiac safety

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Background: Anthracyclines have been crucial chemotherapy for breast cancer treatment. However, its use has been limited by cardiotoxicity. We investigated the long-term outcomes and potential biomarkers associated with cardiac toxicities in breast cancer survivors who received anthracycline.

Methods: We prospectively collected data from 212 early-stage breast cancer patients who received adjuvant doxorubicin-cyclophosphamide (AC) at KCMH from 2007 to 2012. Echocardiography was performed pre-AC and within 3 months post-AC in 177 patients. Cardiac MRI (CMR) was conducted in asymptomatic patients (n=49) between July and December 2022 to assess long-term cardiac outcomes. We analyzed plasma microRNA expression using the Nanostring platform at pre-AC and before 2nd cycle of AC of 18 patients who had decline of LVEF $>$10% (n= 9) and $\leq$10% LVEF (n =9).

Results: The mean age of breast cancer diagnosis was 51$\pm$9 years with a median follow-up of 11 years [6-12]. The mean cumulative doxorubicin was 223.3$\pm$19.8 mg/m^2. At end-AC evaluation, 43 patients (24.3%) and 15 patients (8.5%) had decreased LVEF by 10-20% and $>$20% respectively. 32 patients (18%) received subsequent anti-HER2 therapy. 8 patients (3.7%) had arrhythmia (n=6) and cardiomyopathy (n=2) in long-term follow-up. The miR-16-5p, miR-25-3p, miR-873-5p, miR-19b-3p, and miR-30d-5p were the top 5 microRNAs that overexpressed in end-AC LVEF decline $>$10% with the fold change of 1.77-2.99. There was no difference in long-term CMR findings, including LVEF, LVEDVI, LVESVI, LV mass index, RVEF, T1 mapping, and strain in asymptomatic patients with end-AC LVEF decline $>$10% vs. $\leq$10%. Abnormal scars

were found in 8 patients who had end-AC LVEF decline >10% (n=7) vs. ≤10% (n=1). All were located at the RV insertion site or mid-wall.

Table: 259P

LVEF at pre-AC, end-AC, and long-term CMR

LVEF	End-AC LVEF decline >10% (n = 16)	End-AC decline ≤10% (n = 30)	p-value
Pre-AC echocardiogram	75.2% +/- 7.2%	68.4% +/- 5.2%	<0.01
End-AC echocardiogram	62.7% +/- 6.5%	68.1% +/- 5.3%	<0.01
Long-term CMR	60.3% +/- 4.9%	60.6% +/- 5.3%	0.87

Conclusions: Our study demonstrated acceptable long-term cardiac outcomes in early-stage breast cancer patients who received ≤4 cycles of AC. Potential plasma micro-RNAs were identified and will be further studied in more patients.

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260P Oncology efficacy of gonadotropin-releasing hormone agonist in hormone receptor-positive very young breast cancer patients treated with neoadjuvant chemotherapy

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Background: Breast cancer in young women has been shown to have an aggressive behavior and poor prognosis. This study aimed to evaluate the outcomes of hormone-receptor (HR)-positive young breast cancer patients treated with neoadjuvant chemotherapy (NAC) and the oncologic efficacy of gonadotropin-releasing hormone (GnRH) agonist.

Methods: This was a retrospective study on a prospectively collected cohort. We included 1123 patients who, between January 2006 and June 2018, were diagnosed with invasive breast cancer and treated with NAC followed by curative surgery at 000. Among patients with HR-positive and human epidermal grow factor 2 (HER2)-negative breast cancer, we analyzed the characteristics and oncology outcomes between the patients equal to or younger than 35 years and the patients older than 35 years.

Results: Among 288 patients with NAC and strong HR-positive/HER2-negative breast cancer, 72 patients were equal to or younger than 35 years of age, and 213 patients were older than 35 years of age. The median follow-up is 74.0 months. There was no statistically significant difference in disease free survival (DFS, $p = 0.261$) and overall survival (OS, $p = 0.625$) between the patients equal to or younger than 35 years and the patients older than 35 years. The two groups differed in that the GnRH agonist was used more frequently in the group of patients equal to or younger than 35 years than in the other group (52.4% vs. 11.2%, $p<0.001$). Interestingly, for the DFS according to the GnRH agonist in the group of patients equal to or younger than 35 years, patients treated with the GnRH agonist had better DFS ($p = 0.016$).

Conclusions: GnRH agonists might improve the DFS rate of HR-positive/HER2-negative breast cancer in the equal to or younger than 35 years group of patients with NAC.

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261P Dysregulation of immune checkpoint proteins in newly- diagnosed early breast cancer patients undergoing neoadjuvant chemotherapy: A comparison between TNBC and non-TNBC patients

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Background: Breast cancer is associated with up-regulation or down-regulation of proteins in the immune system, to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (sICMs) can be measured in human plasma. The study aimed to measure the systemic levels of a series ICMs at diagnosis, post-neo-adjuvant chemotherapy (NAC) and post-surgery in newly- diagnosed BC patients (pts) and compare the biological behaviour of these sICMs between TNBC and non-TNBC patients.

Methods: Soluble ICMs were measured using multiplex bead array technology in plasma from 72 BC pts and 45 healthy controls. Data were prospectively obtained and levels were compared between pre-treatment, post-NAC, and post-surgery using non-parametric tests (Mann-Whitney & Kruskal-Wallis).

Results: Following NAC, the plasma levels of six soluble co-stimulatory checkpoints (CD28, CD40, ICOS, CD27, CD80, GITR), all involved in the activation of CD8+ cytotoxic T cells, were significantly increased ($p < 0.04$-$p < 0.00001$). Four of the soluble co-inhibitory checkpoints (LAG-3, PDL1, TIM-3 and HVEM) increased significantly post-NAC. PD-1 remained unchanged, while BTLA and CTLA-4 decreased significantly ($p < 0.03$ and $p < 0.00001$, respectively). Normalization of sICM seemingly indicates a reversal of systemic immune dysregulation following the administration of NAC in early BC. In contrast, recovery of immune homeostasis may explain the increased levels of several negative checkpoint proteins, albeit with the exceptions of CTLA-4 and PD-1.

Conclusions: This study demonstrates low levels of co-stimulatory and co-inhibitory sICMs in newly-diagnosed, non-metastatic BC pts. Following treatment with NAC, the sICMs levels increase substantially, except CTLA-4. In the case of co-stimulatory sICMs, these novel findings are indicative of an immune-restorative mechanism. The pattern of co-inhibitory sICMs (elevated levels of PD-L1, LAG-3, TIM-3 and HVEM), might be indicative of immune-therapeutic resistance, underscoring the augmentative immune-therapeutic promise of targeting these molecules, either individually or in combination, to improve the outcome of pts with early BC.

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262P Pragmatic clinical trial assessing response to neoadjuvant taxotere and trastuzumab in Nigerian women with HER2-positive breast cancer (ARETTA): First report from the Nigerian breast cancer study group

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Background: There is unacceptably low level of oncology clinical trials in Nigeria, the country with the highest burden of breast cancer in Africa. This has been attributed to poor research infrastructure and trained personnel. This study was designed to assess the feasibility of establishing a robust platform for multi-institutional biomarker driven oncology clinical trials to improve quality of cancer care in Nigeria.

Methods: One-stage phase II single arm design in women with HER2-positive breast cancer with clinical stages IIA to IIIC (AJCC 2009). All patients received 4 cycles of docetaxel + Herceptin SC. Breast ultrasound (USS) was done at diagnosis and after

every 2 cycles of neoadjuvant phase. Those with complete clinical response by USS after 4 cycles had surgery. Those with partial response or stable disease (operable) switched to FEC for additional 3 cycles before surgery. All responders received 18 cycles of Herceptin SC. Adjuvant treatment included hormonal therapy as indicated. Radiation therapy was administered as per institutional practice.

Results: Study was initiated in April 2020 at onset of the pandemic and completed accrual in August 2022. Forty-seven of 53 enrolled patients (pts) were evaluable; 4 pts withdrew consent and 2 refused surgery. The median age was 50yrs (range 25-71 yrs.); Fifty-five percent were premenopausal. Majority were clinical stage III (60%), 58% ER- and 60% PR-. Twenty-five of 47 (53.2%) evaluable pts had pathological complete response (pCR) [including 6 pts (12.8%) after 4 cycles of docetaxel + Herceptin SC]. Treatment was well tolerated with Grade 3 toxicities of myelosuppression 6 (12.8%), diarrhea 1 (2.1%) and hepatic toxicity 2 (4.2%). The maximum reductions in LVEF were 20% and 26% in 2 pts respectively but without cardiac symptoms.

Conclusions: The study met its primary endpoint with pCR rate of 53% and manageable toxicity. To our knowledge, this is the first investigator initiated multi-institutional biomarker driven oncology clinical trial ever conducted in sub-Sahara Africa, paving the way for future pragmatic patient-centric biomarker informed clinical trials in populations of African Ancestry.

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263P Efficacy and safety of neoadjuvant chemotherapy combination with pembrolizumab in triple-negative breast cancer: Real-world data

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Background: Neoadjuvant chemotherapy (NAC) with the addition of Pembrolizumab (anti-PD1) is the current standard of care for early-stage II-III triple-negative breast cancer (TNBC). Although immunotherapy improves efficacy, toxicity rates remain a paramount parameter to consider since many of the events are long-lasting for this subset of patients (pts) treated with a curative intent.

Methods: We conducted a retrospective analysis of the medical records of 95 pts with early-stage TNBC treated with NAC and Pembrolizumab, between April 2022 and April 2023 in our institution. At the time of this submission, the toxicity analysis is available for 74 pts and efficacy for 64 pts. A complete analysis of 95 pts will be presented at ESMO. Treatment-related toxicities are reported according to the common terminology criteria for adverse events (CTCAE) v5.0.

Results: The cohort currently comprises 74 female patients, with a median age of 50 years [20-74]; 52% were premenopausal, and 20% harboured a deleterious *BRCA* germline mutation. Efficacy analysis (n=64): Pathologic complete response (pCR) rate was 56 % (n=36). The rate of pCR in pts with BRCA1/2 germline mutations was 80% (n=12). Toxicity analysis (n=74): We reported 376 toxicity events, of which 27% were grade 3-4. Most events were attributed to chemotherapy (55%). The immune-related adverse events (irAE) rate was 26%. A total of 35% of pts discontinued treatment due to toxicity, most commonly: liver toxicity, recurrent severe haematological and severe skin toxicities; while 50% of pts required dose reductions. The most common grade 3-4 AEs were neutropenia in 49% of pts and hepatic toxicity in 30% of cases. Immune-mediated thyroid dysfunction occurred in 25.7%, adrenal insufficiency was witnessed in 5%(4) of pts and hypophysitis in 4%(3). Immune-mediated myocarditis was witnessed in 1 elderly patient.

Conclusions: In this real-life cohort of early-stage TNBC patients treatment with a chemo-immunotherapy combination in the neoadjuvant setting was effective. However, we witnessed an important rate of treatment discontinuation due to toxicity. The impact on the quality of life of these patients should be carefully evaluated, especially in regard to permanent toxicities.

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Disclosure: C. Baldini: Financial Interests, Personal, Advisory Role: Bicycle therapeutics, Rising Tide Fundation, ITEOS; Financial Interests, Institutional, Principal Investigator: Abbvie, Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beige; Financial Interests, Institutional, Research Grant: AstraZeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi; Non-Financial Interests, Institutional, Product Samples: AstraZeneca, Bayer, BMS, Boringher Ingelheim, GSK, MedImmune, Merck, NH TherAGuiX, Pfizer, Roche. S. Champiat: Financial Interests, Personal, Invited Speaker: Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Eisai, Genmab, Janssen, Merck, Merck Serono, Novartis and Roche; Financial Interests, Personal, Other, Principal Investigator of Clinical Trials: AbbVie, Amgen, Boehringer Ingelheim, Cytovation, Eisai, Imcheck Therapeutics, Molecular Partners Ag, Merck, Ose Pharma, Pierre Fabre, Sanofi Aventis, Sotio A.S, Transgene; Financial Interests, Personal, Advisory Board: Alderaan Biotechnology, Amgen, AstraZeneca, Avacta, Celanese, Domain Therapeutics, Ellipses Pharma, Genmab, Immunicom, Inc., Nanobiotix, Nextcure, Oncovita, Pierre Fabre, Seagen, Tatum Bioscience, Tollys SAS, UltraHuman8; Financial Interests, Personal, Other, Travel and congress: Amgen, AstraZeneca, Bristol Myers Squibb, Merck, Ose Pharma, Roche, Sotio; Financial Interests, Institutional, Other, As part of the Drug Development Department (DITEP) =Principal/sub-Investigator of Clinical Trials: Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Adaptimmune, AdlaiAstex Pharmaceuticals, AstraZeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, BicycleTx Ltd, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Casi Pharmaceuticals, Inc, Celgene Corporation, Cellcentric, Chugai Pharmaceutical Co, Cullinan-Apollo, Curevac, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Exelixis, Faron Pharmaceuticals Ltd, Forma Tharapeutics, Gamamabs, Genentech, GSK, H3 Biomedicine, Hoffmann La Roche Ag, Imcheck Therapeutics, Incyte Corporation, Imcheck Therapeutics, Incyte Corporation, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Iteos Belgium SA, Janssen Cilag, Janssen Research Foundation, Janssen R&D LLC, Kura Oncology, Kyowa Kirin Pharm. Dev, Lilly France, Loxo Oncology, MedImmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Genomics, Ose Pharma, Pfizer, PharmaMar, Pierre Fabre Medicament, Relay Therapeutics, Inc, Roche, Sanofi Aventis, Seattle Genetics, Sotio A.S, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Transgene S.A, Turning Point Therapeutics, Xencor; Financial Interests, Institutional, Research Grant, As part of the Drug Development Department (DITEP) =Research Grants: AstraZeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Pfizer, Roche, Sanofi; Non-Financial Interests, Institutional, Product Samples, As part of the Drug Development Department (DITEP) =Non-financial support (drug supplied): AstraZeneca, BMS, Boehringer Ingelheim, GSK, MedImmune, Merck, NH TherAGuiX, Pfizer, Roche. B. Pistilli: Financial Interests, Institutional, Advisory Board: AstraZeneca, Seagen, Lilly, Daiichi Sankyo, MSD; Financial Interests, Institutional, Invited Speaker: Gilead, Novartis; Financial Interests, Personal, Advisory Board: Pierre Fabre, Daiichi Sankyo; Financial Interests, Personal, Other, travel support: AstraZeneca, Pierre Fabre, MSD, Daiichi Sankyo; Financial Interests, Institutional, Steering Committee Member: AstraZeneca, Novartis; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Local PI: AstraZeneca, Gilead, Seagen, MSD, Novartis; Financial Interests, Institutional, Funding: Daiichi Sankyo; Non-Financial Interests, Project Lead: UNICANCER. J.T.M.L. Ribeiro: Financial Interests, Personal, Advisory Board: Gilead Sciences, Inc.; Financial Interests, Institutional, Advisory Board: AstraZeneca; Financial Interests, Personal, Invited Speaker: eESO. All other authors have declared no conflicts of interest.

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264P Tumor-infiltrating lymphocytes (TILs) for prediction of response to platinum-based neoadjuvant chemotherapy (NACT) in triple-negative breast cancer (TNBC): Final analysis

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Background: According to several previous trials, event-free survival (EFS) in patients with TNBC is improved when carboplatin is added to NACT. Stromal TILs represent an important predictive and prognostic biomarker in patients with breast cancer. We are now reporting the analysis of EFS in patients with TNBC who received NACT $\pm$ carboplatin regarding TILs status.

Methods: The clinical data were obtained from 132 patients diagnosed with TNBC (ER&PgR<10%) and treated with either anthracycline-taxane NACT (n=68) or carboplatin-based chemotherapy (n=64) from 2017 to 2022 at N.N. Petrov National Medicine Research Center of Oncology. TILs were evaluated in FFPE tumor tissue samples stained with H&E at baseline biopsies according to guidelines from the International TILs Working Group. EFS was estimated by the Kaplan-Meier method and compared between groups by log-rank test. Multivariate analysis for EFS was performed using Cox's proportional hazards regression model, covariates included TILs level (<40 vs. $\geq$40), NACT, nodal status, BRCA status and pCR.

Results: High TILs were associated with significantly higher 5-year EFS (94.3% vs 56.1% HR=0.119, 95%CI 0.02-0.88, p=0.037). Patients with pCR had a significantly better 5-year EFS (74.5% vs 53.2%, HR=0.231, 95%CI 0.09-0.58, p=0.002). 5-year EFS rates were similar for both platinum-based and standard NACT groups (68.6% and 61.9%, respectively HR=0.537, 95%CI 0.24-1.19, p=0.124).
5-year EFS for platinum-based NACT was 100% vs 84.6% in the standard NACT group (HR=1.374, 95%CI 0.66-2.88, p=0.40) in patients with high TILs, compared with patients with low TILs levels EFS was lower 61.3% vs. 56.9%, respectively (HR=1.602, 95%CI 0.71-3.61, p=0.256). In univariate analysis, the nodal status, pCR, and TILs level were significant predictors of EFS. In multivariate analysis, only pCR (p=0.006) and TILs level (p=0.048) are two independent predictors of EFS.

Conclusions: EFS is numerically lower in the low TILs tumors which justifies the escalation of the NACT regimen. Treatment de-escalation may be considered in patients with high TILs level. Further research in larger datasets is needed to validate these hypothesis generating findings.

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265P Effect of HER2-low-positive status on neoadjuvant chemotherapy and survival outcome of breast cancer: A 10-year dual-center retrospective study

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Background: Various novel HER2-targeted antibody-conjugated drugs (ADCs) have shown satisfactory antitumor activity in HER2-low-positive breast cancer (BC). The effect of HER2 status on neoadjuvant chemotherapy (NAC) and survival outcome is controversial. It is urgent to clarify whether HER2-low-positive tumors have unique biological behavior and should be considered a new molecular subtype. In our study, a 10-year dual-center retrospective research was conducted to analyze the effect of HER2-low-positive status on NAC and survival outcome of BC.

Methods: We screened eligible BC patients and collected relevant information at the First Hospital of Jilin University and the the First Affiliated Hospital of Xi'an Jiaotong University from January 2010 to December 2020. The primary outcome indicator was pathologic complete response(pCR). The secondary outcome indicators were overall survival (OS) and disease-free survival (DFS).

Results: A total of 1027 patients were included in our study cohort, and 66.0% (678/1027) had HER2-low-positive tumors. Compared to HER2-zero, HER2-low-positive patients tended to have more lymph node metastasis, a larger proportion of hormone receptor (HR)-positive tumors, and a lower proliferation rate (Ki-67). The pCR rate of HER2-low-positive was lower than that of HER2-zero patients (19.3% vs 21.6%), especially in the HR-positive subgroup (12.00% vs 20.29%). However, multivariate logistic regression analysis showed that HER2 status was not an independent factor for predicting pCR. HER2-low-positive patients had a higher OS rate in the HR-positive subgroup. The Cox regression model analysis suggested that HER2-low-positive status did not affect the survival outcomes, regardless of DFS (p=0.308) or OS (p=0.066).

Conclusions: HER2-low-positive tumors have unique clinical and pathological characteristics, with a lower pCR rate in the HR-positive subgroup and better survival in the HR-negative subgroup compared to HER2-zero tumors. However, HER2-low-positive status is not an independent predictor of pCR or survival outcome. The authors have equally contributed to the study.

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266P Discontinuation rate and serious adverse events of chemoimmunotherapy as neoadjuvant treatment for triple-negative breast cancer: A systematic review and meta-analysis

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Background: Combination of chemotherapy plus immune checkpoint inhibitors (ICIs) has recently shown efficacy in triple-negative breast cancer (TNBC), and thus, has been introduced in clinical practice in both the advanced and early disease stage. However, few data are available regarding the extent and the potential consequences of discontinuation rate and serious adverse events of these treatments, especially in the neoadjuvant setting. Herein, we performed a comprehensive systematic review and meta-analysis to assess discontinuation rate and serious adverse events of chemoimmunotherapy compared to chemotherapy alone in phase II and III neoadjuvant clinical trials in TNBC.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, EMBASE, Cochrane Library, and PubMed/ Medline were searched for articles published from June 2008 to March 2023. The outcomes of interest were discontinuation rate, serious adverse events, and grade 3-4 adverse events.

Results: Overall, 4 studies were included in the analysis. The pooled Odds Ratios (ORs) for discontinuation rate and serious adverse events were 1.26 (95% CI, 0.78-2.06) and 1.79 (95% CI, 1.4-2.28), respectively, in patients receiving chemoimmunotherapy versus chemotherapy alone as neoadjuvant treatment for TNBC. A higher risk of grade 3-4 adverse events was reported in the chemoimmunotherapy group (OR 1.30; 95% CI, 1.07-1.59). The analysis was associated with substantial heterogeneity and the risk of discontinuation rate was strongly conditioned by the KEYNOTE-522 trial.

Conclusions: Our findings support the design of clinical trials which could be specifically focused on safety and treatment adherence, as well as the potential impact on outcome and quality of life in TNBC patients receiving neoadjuvant treatment. Careful monitoring of tolerability remains a crucial need in this clinical setting.

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267P Pathological complete response after neoadjuvant chemotherapy plus pertuzumab and trastuzumab for HER2+ early breast cancer: Real-world data from NeoPowER study

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Background: The addition of pertuzumab (P) to trastuzumab (H) and standard chemotherapy (CT) as neoadjuvant treatment (NaT) for patients (pts) with HER2 positive (HER2+) breast cancer (BC), has shown to increase the pathological complete response (pCR) rate, without main safety concerns. The aim of multicentric NeoPowER trial is to evaluate safety and efficacy of P+H+CT in a real world population.

Methods: We retrospectively reviewed the electronic medical records of stage II-III, HER2+ BC pts treated with preoperative CT+H±P. The pts who received P+H+CT in 5 Emilia Romagna oncology centers (Modena, Bologna Bellaria, Bologna S.Orsola, Meldola, Rimini) between 2017-2022, were compared with a historical group who received H+CT (control) at Modena Cancer Center between 2007-2021. Clinicopathological variables were collected. Univariate and multivariate analysis were performed to assess the impact of covariates on pCR. Results were expressed as odds ratios (OR).

Results: 259 pts were included in the analysis, 125 (48%) received P+H+CT. Median age was 52 years, 63% were node-positive and 62% had hormone receptors positive (HR+). Features were balanced in the two groups, 62% of pts in the P+H+CT cohort had a Ki67 $\geq$ 30%, vs 43% in the control. All pts received preoperative taxane-based CT: 82% and 45% of pts also received anthracyclines, in the control and P+H+CT respectively. P+H+CT pts achieved higher pCR rate than the control: 46% vs 40% (p=0.462). At univariate analysis, HR negative (OR=3.79 p<0.001), Ki67 $\geq$ 30% (OR=1.29 p=0.04) and the use of preoperative anthracyclines (OR=1.72 p=0.04), were statistically related to pCR. Only ER expression (OR: 0.97 p=0.004) confirmed its statistical relation to pCR at multivariate analysis.

Conclusions: NeoPowER study confirms the efficacy of neoadjuvant chemotherapy combined with dual HER2 directed therapy: a higher pCR rate is achievable in case of HR negative and ki67$\geq$30% in pts receiving neoadjuvant P+H+CT, when compared to H+CT.

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268P Evaluating the efficacy of adjuvant capecitabine in triple-negative breast cancer patients with residual disease: A real-world evidence study

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Background: In early breast cancer, residual disease after neoadjuvant chemotherapy is considered an important prognostic factor, especially for triple-negative breast cancer (TNBC) and HER2-positive patients. The CREATE-X study demonstrated a survival benefit of adjuvant capecitabine (adjC) for these patient groups, particularly in TNBC. Researchers have been trying to find the appropriate population for adjC as Real-World Evidence (RWE). However, RWE in the Asian population was lacking, and previous RWE studies were limited in number. In addition, these studies did not include patients who received neoadjuvant immunotherapy treatment, while the Keynote-522 trial demonstrated the benefit of immunotherapy in early TNBC. Therefore, we evaluated the advantages of adjC in non-pCR TNBC patient group by using RWD.

Methods: We conducted a retrospective analysis of 1,033 TNBC patients who received neoadjuvant treatment at Samsung Medical Center between 2018 and 2023, using de-identified, anonymous data from the institutional Clinical Data Warehouse. Among these patients, we identified 403 patients who received at least one cycle of adjC, while 36 received no adjuvant treatment. Residual Cancer Burden (RCB) classification were available for 399 patients. The primary outcome of the study was Disease-Free Survival (DFS). We conducted a survival analysis using Kaplan-Meier method.

Results: The median DFS has not yet been reached. The disease risk of the adjC group tended to be lower than that of the no adjuvant treatment group, but the difference was not statistically significant (Hazard ratio(HR), 0.52; p-value=0.083). At 36 months, 86% of patients in the adjC group were disease-free or alive, compared to 76% of patients in the no adjuvant treatment group. Compared to the RCB-I group (n=114, 28.4%), the HR for the RCB-II group (n=233, 58.5%) was 1.40, and the for the RCB-III group (n=52, 13.1%), it was 5.88 ($p<0.0001$). The DFS at 36 months was 90%, 89%, and 67% for the RCB-I, II, and III groups, respectively.

Conclusions: In this study, adjC demonstrated a potential survival benefit for non-pCR TNBC patients. Subgroup analysis based on RCB classification indicated a higher risk associated with higher RCB class.

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269P Achieving treatment goals in elderly breast cancer patients with neoadjuvant chemotherapy: A remarkable insight

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Background: Neoadjuvant chemotherapy (NAC) is widely used for locally advanced breast cancer, including HER2-positive and triple-negative subtypes. However, the impact of age on treatment response remains uncertain. This study aims to investigate treatment outcomes in elderly breast cancer patients receiving neoadjuvant chemotherapy.

Methods: A retrospective analysis was conducted on breast cancer patients who underwent neoadjuvant treatment at two tertiary centers between 2010 and 2021. Patients were divided into two groups based on age: $\geq$65 years and $<$65 years. Pathologic response and surgical outcomes were compared between the groups.

Results: A total of 535 patients were included in the study, with 12% aged $\geq$65 years. There were no statistically significant differences in the clinicopathological characteristics between older and younger patients. The overall rate of receiving anthracycline-based chemotherapy (CT) in the entire population was 97.6%, with ddAC used more in the younger patients (71.7% vs 38.5%, $p<0.001$). Breast-conserving surgery and sentinel lymph node dissection were comparable between the groups. In older patients, the rate of breast downstaging was 73.5% and the rate of axillary downstaging was 70.6%, with no statistically significant difference compared to younger patients. A comparison of the groups in terms of pathological complete response revealed rates of 26.6% in younger patients and 33.3% in older patients ($p>0.05$). The rate of grade 3-4 toxicity was statistically higher in elderly patients (71% vs. 46.4%, $p<0.01$). No treatment-related deaths were observed. The median follow-up period was 50 months. Recurrence occurred in only 84 (17%) patients, with a recurrence rate of 10.4% in elderly patients compared to 17% in the other group ($p=0.17$).

Conclusions: The study suggests that elderly patients achieve similar outcomes to younger patients, indicating that age alone should not be a basis for undertreatment. Further research focusing on personalized approaches for the geriatric population is needed.

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270P Influence of neoadjuvant chemotherapy-induced short-term amenorrhea on pathologic response and treatment outcome in ER+HER2- breast cancer

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Background: Premenopausal women experience temporary ovarian function suppression (OFS) during the period of chemotherapy. In ER+ breast cancer, chemotherapy-induced temporary OFS may offer anti-estrogenic effect in addition to direct cytotoxic anti-tumor effect. It is unclear whether anti-estrogenic effect by temporary OFS during neo-adjuvant chemotherapy (NAC) enhance anti-tumor effect. Based on pathologic complete response (pCR) and complete cell-cycle arrest (CCCA), we compared pathologic response and outcomes between younger and older patients with ER+HER2- breast cancer treated with NAC.

Methods: Between 2007 January and 2021 June, we retrospectively identified 1,178 patients with ER+HER2- breast cancer who underwent NAC in the Gangnam Severance Hospital and the Asan Medical Center. We compared the pCR rate according to age under 45 and over 55 and investigated durations of NAC, clinical stage, and Ki-67. Pathologic complete response was defined as no invasive residual disease in both breast and axillae. In addition, we collected available Ki67 expression in surgical specimen after NAC. We defined low Ki67 with a cutoff of 2.7%. The recurrence-free survival was evaluated in patients with post-NAC Ki67.

Results: In all 1,178 patients, the pCR rate was 1.9% (22/1,178). The rate was 1.4% (8/552) in younger patients (age $\leq$45), whereas it was 3.6% (9/250) in older patients (age $\geq$55) ($p=0.063$, Chi-square test). In 524 patients who received NAC consisting of anthracyclines and taxanes with a duration of NAC longer than 6 months, the pCR rate did not differ between the younger patients and the older (2.1%, 5/243 vs. 2.8%, 3/106; $p=0.703$). In patients with post-NAC Ki67, the CCCA rates were 66.2% (307/464) in the younger and 39.8% (86/216) in the older, respectively ($p<0.001$). Survival analyses showed that, compared to patients with CCCA, those without CCCA experienced a significant decrease in RFS in both younger and older women.

Conclusions: While short-term OFS resulting from NAC led to a higher rate of CCCA in premenopausal women, younger women had notably poorer survival outcomes compared to older women. Among premenopausal women, achieving CCCA was associated with a slight improvement in treatment outcomes.

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271P First clinical demonstration of the predictive value of tissue nanomechanical signature in breast cancer patients in neoadjuvant therapy setting

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Background: Structural remodeling of cells and extracellular matrix (ECM) during cancer initiation and progression are accompanied by substantial biomechanical alterations, which can be measured by Atomic Force Microscopy (AFM). Increasing (pre)- and clinical evidence demonstrate the importance of cancer biomechanics in mediating therapy response. Incorporating AFM measurements of clinical biopsies within standard of care is thus a promising avenue to leverage tissue mechanics as prognostic and predictive biomarker for solid cancers.

Methods: We conducted a single center, blinded, prospective study to measure a multiparameter nanomechanical signature (NS) of response to neoadjuvant therapy (NAT) in breast cancer (BC). Between 2016 and 2019, 588 fresh, baseline, clinical breast biopsy samples from 545 patients were measured using the AFM based Automated and Reliable Tissue Diagnostics (ARTIDIS) investigational device — ART-1, within routine clinical setting in the Breast Clinic, University Hospital Basel. 35 patients received NAT: combination chemotherapy (CHT) (n=30) and endocrine NAT (n=5). Study endpoints were radiological complete response (rCR) prior and pathological complete response (pCR) after surgery. NS data has been analyzed in an automated manner using proprietary ARTIDISNet software platform. 10 y follow up is ongoing.

Results: The ARTIDIS NS of response to NAT in BC showed 100% negative predictive value (NPV) and 89% positive predictive value (PPV) with 93% of accuracy for patients receiving CHT, independent of molecular subtype or treatment regimen. Sensitivity was 100% and specificity was 85% (AUC=0.91). When 5 patients with endocrine NAT were included, performance was decreased, meaning: NPV=92%, PPV=91, Sensitivity = 95 and Specificity = 85 (AUC=0.83).

Conclusions: NS can be prospectively used in clinical settings to predict response to NAT in BC. Mechanistically, these results highlight the importance of cell and TME mechanics in modulating therapy response. Furthermore, these results are being validated in a multicenter prospective study (ANGEL) currently enrolling 2706 patients with the aim to support implementation of the ARTIDIS NS into routine clinical practice.

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272P Primary prevention of bone fractures in patients (pts) with hormone receptor (HR)+ early breast cancer (EBC) during adjuvant hormonal therapy (HT): The predict & prevent project (P&P)

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Background: High rate of clinical fractures was reported during adjuvant HT trials (9-14% in BIG 1-98, ATAC, IES). Since 2015, in Italy, bisphosphonates and denosumab are reimbursed for prevention of bone fractures in EBC HR+ postmenopausal pts receiving HT, regardless of T-score values (Note 79 of AIFA-Agenzia Italiana del Farmaco). In 2019, these drugs were administered only in 25% of potentially beneficiary pts. The P&P is a nationwide Bone Health (BH) management project designed to improve adherence to recommendations regarding fracture risk assessment and risk prevention measures in pts receiving HT for HR+ EBC.

Methods: The BH management model P&P was developed in 10 Italian cancer centres and includes: 1- training of multidisciplinary team and presentation of a BH management model by the oncologist (with referral to the Bone Specialist if osteoporosis); 2- implementation of this model in every centre; 3- evaluation, after 12 months, of rate of EBC HR+ pts in postmenopausal status (natural, surgical, secondary to chemotherapy or hormonal blockage) assessed for BH within 30 days from the start of adjuvant HT; 4- evaluation, after 12 months, of rate of EBC HR+ pts receiving therapy within 90 days from the start of adjuvant HT, according to the criteria for reimbursement by AIFA.

Results: At 12 months after implementation of P&P, data are available from 6 centres (IRCCS Negrar, Ancona Hospital, IRCCS San Martino Genova, Poliambulanza Brescia, Cardarelli Napoli, Papa Giovanni XXIII Bergamo) in 1,551 postmenopausal EBC HR+ pts. The first analysis reports that 83% of EBC HR+ patients who started adjuvant HT were assessed for BH within 30 days compared to 43% in the 2019 national survey and 68% of pts started bisphosphonates/denosumab compared to 25% in the 2019 national survey.

Conclusions: Implementation of the P&P model has been shown to increase the rate of postmenopausal EBC HR+ pts on adjuvant HT assessed for BH and treated with bisphosphonate/denosumab to reduce the risk of bone fractures. A new project is ongoing to assess the rate of fractures in Italian pts after the approval of Note 79 by AIFA.

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273P A preoperative window-of-opportunity (WOO) study of imlunestrant in ER+, HER2- early breast cancer (EBC): Final analysis from EMBER-2

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Background: Imlunestrant is an investigational, next-generation, oral SERD designed to deliver continuous ER target inhibition, including in *ESR1*-mutant BC. Imlunestrant monotherapy demonstrated favourable safety, pharmacokinetics, and preliminary efficacy in patients (pts) with heavily pre-treated ER+ advanced BC (Jhaveri ASCO 2022). We present final pharmacodynamic (PD) biomarker data from the preoperative EMBER-2 WOO study (NCT04647487), including the expanded data at the 200 mg dose level, evaluating imlunestrant in ER+, HER2- EBC.

Methods: Post-menopausal women with stage I—III operable ER+, HER2- untreated EBC ≥1 cm were enrolled to imlunestrant 200, 400 (RP2D), or 800 mg once daily for approximately two weeks up to the surgery date. Pre- and on-treatment tumor samples were compared for changes in PD biomarkers. Primary endpoint was change in ER expression by IHC. Secondary endpoints were change in progesterone receptor (PR) expression and Ki-67, safety, and tolerability.

Results: Seventy-five pts were evaluable for ER expression (200 mg: n = 22; 400 mg: n = 27; 800 mg: n = 26). Baseline characteristics were similar across cohorts, with a median age of 64 years, 69% invasive ductal carcinoma, 30% invasive lobular carcinoma, 1% other, 55% stage I, 40% stage II and 5% stage III. Among evaluable pts, relative reduction in PD biomarkers after a median of 16 days of treatment are presented in the table. There was no significant difference in PD biomarker modulation between imlunestrant doses or tumor histology. Imlunestrant was well tolerated..

Conclusions: Imlunestrant demonstrated evidence of consistent and robust target engagement across all evaluated doses and was well tolerated in an EBC population, supporting adjuvant development in the EMBER-4 study.

Clinical trial identification: NCT04647487.

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Table: 273P Reduction in PD biomarkers from baseline and safety

Endpoint	200 mg	400 mg	800 mg	Total
ER (N=75)				
n (%)	22 (29)	27 (36)	26 (35)	**75 (100)**
GMPC - % (90% CI)	-89 (-96, -72)	-82 (-91, -60)	-70 (-78, -59)	**-81 (-87, -72)**
PR (N=72)				
n (%)	20 (28)	26 (36)	26 (36)	**72 (100)**
GMPC - % (90% CI)	-85 (-97, -37)	-76 (-90, -38)	-82 (-92, -60)	**-81 (-89, -66)**
Ki-67 among pts with baseline Ki-67 >5% (N = 59)				
n (%)	20 (34)	22 (37)	17 (29)	**59 (100)**
GMPC - % (90% CI)	-70 (-80, -56)	-71 (-80, -57)	-78 (-84, -70)	**-73 (-78, -67)**
All-grade treatment related adverse events (TRAEs) ≥5% - %	Nausea — 11 Diarrhea — 7 Dizziness — 7 Fatigue — 7 Hot flush — 7	Fatigue — 13 Hot flush — 7	Diarrhea — 18 Nausea — 11 Fatigue — 7 Hot flush — 7	**Fatigue — 9** **Diarrhea — 8** Hot flush — 7 Nausea — 7
Grade ≥3 TRAEs - %	0	0	0	**0**
Discontinuations due to AEs	0	0	0	**0**

N = number of biomarker evaluable pts; n = number of pts in category; GMPC = geometric mean percent change.

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274P Impact of dose reductions on efficacy of adjuvant abemaciclib for patients with high-risk early breast cancer (EBC): Analyses from the monarchE study

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Background: Abemaciclib is approved as adjuvant therapy for HR+, HER2-, high risk EBC based on clinically significant improvements in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS), which were maintained and deepened after the 2-year treatment period was completed. In monarchE, 44% of patients required dose reductions of abemaciclib to proactively manage adverse events. In abemaciclib MBC trials, similar rates of dose reductions did not compromise PFS (Rugo, 2021). Here we present the exploratory analyses to investigate the impact of dose reductions on efficacy in monarchE.

Methods: In monarchE, up to 2 abemaciclib dose reductions were permitted prior to discontinuation. Pts treated with abemaciclib were classified into 3 equal-sized subgroups according to their abemaciclib relative dose intensity (RDI), and IDFS rates were estimated within each subgroup. A time-dependent Cox proportional hazard (PH) model (Therneau, 2000) was also implemented to assess the impact of dose levels over time on IDFS.

Results: Among the 2791 pts treated with abemaciclib, 832 (30%) had one and 389 (14%) had two dose reductions. Patients $\geq$65 years old, or those with $\geq$4 pre-existing co-morbidities were more likely to have dose reductions. Across the 3 RDI groups ($\leq$66% vs 66%-93% vs $\geq$93%), 4-year IDFS rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest). According to the time-dependent model, the effect of abemaciclib is similar when staying at the full 150mg dose compared to being dose reduced to either 100mg or 50mg (HR = 0.905; 95% CI = 0.727, 1.125).

Conclusions: Consistent with observations in the metastatic setting, the efficacy of adjuvant abemaciclib in monarchE was not compromised by dose reductions. Therefore, dose reductions should be considered as a safe and effective way to manage toxicity and retain patients on treatment, in order to maintain benefit from adjuvant abemaciclib in combination with endocrine therapy.

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275P Clinical and molecular impact of neoadjuvant chemotherapy (NACT) or endocrine therapy (NET) on hormone receptor positive (HR+)/HER2-negative (-) breast cancer (BC)

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Background: Clinicopathological and molecular features of HR+/HER2- BC associated with response and survival following NACT or NET have been poorly characterized.

Methods: A total of 186 patients with early-stage HR+/HER2- BC treated with NACT (52.2%) and NET (47.8%) at the Hospital Clinic of Barcelona between 2014-2018 were evaluated. Associations with pathologic complete response (pCR), event-free survival (EFS) and overall survival (OS) were assessed with logistic and Cox regressions, where appropriate. Intrinsic subtypes (IS), risk of relapse (ROR) and selected genes' expression before and after neoadjuvant treatment (NAT) were assessed with a research-based PAM50. SAM analyses were carried out. Significance was set at $p \leq 0.05$ and false discovery rate (FDR)$\leq$5%.

Results: The pCR rates following NACT and NET were 18.6% and 3.4%, respectively. NACT (adjusted odds ratio [aOR]: 6.26, p=0.044) and non-Luminal IS (aOR: 8.89, p=0.021) were independently associated to pCR. Both NAT strategies reduced PgR and Ki67 levels significantly ($p<0.001$ all). After NAT, a significant ($p<0.001$) larger proportion of tumor samples were Luminal A/Normal-like (95.1% vs 55.3% at baseline) and ROR-low (78.8% vs. 22.9% at baseline). Both treatments induced the upregulation of selected immune genes and Basal-like-related genes/signature and downregulation of Luminal, proliferation and HER2-related genes/signatures (FDR<5% all). At a median follow-up of 64.0 months, 5-year EFS and OS were 90.4% and 95.0% with no significant difference based on NAT strategy (71.9% NET patients did not receive posterior CT). After adjusting for NAT cohort and significant factors at univariate analyses, including IS switch, only reduction of the proliferation signature remained significantly associated with better EFS (p=0.011) and OS (p=0.014). Similar results were observed with reduction of ROR for EFS (p=0.034), but not OS.

Conclusions: This study suggests that molecular downstaging induced by NACT or NET follows similar biological patterns and is associated with favorable survival outcomes, supporting molecular-driven neo-/adjuvant strategies, as tested in the ongoing RIBOLARIS phase II trial (NCT05296746).

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276P Development and external validation of an artificial intelligence (AI)-based machine learning model (ML) for predicting pathological complete response (pCR) in hormone-receptor (HoR)-positive/HER2-negative early breast cancer (EBC) undergoing neoadjuvant chemotherapy (NCT)

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Background: In HoR-positive/HER2-negative EBC pCR rates are low and ML algorithms could help to predict pCR using clinical and pathological characteristics.

Methods: Patients with EBC receiving NCT followed by surgery were included in the training/validation cohorts (TC/VC). pCR was defined as absence of residual invasive cancer on pathologic breast specimen and lymph nodes (ypT0/is ypN0). Eight ML models (c5.0, k-nearest neighbour, random forest [RF], neural network, support vector machine [linear/radial], boosted trees and boosted logistic regression) were trained and tuned. A stratified ten-fold cross-validation was used and models' performance was evaluated using the area under the receiver operation characteristics curve (AUC), sensitivity and specificity.

Results: 572 patients were included in the TC and 87 achieved pCR (15%, 95% CI 12-18%). Ten variables (menopausal status, age, histology, grade, clinical T/N, ER/PgR, Ki67 and HER2 [zero/low]) were included according to multivariate analysis and clinical relevance. The RF algorithm had the best performance: AUC 0.77, 95% CI 0.71-0.83; sensitivity 0.86 (95% CI 0.82-0.88) and specificity 0.56 (95% CI 0.46-0.66). Variables with the highest importance were Ki67, ER/PgR status, age and nodal status. 293 patients were included in the VC and 24 achieved pCR (8%, 95% CI 6-12%). The RF algorithm had an AUC of 0.71 (95% CI 0.61-0.81), sensitivity of 0.29 (95% CI 0.13-0.51) and specificity of 0.90 (95% CI 0.86-0.94). With a median follow-up of 53.3 and 57.7 months for DFS and OS, patients whose pCR was predicted by the model had longer DFS (HR 0.51, 95% CI 0.31-0.83, *p*=0.003) and OS (HR 0.48, 95% CI 0.29-0.79, p=0.001). A one percentage increase in the probability of predicted pCR was significantly associated with longer DFS (HR 0.992; 95% CI 0.986-0.999, p=0.02) and OS (HR 0.992, 95% CI 0.985-0.998, p=0.01).

Conclusions: The ML algorithm has the potential to predict pCR in HoR-positive/HER2-negative patients undergoing NCT, thus supporting clinicians to individualize treatment for EBC.

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277P Fat body mass independently predicts incident vertebral fractures in breast cancer patients given adjuvant aromatase inhibitor therapy and denosumab

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Background: Women with early breast cancer (EBC) receiving adjuvant aromatase inhibitors (AIs) are frequently given denosumab (Den) with the aim to both reducing fracture risk and preventing disease recurrence. However, a proportion of these patients still experience fragility fractures despite Den, and risk factors in women treated with upfront AIs and Den have never been explored.

Methods: Dual-X-ray absorptiometry (DXA) at baseline conditions and after 18 months was performed in 237 consecutive patients undergoing adjuvant therapy with AIs and Den (60 mg subcutaneously every 6 months), recruited at the Breast Unit of the ASST-Spedali Civili of Brescia. The following baseline parameters were evaluated to predict the risk of vertebral fracture (VF) as assessed by a morphometric approach on DXA images: age, body mass index (BMI), history of previous fractures, family history of fractures, smoking, alcohol consumption, FRAX score, DXA-derived bone mineral density (BMD), trabecular bone score (TBS), percentage fat body mass (% FBM), lean body mass (LBM), appendicular mass index (ALMI).

Results: Seventeen out of 237 (7%) reported incident VFs after 18 months of AIs therapy. At the univariate analysis, incident VFs were significantly associated with high FRAX score (Odd Ratio [OR]: 3.786, 95% Confidence interval [CI]: 1.039-13.790), previous VFs (OR: 3.217, 95% CI: 1.185-8.736), high %FBM (OR 5.174, 95% CI: 1.418-18.873, p=0.013), high android fat (OR 9.580, 95% CI: 1.174-78.209, p=0.035) and low ALMI/FBM ratio (OR 0.252, 95% CI: 0.078-0.818, p=0.022). Only high %FBM was independently associated to incident VFs at multivariate analysis.

Conclusions: FBM is an independent risk factor for VFs in EBC patients treated with adjuvant AIs and Den. A supervised physical activity aiming at avoiding obesity and potentiating LBM could synergize with Den in preventing AI-induced bone fragility.

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278P Association between tamoxifen and endoxifen plasma levels and clotting proteins in patients with primary breast cancer

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Background: Tamoxifen is effective for the adjuvant treatment of primary breast cancer, but increases the risk for venous thromboembolism. Tamoxifen decreases anticoagulant proteins, including antithrombin (AT), protein C (PC) and tissue factor pathway inhibitor, and increases thrombin generation (TG). However, the relation between levels of both tamoxifen and its active metabolite endoxifen and coagulation is unknown. To gain insight in the prothrombotic effects of tamoxifen and to guide safe dose-escalation, which may be performed in case of sub-therapeutic endoxifen levels, we studied the association between tamoxifen and endoxifen levels and various clotting proteins.

Methods: Tamoxifen and endoxifen levels were measured in 148 patients from the prospective TOTAM study (NL6918) after 3 months (m) and 6m of tamoxifen treatment. Plasma levels of the anticoagulants AT and PC, the procoagulant tissue factor (TF), and TG parameters were determined at both timepoints if samples were available (n=65-138 per analysis). Levels of clotting proteins and TG parameters were compared between: 1) quartiles of tamoxifen and endoxifen levels with ANOVA or Kruskall-Wallis with Dunnett's test, and 2) 3m and 6m of treatment in patients without dose adjustments with paired sample t-tests or Wilcoxon signed rank tests.

Results: After 3m of tamoxifen, levels of AT, PC, TF and TG parameters were not associated with tamoxifen nor endoxifen levels. At 6m, median TF levels were lower in patients in the 3rd (45 [range: 101] pg/mL), and 4th (50 [90] pg/mL) endoxifen quartiles compared to the 1st (lowest) quartile (70 [143] pg/mL) (adjusted *P* of 0.024 and 0.012, respectively), but no differences in anticoagulants or TG were observed. An increase in both median TF levels (3m: 46 [94], 6m: 54 [143] pg/mL, $P<0.001$) and TG parameters was observed at the 6m treatment period, while the AT and PC levels remained stable.

Conclusions: Our results indicate that higher tamoxifen and endoxifen levels are not associated with increased coagulation system activation, suggesting that both tamoxifen dose-escalation and high endoxifen levels do not have an additional prothrombotic effect. The time-dependent effect of tamoxifen on coagulation warrants further study.

Clinical trial identification: NL6918.

Legal entity responsible for the study: The authors.

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279P Early changes in bone turnover biomarkers during AI therapy are related to loss bone mineral density, data of the B-ABLE cohort

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Background: Aromatase inhibitors (AI) are the preferred hormonal therapy in postmenopausal women with early breast cancer (eBC). Bone turnover markers (BTM) provide dynamic information about the accelerated bone remodeling in patients taken AI. Here we described early changes in BTM during the first year of AI therapy in patients included at B-ABLE cohort.

Methods: B-ABLE cohort includes 1071 postmenopausal women with eBC, candidates to receive AI. PTH, Vit D and BTMs including carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX), amino-terminal crosslinked telopeptide of type 1 collagen (NTX), procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (BAP) and osteocalcin (OC), were evaluated previous AI therapy, at 3 months, and then annually. Bone mineral density (BMD) was assessed by DXA (at lumbar spine (LS) and femoral neck (FN)) baseline and annually. Here we report data of early changes in BMTs the first year of AI and its relation with BMD at 12 months in 768 women receiving AI as single agent or switching from tamoxifen, no treated with antiresorptive agents.

Results: The median age was 60 years, BMI was 29.15 and 18% are current smokers. 30% were switching from tamoxifen and 54.3% received Chemotherapy. 62% have osteopenia, 0.5% osteoporosis, and 4% of patients had fragility fractures at baseline. Baseline BTM were CTX 0.44ng/ml, NTX 45.09ng/ml, P1NP 60.14ng/ml, OC 6.05ng/ml, BAP 13.44mcg/l. In patients with osteopenia, BTM were higher compared with patients with normal DXA ($p< 0.005$) at baseline and at 3 months. Early changes in FAO (p=0.001) and CTX (p=0.001) were correlated with higher risk of LS and FN BMD loss (Table).

Table: 279P Association of BMD loss at 12 months with bone remodelling markers at 3 months of AI treatment

Changes in BTMs at 3-mo	LS 12-mo OR (95% CI)	FN 12-mo OR (95% CI)
CTX	3.13 (1.94-5.04)	2.45 (1.56-3.83)
NTX	1.81 (0.93-3.60)	1.13 (0.58-2.12)
P1NP	1.90 (0.86-4.22)	1.16 (0.60-2-24)
OC	1.21 (0.77-1.92)	1.06 (0.68-1.66)
BAP	2.086 (1.43-2.49)	2.01 (1.43-2.81)

Conclusions: Early dynamic changes in CTX and BAP are related to bone loss at 12 month in LS and FN.

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280P Adjuvant aromatase inhibitors in patients with PIK3CA mutation early breast cancer

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Background: Phosphatidylinositide-3-kinase (PI3K) regulates proliferation and apoptosis and; somatic *PIK3CA*-mutations may activate these processes. In a prospective cohort study of early breast cancer (eBC) patients, in case of somatic *PIK3CA*-mutation we observed resistance to aromatase inhibitor (AI) therapy *(Reinhardt K et al., Breast Cancer Res Treat 2022;196:483—493).* This study is aimed at validating these findings in a second cohort.

Methods: We studied a unicentre cohort of 262 patients with steroid hormone receptor-positive, HER2-negative eBC, who were planed to be treated with endocrine therapy only: aromatase inhibitor (AI, n=183) or Tamoxifen (TAM, n=69), AI and TAM (n=9), Fulvestrant (n=1) and tested the three most common somatic PIK3CA gene mutations (H1047R, E545K, E542K) by qPCR. The primary endpoint was recurrence-free survival (RFS), secondary endpoint overall survival (OS). Median follow up was 62 months.

Results: The *PIK3CA*-mutation rate was 42% (110 of 262). Overall, there was no difference considering RFS between patients with AI (n=183) and TAM (n=69) therapy (5 yrs-RFS 91.7% in both groups). Patients of the AI group harbouring a somatic PIK3CA mutation (n=75) had non-significantly more RFS related events compared to patients with PIK3CA wildtype (n=108): 5 yrs-RFS 89.5% (95% CI 82.1-97.0) versus 93.2% (95%CI 87.9 - 98.5), respectively (HR=1.2, 95%CI 0.461-2.961; n.s.). After 5 yrs, 91.2% (95% CI 84.5 — 97.9) of the patients with PIK3CA mutation were alive and 94.4% (95% CI 89.7 — 99.1) of patients without PIK3CA mutation, respectively (HR=1.3, 95% CI 0.453-3.447; n.s.). In the group of patients who were treated with TAM only (n=69), no interaction was observed between PIK3CA mutation and RFS or OS, respectively.

Conclusions: Although we observed a trend that AIs are less effective in patients with PIK3CA mutated tumours, formal validation is still lacking. Further data including prospective studies are required.

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281P Cyclin-dependent kinase 4/6 inhibitors combined with endocrine therapy for hormonal receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: A meta-analysis of randomized clinical trials

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Background: The use of cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors combined with endocrine therapy (ET) has recently emerged in the early stages breast cancer (eBC) treatment landscape. The present analysis aims to clarify the efficacy and safety of this treatment for hormonal receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER-) patients in the early stages of breast cancer (eBC).

Methods: PubMed, Scopus, Web of Science, Cochrane, and the Central Register of Clinical Trials were systematically searched for studies using CDK4/6 inhibitors with ET in patients with HR+/HER- early breast cancer (I-IIIA stage). For the meta-analysis, statistical analysis was performed using RStudio v 4.4.2. Heterogeneity was examined with Cochran Q test and I^2 statistics and p-values inferior to 0.10 and I>25% were considered significant for heterogeneity. The p-value< 0.05 was considered statistically significant.

Results: This study included 9345 patients from six randomized clinical trials. Ductal (87%) and lobular (10%) were the most common, and 53% of women were postmenopausal. Lymph node status data revealed that 9% had N0 status, 72% had N1 status, and 19% had ≥ N2 status. In a pooled analysis, the invasive disease free survival (iDFS) was 82% (95% CI, 0.64-1.06), and the overall survival rates were consistent across the studies, with 12-month rates at 1.00 (95% CI 0.99-1.01), 24-month rates at 1.00 (95% CI 0.99-1.01), 36-month rates at 1.01 (95% CI 0.93-1.10), and 48-month rates at 1.04 (95% CI 0.91-1.19). The most common treatment-related adverse events (AE) included neutropenia (78.1%), leukopenia (51.6%), fatigue (37.6%), diarrhea (31.4%), anemia (30.5%), and arthralgia (29.3%). Any grade 3 adverse events were observed in 2.44 (95% CI 0.84-7.08) and grade 4 in 1.39 (95% CI 0.15-12.68).

Conclusions: This meta-analysis reinforces the antitumor activity of the combination of CDK4/6is with ET in patients with eBC, regardless of iDFS rate. Despite high rates of serious adverse events related to treatment, most were manageable.

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282P Analysis of Prosigna in hormone receptor-positive early-stage breast cancer cohort after 8 years of experience at a single institution

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Background: Molecular signatures are recommended in HR+, HER2- early-stage breast cancer (EBC) to guide decisions for adjuvant treatment. Prosigna® is a standardized test based on the PAM50 gene signature with provides information on risk of recurrence and permits intrinsic subtype classification of tumor. The study aimed to evaluate the clinical impact of adopting Prosigna® assay after 8y.

Methods: A retrospective study of patients (pts) with ER+, HER2- EBC was carried out between 2015 and 2023 in a single center. Gene expression analysis of tumors was performed with PAM50/Prosigna® (NanoString Technologies, Seattle, WA, USA).

Results: 232 pts were included. All were node-negative. The median age was 55y (32-80) and 152 (65.5%) were postmenopausal. Risk of Recurrence (ROR) risk groups were as follows: low ROR: 97 (42%); intermediate ROR: 76 (33%); high ROR: 59 (25%). Intrinsic Subtype Reclassification: According to immunohistochemistry (IHC), 102 tumors (44%) were initially classified as luminal A and 130 (56%) as luminal B. After PAM50, 144 tumors (62%) were classified as luminal A, 86 (37%) as luminal B and 2 (0.01%) as HER2-E. The discordance rate for luminal B by IHC is noteworthy. 67 (52%) were reclassified as luminal A after PAM50. Impact on decision making: Prosigna® led to a treatment decision change in 64 pts (28%). Chemotherapy (CT) was added in 36 (27%) of the 132 pts (57%) initially assigned to hormonal therapy (HT). Of 100 pts (43%) initially assigned to HT-CT, 28 pts (28%) finally received HT alone. Follow-up: With a median follow-up of 48 months and a maximum follow-up of 90 months, no recurrence of the disease has been reported.

Conclusions: The use of gene expression platforms such as Prosigna ® directly impacts treatment decision making, allowing the selection the best adjuvant treatment adapted to the de risk of recurrence, without having registered any relapse so far in our HR+, HER2- EBC and node-negative patients. In addition, it seems that the intrinsic subtype determined by Prosigna® assay cannot be replaced by IHC parameters.

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283P Patient profiles treated with extended adjuvant neratinib in the early access registry study: NEAR study

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Background: Neratinib is an oral pan-HER TKI approved in 2018 in Europe in adult patients with HR+ HER2+ early breast cancer (eBC) who completed adjuvant trastuzumab-based therapy. The approval is based on the phase III ExteNET trial that demonstrated clinically meaningful benefit for neratinib vs. placebo in this population, including significantly improved 5-year iDFS (Δ5.1%, HR 0.58, 95% CI 0.41-0.82). An Early Access Program (EAP) was initiated in Europe in 2017 and provided access to individual patients for extended adjuvant neratinib based upon the ExteNET protocol while neratinib was awaiting product approval and availability in multiple countries. Since ExteNET, the treatment landscape of HER2+ eBC has evolved and there is a need to document the clinical profile, the tolerability, and the effectiveness of patients treated with neratinib in a real-world setting.

Methods: This is a multicenter, retrospective, observational, longitudinal study in Croatia, France, Belgium, Spain and Italy. Eligible patients will be selected among those having received at least one dose of neratinib in the EAP, between 01/08/17 and 31/12/20. The aim of the study is to describe the characteristics of patients receiving neratinib and its use in the real world. Demography and clinical profiles of patients are presented.

Results: As of 30/01/23, 108 patients were included in the Full Analysis Set. Median age at neratinib initiation was 48.0 years and 37.4% of patients were premenopausal. 29.6% of patients had cT1 and 46.3% had cT2. Two-thirds of patients were N+ and three-quarters had stage II + III tumours. Overall, 85.2% of patients had HR+ eBC. 41.7% of patients had upfront surgery followed by adjuvant therapy while 58.3% received neoadjuvant therapy first; of them 19.0% achieved a pathological complete response. In the neoadjuvant setting, most patients received trastuzumab + pertuzumab (58.7%) and trastuzumab (31.7%), whereas in the adjuvant setting, anti-HER2 treatment mainly consisted of trastuzumab (79.6%).

Conclusions: Patients treated in this EAP reflected the profile of patients who were expected to receive extended adjuvant neratinib during the observational period, which included the use of more recent (neo)adjuvant treatments.

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284P Prognostic and predictive impact of uPA/PAI-1 in early breast cancer

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Background: The prognostic marker uPA/PAI-1 is recommended by international guidelines for treatment decisions in node-negative breast cancer (BC). This study is aimed at validating the prognostic impact of uPA/PAI-1 by using a daily routine cohort and to consider the predictive impact with regard to chemotherapy in HR+ /HER2- breast cancer.

Methods: In a multicentre cohort study (PiA-study, Prognostic assessment in routine Application n=1,270, NCT 01592825), the concentrations of uPA and PAI-1 in fresh tumour tissue (n=813) were prospectively determined by ELISA (FEMTELLE®, Bio-Medica Diagnostics GmbH). The first objective was the association of uPA/PAI-1 with recurrence-free Interval (5 yrs RFI) and overall survival (5 yrs OS). As the second objective, we evaluated the impact of uPA/PAI-1 as a predictive factor for adjuvant chemotherapy in the intermediate risk group, which was defined as HR+, HER2-, G2, ≥35 yrs., 0-3 positive lymph nodes. Median follow-up was 60.3 months (1-129).

Results: After 5 years of observation, 96.7% (95% CI 94.5-98.9) of patients with low uPA/PAI-1 were without any RFI event compared to 87.2% (95% CI 84.1-90.3) with high uPA/PAI-1 (aHR 2.6, 95% CI 1.293-5.227, p=0.001). Also considering OS, a significant difference was detected; with low uPA/PAI-1, 93.9% (95% CI 91.0-96.8) were alive after 5 years (aHR 2.38, 95% CI 1.359-4.156) compared to 82.9% (95% CI 79.1-86.4) with high uPA/PAI-1. With regard to the intermediate risk group (n=378), even without chemotherapy, less than 1% of patients with low uPA/PAI-1 (n=120) had an RFI event. While patients with high uPA/PAI-1 had a significantly higher risk of disease-related events over the entire observation time (aHR 4.27, 95% CI 1.132-16.124). If patients were treated with adjuvant chemotherapy (n=181), uPA/PAI-1 had no further prognostic significance. Patients with high uPA/PAI-1 benefited significantly from adjuvant chemotherapy compared to patients without chemotherapy (aHR 0.21, 95% CI 0.076-0.600).

Conclusions: These real-world cohort data confirm that uPA/PAI-1 can routinely be used as an independent prognostic factor for decisions about adjuvant chemotherapy and underline the assumption that uPA/PAI-1 might be predictive for the effect of adjuvant chemotherapy.

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Legal entity responsible for the study: M. Vetter and E. Kantelhardt.

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285P Treatment patterns and clinical outcomes of germline BRCA mutation (gBRCAm)-associated breast cancer (BC): A matched, case-control study

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Background: Up to 10% of early BC occur in gBRCAm carriers. Whether gBRCAm-related and sporadic BC have different outcomes is controversial.

Methods: Consecutive patients (pts) who underwent surgery for BC at Dana-Farber Brigham Cancer Center between 1/2016 and 8/2021 and had known gBRCA status were included. gBRCAm cases were matched 1:3 with non-gBRCAm controls by age groups, stage, hormone receptor (HR) status and year of diagnosis. HER2-negative BC were excluded. Clinicopathologic features, treatments, and outcomes of gBRCAm carriers and non-gBRCAm controls were compared.

Results: We identified 189 gBRCAm (107 *BRCA1,* 82 *BRCA2*) carriers and 567 matched non-gBRCAm controls. Median age was 43 years (yrs) in carriers and 46 yrs in controls. Most pts had stage I (41.7%) or II (44.7%) BC; 55% of BC were HR+ (38 in *gBRCA1*m, 66 in *gBRCA2m;* 312 in non-gBRCAm). Compared to controls, gBRCAm carriers had higher tumor grade ($p<0.001$), higher recurrence score in HR+ (median 25 vs 19, $p<0.001$), were more likely to receive chemotherapy (CT) (81 vs 67.4%, $p<0.001$), including platinum-based regimens (17.6 vs 9.2%, $p=0.007$). 11 gBRCAm carriers and 3 controls received PARPi. At a median follow up of 42.3 months, invasive disease-free survival (iDFS) and relapse-free survival (RFS) did not differ between gBRCAm and controls after adjusting for age, grade, and CT administration (Table). In triple-negative BC (TNBC), risk of relapse was lower for gBRCAm vs controls ($p=0.025$).

Table: 285P

	N (%)	Events	3-yr IDFS	Adjusted hazard ratio [95% CI]	p-value
All	746 (100)	95	gBRCAm = 88.4% [83.3, 93.9] Non-gBRCAm = 88.9% [86.2, 91.7]	0.82 [0.46,1.44]	0.49
HR+ BC	411 (55)	47	gBRCAm = 88.4% [83.3, 93.9] Non-gBRCAm = 88.9% [86.2, 91.7]	1.44 [0.55, 3.81]	0.46
TNBC	335 (45)	48	gBRCAm = 91.8% [85.6, 98.5] Non-gBRCAm = 84.3% [79.7, 89.3]	0.53 [0.22, 1.31]	0.17
	N (%)	**Events**	**3-yr RFS**	**Adjusted hazard ratio [95% CI]**	**p-value**
All	748 (100)	83	gBRCA = 92.2% [87.8, 96.9] Non-gBRCA = 89.4% [86.8, 92.2]	0.57 [0.30, 1.08]	0.085
HR+ BC	412 (55)	40	gBRCA = 90.6% [84.1, 97.6] Non-gBRCA = 93.6% [90.7, 96.5]	1.14 [0.41, 3.21]	0.80
TNBC	336 (45)	43	gBRCA = 94.4% [89.1, 100.0] Non-gBRCA = 84.3% [79.7, 89.3]	0.25 [0.07, 0.84]	**0.025**

Conclusions: Pts with BRCA-associated BC have higher-risk pathologic features and are more often treated with CT compared to matched non-gBRCAm BC. After adjusting for treatment and clinicopathologic variables, short-term outcomes did not differ in gBRCAm carriers vs controls overall. However, in TNBC pts, risk of relapse was significantly lower among carriers than controls. Our results provide risk estimates for gBRCAm carriers that could inform the design of future clinical trials.

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F. Lynce: Financial Interests, Personal, Advisory Board: Pfizer, AstraZeneca; Financial Interests, Personal, Invited Speaker: ION; Other, Institutional, Principal Investigator: AstraZeneca, CytomX, Cyclacel, Genentech, Eisai, Incyte. All other authors have declared no conflicts of interest.

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286P Prognostic role of HER2 expression in patients with ER-positive/HER2-negative breast cancer: Results from a population-based cancer registry study

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Background: Estrogen Receptor (ER)-positive (+)/Human Epidermal Growth Factor Receptor 2 (HER2)-negative (-) breast cancers (BCs) express variable protein levels of HER2, which can influence prognosis.

Methods: This cohort study was conducted using data on all consecutive patients (pts) diagnosed with BC between 2005 and 2017, which were systematically and prospectively collected by the Emilia-Romagna Cancer Registry (Provinces of Piacenza, Parma, Modena, and Ferrara), Italy. The study included 13527 pts with ER+/HER2- BC. Tumors were classified by HER2 IHC score (0 [n=7155], 1+ [n=5186], or 2+ with negative FISH [n=1186]). Comparisons of clinicopathologic characteristics and disease outcome were performed.

Results: BCs with late-stage diagnosis, high histological grade, or high proliferative rate were more likely to be HER2 1+ or 2+/FISH- in comparison with earlier stage, low-grade, or low-proliferative tumors (lower bounds of 95% confidence intervals [CIs] for odds ratios [ORs] > 1). BCs with high expression of ER (≥ 80% [n=12383]) were more enriched with HER2 1+ (OR 1.39; 95%CI, 1.2-1.6) or 2+/FISH- tumors (OR 1.26; 95%CI, 1.0-1.6) than ER-low/moderate (1-79% [n=1144]) ones. The 5-year overall survival (OS) for HER2 1+ BCs was lower than that for HER2 0 or 2+/FISH- tumors ($P = 0.0018$). This finding was confirmed also after stratification by ER status (low/moderate and high expression; $P = 0.07$ and 0.007, respectively).

Conclusions: The worse prognostic impact of HER2 expression in pts with ER-positive/HER2-negative BCs seems to be restricted to HER2 1+ tumors. The better outcome observed in pts with HER2 2+/FISH- BCs may be related to the known FISH-negative (HER2-non-amplified) status of this subgroup. These findings may help identify optimal patient inclusion criteria for clinical trials with novel anti-HER2 therapies in ER-positive/HER2-negative disease.

Legal entity responsible for the study: A. Musolino on behalf of the Emilia-Romagna Cancer Registry.

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Disclosure: A. Musolino: Financial Interests, Personal, Advisory Board: Roche, Novartis, Gilead, AstraZeneca; Financial Interests, Institutional, Coordinating PI: Roche; Financial Interests, Institutional, Research Grant: Lilly; Financial Interests, Institutional, Funding: Seagen; Non-Financial Interests, Principal Investigator: Roche, Lilly, Gilead, Novartis. All other authors have declared no conflicts of interest.

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287P Perturbation and stability of PAM50 subtyping in population-based primary invasive breast cancer

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Background: PAM50 gene expression subtypes represent a cornerstone in molecular classification of breast cancer and are included in risk prediction models to guide therapy. We aimed to illustrate the impact of included genes and biological processes on subtyping while considering a tumor's underlying clinical subgroup defined by ER, PR and HER2 status.

Methods: We used a population-representative and clinically annotated primary breast tumor cohort of 6233 samples profiled by RNA sequencing and applied a perturbation strategy of excluding co-expressed genes (gene sets) from the PAM50 centroids followed by nearest centroid classification.

Results: We demonstrate how PAM50 nearest centroid classification depends on biological processes present across, but also within, ER/PR/HER2 subgroups and PAM50 subtypes themselves. Our analysis highlights several key aspects of PAM50 classification. Firstly, we observed a tight connection between a tumor's nearest and second nearest PAM50 centroid. Additionally, we show that second-best subtype is associated with overall survival in ER-positive, HER2-negative, and node-negative disease. We also note that *ERBB2* has little impact on PAM50 classification in HER2-positive disease regardless of ER-status, that the Basal subtype is highly stable in contrast to the Normal subtype, and that the LumB subtype classification is mainly reliant on expression of proliferation-related genes and low expression of keratin-associated genes.

Conclusions: Improved consciousness of the commonly used PAM50 subtyping scheme will aid in our understanding and interpretation of breast tumors that have seemingly conflicting PAM50 classification when compared to clinical biomarkers. Our study adds further support in challenging the common misconception that PAM50 subtypes are distinct classes by illustrating that PAM50 subtypes in tumors represent a continuum that may have clinical implications.

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288P Prognostic factors in nonmetastatic HER2 'low' & HER2 'negative' breast cancer: Single institute experience

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Background: Human epidermal growth factor-2 (HER2) low breast cancer is a novel entity that differs from HER2-negative ones. We evaluated prognostic factors in HER2 low & compared with HER2-negative breast cancer retrospectively.

Methods: Estrogen receptor (ER) +/ progesterone receptor (PR) +, HER2 low and HER2-negative patients without distant metastasis were included.

Results: 444 (HL n:209, HN n:235) patients were evaluated. Median follow-up was 47 months. Most (59%) were postmenopausal. 121 (27.3%) had immunohistochemistry (IHC) score 1, 88 (19.8%) had IHC score 2 (SISH -). Mean age was 54.5 vs 53.3 years. Stage 2 (35.8%) & grade 2 (49.3%) were most common. Median ER/PR/ki67 were 95/60/25% for HER2 low & HER2 negative. 375 patients had chemotherapy, most (86%) had adjuvant chemotherapy. 40 (9%) had relapse & most (n: 31, 77.5%) had distant relapse. HER2-negative patients tended to have higher relapse rate (11.5% vs 6.2%, p:0.053). 5 year-disease free survival (DFS) was shorter for patients with HER2 negative (83.4% vs 90.8%), positive lymph nodes ≥10 (63.2% vs 92.3%), ECE + (75.4% vs 91.5%), ki67≥20% (70.2% vs 83.9%) (p: 0.021, p:0.008, p:0.004, p:0.026) (Table). Stage was inversely correlated with DFS (p: 0.001). HER2 status [HR: 0.43 (95% CI: 0.20 −0.94), p=0.035] & ki67 [OR: 2.99 (95% CI: 1.21−7.36), p=0.017] were significant prognostic factors in multivariate analysis. Overall survival (OS) data was immature..

Conclusions: HER2 low breast cancer patients, especially with ki67 <20% had better DFS, Most patients had IHC score 1.

Table: 288P Survival according to clinical & pathological features

	5-year DFS (%)	Median DFS (95% CI)	p-value	5-year OS (%)	Median OS (95% CI)	p-value
Age						
<55	85.5	NR	0.316	98	NR	0.579
≥55	89.7	128.2 (88.4-167.9)		95.2	NR	
Menopausal status						
Premenopausal	89.2	NR	0.599	97.6	NR	0.523
Postmenopausal	85.7	128.2 (95.3-161.1)		96.1	NR	
Ki67						
<20	83.9	NR	**0.026**	96.2	NR	0.441
≥20	70.2	NR		96.6	NR	
HER2 status						
Negative	83.4	121.8 (93.6-150.1)	**0.021**	97.1	NR	0.214
Low	90.8	NR		96.7	NR	
Posivite Lymph node						
<10	92.3	156.1 (124.3-187.9)	**0.008**	96.6	NR	0.946
≥10	63.2	NR		97.2	NR	
Stage						
Stage 1	99	NR	**0.001**	97.4	NR	0.463
Stage 2A	91.4	NR		95.2	NR	
Stage 2B	88	121.8 (69.3-174.4)		96	NR	
Stage 3	73.8	128.2 (70.3-186.1)		97.9	NR	
ECE						
ECE (-)	91.5	NR	**0.004**	95.6	NR	0.714
ECE (+)	75.4	108.8 (40.3-177.2)		97.9	NR	

Legal entity responsible for the study: Clinical of Medical Oncology.

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289P Results of the window-of-opportunity clinical trial D-BIOMARK: Study of biomarkers of the antitumor activity of denosumab and its role as a modulator of the immune response in early breast cancer

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Background: Inhibitors of the Receptor Activator of NF*k*B (RANK) pathway, such as denosumab, have been shown to prevent breast cancer (BC) in preclinical models by reducing proliferation and tumor cell survival. Recent studies suggest that RANK pathway inhibition enhances the anti-tumor immune response. This study aimed to evaluate the antiproliferative, proapoptotic (primary endpoints), and immunomodulatory activity (exploratory endpoint) of denosumab in early BC.

Methods: D-BIOMARK study (NCT03691311) was a randomized window-of-opportunity trial designed to evaluate the biological effects of single-agent denosumab in early BC. Sixty patients with early HER2-negative BC were enrolled, 2:1 randomization to experimental (two doses of 120mg of denosumab separated by 7 days before surgery) or control (no treatment) group. Paired samples (core-biopsy and surgical specimen) were obtained from each patient for comparison of Ki67 (proliferation), Cleaved Caspase-3 (cell survival), and tumor infiltrating lymphocytes (TILS) according to international guidelines. Pre *vs*. post values were compared using a paired t-test.

Results: A total of 58 evaluable patients were analyzed, 10 with triple-negative breast cancer (TNBC), 27 premenopausal and 31 postmenopausal. Denosumab reduced free RANKL (sRANK) levels in patient's serum but did not reduce tumor cell survival or proliferation. Denosumab increased TILS in all patients, except TNBC (n=6) while differences in the control group did not reach statistical significance. When considering clinically significant increases in TILS (5% or 10%), no differences were found between both groups. No associations were found between basal sRANKL and an increase in TILS..

Conclusions: Denosumab did not affect tumor cell survival nor proliferation in early BC but may have an immunomodulatory effect that warrants further investigation.

Clinical trial identification: NCT03691311.

Legal entity responsible for the study: The authors.

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290P Metabolomic profiling and response to neoadjuvant therapy (NAT) in early breast cancer (EBC)

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Background: The presence of residual disease (RD) after NAT is correlated with a poor outcome in EBC patients. New strategies are required to early identify patients who will not achieve a pathological complete response (pCR). Metabolomics may represent an innovative technology to identify host-related factors correlated with treatment outcome. In this study, we evaluated the predictive ability of metabolomics combined with machine learning in EBC patients receiving NAT.

Methods: Untargeted metabolomic analysis was performed in EBC patients candidates for NAT at our institution. Plasma samples were collected at baseline, before start of treatment. Small molecules were extracted, derivatized and then analysed using bi-dimensional gas chromatography/mass spectrometer (GCxGC-MS). The metabolomic profiling was then evaluated according to response to therapy (pCR versus RD). A machine learning approach was implemented with Boruta features selection algorithm combined with genetical algorithm as classifier, on a training set of 69 samples and validated on the remaining 27.

Results: From 12/2020 to 05/2023, 109 EBC patients have been enrolled (26 ER+, 45 HER2+, 38 TN); surgery was performed in 96 patients so far, with an overall pCR of 51% (ER+ 19%, HER2+ 51%, TN 55%). 61 small molecules were expressed ($p<0.05$ and Fold Change FC >1.3) between patients in pCR or RD. By multivariate analysis patients with RD showed higher levels of unsaturated fatty acids, as eicosatrienoate (FC=6), 9-decenoic acid (FC=2.2) and 17-octadecynoic acid (FC=2.2) and lower levels of fatty acids, as hexadecenoic acid (FC >100), doconexent (FC=69.5), 9,11-conjugated linoleic acid (FC=5.2), circulating glucose (FC=71) and glucopyranose (FC=23). Pathway analysis revealed the involvement of amino and fatty acid metabolism. A prediction model, combining metabolomics and machine learning, was implemented on 35 metabolomic probes and correctly identified the type of response with an accuracy of 95%.

Conclusions: Our data indicate that host-related metabolomic signatures may identify patients with EBC failing to achieve a pCR after NAT. We identified several fatty acids, amino acids and small molecules that can be modulated through diet. Possible effects by BC subtype are being investigated.

Legal entity responsible for the study: A. Gennari.

Funding: AIRC.

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Table: 289P

Response variable	Mean Pre	Mean Post	Control *p*-value	Mean Pre	Mean Post	Experimental *p*-value
sRANKL pg/ml N=58	0.10	0.12	**0.25**	0.01	0.00	**<0.01**
Ki-67 % N=58	24.52	29.19	**0.05**	20.59	25.24	**0.01**
CLEAVED-CASPASE 3 H-score N=58	1.66	2.24	**0.05**	2.56	1.98	**0.24**
TILS % N=58	7.42	12.24	**0.06**	7.35	12.94	**<0.01**
TILS % within Luminal BC N=48	8.17	11.78	**0.18**	6.13	10.80	**0.01**
TILS % within TNBC N=10	4.250	14.250	**0.24**	13.667	24.000	**0.08**
TILS % within premenopausal patients with luminal BC N=26	10.68	12.60	**0.64**	7.31	12.73	**0.05**
TILS within postmenopausal patients with luminal BC =22	8.17	11.77	**0.06**	4.87	8.75	**0.04**

291P Prognostic implications of HER2 gain in patients with HR+/ HER2- breast cancer (BC) and TNBC after neoadjuvant chemotherapy (NAC)

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Background: Residual disease (RD) after NAC is a well-established risk factor for recurrence in patients (pts) with triple-negative breast cancer (TNBC) or high-risk hormone receptor-positive (HR+)/ HER2-negative (-) BC. Biologic and prognostic significance of HER2 gain on RD after NAC are unknown. We sought to determine invasive disease-free survival (IDFS) in patients with HER2 gain in a cohort of consecutive patients with HER2(-) BC treated with NAC.

Methods: We identified pts with HER2(-) BC treated with NAC followed by surgery at our institution between 8/2019 and 12/2021. Pathologic complete response [pCR] (ypT0/is ypN0) rates and HER2 status pre- and post-NAC were assessed, the latter by 2018 ASCO/CAP guidelines. HER2-low was defined as IHC 1+ or IHC 2+, FISH non-amplified. IDFS was analyzed using the Kaplan-Meier method and differences assessed by log-rank test. Chi-square, Fisher's exact, Wilcoxon rank sum test, and logistic regression were used to evalute baseline features associated with HER2 gain. Any *p*-value less than 0.05 was deemed to be statistically significant.

Results: We included 528 HER2(-) pts [274 (52%) HR+/HER2- and 252 (48%) TNBC]. Overall, pCR was achieved in 40% of TNBC and 9% of HR+/HER2(-). The median follow-up was 17.5 months (14.5-21.3). Among 401 pts with RD, the rate of HER2 gain was 5% (20/401) (Table). HER2-low and HR+ status assessed on initial biopsy were independently associated with HER2 gain on the surgery sample with OR=3.05 (95% CI:1.07-10.9) and OR=4.09 (95%CI: 1.02-27.5), respectively, while high grade was not (OR=0.68; 0.24-1.78). After surgery, all but two pts with HER2 gain received anti-HER2 therapy. The 2-year IDFS rate was 100% in pts with HER2 gain and 85% (95%CI: 81-90%) in pts with HER2(-) RD (p=0.07).

Conclusions: HER2 gain after NAC was a rare event, more commonly occurring in pts with HR+/HER2(-) BC compared to TNBC, likely related to HER2 heterogeneity. Optimal adjuvant regimen remains to be established..

Table: 291P Details of patients with HER2 gain

	HR status	HER2 biopsy			HER2 surgery			Post-NAC
Pts	(+/-)	IHC	F ratio	F CN	IHC	F ratio	F CN	therapy
1	-	2+	1.6	5.6	3+	/	/	TH
2	-	1+	/	/	2+	3.36	7.6	Pembro/HP
3	+	2+	1.2	3.3	2+	1.94	7.7	AI
4	+	1+	/	/	2+	3.35	8.4	V/HP, AI
5	+	1+	/	/	2+	2.6	5.4	V/HP, AI
6	+	1+	/	/	2+	3.1	6.1	HP/AI
7	+	2+	1.5	3.3	2+	2.04	7.49	THP
8	+	1+	/	/	2+	2.58	5.6	T-DM1
9	+	1+	/	/	2+	3.12	8.45	Cape/HP
10	+	2+	1.2	3.44	2+	2.27	5.17	HP/AI
11	+	0	/	/	2+	3.72	7.67	Carbo/HP, AI
12	+	0	/	/	3+	/	/	HP/AI
13	+	1+	/	/	2+	1.8	6.3	HP/AI
14	+	0	/	/	3+	/	/	CMF/HP, OS/AI
15	+	1+	/	/	2+	2.7	4.14	Cape/H, AI
16	+	1+	/	/	3+	/	/	T-DM1, HP/AI
17	+	2+	1.7	5.4	2+	2	5.4	HP/AI
18	+	2+	1.5	2.9	2+	2.9	6.1	HP/AI/OS
19	+	1+	/	/	2+	2.3	6.2	HP/AI/OS
20	+	0	/	/	2+	1.6	6.8	AI/Abema

F: FISH test; CN: copy number; V: vinorelbine; T: paclitaxel.

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292P Unlocking the potential of circulating miRNAs in predicting response to neoadjuvant chemotherapy in breast cancer: A systematic review and meta-analysis

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Background: The potential role of circulating miRNAs as biomarkers for breast cancer (BC) has been widely reported. However, the large discrepancy between studies prevents the feasibility of implementing circulating miRNAs in routine clinical practice. In BC patients undergoing neoadjuvant chemotherapy (NAC), the ability to anticipate response could lead to improve prognosis by individualizing post-NAC approach. In this scenario, the present meta-analysis aims to quantify and clarify circulating miRNAs' predictive role for NAC response in BC patients.

Methods: We conducted a comprehensive literature search in 5 main medical databases until 16th February 2023, along with additional research sources. The systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and we applied the Cochrane recommended methodology for prognostic factor studies. We quantitatively pooled the effect sizes of each study by applying a random-effects model to consider within and between-study variances. Cochrane Q test (significance at 0.05) and I^2 value were used to assess between-study heterogeneity. The Prediction Model Risk Of Bias Assessment Tool evaluated studies' bias risk.

Results: The meta-analysis included 15 studies, with a total of 1521 early BC patients. Overall, our findings support the hypothesis that circulating miR-21-5p and miR-155-5p may act as predictive biomarkers. Pooled area under the curve values were 0.72 (95% confidence interval (CI) 0.59-0.86, $p < 0.05$) and 0.67 (95% CI 0.53-0.81, $p < 0.05$), respectively, thus indicating an acceptable predictive ability in anticipating NAC response.

Conclusions: To our knowledge, this is the first systematic review and meta-analysis that provides a quantitative synthesis of the predictive value of circulating miRNAs for NAC response in BC patients. However, due to the limited number of studies included in the meta-analyses and the high clinical and statistical heterogeneity, further studies are needed to confirm the predictive power of circulating miR-21-5p and miR-155-5p.

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294P Prognostic significance and evolution of HER2 zero, HER2 low and HER2 positive in breast cancer after neoadjuvant treatment

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Background: With the development of anti-HER2 targeted antibody-drug conjugates, HER2 low has attracted a lot of attention in breast cancer (BC). It's significant to study the pathological response of HER2 zero, HER2 low and HER2 positive BC after neoadjuvant treatment and the HER2 status evolution.

Methods: A retrospective study was conducted at National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Data from patients who were diagnosed with BC between 2015 and 2021 at our center and who had received neoadjuvant treatment were collected. The pathological complete response (pCR) rate of HER2 zero, HER2 low, and HER2 positive was analyzed. And the analysis of HER2 status evolution were carried out.

Results: 1173 patients with BC who had received neoadjuvant treatment were collected. 11.85% of the patients (n=193) achieved pCR, and 88.15% of the patients (n=1034) were non-pCR. Among 526 patients with available baseline biopsy reports and matched pathological reports after neoadjuvant treatment, HER2 low BC was related to the lowest rate of pCR, followed by HER2 zero and HER2 positive BC (13.79% vs. 20.00% vs. 40.20%, respectively, p=0.000). Of the 526 patients, 381 were hormone-receptor-positive BC, and 145 were triple-negative breast cancer (TNBC) on baseline biopsy. In 381 patients with hormone-receptor-positive BC, HER2 low BC was also related to the lowest rate of pCR, followed by HER2 zero and HER2 positive BC as well (9.14% vs. 12.28% vs. 36.22%, respectively, p=0.000). A similar trend was also observed in TNBC without a statistically significant difference. On the converting of HER2 zero, HER2 low and HER2 positive before and after neoadjuvant treatment, HER2 zero has the highest discordance rate and 58.21% of HER2 zero on baseline biopsy converted into the other two types after neoadjuvant treatment. The conversion rates of HER2 low and HER2 positive on baseline biopsy were 28.10% and 14.43%, respectively.

Conclusions: Compared with HER2 zero and HER2 positive, HER2 low has the lowest pCR rate after neoadjuvant treatment. Besides, HER2 zero had the highest incidence of conversion to other HER2 statuses after neoadjuvant treatment.

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295P ESR1, PGR, ERBB2, MKI67 single gene analysis in neoadjuvant-treated early breast cancer patients

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Background: Currently, early breast cancer (eBC) is classified by using clinical and histopathological factors that are often considered insufficient for individualised therapy. This study is aimed at examining whether single gene mRNA expression of ESR1, PGR, ERBB2 and MKI67 can be used instead of histopathological analysis in high-risk eBC.

Methods: For this study, a sample of high-risk patients who were treated with neoadjuvant chemotherapy was selected from a prospective, multicentre cohort of 1,270 eBC patients (PiA, Prognostic Assessment in routine application, NCT 01592825). Histopathological data for ER, PgR, HER2 and Ki67 were taken from the routine results from pre-treatment core needle biopsies. Single gene mRNA expression analysis of ESR1, PGR, ERBB2 and MKI67 and intrinsic subtyping (PAM50) were generated by multiplex hybridisation method (nCounter, NanoString ®) using formalin fixed tumour material. Cut-off values were determined by ROC-analysis.

Results: A strong correlation for ESR1, PGR and ERBB2 with corresponding histopathological results (IHC/ISH) was demonstrated (Pearson's r= 0.701, r=0.716, and r= 0.669, respectively; all p<0.001). After dichotomisation positive predictive value was 98%, 92%, and 92%, resp. Overall percent agreement was 94.5%, 92.8% and 90.8%, resp. Cohen's Kappa showed high inter-reliability (κ=0.888, κ=0.856, κ=0.766 resp, all p<0.001). Odds ratio also indicates an association of single gene mRNA-expression with complementary histopathological and intrinsic subtypes (p<0.05). Single gene mRNA expression data of all four genes (including MKI67) was used to classify the tumours following the surrogate definitions by the St. Gallen International Expert Consensus and demonstrated concordance with histopathological groups and intrinsic subtypes.

Conclusions: Single gene mRNA expression analysis for ESR1, PGR, ERBB2 and MKI67 is feasible and, in our sample, the results show a strong correlation to the corresponding histopathological results. Single gene expression may be used as an alternative to standard histopathological analysis. In addition, also subtyping can be performed by using single gene data; however, the clinical reliability has still to be proven.

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Legal entity responsible for the study: M. Vetter and E. Kantelhardt.

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296P Identification of metabolism-related therapeutic targets to improve response to neoadjuvant chemotherapy in early breast cancers

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Background: Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) is known as a prognostic factor correlated with improved EFS and OS. Better prediction of pCR would allow better patient and treatment selection. We aim to reveal specific transcriptomic and metabolic signatures correlated with distinct responses to NAC based on patient diagnostic biopsies. We also compared metabolic profiles of *in vitro* models.

Methods: We performed bulk-RNA sequencing on 95 samples from diagnostic biopsies from all subtypes of early BC treated with NAC (NCT03314870 study). Early triple-negative BC cell lines (HCC38, HCC1143, HCC1937) and patient-derived tumor organoids were cultured for drug testing, RT-qPCR and metabolomics studies using Seahorse bioenergetic analyzer.

Results: Transcriptomic analyses showed a down-regulation of genes related to tumor cell metabolism such as genes involved in the glycolysis (e.g. *STC2,* FDR = 0.05) in non-responding patients (n=39). Gene set enrichment analysis (hallmark and KEGG pathway databases) showed a down-regulation of the glycolysis and the oxidative phosphorylation pathways in non-responding patients (adjusted p-value <0.05). In 2D cell cultures, the HCC1937 cell line showed resistance to paclitaxel and a higher glycolysis profile than the HCC38 and HCC1143 cells. Exposure to epirubicin or paclitaxel decreased the glycolysis in HCC38 and HCC1937 cell lines, while a decrease in the oxidative phosphorylation was observed in all 3 cell lines. A triple-negative organoid model (BCO17), initiated from a treatment naive tumor, showed resistance to epirubicin and paclitaxel. In BCO17, exposure to epirubicin or paclitaxel did not change the glycolysis or oxidative phosphorylation profile. Targeting glycolysis with 2-deoxy-2-glucose (2DG) in monotherapy showed 50% of cell mortality in a 2D and organoid models, while combination of 2DG with epirubicin and paclitaxel did not increase the cell mortality.

Conclusions: Glycolysis and oxidative phosphorylation are involved in non-response to NAC in early breast cancer. 2D and organoid models with distinct chemotherapy sensitivity showed different metabolic profiles that may be explored in drug development.

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297P Prognostic and predictive impact of NOTCH1 in early breast cancer

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Background: The notch signalling pathway is considered to be an interesting prognostic and predictive marker in breast cancer as it is involved in proliferation, invasiveness and chemotherapy resistance.

Methods: From a prospective, multicenter cohort (Prognostic Assessment in Routine Application (PiA), 2009-2011, NCT01592825) of 1,270 breast cancer patients with a median follow-up of 60 months, the relative mRNA expression of NOTCH1 was determined in 414 tumour samples by qPCR. The primary objective was the evaluation of NOTCH1 mRNA expression and its association with patients and tumour characteristics. The secondary objectives were the associations with recurrence-free interval (RFI), overall survival (OS), and the predictive value of NOTCH1 mRNA expression with regard to adjuvant chemotherapy.

Results: Within our study, high NOTCH1 expression was detected in one-third of the tumours. We observed a significant prognostic impact of high NOTCH1 expression with regard to RFI (adjusted hazard ratio 2.1, 95% CI 1.077−4.118). Patients with high NOTCH1 expression and chemotherapy (n = 86) had a worse clinical outcome compared to those without chemotherapy with an adjusted 3.1 higher risk for disease-related events (RFI events, 95% CI 1.321−7.245, p = 0.009).

Conclusions: In summary, in our cohort for NOTCH1 we showed a prognostic and, particularly, a significant predictive impact. We observed that tumours with high NOTCH1 expression seem to be less sensitive to cytotoxic treatment. Therefore, we postulate, that downregulation of the Notch signalling pathway, e.g. with y-secretase inhibitors, may improve the efficacy of breast cancer therapy by restoring chemosensitivity.

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Legal entity responsible for the study: E. Kantelhardt, M.Vetter.

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298P Association of luminal-androgen receptor (LAR) subtype with low HER2 in triple-negative breast cancer

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Background: Low level of HER2+ breast cancer, a subset of HER-2 negative, accounts for about 50-60% of breast cancer. A recent publication highlighting the improved survival outcomes with trastuzumab deruxtecan in this group has raised the need to redefine low HER2+ breast cancer in the context of molecular characterization. In triple-negative breast cancer (TNBC), we compared molecular TNBC subtype, PAM50 subtypes, and clinical-pathological characteristics between the low HER2 and zero HER2 groups.

Methods: A study population included two cohorts with early TNBC. The adjuvant cohort consisted of 199 TNBC patients who underwent upfront surgery, while the neoadjuvant cohort comprised 124 TNBC patients treated with neoadjuvant chemotherapy (NAC). Transcriptome analysis was conducted in the adjuvant cohort to determine the TNBC molecular subtype and PAM50 types. Tumor-infiltrating lymphocyte (TIL) levels, PD-L1, and Ki67 expression were evaluated in both cohorts, along with recurrence-free survival (RFS) and event-free survival (EFS) investigations in each cohort.

Results: In 199 patients with transcriptome analysis, 66 (33.2%) had low HER2 disease, while 133 (66.8%) had zero HER2 tumors. The rates of luminal androgen receptor (LAR) and HER2-E subtypes were 13.1% (26/199) and 7.0% (14/199), respectively. Comparing the two groups, low HER2 tumors showed higher rates of LAR (22.7% vs. 8.5%, p=0.006) and HER2-E (15.2% vs. 3.3%, p=0.016), while other characteristics such as TIL, PD-L1, ROR-P score, and Ki67 did not differ between the two groups. In the neoadjuvant cohort, 31 (25.0%) had low HER2 disease while 93 (75.0%) had zero HER2 tumors, and there were no significant differences in TIL, PD-L1, and Ki67 expression between the two groups. Furthermore, low HER2 status did not significantly affect RFS and EFS in either cohort.

Conclusions: Low HER2 status in TNBC is distinctly associated with enriched LAR and HER2-E subtypes. However, other characteristics such as TIL, PD-L1, and Ki67 expression, as well as survival outcomes, were found to be similar between the two groups.

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299P Single-cell transcriptomic analysis reveals specific luminal and T cell subpopulations associated with response to neoadjuvant therapy in early-stage breast cancer

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Background: Neoadjuvant therapy (NAT) remains the standard of care for most early-stage breast cancer (BC) patients, especially in HER2+ and triple-negative (TNBC) subtypes. Patients who do not achieve pathological complete response (pCR) present an increased risk of disease recurrence. Here, we applied single cell RNA sequencing (SCS) to investigate tumor and immune landscape for the identification of predictive biomarkers of response to NAT.

Methods: Twenty-one BC patients treated with NAT were included in the study. Pretreatment biopsies, matched residual disease and adjacent normal tissue samples were prospectively collected for all patients. After tissue dissociation, single cell RNA profiles were investigated using the Chromium Next GEM Single Cell 5' kit (10X Genomics). After removing batch effect using Seurat integration, cell clusters were annotated based on the expression of specific marker genes. Epithelial luminal cells (KRT18+/KRT19+) were classified as malignant or non-malignant using copy number profiles computed by inferCNV. Wilcoxon rank sum test was used to compare cell proportions between pCR and non-pCR groups.

Results: pCR rates were 61.5% (8/13), 100% (4/4) and 25% (1/4) in TNBC, HER2+ and Luminal B patients respectively. A total of 21 TNBC, 6 HER2+ and 6 Luminal B samples were profiled with SCS. Malignant luminal epithelial cells were classified in luminal progenitor (LP) (KIT+/SLPI+/KRT5^{low}), luminal mature (LM) (KIT-/SLPI-/KRT5-) and luminal cycling cells (LC) (MKI67+/TOP2A+). Patients achieving pCR had a higher fraction of LC cells at baseline, considering all BC subtypes ($p<0.05$). Enrichment of LP cells at baseline was observed in TNBC patients achieving pCR ($p<0.05$). T cells reclustering further identified four CD4+ subtypes. Of note, lower proportions of FOXP3+ regulatory T cells and RORC+/CCR6+ Th17 cells at baseline were associated with a better response to NAT both in TNBC and HER2+ patients ($p<0.05$).

Conclusions: Our study showed substantial heterogeneity at the single cell level with specific cell types being associated with response to neoadjuvant chemotherapy, towards an improved BC care.

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300P Correlation of PD-L1 protein and mRNA expression and their prognostic impact in triple-negative breast cancer

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Background: PD-L1 expression is determined by immunohistochemical (IHC) analyses. PD-L1 positivity can differ depending on the used antibody. The aim of this study was to evaluate the correlation of IHC and mRNA PD-L1 expression and their associations to prognosis.

Methods: For this analysis, 85 TNBC samples from a prospective cohort of breast cancer patients (n=1,270, PiA Prognostic Assessment in routine application, NCT 01592825) were eligible. IHC was performed using CAL10 antibody (BioCare), ≥1% staining was considered PD-L1 positive for immune cell score (IC), tumour proportion score (TPS) and combined positive score (CPS). For analysis of mRNA expression, microarray analysis was performed (Affymetrix®, HG U133 Plus 2.0, probesets #1: 223824, #2: 227458, detecting different transcripts of the PD-L1 gene); maximum likelihood method was used for cut off determination. Correlations with IHC and TILs were tested using Spearman's rank correlation. Survival analysis included recurrence free interval (RFI) and overall survival (OS), considering only those patients who received chemotherapy (n=76). Median follow up was 73 months (20-127).

Results: In IHC analysis, half of the samples were classified PD-L1 positive for IC and CPS (50.6% and 49.4%) and only 23.5% considering TPS. In probeset #1, 63.5% were determined PD-L1 positive, no correlation to the IHC scores, TILs and probeset #2 was shown. In probeset #2 only 34.1% showed a PD-L1 positivity and had a strong correlation to the IHC scores and to TILs ($p<0.01$). PD-L1 positivity had no impact on survival when determined by IHC scores or probeset #2. In contrast, patients with high PD-L1 expression in probeset #1 had a more favourable 7-years RFI probability (84.6% vs 64.3%). Low PD-L1 expression showed higher risk for recurrence in univariate (2.68, 95%CI 1.089-7.532) and multivariate analysis (3.43, 95%CI 1.294-9.080, adjusted to nodal status). Considering OS only a trend was shown (HR 1.445, 95%CI 0.570-3.662).

Conclusions: In our cohort, the PD-L1 mRNA analysis detected additional PD-L1 positive tumours compared to IHC analysis. For validation of the prognostic impact and to examine the predictive value considering therapy with immune checkpoint inhibitors, further studies are warranted.

Clinical trial identification: NCT01592825 release date 16.12.2009.

Legal entity responsible for the study: M. Vetter, E. Kantelhardt.

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301P Epigenetic modifications of IL-17 gene in patients with early breast cancer and healthy controls

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Background: During malignant transformation, the composition and expression of cell surface molecules are changing allowing recognition by the host immune system. Interleukin 17 (IL-17) is an inflammatory mediator involved in all phases of the inflammatory process and tumour development and progression. The aim of this study was to determine the IL-17 gene methylation level and IL-17 serum concentration in patients with different surrogate subtypes of early breast cancer (eBC) and healthy controls (HCs).

Methods: Peripheral blood samples were obtained from a consecutive series of 130 female patients treated at the University Hospital Centre (UHC) Zagreb, Croatia, and 30 female HCs. The level of methylation of four CpG dinucleotide loci (CPG1, CPG2, CPG3, CPG4) in the promoter region of the IL-17 gene was measured by pyrosequencing with prior bisulfite conversion, while serum IL-17 concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Blood samples, clinical and histopathological data were collected with prior UHC Zagreb 02/21 AG Institutional Review Board approval.

Results: According to the Mann-Whitney test, the HCs methylation level of the promotor region of the *IL-17* gene differed significantly from the BC patients ($p = 0.0011$), together with the methylation level of four individual CpG loci, also (p values; CPG1 0.0067; CPG2 0.0018; CPG3 CPG 0.0029; CPG4 0.0032, respectively). There was a statistically significant difference according to the Kruskal-Wallis test in CPG3 locus methylation among BC surrogate subtypes (p=**0.010**), whereas no difference in the methylation of the other three loci was observed. Preoperative IL-17 serum concentration was significantly higher in patients with HER-2 enriched and triple-negative eBC (Kruskal-Wallis test, p=**0.022**).

Conclusions: This study confirmed differences in epigenetic modification of *IL-17* gene in women with eBC compared to HCs. Differences in the IL-17 gene methylation and IL-17 serum concentration in patients with different subtypes of BC were observed. Further research is planned to define the impact of IL-17 on eBC outcome in this cohort.

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302P Clinicopathological features and outcomes of pregnancy associated breast cancer: Case control study -single institution experience

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Background: Globally, breast cancer ranks among the primary contributors to the incidence and mortality rates of cancer. Pregnancy-Associated Breast Cancer (PABC) is an infrequent occurrence among young patients (≤45 years), characterized by diagnosis of breast cancer during pregnancy or within a year after delivery. In recent meta-analysis study, PABC patients showed higher mortality than control group. This retrospective case-control study aimed to assess the outcomes of PABC vs non-pregnancy-associated breast cancer (NPABC). The primary outcome measure was overall survival (OS), and secondary outcome measures included disease-free survival (DFS) and recurrence-free survival (RFS).

Methods: A retrospective case-control study was conducted at Shefa El Orman Hospital (SOH) from 2016 to 2021, on patients who met PABC criteria and were under follow-up for at least 3 years. Data collection was carried out using SOH Cancer Registry. 54 PABC patients cross matched with an equal number of control NPABC (≤45 years of age) with a 1:1 ratio. Statistical analysis was conducted through SPSS software. The Chi-square $\chi 2$ test was employed to conduct a comparative analysis of frequency distributions for categorical variables.

Results: Total of 54 PABC patients and equal number of control subjects. The median age of PABC cohort = 33 (IQR: 23-42), which did not differ significantly from NPABC (34, IQR: 22-42; p=0.650). PABC demonstrated a higher likelihood of presenting with metastasis at initial diagnosis compared to those NPABC (metastatic: 66.7% vs. 33.3%, p=0.018). PABC patients exhibited a noteworthy contrast in advanced stages during diagnosis, particularly in stage III and IV, in comparison to NPABC patients (61.1% vs 40.7%, p=0.021). Additionally, PABC patients showed an inferior median OS rate (48.9% vs 69.3%, p=0.085) compared to NPABC.

Conclusions: In conclusion, a significant difference exists between the OS and clinicopathological characteristics of PABC patients compared to NPABC. Furthermore, PABC patients exhibited an advanced stage of the disease upon presentation. Larger cohort studies are necessary to evaluate the treatment efficacy and to acquire molecular indicators that may impact the disease outcomes.

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303P Differential prognostic role of PDGFRA alterations in breast cancer subtypes

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Background: The platelet — derived growth factor (PDGF) signaling pathway and its main representative, PDGF receptor alpha is reportedly expressed in early breast cancer and has been associated with aggressive tumor features and worse outcomes. The aim of this study was to examine the prognostic relevance of *PDGFRA* molecular alterations across different breast cancer subtypes.

Methods: Patients with a diagnosis of non-metastatic, invasive breast carcinoma from The Cancer Genome Atlas (TCGA), including estrogen receptor (ER)-positive (n=594), ER-negative (n=174), human epidermal growth factor receptor 2 (HER2)-positive (n=120), and triple-negative (n=82) cohorts were interrogated for presence of somatic molecular alterations in *PDGFRA* gene. Kaplan Meier survival analysis was used to determine the associations between altered *PDGFRA* and disease-free survival (DFS).

Results: Sixty patients (10%) from the ER-positive cohort had altered *PDGFRA*, including 2 patients with gene amplification, 3 with missense mutations, 1 with homologous deletion and 55 with elevated mRNA expression. These patients had a longer DFS compared to those with unaltered PDGFRA (not reached vs 168 months, log-rank p=0.04). In the ER-negative cohort, 24 patients (14%) had tumors harboring *PDGFRA* alterations including 5 amplifications, 2 missense and 1 nonsense mutation, and high mRNA (n=16). There was a trend towards a shorter DFS in these patients (p=0.23). Within the HER2-positive cohort, 11 patients (9%) had somatic gene amplifications (n=1), missense mutation (n=1), and elevated mRNA (n=9). These patients experienced a significantly worse DFS (56 months vs not reached, p<0.001). Among TNBC patients, 10 (12%) were characterized by *PDGFRA* amplification (n=2), missense (n=2) and nonsense (n=1) mutations, and high mRNA (n=5). This group also featured a non-significant trend towards worse DFS (p=0.39).

Conclusions: *PDGFRA* molecular alterations in early breast cancer are mainly characterized by amplification and increased transcript levels. Their prognostic utility is variable depending on the hormone receptor- and HER2-status. An intriguing association with favorable prognosis in ER-positive cohort was found that merits further investigation.

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304P Generalizability of 313-SNP PRS for breast cancer risk in non-European ancestries

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Background: Polygenic risk scores (PRS), which summarize the combined effect of multiple common risk variants, have been associated with elevated breast cancer risk in patients who lack any identifiable monogenic risk factors. One of the most well-validated PRSs in breast cancer to date is PRS313, which was developed from a Northern European biobank (n = 33,673 cases and n = 33,381 controls). However, subsequent work has demonstrated an attenuated effect of PRS313 in African females, raising generalizability concerns. In this work, we further investigate the generalizability of the PRS313 for American women of European (EA), African (AFR), Asian (EAA), and Latinx (HL) ancestry within one institution, leveraging a singular EHR system, genotyping platform, and quality control process.

Methods: Participants were females drawn from the UCLA ATLAS Biobank (N=18,627) from 2018-2023. SNPs were genotyped on a genome-wide array and imputed to the TOPmed reference panel. Breast cancer cases and controls were identified using ICD9 and ICD10 coding. We previously identified 5 Genetically Inferred Ancestries (GIA) based on Principal Component Analysis (PCA) and k-means clustering including African Americans (AA), Hispanic Latino Americans (HLA), East Asian Americans (EAA), European Americans (EA). Breast cancer subtypes were identified based on prescription patterns.

Results: We found that the PRS313 achieved overlapping AUCs in females of Lantix (AUC, 0.68; 95% CI, 0.65-0.71) and European ancestry (AUC, 0.70; 95% CI, 0.69-0.71) with lower AUCs for the AFR and EAA populations (AFR: AUC, 0.61; 95% CI, 0.56-0.65; EAA: AUC, 0.64; 95% CI, 0.60-0.680).

Conclusions: In summary, we found that PRS313 was significantly associated with breast cancer in American females of Hispanic and East Asian ancestry but with attenuated accuracy in women of African descent. Our results are consistent with prior studies on PRS313 and further highlight the need for ethnically diverse cohorts in developing and implementing polygenic risk scores.

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305P Prognostic implications of HER2 changes after neoadjuvant chemotherapy in patients with HER2-zero and HER2-low breast cancer

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Background: Transition of HER2 status after neoadjuvant chemotherapy (NAC) has frequently been reported previously; however, few study has focused on HER2-low breast cancer. Here, we evaluated the HER2 transition proportion among HER2-zero and HER2-low breast cancer cases post-NAC and the impact of clinical outcome after our initial report on pathologic complete response, long term outcomes and recurrence pattern in between two groups after neoadjuvant chemotherapy (S Kang, European Journal of Cancer, 2022).

Methods: We retrospectively reviewed HER2-zero and HER2-low breast cancer patients who underwent NAC and surgical resection during 2014—2018 at Asan Medical Center. We included 1288 patients who had paired pre- and post-therapeutic HER2 status results. HER2-zero was defined as immunohistochemistry (IHC)0, and HER2-low was defined as IHC1+ or IHC2+, with in situ hybridization-negativity.

Results: Of patients who were HER2-zero pre-NAC(n=650), 68% and 29% of patients were HER2-zero and HER2-low, respectively, post-NAC. Among patients who were HER2-low pre-NAC(n=638), 32% of patients showed HER2 changes, and 59% of patients had a constant HER2-low status post-NAC. Patients with constant HER2-low or transitions from HER2-low to zero had a higher proportion of hormone-receptor [HR] positivity (84% and 79%) than those with changes from HER2-zero to low (77%) or with constant HER2-zero (56%), respectively. Multivariable logistic regression analysis revealed that patients with HR positivity had a higher probability of gaining HER2-low expression than those with HR negativity (Odds ratio 2.48). No significant differences were observed in terms of overall survival and disease-free survival between patients with and without HER2-changes according to hormone receptor status, except in the post-therapeutic HER2-low HR-negative subset.

Conclusions: Temporal heterogeneity of HER2-low expression is observed in substantial portions of post-NAC breast cancer patients. Clinical outcomes show no significant associations, except in the post-therapeutic HER2-low, HR-negative subset. Prognostic implications of HER2 transition in HER2-low breast cancer require further investigation.

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306P Multiplexed immunofluorescence (mIF) to select patients with HER2+ breast cancer (BC) having an excellent outcome without chemotherapy (chemo): A substudy of the PERNETTA trial (SAKK22/10-UCBG-BOOG)

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Background: PERNETTA trial randomized 210 HER2+ BC patients (pts) to 1st-line trasutuzmab-pertuzumab (T-P) alone or combined with chemo. In the final analysis (median follow-up 63 months), pts with chemo had longer progression free survival (PFS), but similar overall survival (OS) at 2 years. In this ancillary study, we aimed to identify immune biomarkers predicting for long PFS in pts with the chemo-free anti-HER2 strategy.

Methods: Six good and 6 poor responders were selected in each study arm, based on their PFS (total 24 pts); 77 proteins were assessed using GeoMx digital spatial profiling technology in these 24 samples, in the Immune Landscape Laboratory of the Ludwig Institute in Lausanne. Proteins discriminating good versus poor responders were selected to construct a panel of 7 proteins, which was then tested by mIF in the 142 available pts' samples. After high-definition scanning, the tissue images were analyzed by IFQuant software and the results correlated with pts' PFS and OS by stratification cox regression.

Results: CD8, GrzB, BCL2, CD44, MET, DAPI, and CK were selected for the final panel. In the chemo-free arm, pts with low expression of CD8-GrzB in stroma or CD8-MET in tumor had similar PFS as pts receiving chemo (p=0.8 and 0.4) and significantly better than the pts with high expressions (p=0.03 and 0.05). Pts without chemo and with low expression of CD8-MET in tumor showed a better OS than the pts with high expression (p=0.02) and even better than the pts having received chemo (p=0.04). In addition, different combined expressions of these biomarkers in stroma and in tumor were able also to discriminate pts with good versus poor outcome in arm A, arm B or whole study population.

Conclusions: Immunity plays a significant role in the efficacy of anti-HER2 treatments. mIF allowing to assess simultaneously several biomarkers presence, intensity and location seems to permit selecting pts with HER2+ advanced stage BC having an excellent outcome in terms of PFS and OS without chemo in 1st line. If validated these biomarkers may contribute to treatment de-escalation and quality of life improvement.

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Legal entity responsible for the study: Lausanne University Hospital, Prof. Lana Kandalaft.

Funding: Roche provided an unrestricted funding.

Disclosure: K. Zaman: Financial Interests, Institutional, Advisory Board: AstraZeneca, Daiichi, Lilly, Pierre Fabre, Gilead, MSD, Novartis, Seagen, Viatris; Financial Interests, Institutional, Funding, Translational study: Roche; Financial Interests, Institutional, Steering Committee Member: Pierre Fabre; Financial Interests, Institutional, Other, Member of the IDMC of an international trial: Roche; Financial Interests, Institutional, Steering Committee Member, Member of the Steering committee of an international study: Daiichi; Non-Financial Interests, Advisory Board: Swiss Group for Clinical Research Against Cancer (SAKK), Executive Committee of the MINDACT trial; Non-Financial Interests, Member, Representative of SAKK Breast Group: Breast International Group (BIG); Non-Financial Interests, Member: EORTC Breast Group; Other, Unrestricted funding for organization of academic symposium: Agendia, AstraZeneca-MSD, Daiichi, Eisai, Exact Sciences, Lilly, Pierre Fabre, Gilead, Novartis, Pfizer, Roche, Seagen, Viatris, Vifor; Other, Support for participation in international congress: AstraZeneca, Daiichi, Gilead, Pierre Fabre, Roche, Lilly. J. Huober: Financial Interests, Institutional, Research Funding: Celgene, Novartis, Lilly; Financial Interests, Personal, Invited Speaker: Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Celgene, Eisai, AbbVie, Seagen, Gilead, Daiichi; Financial Interests, Institutional, Advisory Board: Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Celgene, AbbVie, Seagen, Gilead; Financial Interests, Institutional, Other, travel grant: Roche, Pfizer, Novartis, Daiichi. P. Weder: Financial Interests, Institutional, Other, travel grants: Roche. All other authors have declared no conflicts of interest.

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307P Identifying new biological subgroups of triple-negative breast cancer using next-generation integrative clustering pipeline

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Background: Early triple-negative breast cancer (eTNBC) is molecularly heterogenous, with differential prognosis. We aimed to identify new biological subgroups (B-grp) of eTNBC via an integrative clustering pipeline (ICP) and evaluate the clinical value of these B-grp in a large randomised clinical trial.

Methods: TACT2 was a phase 3, randomised trial testing adjuvant accelerated versus standard Epirubicin in early breast cancer. From TACT2, 551 eTNBC tumours were stratified into training (n=367) and testing (n=184) by treatment arm. Expressions of 758 genes (GE) and Triple-Negative Subtypes (TNS; Burstein CCR 2015) of tumour were profiled by nCounter@ Breast Cancer 360TM. Immunohistochemistry expressions (IHC) of HER2, EGFR and CK5/6 were assessed. Clinicopathological features (ClinPath) included age, nodal status, tumour size and grade. The ICP included random forest (RF) and 9 unique clustering methods with hypergeometric test to reconcile clustering results to a final output. Survival endpoint was time to recurrence (TTR) for multivariable cox regression (mCox), of which the goodness-of-fit was assessed by chi-square, brier score and integrated calibration index.

Results: The ICP returned 4 B-grp using GE, IHC and ClinPath of the training set. GE was the main factor of clustering, summarising B-grp into immune-enriched (IM), Luminal-AR (LAR), mesenchymal like (MES) and basal like (BL). IM and LAR contained mainly TNS-BLIA and TNS-LAR, respectively. Both MES and BL comprised TNS-BLIA, TNS-BLIS and TNS-MES. The RF was trained using GE as unimodal single-sample predictor to assign the B-grp on the testing set. Adding B-grp to ClinPath yielded more accurate 5-year TTR prediction for test samples when compared to TNS (Table).

Table: 307P Comparing the goodness-of-fit of three mCox models using chi-square, brier score and integrated calibration index

	ClinPath	ClinPath + TNS	ClinPath + B-grp
Chi-square	19.27	**59.98**	32.29
Chi-square (against the ClinPath model)	-	**40.71** ($p < 0.0001$)	16.02 ($p = 0.001$)
Brier score	0.1477	0.1544	**0.1425**
Integrated calibration index	0.021	0.064	**0.019**

Brier score is the mean square difference between the true classes (0 = no recurrence, 1 = recurrence) and the predicted probabilities at given time point. Integrated calibration index is the weighted absolute difference between the calibration curve and the diagonal line of best fit.

Conclusions: We identified 4 eTNBC B-grp based on distinct biology which provided more accurate 5-year TTR prediction in addition to ClinPath than TNS. The association of the B-grp with survival for other treatments could be further evaluated.

Clinical trial identification: NCT00301925.

Legal entity responsible for the study: The Institute of Cancer Research and Lothian Health Board.

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AG, Biotheranostics, Inc., RNA Diagnostics, Inc., oncoXchange/MedcomXchange Communications Inc, OncoCyte Corporation, Ontario Institute for Cancer Research, AstraZeneca, Cerca Biotech; Financial Interests, Personal, Advisory Board: MedcomXchange Communications Inc; Financial Interests, Personal, Other, Honoraria: MedcomXchange Communications Inc; Financial Interests, Personal, Research Funding: Thermo Fisher Scientific, Genoptix, Agendia, NanoString Technologies, Inc., Stratifyer GmbH, Biotheranostics, Inc., Exact Sciences; Other, Personal, Other, CIN4 predicts benefit from anthracycline, National Phase Application, (Canada, Jan. 11, 2017): Patent - Applied; Other, Personal, Other, Systems, Devices and Methods for Constructing and Using a Biomarker, National Phase Application, 15/328,108 (United States, Jan. 23, 2017); 15824751.0 (Europe, Jan. 12, 2017); (Canada, Jan. 12, 2017): Patent - Applied; Other, Personal, Other, Immune Gene Signature Predicts Anthracycline Benefit, PCT (international application), PCT/CA2016/000305, Filing date: Dec. 7, 2016: Patent - Applied; Other, Personal, Other, Gene Signature of Residual Risk Following Endocrine Treatment in Early Breast Cancer (Patent Title), National Phase Application, Patent application number 3007118 (Country of Filing: Canada — Patent Application Date: 06/01/18): Patent - Applied; Other, Personal, Other, A Molecular Classifier for Personalized Risk Stratification for Patients with Prostate Cancer (Invention Title), PCT International Application No.: PCT/CA2021/050837, International Filing Date: June 18, 2021: Patent - Applied; Other, Personal, Other, CIN4 predicts benefit from anthracycline (Invention Title), National Phase Application, Patent number: 11214836 (Country: United States, Date: Jan. 4, 2022); 3169815 (Europe, Dec. 23, 2020): Patent - Granted; Other, Personal, Other, Targeting the Histone Pathway to Detect and Overcome Anthracycline Resistance (IP Title), National Phase Application, Patent number: 2016800728463 (Country: China, Date: Aug. 27, 2021); 11,015,226 (United States, May 25, 2021); 3359508 (Europe, Sept. 9, 2020); 3,000,858 (Canada, Sept. 27, 2022): Patent - Granted; Other, Personal, Other, Gene Signature of Residual Risk Following Endocrine Treatment in Early Breast Cancer (Patent Title), National Phase Application, Patent number: 2016368696 (Country: Australia, Date: Mar. 10, 2022); 2016800813945 (China, Mar. 18, 2022); 3387168 (Europe, May 12, 2022); 7043404 (Japan, Mar. 18, 2022); 11,566,292 (United States, Jan.31, 2023): Patent - Granted; Other, Personal, Other, Disclosure Name: A Molecular Classifier for Personalized Risk Stratification for Patients with Prostate Cancer, Date: 21/08/2019: Invention Disclosure. M.C.U. Cheang: Financial Interests, Personal, Funding: NanoString Technologies; Financial Interests, Personal, Advisory Role: Veracyte; Other, Personal, Licencing Fees or royalty for IP, Breast Cancer Classifier: US Patent No. 9,631,239.: Patent. All other authors have declared no conflicts of interest.

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308P Regression-based deep-learning predicts breast cancer recurrence risk score from pathology slides

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Background: Breast cancer (BC) treatment decisions can be challenging, particularly in patients with early-stage hormone receptor-positive/HER2-negative (HR+/HER2-) tumors. Prognostic assays, such as the 21-gene recurrence score assay (Oncotype DX), are used to determine individual patient risk of recurrence and guide decision on whether to administer adjuvant chemotherapy or not. However, these tests are costly and time-intensive to perform. Deep-Learning (DL) can predict molecular biomarkers from routine hematoxylin and eosin (H&E) pathology slides, potentially serving as an inexpensive and accessible pre-screening tool. We aim to use DL for the outcome prediction of the Oncotype DX test.

Methods: We trained a DL-based regression model in a weakly-supervised manner to detect Oncotype DX risk score directly from routine H&E-stained pathology slides in a large (n=5,303) cohort of early-stage HR+/HER2- BCs from Memorial Sloan Kettering (MSK). We then externally validated the model onto The Cancer Genome Atlas (TCGA) BC cohort for which Oncotype DX scores were available (n=100). The model was evaluated using the Pearson's correlation coefficient r. Moreover, the recurrence score was divided into low ($<$11) and intermediate/high ($\geq$11) risk groups, enabling evaluation via the area under the receiver operating characteristic curve (AUROC).

Results: The model yielded a significant r of 0.59 ($p<0.0001$) on the test set of the training cohort of MSK BCs and 0.58 ($p<0.0001$) on the external cohort of TCGA BCs. When binarizing the predictions into intermediate/high and low recurrence risk groups, we found that the model was particularly accurate for identifying patients with intermediate/high risk scores, reaching an AUROC of 0.87 ($\pm$ 0.04) and 0.79 ($\pm$ 0.03) in the MSK and TCGA cohort, respectively.

Conclusions: We developed a DL-model that can accurately predict Oncotype DX score from routine pathology slides, offering a cost-effective and time-efficient pre-screening tool for identifying a high-risk subgroup HR+/HER2- early BCs and to democratize the access to complex but clinically useful biomarkers. This approach could support informed treatment decisions by accurately determining recurrence risk, ultimately improving patient outcomes.

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309P Machine learning-based characterization of tumor-immune microenvironment at a spatial and multiplexed resolution in early breast cancer: A sub-study of the EORTC 10994/BIG 1-00 randomized phase III trial with long-term follow-up

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Background: Data support the role of immune infiltrate in breast cancer (BC) prognosis and therapy prediction. The aim of this study was to characterize the immune landscape in early BC at a multiplex and spatial resolution using machine learning (ML)-based algorithms and investigate its potential prognostic value.

Methods: Tissue microarrays (TMA) were constructed from pretreatment samples from patients enrolled in the EORTC 10994/BIG 1-00 neoadjuvant randomized phase III trial (taxane/anthracycline vs FEC). An automated algorithm for digital TIL (dTIL) quantification was applied on H&E stained TMA. Multiplex fluorescent immunohistochemistry (mfIHC) was performed for an immune antibody panel and cell phenotyping/localization was applied with a ML-based software. *TP53* mutational status was available for a subset of patients. Logistic and Cox regression models investigated the association of immune-related metrics with pathological complete response (pCR) and progression-free survival (PFS), respectively.

Results: Median follow-up was 11.4 years. 587 patients had dTIL and 478 had mfIHC data. Among the dTIL variables, easTIL [sum of TIL area (mm^2)/stroma area (mm^2)] were higher in the triple-negative subtype and an independent predictor of pCR (ORadj= 1.59, 95% CI 1.00 — 2.54, p=0.05) in the whole cohort. No significant association with PFS was noted. However, a significant interaction was observed between esTIL (TIL/stromal cells) and *TP53* mutational status (p= 0.028); higher esTIL abundance was prognostic for worse PFS only in patients with *TP53* wild-type tumors. CD8+ T-cells were the most abundant cell subset in both tumor and stroma compartments. Expression of total CD4+ (ORadj= 1.79, 95% CI 1.07 — 2.97, p=0.026) and intra-tumoral CD8+ T-cells (ORadj= 1.83, 95% CI 1.05 — 3.20, p=0.033) was independently associated with improved pCR.

Conclusions: Our data indicate that ML-based models could be used for studying the immune infiltrate in BC. Abundance of dTIL and spatial distribution of immune markers contain prognostic information, which might depend on *TP53* mutational status. Further validation is warranted.

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Legal entity responsible for the study: European Organisation for Research and Treatment of Cancer (EORTC).

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Non-Financial Interests, Officer: EORTC; Financial Interests, Personal, Other, Travel Grants: Roche, Gilead. D. Rimm: Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, Cell Signaling Technology , Cepheid, Danaher, GSK, Konica/Minolta, Lilly, Merck, Monopteros, Nanostring, PAI-GE.AI, Regeneron, Roche, Ventana; Financial Interests, Personal, Advisory Role: Fluidigm, Immunogen, NextCure, Odonate, Sanofi, Verily; Financial Interests, Institutional, Other: Amgen, Cepheid, Navigate BioPharma, NextCure, Konica/Minolta, Akoya; Financial Interests, Personal, Royalties: Rarecyte. D.A. Cameron: Financial Interests, Institutional, Advisory Board: Roche, Pfizer, AstraZeneca, Daiichi Sankyo, SeaGen, Synthon, Zymeworks; Financial Interests, Institutional, Other, Have done advisory boards, spoken at a webinar and involved in a manuscript with Lilly - all recompense to my institution: Lilly; Financial Interests, Institutional, Other, Have done advisory boards and been involved in a health economic analysis and publication. All recompense to my institution: Novartis; Financial Interests, Institutional, Coordinating PI, funding and drug for UK participation in a French led Novartis funded study. Institutional funding received for consultancy work: Novartis; Non-Financial Interests, Principal Investigator, one of three PIs for the Ameera-6 trial - which has now closed early as the company have stopped all development of the drug: Sanofi; Other, Chair of the board of this small Scottish charity for secondary breast cancer: Make Seconds Count; Other, Chair of the Board of B.I.G. - a group of international breast cancer research groups: Breast International Group; Other, Chair of the European Breast Cancer Council which organises the bi-annual EBCC meetings: EBCC. J. Bergh: Financial Interests, Institutional, Advisory Board: Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, Sanofi-Aventis; Financial Interests, Personal, Other, Co-author on a chapter in UpToDate on prognostic and predictive factors in early, non-metastatic breast cancer. Honoraria to Asklepios Medicine HB: UpToDate; Financial Interests, Personal, Stocks/Shares, consultant for this diagnostic company in early development: Stratipath . H. Bonnefoi: Financial Interests, Personal, Advisory Board: AstraZeneca/ Daiichi Sankyo; Financial Interests, Institutional, Coordinating PI, UCBG3-06 prospective study: Bayer. T. Foukakis: Financial Interests, Institutional, Invited Speaker: Roche, AstraZeneca, Gilead Sciences; Financial Interests, Personal, Advisory Board: Novartis, Veracyte, Exact Sciences, Affibody; Financial Interests, Personal, Invited Speaker: Pfizer; Financial Interests, Personal, Royalties, Authorship of two chapters in UpToDate: Wolters Kluwer; Financial Interests, Institutional, Coordinating PI, Clinical trial support (research grant and study drug): Pfizer, AstraZeneca; Financial Interests, Institutional, Coordinating PI, Clinical trial support (research grant and study drug): Novartis. All other authors have declared no conflicts of interest.

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310P Longitudinal evaluation of circulating tumour DNA in early breast cancer using a plasma-only methylation-based assay

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Background: Plasma-only ctDNA detection is a strategy to identify molecular residual disease (MRD) in early breast cancer (EBC). MRD-positivity in the absence of clinical/radiographic disease may have prognostic implications and enable intervention prior to clinical recurrence.

Methods: Plasma samples from baseline, perioperative, adjuvant and follow-up timepoints were collected in patients with estrogen receptor positive/HER2-negative (ER+) and triple-negative (TN) breast cancer treated with neoadjuvant chemotherapy (2015 onward). Samples were analyzed using the Guardant Reveal pan-tumor assay on the INFINITY™ platform. Clinical/pathologic characteristics and recurrence outcomes were collected. ctDNA/MRD-positivity was defined as a methylation score > 0.

Results: 270 timepoints (median 3 per patient, range: 1-9) were analyzed from 83 patients with ER+ (n=38) and TN (n=45) EBC; 95% (256/270) produced successful results. Baseline positivity rate was 67.5% (54/80) in all patients (66.7% in ER+, 68.2% in TN). Nine patients had a mutation called at baseline (7 *PIK3CA*; 1 of *TP53*, *FGFR1*, *BRAF*, *GATA3*, or *NOTCH2*). Larger tumor size (p=0.014) and nodal involvement (p=0.011) were associated with baseline test positivity. 17/83 (20.5%) patients have had a clinical recurrence (13 distant, 4 local). 14/17 (82.3%) patients with recurrence had a positive test at baseline (2 negative, 1 fail) and baseline methylation scores were higher in patients with recurrence (p=0.0032). Seven of 8 patients with recurrence had a positive sample collected at or prior to clinical recurrence with lead time of up to 5.1 months. Four patients with no documented recurrence had a positive test at their last follow up [range: 4.7-19.1 months from last test] with methylation scores lower than those of patients with recurrence (p=0.012). Any ctDNA positivity in follow up after surgery was strongly associated with a risk of recurrence (HR = 7.02, 95%CI: 1.82-27.2, p=0.001).

Conclusions: This longitudinal evaluation of a plasma-only methylation based ctDNA assay demonstrates ctDNA detection and dynamic changes in a large EBC cohort. Potential prognostic and predictive applications warrant further evaluation.

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311P Multinational survey study assessing genetic testing and counselling among patients (pts) with breast cancer (MAGENTA): Results on the genetic counselling experience

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Background: Despite genetic testing (GT) and counselling (GC) being key in breast cancer (BC) risk assessment, GC uptake rates are low even among pts undergoing GT. A global survey was conducted among pts with BC to identify the gaps in the GC experience and to propose strategies to fill them.

Methods: A steering committee comprising of pts and pt advocates co-developed a 38-question survey, which was offered to pts in Argentina, Australia, Brazil, Egypt, India, Malaysia, Mexico, Russia and Taiwan in local languages, through social media. The questions pathway was dependent on response to prior questions. Chi-square test was used to assess significance between responses, if applicable.

Results: The final analysis set (FAS) included responses from 1176 respondents with a > 90% completion rate of survey questions. In the FAS, 737 (63%) respondents reported having undergone GT. Most respondents in the FAS (768/1061; 71%) rated their awareness level of GT/GC (before BC diagnosis) as between 'very low' to 'moderate'. Among pts undergoing GT, 616 respondents responded to the question enquiring on the resources available to them to guide their GT experience, beyond their oncologist. These were the genetic counsellor (295/616; 48%), pt support groups (232/616; 38%) and websites (217/616; 35%). Among the 439 respondents who did not undergo GT, 174 (40%) were offered GT by their doctor but did not take it. The table shows the level of understanding of GC reimbursement eligibility among the respondents.

Table: 311P

Question	Population	No. of respondents	Response [n (%)]		
			Yes	No	I don't know
Did you receive any GC?*	Tested	737	327 (44)	266 (36)	86 (12)
	Not tested	439	31 (7)	277 (63)	46 (11)
Should you qualify, is the cost of GC for breast cancer reimbursed in your country?	FAS	1176	302 (26)	174 (15)	372 (32)
	Tested	737	325 (44)	129 (18)	283 (38)
	Not tested	439	82 (19)	120 (27)	237 (54)

*Statistically significant difference (p<0.00001) between tested and not tested pts

Conclusions: Most pts with BC are not offered GC, which significantly correlates with GT uptake. Since poor awareness of GC is a critical gap, improving GC services and pt education through pt advocates and online tools may increase GT rates, offering a more impactful GT experience for pts and their families.

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312P Prediction model of breast cancer patient's neoadjuvant treatment outcome using breast cancer organoids cultured from core needle biopsies

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Background: The incidence of breast cancer is steadily increasing, and many patients receive adjuvant chemotherapy before or after surgery. In particular, neoadjuvant drug therapy is commonly used to suppress microinvasive before surgery. In this study, the patient-derived organoids (PDOs) from breast cancer patient's biopsies were used for drug sensitivity test. To predict patient's neoadjuvant treatment outcome, we propose a new drug sensitivity evaluation method based on multi-factors such as Area Under Curve (AUC) of dose response curve, organoid growth rate.

Methods: Patient cells were obtained from core needle biopsy before surgery and mechanically dissociated before being mixed with extracellular matrix (ECM) to generate PDOs. Anti-cancer drug sensitivity testing was performed on these PDOs using a pillar-based organoid system, which involved single or combination treatments with anti-cancer drug with 384 plate-based high throughput screening. Area Under Curve (AUC) values of the dose-response curves (DRC) and organoid growth rate were calculated by pillar-based organoid system.

Results: The proposed multi-factor prediction model was verified by comparing drug sensitivity test with patient's neoadjuvant outcome. We performed drug sensitivity test of 79 breast cancer patients. So far, 13 patients have finally been evaluated for neoadjuvant treatment results. Multi-factor prediction model (***C***ancer ***O***rganoid-based ***D***iagnosis ***R***eactivity ***P***rediction, CODRP) shows 83 % sensitivity and 85 % specificity while conventional prediction model using only AUC shows 50 % sensitivity and 71 % specificity.

Conclusions: Therefore, Multi-factor prediction model (CODRP) may provide useful supplementary diagnostic information for individual breast cancer patients by selecting optimal anticancer drug candidates for patient treatment.

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313P Intrinsic subtypes in a cohort of early breast cancer patients

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Background: Breast cancer is a heterogeneous disease with regard to diagnosis, therapy and survival. Complementary to the histopathological classifications of the tumours, molecular biological tests specify individualised therapy recommendations. Our aim was to classify tumours into intrinsic subtypes and to analyse the association of grouping with disease progression.

Methods: Intrinsic subtypes were determined from 1,070 tumours by mRNA expression profiling (PAM50 algorithm) from fresh tumour tissue or FFPE tissue in a prospective, multicenter cohort study (n=1,270; NCT 01592825). mRNA expression evaluation was performed either by nCounter®NanoString or GenChip™ HG U133 Plus 2.0 or BioMark™ Fluidigm. Endpoints were recurrence free interval (RFI) and overall survival (OS). Median follow-up time was 60.3 months. Survival analyses were done by Kaplan-Meier method and Cox model adjusting for age, nodal status, tumour size, and tumour differentiation.

Results: The PAM50 analysis resulted in 44.9% in Luminal A (n=480), 23.9% Luminal B (n=256), 14.4% HER2-enriched (n=154), and 16.8% in Basal-like (n=180). In the total cohort, 89.9% (95% CI 87.9-91.9) of patients were free of RFI event and 87.5% (95% CI 85.3-89.7) were alive at 5 years of observation. Of patients with a Luminal A tumour, 93% were free of RFI event (95% CI 88.1-97.9). The remaining patients had a substantially higher risk of RFI events: Luminal B, HR=3.3 (95% CI 1.78-6.01); HER2-enriched, HR=3.8 (95% CI 2.01-7.21); Basal-like, HR=4.7 (95% CI 2.53-8.7). In the Cox model, only tumour size (HR=2.5) and nodal status (HR=2.2) had a significant additional prognostic impact. Also with regard to OS, PAM50 subtypes, tumour size, and nodal status were the only significant prognostic factors.

Conclusions: Even after guideline-based therapy, the intrinsic subtypes still have prognostic significance. Nearly half the patients can be identified as Luminal A with an excellent course of disease, whilst patients with Luminal B, HER2-enriched, Basal-like still have a substatial risk of recurrence, requiring further improvement of therapy concepts.

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314P Concordance of somatic variants between circulating tumor DNA and tissue in patients with breast cancer

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Background: Analysis of circulating tumor DNA (ctDNA) is a noninvasive method for detecting somatic variants. However, the sensitivity of ctDNA is limited by the dilution of ctDNA with cell-free DNA from non-cancer cells. In this study, we evaluated the concordance of somatic variants between ctDNA and tissue in patients with breast cancer to assess the clinical usefulness of ctDNA testing.

Methods: Paired plasma and tissue samples at the diagnosis were collected from 29 patients with breast cancer. Next-generation sequencing targeting 49 genes was performed on both plasma and tissue samples and the concordance between plasma and tissue was evaluated.

Results: A total of 140 variants were detected in paired tissue and plasma samples of 29 patients. Among them, 66.4% (93/140) of variants were detected only in tissue, 14.3% (20/140) of variants were detected only in plasma, and 19.3% (27/140) of variants were detected in both samples. The median variant allele frequency of concordant and discordant variants in ctDNA was 1.5% and 0.6%, respectively. Actionable variants were detected in four genes: *BRCA1*, *BRCA2*, *ERBB2*, and *PIK3CA*. For 29 patients, the overall concordance rate for detecting actionable variants was 65.5% (19/29), with individual gene concordance rates of 96.6% (28/29) for *BRCA1*, 93.1% (27/29) for *BRCA2*, 79.3% (23/29) for *ERBB2*, and 79.3% (23/29) for *PIK3CA*. The overall sensitivity and specificity were 41.2% and 100%, respectively.

Conclusions: ctDNA testing showed a high concordance and specificity in detecting actionable variants. It can be used as a complementary test to tissue biopsy for selecting appropriate therapeutic agents.

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315P Multinational survey study assessing genetic testing and counselling among patients (pts) with breast cancer (MAGENTA): Results on perceptions on testing

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Background: Genetic testing (GT) is vital in the risk assessment of breast cancer (BC) and along with genetic counselling (GC), may inform treatment decisions. However, fewer than one-third of patients (pts) with BC undergo GT. A multinational survey was conducted for a deeper understanding of the barriers in the uptake of GT and GC. Results from this survey, focusing on awareness and pts' perceptions towards GT and GC have been reported here.

Methods: A steering committee comprising of pts and pt advocates co-developed a 38-question online survey, which was launched in local languages for pts in Argentina, Australia, Brazil, Egypt, India, Malaysia, Mexico, Russia and Taiwan, through different social media platforms. The questions pathway was determined based on response to certain questions on GT & GC uptake. Percentage responses to a response option was calculated against the number of respondents for that question.

Results: The final analysis set (FAS) included responses from 1176 participants with more than 90% completion rate of survey questions. Median age among respondents in the FAS was 42 years (IQR: 35, 49) at the time of BC diagnosis. Among survey respondents, 63% (737/1176) had undergone GT, and 37% (439/1176) did not undergo GT. The table lists select questions on some aspects of the GT experience as well as perceptions of testing. .

Conclusions: There are critical gaps in the awareness of GT among pts and the public, along with gaps in perceived value and access to GT, with notable variance between the tested and the non-tested populations. Strategic action is needed to overcome the barriers to GT and to improve the pt experience.

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316P Comprehensive characterization of the HER2-enriched intrinsic molecular subtype in ER-positive HER2-negative breast cancer

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Background: Breast cancer that is estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) can be further stratified into intrinsic molecular subtypes by employing PAM50-based gene expression profiling. Despite its association with poor outcome, the HER2-enriched (HER2E) subtype currently holds no implications for clinical treatment decisions due to a lack of insight into its distinguishing features. Therefore, we aimed to evaluate the response of patients to conventionally administered therapies and identify molecular features to inform therapy optimization.

Methods: Two primary breast cancer cohorts provided clinical, transcriptomic, and genomic data on ER+/HER2- cases: SCAN-B 4413 (HER2E: 89, Luminal A (LumA): 3049, Luminal B (LumB): 1349) and METABRIC 1227 (HER2E: 58, LumA: 601, LumB: 340), including whole genome sequencing data for 32 HER2E cases. Focal points were analyses based on overall survival and invasive disease-free survival (IDFS),

Table: 315P

Question	Response		No. of respondents/Total no. of respondents to the question (%)	
How would you rate the awareness levels of GT/GC of yourself, before diagnosis?	Moderate to very low		758/1061 (71)	
Should all pts diagnosed with BC undergo GT first before starting treatment?	Yes	Underwent GT Did not undergo GT	603/849 (71)	460/625 (74) 143/224 (64)
How willing would you be to have your children and other family members undergo GT?	Very willing	Underwent GT Did not undergo GT	371/1176 (32)	322/737 (44) 49/439 (11)
What was your main reason for not undergoing GT?	I was not offered GT		282/394 (72)	
What are the main barriers to GT for you and your family? (Top 2)	Cost Lack of understanding		210/425 (49) 163/425 (38)	

differential gene expression, pathway enrichment, mutational frequencies and signatures, and copy number alterations.

Results: Clinicopathological analyses highlighted HER2E breast cancer to be a small subgroup associated with worse prognoses than other luminal PAM50 subtypes, regardless of whether patients were treated with endocrine therapy (E) or both endocrine and chemotherapy (EC), independent of tumor size, grade, age, and lymph node status (IDFS; E: HR 4.0, CI95 2.0-7.8; EC: HR 2.8; CI95 1.16-6.9; LumA as reference). Furthermore, HER2E tumors were larger and higher graded than LumA tumors. Next to highly proliferative characteristics akin to LumB, HER2E tumors were distinguished by their low *ESR1* expression, high *FGFR4* expression, high immune response, and high frequency of *TP53* mutations.

Conclusions: The HER2E subtype within ER+/HER2- disease is a small but clinically relevant patient subgroup that is not constituted by misclassified cases and is less ER dependent than other luminal subtypes. It does not represent a distinct biological entity, but it is nevertheless associated with potentially targetable molecular features, for instance in form of a high immune response and high *FGFR4* expression.

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317P Awareness of genomic testing among patients with breast cancer in Europe

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Background: Genomic testing, involving expression profiling of tumour tissue removed from patients with breast cancer, is a powerful tool to help choose the most appropriate treatment for individual patients. The objective of this study was to evaluate awareness of genomic cancer testing in five European countries (France, Germany, Italy, Spain, and the United Kingdom), with a focus on women with breast cancer.

Methods: The survey was initiated by Cancer Patients Europe (CPE) as part of its my Cancer my Concern (myC) initiative and was developed with a panel of oncologists and patient association representatives. Participants were recruited by e-mail and through a social media campaign. They responded to a 42-question internet survey (Survey Monkey) which took ∼10 minutes to complete..

Results: Of 1,383 participants completing the survey, 566 women with HR+ and HER2- breast cancer who were eligible for genomic testing were analysed. 245 (43.3%) were aged 50-59 years and 381 (67.3%) had received higher education. 238 participants (42.1%) had heard about genomic testing; only 122 (21.6%) were told that they were eligible for it and 104 (18.4%) were told the reasons for the test. The majority (N = 479; 84.6%) considered that they did not have sufficient information to make a decision about genomic testing and only 139 (24.6%) actually decided to take a test. Overall, 234 (41.3%) would have liked to have received more information on treatment options, and 246 (43.5%) more information on additional testing. 464 participants (82.0%) sought more information on their disease. The principal sources of information on breast cancer management were healthcare professionals (N = 363; 64.1%), internet (N = 351; 62.0%), and patient associations (N = 117; 20.7%). For the majority (N = 398; 70.3%), the healthcare professional did not provide advice on where to find more information.

Conclusions: This study demonstrates that awareness of and access to genomic testing for breast cancer in Europe is sub-optimal. Healthcare professionals need to improve communication with patients regarding genomic testing and involve them in shared decision-making. Patient associations should also act as a portal for providing information on genomic testing.

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318P Evaluation of novel diagnostic kits using the semi-dry dot-blot method combined for detecting metastases in sentinel lymph nodes of patients with breast cancer: A multi-center prospective study

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Background: The semi-dry dot-blot (SDB) method, a diagnostic procedure for detecting lymph node (LN) metastases using anti-cytokeratin (CK) antibody, is based on the theory that epithelial components such as CK are not found in normal LNs. Thus, metastases are diagnosed on basis of the presence of CK in lavage fluid of sectioned LNs. We prospectively evaluated novel SDB kits that use a newly developed anti-CK19 antibody and an automatic reader for diagnosing sentinel LN metastases in patients with breast cancer as a multi-center study.

Methods: We obtained 924 sentinel LNs dissected between January 2021 and December 2021 at six institutes in Japan. We excluded patients with neoadjuvant chemotherapy and neoadjuvant endocrine therapy. These LNs were sliced at 2-mm intervals and washed with PBS. Cells suspended in the lavage fluid of sliced LNs were centrifuged and lysed to extract protein. The extracted protein was applied to the SDB kit to diagnose LN metastasis using an automatic reader that evaluates absorbance. Washed LNs were blindly examined using intraoperative and permanent histological examination. Diagnoses based on SDB kit were compared with diagnoses made by permanent histological examination of the LNs. Primary endpoints were sensitivity, specificity, and overall agreement of the SDB kit for distinguishing macrometastases from non-macrometastases.

Results: Ninety-four of the 924 LNs were assessed as macrometastases, 40 as micrometastases and 790 as negative by histological examination. With a borderline CK19 absorbance of 11.9 milli-absorbance for detecting macrometastases with 0.989 Area Under the Curve, the sensitivity, specificity, and overall agreement of the SDB kit were 94.7%, 98.3%, and 97.9%, respectively. Furthermore, the kits and the automatic reader yielded diagnoses in approximately 20 min at a cost of less than 30 EUR for the SDB kit and less than 3,000 EUR for the automatic reader.

Conclusions: The kits with an automatic reader used in our study were accurate, quick, and cost-effective in diagnosing LN metastases without loss of LN tissue, and were especially useful for detecting distinguish macrometastases.

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319P The impact of low HER2 expression on clinical significances and outcomes in patients with HER2-negative early breast cancer

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Background: HER2-low, defined by immunohistochemically (IHC) 1+ or 2+ with negative in situ hybridization (ISH), has recently attracted attention as a novel classification in determining treatment strategies in HER2-negative metastatic breast cancer (BC). However, clinical significance of this new subcategory in early-stage BC and testing methodologies of HER2-low remain unclear.

Methods: We retrospectively reviewed the clinical data of 1,359 patients with HER2-negative BC at stage I-III between January 2008 and December 2017 in our institute. They were classified into HER2-low (n=455) and HER2-0 (n=904) subgroups according to IHC assay or gene amplification on ISH. We compared the difference in clinicopathological characteristics, recurrence-free survival (RFS), and overall survival (OS) between these subgroups. Since three different immunostaining kits (HercepTest; Dako (i), Bond III stainer (Leica Biosystems) (ii), Ventana ultra View PATHWAY HER2/neu (4B5) (iii)) were used in defining HER2 expression depending on period, we also evaluated the frequency of HER2 expression level by immunostaining kits.

Results: The median age was 57 (range 24—87) and the median follow-up period was 77 months (range 1.1—175.6). The number of patients at clinical stage I, II, and III was 790, 462, and 107, respectively. The HER2-low subgroup tended to have lower histological grade ($p < 0.01$) and higher frequency of hormone receptor positivity ($p < 0.01$) compared to the HER2-0 subgroup. There were no statistically significant

differences in RFS (p = 0.95) or OS (p = 0.87) between two subgroups. Intriguingly, there were significant differences in the percentages of HER2-low and HER2-0, depending on the immunostaining kits (42.2% vs 57.8% (i), 84.5% vs 15.5% (ii), 87.9% vs 12.1% (iii)).

Conclusions: In this study, there was no prognostic difference based on HER2 expression status in HER2-negative early-stage BC, but there was a frequency difference in determining HER2-low and HER2-0 depending on the immunostaining kits. While there are many assays for HER2 evaluation approved in the practice, an appropriate companion diagnosis for HER2-low seems to be critical to select patients who may benefit from newer treatment such as Trastuzumab Deruxtecan.

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320P Clinical and pathological characteristics of breast cancers switching from early luminal-like to metastatic triple-negative phenotype

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Background: Loss of hormone receptors (HR) at breast cancer (BC) metastatic relapse has been reported. Few data are available on the clinicopathologic features associated with HR loss and its prognostic impact.

Methods: We retrospectively identified a cohort of 51 patients (pts) with primary HR+/HER2- BC and triple-negative (TN) metastasis (LUM-TN) along with two control cohorts of paired HR+/HER2- and TN on both primary and metastatic samples (LUM-LUM, n=50; TN-TN, n=49). Clinical features and outcomes were retrieved from medical charts. HR and HER2 status were independently reviewed by two pathologists on all archival samples. Estrogen receptor (ER) expression between 1% and 10% was considered as ER-low. Cox-proportional hazard models were used to assess the impact of variables on distant metastasis-free survival (DMFS) and overall survival (OS).

Results: The three cohorts had no difference in median age, menopausal status nor stage at diagnosis. Pts in LUM-TN cohort had a higher frequency of invasive lobular (20% vs 10% vs 2%, p=.03), primary ER-low BCs (22% vs 0% vs 0%, p<.001) and locoregional relapse (18% vs 0% vs 2%, p<.001) than pts in the LUM-LUM and TN-TN cohorts. Metastatic samples from pts in LUM-TN and LUM-LUM cohorts were more frequently HER2-low than those in TN-TN cohort (57% vs 66% vs 24%, p<.001). At univariate analysis, pts with LUM-TN switch had a longer DMFS compared to the TN-TN (median DMFS 62 vs 18 months; HR 3.35, 95%CI 2.2-5.1, p<.001), but similar to the LUM-LUM cohort (median DMFS 62 vs 64 months; HR 0.95, 95%CI 0.6-1.41, p<.8). The DMFS difference was not significant after adjusting for other variables, including grade and ER-low status. Median OS was significantly lower for pts in LUM-TN (median OS 93 vs 139 months; HR 2.3, 95%CI 1.3-4.1, p<0.004) and TN-TN cohorts (median OS 47 vs 139 months; HR 3.4, 95%CI 1.1-10.7, p<0.03) when compared to the LUM-LUM cohort, independently from other clinicopathologic features.

Conclusions: HR loss at metastatic relapse is frequent in lobular and ER-low primary BCs. Pts with HR loss have similar DMFS compared to pts with maintained HR expression, but apparently reduced OS. Further investigation on biological mechanisms underpinning the LUM-TN phenotype switch is ongoing.

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321P Non-BRCA variants in hereditary breast and ovarian cancer patients in the northern Mexico population

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Background: Hereditary cancer syndromes explain 5-10% of all cancer cases. Germline pathogenic variants in BRCA1 and BRCA2 genes (BRCA) are present in 2-3% of all breast cancer (BC), and 15% of all ovarian cancer (OC) cases. BRCA1 and BRCA2 pathogenic variants (PV) represent 25-28% of BC and 40% of OC patients with a positive familial history. BRCAs are the most studied genes for the prevalence, family history, preventive surgeries, and target treatment options in both BC and OC. There are other genes, important in the diagnosis, pathogenesis, and treatment options of the patients: TP53, PALB2, CHEK2, among others. This study aims to identify the prevalence of non-BRCA genes related to the development of hereditary breast and ovarian cancer syndrome in patients of Northeast Mexico.

Methods: This is a multicenter study that recruited patients from two reference oncology centers in Nuevo Leon, Mexico: the CECIL (The CUCC Early Cancer Detection Clinic) Hereditary Cancer Registry and Hereditary Cancer Program from Tec Salud. From March of 2016 to March of 2023, a total of 872 patients meeting NCCN criteria were evaluated by Medical Geneticists from both centers and were tested with NGS multigene cancer panels.

Results: A total of 665 (76.26%) patients with a clinical diagnosis of HBOC (Hereditary Breast Hereditary Cancer Syndrome) were included. We found 310 (46.6%) patients had at least one variant, 180 (58%) with at least one pathogenic variant, and 130 (41%) with a VUS (a variant of uncertain significance). BRCA1 was found in 79 (43.8%) and BRCA2 in 32 (17.7%) of all PV. Non-BRCA PV were found in 69 (38.3%) patients: 4 ATM, 2 BLM, 3 BRIP1, 22 CHEK2, 4 CDKN2A, 5 MUTYH, 10 PALB2, 4 RAD51C, 2 SDHA, 2 TP53, 2 WRN, CDH1, CDK4, DICER, MSH3, NBN, PTEN, RAD50, USH2A one of each. Is remarkable that 19 of the 22 patients with CHEK2 and 5 of the 10 patients with PALB2 had the recurrent PV c.707T>C and c.2167_2168del, respectively.

Conclusions: Non-BRCA PV in Northern Mexico correspond to one-third of the BC and OC cases, including HRD (homologous recombination deficiency) genes. HDR patient carriers are potential targets of iPARP therapies. This project reinforces the fact that multigene panels should be employed to ensure a complete diagnosis in hereditary cancer patients.

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322P Clinicopathological characteristics and genomic profiling of pure mucinous breast cancer

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Background: Pure mucinous breast cancer (PMC) is a rarely seen histological type with favorable prognosis. Nevertheless, cases with recurrence have been reported and diagnosed in clinical practice. The recurrent patterns and mechanisms of PMC are unknown. Thus, in this study, we aim to discover the prognostic factors of PMC and reveal the genomic profiling of PMC with positive lymph nodes.

Methods: A total of 166 cases diagnosed as PMC were included. We compared the clinicopathologic characteristics across different groups using Mann-Whitney U test or chi square test according to variables. 21-gene assay was done in 10 patients with recurrence and 20 TNM staging-matched patients. Whole-exon sequencing was done in 12 PMC primary tumor and 4 positive lymph nodes. We compared the genomic alterations between two groups in single nucleotide polymorphism, copy number variation and enriched pathways.

Results: The median age at diagnosis was 45 years old in total 166 patients. After median follow-up of 84 months, 21/166 patients developed recurrence with/without distant metastasis. The significant different factors between patients with recurrence and without recurrence were tumor size, lymph node status and TNM staging. 21-gene recurrence scores were not statistically significant between two groups. Whole-exon sequencing showed that lymph node-positive(LNP) PMC primary tumors were more recurrently with mutations of ADCY10 (3/6) and SHANK3 (3/6), while lymph node-negative(LNN) PMC did not harbor these genes. Moreover, LNP group

prevalently harbored gains of 15q23, 17q23.2, 20p11.21 and loss of 21p11.2, while LNN group did not harbored any of these copy number variations. In terms of pathway enrichment, LNP group was involved in several pathways but LNN group was not enriched in any pathways.

Conclusions: Overall prognosis is good in PMC. TNM staging is an important prognostic factor of PMC. PMC with positive lymph node more recurrently harbored gains of 15q23,17q23.2, 20p11.21 and loss of 21p11.2. More researches, especially integration of multi-omics studies, are needed in revealing the underlying mechanism of lymph node metastasis in PMC.

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323P Macrophage population analysis of the breast cancer microenvironment within the context of seroma formation after mastectomy (SerMa pilot study)

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Background: The primary goal of the SerMa pilot study was to identify possible immunological/inflammatory factors related to seroma formation after mastectomy and first diagnosis of breast cancer. CD68 is a common marker for tumor-associated monocytes and macrophages in general. CD163 is used to detect M2-polarized macrophages. Both are known to have an influence on defense reactions and wound healing due to their immunomodulatory effect. Thus, the aim of this evaluation was to evaluate whether a correlation can be shown within the context of postoperative seroma formation.

Methods: From 100 patients meeting the criteria of the study, tumor tissue of 80 patients was available for evaluation. Immunohistochemical antibody staining against CD68 and CD163 was performed, and two groups were compared: Patients with and without seroma formation. The number of macrophages in the tumor microenvironment was manually quantified at three sites representative of each specimen in the entire field of view at a magnification of 40x lens. The mean value of the three areas was used for further analysis.

Results: For CD68, the range of the mean value was from 0 to 354 macrophages. The number of CD68-positive macrophages was significantly increased (p=0.036) in patients with seroma development (mean=45.31) compared to those without (mean=34.31). For CD163, the range extends from 0 to 309 macrophages. Again, the number of CD163-positive macrophages was significantly increased (p=0.027) in patients with postoperative seroma formation (mean=45.57) compared to patients without (mean=33.99).

Conclusions: These data demonstrate a significant correlation of CD68 and CD163 positive macrophages in the tumor microenvironment and seroma formation in the breast after mastectomy. This study was the first to investigate these possible relationships. As highly associated with immunological processes, the significant higher detection of CD68 and CD163 within the population of "Seroma developers" supports our study group's previously published results on the identification of immunological markers in seroma fluid and thus the hypothesized relationship of seroma formation based on immunological/inflammatory processes.

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324P Nodal underestimation rate in early-stage ER+/HER2- breast cancer patients with limited positive sentinel lymph nodes in the era of precise medicine: A real-world multicenter analysis from 40 institutions in China

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Background: Emerging data show more estrogen receptor-positive/ human epidermal growth factor receptor 2-negative (ER+/HER2-) early breast cancer patients with 1-3 positive sentinel lymph nodes (SLNs) omitted axillary lymph node dissection (ALND) but received adjuvant radiation therapy, which led to equivalent locoregional and distant disease control. In this study, we aimed to evaluate whether sentinel lymph node biopsy (SLNB) only can provide accurate lymph node staging to select candidates for multigene assay testing and adjuvant CDK4/6 inhibitor treatment in ER+/HER2- breast cancer patients with 1-3 positive SLNs.

Methods: Consecutive patients with cT1-3N0, ER+/HER2- disease, and 1-3 positive SLNs were retrospectively included from the multicenter Shanghai Jiao Tong University-Breast Cancer Database. The nodal underestimation rate (NUR) was calculated in patients receiving SLNB+ALND in the overall population and in potential candidates for multigene assays and CDK4/6 inhibitors according to the RxPONDER, MINDACT, and monarchE trials.

Results: Among the 3672 patients included, 24.1% received SLNB only. The overall NUR was 9.5%. For those who met the inclusion criteria for the RxPONDER, MINDACT, and monarchE trials, positive non-SLNs were found in 3.0%, 3.5%, and 3.7% of the patients, respectively. The low NUR was not influenced by breast surgery modality. Additional ALND upon SLNB brought no survival benefit for eligible patients of these trials (RFI P=0.090; OS P=0.772).

Conclusions: ALND can be safely omitted in cT1-3N0, ER+/HER2- breast cancer patients with 1-3 positive SLNs when selecting candidates for multigene assays testing and adjuvant CDK4/6 inhibitor treatment.

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325P Impact of breast tumour location on axillary nodal involvement, chemotherapy use, and survival

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Background: Axillary level I-II node (ALN) status is used to stratify breast cancer risk and inform systemic therapy decisions. We sought to investigate the association of breast tumour location with ALN involvement, use of chemotherapy, and breast cancer-specific survival (BCSS).

Methods: Patients diagnosed with stage T1-2 M0 breast cancer from 2004 to 2019 were identified from the SEER 17 registries database. Tumour locations were classified as outer quadrant, inner quadrant, or central. Covariates were age, race, median household income, year of diagnosis, tumour size, histology, grade, and ER/PR/HER2 status. Propensity score weighting with Bayesian additive regression trees was used to balance covariates between tumour locations. Doubly robust estimation was then performed with multivariable logistic and Cox regressions to assess the association of tumour location with binary outcomes and BCSS, respectively.

Results: A total of 453,387 patients with a median follow-up of 70 months were eligible for analysis, of whom 293,070 (65%) had outer quadrant tumours, 127,237 (28%) had inner quadrant tumours, and 33,560 (7%) had central tumours. After propensity score weighting, the rates of ALN metastases for outer quadrant, inner quadrant, and central tumours were 28.2%, 20.2%, and 32.6%, respectively. Chemotherapy was given to 38.0%, 36.5%, and 38.8% of patients. Ten-year BCSS were 91.6%, 91.0%, and 90.5%. Compared to outer quadrant tumours, inner quadrant tumours had lower odds of ALN metastases (OR 0.62; 95% CI 0.61-0.63; P<0.001) and central tumours had higher odds (OR 1.30; 95% CI 1.26-1.33; P<0.001). Similarly, inner quadrant tumours had lower odds of receiving chemotherapy (OR 0.90; 95% CI 0.88-0.91; P<0.001) while central tumours had higher odds (OR 1.07; 95% CI 1.04-1.10; P<0.001). BCSS was worse in both inner quadrant (HR 1.07; 95% CI 1.04-1.10; P<0.001) and central (HR 1.10; 95% CI 1.04-1.15; P<0.001) tumours.

Conclusions: The risk of ALN metastases from breast cancer varies with tumour location. Inner quadrant tumours have worse BCSS than outer quadrant tumours despite a lower risk of ALN metastases. Reliance on ALN staging without consideration

of tumour location may lead to treatment decisions that are inconsistent with breast cancer risk.

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326P Sentinel lymph node mapping in breast cancer: Evaluating the dual-tracer method with indocyanine green and radioisotope

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Background: Indocyanine green (ICG) has the potential to improve sentinel lymph node (SLN) mapping. This current cohort study was designed to assess the value of ICG using a new ICG handheld system with radioisotope (RI) in patients with early breast cancer undergoing SLN biopsy.

Methods: A prospective self-controlled trial compared the detection efficacies of ICG and RI was conducted. Concordance (ICG and RI-positive cases divided by RI-positive cases) and reverse concordance (ICG and RI-positive cases divided by ICG-positive cases) were documented and adverse event were also assessed.

Results: Of 69 patients (median age 56.7 (range 33-85), median BMI 22.6 (range 17.0 − 44.5)) enrolled between 2019 and 2021, 71 SLN biopsies were performed. Sixty-one (85.9%) underwent upfront surgery, while ten (14.1%) were given neoadjuvant treatment. Thirty-four breast-conserving surgeries (BCS) (47.9%), 33 mastectomies (46.5%) and four cryotherapies (5.6%) were performed. No adverse event nor skin staining were reported. The SLN identification rate was 87.3% (62/71) for ICG and 95.8% (68/71) for RI (p=0.13). Dual tracer method resulted in 97.2% successful identification, significantly superior to ICG alone (p=0.04, OR 5.0, CI 1.0-24.1) and and was in line with the reported rate of 96.7% (94.3-99.1)[1] by blue dye and RI. Concordance and reverse concordance rates were 89.7% and 98.4%, respectively. A median of 2 lymph nodes was detected by both ICG (range 0 − 6) and IR (range 0 − 5) with no statistical difference (p=0.60). Of 10 cases with 13 metastatic nodes confirmed by histology, both ICG and RI achieved 100% concordance rates. Breast conserving treatments had a higher ICG failure rate compared to mastectomy (21.1% vs 3.0%, p=0.05, OR 8.5, CI 1.0-72.4). In addition, among three cases with prior surgery, two failed ICG SLN identification. Meanwhile, age, BMI, tumour location, multifocality, neoadjuvant treatment, and ICG volume showed no significant correlation with ICG detection rate.

Conclusions: The combined use of ICG and RI ensures adequate SLN identification without problems known with the use of blue dye, such as skin staining and anaphylaxis. A higher failure rate was noted in patients with breast-conserving treatments for ICG tracing.

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327P Defining ≥10% radioisotope-hot stained nodes as sentinel lymph nodes by "blue dye + radioisotope" dual-tracer method for sentinel lymph node biopsy leads to the overdetection and excessive excision

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Background: Sentinel lymph node biopsy (SLNB) has been widely used to assess axillary staging. In clinical practice, it is crucial to define sentinel lymph node (SLN) and determine whether the detected nodes are SLNs during the process of SLNB. It is important to consider whether currently existing consensus on SLNB method which is dual-tracer technique may lead to the excessive and unnecessary removal of negative nodes. In addition, no uniform measurable and objective index has been established to define intra-operation palpable nodes, the excision of which may increase the random detection of SLN. The purpose of this study was to optimize the specific method of SLNB.

Methods: To propose an optimal cut-off value for "radioisotope+bule dye" dual-tracer method, the detailed information of (BC) patients who had no clinical node involvement and underwent SLNB from November 2010 to February 2021 was prospectively collected in the breast surgery department of West China Hospital. We analyzed the site and size, radioactivity, the status of blue dye and the pathological results of each node detected of each patients.

Results: A total of 4985 lymph nodes from 1595 BC patients were identified. Only 11.57% (577/4985) SLNs were defined as pathologically positive, resulting in 88.43% (4408/4985) negative nodes removed excessively. By gradually increasing the threshold of radioisotope count in comparison to the hottest SLN, we found that when elevating the cut-off value from 10% to approximately 60%, 17.3% of lymph nodes were spared removal, among which only 0.88% were missed positive SLNs. Raising the optimal cutoff value of radioisotopes to 60% and exempting palpable nodes at the same time could reduce the number of nodes detected by 30.81% with only 1.75% missed positive SLNs. Additionally, multivariate analysis in our study showed that larger tumor size and higher clinical N stage was significantly positively associated with SLN metastasis.

Conclusions: Raising the optimal cut-off value of radioisotope to 60% and exempting palpable nodes may be considered as a potential alternative method to avoid removing excessive negative nodes in SLNB.

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328P Frequency of radiotherapy-induced malignancies in Li-Fraumeni syndrome patients with early breast cancer and influence of the radiotherapy technique

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Background: Breast cancer (BC) is the most common malignancy in female patients (pts) with Li-Fraumeni Syndrome (LFS). These pts are at increased risk of other malignancies, including radiotherapy-induced malignancies (RIM) that are those occurring in a previously irradiated field. We aimed to evaluate the frequency of RIM and other oncologic outcomes of LFS pts with eBC.

Methods: We evaluated pts with a germline pathogenic/likely pathogenic variant of TP53 (LFS) diagnosed with eBC and followed by the Hereditary Cancer Team of a single cancer center between Dec/99 and Apr/23. The primary endpoint was the frequency of RIM among pts treated with adjuvant RT.

Results: Forty-nine pts were evaluated. Median age was 39 years (range 21 - 62); 79% were ER-positive; 35% HER2-positive; 35% stage I and 27% stage II; and 71% had TP53 R337H variant. Most pts (87%) were unaware of the LFS at the time of BC treatment. Regarding treatment, 62% underwent a mastectomy, 66% (neo)adjuvant chemotherapy, and 62% RT. The use of RT was more common after conservative surgery as expected (87% vs 46% with mastectomy, P=0.010). Oncologic outcomes are summarized in the table. Among 30 pts treated with RT, 4 (13.8%) developed RIM in the irradiated field (3 soft tissue malignancies and 1 BC). The occurrence of RIM was not influenced by RT dose ($\leq$ 40.8 or $>$ 40.8), but was influenced by the type of RT. RIM was observed in 100% with 2D RT (n=2/2), 100% (n=1/1) with volumetric modulated arc therapy (VMAT), 6% (n=1/16) with 3D RT, and 0% with intensity-modulated RT (n=0/1) (P=0.007).

Table: 328P

	Radiotherapy (n=30)	No radiotherapy (n=18)	P
Local recurrence	2 (6.7%)	1 (5.6%)	1.000
Distant recurrence	5 (16.7%)	1 (5.6%)	0.388
Contralateral BC	5 (16.7%)	2 (11.1%)	0.696
Second neoplasia	15 (50%)	5 (27.8%)	0.226
RIM	4 (13.8%)	-	-

Conclusions: Our study confirms an alarming rate of RIM after adjuvant RT, highlighting the need for a careful risk-benefit evaluation for the indication of RT, which should be preferentially avoided if possible. Despite the small numbers in each subgroup, the risk of RIM seemed to be influenced by the RT technique, with higher rates with 2D RT and VMAT. Early TP53 testing is crucial to guide the BC treatment plan.

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329P Pulmonary function and lung fibrosis up to 12 years after breast cancer radiotherapy

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Background: Breast cancer (BC) radiotherapy (RT) may induce lung damage ranging from radiological changes only to respiratory failure. The evidence of long-term radiation fibrosis (RF) and its impact on lung function and patients reported dyspnea is scarce. The aim of the present study was to evaluate lung function from before RT to up to 12 years after treatment and identify predictors for long-term RF and reduced lung function.

Methods: BC patients (n=250) referred to postoperative RT (2 Gy x 25) were enrolled in a prospective cohort study from February 2007 to October 2008. All assessments were conducted through clinical controls before RT (baseline), at 3, 6 and 12 months and at long-term follow- up ranging from 7-12 years after RT. Lung function was assessed by the pulmonary function tests (PFT) Vital capacity (VC), Forced Expiratory volume in 1second (FEV1), Forced Vital Capacity (FVC) and diffusion capacity for carbon monoxide (DLCO). RF was diagnosed by High Resolution Computer Tomography scans and graded in accordance with the CTCAE version 3.0 criteria. Patient reported dyspnea was assessed by the EORTC QLQ-C30.

Results: VC, FVC, FEV1 and DLCO declined at 3 months after RT and remained low at long-term follow-up except for DLCO which increased up to 12 years after RT. VC, FEV1, and FVC changes from baseline differed between patients treated with chemotherapy and those not treated with chemotherapy. FEV1 changes from baseline differed between locoregional and local radiated patients. A decline in VC, FEV1, and FVC 3 months after RT predicted a decline in PFT up to 12 years (p=0.020, p=0.004, and p=0.020, respectively). At long-term follow-up age was the only patient and treatment-related factor associated with RF (p=0.021). RF was observed in 144 patients (91%), of which 129 (81%) had fibrosis Grade 1 and 15 (9%) had fibrosis Grade 2. 61 (35%) patients reported dyspnea, mainly grade 1.

Conclusions: Pulmonary function deteriorated in the first year and up to 12 years after BC RT. An early decline in VC, FVC and FEV1 predicted further decline at long-term follow-up. RT. Chemotherapy and locoregional RT predicted a decrease in PFT in the first year and for up to 12 years after RT. Older age was associated with RF at long-term follow-up. Few patients reported severe dyspnea.

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330P Effect of radiotherapy in deep inspiration in patients with left breast cancer: Does the size of the target area affect the dose for the most crucial organs at risk?

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Background: After radiotherapy (RT) to the left breast, the long-term risk of developing various cardiovascular diseases may increase. In our study, we present how deep inspiration treatment changes the doses of organs at risk (OAR), especially the heart. Furthermore, we examined if there is a relationship between the size of the irradiated target area and the dose on the heart.

Methods: From May 2016 to August 2020, 503 patients with left-sided breast cancer underwent RT at our institute. Since May 2018, we have treated our patients in deep breathing (DIBH) using the "voluntary breath-hold" technique. We compared the D_{mean} and D_{max} values for the most critical OAR (left lung, heart, left ventricle, LAD-left anterior descending artery) based on the two treatment methodologies. Subsequently, both groups were then further subdivided into whether the treatment was given by standard fractionation or hypofractionation and created 3-3 groups based on the size of the target area (PTV).

Results: In patients treated with normal fractionation in DIBH vs. without, the doses of the OARs were the following: lung D_{mean}: 9.3 Gy vs. 9.96 Gy (p=0.029), left ventricle D_{mean}: 3.52 Gy vs. 7.56 Gy (p=2.69E-27), heart D_{mean}: 2.78 vs. 5.31 (p=1.11E-24), LAD D_{mean} 12.17 vs. 25.91 Gy (p=4.63E-24) respectively. In the hypofractionated group with vs. without DIBH the values were lung D_{mean}: 7.43 Gy vs. 8.08 Gy (p=0.17), left ventricle D_{mean}: 3.48 Gy vs 6.4 Gy (p=2.64E-10), heart D_{mean}: 2.64 vs 4.62 (p=2.96E-08), LAD D_{mean} 11.46 vs 18.35 Gy (p=3.37E-06) respectively. In the standard fractionated group, the average doses for each structure decreased mostly in women with large breast sizes after DIBH treatment. Generally, as the breast size increases, the values of the left ventricle, heart, and LAD increase, whilst the values of the lungs decrease. Although, a significant difference could only be detected in a few categories.

Conclusions: DIBH RT of the left breast significantly reduces radiation exposure to crucial OAR than free-breathing radiation therapy. At the same time, the coverage of the target area does not change, and our results suggest that this benefit is most pronounced in patients with large breast sizes.

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331P miR-21 and miR-34a as biomarkers of radiotherapy skin adverse events in ductal carcinoma in situ

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Background: Ductal carcinoma *in situ* (DCIS) is a non-invasive type of breast cancer treated with surgery and adjuvant radiotherapy (RT). RT improves local disease control, but also causes adverse effects. Molecular factors could contribute to interindividual variability in the incidence of skin adverse events after RT. Radiation exposure can affect expression of miRNAs, small non-coding RNAs involved in post-transcriptional regulation of gene expression. Our aim was to evaluate whether miR-21 and miR-34a expression changes after RT and if miRNA expression is associated with skin adverse events of RT in patients with DCIS.

Methods: Our prospective study included 119 patients with DCIS treated with adjuvant RT. Skin adverse events were assessed using Common Terminology Criteria for Adverse Events (CTCAE) v.5 immediately after RT and six months after RT. MiRNA was isolated from plasma before and after RT and quantitative PCR was used to determine miR-21 and miR-34a expression. Non-parametric tests and logistic regression were used in statistical analysis.

Results: Immediately after RT, 5.7% patients had grade 2 skin adverse events, while 26.1% patients experienced grade 2 adverse events after six months. More skin adverse events after six months were observed in smokers (p=0.036). After RT, the expression of miR-21 (p=0.001) and miR-34a (p<0.001) was significantly increased. Patients with a greater increase in miR-34a expression after RT were more likely to have a higher grade of skin adverse events immediately after RT, even after adjustment for clinical parameters (OR_{adj}=1.13; 95% CI_{adj}=1.02-1.26; p_{adj}=0.026). Similarly, greater increase in miR-34a expression was associated with more adverse events six months after RT, but the association was only significant adjustment for clinical parameters (OR_{adj}=1.13; 95% CI_{adj}=1.01-1.27; p_{adj}=0.035). Expression of miR-21 was not associated with skin adverse events.

Conclusions: Our results suggest that miR-21 and miR-34a expression increases after RT and miR-34a expression might serve as a biomarker of RT skin adverse events. Research grants: ARRS J3-1753, ARRS J3-2527, P1-0170 and P3-0321.

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332P Early prediction of residual cancer burden to neoadjuvant chemotherapy in breast cancer by longitudinal MRI-based multitask learning: A multicenter cohort study

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Background: Neoadjuvant chemotherapy (NAC) has been a standard treatment for locally advanced breast cancer (BC). However, the high heterogeneity of BC results in various tumor response. Therefore, there is a growing need for early assessment of tumor response, particularly for insensitive BC, to guide personalized treatment. We

aim to develop a longitudinal radiomics multitask model to accurately predict RCB score in the early stage of NAC for breast cancer.

Methods: A total of 1048 patients with breast cancer receiving NAC across four institutions were retrospectively enrolled. We collected longitudinal MRI sequences at the pre-NAC and mid-NAC timepoints, and extracted 21804 radiomics features per patient. We used a multitask learning strategy to predict RCB score (RCB 0-I, II and III). The Mann-Whitney U-test, Spearman analysis, the least absolute shrinkage and selection operator regression and Boruta method were used to perform feature selection. We developed various base machine learning models, followed by an ensemble stacking method to integrate the base model outputs. The multitask learning model was subsequently verified in three independent external validation cohorts.

Results: Of the total patients, 442 (42.18%) reached RCB 0-I, 462 (44.08%) reached RCB II and 144 (13.74%) reached RCB III. 17 and 19 significant features were selected for two independent tasks. For identifying RCB 0-I and RCB II-III, the multitask model reached an area under the curve (AUC) of 0.932 in primary cohort, and AUCs of 0.890, 0.919 and 0.911 in the external validation cohorts. It also identified RCB II and RCB III with an AUC of 0.916 in primary cohort, and AUCs of 0.870, 0.899 and 0.871 in external validation cohorts.

Conclusions: The longitudinal radiomics multitask learning model is a noninvasive tool to predict RCB score for breast cancer, and help clinical decision-making in the early stage of NAC.

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333P Evaluation of a composite PET/CT and HER2 tissue-based biomarker to predict response to neoadjuvant HER2-directed therapy in early breast cancer (TBCRC026)

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Background: Early metabolic change on FDG PET/CT was predictive of response to neoadjuvant trastuzumab/pertuzumab (HP) in TBCRC026, with high negative predictive value (NPV) suggesting a lack of decline in SULmax at cycle 1 day 15 (C1D15) best predicts those who will not achieve pathological complete response (pCR) with HP alone. We hypothesized that a composite biomarker incorporating both PET and HER2 tissue-based biomarkers could improve biomarker performance in this setting.

Methods: Patients with stage II-III ER-negative/HER2-positive breast cancer received neoadjuvant HP. PET/CT was performed at baseline and C1D15. Promising imaging biomarkers included $\geq$40% SULmax decline between baseline and C1D15, and C1D15 SULmax $\leq$3 (n=83 evaluable). Baseline tissue-based biomarkers included HER2-enriched intrinsic subtype (72%, 46/64 available; Nanostring [NS] BC360), log2 tumor HER2 protein abundance (median 13.5, range 7.1-15.9; NS GeoMxTM DSP), HER2 3+ (83%, 64/77; immunohistochemistry central review). Logistic regressions were used to construct prediction models for pCR with the composite HER2/PET biomarker. Overall discriminatory power of the predictive model was evaluated using the C statistic. Sensitivity and specificity were evaluated at the optimal cut-off point determined by maximizing Youden's index in the receiver operating characteristic (ROC) analysis.

Results: Factors most predictive for response (pCR 22%, PMID 33999652) in single predictor models included D15 SULmax (OR 0.43; p=0.007, c=0.77), % reduction in SULmax (OR 1.03, p=0.006, c=0.72) and tumor HER2 protein abundance (OR 1.75; p=0.01, c=0.76). The composite of D15 SULmax and % reduction in SULmax combined with their interaction term, had improved probability (c=0.89 from c=0.78), with high sensitivity (100%) and NPV (100%). The addition of tumor HER2 protein did not further improve prediction power (c=0.90).

Conclusions: The composite HER2/PET biomarker had high prediction power for pCR, however was not superior to the prediction power of PET/CT alone. These data suggest clinical trials informed by early FDG PET/CT biomarkers warrant further evaluation to personalize breast cancer care.

Clinical trial identification: NCT01937117.

Legal entity responsible for the study: Translational Breast Cancer Research Consortium.

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334P The contribution of nurses in early detection of breast cancer in Cameroon

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Background: Compared to global figures, breast cancer mortality to incidence ratio is worst in Sub Saharan Africa where about 80% of patients present with locally advanced and metastatic disease at diagnosis. In Cameroon, breast cancer is the commonest cancer with 4,170 cases recorded each year constituting 20.1% of all cancers diagnosed. Late disease presentation is attributed to poor awareness, absence of organized early detection programs, and inadequate facilities for accurate and timely diagnosis and treatment. Our objective was to investigate the role that nurses involved in cervical cancer screening/prevention can play in early detection of breast cancer in Cameroon.

Methods: The nurses involved in cervical cancer screening/prevention in a large faith-based healthcare organization called the Cameroon Baptist Convention Health Services (CBCHS) were trained to do clinical breast exams (CBE) for women aged 21 years and over, and also trained on breast tissue collection for pathology processing and examination. Clients with abnormal breast findings were provided Fine Needle Aspirations (FNA), TruCut biopsies or referred for ultrasound and/or mammography depending on the clinical presentation.

Results: Between January 2020 and December 2022, a total of 16,038 women age range (14-99) years were provided CBE with a mean and median age of 40.4 and 39, respectively. Among these, 750 (4.7%) had abnormal findings. Among those with

abnormal findings, 397(52.9%) had breast masses for which 213 (53.7%) had TruCut biopsies and FNA and the others were either referred or had previously established diagnosis. From the 213 Tru-Cut biopsies and FNA's done, 76 (35.7%) showed a pathology diagnosis of invasive breast cancer while the others showed: acute mastitis 3 (2.9%), fibroadenoma 25 (11.7%), benign mass 83 (39.0%), non-diagnostic 12 (5.6%) and other diagnosis 19 (8.9%).

Conclusions: Nurses can play a key role in early detection of breast cancer if they are trained, and this can greatly reduce the number of women seen with late stage disease and also reduce mortality rates.

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335P Real-world data: Correlation of radiological and pathologic complete response after neoadjuvant treatment of breast cancer

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Background: Neoadjuvant chemotherapy (NAC) of newly diagnosed breast cancer is used to improve resectability, reduce the extent of breast and axillary surgery and improve overall survival. Accurate assessment of locoregional response to NAC is important for surgical planning. Radiological method of choice is post-treatment breast magnetic resonance imaging (MRI), which determines the rate of response according to RECIST criteria. The primary indicator of outcome of NAC is pathologic complete response (pCR). This study aimed to compare radiologic and pathologic complete response rates after neoadjuvant treatment of early breast cancer.

Methods: A retrospective study of 259 breast cancer cases who received NAC between 01.01.2020 and 31.12.2021 at University Hospital Centre Zagreb was conducted with prior Ethics Committee approval. Radiological and pathohistological characteristics of the tumor at the time of diagnosis and after neoadjuvant treatment were analyzed using the Hospital information system (BIS). Furthermore, post-neoadjuvant therapy MRI findings were correlated with the postoperative pathohistological findings. Sensitivity, specificity, accuracy, and positive predictive value of radiologic complete response (rCR) as a predictor of pCR were calculated.

Results: Complete data was available for 94.98% (246/259) of patients. In 62 (25.20%) patients, rCR was recorded, radiologic partial response (rPR) in 150 (60.98%), stable disease in 22 (8.94%), and progressive disease in 9 patients. In 78 (31.71%) patients pCR was achieved, 46 (58.97%) were also classified as rCR, while 32 (41.03%) of those showed a radiological stable disease or rPR. Out of the 62 patients with rCR, 16 (25.81%) did not achieve pCR. The sensitivity and specificity of rCR were 90.48% and 58.97%, respectively, while positive predictive value was 82.61%. The overall accuracy of breast MRI in predicting pCR was 80.49%.

Conclusions: Although the sensitivity of breast MRI in predicting pCR was high, the specificity was low with only moderate overall accuracy. Low specificity can lead to an incorrect choice of breast surgery, therefore a better method of evaluation is necessary.

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336P Dual-mode near-infrared multispectral imaging system equipped with deep learning models improves the identification of cancer foci in breast cancer specimens

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Background: For surgically resected breast cancer samples, it is challenging to perform specimen sampling by visual inspection, especially when the tumor bed shrinks after neoadjuvant therapy in breast cancer.

Methods: We developed a dual-mode near-infrared multispectral imaging system (DNMIS) to obtain richer sample tissue information by acquiring reflection and transmission images covering visible to NIR-II spectrum range (400—1700 nm). Additionally, artificial intelligence (AI) was used to segment the rich multispectral data. 80 breast cancer samples were collected to verify the advantage of DNMIS in assisting pathologists to identify tumor beds.

Results: DNMIS demonstrated better tissue contrast and eliminated the interference of surgical inks on the breast tissue surface, helping pathologists find the tumor area which is easy to be overlooked with visual inspection. Statistically, AI-powered DNMIS provided a higher tumor sensitivity (95.9% vs visual inspection 88.4% and X-rays 92.8%), especially for breast samples after neoadjuvant therapy (90.3% vs visual inspection 68.6% and X-rays 81.8%).

Conclusions: We infer that DNMIS can improve the breast tumor specimen sampling work by helping pathologists avoid missing out tumor foci.

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337P Comparison of fused diffusion-weighted imaging using unenhanced MRI and abbreviated post-contrast-enhanced MRI in patients with breast cancer

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Background: To determine the percentage of breast cancers detectable by fused diffusion-weighted imaging (DWI) using unenhanced magnetic resonance imaging (MRI) and abbreviated post-contrast-enhanced MRI.

Methods: Between October 2016 and October 2017, 194 consecutive women (mean age, 54.2 years; age range, 28-82 years) with newly diagnosed unilateral breast cancer who underwent preoperative 3.0 T breast MRI with DWI were evaluated. Both fused DWI and abbreviated MRI images were independently reviewed by two radiologists for the detection of index cancer (which showed the most suspicious findings in both breasts), location, lesion conspicuity, lesion type, and lesion size. Moreover, the relationship between cancer detection and histopathological results of surgical specimens were evaluated.

Results: Index cancer detection rates were comparable between fused DWI and abbreviated MRI (radiologist 1: 174/194 [89.7%] vs. 184/194 [94.8%], respectively, $P = 0.057$; radiologist 2: 174/194 [89.7%] vs. 183/194 [94.3%], respectively, $P = 0.092$). In both radiologists, abbreviated MRI showed a significantly higher lesion conspicuity than fused DWI (radiologist 1: 9.37 ± 2.24 vs. 8.78 ± 3.03, $P < 0.001$; radiologist 2: 9.16 ± 2.32 vs. 8.39 ± 2.93, $P < 0.001$). The κ value for the interobserver agreement of index cancer detection was 0.67 on fused DWI and 0.85 on abbreviated MRI. For lesion conspicuity, the intraclass correlation coefficients were 0.72 and 0.82 on fused DWI and abbreviated MRI, respectively. Among the histopathological factors, tumor invasiveness was associated with cancer detection on both fused DWI ($P = 0.011$) and abbreviated MRI ($P = 0.004$, radiologist 1), lymphovascular invasion was associated with cancer detection on abbreviated MRI ($P = 0.032$, radiologist 1), and necrosis was associated with cancer detection on fused DWI ($P = 0.031$, radiologist 2).

Conclusions: Index cancer detection was comparable between fused DWI and abbreviated MRI, although abbreviated MRI showed a significantly better lesion conspicuity.

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338P Breast cancer follow-up: A population-based cohort study

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Background: Breast cancer (BC) survivorship guidelines recommend follow-up (F/U) with a schedule of physician visits and annual mammography. However, literature reflects an increasing reliance on advanced imaging. Our goal was to analyze BC F/U practice with its roots and effects at a population level.

Methods: We included women ≥18 years with early BC undergoing surgery between 2012-2014. We accessed the data warehouse of Lombardy Region in Italy. After calculating the annual frequency of each imaging *per* patient, we included the derived covariates in unsupervised clustering to set three statistically different groups with increasing F/U intensity, ie minimal, moderate and maximal. We used the Kaplan-Meier method for overall survival (OS) estimates and the Cox model for multivariable analysis.

Results: Overall 28,775 women entered the study, median age was 61 years (IQR 49-72), median time since diagnosis 87.6 months (IQR 77.7-97.9), 69.7% had breast-

conservative surgery. Of the 862,955 exams prescribed in the 5 years after surgery, 12.8% were mammograms. Ultrasound (64.7%) was the most common non recommended imaging, followed by computed tomography (11.7%), magnetic resonance (6.2%), and bone scan (4.6%). Intensive F/U was more likely after triple negative (30.1%) and HER2 positive (27.8%) than luminal-like BC (13.1%). Surveillance intensity decreased over time, resulting in 56% of BC survivors having minimal F/U from the third year after surgery onwords. At a 12 month landmark analysis, OS was 80.8%, 87.4% and 66.2% in women having minimal, medium, and maximal intensive F/U. The survival benefit of medium intensive F/U was significant in luminal-like; whereas, the negative effect of maximal intensive F/U extended to all subtypes and was independent of age, surgery, adjuvant and radiotherapy (HR 2.16, 1.99-2.36).

Conclusions: Use of non recommended imaging is common after BC surgery and increases with increasing risk of relapse. Due to the retrospective nature of our study, survival findings are only hypotheses generating. While intensive F/U possibly included women with poor prognostic factors not accounted for by the adjustment, medium intensive F/U might have allowed for timely/curative intervention of recurrent BC. Data overall offers an opportunity to discuss current F/U strategies.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori.

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Disclosure: S. Di Cosimo: Financial Interests, Personal, Other, Ad hoc project/protocol reviewer: MEDSIR; Financial Interests, Personal, Advisory Board, Treatment of HER2-positive breast cancer: Pier Fabre; Financial Interests, Personal, Other, Medical meeting material setup and distribution; Speaker Bureau: IQVIA. All other authors have declared no conflicts of interest.

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339P An online mindfulness-based stress-reduction (MBSR) intervention for breast cancer (BC) survivors: A randomized trial

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Background: Recent literature has proposed MBSR as an intervention that can decrease symptom burden in oncologic patients. However, there is paucity of data on the effect of online-delivered interventions despite the potential of this modality to improve access and adherence to treatment. The aim of this study was to study the effects of an online MBSR intervention on BC survivors.

Methods: Women aged $\geq$18 years, diagnosed with stage 0-III BC at least 1 year prior to inclusion and not undergoing active treatment were invited to participate. Those with mild anxiety were randomized to an online MBSR intervention or waitlist (WL). The MBSR intervention consisted of 8 weekly sessions of meditation guided by a certified instructor. Measured outcomes included anxiety (GAD-7), depression (PHQ-9), worry about disease recurrence (CWS), fatigue (FACIT-F), insomnia (ISI), and vasomotor symptoms (MENQOL). Assessments were done at baseline, 2 months, 5 months, and 8 months.

Results: A total of 97 patients with a median age of 45 years (IQR: 40-51) and a median of 24 months (IQR: 15-36) after diagnosis were included. 66 were randomized to MBSR and 31 to WL. Most participants were married (54%), had public health insurance (49%), and were diagnosed with stage III (33%) or II (32%) BC. Linear mixed models controlling for health insurance, education, and stage showed that MSBR led to significant reductions in anxiety (GAD-7 -3.76, $p<0.01$), depression (PHQ-9 -4.17 points, $p<0.01$), cancer worry (CWS -2.59 points, $p<0.05$), fatigue (FACIT-F -4.15 points, $p<0.05$), and insomnia (ISI -4.10 points, $p<0.01$) at the 8 months follow-up, but not vasomotor symptoms (MENQOL score +0.51 points, $p=0.42$). Adjusted mean scores are shown in the Table.

Table: 339P

Questionnaire	Group	Baseline	8 months
GAD-7	MSBR	10.3	5.6
	WL	11.1	9.4
PHQ-9	MSBR	11.3	6.1
	WL	12.8	10.3
FACIT-F	MSBR	13.7	8.5
	WL	14.9	12.7
CWS	MSBR	14.4	11.0
	WL	14.0	13.6
ISI	MSBR	13.9	8.2
	WL	13.1	12.3
MENQOL	MSBR	4.4	3.1
	WL	3.9	2.6

Conclusions: An online MBSR intervention demonstrated a statistically significant and persistent reduction in anxiety and depression symptoms in BC survivors. This modality offers BC patients better access to interventions with the potential to improve their quality of life.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: J. Gutiérrez-Ornelas: Financial Interests, Personal, Financially compensated role, Director: Centro Mindfulness Monterrey. A. Platas: Non-Financial Interests, Personal, Member of Board of Directors: MILC - Médicos e Investigadores en la Lucha contra el Cáncer de Mama. H.C. Verduzco-Aguirre: Financial Interests, Personal, Other, Research honoraria: Celulicity; Financial Interests, Personal, Other, Travel grants: Asofarma, AstraZeneca. C.M. Villarreal Garza: Financial Interests, Personal, Invited Speaker: MSD Oncology, Novartis, Pfizer, AstraZeneca Mexico, Lilly; Financial Interests, Personal, Research Grant: Pfizer; Financial Interests, Personal, Advisory Board: Lilly, AstraZeneca Mexico, MSD Oncology; Non-Financial Interests, Personal, Member of Board of Directors: MILC - Médicos e Investigadores en la Lucha contra el Cáncer de Mama. All other authors have declared no conflicts of interest.

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340P Novel application of spatial analyses to investigate environmental factors and hormone receptor-positive breast cancer

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Background: Incidence of hormone receptor-positive (HR+) breast cancer (BC) is increasing. With environmental factors associated with HR+ tumors, we used spatial analysis to identify regions with excess HR+ BC.

Methods: Surveillance data for 38,944 women with a primary diagnosis of BC with reported HR status during 2000-18 and no prior cancers were obtained from the Iowa Cancer Registry. HR+ tumors were defined as those that were estrogen receptor-positive or progesterone receptor-positive. Spatial patterns in HR+ BC/1,000 women and as a proportion of all women with BC with known HR status were examined by county (n=99) for premenopausal aged (15-49 years; n=7,935) and post-menopausal aged ($\geq$50 years; n=31,009) women; proportions were analyzed using logistic regression with spatial correlation via intrinsic conditional auto-regressive models at the county level and general additive models (GAMs) at the residence level (premenopausal, n=7,930; postmenopausal, n=30,988).

Results: HR status was classified for 38,944 women (premenopausal: 6,188 HR+, 1,747 HR-; postmenopausal: 26,190 HR+, 4,819 HR-). Across all counties, rates of HR+ BC ranged from 4.9-17.1/1,000 premenopausal women, representing 57.6-96.8% of BC cases among these women and a state average of 78.0%. Respective values were 29.3-61.1/1,000 postmenopausal women, 75.6-92.6%, and 84.5%. The top 21 counties with the highest estimated proportions of HR+ BC after spatial smoothing within each age group represented 25.3% of all premenopausal women and 21.2% of all postmenopausal women in Iowa. Twelve (57.1%) of these counties overlapped between age groups; two counties were elevated above the respective state averages for both age groups, with 95% probability. GAMs indicated similar areas of increased probability of HR+ BC.

Conclusions: Findings suggest some spatial overlap in proportions of incident HR+ BC between pre- and postmenopausal women. This overlap may indicate shared environmental risk factors for HR+ BC between age groups in these regions. Our analytical approach provides a model that can be applied across broader geographic regions. Future analyses will explore temporal differences in these incident cancers.

Legal entity responsible for the study: University of Iowa.

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Disclosure: A. Thomas: Financial Interests, Personal, Advisory Board, One time Ad Board: AstraZeneca, Genentech; Financial Interests, Personal, Stocks/Shares: Pfizer, Bristol Myers Squibb, Gilead Sciences, Johnson and Johnson, Doximity; Financial Interests, Personal, Royalties, Husband: UpToDate; Financial Interests, Institutional, Local PI: Sanofi, Merck. All other authors have declared no conflicts of interest.

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341P Impact of environmental temperature on clinical outcomes of early-stage breast cancer (BC)

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Background: Preclinical evidence using mouse model suggests that thermal/cold stress increases tumor growth by modulating the tumor microenvironment; however, the clinical relevance of temperature on BC outcomes is unknown. Studies show that residing in cold regions is associated with higher incidence of BC. We aim to study the impact of environmental temperature on the pathological complete response (pCR) and survival of early-stage BC patients (pts).

Methods: A multi-institutional study was conducted within the Oncology Research Information Exchange Network. We analyzed the clinical and genomic data for early-stage BC pts from 12 centers in the United States from different environment zones (5 warm (W) and 7 cold (C)) (based on average annual regional temperature obtained from National Centers for Environmental Information). Cox regression was used to measure the association of climate and overall/relapse-free survival (OS/RFS) after adjusting for confounders.

Results: Out of the 1,304 early-stage BC pts, 271 pts received neoadjuvant chemotherapy (NAC) (186 W, 85 C). Higher clinical T- and N-stages were observed in pts from W compared to C regions ($p<0.001$). Pts residing in C regions had more comorbidities (57.6% vs 48%, $p<0.001$). Pts in W regions had higher pCR, though not statistically significant (8% vs 2.5%, $p= 0.1$). The OS (univariate (UV) HR= 0.48, 95% CI 0.27-0.64, $p <0.001$; multivariate (MV) aHR= 0.56, 95% CI 0.32 - 0.96, $p= 0.03$) and RFS (UV HR= 0.51, 95% CI 0.38 - 0.68, $p<0.001$; MV aHR= 0.52, 95% CI 0.36 - 0.75, $p= 0.0005$) were higher in pts from W compared to C regions (Table). The OS (aHR= 0.35, $p= 0.02$) and RFS (aHR= 0.49, $p= 0.02$) of pts who received NACT were also higher in W regions.

Table: 341P

Regions (n)	5-yr OS (95% CI)	Median OS (months) (95% CI)	5-yr RFS (95% CI)	Median RFS (95% CI)	p-value
Cold (782)	83 (76-86) %	157.7 (116.6-NR)	69 (62-76) %	108.4 (88.9-147.8)	<0.001
Warm (522)	95 (92-97) %	214.7 (205.3-NR)	83 (79-87) %	250.4 (129.9-250.4)	

Conclusions: Early-stage BC pts living in cold have worse OS and RFS compared to warm regions. Larger studies are warranted to validate these interesting findings and further research focusing on therapeutic strategies to abrogate this outcome disparity by temperature is needed.

Legal entity responsible for the study: A.M. Roy.

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342P Fertility preservation in young breast cancer patients: Patient's knowledge and perception

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Background: This study aimed to assess breast cancer (BC) patients' knowledge and perception of fertility risks and preservation, and to determine factors that impact fertility preservation(FP) patient decision making.

Methods: We performed a cross-sectional study including 70 BC patients $\leq$ 45 year-old. Patients were surveyed using a 29 item questionnaire assessing their personal experience and knowledge about fertility risks and FP treatments. A knowledge score (0-12) was calculated with 1 point awarded for each correct answer. Statistical associations between socio-demographic characteristics, personal experience and knowledge score were analyzed.

Results: Mean age was 34 year-old. Thirty-seven patients had a college degree and 80% were married. Previous pregnancy/live birth were reported in 77%/72% of patients. Twenty-seven percent of patients had prior contact with infertility. Fifty-five patients were informed about infertility risks related to BC treatment. Only 62.8% of patients received information about FP treatments. Thirty-five patients were referred to FP consultation of whom 12 patients received FP treatments. Embryos/oocytes freezing were the main used options. The main reasons for skipping FP treatments were lack of pregnancy desire (38.6%) and insufficient provided information (30%). "Complexity of FP procedure" and "fear of delaying cancer treatment" were reported in 8.6% and 4.3% of cases respectively. Mean knowledge score was 6(3 -11). Forty-six percent of patients believed that "FP treatment is related to an increased risk of cancer recurrence". Only 61.4% of patients were aware that "freezed eggs remain available in the future whenever the patient is ready to use them". Most of the patients (81.4%) were aware that having a spouse was not a prerequisite for FP treatment. Knowledge about FP treatments availability and costs was poor with more than half of patients overestimating costs and assuming the lack of FP treatment options. Only 60% of patients were aware of an operational legal framework for FP in Tunisia.

Conclusions: This study showed that FP baseline knowledge in BC patients is generally poor. Patient's access to clear and concise fertility information is the key for effective interventions for fertility preservation.

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Disclosure: All authors have declared no conflicts of interest.

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343P Modulation of the immune system (ImS) during moderate physical activity (mPA) in breast cancer (BC) patients (pts) treated with neoadjuvant chemotherapy (NACT)

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Background: The link between mPA and ImS is known. We studied the effect of mPA on a panel of circulating cytokines (Cy) during NACT in BC pts.

Methods: Pts underwent epirubicin and cyclophosphamide, followed by weekly paclitaxel $\pm$ trastuzumab. Blood samples were collected in pts underwent mPA (TR, Nordic or fit walking, 3 workouts/week, 1 hour each in the 10-12 weeks before surgery) and in pts who declined mPA (UN) at T0, at day 1 of week 6 of paclitaxel (T1, starting point of mPA) and before surgery (T2). 22 Cy: IL1b, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL15, IL17a, IL18, IL21, CCL2, CCL4, CXCL10, CCL22, IFNγ, TGFβ, TNFα, VEGF were measured by Simple Plex Ella™. Differences between the median Cy values were analyzed with Mann-Whitney U test. Comparisons between time points within the same group were analyzed with Wilcoxon signed-rank test. ROC analysis was performed to highlight relevant variables for TR and UN. PCA and PERMANOVA evaluated the impact of mPA on Cy at T1 and T2.

Results: 91 pts have been accrued. 88 pts have been analysed, 68 TR and 20 UN. At T0 IL4 was higher ($p < 0.01$) in UN pts. At T1 IL4 and IL17 were higher ($p < 0.01$) in UN. At T2 higher values ($p < 0.01$) of IL4, IL7, IL17, VEGF in UN. Higher IL21 ($p < 0.01$) in TR. Longitudinal analysis (LA) between T0 and T1 in TR and UN showed increase of INF-γ, IL5, IL15, CCL2, CXCL10, IL17α. UN pts showed also increase of IL6. TR pts showed increase of IL7, IL18 and decrease of IL4, IL13, CCL22. LA between T1 and T2 showed increase of IL21, CCL22, TNFα and decrease of IL6, IL8, IL15 TGFβ in TR pts. UN showed increase of CXCL10 and decrease of IFNγ, IL6, IL8, CCL2, TGFβ. PCA discriminated TR from UN pts at T2 ($p=0.045$ PERMANOVA analysis).

Conclusions: TR and UN pts were similar at T0. LA between T0-T1 showed that CT induced prominent changes in TR suggesting a more plastic ImS. LA between T1-T2 showed significant changes of Cy only in TR supporting a role of mPA in the modulation of the ImS. Overall, CT induced weak changes in UN and more consistent changes in TR pts, suggesting a more efficient ImS and a possible additional effect derived from mPA in TR. PCA at T2 supports these hypotheses showing a significant grouping of TR clearly separate from UN.

Legal entity responsible for the study: O. Garrone.

Funding: Fondazione IRCCS Ca' Granda Ospedale maggiore Policlinico, Milan.

Disclosure: O. Garrone: Financial Interests, Personal, Advisory Board: Eisai, Daiichi Sankyo; Financial Interests, Personal, Speaker, Consultant, Advisor: Pfizer; Financial Interests, Personal, Invited Speaker: Novartis, Lilly. G. Tomasello: Financial Interests, Personal, Advisory Board: Novartis, Lilly, Amgen. All other authors have declared no conflicts of interest.

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344P Epidemiological analysis and overall survival of female breast cancer in a developing middle eastern country over 18 years

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Background: Breast cancer imposes a significant regional and global health burden not only due to being the most prevalent malignancy in females in the Middle East and worldwide, but due to the associated substantial morbidity and mortality. Therefore, the determination of the epidemiological features of breast cancer in the Middle East is of prominent interest given the significant resultant burden associated with breast cancer as it enables for the efficient introduction of effective interventions.

Methods: Data on 20,046 female patients of different nationalities and residing in Jordan diagnosed with breast cancer during the period of 2000-2018 were obtained from the Jordan Cancer Registry. Consequently, comprehensive statistical analysis was performed to establish the epidemiological characteristics of breast cancer in Jordan, including the overall survival and crude incidence.

Results: A total of 20,046 female patients with a mean age of 51.5 ± 12.5 years old were included in the analysis. Only 6.54% of the enrolled patients were smokers at the time of diagnosis. Breast cancer was more commonly affecting the left breast, 46.9% of the patients, than the right breast, 43.5% of the patients, whereas 1.18% of the patients had breast cancer bilaterally. The upper outer quadrant of the breast was the most commonly reported site of tumour location. Moderately differentiated carcinoma was the most commonly encountered grade in 31.4% of the patients, whereas 28.9% had poorly differentiated carcinoma. Regional spread to the lymph nodes was observed in 19.0% of the sample and 13.1% of the patients had distant metastasis, while localized breast cancer was noted in 16.6% of the patients. A statistically significant increase in the crude incidence of breast cancer in females has been observed in Jordan over the 18 years period with a crude incidence estimated effect of 0.46 (P-value<0.001). The overall survival rate was determined to be 95.8%, 83.2%, and 62.8% at 1-year, 3-year, and 5-year interval, respectively.

Conclusions: Breast cancer in Jordan imposes a significant burden due to the significant increase in the crude incidence over the 18-year period, and thus mandating vigorous and vigilant screening and preventative measures.

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345P The effect of early post-operative exercise on shoulder function in breast cancer patients: A randomised controlled trial

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Background: Breast cancer surgery can impair shoulder function, and the effects of rehabilitation exercise during early recovery remain uncertain. This study aims to assess the effectiveness of tailored exercise intervention on shoulder function recovery at one and six months post-surgery.

Methods: A total of 122 breast cancer patients (Stage 0-3) scheduled for surgery were evaluated, and 58 patients (mean age 50.2±6.6 years) were randomly assigned to an exercise or usual care group (1:1). The exercise group underwent five tailored exercise education sessions, starting one day before hospital discharge and continuing for four weeks after surgery. Participants received exercise diaries, online links, and QR codes for home-based workouts. The primary outcome measured the proportion of participants achieving 90% of their pre-surgery shoulder ROM and strength at one and six months post-surgery. Secondary measures included DASH and SPADI scores, physical activity levels, and body composition.

Results: Out of 58 participants, 56 (96.6%) completed the trial, with a 96.6% exercise compliance rate one month after surgery. In the exercise group, 92.9% and 96.2% achieved pre-surgery shoulder strength levels at one and six months post-surgery, respectively, compared to 3.7% and 32.1% in the control group. The exercise group also exhibited significantly lower shoulder pain and disability scores (SPADI) at one and six months after surgery, as well as higher physical activity levels at six months.

Table: 345P Change in shoulder strength among postoperative breast cancer patients

	Affected arm		
	EPET (n=25)	Usual Care (n=26)	*p*
Sum of strength (lb)			
T0	44.1±10.2	47.5±11.1	0.36
T1	23.2±10.3***	23.8±9.4***	0.80
T2	40.4±11.9	28.5±11.9***	**0.001**
T3	45.9±14.7	32.0±11.2***	**<0.001**
T4	51.3±14.0	32.0±9.2***	**<0.001**
T5	61.0±17.1***	38.3±8.4***	**<0.001**

Mean±SD, *P*=represented the results of independent T-test (the p-value adjusted for Bonferroni method (0.05/6=0.0083), *=represented paired t-test [**p<0.01 vs. baseline, ***p<0.001 vs. baseline (p-value adjusted for Bonferroni method)] Abbreviation: early postoperative exercise therapy; EPET

Conclusions: Early implementation of tailored exercise during rehabilitation significantly improved shoulder function beyond pre-surgery levels. This study provides essential insights into the efficacy and safety of early rehabilitation exercises for breast cancer patients during the post-surgery recovery phase.

Clinical trial identification: The Institutional Ethics Review Board of Severance Hospital and WHO International Clinical Trials Registry Platform (ICTRP; KCT0006997) approved the trial.

Legal entity responsible for the study: The authors.

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346P Quality of life (QoL) and toxicity in patients (pts) with hormone receptor-positive, HER2-negative early breast cancer (HR+, HER2− eBC) treated with adjuvant (adj) endocrine therapy (ET) in the CANcer TOxicities (CANTO) study

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Background: ET is the mainstay treatment (tx) for HR+ eBC but they have persistent side effects that negatively affect QoL, leading to early tx discontinuation and compromising outcomes. We describe the incidence of ET toxicity and its QoL impact in CANTO.

Methods: CANTO (NCT01993498) is a prospective, longitudinal cohort study enrolling pts with invasive (cT0-cT3, cN0-3, no metastases) BC from 26 French cancer centres. Pts with HR+, HER2− eBC treated with adj ET were followed for the first 3 years (yrs) after eBC diagnosis. Pt demographics, clinical data, adherence, symptoms and QoL were collected. Questionnaires were administered at baseline (BL), 3−6 months (mo; M0) after primary surgery, chemotherapy or radiotherapy completion (whichever came last), and 12 mo, 36 mo and 60 mo after M0. Descriptive analyses were conducted for frequency of symptoms and mean/median QoL questionnaires summary scores.

Results: Of the 5564 pts who met the inclusion criteria (median age: 57 yrs), 63% were post-menopausal and 52% had stage I eBC at diagnosis. The table shows QoL and toxicity data. Global and functioning QoL remained high at BL and during tx. BC-specific symptoms persisted during tx. Pain was the most prevalent toxicity in the first 3 yrs; prevalence of muscular and joint pain increased over time. Mean intensity of global, muscular and joint pain all remained high over the course of ET (median intensity: ∼6 [0−10 scale]). ET adherence was 81−93% over time; in the first 3 yrs, 23% switched ET and 7% discontinued adj ET; toxicity was the main reason cited.

Table: 346P

	BL	M0	12 mo	36 mo
Mean EORTC QLQ-C30	83	80	79	80
Global health status	68	68	66	66
Physical functioning	91	85	84	85
Role functioning	87	80	82	83
Emotional functioning	65	72	70	71
Cognitive functioning	82	79	77	78
Social functioning	91	83	85	86
Insomnia	43	41	43	42
Fatigue	28	36	35	34
Pain	15	28	30	29
Mean EORTC QLQ-BR23				
Body image	88	75	77	79
Future perspective	49	56	61	64
Sexual functioning	26	26	26	24
Breast symptoms	13	26	20	16
Systemic therapy side effects	11	20	19	18
Arm symptoms	9	21	19	17
Toxicity, %				
Global and back pain	-	71	74	72
Muscular and back	-	32	36	38
Joint and back	-	59	68	70

Conclusions: While global and functional QoL remained high in the first 3 yrs after eBC diagnosis, BC-specific symptoms slightly increased/persisted during ET. This study confirmed long-term toxicity of ET, particularly pain. Better management of symptoms and supportive interventional strategies are needed to further improve QoL in eBC.

Clinical trial identification: NCT01993498, first posted November 25, 2013.

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348P Long-term opioid use following treatment of localized breast cancer: A real-world analysis

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Background: Chemotherapy for early breast cancer (BC) increases the risk of chronic opioid use. Factors associated with new opioid use after (neo)adjuvant chemotherapy for BC are poorly understood.

Methods: We analyzed Elevance Health administrative claims and Cancer Care Quality Program data between 2017-2022. BC patients who underwent surgery and (neo)adjuvant chemotherapy were included. Patients that had claims for either opioids or for medications used to treat neuropathic pain before BC diagnosis were excluded. Long-term use was defined as opioid drug claims lasting at least 3 months within 1 year of follow-up. We explored factors associated with this outcome via logistic regressions, with additional stratification to adjuvant/neoadjuvant groups.

Results: Among 3,353 BC patients, 156 (4.56%) were prescribed long-term opioids during the first year following chemotherapy. Young age, advanced stage, mastectomy (vs. lumpectomy), and higher comorbidity score were associated with long-term opioid usage (Table). Of patients aged $\leq$ 45 (N=442), 8.6% had long-term opioid claims, while patients aged 65-75 (N=653), 2.45% had such claims. When analyzing specific comorbidities, significant associations with opioid use were found for chronic obstructive pulmonary disease (COPD), liver disease, and peptic ulcer in patients treated with neoadjuvant chemotherapy. Rheumatic disease and congestive heart failure were associated with opiod use in patients treated with adjuvant chemotherapy.

Table: 348P Factors associated with long term opioid use

	OR	Confidence interval	p value
Age	0.66	0.55-0.78	1.40E-06*
Lymph node +	1.51	1.02-2.24	4.13E-02
Social determinant index	1.07	0.91-1.26	4.17E-01
Charlson's comorbidity	1.4	1.21-1.64	1.29E-05*
Stage II (ref stage I)	2.16	1.33-3.52	1.93E-03*
Stage III (ref stage I)	1.35	0.72-2.54	3.52E-01
Mastectomy (ref lumpectomy)	2.41	1.52-3.81	1.77E-04*
Mastectomy and lumpctomy (ref lumpectomy)	5.72	3.33-9.8	2.34E-10*
Radiotherapy	0.64	0.43-0.96	2.87E-02*
Hormonal	0.71	0.5-1	5.27E-02
Anti HER2	0.91	0.63-1.31	6.09E-01
Immunotherapy	2.29	0.75-6.97	1.45E-01
Taxans	1.09	0.59-1.99	7.87E-01

Conclusions: This study offers valuable real-world insights into the prevalence and potential risk factors for chronic opioid use during the first year following chemotherapy for BC. Young age, mastectomy and higher comorbidity index were associated with chronic opiod use in this cohort.

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349P The influence of diabetes on taxane-induced neurotoxicity and quality of life in breast cancer patients

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Background: Peripheral neuropathy is one of the long-term complications of diabetes. In breast cancer diabetic patients, this condition can worsen neurotoxic symptoms induced by taxane-based therapy administration. Chemotherapy induced peripheral neuropathy (CIPN) and its influence on patient's quality of life (QoL) is evaluated through certified questionnaires (NCI-CTC, EORTC QLQ-CIPN20, FACT-TAXANE).

Methods: Data from stage I-III breast cancer patients treated with taxane-based therapy between 2018 and 2022 were retrospectively analyzed at the Medical Oncology of the University Hospital of Cagliari. 300 patients, median age 57 years (32-85), followed a schedule of PCT 80mg/m2 $\pm$ 30 weekly per maximum 12 administrations; 43 patients had diabetes (14,3%). Peripheral neuropathy was evaluated by the NCI-CTC scale at every drug administration. QLQ-CIPN20 and FACT-TAXANE questionnaires were collected at baseline, at 4 and 12 weeks of treatment. Kruskal-Wallis test was used to assess relation between neurotoxicity grade and QoL; ANOVA for repeated measures was used to test differences at different timing. Student's T-test was used to analyze differences in diabetic and non-diabetic population.

Results: Neurotoxicity influenced QoL, in both populations, at cycle IV ($p<0.001$) and cycle XII ($p=0.008$). Patients with grade 0, 1 and 2 neurotoxicity reported a QLQ-CIPN20 median score of 32, 34 and 43 at cycle IV respectively, and a median value of 27, 33 and 34 at cycle XII respectively. ANOVA test showed a significant worsening of QLQ-CIPN20 and FACT-TAXANE scores at 4 and 12 weeks vs. baseline ($p<0.001$ for both). Values of QLQ-CIPN20 remained significantly higher in comparison to baseline also at 3 ($p<0.001$), 6 ($p<0.001$) and 12 months ($p<0.001$) follow up. In diabetic population, scores were significantly higher ($p<0.05$) in all neurotoxicity questionnaires, but no difference in QoL was highlighted by FACT-TAXANE, compared to non diabetic patients.

Conclusions: The use of QLQ-CIPN20 and FACT-TAXANE questionnaires identified neurotoxicity onset and its correlation to QoL, yet at an initial phase of treatment. Diabetic patients presented more severe neurotoxicity, without influencing overall QoL.

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350P Quality of life data on sexual relations in early breast cancer patients

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Background: The diagnosis and treatment of breast cancer involves changes in personal, family, social, professional and sexual relationships. In this study we assessed sexual satisfaction in patients with early breast cancer using the validated SEXSAT-Q scale.

Methods: We used the SEXSAT-Q quality of life questionnaire in 60 patients diagnosed with early breast cancer at our centre. Six dimensions were studied: 1. Loss of sexual desire. 2. Alteration of body image. 3. Psychological coping. 4. Discomfort during sexual intercourse. 5. Satisfaction during sexual intercourse. 6. Satisfaction with breast reconstruction. Data were collected in Medical Oncology Department during March 2023.

Results: A sample of 60 patients was selected, aged 26-72 years old, with a median age of 52 years, who had undergone breast cancer surgery, 73.33% by conservative surgery. 20% were premenopausal, 10% were perimenopausal and 70% were menopausal. 35% were being treated with chemotherapy, 56.67% with hormonoterapy and 8.33% with anti-HER2. 78.33% had a stable partner and did not use contraception. 30% of patients were quite or very sad and depressed since starting treatment. 50% of patients believe that the treatment has worsened their body image. 75% reported that during treatment their sexual relations were not satisfactory. 61.67% believe that their sexual desire has decreased and 45% admit having more problems reaching orgasm since diagnosis.

Conclusions: Women with curable breast cancer it is important to know the impact of diagnosis and treatment on the sexual sphere. The SEXSAT-Q questionnaire is a validated scale capable of measuring the sexual satisfaction of our patients.

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351TiP EORTC BCG 1984 — NOBLE: Noeoadjuvant olaparib and durvalumab for patients with BRCA-associated triple-negative breast cancer

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Background: The standard of care for patients with early triple-negative breast cancer (TNBC) is neoadjuvant chemotherapy followed by surgery. Recently, immune checkpoints inhibitors (ICI) added to neoadjuvant chemotherapy have shown efficacy. Among TNBC, BRCA mutations and other homologous recombination deficiency (HRD) signals are relatively frequent. As opposed to other types of breast cancer, HRD TNBC show a high neoantigen load, a large number of tumour infiltrating lymphocytes (TILs), and a high PD-L1 expression. In BRCA/HRD breast cancer, PARP inhibitors (PARPi) exhibit a distinct anticancer activity. In addition, they show immunomodulatory effects by promoting PD-L1 expression and DNA damage, increasing neoantigen load. Chemotherapy-free regimens combining PARPi and ICI result in promising synergistic activity as shown in the metastatic setting, supporting investigation in the neoadjuvant setting.

Trial design: NOBLE is an EORTC phase 2, randomized, multicentre, open label, clinical trial. It includes a minimax Simon's two-stage design with an early feasibility step. Eligible patients must have early TNBC harbouring a tumoral (t)BRCA1/2 mutation, or another HRD signal based on methylation. Following central screening for tumoral BRCA/HRD (Institute Curie, 455 patients), 152 patients will be randomized between olaparib vs olaparib and durvalumab for 4 cycles of neoadjuvant treatment. Thereafter, patients will undergo surgery. All patients will be followed-up to 2 years (y) after surgery. The trial will be conducted in 3 steps (screening/randomization): Step 1 — Feasibility (60/20): to assess the central testing failure rate, the turn-around time for central testing and the prevalence of tBRCA/HRD; Step 2 (193/64) — Futility; and Step 3 (202/152) — Expansion of recruitment. The primary endpoint is the rate of pathologic complete response at the time of surgery, defined as ypT0/is ypN0. Secondary endpoints are response based on RECIST v1.1, surgery rate, 2-y event-free-survival, 2-y overall survival, safety, and quality of life. The study is expected to be activated in early autumn 2023 and the primary endpoint will be available approximately 5 years after the screening of the first patient.

Clinical trial identification: EudraCT 2022-003594-33. NCT05209529.

Legal entity responsible for the study: EORTC.

Funding: EORTC is the legal sponsor of the study. AstraZeneca provided an educational grant.

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352TiP Neoadjuvant chemo-immunotherapy plus/minus fasting-like approach in stage II-III triple-negative breast cancer patients: The phase II randomized BREAKFAST-2 trial

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Background: Despite remarkable improvements in early-stage Triple-Negative Breast Cancer (TNBC) treatment with neoadjuvant chemoimmunotherapy (CT-IO), a considerable proportion of TNBC patients (pts) still experience tumor relapse after surgery. Preclinical studies indicate that TNBC is exquisitely sensitive to fasting-like approaches (FLAs), and we have recently shown that cyclic FLA boosts systemic and intratumor immunity in cancer patients. We hypothesize that combining FLA with preoperative CT-IO can increase pathologic complete response (pCR) rates in pts with stage II-III TNBC.

Trial design: BREAKFAST-2 (NCT05763992) is an open-label, multicentric, randomized, phase 2 trial aimed at investigating the antitumor activity of experimental FLA in combination with standard preoperative CT-IO in pts with treatment-naïve, localized (T1c and N1-2, or T2-4 and N0-2) TNBC. Pts will be randomized in a 1:1 ratio to: a) control arm (standard CT-IO), consisting of 12 administrations of weekly paclitaxel + carboplatin concomitant with 4 triweekly cycles of Pembrolizumab, followed by 4 triweekly cycles of doxorubicin/epirubicin + cyclophosphamide + Pembrolizumab every three weeks; b) experimental arm, consisting of CT-IO + 5-day FLA every three weeks, up to 8 FLA cycles. Then pts will undergo surgery. Key eligibility criteria are: age of 18-75 years, ECOG PS 0-1, BMI > 19 kg/m^2, absence of malnutrition, diabetes, uncontrolled autoimmune disorders, or severe comorbidities. The primary study endpoint is pCR. Hypothesizing that the experimental treatment is able to increase the pCR rate from 65% (historical data with CT-IO alone) to 85%, and assuming an α error of 5% and a power of 85%, a total of 145 patients will be enrolled. Secondary endpoints include: safety and tolerability, compliance, Event-Free Survival (EFS) and Overall Survival (OS). We will combine plasma metabolomics and bulk/single cell RNA-seq analyses to explore the impact of the experimental treatment on systemic and intratumor immunometabolic pathways, as well as to assess the association between immunometabolic changes and clinical outcomes. The trial has started to enroll pts on May 2nd, 2023.

Clinical trial identification: NCT05763992.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan.

Funding: Giuliani Foundation — Fondazione Gianmaria e Sabrina Giuliani; Fondazione IRCCS Istituto Nazionale dei Tumori; AIRC.

Disclosure: C. Vernieri: Financial Interests, Personal, Advisory Board: Novartis, Pfizer, Lilly, Daiichi Sankyo, Lilly, Istituto Gentili; Financial Interests, Personal, Invited Speaker: Novartis; Financial Interests, Institutional, Research Grant: Roche. M.V. Dieci: Financial Interests, Personal, Invited Speaker: Eli Lilly, Exact sciences, Gilead, Seagen, Daiichi Sankyo, Novartis; Financial Interests, Personal, Advisory Board: Novartis, Eli Lilly, Seagen, Exact Science, Daiichi Sankyo, Gilead; Financial Interests, Personal, Other, Consultancy: Pfizer; Financial Interests, Personal, Other, Consultancy on educational project: Roche. M. Lambertini: Financial Interests, Personal, Advisory Board: Roche, AstraZeneca, Lilly, Novartis, Pfizer, Exact Sciences, MSD, Seagen, Gilead; Financial Interests, Personal, Invited Speaker: Takeda, Sandoz, Ipsen, Libbs, Knight, Daiichi Sankyo, Lilly, Pfizer, Novartis, Roche;

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353TiP Phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in breast cancer patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy, Flamingo-01

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Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. In a prospective, randomized, single-blinded, placebo-controlled, multicenter phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived, and was followed for more than 6 months ($p = 0.0338$). Immunotherapy elicited a potent response measured by skin tests and immunological assays. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events observed were considered related to the immunotherapy.

Trial design: This phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up. Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. The patient population is defined by these key eligibility criteria: 1) HER2/neu positive and HLA-A*02 and 2) Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy. The trial objectives are to: 1) Determine if GP2 therapy increases IBCFS, 2) Assess the safety profile of GP2, and 3) Monitor immunologic responses to treatment and assess relationship to efficacy and safety. The study has been initiated in the US with plans to open in Europe.

Clinical trial identification: NCT05232916.

Legal entity responsible for the study: Greenwich LifeSciences. Inc.

Funding: Greenwich LifeSciences, Inc.

Disclosure: S. Patel: Financial Interests, Personal, Ownership Interest: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Stocks/Shares: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Member of Board of Directors: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Officer: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Full or part-time Employment: Greenwich LifeSciences, Inc.. J. Thompson: Financial Interests, Personal, Ownership Interest: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Stocks/Shares: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Officer: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Full or part-time Employment: Greenwich LifeSciences, Inc.. M. Patel: Financial Interests, Personal, Ownership Interest: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Stocks/Shares: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Full or part-time Employment: Greenwich LifeSciences, Inc.. F.J. Daugherty: Financial Interests, Personal, Ownership Interest: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Stocks/Shares: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Member of Board of Directors: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Officer: Greenwich LifeSciences, Inc.; Financial Interests, Personal, Full or part-time Employment: Greenwich LifeSciences, Inc.. M. Rimawi: Other, Personal, Speaker's Bureau: Daiichi Sankyo, Genentech, Macrogenics, Seattle Genetics; Other, Personal, Other, Contracted Research: F. Hoffmann-La Roche Ltd., Pfizer; Other, Personal, Principal Investigator: Greenwich LifeSciences, Inc.

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354TiP A phase III randomised open-label study of extended adjuvant therapy with camizestrant vs standard endocrine therapy (ET) in patients with ER+/HER2− early breast cancer (BC) and an intermediate or high risk of recurrence (CAMBRIA-1)

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Background: Definitive locoregional (surgery ± radiotherapy) and standard adjuvant ET (± chemotherapy or cyclin-dependent kinase 4/6 inhibitor [CDK4/6i]) can achieve cure in many patients (pts) with ER+/HER2− early BC. Nevertheless, a significant proportion of pts with stage I—III disease will experience recurrence to metastatic, incurable disease (5- and 10-year cumulative incidences of recurrence of 8.3% and 14.0%, respectively). There is evidence that incorporating a more effective endocrine therapy after 2 years of standard adjuvant ET can result in clinical benefit for high-risk individuals. Camizestrant is a next-generation oral selective ER degrader and pure ER antagonist. In SERENA-2, camizestrant 75 mg and 150 mg significantly prolonged progression-free survival vs fulvestrant in postmenopausal women with ER+/HER2− advanced BC with disease recurrence or progression after ET. The CAMBRIA-1 study (NCT05774951) is evaluating the potential of extended adjuvant therapy with camizestrant to improve outcomes in pts with ER+/HER2− early BC with an intermediate or high risk of recurrence after definitive locoregional therapy and standard adjuvant ET.

Trial design: This phase 3 randomised, open-label study is enrolling women (pre- or postmenopausal) and men with ER+/HER2− (IHC 0/1+/2+/ISH−) early BC who have completed definitive locoregional therapy and standard adjuvant ET (± CDK4/6i) for ≥2 and ≤5 years (+ 3 months) without disease recurrence. Pts must be considered at intermediate or high risk of recurrence based on clinical, biological and genomic factors. Pts are randomised (1:1) to continue standard ET of the investigator's choice (tamoxifen or aromatase inhibitor ± LHRH agonist) or camizestrant ± LHRH agonist for up to 60 months. The primary endpoint is invasive BC-free survival (STEEP 2.0 criteria). Secondary endpoints include invasive disease-free survival and distant relapse-free survival (STEEP 2.0 criteria), overall survival, safety, and health-related quality of life. Approximately 4300 pts will be randomised; enrollment is ongoing.

Clinical trial identification: NCT05774951.

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Pharmaceuticals, K-Group Beta, Kind Pharmaceuticals, Loxo Oncology, Oncothyreon, Orum Therapeutics, Prelude Therapeutics, Profound Bio, Relay Therapeutics, Tolmar, Torque Therapeutics. S. Loibl: Financial Interests, Institutional, Advisory Board, Member: Amgen, AstraZeneca, BMS, Celgene, EirGenix, GSK, Lilly, Pierre Fabre, Roche, SeaGen, Abbvie, Sanofi, Gilead, Merck, Novartis, Relay Therapeutics; Financial Interests, Institutional, Invited Speaker: AstraZeneca, DSI, Novartis, Pfizer, Roche, Gilead, Seagen; Financial Interests, Institutional, Advisory Board: DSI, Pfizer, Olema; Financial Interests, Personal, Invited Speaker: Medscape; Financial Interests, Personal, Full or part-time Employment, CEO: GBG Forschungs GmbH; Financial Interests, Institutional, Invited Speaker, Ki67: VM Scope GmbH; Financial Interests, Institutional, Research Grant: AstraZeneca, Celgene, Novartis, Immunomedics/Gilead, Pfizer, Roche, Daiichi-Sankyo; Financial Interests, Institutional, Funding: AbbVie, Molecular Health; Financial Interests, Personal, Other, PIPenelope/Padma: Pfizer; Financial Interests, Personal, Other, SC PALOMA3: Pfizer; Financial Interests, Personal, Other, SC SOLAR1: Novartis; Financial Interests, Personal, Other, SC ASCENT: Immunomedics/Gilead; Financial Interests, Personal, Other, SC HERCLIMB: SeaGen; Financial Interests, Personal, Other, SC Katherine: Roche; Financial Interests, Personal, Other, SC Capitello; EC Cambria 1: AstraZeneca; Financial Interests, Personal, Other, SC Inavo: Roche; Financial Interests, Personal, Other, SC Destiny B05; SC Destiny B09: Daiichi Sankyo; Non-Financial Interests, Principal Investigator, After publication of primary endpoint: PI Aphinity; Non-Financial Interests, Advisory Role, Group in Germany responsible for breast cancer guidelines: AGO Kommission Mamma; Non-Financial Interests, Member, Member guideline committee; past chair in ESMO Breast: ESMO; Non-Financial Interests, Member, German Gynaecological Oncology society: AGO; Non-Financial Interests, , Member, German Cancer Society: DKG; Non-Financial Interests, Member: ASCO; Other, Other, EP14153692.0No financial interest, Institutional: Patent; Other, Other, EP21152186.9No financial interest, institutional: Patent; Other, Other, EP15702464.7No financial interest, institutional: Patent; Other, Other, EP19808852.8 No financial interest, Institutional: Patent. N. Niikura: Financial Interests, Personal, Invited Speaker: AstraZeneca, Pfizer, Daiichi Sankyo, Chugai, Eli Lilly, MSD; Financial Interests, Personal and Institutional, Research Grant: Chugai, Eisai, Nippon Kayaku; Financial Interests, Personal and Institutional, Coordinating PI: Daiichi Sankyo. K.S. Saini: Financial Interests, Personal, Full or part-time Employment: Fortrea Inc.; Financial Interests, Personal, Stocks/Shares: Fortrea Inc., Labcorp Inc.; Financial Interests, Personal, Advisory Board: European Commission; Financial Interests, Personal, Ownership Interest: Quantum Health Analytics (UK) Ltd.; Non-Financial Interests, Personal, Other, Honorary Clinical Fellow: Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. I. Gioni: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. T. Klinowska: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. I. Mayer: Financial Interests, Personal, Advisory Board: AstraZeneca, Lilly, Puma, Macrogenics, Sanofi; Financial Interests, Personal, Full or part-time Employment, since 12/2021: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca; Financial Interests, Institutional, Research Grant: Genentech, Pfizer; Non-Financial Interests, , Member: ASCO, AACR. M. Stuart: Financial Interests, Personal and Institutional, Other, I provided consultancy support for AZ: AstraZeneca. E.I. Syta: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. A. Walding: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. T. Bachelot: Financial Interests, Personal, Advisory Board: Roche, Novartis, AstraZeneca, Pfizer, Seagen, Daiichi Sankyo; Financial Interests, Institutional, Advisory Board: Lilly; Financial Interests, Institutional, Research Grant: Novartis, Roche, AstraZeneca, SeaGen, Pfizer; Financial Interests, Personal, Invited Speaker: Roche; Financial Interests, Institutional, Invited Speaker: AstraZeneca. All other authors have declared no conflicts of interest.

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355P Reduction of anthracycline use with a combined imaging and pathology prediction model in the neoadjuvant I-SPY2 trial

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Background: The I-SPY2 Trial is a randomized phase II platform trial testing novel neoadjuvant therapies. Serial MRI and pathology are used to evaluate response. New agents (+/- taxane) are tested in a 12 week (wk) treatment block, followed by Adriamycin/Cytoxan (AC). We sought to determine whether MRI functional tumor volume (FTV)-based predictive models, in conjunction with breast core biopsy, could identify early responders who had reached pCR and thus proceed to surgery without receiving AC, sparing them additional toxicity. The "predicted Residual Cancer Burden" (preRCB) models were developed using retrospective I-SPY data and prospectively tested in I-SPY2.

Methods: Eligible patients (pts) were required to be on preRCB-designated treatment arms and consented to participate in the optional preRCB process. PreRCB included breast MRI at baseline, wk 3 and wk 12 of the initial I-SPY2 treatment block and a clinical core biopsy of the tumor bed at 12-weeks. Pts who met combined preRCB criteria (predicted probability of pCR above threshold in a subtype specific FTV model and no invasive tumor on breast biopsy) were eligible to proceed to surgery without AC after return of results (ROR) and consultation with their clinician.

Results: From 1/20-6/22, 172 pts underwent preRCB and completed surgery. 51/172 (30%) met combined MRI/biopsy preRCB criteria and 40/51 proceeded to surgery without AC (Table). 96% (49/51) pts who met preRCB criteria had RCB0/1 vs. 48% (57/120) of pts who did not meet criteria (OR 27 [6.5-235]; Fisher's exact test p=1.04E-10). Overall, preRCB led to a 24% reduction in AC use without significant difference in RCB0/1 rate between those with and without AC (p=1).

Conclusions: Implementation of preRCB in I-SPY2 identified patients with pCR prior to AC. High uptake of early surgery recommendations led to reduced use of AC while maintaining optimal outcome. I-SPY 2.2 is testing next-generation models to enable further optimization.

Table: 355P

PreRCB met (n=51)				PreRCB not met (n=120)			
No AC 40/51 (78%)		Received AC 11/51 (22%)		No AC 22/120 (18%)		Received AC 98/120 (82%)	
RCB 0/1	RCB 2/3	RCB 0/1	RCB 2/3	RCB 0/1	RCB 2/3	RCB 0/1	RCB 2/3
38 (95%)	2 (5%)	11 (100%)	0 (0%)	12 (55%)	10 (45%)	45 (46%)	53 (54%)

Clinical trial identification: NCT01042379.

Legal entity responsible for the study: Quantum Leap Healthcare Collaborative.

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356P Prognostic value of the residual cancer burden after neoadjuvant chemotherapy for invasive lobular breast cancer: An international pooled cohort study

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Background: Residual Cancer Burden (RCB) after neoadjuvant chemotherapy (NAC) has been validated to predict event-free survival (EFS) across breast cancer subtypes but its prognostic ability has not been specifically studied for invasive lobular carcinoma (ILC).

Methods: We studied patient-level data (histologic subtype, RCB, and EFS) from a previously published pooled cohort from 12 institutions in the US and Europe. ILC was defined by local institutional protocols. Characteristics in pure ILC vs. non-ILC were compared using t-test or chi-squared test. Associations between continuous RCB index and EFS were assessed in both groups with mixed effect Cox models and multivariable analyses. Recursive partitioning was used in an exploratory model to stratify prognosis by individual clinicopathologic variables and the components of RCB.

Results: Of 5161 patients, the diagnosis was ILC in 216 (4.2%) and non-ILC in 4945. ILC cases were older, had lower grade, higher tumor (T) category, and more hormone receptor (HR) positive HER2 -negative subtype (73.6% vs 36.4%) (all p-values <0.05). Pathologic complete response (pCR/RCB 0) was achieved in 10.6% of ILCs and 33.4% of non-ILC (2.5% and 11.8% respectively among HR+HER2- cases, $p<0.0005$). Increased RCB index was significantly associated with worse EFS in both ILC and non-ILC ($p<0.05$) and remained prognostic when adjusted for age, grade, T category, baseline nodal status, and receptor subtype. While continuous RCB index had a linear relationship with probability of EFS event (log scale) in non-ILC, this relationship was non-linear in ILC cases; for ILC, prognosis was similar for RCB index ≤ 1.9, with increasing risk for RCB index >1.9. Recursive partitioning demonstrated residual tumor cellularity as most prognostic in ILC, followed by number of positive nodes and tumor dimensions.

Conclusions: While pCR rate after NAC is low in ILC, RCB retains prognostic value, with residual cellularity providing the most information. RCB index values ≤ 1.9 had similar prognosis to pCR. These results underscore the utility of RCB for evaluating NAC response in those with ILC for clinical management and as an endpoint for clinical trials.

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Cameron: Financial Interests, Institutional, Advisory Board: Roche, Pfizer, AstraZeneca, Daiichi Sankyo, SeaGen, Synthon, Zymeworks; Financial Interests, Institutional, Other, Have done advisory boards, spoken at a webinar and involved in a manuscript with Lilly - all recompense to my institution: Lilly; Financial Interests, Institutional, Other, Have done advisory boards and been involved in a health economic analysis and publication. All recompense to my institution: Novartis; Financial Interests, Institutional, Coordinating PI, funding and drug for UK participation in a French led Novartis funded study. 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357P Prediction of pathologic response to neoadjuvant chemotherapy (NAC) using diffuse optical breast scanner (DOB-Scan) in patients with locally advanced breast cancer (LABC)

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Background: No modality exists to accurately predict pathologic response to chemotherapy prior to surgery in patients with LABC receiving NAC. The objective of this study is to use the novel DOB-scan to evaluate the pathologic response of breast cancer to NAC before surgery.

Methods: The study aims to enroll 90 patients and recruitment is ongoing. An eligible patient had a diagnosis of LABC and was recommended NAC followed by resection. DOB-Scan used near-infrared light to examine healthy and breast cancer tissue prior to NAC, at clinic visit prior to each WNAC cycle, and after NAC was completed. Palpated tumour size was measured at the same time; ultrasound (US) was performed prior to NAC start, halfway, and after final NAC. After surgery, the specimens were reviewed by reference pathologist and assigned the pathologic Residual Cancer Burden (pRCB) class (Symmans et al. JCO 2007 ; Yau et al. SABCS 2019). We calculated the optical RCB (oRCB) class by determining the minimum reflectance that correlated with maximum absorption on DOB-Scan after the last NAC prior to surgery. Correlation between pRCB and oRCB was modelled to fit a linear regression.

Results: 60 patients have been enrolled; data from 30 patients who completed NAC and surgery were included in this interim analysis. Median age was 58 (range 29-72); all but 1 had ductal carcinoma; 22 had axillary lymph node(s) involved. Median longest diameter of the primary tumour on US was 2.3 cm (range 0.7-18). Final size by palpation or US indicated response to NAC, but did not correlate with pRCB. The oRCB clustered linearly with pRCB (pRCB $=$ 4.4 x oRCB), with a sensitivity of 97% and a specificity of 100%. Artificial-intelligence rendered noise reduction of oRCB increased the sensitivity to nearly 100%.

Conclusions: Early results suggest that the oRCB can predict final pathologic response more accurately than palpation or US during NAC. Lower oRCB indicated better response to NAC, with the ability to predict pRCB and pathologic complete response prior to resection. DOB-Scan can be used as a point-of-care hand-held instrument to assess tumour response and assist with treatment decisions in patients receiving NAC.

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358P Major adverse cardiovascular event outcomes of adjuvant taxane + anthracycline versus taxane-based chemotherapy in older adults with triple-negative breast cancer: A SEER-Medicare study

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Background: Triple-negative breast cancer (TNBC) is regarded as relatively more aggressive compared to other subtypes of breast cancer with characteristic metastatic patterns and poor prognosis. The standard of care for TNBC has historically been anthracycline and taxane-based chemotherapy (ATAX). Despite its effectiveness, anthracyclines carry a small but important risk of cardiotoxicity, which is a concern in older women. The purpose of this study was to evaluate major adverse cardiovascular events in older women with TNBC.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified 2,215 women with TNBC diagnosed at age $>$ 65 between 2010-2015. We compared patient and clinical characteristics according to adjuvant chemotherapy regimen (ATAX versus TAX). Logistic regression was performed to estimate the odds ratios (OR) and 95% confidence intervals (CIs), Kaplan Meier survival curves were generated to estimate three-year overall survival (OS) and cancer specific survival (CSS). Cox proportional hazards models were used to analyze OS and CSS while controlling for patient and tumor characteristics. MACE was defined as acute myocardial infarction, heart failure, potentially fatal arrhythmia, and cerebral vascular incidence. Few patients experienced a cardiac death and therefore this was excluded in the analysis.

Results: Of the 2,215 patients in our cohort, a majority of patients 1334 (60.26%) received TAX compared to ATAX 881 (39.78%). Patients who received ATAX were not more likely to experience cardiac outcomes such as acute myocardial infarction (OR 1.10, 95% CI [0.66, 1.82], p=0.724), heart failure (OR 0.73, 95% CI [0.52, 1.05], p=0.09), CVA (OR 0.76, 95% CI [0.45, 1.29], p=0.31), or potentially fatal arrhythmia (OR 0.66, 95% CI [0.29, 1.50], p=0.32) when controlling for traditional risk factors. Among patients who experienced a cardiac outcome, there was no difference in OS or CSS in patients who received TAX vs ATAX (HR 1.18, 95% CI [0.46-2.98], p=0.74 and HR 1.39, 95% CI [0.38 $-$ 5.11] p=0.62).

Conclusions: Among older women with TNBC, receipt of adjuvant chemotherapy with ATAX was not associated with increased risk of adverse cardiac outcomes. For those who experienced a cardiac event, there was no difference in survival amongst those who received TAX compared to ATAX.

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359P Unveiling the factors influencing exercise engagement in breast cancer patients: Insights from the early recovery phase

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Background: Although engaging in exercise after breast cancer surgery (BCS) has been shown to facilitate faster recovery, factors influencing exercise participation during the early recovery phase remain unclear in breast cancer patients. Therefore, this study aimed to explore the perceptions, attitudes, and barriers to exercise in breast cancer patients immediately after surgery and up to 4 weeks post-surgery.

Methods: A descriptive qualitative research method was employed to investigate this topic. A purposive sample of 33 breast cancer patients was selected, and each participant was interviewed three times over a one-month period after surgery.

Results: We found physical constraints and psychological resistance were identified as barriers to exercise. Postoperative physical symptoms (pain, range of motion, lack of fitness, and seroma) and surgical drains were identified as physical constraints. Participants also faced psychological resistance such as concerns about side effects, lack of willpower, and fear of pain. Furthermore, a lack of trustworthy information regarding the timing of exercise initiation and proper types of exercise after surgery was identified as a psychological resistance.

Conclusions: The identified barriers, both physical and psychological, should be taken into consideration when developing strategies to motivate and support patients in engaging in exercise. The identified barriers, both physical and psychological, should be taken into consideration when developing strategies to motivate and support patients in engaging in exercise.

Clinical trial identification: This study involves human participants and was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2018-1094).

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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360P Neoadjuvant inetetamab combined with pertuzumab, paclitaxel and carboplatin for locally advanced HER2-positive breast cancer: Primary analysis of a phase II study

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Background: Inetetamab is a neotype HER2-targeted monoclonal antibody with amino acids modified Fc segment which optimizes the antibody-dependent cellular cytotoxicity effect. However, robust evidence evaluating the combination of inetetamab combined with pertuzumab, paclitaxel and carboplatin (TCbIP) for neoadjuvant therapy is still lacking. This study aimed to evaluate the efficacy and safety of TCbIP as a neoadjuvant therapy for patients with locally advanced (LA) HER2-positive breast cancer.

Methods: This phase II trial included female patients with histologically confirmed stage IIA to IIIC HER2-positive primary invasive breast cancer. Eligible patients received TCbIP treatment every three weeks for a maximum of six cycles followed by surgery. The primary endpoint was pathologic complete response (pCR, ypT0/is ypN0) rate. Key secondary endpoints included near pCR (npCR, residual breast disease $<$1cm) rate, objective response rate (ORR) and safety.

Results: From November 2021 to May 2023, 28 patients were enrolled in the trial. One patient received one cycle of the study treatment and was lost to follow-up without surgery, and four patients received one cycle of the study treatment and were still in treatment, leaving 23 patients in the ITT population. Among these 23 patients (82.6% in stage III), 16 patients completed the study treatment and surgery (PP population) and six patients were still undergoing neoadjuvant treatment. The ORR was 91.3% (21/23) in the ITT population and 93.8% (15/16) in the PP population. Among the 16 patients in the PP population, 10 patients (62.5%) achieved pCR. A total of 14 patients (87.5%) achieved npCR. For patients with hormone receptor (HR) negative and positive tumors, the pCR rates were 88.9% (8/9) and 28.6% (2/7), respectively. The most common grade 3 adverse event was neutropenia (25.0%). No significant reduction in the left ventricular ejection fraction was observed in any patient.

Conclusions: Neoadjuvant therapy with TCbIP has shown promising efficacy and manageable toxicity in patients with HER2-positive LA breast cancer.

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Table: 359P Themes, codes, and categories from the interviews

Categories	%(n)	Codes	%(n)	Theme	%(n)
Physical constraints	100% (33)	Postoperative physical symptoms	100% (33)	Pain at the surgery site	87.9% (29)
				Limited range of motion	66.6% (22)
				Lack of fitness	33.3% (11)
				Seroma	12.2% (4)
		Operation derived condition	45.4% (15)	Drain	45.5% (15)
Psychological resistance	48.5% (16)	Perception and attitude	54.5% (18)	Concerns about side effects	42.4% (13)
				Lack of willpower	15.2% (5)
				Fear of pain	15.2% (5)
		Concerns due to lack of trustworthy exercise information	54.5% (18)	Concerns regarding the exercise timing being inappropriate	42.4% (14)
				Discouragement from others	18.2% (6)

361P A phase II study of fulvestrant combined with chemotherapy in the neoadjuvant treatment of HR+/HER2- locally advanced breast cancer

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Background: HR+/HER2- breast cancer are less sensitive to neoadjuvant chemotherapy (NCT), with a low objective response rate (ORR) of approximately 65% and a much lower pathological complete response (pCR) rate ranging from 5% to 10%. This phase 2 study aims to evaluate the efficacy and safety of adding fulvestrant to NCT in patients (pts) with HR+/HER2- breast cancer, and to investigate the predictive value of ^{18}F-FES PET/CT for effectiveness.

Methods: In this single-arm phase 2 study, eligible pts were female with histologically confirmed HR+/HER2- locally advanced breast cancer (IIB-IIIC). Pts received fulvestrant (500 mg, on days 0, 14, 28, then every 28 days thereafter, every 4 weeks for six cycles) plus AC-T regimen, followed by surgery. Premenopausal women received a concomitant GnRH analogue. Pts underwent ^{18}F-FES PET/CT examination at baseline. The primary endpoint was ORR. Secondary endpoints include tpCR (ypT0/is ypN0), overall survival (OS), and safety.

Results: From Dec 2020 to Sep 2022, 36 pts were enrolled. The median age was 53 years (range, 35-67), 78% were ECOG PS 1, 69% were postmenopausal, 92% were nodal involved, and 83% had stage III. After neoadjuvant therapy, the ORR and DCR were 86.1% (95% CI, 70.5%-95.3%) and 100% (95% CI, 90.3%-100.0%), respectively. All pts completed surgery, with a tpCR rate 8.3% (3/36; 95% CI, 1.8%-22.5%). 29 (80.6%; 95% CI, 64.0%-91.8%) pts had pathological tumor response [Miller-Payne (MP) grade $\geq$3]. Grade $\geq$3 treatment-emergent adverse events (TEAEs) occurred in 22% (8/36). The most common TEAEs were neutropenia (13.9%) and leukopenia (8.3%). Among the 36 pts, 24 completed ^{18}F-FES PET/CT scan at baseline. The average SUV_{max} in primary breast lesions was 4.17 (range 1.00-12.80). The SUV_{max} was significantly associated with MP grade (R=0.82, p=8.4e-07). The SUV_{max} of the primary tumor from pts with MP grade 2/3 was significantly lower than those in pts with MP grade 4/5 (p=2.33e-05).

Conclusions: The addition of fulvestrant to NCT showed manageable toxicity and promising antitumor activity for pts with HR+/HER2- locally advanced breast cancer. The SUV_{max} of ^{18}F-FES PET/CT was positively correlated with patient efficacy.

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Legal entity responsible for the study: The authors.

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362P CYBERNEO trial: Update of results at 14 years of follow-up

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Background: The purpose of the phase I "CYBERNEO" trial was to define the efficacy of the CyberKnife®(CK) for locally advanced (stage III) breast tumors combined to a neo-adjuvant treatment with chemotherapy for patients for whom a conservative surgery could not be considered at the onset. Neoadjuvant chemotherapy (NAC) consisted of 6 cycles: 3 cycles of docetaxel and 3 cycles of 5-fluorouracil-epirubicin-cyclophosphamide (FEC). CK was performed during the second cycle of chemotherapy. Breast surgery was performed six to eight weeks later and conventional breast irradiation without boost, afterwards. The main objective was to define the maximum tolerated dose of hypofractionated radiotherapy concurrent with NAC.We present an updated survival data for patients included in this trial and we evaluate the late toxicities of this combination.

Methods: We updated the survival data of 25 patients treated for a stage III breast cancer between 2007 and 2009 at the Antoine Lacassagne Center in Nice and included in the CYBERNEO trial by recording late toxicities and esthetic results.

Results: With a median follow-up of 12 years, 95% CI [10-14], 19 patients (76%) were in remission, 1 patient had a controlled axillary lymph node relapse (4%) band 5 patients (20%) died due to metastatic progression within a median of 5 years after treatment (min: 1, max: 9). Nine patients (36%) had a complete histological response (pCR). The highest percentage of pCR was in the group of patients treated in the 4th stage (28.5 Gy in 4 fractions). Overall survival at 14 years was 71%, 95% CI [53%-94%]. Two patients developed chronic radiation toxicity during follow-up with a fibrosis (8%), of which one was in the 4th stage and one in the 5th stage (31.5 Gy). Three patients (12%) had a change of prosthesis after treatment which for one patient was 24 months after the end of support.

Conclusions: The updated results of the CYBERNEO trial with 14 years of follow-up confirm the satisfactory results in terms of local control with an excellent long-term safety profile.

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363P High adipocytokines and IL-18bp serum levels are associated with lower objective response rate after neoadjuvant treatment in breast cancer patients with metabolic syndrome

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Background: Metabolic syndrome (MetS) has been identified as a factor related to a worse prognosis in breast cancer. However, the association between adipocytokines and IL-18bp serum levels, MetS, and breast cancer is not demonstrated.

Methods: We prospectively evaluated 151 women with breast cancer eligible for neoadjuvant chemotherapy (NAC). We studied adipocytokines (resistin and leptin) and IL-18bp serum levels and their association with MetS, patients' clinical and laboratory data, and clinical and pathological responses after NAC. Data analysis used the Fisher/Chi-Square and Mann-Whitney Tests (SPSS v20.0, $p<0.05$). Study approval number 5.332.237.

Results: 134 subjects (95.7%) achieved clinical objective response (complete + partial). Among the 151 patients evaluated, 82 (54.3%) had MetS, with HDL-C <50 mg/dl being the most frequent criterion (n=72, 87,8%). Age>45 years, postmenopausal status, obesity, NAC dose reduction, and delay in performing surgery were more associated with the MetS group ($p<0.01$). MetS breast cancer patients with high resistin levels presented with positive lymph nodes (97%), >=88 cm waist circumference (94%), and invasive breast carcinoma of no special type (100%) versus the group with low levels of resistin ($p<0.05$). Additionally, high IL-18bp levels were associated with non-luminal A breast cancers (94%) versus 73% of patients with IL-18bp low levels ($p<0.05$). Leptin was elevated in patients with hyperglycemia and hypertriglyceridemia, while IL18-bp levels increased in subjects with HDL-C < 50md/dl ($p<0.05$). The higher frequency of objective response was associated with no need for dose reduction and low serum IL-18bp concentration ($p<0.05$).

Conclusions: High adipocytokines and IL-18bp serum levels are associated with lower objective response rates after neoadjuvant treatment in breast cancer patients with metabolic syndrome.

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365P Effectiveness and safety of human type 5 recombinant adenovirus (H101) in malignant tumor with malignant pleural effusion and ascites: A multicenter, observational, real-world study

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Background: Human type 5 recombinant adenovirus (H101) has shown promising efficacy in malignant serous effusion (MSE), but evidence is limited. The purpose of this study was to analyze the effectiveness and safety of H101 in Chinese patients

with malignant pleural effusion and ascites (MPE/MA) in the real world, so as to guide clinical use of H101.

Methods: This multicenter, observational, real-world study recruited patients with MPE or MA caused by malignant tumor receiving H101-containing treatment between January 2020 and June 2022 across 5 hospitals. Effectiveness was evaluated by overall remission rate (ORR), and safety was evaluated based on adverse events (AEs). Subgroup analysis was performed on patients grouped according to tumor type, the volume of MPE and MA, and dosage of H101.

Results: A total of 653 eligible patients were enrolled in this study, among whom 467 received H101 monotherapy and 176 received H101 combined with chemotherapy. In H101 monotherapy group, the decrease of MPE or MA was achieved in 282 (60.4 %) patients, 176 (37.7%) patients showed no change in volume of MPE or MA, and 9 (1.9%) patients showed an increase, yielding an ORR of 60.4% (282/467). The ORR for the combination therapy group was 60.2% (106/176), with 106 cases of PR, 69 cases of NC and 1 case of PD. Subgroup analyses based on tumor type, volume of MPE and MA, and dosage of H101 all showed high ORR, approximately 60%. The main AEs associated with H101-containing regimens were fever, nausea and vomiting. No serious AEs occurred in both groups.

Conclusions: Encouraging clinical benefits and manageable toxicity of H101 against MPE and MA were observed in the real-world clinical setting, indicating that the H101-containing regimen is reliable, safe, and feasible, providing a novel and effective option for the treatment of this disease.

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366P Artificial intelligence (AI)-powered assessment of complete and intense human epidermal growth factor receptor 2 (HER2)-positive tumor cell proportion in breast cancer: Predicting fluorescence in situ hybridization (FISH) positivity and response to HER2-targeted therapy

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Background: The level of expression of HER2 is important in predicting response to HER2-targeted therapies. HER2 expression level is classified in groups (3+ positive, 2+ equivocal, and 1+ or 0 negative) or quantified as an H-score based on the proportion of tumor cell intensity (complete and intense [strong positive], weak to moderate complete [moderate positive], incomplete and faint/barely perceptible [weak positive]). If the case is classified as 2+ equivocal, an additional test such as Fluorescence In Situ Hybridization (FISH) test is performed to confirm the positivity. In this study, we aim to figure out that the complete and intense HER2-positive tumor cell proportion can predict both FISH positivity and response to HER2-targeted therapy, compared to the H-score.

Methods: Lunit SCOPE HER2, an AI-powered HER2 analyzer that identifies and quantifies HER2 IHC according to staining intensity of tumor cells, was used to evaluate the HER2 status of breast cancer cases (n=205) from Kyung Hee University Hospital. They consisted of 41 3+, 163 2+, and 1 1+, as interpreted by pathologists. Of these, 171 had FISH results, and 44 received HER2-targeted therapy as neoadjuvant (n=25) or as palliative (n=19). The proportion of strong positive tumor cells or the H-score by the AI-powered HER2 analyzer was assessed to predict clinical outcomes.

Results: Among all cases, FISH positivity was 20.5%, pathologic complete response (pCR) after neoadjuvant therapy was 40.0%, and complete/partial response during palliative therapy was 68.4%. The proportion of strong positive tumor cells was a better predictor of FISH positivity and response compared to H-score (Area under the curve: 0.784 vs. 0.688 for FISH, and 0.872 vs. 0.859 for response). Prediction of pCR was equivalent for both (0.773). The DeLong test showed a significant difference in the prediction of FISH positivity (p=0.023).

Conclusions: This study showed that AI analysis of breast cancer HER2 expression, specifically the proportion of strong positive tumor cells, can predict FISH and therapy response better than the H-score.

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367P Sentinel lymph node biopsy (SLNB) in patients with locally advanced breast cancer (LABC): Descriptive, inferential and survival analysis

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Background: The objective was to perform a descriptive, inferential and overall survival analysis of patients with LABC who underwent SLNB.

Methods: Retrospective study(January/12-December/22) in patients with LABC selected for SLNB with: initial clinical and radiological tumor and lymph node staging(TNM-AJCC-7&8-Edition), histological types, prognostic tumor markers, with evaluation of the response(radiological & pathological) of the tumor and lymph nodes after neoadjuvant chemotherapy(NACT). We performed a descriptive, inferential and survival analysis.

Results: 141patients with LABC met inclusion criteria: 128(91%)Infiltrating Ductal Carcinoma, 7(5%)Infiltrating Lobular Carcinoma, 2(1%) Infiltrating Ductal Carcinoma in-situ, and 1case(1% each) of: tubular, medullary, mucinous and colloid carcinoma. The TNM staging before NACT was: T1:14(9.9%)patients; T2:95(67.4%); T3:27(19.2%) and T4:5(3.5%). 89(63.1%)patients were cN(+) and 52(36.9%) were cN(0). Intrinsic subtypes were: Luminal-A 10(7.1%) patients, Luminal-B 26(18.4%); Luminal-B-Her2 34(22%); Her2 31(28.4%) and 40(24.1%)Triple negative. Histological grades (HG) were: grade I 5(3.5%)patients, grade II 53(37.6%), and grade III 83(58.9%). We obtained 46(32.6%)SLNB(+), 85(60.3%)SLNB(-) and in 10(7.1%)there was no migration (NM). We performed 93 lymphadenectomies(LDN): 44 SLNB(+); 39 SLNB(-) and 10-NM. We obtained 29LDN(+):19SLNB(+), 6NM and 4SLNB(-). We obtained 64LDN(-): 25SLNB(+), 4NM and 35SLNB(-). 8-patients died: 3LDN(+): 2SLNB(+) and 1NM; 4-LDN(-): 2SLNB(+) and 2SLNB(-); and 1 SLNB(-) without LDN. 46-patients(51.7%) went from cN(+) to pN0. In the inferential analysis we found a statistically significant correlation between the SLNB result and the intrinsic subtype ($p<0.001$), with Luminal-B-Her2 subtypes and triple negative patients as those with the most SLNB(-) results. Detection rate(DR) was 95.3%. False negative rate (FNR) was 8%, considering SLNB(+) as a true positive. The survival time for patients with SLNB(+) was 111 months, for SLNB(-) it was 127 months ($\pm$2.4) and for patients with NM it was 95 months.

Conclusions: Our DR was 95%, FNR was 8%, mortality was 5%, and overall survival with SLNB(-) was 127 months.

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368P Impact of PET-CT-determined sarcopenia on survival and pathological complete response in breast cancer patients with neoadjuvant chemotherapy

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Background: Neoadjuvant chemotherapy (NACT) is a frequently used treatment method in breast cancer. Achieving pathological complete response (pCR) is one of the surrogate marker for long-term survival. Sarcopenia is considered a poor prognostic factor in breast cancer. The association between pCR and sarcopenia has not been fully elucidated in neoadjuvant setting in breast cancer. It was aimed to evaluate the effect of sarcopenia on pCR and overall survival (OS) in breast cancer patients with NACT.

Methods: Patients with NACT between 2014 and 2021 were included in the study. SMI (skeletal muscle index), VFA (visceral fat tissue area), sarcopenic obesity (VFA/SMI) were determined at the level of the third lumbar vertebra on PET-CT images before and after NACT. Patients were categorized according to pCR. The relationship between pCR and clinicopathological features and PET-CT parameters were evaluated by logistic regression analysis. Kaplan-Meier method was used for survival analysis.

Results: The medical records of 56 patients who received NACT were reviewed and twenty-three patients who met the inclusion criteria were included in the study. They were classified as sarcopenic according to the previously determined cutoff value for sarcopenia (SMI: 38.9 cm2/m2). Sarcopenia was present in 50% of patients. Post-NACT sarcopeni was found in 20% of the patients. The rate of post -NACT sarcopenic obesity was %27.3. pCR was achieved in 28.3% of patients. Sarcopenia was not associated with clinicopathologic features, pCR and OS. There was no association between clinicopathologic factors and pCR. Recurrence, post treatment high VFA, and post treatment sarcopenic obesity were significantly associated with survival. In multivariate analysis post treatment high VFA level was significantly associated with increased mortality (HR: 3.278 CI: 95% (1.143-9.401), p= 0.027).

Conclusions: Dynamic follow-up for sarcopenic obesity and visceral adipose tissue increase may improve the survival in breast cancer with NACT. Further prospective studies will be elucidated the relationship between breast cancer and sarcopenia.

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369P The impact of germline BRCA mutations in locally advanced, triple-negative breast cancer (TNBC) treated with platinum-based neoadjuvant chemotherapy

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Background: Whether germline BRCA (gBRCA) mutation affects prognosis and whether it has implications on treatment decision in the neoadjuvant setting is unclear.

Methods: Two centers retrospective cohort study comprising all women with early-stage TNBC who completed genetic testing and were treated with neoadjuvant chemotherapy with dose-dense chemotherapy containing carboplatin, between 10.2014 and 3.2020. Clinico-pathological features and data on dose reduction and delays were collected. Data on outcomes including pathological complete response (pCR), overall-survival (OS) and disease-free survival (DFS) were also calculated. Differences of these variables by gBRCA status were investigated.

Results: Sixty-four 64 women were included in the final analysis, of which 31 had pathogenic gBRCA mutation and 33 were gBRCA wild-type. Clinico-pathological characteristics and dose density and intensity were similar between both groups. Among gBRCA mutated patients, 23/31 (74%) achieved pCR, compared to 17/33 (51%) in the non-mutated, p=0.035. At a median follow-up of 30 months, gBRCA mutated women had significantly favorable OS (HR=8.64, 95% CI 1.08-69.21, p=0.042) and a trend for a favorable DFS (HR=7.4, 95% CI 0.91-60.27; p=0.062). The favorable OS for gBRCA mutated women remained significant in multivariate analysis (p=0.029) and was noted regardless to pathological response (p=0.01).

Conclusions: Compared to non-mutated, gBRCA mutated women with locally advanced TNBC treated with neoadjuvant chemotherapy containing carboplatin had a higher pCR rate and better outcome. Whether gBRCA mutation has a role in deescalating treatment in this population, should be further investigated.

Legal entity responsible for the study: The authors.

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370P LYMPHA surgery to reduce lymphedema following axillary node clearance: A new study at a London plastics centre

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Background: LYMPHA is a relatively new surgical technique that dramatically reduces the incidence of lymphedema following axillary node clearance in breast cancer patients. The technique identifies dominant lymph vessels draining the arm with the aid of dye and, following clearance of the axillary nodes, anastomosing lymphatic vessels to a branch of the axillary vein to enable free drainage of lymphatic fluid. Not currently widely available to breast cancer patients in the UK, this simple surgical procedure carried out at the time of axillary node clearance has been shown to reduce the incidence of lymphedema from 25% to 4%. We report on the establishment of a LYMPHA service at a major London Plastics Centre and first 2 years of its outcomes.

Methods: Suitable patients were referred to plastics by the breast surgery team and seen preoperatively to discuss LYMPHA. Upon agreeing to the procedure, pre-operative measurements of arm volume and arm bioimpedance were completed as well as screening questionnaires on symptoms of lymphedema. Subsequent to the procedure the two measurements and the questionnaires were repeated at 1, 3, 6, 12 and 24 month intervals.

Results: Of 16 patients that have undergone the LYMPHA procedure 0 have experienced signs or symptoms of lymphedema to date. One patient suffered temporary swelling of the arm 1-month post-op which subsequently resolved. No patients have suffered any complications relating to LYMPHA. 1 patient withdrew due to metastatic disease recurrence. The patients enrolled have been followed up for between 3-23 months with a current mean follow up time of 12.61 months.

Conclusions: Our findings thus far support current evidence that LYMPHA surgery is both safe and effective in reducing the incidence of lymphedema. This pilot study is currently being developed into an RCT which will add to the evidence base of this relatively niche area of plastic surgery.

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371P Adherence to standardized and structured electronic symptom reporting (ePRO) via mobile app in HER2-positive breast cancer treated with HER2 biosimilar trastuzumab

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Background: The treatment of HER2+ breast cancer (BC) patients with Herceptin® was the standard for more than a decade. Development of trastuzumab biosimilars has prompted the demonstration of clinical equivalency to the reference biosimilar and safety. So far, adherence to dynamic standardized and structured real-world assessment of wellbeing and symptoms, via ePROs in patients treated with the HER2 biosimilar Ogivri® has not been reported. We assess the adherence of ePROs using the medidux app (previously: consilium care) and perform a comparative analysis of ePROs obtained from HER2+ BC patients in two studies where Herceptin® was administered (NCT02004496, NCT03578731).

Methods: In this 6 week observational study, patients were treated with trastuzumab (Ogivri®) +/- Pertuzumab, +/- Chemotherapy +/- anti-hormones. Patients used the medidux™ app to record well-being, symptoms (according to CTCAE), EQ-5D-5L, trail maker test and vital parameters and intake of medication in a standardized manner. Patients also received a pop-up reminder in case of missing data entries after 3 days. Previously obtained ePROs from 38 patients treated with Herceptin® similar therapeutic settings were used for comparative analysis.

Results: From 53 female patients included in this trial so far, there was only one drop out. About 60% of patients continued to use the app after the observational 6 weeks period. Close to 10`000 symptom entries were recorded with an average of $>$ 2 symptoms/day. Of the more than 90 individual symptoms, the most common reported were fatigue, taste disorder, diarrhea, nausea, dry mucosa, joint discomfort, tingling, headache and appetite loss. Results available from $>$70% of all data sets suggests that patients symptoms were reported in a similar incidence and score as from the comparative analysis of Herceptin®. Adherence to the app use and electronic recording of symptoms was continued in average for another 3 months after the end of observation without clear correlation to age or symptom severity.

Conclusions: The majority of patients continued the ePRO app use after end of study participation. Only 1 drop out (from 53 pats) was noted in this propsective observational study.

Clinical trial identification: SNCTP000004711.

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372P Prevalence of BRCA1 and BRCA2 mutation among Indian breast cancer patients: A multicentre cross-sectional study

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Background: Germline mutations in breast cancer susceptibility genes 1 or 2 (gBRCA1/2mut) increase predisposition to breast cancer. Previous Indian breast cancer studies suggest gBRCAmut prevalence of 18.6-36.2%, but data are either single-centre or in patients selected by family history, histopathological subtype or age.

Methods: This was a prospective,cross-sectional,multicentre, study conducted in 14 institutions across India among patients with newly diagnosed stage I to IV breast cancer who had not yet completed 1st- line treatment and were not enriched for gBRCAmut. Based on previous Indian data, a sample size of 313 was estimated to be adequate. Germline BRCA 1/2 testing was performed in a single central laboratory in blood sample-derived DNA by next-generation sequencing (NGS), with reflex multiplex ligation probe amplification (MLPA) in patients who were -ve on NGS or were detected with Variant of Unknown Significance (VUS).

Results: Between June 2022 and Feb 2023, 304 patients were recruited in the study with a median age of 46 (22-83) years.The prevalence of pathogenic or likely pathogenic (P/LP) gBRCA 1/2 mutation was 27 (8.8%, 95%CI 6.18-12.61%) in the full study population. P/LP gBRCAmut prevalence in patients with ER/PR+/HER2 negative, HER2 positive and TNBC were 10/123 (8.13%, 95% CI 4.48-14.32), 2/80 (2.5%, 95% CI 0.69-8.66), and 15/102 (14.8%, 95% CI 9.12-22.85) respectively; in patients $\leq$ 50 years and $>$50 years were 20/194 (10.31%, 95% CI 6.77-15.39) and 7/110 (6.37%, 95% CI 3.12-12.56) respectively; in patients with and without relevant family history were 10/35 (28.57%, 95% CI 16.33-45.05) and 17/269 (6.32%, 95% CI 2.57-7.63), respectively; and in patients with stage I-III and stage IV disease were 22/235 (9.36%, 95% CI 6.26-13.77) and 5/68 (7.35%, 95% CI 3.18-16.09), respectively. The majority of P/LP gBRCAmut were in BRCA1 (16/304, 5.26%, 95%CI 3.04-8.4%), of whom 12/16 (75.0%) patients had TNBC, while 11/304 (3.62%) patients had gBRCA2mut of whom 7/11 (63.63%) had ER/PR+/HER2 -negative disease and 4/11 (36.37%) were TNBC.

Conclusions: Less than 10% of unselected newly diagnosed Indian breast cancer patients have P/LP gBRCA mutations. Younger age, TNBC subtype and positive family history enrich for such mutations.

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Gupta: Financial Interests, Personal, Other, Member of various committees related to guidelines, drug pricing, others: Indian Council of Medical Research, Government of India; Financial Interests, Personal, Other, Member of Scientific Committee on nano-biosensors for healthcare applications: Council of Scientific and Industrial Research, Government of India; Financial Interests, Personal, Other, Scientific committee member for appraisal of scientific projects submitted to DBT for funding.: Department of Biotechnology, Government of India; Financial Interests, Personal, Other, Scientific committee member for appraisal of scientific projects submitted to India Alliance for funding. India Alliance is a partnership between Wellcome Trust and Department of Biotechnology (Government of India) to fund healthcare related research in India.: India Alliance; Financial Interests, Institutional, Other, Steering Committee member for a global clinical trial (CLEE011A2207). 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Honoraria to institution.: Roche Products (India) Private Limited; Financial Interests, Institutional, Invited Speaker, Chairperson, panelist, or speaker at a 3 meetings/roundtable. Honoraria to institution: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Invited Speaker, Chairperson at 2 conferences/meetings. Honoraria to institution: Eli Lilly & Company (India) Limited; Financial Interests, Institutional, Invited Speaker, Invited speaker in a conference. Nag Foundation is a not-for-profit registered society working in the field of cancer: Nag Foundation; Financial Interests, Institutional, Invited Speaker, Invited panelist in a meeting. Honorarium to institution.: Eisai Company Limited; Financial Interests, Institutional, Invited Speaker, Invited speaker. Honorarium to institution: Omnicuris Healthcare Private Limited; Financial Interests, Institutional, Invited Speaker, Invited panelist at a conference. 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Hoffmann-La Roche Ltd; Financial Interests, Institutional, Coordinating PI, National coordinating PI of a multi-omics study in ER positive breast cancer: Department of Biotechnology, Government of India; Financial Interests, Institutional, Local PI, EGC002: Phase III, Randomized, Multicenter, Double-blind Study to Compare Efficacy and Safety of EG12014 (EirGenix Trastuzumab) with Herceptin® as Neoadjuvant Treatment in Combination with Anthracycline/Paclitaxel-based Systemic Therapy in Patients with HER2-positive Early Breast Cancer: EirGenix Inc.; Financial Interests, Institutional, Local PI, Protocol No. - CLEE011A3201C : A phase II randomized study of the combination of Ribociclib plus goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor positive/HER2-negative inoperable locally advanced or metastatic breast cancer - RIGHT Choice Study: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - D9100C00001 : A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer (CALLA): AstraZeneca Pharma India limited.; Financial Interests, Institutional, Local PI, Protocol No. - CLEE011A2207 : A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Local PI: Glenmark Pharmaceuticals Ltd.; Financial Interests, Institutional, Coordinating PI, Protocol No. - D0816R00025 : A Prospective, Multicentre, Phase-IV Clinical Trial of Olaparib in Indian Patients with Platinum Sensitive Relapsed Ovarian Cancer who are in Complete or Partial Response Following Platinum Based Chemotherapy and Metastatic Breast Cancer with Germline BRCA1/2 Mutation (SOLI Study): AstraZeneca Pharma India Limited; Financial Interests, Institutional, Local PI, Protocol No. - D9670C00001 : A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - D3614C00001 : A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Paclitaxel Versus Placebo + Paclitaxel as First-line Treatment for Patients with Histologically Confirmed, Locally Advanced (Inoperable) or Metastatic Triple-Negative Breast Cancer (TNBC).: AstraZeneca Pharma India Limited; Financial Interests, Institutional, Local PI, PIK3CA Registry- A descriptive study of PIK3CA mutations in patients with HR+/Her2- advanced breast cancer.: NOVARTIS HEALTHCARE PRIVATE LIMITED; Financial Interests, Institutional, Local PI, Protocol No. - D967JC00001 : A Phase 1b/2 Multicentre, Open-label, Modular, Dose-finding and Dose-expansion Study to Explore the Safety, Tolerability, and Anti-tumour Activity of Trastuzumab Deruxtecan (T-DXd) in Combination with other Anti-cancer Agents in Patients with HER2-positive Metastatic Breast Cancer (DESTINY-Breast07): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, D9311C00001 ''A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E): AstraZeneca; Financial Interests, Institutional, Local PI, WO42633 A phase III, randomized, double-blind,placebo-controlled clinical trial to evaluate the efficacy and safety of adjuvant atezolizumab or placebo and trastuzumab emtansine forher2-positive breast cancer at high risk of recurrence following preoperative therapy (ASTEFANIA study): Roche Products (India) Pvt. Ltd.; Financial Interests, Institutional, Local PI, MO42921 A multi-country observational retrospective study to evaluate the prevalence of pd-l1 and its role in patients with tnbc treated with systemic therapy (VANESSA): Roche Products India Pvt Ltd.; Financial Interests, Institutional, Local PI, Cost-effectiveness Analysis & Value-Based Pricing for Anti-Cancer Drugs: Implications for Patients, Industry, Insurer and Regulator: Department of Health Research, Ministry of Health and Family Welfare, New Delhi; Financial Interests, Institutional, Coordinating PI, Coordinating PI for Multi-Omics Analysis to Decipher Mechanisms of Hormone Resistance in Breast Cancer: Department of Biotechnology, Government of India; Financial Interests, Institutional, Coordinating PI, Mapping of Breast Cancer: Department of Science and Technology, Government of India; Financial Interests, Institutional, Local PI, Protocol No. - ECTS/16/002 : A multicentric open label phase II safety and efficacy study of ormeloxifene in tamoxifen resistant metastatic/recurrent breast cancer patients.: HLL Lifecare Limited (A Government of India Enterprises); Financial Interests, Institutional, Coordinating PI, Protocol No. - D0818R0000 : Protocol no. D0818R00001- A Non-interventional, multicentre study to assess prevalence of BRCA1 and BRCA2 mutation among ovarian, primary peritoneal and fallopian tube cancer patients in India (BRCA study): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - 1000-16 : An Open Label, Single Arm, Multicentric, Phase IV study to evaluate the safety and efficacy of Bevacizumab of Intas Pharmaceuticals Limited in approved indications: Intas Pharmaceuticals Ltd; Financial Interests, Institutional, Local PI, Protocol No. - Protocol no: 471-13 : "A Prospective, Adaptive, Randomized, Open-Label, Multicenter Clinical Trial to assess the Efficacy and Safety of Fixed Dose Combination of Capecitabine & Cyclophosphamide in Patients of Metastatic Breast Cancer with failure of Anthracycline and/or Taxane Chemotherapy: Intas Pharmaceuticals Ltd; Financial Interests, Institutional, Local PI, Protocol No. - MO39196: A phase III, Multicentre, randomised, double-blind, placebo controlled study of Atezolizumab (anti-PD-L1 antibody) in combination with paclitaxel compared with placebo in combination with paclitaxel for patients with previously untreated, inoperable locally advanced or metastatic Triple Negative Breast Cancer.: Roche Products (India) Pvt. Ltd; Financial Interests, Institutional, Local PI, Protocol No. - CBYL719C2301 : A phase III randomized double-blind, placebo controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment: Novartis Healthcare Pvt. Ltd.; Non-Financial Interests, Member of Board of Directors, This is a not-for-profit registered organization which aims to create large databases of genomic and other 'omic' data in breast and other cancers.: Indian Cancer Genome Atlas; Non-Financial Interests, Leadership Role, General Secretary of this non-governmental organization (It is a not-for-profit) which aims to help underprivileged patients with breast and gynecological cancers and promotes research and educational activities in these themes.: Women's Cancer Initiative - Tata Memorial Hospital; Non-Financial Interests, Leadership Role, President-Elect of ISMPO which is the largest professional organization of medical oncologists in India. It is a not-for-profit registered society.: Indian Society of Medical and Paediatric Oncology (ISMPO). All other authors have declared no conflicts of interest.

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373P Impact of comorbidities on real-world (rw) clinical outcomes of patients (pts) with hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2-) advanced breast cancer (ABC) treated with palbociclib and enrolled in POLARIS

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Background: Palbociclib is used to treat HR+/HER2− ABC with an aromatase inhibitor as first line of therapy (1LOT) or with fulvestrant in pts whose disease progressed on endocrine therapy. Limited information exists on comorbidities' impact on rw clinical outcomes in these pts.

Methods: POLARIS is a prospective observational study of pts with HR+/HER2− ABC receiving palbociclib in clinical practice in the US and Canada. Rw progression-free survival (rwPFS) and overall survival (OS) for pts with clinically relevant comorbidities and by Charlson Comorbidity Index (CCI) score were descriptively summarized.

Results: 1250 pts were enrolled (median age 64 y; 99% female; 27% de novo metastatic diagnosis; 32% bone-only; 40% visceral metastases). Of these, 908 (73%) received palbociclib as 1LOT and 342 (27%) as $\geq$ 2LOT. Pts had a median (range) of 2 (0−9) comorbidities; 5% had 0, 56% had 1−2, 32% had 3−4, and 7% had >4. Median OS (months; 95% CI) for pts with CCI scores of 0, 1−2, and 3+ were 48.8 (37.3−NE), NR (43.0−NE), and 34.3 (29.1−44.1) in 1LOT and 39.5 (30.6−50.5), 35.2 (26.5−41.6), and 31.6 (20.9−45.2) in $\geq$ 2LOT, respectively. Median rwPFS for CCI scores and certain comorbidities are shown (Table).

Conclusions: Pts with HR+/HER2− ABC receiving palbociclib and CCI scores 0 and 1−2 had similar rwPFS and OS regardless of LOT. Pts with CCI score 3+ had shorter rwPFS and OS in the 1LOT, and similar rwPFS but shorter OS in the $\geq$ 2LOT than pts with score 0−2. Pts with cardiac disorders in the 1LOT and blood and lymphatic disorders in the $\geq$ 2LOT had shorter rwPFS, while other subgroups achieved generally comparable clinical outcomes. Understanding potential impact of comorbidities on clinical outcome in the rw is important for treatment decision-making. Larger rw studies may be needed to further assess the true impact of these comorbidities.

Table: 373P rwPFS in pts with HR+/HER2− ABC by comorbidities and LOT

Subgroups	1LOT (n=908)		≥ 2LOT (n=342)	
	n (%)	Median rwPFS, months (95% CI)	n (%)	Median rwPFS, months (95% CI)
CCI score				
0	276 (30)	20.3 (17.1−24.8)	101 (30)	13.9 (7.4−19.7)
1−2	493 (54)	24.7 (20.2−29.5)	189 (55)	13.1 (9.0−17.5)
3+	139 (15)	16.8 (12.4−21.9)	52 (15)	13.2 (8.0−24.0)
Comorbidities				
Vascular	496 (55)	23.7 (19.5−28.1)	183 (54)	13.1 (8.7−17.2)
Psychiatric	240 (26)	19.6 (15.2−27.2)	92 (27)	13.2 (9.4−24.0)
Metabolic and nutritional	173 (19)	19.6 (14.8−24.0)	55 (16)	14.9 (6.7−23.7)
Blood and lymphatic system	147 (16)	16.8 (12.2−20.8)	83 (24)	8.6 (4.8−11.7)
Cardiac	32 (4)	12.5 (8.5−34.1)	12 (4)	11.6 (2.9−42.8)

Clinical trial identification: NCT03280303.

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374P Evaluation of symptom severity, tolerability, and physical function in the I-SPY2 trial

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Background: Patient-reported outcomes (PROs) are a valuable component to understand treatment tolerability and toxicity. We have implemented an electronic system for monitoring PROs and quality of life (QOL) for patients enrolled in the I-SPY2 trial, a phase II trial evaluating the effect of novel neoadjuvant therapies for breast cancer. We associated patient demographic factors with symptoms, decline in physical function (PF), and tolerability to treatment.

Methods: Study population for this analysis includes 259 enrolled patients receiving combinations of experimental immunotherapy and chemotherapy. Patients completed PRO-CTCAE/PROMIS/FACT surveys reflecting symptom severity, symptom frequency, tolerability of drug, and physical function at baseline through follow up (12 months). CTCAE 5.0 was collected weekly at these timepoints to assess adverse events (AE). Odds ratio and regularized multi-variate regression was used to evaluate early symptoms predictive of a clinically significant decline in PF from baseline to post-treatment follow-up.

Results: Of 259 patients, 160 (58%) were White, 13 (5%) were Asian, 26 (10%) were African American (AA), and 25 (9.3%) were Hispanic. 25% of all patients had a clinically significant decline in PF between baseline and pre-surgery/follow-up. Symptom predictors of decline included high frequency of diarrhea and severity of joint pain. African American (AA) patients had higher severity of joint pain than White patients (OR = 14.9, $P < 0.05$). Within the first 12 weeks of treatment, AA patients and non-white (NW) patients were more likely to report severe vomiting than White patients (OR =13.22 and 12.72, $P < 0.05$ and $P < 0.03$ respectively). Overall, patients that reported lower tolerance to therapy had higher grade of AE. While patients with low-grade adverse events were less bothered by their side effects at follow-up, higher grade adverse events such as hypothyroidism impacted distress levels by more than double.

Conclusions: Among I-SPY2 participants, when higher grade of symptoms is persistent through follow up, it impacts physical function and tolerability even after end of therapy. Our study can allow physicians to be more diligent in active and post treatment monitoring.

Clinical trial identification: NCT01042379.

Legal entity responsible for the study: I-SPY2 Trial Investigators.

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375TiP A phase I, 2-part, multicenter, first-in-human dose-escalation and dose-expansion study of DS-1103a with trastuzumab deruxtecan (T-DXd) in patients with advanced solid tumors

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Background: Immune checkpoint inhibitors have improved outcomes for patients with various cancer types, yet most experience disease progression. Growing evidence supports that myeloid cells, such as macrophages, play a major role in inhibiting tumor progression. Macrophage and cancer cell interaction can be inhibited by the SIRPα-CD47 pathway. Blocking this pathway may restore antitumor immune functions of macrophages and reduce tumor growth. DS-1103a, a recombinant humanized IgG4 anti-SIRPα antibody, blocks this pathway by binding to the major human variants of SIRPα. T-DXd, an antibody-drug conjugate consisting of an anti-HER2 antibody and topoisomerase I inhibitor payload, is approved for various cancers. In nonclinical studies, DS-1103a enhanced the trastuzumab-induced antibody-dependent cellular phagocytosis, suggesting a potential benefit of the combination. This study will assess the preliminary safety and efficacy of DS-1103a + T-DXd in advanced solid tumors.

Trial design: This phase 1, global, multicenter, first-in-human, 2-part, dose-escalation, and dose-expansion study (NCT05765851) plans to enroll up to 78 patients. Part 1 (dose-escalation [based on BOIN design]) will enroll patients with pathologically documented HER2-expressing (IHC1+ or greater) or HER2-mutated (activating mutation) advanced solid tumors not amenable to standard of care. Part 2 (dose-expansion) will enroll patients with HER2-low (IHC2+/ISH- or IHC1+ [ISH- or untested]) breast cancer who received 1-2 prior lines of chemotherapy in the recurrent or metastatic setting. DS-1103a monotherapy will be administered for Cycle 1 of Part 1, DS-1103a + T-DXd for all other 21-day cycles and during Part 2. The evaluation period for dose limiting toxicity will be before Cycle 3 in Part 1. Primary endpoints include the safety and tolerability of the combination in both parts, determining the recommended dose of DS-1103a in combination for expansion in Part 1, and assessing the objective response rate in Part 2. Secondary endpoints include the antitumor activity of DS-1103a + T-DXd, pharmacokinetic profile of DS-1103a, and incidence of antidrug antibodies against DS-1103a.

Clinical trial identification: NCT05765851.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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BREAST CANCER, METASTATIC

376O Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Updated survival results of the randomized, phase III DESTINY-Breast04 study

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Background: DESTINY-Breast04 (NCT03734029) assessed T-DXd vs TPC in pts with HER2-low mBC (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization−). At primary data cutoff (DCO; January 11, 2022), median overall survival (mOS) for the full analysis set (FAS = hormone receptor-positive [HR+] and hormone receptor-negative [HR−]) was 23.4 months (mo) for T-DXd vs 16.8 mo for TPC (hazard ratio, 0.64; $P = 0.001$), with 18.4 mo median follow-up (F/U). Here, we report results from a preplanned further F/U (DCO, March 1, 2023).

Methods: Pts were randomly assigned 2:1 to T-DXd or TPC. At the updated DCO, analyses of OS (HR+ and FAS), progression-free survival (PFS) by investigator (HR+ and FAS), and safety were conducted.

Results: At DCO, median F/U was 32 mo. Median treatment duration was 8.2 mo (range, 0.2-39.1 mo) for T-DXd and 3.5 mo (range, 0.3-19.7 mo) for TPC. Efficacy results are shown in the table. Grade ≥3 treatment-emergent adverse events (TEAEs) were lower in T-DXd vs TPC (54.4% vs 67.4%). The most common TEAEs were gastrointestinal or hematological in nature; all-grade nausea (T-DXd: 76.0%; TPC: 30.2%) and vomiting (T-DXd: 40.7%; TPC: 13.4%) were most common for T-DXd and decreased neutrophil count (T-DXd: 22.1%; TPC: 36.0%) was most common for TPC. Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 for the T-DXd vs TPC arm, respectively. No new adjudicated drug-related interstitial lung disease/pneumonitis events were reported with longer F/U (primary DCO: 45 pts [12.1%] for T-DXd; 1 pt [0.6%] for TPC).

Conclusions: Results from the 32-mo median F/U for DESTINY-Breast04 confirms the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low mBC, regardless of HR status. Similar to the primary analysis, the overall safety profile was generally manageable with longer duration of treatment exposure.

Clinical trial identification: NCT03734029.

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Table: 376O Summary of efficacy results

	HR+		FAS	
	T-DXd n = 331	TPC n = 163	T-DXd N = 373	TPC N = 184
mOS, mo (95% CI)	23.9 (21.7-25.2)	17.6 (15.1-20.2)	22.9 (21.2-24.5)	16.8 (14.1-19.5)
mOS Hazard ratio (95% CI)	0.69 (0.55-0.87)		0.69 (0.55-0.86)	
OS rate at 24 mo, %[a] (95% CI)	49.0 (43.3, 54.5)	35.1 (27.3, 43.0)	47.3 (41.9, 52.4)	32.0 (24.8, 39.3)
OS rate at 36 mo, %[a] (95% CI)	26.5 (20.7-32.7)	16.9 (10.2-25.0)	26.2 (20.8-31.9)	16.3 (10.3-23.6)
mPFS by investigator, mo (95% CI)	9.6 (8.4-10.0)	4.2 (3.4-4.9)	8.8 (8.3-9.8)	4.2 (3.0-4.5)
mPFS Hazard ratio (95% CI)	0.37 (0.30-0.46)		0.36 (0.29-0.45)	

m, median.
Estimated and CI for OS rate at the specified time point are from Kaplan-Meier analysis.

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377O A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03

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Background: T-DXd is approved for treatment of pts with HER2+ unresectable or mBC who have received ≥1 prior anti-HER2-based regimens. We report exploratory pooled efficacy and safety data of T-DXd vs comparator (comp) in pts from DB-01, DB-02, and DB-03 with treated/stable (treated) and untreated/active (untreated; from DB-02/-03) BMs at baseline, as defined by the US FDA (FDA 2020).

Methods: DB-01/-02 enrolled pts who were resistant/refractory to trastuzumab emtansine (T-DM1); DB-03 included pts previously treated with trastuzumab and taxane. T-DXd data and ad hoc exploratory intracranial analyses were pooled from DB-01/-02/-03. Comp data, physician's choice chemotherapy and T-DM1, were pooled from DB-02 and -03, respectively. Endpoints were intracranial (IC) objective response rate (ORR; complete [CR] or partial response [PR] in brain) per blinded independent central review (BICR) by RECIST, IC duration of response (DoR), central nervous system-progression-free survival (CNS-PFS) by BICR, and safety.

Results: Of the 148 pts with BMs at baseline who received T-DXd, 104 (70.3%) had treated and 44 (29.7%) had untreated BMs. Pts had a median of 3 (range, 1.0-14.0) prior regimens in the metastatic setting. Median treatment duration was 12.7 mo (range, 0.7-45.1) with T-DXd and 5.6 mo (range, 0.1-43.0) with comp. Efficacy data are in the Table. Any-grade drug-related treatment-emergent adverse events (TEAEs), drug-related grade ≥3 TEAEs, and serious drug-related AEs were observed in 94.5%, 43.2%, and 13.0% of pts with T-DXd, vs 94.0%, 36.1%, and 7.2% with comp, respectively.

Conclusions: T-DXd exhibited robust IC responses in pts with treated and, notably, untreated BMs vs comp. Although pt numbers were small and not statistically tested, numerically longer median IC-DoR and CNS-PFS were observed in pts with untreated BMs with T-DXd. Safety was acceptable and generally manageable with T-DXd.

Clinical trial identification: NCT03248492; NCT03523585; NCT03529110.

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Table: 377O IC efficacy summary

	T-DXd (N = 148)		Comp (N = 83)	
	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
CR	17 (16.3)	7 (15.9)	2 (3.4)	0
PR	30 (28.8)	13 (29.5)	14 (24.1)	3 (12.0)
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
NE	4 (3.8)	5 (11.4)	1 (1.7)	2 (8.0)
Missing	2 (1.9)	3 (6.8)	6 (10.3)	0
IC-ORR (CR + PR in brain), n (%)	47 (45.2)	20 (45.5)	16 (27.6)	3 (12.0)
IC-DoR, median, mo (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	2.8 (2.7-NE)
CNS-PFS, median (95% CI)	12.3 (11.1-13.8)	18.5 (13.6-23.3)	8.7 (6.3-11.8)	4.0 (2.7-5.7)

NE, not evaluable.

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378O Persistence under abemaciclib and endocrine treatment (ABA+ET) in patients with advanced breast cancer (aBC): First results of the randomized IMPACT trial comparing patient coaching with the MASCC oral agent teaching tool (MOATT) versus local routine patient coaching (LC)

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Background: Recent studies showed the positive impact of supportive care programs on patients. Possible benefits include the prevention of incorrect medication intake, a decrease of treatment-related symptoms and the reduction of hospitalization due to adverse events. MOATT is a standardized patient coaching program which might be suitable to improve the therapy management of BC patients with oral treatments. Aim of this study was to investigate the impact of MOATT on persistence and therapy management under ABA+ET.

Methods: IMPACT (NCT04030728) was a prospective randomized, controlled trial in patients with hormone receptor positive, HER2-negative aBC treated with ABA+ET. Patients were randomized to LC vs. MOATT. Primary endpoint was the persistence rate after 24 weeks of treatment. Further endpoints included compliance rate, the number of dose reduction and dose interruptions.

Results: A total of 211 patients were randomized between 06/20 and 02/22. Persistence probability after 24 weeks was 0.71 (95%CI 0.63-0.81) with LC and 0.82 (95%CI: 0.74-0.90) with MOATT (hazard ratio: 0.59 (95%CI: 0.32-1.07; $p_{log\text{-}rank} = 0.078$). Disease progression or death were the main reasons for therapy discontinuation in 14 cases in the LC arm and in 10 cases in the MOATT arm. A decision for a permanent discontinuation of ABA in the first 24 weeks was seen in 14 patients (14.1%) in the LC arm and 8 Patients (7.8%) in the MOATT arm. Dose reductions were planned in 24.5% of patients with LC and in 17.2% of patients in the MOATT arm. Therapy interruptions were planned in 14.9% of LC-patients and 10.1% in the MOATT arm.

Conclusions: The risk of therapy discontinuation within the first 24 weeks of treatment is clinically relevant. Coaching with MOATT reduced the probability for permanent therapy discontinuations by about 40% during the first 6 months of therapy. Standardized patient coaching improved therapy management of oral cancer therapies like abemaciclib. Patient coaching might be very useful to improve therapy management also in the adjuvant breast cancer setting.

Clinical trial identification: NCT04030728 and July 24, 2019.

Legal entity responsible for the study: Onco Medical Consult GmbH, Tennelbachstr. 59, D-65193 Wiesbaden.

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381O First-in-human/phase I trial of HS-20089, a B7-H4 ADC, in patients with advanced solid tumors

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Background: B7-H4, a transmembrane glycoprotein in the B7 superfamily, has limited expression in normal tissues but is highly expressed in various cancers. HS-20089 is a novel B7-H4 directed antibody-drug conjugate (ADC) with a drug to antibody ratio of 6. We conducted a first-in-human phase I trial to evaluate the dose-limiting toxicity (DLT), safety, tolerability, pharmacokinetics, and efficacy of HS-20089 in patients (pts) with advanced solid tumors refractory to standard therapy.

Methods: Eligible pts were enrolled in sequentially escalating dose cohorts (0.7 to 7.2 mg/kg) of HS-20089 administered intravenously every 3 weeks. The accelerated titration combined with Bayesian optimal interval (BOIN) was used as the dose escalation schedule in this phase I dose escalation trial.

Results: As of Apr. 11th, 2023, 44 pts with advanced solid tumors (41 breast cancers, 2 ovarian cancers, and 1 endometrial cancer) received HS-20089 treatment. Three DLTs were observed in 2 pts (both in 7.2 mg/kg). The most common treatment-emergent adverse events ($\geq$20%) were leukopenia, neutropenia, nausea, anemia, thrombocytopenia, vomiting, fatigue, increased alanine aminotransferase, anorexia, increased aspartate aminotransferase and hyponatremia. No interstitial lung disease and infusion reaction were reported. Of 33 response-evaluable pts, 8 partial responses (PRs) were observed in pts treated with HS-20089 (response rate: 24.2%), including 3 confirmed PRs and 5 PRs awaiting confirmation. The disease control rate was 63.6%. In the subset of 16 triple-negative breast cancer (TNBC) pts, 6 PRs were observed (response rate: 37.5%), including 2 confirmed PRs and 4 PRs awaiting confirmation. At potential target therapeutic dose (4.8 and 5.8 mg/kg), 5 PRs of 12 pts were observed (response rate: 41.7%) in TNBC. The patient achieving PR with the longest treatment duration of 403 days remains on treatment in 0.7 mg/kg cohort.

Conclusions: Based on data from the ongoing study, HS-20089 was well tolerated and showed antitumor activities in advanced solid tumors, with encouraging clinical efficacy in TNBC.

Clinical trial identification: NCT05263479.

Legal entity responsible for the study: Hansoh Pharmaceutical Group Co. Ltd.

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379MO Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/ metastatic triple-negative breast cancer (a/mTNBC): Updated results from BEGONIA, a phase Ib/II study

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Background: BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study in 1L a/mTNBC, evaluating D, an anti—PD-L1 antibody, plus novel therapies, including Dato-DXd, an antibody-drug conjugate made of a anti-TROP2 antibody covalently linked via a cleavable linker to a topoisomerase I inhibitor payload. Early data from BEGONIA Arm 7, Dato-DXd + D, showed promising responses. Updated results, including response duration (DoR), are reported.

Methods: Patients (pts) with unresectable a/mTNBC eligible for 1L treatment were enrolled, regardless of PD-L1/TROP2 expression, and received Dato-DXd 6 mg/kg IV + D 1120 mg IV Q3W until progression or unacceptable toxicity. PD-L1, assessed by the VENTANA PD-L1 (SP263) Assay, was high if ≥10% of the tumor area was populated by PD-L1—expressing tumor or immune cells. Primary endpoints were safety and tolerability. Secondary endpoints included investigator-assessed ORR, PFS (RECIST v1.1), and DoR.

Results: As of 2 Feb 2023, 62 pts received Dato-DXd + D (29 ongoing). Median follow-up was 11.7 (range 2—20) months (mos). At baseline, median pt age was 53 years; 60% had visceral metastases; 87% had PD-L1—low expression. Confirmed ORR was 79% (95% CI, 67—88); 6 (10%) pts had complete and 43 (69%) had partial responses. Response to treatment was irrespective of PD-L1 expression level. Median DoR was 15.5 mos (95% CI, 9.9—not calculable [NC]). Median PFS was 13.8 mos (95% CI, 11—NC). Nausea and stomatitis were the most common adverse events (AEs; 40 [65%] each). Any Grade (G) 3/4 AEs occurred in 35 (57%) pts and serious AEs in 14 (23%). Low rates of anemia (9 [15%]), diarrhea (8 [13%]), and neutropenia (3 [5%]) occurred. Adjudicated treatment-related interstitial lung disease/pneumonitis occurred in 3 (5%) pts (2 G2; 1 G1). No deaths due to treatment-related AEs occurred. 10 (16%) pts discontinued any study drug due to AEs. No new safety signals were reported.

Conclusions: Dato-DXd combined with D continues to demonstrate manageable safety and compelling high, durable response rates in 1L a/mTNBC. Further investigation is warranted. Translational data analysis is ongoing. Funding: AstraZeneca/ Daiichi Sankyo.

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380MO SKB264 (MK-2870) in previously treated hormone receptor-positive (HR+)/ HER2-negative metastatic breast cancer (mBC): Results from a phase I/II, single-arm, basket trial

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Background: TROP2 is commonly overexpressed in HR+/HER2- mBC and associated with poor prognosis. SKB264 is a novel anti-TROP2 ADC developed using sulfonyl pyrimidine-CL2A-carbonate linker to conjugate its payload, a belotecan-derivative topoisomerase I inhibitor, to achieve an average Drug-to-antibody Ratio (DAR) of 7.4. This is the first report of results from a phase II cohort in patients (pts) with HR+/ HER2- mBC.

Methods: Pts with HR+/HER2- (including HER2-low and HER2-zero) mBC received SKB264 at a dose of 5 mg/kg Q2W until progression or unacceptable toxicity. Eligibility included progression on endocrine-based therapy and at least one prior chemotherapy for mBC. Tumor assessment was performed every 8 weeks per RECIST v1.1 assessed by investigator.

Results: As of data cut-off (April 12, 2023), 41 pts (median age 50 yrs [34-66], 61% ECOG PS 1) were enrolled. Median follow-up was 8.2 months (mo). Treatment-related adverse events (TRAEs) of ≥ Grade 3 were reported in 48.8% (20/41) of pts. The most common ≥ Grade 3 TRAEs (≥ 5%) were neutrophil count decreased (36.6%), white blood cell count decreased (22%), anemia (14.6%), platelet count decreased (9.8%) and GGT increase (7.3%). TRAEs led to dose reduction in 17.1% (7/41) of pts. No neuropathy or drug-related ILD/pneumonitis was reported. No TRAEs led to treatment discontinuation or death. Of 38 pts evaluable for response assessment, 47% of pts had primary endocrine resistance; 79% of pts had received ≥2 prior chemotherapy for metastatic disease, and prior treatments included taxane (100%), and CDK 4/6 inhibitors (65.8%). The ORR was 36.8% (14/38, 12 confirmed PR and 2 unconfirmed PR) and DCR was 89.5%, median DoR was 7.4 mo (range, 4.2 to 14.9+), 6-mo DoR rate was 80%. Median PFS was 11.1 mo (95% Cl: 5.4, 13.1), and 6-mo PFS rate was 61.2%.

Conclusions: SKB264 at 5 mg/kg demonstrates a manageable safety profile and promising antitumor activity in pts with pre-treated HR+/HER2- mBC. Two phase 3 studies are currently planned in HR+/HER2- mBC, one in China for pts after at least one chemo for mBC and a second global for pts previously untreated with chemo for mBC, both comparing SKB264 vs investigator selected chemo.

Clinical trial identification: NCT04152499.

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382MO Updated results from the phase I/II study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer

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Background: OP-1250 is a small molecule CERAN/SERD with antitumor activity in breast cancer (BC) xenograft models, including *ESR1*/*PIK3CA* mutations and brain metastasis. OP-1250 was administered at 30—300 mg daily (qd) in the dose-escalation part of a phase 1 study. Maximum tolerated dose was not reached and no dose-limiting toxicities occurred. OP-1250 at 60 mg and 120 mg was assessed in the dose-expansion part. Based on safety, pharmacokinetics, and preliminary antitumor activity, 120 mg qd was selected as the recommended phase 2 dose. Here we present the phase 1/2 study data (phase 2 is ongoing).

Methods: Pts with measurable and nonmeasurable disease were included. Eligible women (any menopausal status) and men had received $\leq$4 lines of endocrine therapy (ET) and $\leq$1 line of chemotherapy for metastatic disease. Pts with stable brain metastasis had to have $\geq$1 prior line of ET and $\leq$3 prior lines of chemotherapy (both for metastatic disease). Tumor assessment (RECIST v1.1) occurred every 8 weeks (NCT04505826).

Results: By March 17, 2023, of 86 pts on OP-1250 (120 mg), 66% had $\geq$2 prior lines of ET, 30% prior chemotherapy, 67% prior fulvestrant, and 98% prior cyclin-dependent kinase 4/6 inhibitors (CDK4/6i); 45% (34/75) of pts with available baseline ctDNA had *ESR1* mutations. The most common ($\geq$15% of pts) all-grade treatment-emergent adverse events (AEs) were nausea, vomiting, neutropenia, fatigue, headache, constipation, and diarrhea. The most common grade 3/4 treatment-related AEs were neutropenia (9%), nausea (3%), and vomiting (3%). Neutropenia was reversible; 3 pts with grade 4 neutropenia were rechallenged at a lower dose without recurrence. There were 4 partial responses (3 confirmed) with a clinical benefit rate of 40% (23/57). In pts with an *ESR1* mutation, CBR was 50% (11/22). D[NZ1] [NZ2] ata continue to mature and updated data will be presented.

Conclusions: OP-1250 (120 mg qd) was well tolerated with promising efficacy in heavily pretreated pts, including pts progressing on fulvestrant and CDK4/6i. A phase 3 monotherapy study in metastatic BC (second/third line) is planned in 2023.

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383MO Imlunestrant with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase Ia/b EMBER study

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Background: Imlunestrant is an investigational, next-generation, oral SERD designed to deliver continuous ER target inhibition, including in *ESR1*-mutant BC. In the first-in-human phase 1a/b EMBER study, imlunestrant demonstrated favorable safety, pharmacokinetics (PK), and clinical benefit rate when administered as monotherapy (Jhaveri ASCO 2022) or with abemaciclib (Jhaveri SABCS 2022). We present the first clinical data of imlunestrant with everolimus or alpelisib and updated imlunestrant monotherapy data from the EMBER study (NCT04188548).

Methods: Patients (pts) received imlunestrant alone as part of the phase 1a (escalation) or 1b (expansion), or with everolimus or alpelisib in 1b. Key phase 1b eligibility

included ER+, HER2- aBC, prior endocrine therapy (ET) sensitivity, ≤2 prior therapies, and a *PIK3CA* mutation (alpelisib arm only). Assignment to phase 1b treatment arms was made by investigators. Men and premenopausal women received GnRH agonist. Key endpoints included RP2D, safety, PK, ORR (complete response [CR] plus partial response [PR]) and CBR (CR or PR, or stable disease ≥24 weeks) per RECIST v1.1.

Results: As of 6 Oct 2022, 114 pts received imlunestrant monotherapy, 42 pts received imlunestrant + everolimus, and 21 pts received imlunestrant + alpelisib. Baseline characteristics were similar across combination cohorts; 46% pts had visceral disease and 46% had an *ESR1* mutation at baseline. Median number of prior aBC therapies in combination cohorts was: 1 (range 1-2); including prior ET (100%), CDK4/6i (100%), fulvestrant (35%) and chemo (17%). No cardiac or ocular toxicity was seen. Safety and preliminary efficacy are presented (Table).

Table: 383MO Safety and preliminary efficacy

Endpoint	Imlunestrant monotherapy (n=114)	Imlunestrant + everolimus (n=42)	Imlunestrant + alpelisib (n=21)
All-grade treatment emergent AEs (TEAEs) - %	Nausea — 40 Fatigue — 32 Diarrhea — 31	Diarrhea — 55 Fatigue — 45 AST increase — 38	Diarrhea — 86 Rash — 67 Hyperglycaemia - 62
Grade ≥3 treatment related AEs (TRAEs) - %	5 Fatigue — 2 Neutropenia — 2	19 Hypertriglyceridemia — 5 AST increase — 5	62 Rash — 43 Hyperglycemia - 10
Dose reductions due to TRAEs - %			
Imlunestrant alone	2	0	0
Everolimus/alpelisib alone	N/A	12	24
Both	N/A	2	14
Discontinuations due to TRAEs - %			
Imlunestrant alone	0	0	0
Everolimus/ alpelisib alone	N/A	2	29
Both	N/A	0	0
ORR (%)	7/75 (9)	6/28 (21)	6/12 (50)
CBR (%)	48/114 (42)	26/42 (62)	13/21 (62)

AEs = adverse events.

Conclusions: Imlunestrant alone or in combination with everolimus or alpelisib demonstrated robust efficacy in pts with pre-treated ER+, HER-2 aBC. Toxicities were consistent with the known safety profile of both alpelisib and everolimus.

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Hamilton: Financial Interests, Institutional, Other, Consulting/Advisory Role: Genentech/Roche, Novartis, Lilly, Pfizer, Mersana, iTeos, Janssen, Loxo, Relay Therapeutics, Olema Pharmaceuticals, Orum Therapeutics, Stemline Therapeutics, AstraZeneca, Daiichi Sankyo, SeaGen, Ellipses Pharma, Greenwich LifeSciences, Tubulis, Verascity Science, Theratechnologies; Financial Interests, Institutional, Research Grant: Oncomed, Genentech/Roche, Zymeworks, Rgenix, Arqule, Clovis, Millennium, Acerta Pharma, Sermonix Pharmaceuticals, Black Diamond, Karyopharm, Curis, Syndax, Novartis, Boehringer Ingelheim, Immunomedics, FujiFilm, Taiho, Deciphera, Molecular Templates, Onconova Therapeutics, Dana Farber Cancer Inst, Hutchinson MediPharma, MedImmune, SeaGen, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Merus, Regeneron, Arvinas, StemCentRx, Verastem, eFFECTOR Therapeutics, CytomX, InventisBio, Lycera, Mersana, Radius Health, Abbvie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, PharmaMar, Olema, Immunogen, Plexxicon, Amgen, Akesobio Australia, Shattuck Labs, ADC Therapeutics, Aravive, Atlas MedX, Ellipses Pharma, Incyte, Jacobio, Mabspace Biosciences, ORIC Pharmaceuticals, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Repertoire Immune Medicine, Treadwell Therapeutics, Accutar Biotechnology, Artios, BeiGene, Bliss BioPharmaceuticals, Cascadian Therapeutics, Context Therapeutics, Cullinan, Dantari, Duality Biologics, Elucida Oncology, Infinity Pharmaceuticals, K-Group Beta, Kind Pharmaceuticals, Loxo Oncology, Oncothyreon, Orum Therapeutics, Prelude Therapeutics, Profound Bio, Relay Therapeutics, Tolmar, Torque Therapeutics K. 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Hoffmann - La Roche Ltd, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Piere Fabre, PintPharma, Puma, Roche Farma, Sanofi-Aventis, SeaGen, Zymeworks, Genentech, Innoup, Millenium, Pharmalex Spain SLU; Financial Interests, Personal, Other, SC: Byondis B.V., Glaxo, Macrogenics, Menarini, Merus, Synthon Biopharpaceuticals; Financial Interests, Institutional, Research Grant: AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Cytomx Therapeutics, Daiichi Sankyo, Eli Lilly and Company, F. 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Meniawy: Financial Interests, Personal, Other, Honoraria: AstraZeneca/MedImmune; Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca/MedImmune; Bristol Myers Squibb; GSK; Novartis; Financial Interests, Institutional, Research Funding: AstraZeneca/MedImmune; Bayer; BeiGene; Bristol Myers Squibb; Incyte; Merck Serono; Regeneron; Roche/Genentech; Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Bristol Myers Squibb. F. Bacchion, R. Ismail-Khan, Y. Li, S.T. Estrem, B. Nguyen: Financial Interests, Personal, Stocks or ownership: Eli Lilly and Company; Financial Interests, Personal, Full or part-time Employment: Eli Lilly and Company. All other authors have declared no conflicts of interest.

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384MO Final overall survival analysis for fulvestrant vs anastrozole in endocrine therapy (ET)-naïve, hormone receptor-positive (HR+) advanced breast cancer (FALCON)

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Background: The phase 3 international, randomised, double-blind FALCON trial (NCT01602380) met its primary endpoint showing a statistically significant improvement in progression-free survival (PFS) with fulvestrant vs anastrozole as a first-line treatment for HR+ advanced breast cancer (BC). PFS improvement was confined to non-visceral disease (HR=0.59 [95% CI 0.42—0.84]) vs visceral disease (HR=0.99 [95% CI 0.74—1.33]). At the primary analysis, interim overall survival (OS) data were immature (31%). Here we report the prespecified final analysis of OS.

Methods: Postmenopausal women with ET-naïve, HR+/HER2— locally advanced or metastatic BC were randomised 1:1 to fulvestrant (500 mg, Days 0, 14 and 28, then monthly thereafter) or anastrozole (1 mg, daily). Secondary endpoints of OS, safety, and quality of life (QoL) are reported. The final OS analysis was triggered at a threshold of 65% maturity and ≥8 years since the last patient was enrolled, with an available 1-sided alpha of 0.01845.

Results: In the overall population (462 patients; 68% maturity; cut-off 11 July 2022), median OS was 44.8 months with fulvestrant vs 42.7 months with anastrozole (HR=0.97 [95% CI 0.77—1.21]; p=0.7579). Median OS across prespecified subgroups was consistent with the overall population. In patients with non-visceral disease, a 15% reduction in the risk of death was observed with fulvestrant vs anastrozole, although statistical significance was not reached (Table). No meaningful differences were seen in QoL. No new safety signals emerged.

Table: 384MO Median OS for visceral and non-visceral disease [DCO 11 July 2022]

	Median OS, months		HR (95% CI)
	Fulvestrant	Anastrozole	
Non-visceral disease	n=95 65.2	n=113 47.8	0.85 (0.60−1.20)
Visceral disease	n=135 37.2	n=119 40.7	1.06 (0.80−1.42)

CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.

Conclusions: At the final analysis of FALCON, no significant difference in OS was seen between fulvestrant and anastrozole in ET-naïve postmenopausal women with HR+/HER2− locally advanced or metastatic BC. The positive trend observed in OS for fulvestrant in non-visceral disease compared with visceral disease is consistent with the primary analysis.

Clinical trial identification: NCT01602380.

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385MO A multicenter, open-label, dose escalation and expansion study of DP303c in patients with HER2-positive pre-treated advanced solid tumors

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Background: DP303c is a HER2-targeting ADC with a cleavable linker-MMAE payload. Pre-clinical study demonstrated similar to or better antitumor activity than T-DM1 in xenograft models. Here we present the safety and efficacy of DP303c in patients (pts) with HER2-positive pre-treated advanced solid tumors.

Methods: Adult pts with HER2-positive advanced solid tumors who were not eligible to receive standard of care (SoC) or had no SoC, or failed SoC were recruited. This phase I study consisted of dose escalation with a modified 3+3 design at DP303c 0.5, 1.0, 2.0, 3.0 and 4.0 mg/kg, and then dose expansion at 3.0 mg/kg, intravenously administered every 3 weeks. The primary endpoints were safety and RP2D.

Results: As of 28 Feb 2023, 94 pts were enrolled in dose escalation (22 pts) and dose expansion (72 pts). The median follow-up was 11.98 months (mo). Median age was 51.5 yrs (range: 28-73). Tumor types were breast cancer (BC, 68 pts), colorectal cancer (10 pts), gastric cancer (9 pts) and others (7 pts). ECOG PS was 0 in 15 pts (16.0%), and 1 in 79 pts (84.0%). All 94 pts received $\geq$ 1 prior line of systemic therapy. 65 pts (95.6%) with BC received $\geq$ 2 prior lines of systemic therapy. One dose limiting toxicity [Grade (G) 3 eye pain] was observed in 4.0 mg/kg with 3.0 mg/kg selected as expansion dose. Treatment-related adverse events (TRAEs) of any grade occurred in all 94 pts, in which 34 (36.2%) were G $\geq$ 3. The most common G $\geq$ 3 TRAEs were vison blurred (16.0%), xerophthalmia (6.4%), and neuropathy peripheral (3.2%). No treatment-related death occurred. Among 91 efficacy evaluable pts, ORR and DCR were 42.9% (95%CI: 32.5-53.7) and 68.1% (95%CI: 57.5-77.5). The median PFS and DoR were 4.44 mo (95%CI: 3.35-6.44) and 10.97 mo (95%CI: 3.98-NA) for all 94 pts. The minimal effective dose was 1.0 mg/kg in BC. Among 66 efficacy evaluable pts with BC, ORR and DCR were 51.5% (95%CI: 38.9-64.0) and 77.3% (95%CI: 65.3-86.7). The median PFS and DoR were 6.44 mo (95%CI: 4.14-8.51) and 10.97 mo (95%CI: 3.98-NA) for all 68 pts with BC.

Conclusions: DP303c demonstrated promising anti-tumor activity with acceptable safety in pts with pre-treated advanced solid tumors, especially BC. The pivotal phase II study in pts with BC is ongoing.

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Legal entity responsible for the study: The authors.

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386MO Trastuzumab duocarmazine versus physician's choice therapy in pre-treated HER2-positive metastatic breast cancer: Final results of the phase III TULIP trial

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Background: Trastuzumab duocarmazine (T-Duo, SYD985) is a HER2-targeting antibody-drug conjugate comprised of trastuzumab bound to the DNA alkylating agent duocarmazine with a drug-antibody ratio of 2.4 to 2.8. TULIP is a randomized, international, multicenter, phase 3 study in patients with pre-treated HER2-positive metastatic breast cancer (MBC). The initial analysis of the primary endpoint progression free survival (PFS) showed a clinically meaningful and statistically significant difference in favor of T-Duo versus physician's choice (PC) (Saura *et al.*, ESMO 2021). At that time, preliminary overall survival (OS) data were reported. Final OS and updated secondary outcomes are reported here.

Methods: The TULIP trial randomly assigned patients with HER2-positive locally advanced or MBC with $\geq$2 previous HER2-targeting MBC regimens or pretreated with T-DM1, in a 2:1 ratio between T-Duo (1.2 mg/kg q3w) and PC. PC could be either trastuzumab combined with capecitabine or vinorelbine or eribulin or lapatinib plus capecitabine. The primary endpoint was PFS by blinded, independent, central review. Key secondary endpoints are PFS by investigator, OS, overall response rate, QoL, duration of response and safety.

Results: A total of 291 patients were randomized to the T-Duo group and 146 to the PC group. At the data cut off, the median follow-up of the T-Duo and PC groups were 35.6 months and 32.0 months, respectively. Median OS was 21.0 months in the T-Duo group and 19.5 months in the PC group. The hazard ratio was 0.87 (95% CI 0.68, 1.12) p=0.236. The 1-year survival estimate was 70% in the T-Duo group and 68% in the PC group. The primary endpoint PFS (7.0 vs 4.9 months, HR 0.63, p=0.002) and other secondary efficacy outcomes did not change in this analysis compared to the initial analysis. No new safety findings were observed with longer follow-up.

Conclusions: T-Duo showed a meaningful and statistically significant improvement in PFS in patients with pre-treated HER2-positive MBC. The final OS results confirm a trend towards a numerically prolonged OS (statistically non-significant) in the T-Duo group compared with PC group. Safety was aligned with the primary analysis, with no new signals identified.

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AstraZeneca, Lilly, Novartis, Pfizer, Roche/Genentech, GSK, Zentalis pharmaceuticals, Repare therapeutics, GSK, Relay therapeutics, Gilead, Inivata, Guardant, Exact Sciences; Financial Interests, Institutional, Funding: AstraZeneca, Pfizer, Roche/Genentech, Merck Sharpe and Dohme, Invitae, Inivata, Personalis, Natera; Financial Interests, Institutional, Other, provision of materials: BioRad; Financial Interests, Institutional, Other, Provision of assays: Guardant Health. J. O'Shaughnessy: Financial Interests, Personal, Advisory Board: Abbvie, Agendia, Amgen, Aptitude Health, AstraZeneca, Bristol Myers Squibb, Celgene, Eisai, G1 Therapeutics, Genentech, Immunomedics, Ipsen Biopharmaceuticals, Lilly, Merck, Myriad, Novartis, Ondonate, Pfizer, Puma, Prime Oncology, Roche, Seattle Genetics, Syndax, Carrick Therapeutics, Daiichi Sankyo, Gilead Sciences, Ontada, Pierre Fabre Pharmaceuticals, Samsung Bioepis, Sanofi. 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X. Song: Financial Interests, Personal, Advisory Board: EMD, BMS, Novartis, Pfizer, merck; Financial Interests, Institutional, Local PI: AstraZeneca, BMS, Gilead, Novartis, Pfizer, Roche, Seagen. N. Koper: Financial Interests, Personal, Full or part-time Employment, VP Clinical Development: Byondis B.V.. C. Saura Manich: Financial Interests, Personal, Advisory Board: AstraZeneca, Boehringer Ingelheim, Bristol Meyers Squibb, Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann - La Roche Ltd, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Piere Fabre, PintPharma, Puma, Roche Farma, Sanofi-Aventis, SeaGen, Zymeworks, Genentech, Innoup, Millenium, Pharmalex Spain SLU; Financial Interests, Personal, Other, SC: Byondis B.V., Glaxo, Macrogenics, Menarini, Merus, Synthon Biopharpaceuticals; Financial Interests, Institutional, Research Grant: AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Cytomx Therapeutics, Daiichi Sankyo, Eli Lilly and Company, F. Hoffmann-La Roche Ltd, Genentech, GSK, Immunomedics, Innoup Farma, Macrogenics, Menarini Ricerche, Merus, Novartis, Pfizer, Puma, Roche, Sanofi-Aventis, Seattle Genetics; Financial Interests, Institutional, Coordinating PI: Byondis B.V.; Non-Financial Interests, Member: Spanish Society of Medical Oncology (SEOM), American Society for Clinical Oncology (ASCO), Geicam (Spanish Breast Cancer Research Group), European Society for Medical Oncology (ESMO), Sinology Society of the Official College of Physicians of Barcelona (COMB); Non-Financial Interests, Member, Junta Directiva y Comité Científico: SOLTI group (Academic research group in breast cancer). All other authors have declared no conflicts of interest.

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387MO First results of the SOLTI-1903 HOPE's patient-centric molecular screening program in advanced breast cancer

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Background: The SOLTI-1903 HOPE study aims to assess the feasibility of a molecular screening program promoting active participation of patients with Advanced Breast Cancer (ABC) in the management of their disease to better characterize the genomic landscape of ABC and to facilitate pt access to matched-targeted therapies in Spain.

Methods: HOPE (NCT04497285) is a patient-centric study where pts diagnosed with ABC lead their inclusion, participation, and follow-up through a digital tool (DT). They report clinical information and provide archival tumor samples to be analyzed by FoundationOne CDx. At progression disease, patients undergo a liquid biopsy with the Guardant360 panel. Clinical and genomic information is discussed by a Molecular Advisory Board (MAB) that issues a report explaining the alterations and enumerating potentially useful targeted treatments. Then, participants record disease evolution in the DT for 2y. The primary objective is to assess the real-world clinical practice of integrating molecular profiling into the Standard of Care management of pts with ABC.

Results: Between Oct 2020 and Feb 2022, 604 patients were included in the study, and the median age was 51 ys (range 27-82y). The most common reported IHC subtype was ER+/HER2- (74%), followed by HER2+ (14%) and triple negative (12%). 512 tumor samples were received from 423 patients, and DNA-seq results with positive results were obtained in 298 (58%) cases. Common alterations were PIK3CA mut (34%), CCND1 amp (27%), and TP53 mut (26%). Blood extractions were obtained from 378 patients, and ctDNA detection was observed in 303 (80%) cases. Frequently mutated genes were PIK3CA (38%), TP53 (38%), and ESR1 (29%). As of April 2023, the MAB reviewed 306 cases, observing at least one ESCAT I-III alteration in 75% of cases. Of these, only 15% were already known before HOPE. After a mean follow-up of 1.3ys, 20% of ABC cases discussed received a targeted treatment.

Conclusions: Patient-centric molecular screening programs implemented on a nationwide level are viable, have the potential to impact treatment decisions in a subgroup of patients and seems more efficient to bring patients to receive treatments targeted to the identified alterations.

Clinical trial identification: NCT04497285.

Legal entity responsible for the study: SOLTI Cancer Research Group.

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388P Subgroup analysis of patients (pts) with HER2-low metastatic breast cancer (mBC) with brain metastases (BMs) at baseline from DESTINY-Breast04, a randomized phase III study of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC)

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Background: The DESTINY-Breast04 trial (NCT03734029) demonstrated significantly improved progression-free survival (PFS) and overall survival (OS) in pts with HER2-low mBC treated with T-DXd vs TPC. Consistent efficacy was also demonstrated in pts with BMs at baseline with T-DXd vs TPC. In this exploratory analysis, we provide additional intracranial (IC) efficacy data in pts with BMs at baseline.

Methods: Pts with centrally confirmed HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization−) mBC who were previously treated with 1 or 2 lines of chemotherapy were randomized (2:1) to T-DXd or TPC. Pts with investigator-assessed clinically stable and treated BMs at baseline were eligible, and exploratory analyses of IC clinical activity were completed. Analysis was based on central review of brain MRI or CT scans. Endpoints included IC objective response rate (ORR) by blinded independent central review (BICR), best overall response, clinical benefit rate, disease control rate, and IC PFS by BICR.

Results: Of 35 pts with BICR-assessed BMs at baseline, 24 pts received T-DXd and 11 received TPC. Like the full dataset, most pts with BMs at baseline had hormone receptor-positive tumors (T-DXd, 75.0%; TPC, 72.7%). Of those pts who received $\geq$1 dose of trial drug, median treatment duration was 6.6 mo (mo; range, 0.3-24.3 mo) for T-DXd (n = 24) and 1.4 mo (range, 0.4-17.4 mo) for TPC (n = 9); 20.8% and 11.1% of these pts remained on T-DXd and TPC for >12 mo, respectively. IC response data are shown in the table. Median IC PFS by BICR for T-DXd was 9.7 mo (95% CI, 4.4-15.1 mo) vs not evaluable for TPC, due to small pt numbers.

Table: 388P Summary of intracranial responses

	T-DXd n = 24	TPC n = 11
Intracranial confirmed ORR (CR + PR), n (%) [95% CI][a]	6 (25.0) [9.8-46.7]	0 [0-28.5]
Best overall intracranial response, n (%)		
CR	4 (16.7)	0
PR	2 (8.3)	0
SD	12 (50.0)	7 (63.6)
PD	0	1 (9.1)
NE	1 (4.2)	0
Missing[b]	5 (20.8)	3 (27.3)
Clinical benefit rate (CR + PR + (>6 mo) SD), n (%) [95% CI][a]	14 (58.3) [36.6-77.9]	2 (18.2) [2.3-51.8]
Disease control rate (CR + PR + SD), n (%) [95% CI][a]	18 (75.0) [53.3-90.2]	7 (63.6) [30.8-89.1]

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. [a]Based on Clopper-Pearson method for single proportion. [b]Imaging not performed/available.

Conclusions: In this exploratory analysis, IC responses favored T-DXd over TPC in pts with clinically stable and treated baseline BMs. While only a small number of pts were included here, the IC efficacy data suggest a clinical benefit of T-DXd over TPC.

Clinical trial identification: NCT03734029.

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389P Efficacy and safety analyses by prior lines of chemotherapy from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC)

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Background: SG is a Trop-2–directed antibody-drug conjugate approved for pretreated HR+/HER2- (IHC 0, 1+, or 2+/ISH-) mBC in the US. In the TROPiCS-02 study, SG treatment showed statistically significant improvement in progression-free survival (PFS; hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.53-0.83) and overall survival (OS; HR 0.79; 95% CI 0.65-0.96) vs TPC with manageable safety in pts with pretreated HR+/HER2- mBC (Rugo et al. ESMO 2022). Outcomes worsen with multiple prior lines of chemotherapy (LoT). We present a post-hoc analysis of outcomes with SG vs TPC by prior LoT from TROPiCS-02.

Methods: Pts with HR+/HER2- mBC and $\geq$ 1 endocrine therapy, taxane, and CDK4/6 inhibitor, and 2 to 4 prior LoT for mBC, were randomized to SG (10 mg/kg IV Days 1 and 8, Q3W) or TPC. The primary endpoint was PFS; secondary endpoints included OS, objective response rate (ORR), clinical benefit rate (CBR), and safety. This analysis included pts with 2 vs $\geq$ 3 prior LoT in the metastatic setting.

Results: 543 pts were randomized to SG (n = 272; 113 (42%) had 2 prior LoT, 159 (58%) had $\geq$ 3) and TPC (n = 271; 120 (44%) had 2 prior LoT, 151 (56%) had $\geq$ 3). Baseline characteristics were similar in pts with 2 and $\geq$ 3 prior LoT and across treatments. Median PFS and OS were improved with SG vs TPC irrespective of prior LoT, with HR of 0.61 and 0.82 in pts with 2 prior LoT and 0.72 and 0.78 in pts with $\geq$ 3 prior LoT, respectively (Table). CBR was improved with SG vs TPC in pts with 2 and $\geq$ 3 prior LoT, ORR was improved in pts with 2 prior LoT, and the safety profile was similar in both subgroups (Table).

Table: 389P

Efficacy, ITT	2 Prior LoT		≥3 Prior LoT	
	SG (n=113)	TPC (n=113)	SG (n=159)	TPC (n=158)
Median PFS[a,b] (95% CI), mo	5.7 (4.2-8.5)	4.1 (2.8-5.6)	5.3 (4.0-6.9)	4.0 (2.9-4.4)
HR (95% CI)	0.61 (0.44-0.84)		0.72 (0.54-0.97)	
Median OS[c] (95% CI), mo	15.3 (12.7-19.8)	12.4 (10.4-14.9)	13.9 (12.3-15.5)	10.3 (8.7-12.4)
HR (95% CI)	0.82 (0.60-1.12)		0.78 (0.61-1.01)	
ORR[a,c](95% CI), %	30 (22-39)	16 (10-24)	14 (9-21)	13 (8-19)
CBR[a,c](95% CI), %	41 (32-50)	25 (17-34)	29 (22-37)	20 (14-27)
Safety, all treated, n (%)	**SG (n=112)**	**TPC (n=109)**	**SG (n=156)**	**TPC (n=140)**
Any grade TEAEs[c]	112 (100)	106 (97)	156 (100)	133 (95)
Grade 3/4	79 (71)	58 (53)	113 (72)	92 (66)

[a]Per independent central review. [b]Data cutoff: Jan 3, 2022; [c]Jul 1, 2022.

Conclusions: Regardless of number of prior LoT, SG demonstrated improved efficacy vs TPC in pts with HR+/HER2- mBC, with manageable safety across subgroups. Findings are consistent with the ITT population, demonstrating the potential for pts to benefit from SG in earlier LoT. Table

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390P Vepdegestrant, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer: Update of dose escalation results from a phase I/II trial

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Background: Vepdegestrant (ARV-471), an oral PROTAC ER degrader, was well tolerated and had clinical activity in heavily pretreated patients (pts) with ER+/HER2- advanced breast cancer in the phase 1 dose escalation (data cutoff: Sep 30, 2021) and phase 2 expansion cohort portions of a phase 1/2 study (NCT04072952). We present updated phase 1 dose escalation data after an additional 13 months of follow-up.

Methods: Eligible pts had ER+/HER2- advanced breast cancer, ≥1 prior cyclin-dependent kinase (CDK)4/6 inhibitor, and ≥2 prior endocrine therapies. Primary endpoints were safety, tolerability, and recommended phase 2 dose.

Results: As of Nov 1, 2022, 83 pts (median age: 64 y [range: 36–80]; 99% female) received vepdegestrant (30–700 mg total daily dose). Pts had a median of 4 prior regimens (range: 0–10; 100% prior CDK4/6 inhibitors, 81% prior fulvestrant, and 82% prior chemotherapy [60% in metastatic setting]). There were no dose-limiting toxicities. Treatment-related adverse events were mostly grade 1/2 (Table). Clinical benefit rate (rate of confirmed complete or partial response [PR] or stable disease ≥24 wks) for evaluable pts (n=76) was 37% (95% CI: 26–49). Of 64 pts with baseline measurable disease, 6 had a confirmed and 4 an unconfirmed PR. At data cutoff, 27 pts had treatment for ≥24 wks (7 for ≥48 wks) with 10 pts ongoing. Pharmacokinetics (PK) showed dose-dependent exposure for 30–500 mg daily doses. Substantial on-treatment reductions in mutant *ESR1* circulating tumor DNA levels were observed.

Table: 390P TRAEs reported in ≥10% of pts overall

	30–700 mg total daily dose (n=83)		
	Any grade	Grade 1/2	Grade 3[a]
Any TRAE, n (%)	58 (70)	53 (64)	5 (6)[b]
Nausea	20 (24)	19 (23)	1 (1)
Fatigue	20 (24)	20 (24)	0
Arthralgia	11 (13)	11 (13)	0
Constipation	11 (13)	11 (13)	0
Hot flush	10 (12)	10 (12)	0

[a]No grade ≥4 TRAEs occurred in any pts [b]Other grade 3 TRAEs not listed were headache (n=1), increased aspartate aminotransferase (n=1), increased amylase (n=1), increased lipase (n=1), QT prolongation (n=1), and venous embolism (n=1); pts may have experienced more than one TRAE TRAE=treatment-related adverse event

Conclusions: Vepdegestrant continued to be well tolerated across all doses and showed clinical activity in heavily pretreated pts with ER+/HER2- advanced breast cancer; PK was dose-dependent up to 500 mg daily. Data support further development of vepdegestrant; the ongoing phase 3 VERITAC-2 study (NCT05654623) is evaluating vepdegestrant 200 mg once daily vs fulvestrant.

Clinical trial identification: NCT04072952.

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391P Detrimental effect on overall survival of CDK4/6 inhibitor dose reduction if immortal time bias is considered

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Background: Since 2017, the combination of CDK4/6 inhibitors and endocrine therapy has been the standard first-line treatment for patients diagnosed with hormone-positive/HER2-negative metastatic breast cancer (mBC) in Denmark. Previous analyses, based on randomized phase III studies, have shown that the clinical benefit

remains after CDK4/6i dose reduction, but analyses may have been susceptible to immortal time bias.

Methods: This real-world cohort study is based on electronic health records from 695 patients from the capitol region of Denmark who initiated first-line treatment for mBC with CDK4/6i between May 2017 and October 2022. We used landmark Kaplan-Meier estimates and Cox regression to examine the association of dose reduction with treatment duration and overall survival. Patients were categorized based on dose reduction from the recommended dose prior to the landmark, defined at 3 months after initiation of treatment. Hazard ratios were adjusted for CDK4/6i agent, age, comorbidity, BMI, LDH > ULN, ECOG performance status and visceral metastases.

Results: A total of 530 patients were eligible for inclusion in the landmark analysis and 198 (37%) were categorized into the dose reduction group. Patients with dose reduction were significantly older and more had received prior endocrine therapy. Dose reduction was significantly associated with overall survival and shorter treatment duration, 39.6 vs 55.6 months (95%CI: 35.5-NE vs 49.9-NE) and 19.6 vs. 30.3 months, respectively. Adjusted hazard ratio for death was 1.49 for patients with dose reduction (95% CI: 1.01-2.22).

Table: 391P

Characteristic	Dose reduction, N = 198[1]	Full dose, N = 332[1]	p-value
CDK4/6i			0.14
Abemaciclib	48 (24%)	99 (30%)	
Palbociclib	104 (53%)	145 (44%)	
Ribociclib	46 (23%)	88 (27%)	
Age	72 (63, 78)	67 (58, 75)	<0.001
Primary metastatic	51 (26%)	102 (31%)	0.2
Prior endocrine treatment	144 (73%)	199 (60%)	0.003
Charlson Comorbidity Index[2]			0.3
0	145 (73%)	256 (77%)	
1	31 (16%)	52 (16%)	
2+	22 (11%)	24 (7%)	
Visceral metastasis[3]	41 (55%)	41 (55%)	>0.9
ECOG Performance Status[3]			0.2
0	30 (50%)	45 (66%)	
1	25 (42%)	20 (29%)	
2	5 (8.3%)	3 (4.4%)	
Unknown	15	7	

[1]n (%); Median (IQR). [2]Modified to exclude solid tumors. [3]Manual review of a random sample of 75 patients in each group.

Conclusions: Dose reduction of CDK4/6i within the first 3 months was associated with significantly higher mortality and shorter treatment duration. These findings contrast previous analyses that have shown no effect of dose reduction on treatment efficacy. Consideration of immortal time bias in this study may be a decisive reason for the disparate findings.

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392P The prognostic impact of BMI in patients with HR+/HER2- advanced breast cancer on first-line endocrine therapy with or without a CDK 4/6 inhibitor

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Background: This study aims to determine the prognostic impact of body mass index (BMI) in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC).

Methods: All patients (≥18 years) diagnosed with HR+/HER2- ABC who received first-line endocrine therapy with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor between 2007 and 2020 in the Netherlands were identified from the Southeast Netherlands Advanced Breast Cancer Registry (SONABRE). Patients with a recorded BMI at diagnosis were classified as underweight (BMI: <18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30 kg/m^2). Progression-free survival (PFS) and overall survival (OS) were compared between BMI classes using multivariable Cox regression analyses.

Results: This study included 35 (2.4%) underweight, 580 (39.8%) normal weight, 479 overweight (32.9%), and 362 (24.9%) obese patients. The presence of bone-only metastases increased with a higher BMI, whereas the presence of visceral metastases decreased (p for trend = <0.001). When compared with other BMI classes, underweight patients had a worse WHO performance status (p = <0.001) and were more frequently diagnosed with *de novo* metastatic disease (p = 0.001). Median follow-up time was 60.9 months (interquartile range (IQR): 37.5-96.0). When compared with normal weight patients, no differences in PFS were observed in underweight (hazard ratio (HR)=1.05; 95% confidence interval (CI): 0.73-1.51), overweight (HR=0.90; 95% CI: 0.79-1.03), or obese patients (HR=0.88 (95% CI: 0.76-1.02). However, the OS of underweight patients (HR=1.45; 95% CI: 0.97-2.15) tended to be worse, whereas the OS of overweight (HR=0.99; 95% CI: 0.85-1.16) and obese patients (HR=1.04; 95% CI: 0.88-1.24) was similar to the OS of normal weight patients.

Conclusions: In this cohort of 1,456 patients with HR+/HER2- ABC, overweight and obesity were prevalent, while underweight was uncommon. When compared with normal weight patients, overweight and obese patients did not experience a decrease in either PFS or OS. Interestingly, however, underweight seemed to be an adverse prognostic factor for OS.

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393P Real-world (RW) use patterns, effectiveness, and tolerability of sacituzumab govitecan (SG) for second-line (2L) and later treatment of metastatic triple-negative breast cancer (mTNBC)

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Background: SG is a Trop-2-directed antibody-drug conjugate approved in multiple countries for patients (pts) with mTNBC after ≥ 2 prior systemic therapies (≥ 1 for metastatic disease). In the ASCENT study (NCT02574455) in pts with mTNBC, SG had superior efficacy vs single-agent chemotherapy and a manageable safety profile (Bardia et al. *NEJM* 2021). This study describes RW SG dosing and clinical outcomes in pts with mTNBC treated with SG in 2L and later in the US.

Methods: This retrospective cohort study used de-identified US electronic health records in the ConcertAI database of pts (≥ 18 y) with mTNBC treated with SG in 2L and later from April 2020 to May 2022 to allow for a 3-month minimum data accrual. Clinical outcomes (RW overall survival [rwOS], time to next treatment or death [TTNTD], and RW progression-free survival [rwPFS]) from start of SG (index date) were estimated by Kaplan-Meier methods.

Results: 230 female pts (median age 60 y, 26% Black, 17% ECOG performance status ≥ 2, 66% treated in community settings) were included in the analysis. Median follow-up was 7.2 months (IQR 3.9-11.1). SG RW outcomes for all pts and by SG line (2L and 3L+) are in the Table. Clinical outcomes were similar for all pts and stratified analyses (by race, concomitant G-CSF use, treatment-free interval duration). Of 134 pts (58%) who had G-CSF during SG treatment, 99 (74%) previously received G-CSF. Median time from SG start to G-CSF use was 8.5 days (IQR 8-29). SG was discontinued due to toxicity in 17 pts (7%).

Table: 393P

	2L mTNBC SG n = 77	3L mTNBC SG n = 153	2L+ mTNBC SG N = 230
Median rwOS (95% CI), months*†	13.9 (9.8-NE)	8.4 (7.4-10.3)	10.0 (8.3-11.1)
rwOS rate (95% CI), %			
12-month	51 (37-64)	35 (26-44)	40 (33-48)
24-month	32 (13-54)	20 (11-29)	23 (15-32)
Median TTNTD (95% CI), months†	4.8 (3.2-6.9)	4.4 (3.8-5.5)	4.6 (3.9-5.3)
Median rwPFS (95% CI), months†	4.9 (2.9-6.0)	3.5 (2.7-4.2)	3.8 (3.1-4.3)

IQR, interquartile range; NE, not estimable.
*Kalinsky et al. ASCO 2023 abstr e18879. †Measured from index date.

Conclusions: This RW analysis included patients with mTNBC treated with SG in 2L and later line settings since approval of SG in the US. SG showed survival benefit in this broad patient population. Follow-up duration was short for some pts in this analysis. As data will continue to mature over time, they will provide more insight into RW effectiveness of SG.

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394P CDK4/6 inhibitors in metastatic breast cancer: An Italian real-world experience

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Background: Abemaciclib, ribociclib and palbociclib are CDK4/6 inhibitors (CDKi) that have shown benefit in combination with endocrine therapy (ET) for estrogen receptor-positive (HR+) metastatic breast cancer (mBC). We aimed to compare the effectiveness of CDKi in mBC using twang propensity weight.

Methods: We performed a retrospective study using data from patients (pts) with HR+/HER2- mBC treated with abemaciclib, ribociclib or palbociclib plus ET in endocrine sensitive and resistant setting between July 2014 and March 2022 in 24 hospitals in Italy with at least 1 year of follow up. We used multinomial propensity weight from the twang package to balance baseline characteristics across treatment groups. We estimated the hazard ratios (HR) for progression-free survival (PFS), overall survival (OS). We also compared the grade 3-4 toxicities between the three drugs.

Results: We included 1184 patients (abemaciclib n=158, ribociclib n=326, palbociclib n=700). After twang propensity weight, the treatment groups were well balanced. In the endocrine-sensitive setting PFS was not significantly different between abemaciclib and ribociclib, while palbociclib was associated with shorter PFS compared both to ribociclib (HR 1.41, 95% CI 1.21-1.66, $p<0.001$) and abemaciclib (HR 1.33, 1.12-1.58, $p=0.001$). OS in the palbociclib group was also shorter compared to abemaciclib (HR 1.75, 95% CI 1.35-2.28, $p<0.001$) and ribociclib (HR1.29, 95% CI 1.05-1.58, $p=0.014$). In the endocrine-resistant setting abemaciclib showed a longer PFS compared to ribociclib (HR 0.53, 95% CI 0.44-0.64, $p<0.001$) and albociclib (HR 0.55, 95% CI 0.46-0.66, $p<0.001$) while no difference was observed between ribociclib and albociclib. OS was not significantly different between the three CDKi. Abemaciclib was associated with higher rates of grade 3-4 diarrhea and thromboembolism, palbociclib with anemia and neutropenia, and ribociclib with liver toxicity ($P<0.001$).

Conclusions: Our study showed that abemaciclib, ribociclib in the endocrine-sensitive setting have different efficaciesin terms of PFS and OS compared to palbociclib. In the endocrine'resistant setting abemaciclib showed a better PFS compared to other agents. This evidence coupled with different toxicity profiles that may guide treatment selection.

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395P Interim analysis (IA) of the giredestrant (G) + ipatasertib (IPAT) arm in MORPHEUS Breast Cancer (BC): A phase I/II study of G treatment (tx) combinations in patients (pts) with oestrogen receptor-positive (ER+), HER2-negative, locally advanced/metastatic BC (LA/mBC)

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Background: Many pts with ER+ BC experience disease relapse during/after adjuvant endocrine therapy (ET) or develop resistance due to *ESR1* mutations. G is a highly potent non-steroidal oral (PO) selective ER antagonist and degrader; IPAT is a potent, PO, AKT inhibitor. We present a 16-week IA of G vs. G + IPAT in MORPHEUS BC (NCT04802759).

Methods: Pts with disease progression on 1–2 lines of ET (including a cyclin-dependent kinase 4/6 inhibitor [CDK4/6i]) for LA/mBC were randomised 1:6 to G (30 mg PO daily [QD]) or G + IPAT (400 mg PO QD; Days 1–21 per 28-day cycle) until disease progression/unacceptable toxicity. Primary endpoints were safety and objective response rate (ORR); other endpoints included progression-free survival, overall survival, clinical benefit rate (CBR), disease control rate, duration of response and pharmacokinetics. Genetic alterations were defined using baseline circulating tumour DNA.

Results: As of 17 May 2022, eight and 24 pts (23 evaluable) were enrolled in the G and G + IPAT arms, respectively; 50% (n = 4)/75% (n = 18) received one prior line and 38% (n = 3)/25% (n = 6) received two prior tx lines for LA/mBC. In the overall population the ORR was 0%/17% (n = 4) and stable disease (SD) was 63% (n = 5)/52% (n = 12) in the G and G + IPAT arms, respectively. In pts with AKT signalling alterations (G = 3; G + IPAT = 10), ORR was 0%/30% (n = 3) and SD was 67% (n = 2)/70% (n = 7). Updated data will be presented including longer follow-up and CBR.

Table: 395P

Safety data are % of pts	G	G + IPAT
Tx-related adverse events (TRAEs) Grade 3–4	63% 0	96% 35%
AE/TRAE leading to tx discontinuation	0	9%
AEs leading to dose modification/interruption	13%	52%
Fatal AEs	0	0
Most common TRAEs (≥ 20% incidence rate)	Fatigue; insomnia	Diarrhoea; nausea; constipation; rash; vomiting

Conclusions: Encouraging activity was seen with G + IPAT in pts with disease progression on 1–2 lines of ET (including a CDK4/6i), especially in pts with AKT signalling alterations. G + IPAT was well tolerated, with no unexpected safety signals.

Clinical trial identification: NCT04802759; 17 March 2021.

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396P Real-world treatment and survival outcomes in previously untreated patients with metastatic triple-negative breast cancer (mTNBC) in the United States (US)

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Background: mTNBC is a clinically aggressive disease associated with poor prognosis with a median overall survival (OS) after metastasis of 15.5 mo. Despite improved survival from recent first-line (1L) therapy (Cortes et al. NEJM. 2022), most patients have disease progression. This study aims to describe the unmet need in previously untreated patients with mTNBC in the US.

Methods: This retrospective observational analysis used Flatiron Health de-identified electronic health record data. Pts (aged ≥ 18 years) with mTNBC (defined by American Society of Clinical Oncology/College of American Pathologists guidelines: HER2 IHC0, 1, or 2/ISH-negative; ER/PR negative) who initiated 1L treatment (tx) from January 2011 to May 2022 were included. Pts receiving HER2-targeted or hormone tx, or a clinical trial drug were excluded. Real-world (rw)OS and time to next tx or death (TTNTD) were calculated using Kaplan-Meier method.

Results: The study included 1764 pts (Table). Median time from diagnosis to 1L tx was 0.85 mo. Most pts received CT mono- (46.9%) or combination (36.7%) therapy (Table). Of the 1764 pts, 907 (51%) initiated second (2)L tx (33% had died) and 453 (26%) initiated 3L tx (35% had died). Median rwOS (95% CI) was 11.2 mo (10.7-12.0) with a 1- and 2-year survival rate (95% CI) of 47.5% (45.1-49.9) and 23.9% (21.7-26.1),

respectively. Median TTNTD (95% CI) for 1Ltx was 4.3 mo (4.1-4.5). Stratified analyses by year of mBC diagnosis, tx type, and other factors will be presented.

Table: 396P

Characteristic	Patient population N = 1764
Median age, (IQR), years	60 (51, 70)
Sex, female, %	99.7
Race, % White Black	57..4 20.8
Eastern Cooperative Oncology Group performance status ≥ 2, %	12.4
De novo mBC, %	30.2
1L treatment, % CT monotherapy Capecitabine Taxanes Other CT monotherapy	46.9 18.4 16.9 11.6
CT combination Carboplatin/gemcitabine Cyclophosphamide/doxorubicin Other CT combination PD-(L)1 inhibitor-based regimen	36.7 9.8 8.6 18.3 14.6
Poly (ADP-ribose) polymerase inhibitor- based regimen	0.85

Conclusions: In this rw study, most pts received CT as 1L therapy. Clinical outcomes were poor, and many pts did not receive tx after 1L due to high attrition rates between lines of therapy. These data confirm the unmet need for more efficacious tx options for pts with mTNBC in the 1L setting.

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397P Efficacy and safety of the recombinant humanized anti-HER2 monoclonal antibody-MMAE conjugate RC48-ADC in patients with HER2-positive or HER2-low expressing, locally advanced or metastatic breast cancer: A single-arm phase II study

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Background: Current treatment options for HER2-positive (IHC 3+, or IHC 2+/FISH+) metastatic breast cancer (MBC) at third-line and above have shown limited clinical benefit. There is no recommended HER2-targeting treatment for HER2-low expressing (IHC 2+/FISH-, or IHC 1+) population. Here, we report the efficacy and safety of RC48-ADC in patients with MBC.

Methods: Patients with HER2-positive or HER2-low expressing MBC were eligible and received RC48 2.5 mg/kg every two weeks alone or combined with drugs with different anti-tumor mechanisms, such as immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs) and antiangiogenic compounds. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety.

Results: 76 female MBC patients were enrolled and treated with RC48. 58 patients (76.3%) were HER2-positive and 18 patients (23.7%) were HER2-low expressing. At baseline, 35 patients (46.0%) had liver metastases, 27 patients (35.5%) had brain metastases, and 67 patients (88.1%) had received ≥3 prior chemotherapy regimens. In the overall population, the ORR was 31.6%. The median PFS was 5.7 months. The DCR was 57.9%. In the HER2-positive subgroup, the ORR and mPFS were 34.5% and 6.3 months. In the HER2-low expressing subgroup, the ORR and mPFS were 22.2% and 3.6 months. In addition, the mPFS in the dual drug combination-treated group was longer than that in the single drug treatment group, with mPFS of 7.1 months and 4.6 months, respectively. The most frequently reported adverse events were increased AST (62.4%), increased ALT (61.9%), decreased white blood cell count (42.4%), and fatigue (30.4%), most were grade 1-2 in severity.

Conclusions: RC48-ADC showed consistent efficacy in HER2-positive and HER2-low expressing subgroups. No new safety signals were observed. Coadministration with ICIs, TKIs and antiangiogenic compounds demonstrated substantially enhanced efficacy and could be a future direction of ADC.

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398P A phase Ib/II study of IN10018/FAKi in combination with pegylated liposomal doxorubicin (PLD) and toripalimab in metastatic triple-negative breast cancer (TNBC): IN10018-010

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Background: IN10018 is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK). Preclinical data showed that IN10018 in combination with PLD had synergistic antitumor effect and can further enhance immunotherapeutic effect in TNBC animal model. This study was to evaluate the safety and antitumor activity of IN10018 combined with PLD +/- anti-PD-1 antibody, Toripalimab in metastatic TNBC.

Methods: All enrolled metastatic TNBCs who had failed in 1-2 lines of systemic therapy were assigned to either doublet group: IN10018+PLD or triplet group: IN10018+PLD+Toripalimab. Phase Ib-dose finding part was to identify the recommended phase II dose (RP2D) of triplet combination. Phase II-dose expansion part was to evaluate the primary endpoint of objective response rate (ORR) and secondary endpoints of disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety.

Results: At data cutoff of April 28, 2023, 12 pts received IN10018+PLD and 14 pts received IN10018+PLD+Toripalimab. Median follow-up duration was 7.2 mo (range: 4.9-9.7) in doublet group and 6.0 mo (range: 2.0-10.5) in triplet group. The RP2D was determined as IN10018 100mg qd + PLD 40mg/m^2 q4w + Toripalimab 3 mg/kg q2w. In doublet group, ORR by investigators was 16.7% (95% CI, 2.1-48.4); DCR was 50% (95% CI, 21.1-78.9); median PFS was 3.65 mo (95% CI, 1.77-NA); and median OS was 7.52 mo (95% CI, 5.59-NA). In triplet group, ORR by investigators was 14.3% (95% CI, 3.8-42.8); DCR was 78.6% (95% CI, 49.2-95.3); median PFS was 9.26 mo (95% CI, 3.02-NA); and median OS was not reached. No drug-related death was observed. In doublet group, TEAEs grade ≥3 occurred in 58.3% pts with TEAEs in ≥2 pts being WBC and

neutrophil count decreased; SAE occurred in 2 pts with 1 related to treatment. In triplet group, TEAEs grade ≥3 occurred in 64.3% pts with TEAEs in ≥2 pts being anemia, WBC and neutrophil count decreased; SAE occurred in 5 pts with 4 related to treatment.

Conclusions: The combination of IN10018 with PLD and Toripalimab showed promising antitumor activity in metastatic TNBC. The combination safety profile was comparable to each single agent with no additional safety signal.

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399P Results from a first-in-human phase Ia/b study of LX-039, an oral selective estrogen receptor (ER) degrader (SERD), in postmenopausal patients with ER+, HER2- advanced breast cancer (ABC)

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Background: LX-039 is an oral SERD that blocks ER signaling pathway through receptor antagonism and degradation. LX-039 demonstrated robust antitumor efficacy and good PK profile in preclinical studies.

Methods: This was a multi-center, open-label, first in human, dose escalation and expansion phase I study to evaluate the safety, efficacy and PK/PD profiles of LX-039 monotherapy in postmenopausal patients(pts) with histologically confirmed ER+, HER2- ABC, who had failed ≥1 line endocrine therapy and ≤2 line chemotherapy. The initial dose was 50 mg, sequentially escalated from 100 mg to 1200 mg via traditional "3+3" design. LX-039 was administrated once daily in 28-day cycles until unacceptable toxicity, progression, or withdrawal of consent. ^{18}FES PET/CT scan was undergone on baseline and day 28 after treatment. Primary endpoint was MTD, secondary endpoints included safety, efficacy, and PK/PD.

Results: 44 pts (median age 56.5, ECOG = 1: 88.6%, visceral metastasis: 77.3%) were enrolled. All pts received prior endocrine therapy (range: 1-7 lines, 56.8% fulvestrant) and/or CDK4.6i(40.9%), chemotherapy(54.5%) in the advanced setting. Two pts experienced DLTs: G3 hepatic function abnormal in 1000 mg cohort (1/6) and G4 ALT increased in 1200 mg cohort (1/1), so MTD was not reached. TRAEs were mostly grade 1-2 and experienced by ≥20% of pts were diarrhea (81.8%, G3 15.9%), ALT increased (56.8%, ≥G3 15.9%); AST increased (47.7%, G3 4.5%), fatigue (38.6%), decreased appetite (29.5%), vomiting (29.5%), nausea (27.3%), weight decreased (22.7%). Dose-dependent plasma exposure was seen with an estimated half-life of approximately 7 h. In 29 pts with measurable lesions who received 600 mg or higher doses, 4 pts (13.8%) achieved partial response, with median DOR of 7.4 months. Median PFS in the ITT population was 5.5months (95% CI: 3.5, 5.9). CBR at 24 weeks was 40.0% and DCR was 70.3%. ^{18}FES-PET scan (n = 13) showed that all patients experienced SUV_{max} decrease from baseline with a median reduction of > 70 %.

Conclusions: LX-039 was well tolerated with preliminary anti-tumor activity in ER+, HER2- ABC. RP2D was determined at 600 mg QD and a phase II trial is being planned.

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400P The impact of CDK4/6 inhibitors on bone health: An Italian real-world experience

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Background: Palbociclib, Ribociclib and Abemaciclib, in combination with endocrine therapy (ET), are considered the first-line treatment for hormone-responsive (HR+) disease. Breast cancer frequently metastasizes to the bone with the possible occurrence of skeletal related events (SRE, pathological fractures, hypercalcemia, radiotherapy, spinal cord compression, and orthopaedic surgery).Clinical trials have demonstrated the efficacy of these combination of treatments, but there are limited data on their effect on bone endpoints: time to SRE and skeletal Progression Free Survival (PFS).

Methods: We conducted a retrospective analysis using data from patients (pts) treated with these CDK 4/6 inhibitors (CDKIs) and ET as first- or second-line therapy between July 2014 and March 2023 in 24 hospitals in Italy. Pts had bone metastases at the treatment start. We calculated the propensity weight for each patient based on baseline characteristics using the twang package to reduce selection and confounding bias in observational analyses for the evaluation of time to SRE and Skeletal PFS.

Results: We enrolled 1139 pts (Abemaciclib n=154, Ribociclib = 316, Palbocilib= 668), 562 (49.4%) treated with Denosumab, 235 (20.7%) with zoledronic acid and 341 (30%) did not receive any anti-resorptive therapy. The radiation to the bone was the most frequent SRE that occurred in the 20% of pts. After the twang propensity weight the time to SRE (95% CI) was longer in the Acid zoledronic group than denosumab (P= 0.024). The time to SRE was longer between pts treated with zoledronic acid compared to those who did not receive any bone-targeted agent (P= 0.017). Skeletal PFS (95% CI) was longer in pts treated with zoledronic acid than to Denosumab (39 [35—39] versus 27 [25-32] months, P < 0.001) and then who don't receive therapy (39 [35—39] versus 30 [28-32] months, P < 0.001). There was no significant differences in skeletal PFS between denosumab and none therapy.

Conclusions: Our study suggests that the use of zoledronic acid may lead to a longer time to SRE and skeletal PFS compared to denosumab or no anti-resorptive therapy. These findings can be important for the management of bone metastases in pts with HR+ metastatic breast cancer. Further prospective studies are needed to confirm these results.

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401P Utidelone in combination with etoposide and bevacizumab in HER2-negative breast cancer with brain metastasis (UTOBIA-BM): A prospective, single-arm, phase II trial

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Background: Utidelone, a genetically engineered epothilone analogue, has been proved to be efficacious for advanced breast cancer. However, the effect of utidelone for breast cancer patients(pts) with brain metastasis has not been reported. This trial

was to assess the efficacy and safety of utidelone in combination with etoposide and bevacizumab in HER2-negative breast cancer pts with brain metastasis.

Methods: HER2-negative breast cancer pts with brain metastasis were enrolled and Simon's two-stage optimal trial design was used for this trial (NCT05781633). If more than 3 out of 13 pts show central nervous system (CNS) response, 30 more pts would be further enrolled. Utidelone (30mg/m^2, iv, d1-5), and etoposide (100mg/m^2, iv, d1-3) concurrently with bevacizumab (10mg/kg iv, d1) every 21 days for 6 cycles, with utidelone and bevacizumab maintenance until disease progression or unacceptable toxicity. The primary endpoint was CNS—objective response rate (ORR). Secondary endpoints include CNS-clinical benefit response (CBR), CNS-progression-free survival (PFS), ORR, PFS, CBR, overall survival (OS), and safety.

Results: 17 female pts with a median age of 48 years (range 34-67) were enrolled from August 11, 2022 to March 22, 2023. 11 patients are evaluable for response with median cycles of 6 (2-8) , all of whom are still under treatment. CNS-ORR, CNS-CBR, ORR, CBR were 73% (8/11), 82% (9/11), 27% (3/11) and 55% (6/11), respectively, including a pt with PR for 8 cycles. PFS and OS have not been reached due to a short follow-up time. Therefore, the trial has met the criteria to enter the second stage. The major adverse event (AE) was peripheral neuropathy (PN), primarily classified as sensory. Grade 3 PN was seen in 9% (1/11) of the total patients. Most of the treatment-related AEs were grade 1 or 2 and were considered manageable and reversible. 1 pt experienced utidelone-related dose adjustment. No treatment-related death occurred.

Conclusions: Utidelone in combination with etoposide and bevacizumab has shown anti-tumor activity and manageable toxicity in breast cancer pts with brain metastasis, and a randomized control trial is warrantied.

Legal entity responsible for the study: The authors.

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402P First-line ribociclib (RIB) + endocrine therapy (ET) vs combination chemotherapy (combo CT) in aggressive HR+/HER2− advanced breast cancer (ABC): A subgroup analysis of patients (pts) with or without visceral crisis from the phase II RIGHT choice study

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Background: RIGHT Choice showed a statistically significant median progression-free survival (mPFS) benefit of ≈1 yr with first-line RIB + ET vs combo CT (HR, 0.54; P=.0007) in pts with aggressive HR+/HER2− ABC. As visceral crisis indicates need for a more rapidly efficacious treatment (tx), a subgroup analysis by visceral crisis status was performed.

Methods: Pre/perimenopausal pts (N=222) with no prior systemic therapy for aggressive HR+/HER2− ABC were randomized 1:1 to RIB + letrozole/anastrozole + goserelin or physician's choice of combo CT. Visceral crisis assessment was based on physician's judgment, following ABC 3 guidelines available at the time.

Results: Overall, 116 (RIB + ET, n=61; CT, n=55) and 106 (RIB + ET, n=51; CT, n=55) pts presented with or without visceral crisis, respectively. In pts with visceral crisis, a mPFS of 12.9 mo was seen with RIB + ET vs 11.2 mo with combo CT (HR, 0.87). While in these pts the overall response rate (ORR) numerically favored RIB + ET, the time to treatment failure (TTF) and clinical benefit rate (CBR) were similar in both tx arms (Table). In pts with no visceral crisis, a mPFS benefit was seen with RIB + ET vs combo CT (24.0 vs 12.7 mo; HR, 0.34); also, TTF and CBR favored RIB + ET over combo CT. RIB + ET was associated with lower rates of symptomatic adverse events than combo CT in both groups. These interim results are based on the 12 Apr 2022 data cutoff; final results will be shown at ESMO 2023.

Conclusions: This analysis shows similar PFS and TTF outcomes but greater ORR with RIB + ET vs combo CT in pts with physician-assessed visceral crisis. Clinically meaningful tx benefit with RIB + ET over combo CT was seen in pts with aggressive disease not classified as visceral crisis. These findings support RIB + ET over combo CT in pts with aggressive ABC even in the presence of visceral crisis.

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Honorarium to institution: Seoul National University Hospital; Financial Interests, Institutional, Invited Speaker, Chairperson at a conference. Honorarium to institution.: Lupin Limited; Financial Interests, Institutional, Invited Speaker, Chairperson, speaker, or panelist at 5 conferences/meetings. Honoraria to institution.: Roche Products (India) Private Limited; Financial Interests, Institutional, Invited Speaker, Chairperson, panelist, or speaker at a 3 meetings/roundtable. Honoraria to institution: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Invited Speaker, Chairperson at 2 conferences/meetings. Honoraria to institution.: Eli Lilly & Company (India) Limited; Financial Interests, Institutional, Invited Speaker, Invited speaker in a conference. Nag Foundation is a not-for-profit registered society working in the field of cancer.: Nag Foundation; Financial Interests, Institutional, Invited Speaker, Invited panelist in a meeting. Honorarium to institution.: Eisai Company Limited; Financial Interests, Institutional, Invited Speaker, Invited speaker. Honorarium to institution.: Omnicuris Healthcare Private Limited; Financial Interests, Institutional, Invited Speaker, Invited panelist at a conference. Honorarium to institution.: Cipla Limited, Cadila Pharmaceuticals; Financial Interests, Institutional, Invited Speaker, Invited chairperson at a conference. Honorarium to institution.: Intas Pharmaceuticals Limited; Financial Interests, Institutional, Local PI, CO40016 Titled - A Double Blind, Placebo- Controlled, Randomized Phase III Study of IPATASERTIB in combination with Paclitaxel As a treatment for patients with PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple Negative Breast cancer or Hormone Receptor — Positive, HER2 — Negative Breast Cancer: F. Hoffmann-La Roche Ltd; Financial Interests, Institutional, Coordinating PI, National coordinating PI of a multi-omics study in ER positive breast cancer: Department of Biotechnology, Government of India; Financial Interests, Institutional, Local PI, EGC002: Phase III, Randomized, Multicenter, Double-blind Study to Compare Efficacy and Safety of EG12014 (EirGenix Trastuzumab) with Herceptin® as Neoadjuvant Treatment in Combination with

Table: 402P

Visceral Crisis	Tx Arm	n	mPFS (95% CI), mo	HR (95% CI)	mTTF, mo	HR (95% CI)	ORR, %*	CBR, %*
Yes	RIB + ET	61	12.9 (9.9-25.2)	0.87 (0.51-1.47)	10.3	0.68 (0.43-1.08)	72.1	77.0
	Combo CT†	55	11.2 (8.4-21.0)		10.2		56.4	70.9
No	RIB + ET	51	24.0 (21.1-NR‡)	0.34 (0.18-0.63)	24.0	0.29 (0.17-0.51)	56.9	84.3
	Combo CT†	55	12.7 (8.3-17.5)		8.5		63.6	74.5

*Without image confirmation; †Docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine; ‡Not reached.

Anthracycline/Paclitaxel-based Systemic Therapy in Patients with HER2-positive Early Breast Cancer: EirGenix Inc.; Financial Interests, Institutional, Local PI, Protocol No. - CLEE011A3201C : A phase II randomized study of the combination of Ribociclib plus goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer - RIGHT Choice Study: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - D9100C00001 : A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer (CALLA): AstraZeneca Pharma India limited.; Financial Interests, Institutional, Local PI, Protocol No. - CLEE011A2207 : A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease: Novartis Healthcare Pvt. Ltd.; Financial Interests, Institutional, Local PI: Glenmark Pharmaceuticals Ltd.; Financial Interests, Institutional, Coordinating PI, Protocol No. - D0816R00025 : A Prospective, Multicentre, Phase-IV Clinical Trial of Olaparib in Indian Patients with Platinum Sensitive Relapsed Ovarian Cancer who are in Complete or Partial Response Following Platinum Based Chemotherapy and Metastatic Breast Cancer with Germline BRCA1/2 Mutation (SOLI Study): AstraZeneca Pharma India Limited; Financial Interests, Institutional, Local PI, Protocol No. - D9670C00001 : A Phase 3, Randomized, Multi-center, Open-label Study of Trastuzumab Deruxtecan (T-DXd) Versus Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy in the Metastatic Setting (DESTINY-Breast06): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - D3614C00001 : A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Paclitaxel Versus Placebo + Paclitaxel as First-line Treatment for Patients with Histologically Confirmed, Locally Advanced (Inoperable) or Metastatic Triple-Negative Breast Cancer (TNBC).: AstraZeneca Pharma India Limited; Financial Interests, Institutional, Local PI, PIK3CA Registry- A descriptive study of PIK3CA mutations in patients with HR+/Her2- advanced breast cancer.: NOVARTIS HEALTHCARE PRIVATE LIMITED; Financial Interests, Institutional, Local PI, Protocol No. - D967JC00001 : A Phase 1b/2 Multicentre, Open-label, Modular, Dose-finding and Dose-expansion Study to Explore the Safety, Tolerability, and Anti-tumour Activity of Trastuzumab Deruxtecan (T-DXd) in Combination with other Anti-cancer Agents in Patients with HER2-positive Metastatic Breast Cancer (DESTINY-Breast07): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, D9311C00001 "A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E): AstraZeneca; Financial Interests, Institutional, Local PI, WO42633 A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of adjuvant atezolizumab or placebo and trastuzumab emtansine forher2-positive breast cancer at high risk of recurrence following preoperative therapy (ASTEFANIA study).: Roche Products (India) Pvt. Ltd.; Financial Interests, Institutional, Local PI, MO42921 A multi-country observational retrospective study to evaluate the prevalence of pd-l1 and its role in patients with tnbc treated with systemic therapy (VANESSA): Roche Products India Pvt Ltd.; Financial Interests, Institutional, Local PI, Cost-effectiveness Analysis & Value-Based Pricing for Anti-Cancer Drugs: Implications for Patients, Industry, Insurer and Regulator: Department of Health Research, Ministry of Health and Family Welfare, New Delhi; Financial Interests, Institutional, Coordinating PI, Coordinating PI for Multi-Omics Analysis to Decipher Mechanisms of Hormone Resistance in Breast Cancer: Department of Biotechnology, Government of India; Financial Interests, Institutional, Coordinating PI, Mapping of Breast Cancer: Department of Science and Technology, Government of India; Financial Interests, Institutional, Local PI, Protocol No. - ECTS/16/002 : A multicentric open label phase II safety and efficacy study of ormeloxifene in tamoxifen resistant metastatic/recurrent breast cancer patients.: HLL Lifecare Limited (A Government of India Enterprises); Financial Interests, Institutional, Coordinating PI, Protocol No. - D0818R0000 : Protocol no. D0818R00001- A Non-interventional, multicentre study to assess prevalence of BRCA1 and BRCA2 mutation among ovarian, primary peritoneal and fallopian tube cancer patients in India (BRCA study): AstraZeneca Pharma India Ltd.; Financial Interests, Institutional, Local PI, Protocol No. - 1000-16 : An Open Label, Single Arm, Multicentric, Phase IV study to evaluate the safety and efficacy of Bevacizumab of Intas Pharmaceuticals Limited in approved indications: Intas Pharmaceuticals Ltd; Financial Interests, Institutional, Local PI, Protocol No. - Protocol no: 471-13 : "A Prospective, Adaptive, Randomized, Open-Label, Multicenter Clinical Trial to assess the Efficacy and Safety of Fixed Dose Combination of Capecitabine & Cyclophosphamide in Patients of Metastatic Breast Cancer with failure of Anthracycline and/or Taxane Chemotherapy: Intas Pharmaceuticals Ltd; Financial Interests, Institutional, Local PI, Protocol No. - MO39196 : A Phase III, Multicentre, randomised, double-blind, placebo controlled study of Atezolizumab (anti-PD-L1 antibody) in combination with paclitaxel compared with placebo in combination with paclitaxel for patients with previously untreated, inoperable locally advanced or metastatic Triple Negative Breast Cancer.: Roche Products (India) Pvt. Ltd; Financial Interests, Institutional, Local PI, Protocol No. - CBYL719C2301 : A phase III randomized double-blind, placebo controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment: Novartis Healthcare Pvt. Ltd.; Non-Financial Interests, Member of Board of Directors, This is a not-for-profit registered organization which aims to create large databases of genomic and other 'omic' data in breast and other cancers.: Indian Cancer Genome Atlas; Non-Financial Interests, Leadership Role, General Secretary of this non-governmental organization (It is a not-for-profit) which aims to help underprivileged patients with breast and gynecological cancers and promotes research and educational activities in these themes.: Women's Cancer Initiative - Tata Memorial Hospital; Non-Financial Interests, Leadership Role, President-Elect of ISMPO which is the largest professional organization of medical oncologists in India. It is a not-for-profit registered society.: Indian Society of Medical and Paediatric Oncology (ISMPO). T. Delgar Alfaro: Financial Interests, Personal, Stocks or ownership: Novartis; Financial Interests, Personal and Institutional, Full or part-time Employment: Novartis. J. Wu: Financial Interests, Personal, Stocks or ownership: Novartis; Financial Interests, Personal and Institutional, Full or part-time Employment: Novartis. H. Hu: Financial Interests, Personal and Institutional, Full or part-time Employment: Novartis; Financial Interests, Personal, Stocks or ownership: Novartis. M. Gao: Financial Interests, Personal and Institutional, Full or part-time Employment: Novartis; Financial Interests, Personal, Stocks or ownership: Novartis. Y. 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403P Breast cancer specific survival (BCSS) in HR+/HER2- metastatic breast cancer (mBC) from 2010 to 2019

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Background: Treatment advances, e.g., CDK 4/6 inhibitors (CDK 4/6is) have become standard of care over time in HR+/HER2- mBC in the US since the first approval in 2015. However, whether survival has improved in this patient population post 2015 has not been studied.

Methods: This retrospective study used Surveillance, Epidemiology, and End Results (SEER) registry data to assess BCSS in HR+/HER2- mBC patients from 2010-2019. Kaplan-Meier and Cox Proportional Hazards (CPH) models were used to compare BCSS in two patient cohorts: those diagnosed before (2010-2013 with follow-up [FUP] to 2014), and after (2015-2018 with FUP to 2019) guideline recommendations for CDK 4/6i use.

Results: A total of 11,467 women with de novo HR+/HER2- mBC with a mean age at diagnosis of 62.3 years were included. Unadjusted median BCSS was 39 months for patients diagnosed post 2015 (95% CI: 38-42) and 35 months for patients diagnosed pre 2015 (95% CI: 33-37). After adjusting for age, race & ethnicity, SEER geographic region and site, household income, and marital status, patients diagnosed post 2015 had a 10% reduced risk of BC specific death compared with patients diagnosed pre 2015 (hazard ratio [HR]: 0.90, p<0.01, Table).

Table: 403P Multivariable Analysis of Predictors of BCSS (CPH)*

Variable	HR	95% CI
Diagnosis Date		
Pre 2015 (n=5,304)	Ref.	
Post 2015 (n=6,163)	0.90***	0.85-0.95
Race & Ethnicity		
Non-Hispanic White	Ref.	
Non-Hispanic Black	1.33***	1.22-1.44
Median Household Income		
<$55,000	Ref.	
≥$75,000	0.88**	0.79-0.97
Marital Status		
Never Married	Ref.	
Married/living with domestic partner	0.80***	0.74-0.86

*Not all variables included in the model are shown in this table.
Significant at **p<0.05 and ***p<0.01
Ref: Referent

Conclusions: Using the largest US population-based longitudinal dataset, we observed improvements in BCSS post 2015 in patients with HR+/HER2- mBC. While the limitations of the current analysis prevent attribution to specific treatments, advances such as the introduction of CDK 4/6is in HR+/HER2- mBC may have contributed to population-level improvement in BCSS over time. This is consistent with other RWE studies that have shown an association between CDK4/6i treatment and improved survival.

Legal entity responsible for the study: Pfizer, Inc.

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404P A multicenter, single-arm, open-label trial of birociclib, a CDK4/6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer

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Background: Birociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. This phase II study (NCT04539496) was to evaluate the efficacy and safety of birociclib as single-agent in patients with refractory HR+/HER2- metastatic breast cancer (MBC).

Methods: The patients with $HR^+/HER2^-$ MBC who had progressed after prior endocrine therapy and 1-2 prior chemotherapy regimens in the metastatic setting were eligible. Birociclib 480 mg was administered orally on a continuous schedule twice daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) assessed by Independent Reivew Committee (IRC) per RECIST v1.1. Other endpoints included investigator-assessed ORR,duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety,etc.

Results: 131 patients were enrolled from 29 hospitals in China between 10/2020 and 08/2021. As of Nov 30, 2022, the median duration of follow-up was 19.0 months. Median duration of treatment was 6 months. The majority (84.7%) patients had visceral metastasis, 60.3% of patients had ≥3 metastatic organs. In the metastatic setting, patients had received a median of 3 prior systemic therapies including a median of 1 chemotherapy regimen and 2 endocrine therapy regimens. The main results are shown in the table.

Table: 404P Responses according to RECIST v1.1

BOR n(%)	IRC-assessed N=131	Investigator-assessed N=131
CR	0	1 (0.8)
PR	38 (29.0)	29 (22.1)
ORR (%)[95% CI]	29.0 [21.4, 37.6]	22.9 [16.0, 31.1]
DCR (%)[95% CI]	73.3 [64.8, 80.6]	66.4 [57.6, 74.4]
CBR (%)[95% CI]	42.0 [33.4, 50.9]	39.7 [31.3, 48.6]
mDoR (m) [95% CI]	14.8 [9.5, 16.7]	13.1 [9.4, 14.8]
mPFS (m) [95% CI]	11.0 [7.3,12.9]	8.3 [5.5, 9.3]
mOS (m) [95% CI]	24.3 [24.3, -]	
24m OS rate	62.9%	

The most common treatment-emergent adverse events (TEAEs) were gastrointestinal and hematological toxicity, common to CDK4/6 inhibitors. Most of these AEs were grade 1-2, and manageable with supportive treatments.

Conclusions: In patients with refractory HR+/HER2- MBC who have previously received chemotherapy and endocrine therapy, continuous dosing of single-agent birociclib exhibited promising and sustaining clinical activity with manageable toxicities, thus it provides an alternative orally single-agent therapy.

Clinical trial identification: NCT04539496.

Legal entity responsible for the study: Xuanzhu Biopharmaceutical Co., Ltd.

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405P E7389-LF as a first-line (1L) chemotherapy for patients (pts) with metastatic/advanced HER2-negative breast cancer (HER2− BC): Results from a phase I study dose-expansion part

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Background: E7389-LF is a liposomal formulation of eribulin being tested as 1L chemotherapy in pts with advanced HER2− BC. In an open-label phase 1 study of E7389-LF, a dose-escalation part determined a recommended regimen of 2.0 mg/m^2 once every 3 weeks (Q3W). Here, we present efficacy and safety data from the dose-expansion part in Japanese pts with confirmed metastatic HER2− BC who had not received prior chemotherapy for locally advanced/metastatic disease.

Methods: E7389-LF was administered at 2.0 mg/m^2 Q3W until disease progression, development of unacceptable toxicity, or withdrawal of consent. Efficacy endpoints included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Tumors were assessed by investigators per RECIST v1.1. Additionally, a subanalysis was conducted in pts with luminal BC (hormone receptor-positive [HR+]) and in pts with triple-negative BC (TNBC) who were programmed-death ligand 1-negative (PD-L1−). Adverse events (AEs) were monitored and recorded, and serum biomarkers were explored.

Results: At the data cutoff date (October 26, 2022), of 26 pts who received E7389-LF, 10 (38.5%) had ongoing treatment; 16 pts discontinued due to either disease progression (13 [50%]), AEs (2 [7.7%]), or pt choice (1 [3.8%]). Median age was 59 y (range 35−77); 19 pts (73.1%) had ECOG-PS 0; 22 pts (84.6%) were HR+; 4 pts (15.4%) had TNBC and were PD-L1−. ORR was 30.8% overall (HR+: 27.3%; TNBC and PD-L1−: 50%). Median PFS was 8.1 months (95% CI 4.4−11.1). Median OS was not reached (95% CI not estimable). Treatment-emergent AEs (TEAEs) led to dose reduction in 15 pts and drug discontinuation in 2 pts. TEAEs of grade ≥3 occurred in 25 pts (96.2%), most commonly (>40%) neutropenia (n=20, 76.9%) and leukopenia (n=11, 42.3%). Of 7 pts given prophylactic pegylated granulocyte-colony stimulating factor (peg-GCSF), 0 developed febrile neutropenia (FN). Of the 19 pts without peg-GCSF, 2 (10.5%) had FN. Changes in vasculature- and IFNγ-related serum markers were noted.

Conclusions: E7389-LF showed promising efficacy and a manageable toxicity profile and should be explored as a 1L treatment option for pts with advanced HER2− BC.

Clinical trial identification: NCT03207672.

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406P Phase Ib safety and efficacy of nadunolimab/gemcitabine/carboplatin in mTNBC

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Background: Nadunolimab (Nad; CAN04) is an ADCC-enhanced IgG1 antibody targeting IL-1 Receptor Accessory Protein (IL1RAP) expressed on tumor and stroma cells. Nad blocks downstream IL-1 signaling, including both IL-1α/β signaling. Nad has shown promising clinical activity in PDAC and NSCLC studies. Among breast cancer subtypes, TNBC has the highest IL1RAP expression. TRIFOUR is a phase 1b/randomized phase 2 trial to evaluate NadGC in mTNBC patients (pts). Preliminary safety and efficacy from the phase 1b dose-escalation are presented. Analysis of immunological biomarkers are ongoing.

Methods: Standard 3+3 dose-escalation design was used for phase 1b. mTNBC pts received NadGC on days 1 and 8, in cycles of 3 weeks. Two dose levels (DLs) of Nad (DL1=1 mg/kg; DL2=2.5 mg/kg) were evaluated with standard G (1000 mg/m2) and C (area under the curve 2 mg/mL/min). Nad DL2 was considered the target dose and further dose escalation was not planned.

Results: Phase 1b recruitment is completed with 15 stage IV female pts. Median age was 50 years (32-69), six pts (40%) were pre-/perimenopausal, 14 pts (93%) had visceral disease. BRCA1/2 was known in 47% and was wild type in all. All pts but one received prior (neo)adjuvant therapy; four pts had received platinum. 33% received NadGC as first-line for mTNBC. Overall, 13 patients were evaluable for the DLT period (3 DL1, 10 DL2). Two patients had DLT, both in DL2: one Grade (Gr) 3 febrile neutropenia and one delay >1 week in C2D1 due to Gr3 neutropenia. Gr3/4 AEs in >one pt were neutropenia 47%, thrombocytopenia 33%, anemia 20% and febrile neutropenia 13%. All were considered related by the investigator. At data cut-off, seven pts were still on treatment. Efficacy analysis was available in 12 pts with 1 CR and 5 PR; overall response rate 50% (95% CI: 21-79%).

Conclusions: Nadunolimab at 2.5 mg/kg plus standard G and C is well tolerated and shows promising antitumor activity. Neutropenia is the most frequent toxicity but does not limit treatment. The randomized phase 2 part is currently enrolling with the 2.5 mg/kg dose.

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Clinical trial identification: NCT05181462.

Legal entity responsible for the study: Cantargia AB.

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407P Palbociclib plus endocrine therapy in HR+/HER2- advanced breast cancer patients: Interim results of the PERFORM study

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Background: CDK4/6 inhibitors plus endocrine therapy (ET) are the first-line (1L) standard for patients (pts) with HR+/HER2- advanced breast cancer (ABC). Data from clinical trials have shown high efficacy and good tolerability. Real World Studies are important to support these data and close potential knowledge gaps.

Methods: The prospective, non-interventional PERFORM study is going to enroll 1,900 pts from 320 sites across Germany and Austria to gain further insights on effectiveness, tolerability, patient-reported outcomes (PRO) and longitudinal treatment patterns after 1L treatment with palbociclib + ET. In this second interim analysis (IA 2), response rates and dose modifications in the total population and in age-related subgroups (≥75 years vs <75 years) were investigated.

Results: Between 10/2020 and 09/2022, 938 pts were enrolled and 624 pts had a follow-up of >6 months and were evaluable for analysis. The median age was 68 years (range 33-89), 39% of pts had *de novo* ABC and 11% ECOG ≥2, at inclusion. 30% of patients were ≥75 years of age. Of these, 22% had an ECOG performance status of ≥2 at inclusion compared to 7% of pts <75 years. The rate of *de novo* ABC was higher in pts ≥75 years (44%) than pts <75 years (36%), whereas the number and

distribution of metastases was comparable. Progression-free survival (PFS) rate at 12 months was 71.7%; overall response rate (ORR) and clinical benefit rate (CBR) were 33.2% and 57.4%, respectively. Notably PFS, ORR and CBR were consistent across age groups. Dose modifications were performed in 74.1% of pts ≥75 years vs 61.5% of pts <75 years, respectively; >70% of pts in both subgroups are still on study treatment. Treatment discontinuation rates were comparable in both age groups (28.6% ≥75 years vs 27.3% <75 years), but (serious) adverse event as reason for treatment discontinuation was more frequent in pts ≥75 years (9.2% vs 3.0%).

Conclusions: The IA 2 of PERFORM shows comparable results regarding PFS, ORR and CBR of 1L treatment with palbociclib + ET in pts ≥ and <75 years, even though pts ≥75 years required dose modifications more frequently. These findings are in line with the data of clinical trials and support use of palbociclib based treatment independent of age.

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408P Proxalutamide plus endocrine therapy as a combination therapy in women with HR+/HER2-/AR+ metastatic breast cancer: A phase I study

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Background: This phase I clinical study aimed to assess the safety, efficacy and pharmacokinetic (PK) characteristics of proxalutamide, in combination with Endocrine therapies (ETs), in hormone-receptor (HR)+/human epidermal growth factor receptor 2 (HER2-)/AR+ metastatic breast cancer (mBC).

Methods: In part 1 of the study, patients who progressed on multiple lines of therapy (≥1) were enrolled. Monotherapies were initiated including letrozole (2.5 mg/day on days 1-14) for cohort A, exemestane (25 mg/day on days 1-14) for cohort B, and fulvestrant (intramuscularly 500 mg once on days 1, 15 and 28) for cohort C, followed by proxalutamide 200 mg QD and ETs for in a 28-day cycle. In part 2 of the study, patients who either progressed on or were not tolerant to the first-line therapy were enrolled to receive proxalutamide 200 mg QD plus fulvestrant [cohort D] at a dose of 500 mg once on days 1 and 15 and day 1 of each cycle thereafter. The primary endpoint is safety and tolerability. PK and antitumor activity were also assessed.

Results: Between June 18, 2019 and Sep 5, 2022, 37 (17 in part 1 and 20 in part 2) patients received the combination therapy. No DLTs or drug-related SAEs were reported. The commonly reported Grade ≥3 TEAEs were neutrophil count decreased (3/37, 8.1%), hypokalemia (3/37, 8.1%) and bone marrow suppression (3/37, 8.1%). 6 (15.8%) patients on proxalutamide plus fulvestrant achieved a partial response and 13 (34.2%) patients had stable disease, with an overall disease control rate of 50.0% (95% CI, 33.4%—66.6%; 38.9% in part 1 and 60.0% in part 2). The overall median PFS was 6.4 months (95% CI, 2.7-19.3) for cohort C and 11.0 months (95%CI: 5.5-NA) for cohort D. PK profiles indicated rapid absorption of proxalutamide following a single dose. After multiple doses, proxalutamide and its major metabolite reached steady-state serum concentration levels at day 29 and exhibited a tendency for drug accumulation.

Conclusions: This study suggested a good antitumor activity and safety profile of the combination therapy of proxalutamide and fulvestrant for HR+/HER2-/AR+ mBC patients in the ≥2nd-line settings. Moreover, it may provide survival benefits for these patients, warranting further investigation in a larger population.

Clinical trial identification: CTR20191063.

Legal entity responsible for the study: The authors.

Funding: Suzhou Kintor Pharmaceuticals.

Disclosure: All authors have declared no conflicts of interest.

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409P Treatment of elderly patients (pts; > 75 years) with 1st-line ribociclib (RIB) + endocrine therapy (ET) or endocrine monotherapy in clinical routine: Real-world data from the RIBANNA study (5th interim analysis (IA))

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Background: RIB+ET has demonstrated a statistically significant survival benefit across three phase 3 MONALEESA trials, irrespective of menopausal status, line of therapy, or combination partner. RIBANNA (CLEE011ADE03), a prospective, noninterventional study assessing the efficacy and safety of 1st-line treatment options including RIB+ET in pre-, peri- and postmenopausal women with HR+, HER2— ABC is ongoing in Germany since October 2017. In this 5th IA from RIBANNA, efficacy, safety, and tolerability for elderly pts will be presented.

Methods: Pts were included in accordance with the German tx guideline. For individual age subgroups (≤75 years; >75-80 years; >80 years) efficacy of RIB+ET vs. endocrine monotherapy will be compared by adjusting for baseline characteristics including Charlson comorbidity index. Furthermore, data for patient-reported outcomes (PRO) and treatment-emergent adverse events including time to onset, frequency, dose adjustment and outcome will be analyzed.

Results: At data cutoff Sep 6, 2022, for age subgroup ≤ 75 years, >75-80 years and for age subgroup >80 years data from n=1377 (RIB+ET) respectively n=109 (ET), n=281 (RIB+ET) respectively n=42 (ET), and n=153 (RIB+ET) respectively n=41 (ET) are available. The mean Charlson comorbidity index (standard deviation [SD]) increases with increasing age subgroup in the RIB+ET cohort (0.5 [1.2]; 0.8 [1.4]; 0.8

[1.3]) vs. ET cohort (0.6 [1.2]; 0.9 [1.5]; 0.9 [1.4]) respectively. Excluding interruptions, the mean daily RIB dose decreases with increasing age subgroups (527.7 mg vs. 504.8 mg vs. 471.3 mg). Most relevant differences in mPFS are seen in subgroup >75-80 (HR=0.555; 95% CI: 0.307-1.001; p=0.05). Overall number of treatment-emergent adverse events (all grade) in the RIB+ET cohort were similar between age subgroups (32.33% vs. 29.34% vs. 25.71%).

Conclusions: RIBANNA study showed diverse population characteristics among pts who received RIB tx in a real-world setting. For investigated age subgroups RIB+ET showed high efficacy over ET alone with manageable safety profile without new signals in the clinical routine.

Clinical trial identification: CLEE011ADE03.

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410P Patients treated with pertuzumab followed by T-DM1 for breast cancer in France from 2014 to 2021: A survival analysis of 10,408 patients from the French National Hospital discharge summary database (PMSI)

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Background: Breast cancer represents a major public health issue in which numerous therapeutic advances have been made, particularly for those with HER2 overexpression. The standard of care until mid-2022 has been based on the combination of Trastuzumab - Pertuzumab - Docetaxel in first line, followed by T-DM1 in second line. Limited data are available on survival outcomes of patients receiving these treatments in a real-life setting. We aimed to analyse them in this study.

Methods: We searched the French PMSI (French National Hospital Discharge Summary Database) database and extracted 10,408 patients treated with Pertuzumab between 2014 and 2021, with a C50* code (coding for breast cancer) and with an index stay in a public or private non-profit hospital. We then extracted administrative data, comorbidities, types of metastases and survival. We collected and analyzed the same data for patients receiving T-DM1 after Pertuzumab.

Results: Median survival for patients treated with Pertuzumab was not reached at time of analysis (February 2023). Survival rate at 5 years was 61.9 % (CI95% [60.6, 63.1]). Several risk factors were identified : an intensive care unit stay, age and a code for hydroelectrolytic disorders, metastases (particularly cerebromeningeal, liver, bone, and lung metastases), infection, diabetes, undernutrition and cytopenias. Median survival for patients treated with T-DM1 after Pertuzumab was 2.8 years (CI95% [2.65, 2,99]), with a 5-year survival rate of 36.9% (CI95% [34.6 , 39.4]). Risk factors were : a code for liver or cerebromeningeal metastases, undernutrition, and age.

Conclusions: To our knowledge, this is the largest real-life cohort of patients with breast cancer treated with Pertuzumab followed by T-DM1, and our results are consistent with available data, both from the lead CLEOPATRA and EMILIA studies and other retrospective studies.

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411P Therapy management and safety of 1st-line ribociclib (RIB) + aromatase inhibitor (AI)/fulvestrant (FUL) in clinical routine: Real-world data from the RIBANNA study (5th interim analysis (IA))

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Background: RIBANNA (CLEE011ADE03) is a prospective, noninterventional study assessing the efficacy and safety of RIB+AI/FUL, endocrine therapy (ET) alone, or chemotherapy (CT) in 1L and subsequent therapy lines in pre-, peri- and postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer. Herein we present real-world data on therapy management for RIB, including therapy-related adverse events (AEs), dose adjustment, and efficacy outcomes in special subgroups resulting from the 5th IA from RIBANNA.

Methods: Pre-, peri- and postmenopausal patients within the study were treated according to German treatment guidelines. For the RIB cohort the number of dose adjustments, reason and time until dose adjustment and/or discontinuation will be presented. Effectiveness analysis for PFS in 1L will be performed for patients with and without dose adjustments. Safety analysis and the median time to toxicity will be explored, with focus on AEs of special interest (AESIs): liver toxicity, cardiac events and neutropenia.

Results: At data cutoff Sep 6, 2022, 2581 patients were enrolled in the study (RIB+AI/FUL, n = 2163; ET, n = 237; CT, n = 181). The mean RIB exposure (standard deviation [SD]) in 1L was 597.7 [459.2] days with a mean daily dose of 280.7 [132.3] mg/day and 519.1 [117.4] mg/day including and excluding interruptions, respectively. The unadjusted KM estimate for median PFS was 32.2 months (95% CI, 29.3—34.8) in the RIB + AI/FUL cohort. Regarding the AESIs (all grade): an increased alanine- and aspartate-aminotransferase was recorded in 3.9% (78) and 3.8% (75) of patients, respectively. Similarly, 3.7% (73) of patients had a prolonged QT interval on the electrocardiogram. Neutropenia was documented for 25.8% (511) of the patients, being one of the most frequent treatment-emergent adverse events.

Conclusions: The RIBANNA study encompasses a diverse patient population receiving RIB therapy. Data on the 1L therapy management in real-world settings including dose adjustments, efficacy in special populations and safety will be presented at the conference.

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412P Sacituzumab govitecan versus chemotherapy for metastatic breast cancer: A meta-analysis on safety outcomes

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Background: Although Sacituzumab Govitecan (SG) had a manageable safety profile across clinical trials, this antibody-drug conjugate (ADC) has a specific set of treatment-related adverse events, which may limit adherence to treatment. However, few data are available regarding the comparison of SG versus chemotherapy in breast cancer (BC) patients. Herein, we performed a systematic review and meta-analysis aimed to systematically compare the safety profile of SG versus chemotherapy in phase II and III metastatic BC (mBC) clinical trials.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, all phase II and III randomized clinical trials that compared SG versus chemotherapy in mBC patients were retrieved. The outcomes of interest were grade 3-4, and all grade neutropenia, leukopenia, anemia, nausea, diarrhea, and fatigue in clinical trials comparing SG versus chemotherapy for mBC patients. The risk of alopecia, febrile neutropenia, and treatment discontinuation rate were also assessed.

Results: Two eligible trials were selected in this meta-analysis, encompassing a total of 999 patients (SG=526; chemotherapy=473). The pooled Odds Ratios (ORs) for outcomes such as grade 3-4 and all grade neutropenia, leukopenia, anemia and other nonhematological adverse events showed a higher risk for patients receiving SG versus chemotherapy. No statistically significant differences were observed in grade 3-4 fatigue, all grade nausea, febrile neutropenia and treatment discontinuation due to adverse events.

Conclusions: Despite our research revealing the presence of a higher risk of some adverse events in patients receiving SG than those treated with chemotherapy (e.g., diarrhea), our pooled results suggested no statistically significant differences in terms of treatment discontinuation and febrile neutropenia, which is commonly considered an important and often life-threatening event. Our data, coupled with a statistically significant and clinically meaningful survival benefit, support the use of SG as an important therapeutic option for mBC. Further analysis is needed in the future, and real-world evidence is required to better explore this topic.

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413P Characteristics of patients (pts) with previously treated, oestrogen receptor-positive, HER2-negative advanced breast cancer (ER+, HER2− aBC) who had rapid progression (RP) in acelERA BC

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Background: The phase II acelERA BC study (NCT04576455) compared the oral, selective ER antagonist and degrader (SERD) giredestrant (G) with physician's choice of endocrine therapy (PCET) in previously treated ER+, HER2− aBC. G was not superior to PCET for progression-free survival (PFS) despite a numerical improvement, which was more pronounced in pts with *ESR1* mutations (m). RP (PFS <3 months) has been noted in pts with late-line aBC receiving ET, including oral SERDs. We present exploratory biomarker analyses of circulating tumour (ct)DNA dynamics and characteristics of pts with RP.

Methods: Baseline and Cycle 2, Day 1 ctDNA was evaluated by FoundationOne Liquid CDx. Gene expression was profiled by RNAseq on tumour tissue representing the post-first-line setting (>30 days after aBC diagnosis).

Results: As of 15/07/22, 87/293 pts (30%) with evaluable PFS (10 censored within the first 3 months) had RP. RP did not differ by arm: G 42/145 (29%); PCET 45/148 (30%). Pts with RP were more likely to have received a prior CDK4/6 inhibitor (i; 61% vs. 33%; $p < 0.01$). In pts with *ESR1*m, 35/88 (40%) had RP vs. 30/137 (22%) in pts without. Comparing RP vs. non-RP in pts with *ESR1*m: G2M checkpoint, E2F target and ER gene expression signatures were among those decreased; the proportion of Luminal A PAM50 subtype was increased; and baseline ctDNA levels were significantly higher for pts with RP ($p < 0.01$), with enrichment of *DNMT3A*, *PIK3CA* and *RB1* mutations vs. non-RP. Among pts with *ESR1*m regardless of RP status, those who were CDK4/6i-naive showed meaningful increases in gene pathways associated with inflammatory processes, including IFNα ($p < 0.01$), IFNγ ($p < 0.01$) and IL6 ($p = 0.03$) vs. those with prior CDK4/6i. PFS was improved in pts with undetectable *ESR1*m levels on-treatment, compared with those whose levels increased ($p = 0.03$).

Conclusions: Data suggest that RP occurs regardless of *ESR1*m and is associated with prior CDK4/6i treatment and higher tumour burden, as measured by ctDNA levels. In pts with *ESR1*m, distinct signalling and mutational profiles were observed, dependent on RP status and prior CDK4/6i. Additional observations will inform ongoing pt selection and drug combination research.

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414P Trastuzumab deruxtecan for HER2-positive breast cancer brain metastasis: A systematic review and meta-analysis

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Background: Brain metastases (BMs) affect approximately half of the patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) and holds a poor prognosis. Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate, has shown promising results in patients with breast cancer brain metastases (BCBMs). Thus, we conducted a systematic review and meta-analysis to evaluate the effectiveness and safety of T-DXd in the HER2-positive BCBM population.

Methods: We searched PubMed, Embase, and Cochrane Library databases, as well as ASCO, ESMO, and SABCS websites for clinical trials (CTs) and observational studies evaluating T-DXd in the HER2-positive BCBM patients. Heterogeneity was assessed with the Cochran Q test and I2 statistics. Random effects models were used for all statistical analyses, which were performed using R software (v.4.2.2).

Results: Ten studies were included, six clinical trials (N=189) and four observational studies (N=147), with a total of 336 patients. The mean progression-free survival was 15 months (95% CI 13.9 to 16.1 months). The objective response rate (ORR) was 61% (95% CI 53-68%), and the intracranial (IC)-ORR was 62% (95% CI 55-70%). No significant differences in ORR and IC-ORR were observed between CTs and observational studies (p=0.56, and p=0.46, respectively). The clinical benefit rate (CBR) was 86% (95% CI 72-94%), and the IC-CBR was 69% (95% CI 59-79%). The ORR was 64% (95% CI 53-73%) in the subgroup of patients with stable BMs and 61% (95% CI 49-73%) in patients with active BMs, with no significant difference between groups (p=0.78). Adverse events (AE) of any grade were reported in 98% of cases (95% CI 90-100%). Dose reduction and drug interruption due to AE were reported in 29% (95% CI 10-60%) and 31% (95% CI 19-42%) of cases, respectively.

Conclusions: Our systematic review and meta-analysis supports the intracranial activity of T-DXd in both patients with stable BM and active BM. HER2-positive BCBM patients treated with T-DXd achieved ORR and IC-ORR higher than 50% in the clinical trials setting and in real-world data.

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415P Patterns of time-to-progression intervals across clinical and liquid biopsy (LB) features in hormone receptor-positive (HR+) HER2-negative (HER2-) metastatic breast cancer (MBC) patients (pts) treated with first-line endocrine therapy (ET)

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Background: ET + a CDK 4/6 inhibitor (CDK4/6i) is the standard first-line therapy (1L) for HR+ HER2- MBC. Currently, imaging schedules are arbitrarily derived from clinical trials without margins of personalization. Aim of this study was to analyze the role of clinical and LB features in defining patterns of progression in HR+ HER2- MBC.

Methods: Pts were enrolled in the prospective multicenter CRO-2018-56 trial from January 2018 to January 2023. Serial CT scans and LB were performed. Prognostic factors were tested in terms of progression free survival (PFS) and overall survival (OS) through stepwise Cox regression. Progression distribution was estimated through smoothed hazard function.

Results: Of the 114 enrolled pts, 35% had *de novo* MBC, 15% invasive lobular carcinoma (ILC), 75% PgR+ disease. Bone was the most common metastatic site (75%). Most pts (96%) received ET + CDK4/6i (54% palbociclib, 37% ribociclib, and 9% abemaciclib). At baseline LB, 10% had *ESR1*-mutant (mut) MBC, 24% *PIK3CA*-mut. No *ERBB2* mutations were detected. Median follow up was 34.8 months (mos). Histotype (ILC versus ductal [IDC], HR 5.66, P <0.0001) and liver involvement (HR 2.21, P = 0.027) were significantly associated with worse PFS. Significant prognostic factors for OS were histotype (HR 12.07, P <0.0001), PgR+ (HR 0.19, P = 0.003), *de novo* MBC (HR 6.89, P = 0.04) and *PIK3CA*-mut (HR 3.44, P = 0.03). Marked peak-hazard differences across timepoints were observed to histotypes (55 mos vs 2 mos for IDC and ILC, respectively), PgR status (55 mos for PgR+ vs 1.2 mos for PgR-) and liver involvement (55 mos for liver- vs 7.6 mos for liver+). Consistent distributions were observed for lung and bone involvement, *de novo* MBC, *ESR1*-mut and *PIK3CA*-mut.

Conclusions: Effective disease monitoring should balance the need for appropriate disease characterization while maintaining pts' quality of life. Hazard distribution in HR+ HER2- MBC pts does not reduce overtime, but rather has different patterns across subgroups of interest. Further analyses are planned to define specific subgroups for personalized monitoring strategies.

Clinical trial identification: CRO-2018-56.

Legal entity responsible for the study: IRCCS CRO.

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Disclosure: S. Spazzapan: Financial Interests, Personal, Advisory Board: MSD Italia, Seagen, AstraZeneca; Financial Interests, Personal, Invited Speaker: MSD, Novartis, Mundipharma, AstraZeneca, Eli Lilly; Financial Interests, Personal, Other, Congress registration: Pfizer; Financial Interests, Personal, Other, Tutoring: AstraZeneca; Financial Interests, Personal, Other, congress registration and travel expenses: Pfizer; Financial Interests, Personal, Other, Congress registration and travel expenses: Novartis; Financial Interests, Institutional, Local PI: AstraZeneca. F. Puglisi: Financial Interests, Institutional, Funding: AstraZeneca, Eisai; Financial Interests, Personal, Other: AstraZeneca, Roche, Amgen, Lilly, Novartis, Pfizer. All other authors have declared no conflicts of interest.

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416P Cost-effectiveness of first-line (1L) ribociclib use vs palbociclib in the treatment of postmenopausal women with HR+/HER2− advanced breast cancer (ABC): Analysis based on final overall survival (OS) results of MONALEESA-2 (ML-2) and PALOMA-2 (PAL-2)

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Background: To evaluate cost-effectiveness of ribociclib vs palbociclib, using final ML-2 and PAL-2 OS data, in 1L treatment of postmenopausal women with HR+/HER2− ABC from Canadian payer perspective.

Methods: Partitioned survival model was developed considering 3 states (progression-free survival, progressive disease, and death) with a 1-month cycle length. Hazard ratios (HRs) for PFS and OS for ribociclib vs palbociclib (with letrozole) were derived using an anchored matching-adjusted indirect comparison (MAIC) to adjust for differences in baseline characteristics between ML-2 and PAL-2. Cost inputs included drug acquisition, healthcare resource, subsequent therapies, and adverse

event costs. Trial data and published literature were used to derive utility values. Costs and effects were discounted at 1.5% per year over a lifetime horizon.

Results: Total cost of treatment with ribociclib and palbociclib were $250,004 and $254,052, respectively. For treatment with ribociclib vs palbociclib, quality-adjusted life years (QALYs) were 4.948 vs 3.981, respectively. Ribociclib was the dominant treatment as it was both cost-saving (-$4,048) and more effective (+0.968 QALYs) than palbociclib. Drug cost with ribociclib was found to be $31,819 lower than palbociclib. Probability of ribociclib being cost-effective at $50,000 per QALY was 100%. Ribociclib remained cost-effective when HRs, utilities, ribociclib drug cost, and health state costs were varied.

Conclusions: Post MAIC, significantly longer OS benefit was observed with ribociclib vs palbociclib. Ribociclib remained dominant 1L treatment option over palbociclib. Hence, ribociclib should be the preferred CDK4/6 inhibitor based on the clinical and the economic benefit.

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Funding: Novartis Pharmaceutical.

Disclosure: D. Soliman, K. El Ouagari, C. Biswas, M. Kalra, V. Sharma: Financial Interests, Personal, Full or part-time Employment: Novartis. All other authors have declared no conflicts of interest.

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417P New insights into second-line (2L) choices after CDK4/6 inhibitors (CDK4/6i) in hormone receptor-positive (HR+)/ human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (MBC) patients (pts): Preliminary results of the HERMIONE-13 study

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Background: CDK4/6i with endocrine therapy (ET) still represents the best 1st-line (1L) choice for HR+/HER2- MBC pts. At progression, the optimal subsequent strategy remains an open question. The HERMIONE-13 study aims to describe the efficacy of 2L choices in terms of Progression Free Survival (PFS) and Clinical Benefit Rate (CBR), in HR+/HER2- MBC pts relapsed after CDK 4/6i + ET.

Methods: HERMIONE-13 is a retrospective and prospective multicentric observational trial conducted in 15 Centers in Italy. Data of pts with at least one disease' revaluation during 2L therapy are being collected from January 2016 until January 2024. Here we present the first data of pts enrolled until December 2020.

Results: Among 114 pts enrolled, 16 (14%) were primary endocrine resistant, 70 (61.4%) had visceral metastases and 64 (56%) have received Palbociclib. Median 1L PFS (mPFS) was 11 months (mo) (interquartile range (IQR): 5-18). The 2L preferred choice was a chemotherapy (CHT)-based regimen (69.3%), with a predominance of single agent Capecitabine (22,2%); ET + target therapy (TT) was chosen in 16.7% of pts and ET monotherapy in 14%. An ET-based treatment was more frequently chosen for pts with a PFS$\geq$6 mo to previous CDK4/6i (35.4%), with respect to those with a PFS$<$6mo (13.3%) (P=0.024). A significant improvement in CBR, defined as absence of disease progression at 1st reassessment, was observed with CHT versus ET (20%, P=0.047). Among CHT treatments, a metronomic schedule of oral Capecitabine +/- Vinorelbine +/-Cyclophosphamide was used in 22.8% of pts, with a mPFS of 6 mo.

Table: 417P

	N° of pts (%)	2L mPFS,in mo (IQR)	CBR 2L (%)
All treatment	114	6 (3-10)	55 (48.2)
ET +/- TT	35 (30.7)	5 (3-7)	12 (34.3)
CHT +/- TT	79 (69.3)	6 (4-12)	43 (54.4)
Non-metronomic CHT	61 (77.2)	6 (3-11)	32 (52.5)
Metronomic CHT	18 (22.8)	6 (4-12)	11 (61.1)

Conclusions: In Italy, the preferred 2L treatment after CDK 4/6i remains CHT, especially with single-agent or metronomic schedule. mPFSs of 2L choices are very similar each other, around 6 mo. Further efforts to understand the type of resistance to CDK4/6i are warranted to better select 2L therapy.

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418P Two-year follow-up data on the efficacy and safety of KN026, a HER2-targeted bispecific antibody combined with docetaxel as first-line treatment for HER2-positive recurrent/ metastatic breast cancer

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Background: KN026 is a novel bispecific HER2-targeted antibody. *Fully humanized, IgG1-like antibody binds to two distinct HER2 epitopes, the same domains as trastuzumab and pertuzumab.* Preliminary safety and efficacy results (data as of Aug 18, 2022) were presented at SABCs 2022(PD18-08), showed promising efficacy and tolerability. Herein, we update the 2-year follow-up results.

Methods: Eligible subjects with recurrent/metastatic breast cancer, HER-2 positive and treatment-naive were enrolled. Subjects received KN026 30 mg/kg combined with docetaxel 75 mg/m^2 Q3W until disease progression, unacceptable toxicity, or other reasons. The primary endpoints were ORR and DoR. The secondary endpoints included safety, PFS and OS.

Results: As of data cut-off date (Mar 10, 2023), 57 subjects were enrolled, the median age was 52 y (min:30, max:67), 100% were female, and 91.2 % (52/57) were stage IV. The confirmed ORR within 55 evaluable subjects was 76.4% (42/55) and DoR was 24.0m (95% CI 20.27, NE). The median study follow-up was 24.2m (95%CI:22.80, 25.56). The mPFS was 25.4m (95% CI:17.97, NE) and the mOS was not reached. The OS rates at 12m, 24m and 30m were 93.0% (95% CI:82.37, 97.31), 83.7% (95% CI:70.97, 91.19) and 83.7% (95% CI:70.97, 91.19). The mPFS of subjects with or without visceral metastasis were 23.6m and 28.1m. The mPFS of subjects with or without brain metastasis were 13.7m and 25.4m, respectively. The incidence of KN026-related Grade$\geq$3 TRAE was 38.6% (22/57), including neutrophil count decreased 26.3% (15/57), leucopenia 24.6% (14/57), alanine aminotransferase increased 14.0% (8/57) and others less than 10%. The incidence of serious adverse events was 19.3% (11/57), including febrile neutropenia 5.3% (3/57), leucopenia 3.5% (2/57), and others $\leq$ 2%. There was no KN026 -related death.

Conclusions: KN026 in combination with docetaxel is well tolerated and has shown promising clinical benefit as 1L treatment for HER2-positive BC. After 2 years follow-up, mPFS was 25.4m and the 30-m OS rate was 83.7%, which is very promising. Robustness of efficacy and safety results will be further confirmed in an ongoing randomized phase 3 clinical trial with PTH as control.

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Legal entity responsible for the study: The authors.

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419P Aspire to ASCENT: Real-world outcomes from patients with metastatic triple-negative breast cancer (mTNBC) treated with Sacituzumab govitecan (Saci) in a single academic institution

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Background: Saci is FDA approved for mTNBC and metastatic HR-positive BC based on ASCENT (Bardia et al., NEJM 2022) and TROPiCS-02 (Rugo et al., JCO 2022). In ASCENT, patients with heavily pre-treated mTNBC, including CNS metastases, had improved PFS and OS with Saci. It remains to be seen whether clincial trial results are uniformly applicable to real-world patients. The objectives of this study are to examine patients treated with Saci for mTNBC at our institution and to determine if clinical trial results can be replicated in the real-world setting.

Methods: We retrospectively identified all patients treated with Saci at our institution. Patient demographics, tumor characteristics, response and outcomes were assessed. Statistics are reported descriptively.

Results: From July 2018-June 2022, 188 patients with MBC were treated with Saci at our institution. Of those, 126 patients with mTNBC received at least one dose of Saci. Patients received a median of 2 lines (0-8) of therapy for metastatic disease prior to Saci. At commencement of Saci, 69.8% of patients had visceral metastases and 23% had CNS metastases. The median PFS with Saci was 3 months (0-13). The clinical benefit rate (CR/PR/SD) with Saci was 59.5% and 15% of patients remained on Saci at the time of reporting. The median OS was 21 months (2-50) and the median survival from Saci to death was 6 months (0-33).

Table: 419P Patient and tumor characteristics (n = 126)

Characteristics		n (%)
Median age at diagnosis: Years (range)		52 (27-86)
BRCA1/2 mutation status	Positive	7 (6%)
	None	90 (71%)
	Unknown/Not tested	29 (23%)
Tumor stage at Dx	T1	22 (18%)
	T2	58 (46%)
	T3	15 (12%)
	T4	3 (2%)
	Tx	23 (18%)
	Unknown	5 (4%)
Nodal status at Dx	N0	38 (30%)
	N1	37 (29%)
	N2	15 (12%)
	N3	8 (6.5%)
	Nx	23 (18.5%)
	Unknown	5 (4%)
Metastatic disease at Dx	M0	101 (80%)
	M1	20 (16%)
	Unknown	5 (4%)
Prior systemic therapy	Taxane	119 (94%)
	Anthracycline	92 (73%)
	Capecitabine	77 (61%)
	Platinum	75 (60%)
	Immunotherapy	55 (44%)
	PARPi	19 (15%)

Conclusions: In this real-world series, we report on a patient population similar to that studied in the ASCENT trial. The median PFS was numerically shorter in this series compared to the ASCENT study (3.0 vs 4.8 months) despite our patients being less heavily pre-treated (median 2 vs 4 prior lines). The median OS was numerically longer in this series (21 vs 11.8 months). Further work is ongoing to evaluate real-world outcomes of patients treated with Saci for HR-positive disease and translational work seeks to establish biomarkers of resistance to Saci and other ADCs.

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421P Changes in cell-free DNA after short-term palbociclib and fulvestrant treatment for advanced or metastatic hormone receptor-positive and human epidermal growth factor 2-negative breast cancer

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Background: Here, we investigated the potential predictive and elucidating efficacy of cell-free DNA (cfDNA) changes on clinical outcomes and biological effects, respectively, after short-term palbociclib and fulvestrant treatment for patients with hormone receptor (HR)-positive and human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer (ABC).

Methods: In this secondary analysis of the Japan Breast Cancer Research Group-M07 (FUTURE) trial, blood cfDNA was obtained before palbociclib treatment and on day 15 of cycle one (28-day cycle). Target enrichment was performed using next-generation sequencing; progression-free survival (PFS) was compared based on cfDNA changes between baseline and day 15 of cycle one after combination therapy.

Results: Fifty-six patients (112 paired blood samples) were examined. The median follow-up time was 8.9 months. *PIK3CA* (30.4%, 17/56), *FOXA1* (30.4%, 17/56), and *ESR1* (28.6%, 16/56) were most frequently mutated at baseline. The number of mutated genes was significantly decreased on day 15 compared with that at baseline (paired t-test: P-value = 0.025). No significant difference was observed in PFS (decrease group, 7.9 m vs the others, 9.3 m; log-rank P-value = 0.75; hazard ratio, 1.13; 95% confidence interval, 0.53-2.41). Among patients without previous aromatase inhibitor treatment (n = 15), three (20%) had *ESR1* mutations after progression to fulvestrant.

Conclusions: No significant association was observed between changes in mutated genes after short-term palbociclib and fulvestrant treatment and disease progression; a significant reduction in cfDNA mutation level was observed on day 15 of cycle one. Clinical meanings of cfDNA should be investigated in the future trials.

Clinical trial identification: The study protocol was registered with the University Hospital Medical Information Network, Japan (UMIN000029294) and Japan Registry of Clinical Trials (CRB2200002).

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422P UK real-world data (RWD) of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) use in metastatic breast cancer (MBC)

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Background: Many studies support the use of CDK4/6i in MBC with aromatase inhibitors or fulvestrant. We assessed the efficacy and tolerability of CDK4/6i using RWD.

Methods: RWD was collected retrospectively from 5 UK centres. Patients with a diagnosis of ER+/HER2- MBC treated with a CDK4/6i between Apr 17 and Nov 22 were included. We used Kaplan-Meier statistical analysis to calculate follow-up time, progression free survival (PFS) and overall survival (OS).

Results: 665 patients were included (median age 66 (range 23-92)). 243 (36.5%) were documented as pre- and 343 (51.6%) as post-menopausal. 543 (81.7%) had 1st-line CDK4/6i and 122 (18.3%) had $\geq$ 2nd-line treatment. 536 (80.6%) received Palbociclib (P), 85 (12.8%) Abemaciclib (A) and 44 (6.6%) Ribociclib (R). The median follow-up time was 28 months (range 0-76; IQR 18-41). 1st-line PFS was P - 31 months (25-35), A - 16 months (9-NR) and R - 44 months (21-NR). $\geq$ 2nd-line PFS was P - 12 months (10-29), A - 15 months (11-30) and R - 15.5 months (10-NR). OS data is immature. Overall, 527 (79.2%) patients suffered any grade toxicity (P - 414 (77.2%), A - 72 (84.7%) and R - 41 (93.1%)) and 248 (37.2%) $\geq$Grade 3 ($\geq$G3) (P - 203 (37.9%), A - 22 (25.9%) and R - 23 (52.3%)). The table outlines the most common toxicities by drug and grade. 366 (55%) patients had 1 dose reduction (DR): P - 290 (54.1%), A - 50 (58.8%) and R - 26 (59%). The median time to DR was 2 months (1-63), with no significant difference noticed between CDK4/6i. 113 (17%) patients had >1 DR: P - 96 (17.9%), A - 6 (13.6%) and R - 11 (12.9%).

Table: 422P

Toxicity	P (n=536)		A (n=85)		R (n=44)	
	Any grade (%)	G3 (%)	Any grade (%)	G3 (%)	Any grade (%)	G3 (%)
Neutropenia	38.2	30.3	15.3	7.1	36.4	15.9
Fatigue	37.1	1.9	31.8	2.4	34.1	4.5
Diarrhoea	9.1	0.7	61.2	10.6	15.9	2.3
Mucositis	12.1	0.6	4.8	0	2.3	0
Hepatoxicity	2.8	1.3	1.2	1.2	27.3	20.5
Nausea	9.9	1.3	17.6	5.9	25.0	2.3
Rash	3.2	0	2.4	0	9.1	2.3

Conclusions: This large, RWD-set demonstrates PFS comparable to that of published trial data, but outcomes for A and R are impacted by small numbers and short follow up. $\geq$G3 toxicity was highest for P and R compared to A and lower than previously described, though DR rates were similar, suggesting significant side-effects were experienced. As their use increases and extends to the adjuvant setting, complete and mature RWD examining CDK4/6i toxicity, PFS and OS is required, especially for A and R.

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423P A real-world study on the clinical value of apatinib-based regimens in metastatic triple-negative breast cancer

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Background: Apatinib is an oral, highly potent tyrosine-kinase inhibitor targeting VEGFR2. The published studies have shown probable efficacy and safety. However, the recommended dose of apatinib (500mg/day) is associated with difficult-to-tolerate adverse reactions. To this end, we aim to investigate whether low-dose apatinib (250mg/day) in combination with chemotherapy could benefit metastatic triple-negative breast cancer (mTNBC) in the real-world setting.

Methods: Patients with mTNBC who were treated at Fujian Medical University Cancer Hospital from October 2011 to January 2023 were screened. Patients included in this study were divided into two groups, low-dose apatinib (250mg/day) and/or palliative chemotherapy. Descriptive statistics were used to summarize adverse reactions and demographic data. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method. Secondary outcomes included objective response rate (ORR), disease control rate (DCR), and safety profiles.

Results: A total of 163 patients were included in this study and retrospectively analyzed. The Apatinib-based group (n = 56) showed significant benefits in terms of progression-free survival (PFS) and overall survival (OS) comparing with the chemotherapy-based treatment group (n = 107), with median PFS of 8.5 months (95% CI, 6.6-12.8) versus 2.8 months (95% CI, 2.4-4.4) (HR = 0.33, 95% CI, 0.22-0.50, P < 0.001) and OS of 21.1 months (95% CI, 15.5-NR) versus 10.5 months (95% CI, 9.1-12.8) (HR = 0.28, 95% CI, 0.17-0.47, P < 0.001). The overall response rate (ORR) and the disease control rate (DCR) were 53.6% versus 26.2% (P < .001) and 85.7% versus 44.9% (P < .001), respectively. The second- and later-line subgroup showed significant benefits. The grade 3/4 toxicity of apatinib plus chemotherapy was mainly manifested as neutropenia (8.8%) and hypertension (5.9%). No treatment-related serious adverse events or deaths were reported.

Conclusions: Low-dose apatinib plus chemotherapy showed better survival benefits than chemotherapy alone, with significantly improved non-hematological toxicity and increased patient tolerability for mTNBC. Much more investigation is warranted and necessary for further exploration.

Clinical trial identification: NCT05019690.

Legal entity responsible for the study: The authors.

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424P Pyrotinib plus capecitabine for trastuzumab-resistant, HER2-positive advanced breast cancer: Updated survival results from the phase II PICTURE trial

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Background: Patients with HER2-positive advanced breast cancer and primary resistance to trastuzumab have a poor clinical outcome and lack good evidence to inform clinical decision. Compared with acquired resistance, primary trastuzumab resistance may have different resistance mechanisms, such as intrinsic resistance and HER2

independency. This multicenter phase 2 trial investigated the efficacy and safety of pyrotinib plus capecitabine in this population.

Methods: Patients received pyrotinib 400 mg once daily and capecitabine 1000 mg/m^2 twice a day on days 1-14 of each 21-day cycle until disease progression or intolerable toxicity. Based on the definitions used in prior clinical trials, primary trastuzumab resistance was defined as progression during (neo)adjuvant trastuzumab (subgroup A) or within 12 months of completing (neo)adjuvant trastuzumab (subgroup B), or progression within 6 months after initiation of first-line trastuzumab for advanced disease (subgroup C). The primary endpoint was investigator-assessed progression-free survival (PFS). This report updated survival results.

Results: Between June 20, 2019 and September 19, 2021, 100 patients were enrolled. As of April 31, 2023, the median follow-up duration was 29.7 months (95% CI, 26.9-31.5). Thirty-five deaths occurred, and the estimated median overall survival (OS) was 41.7 months (95% CI, 32.2-not reached). Subgroup B (n=49) had the longest median OS (41.7 months) and PFS (17.8 months). In patients with available data of subsequent anti-HER2 therapy after progression, 61.4%, 38.6%, and 36.4% received monoclonal antibody, tyrosine kinase inhibitor, and antibody-drug conjugate, respectively. The extended follow-up showed unchanged median PFS (11.8 months [95% CI, 8.4-15.1]) and objective response rate (70.0% [70/100]).

Conclusions: The updated OS analysis highlights the long-term efficacy of pyrotinib plus capecitabine in HER2-positive advanced breast cancer patients who have shown primary resistance to trastuzumab. Even in the era of modern anti-HER2 therapies, this clinical setting warrants more investigations to meet unmet needs.

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425P Real world quality of life (QoL) in breast cancer (BC) patients treated with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i)

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Background: Palbociclib, ribociclib and abemaciclib play an important role in the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) BC based on their impressive efficacy; however, there seem to be some differences in toxicity profiles which can adversely affect their QoL. This study aims to evaluate health-related QoL (HRQoL) in advanced BC patients treated with CDK4/6i with the help of digital apps.

Methods: HRQoL was assessed in women with HR+/HER2- metastatic BC treated with CDK4/6i plus endocrine therapy using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire via online platform in Spanish patients with a cut-off date of August 2022.

Results: A total of 264 patients were analyzed. 85% had between 40-69 years. 30% were employed. The most used CDK4/6i was palbociclib (46.2%), followed of ribociclib (39.8%) and abemaciclib (14%). 33% had a dose reduction. 69.7% of patients had received chemotherapy previously; of these, 91.8% consider that their QoL is better with CDK4/6i. Of all patients who are undergoing with CDK4/6i, 87.5% feel content with the treatment. Overall scores from the FACT-B questionnaire were comparable between all CDK4/6i (Table). Notably, 45.9% and 37.8% of patients in the abemaciclib group reported diarrhea and nausea, respectively. Better scores were registered in the palbociclib arm for fatigue, pain, insomnia and better sexual enjoyment.

Table: 425P

FACT-B*	Palbociclib	Ribociclib	Abemaciclib	*p* value
N (%)	122 (46.3%)	105 (39.7%)	37 (14%)	
Age (%)	11 (9.02%)	14 (13.33%)	7 (18.98%)	0,232
≤ 39 years	105 (86.07%)	89 (84.76%)	30 (81.08%)	
40-69 years	6 (4.92%)	2 (1.91%)	0	
≥ 70 years				
Physical well-being, median (range)	22 (4-28)	21 (1-28)	20 (9-27)	0,431
Social/family well-being, median (range)	17 (0-27)	18 (0-24)	18 (5-26)	0,48
Emotional well-being, median (range)	14 (3-24)	10 (0-18)	13 (6-20)	0,005
Functional well-being, median (range)	13.5 (0-26)	14 (1-27)	13 (1-23)	0,855
Breast cancer subscale, median (range)	24 (7-39)	23 (4-35)	20 (13-32)	0,027
Total score, median (range)	90 (24-135)	86 (29-127)	83 (53-104)	0,049

*Higher scores indicate a better QoL.

Conclusions: The CDK4/6i play an eminent role in the therapy of advanced BC; nevertheless, the impact of treatment in QoL should be considered in addition to efficacy and safety, especially in the non-curative setting. Our HR-QoL results seems to confirm those obtained in clinical trials. To our knowledge this is the first study about HR-QoL in HR+/HER2- BC patients treated with CDK4/6i in Spanish real-world setting.

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426P The overall survival data of FUTURE-C-PLUS: Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for advanced, immunomodulatory triple-negative breast cancer, an open-label, single-arm, phase II trial

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Background: Camrelizumab and nab-paclitaxel demonstrated promising anti-tumour activity in metastatic immunomodulatory triple-negative breast cancer (IM-TNBC) in FUTURE trial. Anti-angiogenic agents have been reported to facilitate immune infiltration. Famitinib is a tyrosine kinase inhibitor targeting VEGFR-2, PDGFR and c-kit. The FUTURE-C-PLUS trial (NCT04129996) which added famitinib to camrelizumab and nab-paclitaxel is a single-arm, phase 2 trial evaluating this triplet combinatorial strategy in advanced IM-TNBC. Study design and the primary endpoint ORR has been reported (Zhi-ming Shao, et al. ASCO 2021, Abstract 1007). The final PFS data had been published in Clinical Cancer Research (Clin Cancer Res 2022;28:2807—17). Here, we reported the updated overall survival.

Methods: This study enrolled women aged 18-70 years, with previously untreated, unresectable, locally advanced, recurrent or metastatic IM-TNBC. IM-TNBC was defined as CD8 expression on at least 10% of cells using IHC analysis. Eligible patients received the triple therapy.

Results: Forty-eight patients were enrolled between Oct 2019 and Oct 2020. The median follow-up was 33.1 months (range, 31.8—34.4). 39 (81.3%, 95% CI 70.2-92.3) patients had a confirmed objective response which has been reported in ASCO 2021. At this updating data cutoff (May 1, 2023), the median progression-free survival was 13.6 months (95% CI, 8.4-18.8). While overall survival was 29.4 months (95% CI, 23.3-35.5). The most common treatment-related grade 3 or 4 adverse events were neutropenia (16 [33.3%]), anemia (5 [10.4%]), febrile neutropenia (5 [10.4%]), and thrombocytopenia (4 [8.3%]). No new safety concerns were detected. No treatment-related deaths were reported.

Conclusions: These data, combined with our previous reports, provide further evidence for the triplet combination as an active therapy in advanced IM-TNBC. To our knowledge, this is the best over survival reached in first-line treatment of advanced TNBC. A randomized controlled FUTURE-Super trial (NCT04395989) is ongoing to further validate these findings.

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427P Pyrotinib plus trastuzumab versus pertuzumab plus trastuzumab in patients with HER2-positive metastatic breast cancer: A multicenter, retrospective study

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Background: Pyrotinib has shown to be an effective antitumor agent in HER2-positive metastatic breast cancer (MBC). Pertuzumab, combined with trastuzumab and docetaxel, is the standard first-line dual anti-HER2 therapy for HER2-positive MBC. No

direct comparison has been made between pyrotinib plus trastuzumab (PyroH) and pertuzumab plus trastuzumab (HP) in the treatment of HER2-positive MBC.

Methods: We retrospectively evaluated medical records for all patients with HER2-positive metastatic breast cancer who received PyroH plus chemotherapy or HP plus chemotherapy between 2017 and 2022 at five institutions in China. The primary endpoint was progression-free survival (PFS).

Results: This study included 333 patients, among which 161 received PyroH and 172 received HP. There was no significant difference between the two groups in either first-line or post second-line of systemic treatment (median PFS: 14.46 vs. 22.90 months, p=0.057; 8.67 vs. 7.92 months, p=0.286, respectively). Although HP group showed a significant longer PFS than PyroH group in the overall real-world setting (median PFS: 9.30 vs. 13.01 months, p=0.005), the treatment group is not an independent predictor of PFS in multivariate analysis (HR 1.134, 95% CI 0.710-1.811, p=0.598). PyroH demonstrated a longer PFS than HP when taxane was not utilized (median PFS: 10.12 vs. 8.15 months, p=0.017). In patients with brain metastases receiving first-line treatment, PyroH showed a potential advantage over the HP group, although this difference did not reach statistical significance (median PFS: 14.29 vs. 7.98 months, p=0.955). PyroH group had a higher incidence of grade 3/4 diarrhea (34.3% vs. 3.0%), but the overall incidence of adverse events did not differ between the two groups.

Conclusions: In real-world setting, although HP showed unshakable position when combined with taxane in first-line treatment, PyroH presented comparable effectiveness in post second-line treatment and patients with brain metastasis and even better efficacy in patients without combination of taxane. Toxicities in both groups were tolerable.

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428P Palbociclib dose patterns in Swedish patients with metastatic breast cancer: 5-year update from the SIRI study

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Background: Although palbociclib combined with endocrine therapy is a well-established treatment option in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC), there is limited evidence on patterns of dose reductions in real-world setting. The Swedish Ibrance Registries Insights (SIRI) study investigated real-world dose patterns using a nationwide cohort of palbociclib-treated MBC patients.

Methods: This was a retrospective study utilizing population-based Swedish Health Data Registers. The cohort included all patients $\geq$ 18 years with $\geq$ 1 dispensation of palbociclib from January 2017 – June 2022. Minimum follow-up was 3 months. Starting dose and dose changes for the full population and for different age groups, in total and over time, was investigated.

Results: 2058 patients were identified and the median (IQR) age at treatment initiation was 68.4 (15.7) years. Patients were stratified into three age groups: <50, 50-69, $\geq$70 years, with the following distribution: 9.9%, 46.1%, and 44.0%, respectively. Most patients were initiated on 125 mg (82.0%), with a lower share for older patients ($\geq$70 years; 74.4%). In total, 45.5% of patients had $\geq$ 1 dose reduction, with a higher frequency for older patients ($\geq$70 years; 48.5%). Median (IQR) time to first dose reduction was 2.4 (3.9) months, and 5.9 (7.5) months to second dose reduction, with little variation across age groups. The probability for dose reduction was equal across age groups during the initial 6 months of treatment, whereafter it slightly increased for older patients ($\geq$70 years). For patients starting with lower dose (100 mg) compared to standard dose (125 mg) at treatment initiation, the probability for dose reduction was similar during the first 3 months of treatment, whereafter it increased.

Conclusions: Most Swedish palbociclib-treated patients were initiated on the recommended dose, but a lower starting dose and a higher frequency of dose reductions were observed for older patients. The time to dose reduction was equal across age groups, whereas the probability for dose reduction increased over time for older patients, and for patients with a start dose of 100 mg.

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429P The impact of HER2 status on the efficacy of CDK 4/6 inhibitors: A multicenter study

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Background: The prognostic significance of Human Epidermal Growth Factor Receptor 2 (HER2)-low status in patients with hormone receptor-positive (HR+)/HER2-negative advanced breast cancer (aBC) who receive first-line endocrine therapy combined with cyclin-dependent kinase (CDK) 4/6 inhibitors remains uncertain. Two major studies in this area have yielded conflicting results, indicating the need for further research. Therefore, Our objective is to examine the effect of HER2 status on overall survival (OS) outcomes among patients who are undergoing first-line treatment with CDK 4/6 inhibitors.

Methods: Our study is a multi-center, retrospective, real-world data analysis focusing on patients diagnosed with hormone receptor-positive, HER2-negative metastatic breast cancer who were treated with CDK 4/6 inhibitors as first-line therapy.

Results: Our study included 160 patients from five tertiary hospitals. The median follow-up time was 19.90 $\pm$ 0.82 months, and mOS could not be reached. Of the patients, 83 were included with recurrent metastatic disease. 118 were postmenopausal. 63 patients were treated with palbociclib and 97 were treated with ribociclib. 111 had HER2 negative and 49 had HER2 low status. The median overall survival in the HER2 low group was 49.03 months, while the mOS could not be reached in the HER2-negative group (HR: 0.87, p=0.818). There was no difference in OS between patients treated with palbociclib and ribociclib (p=0.416).

Conclusions: Our study is one of the few with a large sample size, examining the relationship between CDK 4/6 inhibitors' efficacy and HER2 status. Previous research includes two studies with a high number of patients and three with a low number of patients, with inconsistent results in the two larger studies. In our study, which included a significant number of patients, we showed that CDK 4/6 inhibitors had a similar overall survival in the HER2 low group and the HER2-negative group. In our study, there was no significant difference in overall survival between the use of palbociclib and ribociclib.

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430P Real-world patient characteristics and treatment patterns in HR+/HER2+ metastatic breast cancer patients in 5 European countries

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Background: For patients (pts) with HR+/HER2+ metastatic breast cancer (mBC) with no contraindication for chemotherapy (CT), the ESMO mBC Living guidelines recommend first-line CT in combination with dual anti-HER2, followed by endocrine therapy (ET) with dual anti-HER2 agents upon CT completion as maintenance therapy. This study assesses patient characteristics and treatments patterns for adults with HR+/HER2+ mBC in 5 European countries.

Methods: Data were collected using the Adelphi Advanced BC Disease Specific Programme. Oncologists in France, Germany, Italy, Spain, and the UK abstracted data from patient medical records. This study included pts who had previously received

Table: 430P Treatment sequencing in pts with HR+/HER2+ mBC

	Induction regimen				
	ChT + dual anti-HER2	ChT + single anti-HER2	ChT only	Dual anti-HER2	Single anti-HER2
Maintenance regimen	n=372	n=71	n=30	n=14	n=8
ET + dual anti-HER2 (n=273), n (%)	264 (71)	2 (3)	4 (13)	3 (21)	0 (0)
ET + single anti-HER2 (n=130), n (%)	48 (13)	56 (79)	17 (57)	7 (50)	2 (25)
Single anti-HER2 (n=25), n (%)	9 (2)	7 (10)	4 (13)	1 (7)	4 (50)
ET monotherapy (n=21), n (%)	13 (3)	3 (4)	1 (3)	2 (14)	2 (25)
Other* (n=46), n (%)	38 (10)	3 (4)	4 (13)	1 (7)	0 (0)

* Includes dual anti-HER2 and ET + 3 anti-HER2 regimens

induction therapy and were receiving maintenance treatment for HR+/HER2+ mBC at time of data abstraction (July 2022 to February 2023).

Results: 495 pts with HR+/HER2+ mBC were included. At time of data abstraction: mean (SD) age was 62 (9.88) years; 81% had de novo mBC; 63% had visceral metastases; pain was the most common symptom (22%). Among pts who received early-stage BC treatment (n=78), 63% received CT and ≥1 anti-HER2 agent. 89% of pts received CT and a single/dual anti-HER2 agent(s) as 1L regimen for mBC, with 81% of pts then receiving ET and a single/dual anti-HER2 agent(s) as a maintenance regimen (Table). CT only was received by 6% of the sample as an induction regimen, with 70% then receiving ET and a single/dual anti-HER2 agent(s) as a maintenance regimen. The remaining 4% of pts received a single/dual anti-HER2 agent(s) as an induction regimen, with single anti-HER2 +/- ET the most common maintenance regimens.

Conclusions: Most pts were de novo mBC, with two thirds of the population having visceral metastases. While most pts in our study received treatment aligned with ESMO guidelines, some regimens did not align to the guidelines. Further investigation is required to understand the factors that drive treatment decisions and adherence to the guidelines.

Legal entity responsible for the study: Adelphi Real World.

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431P Distribution and prognostic role of HER2 status of circulating tumor cells (CTCs) and tumor-derived extracellular vesicles (tdEVs) in HER2- metastatic breast cancer (MBC) patients (pts)

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Background: CTCs and tdEVs predict clinical outcome in MBC pts. The detection of HER2+ CTCs has been associated with poor prognosis in HER2- MBC. In the blood of MBC pts, it is also possible to detect cytokeratin negative (CK-) CTCs. The clinical significance of HER2 expression in CK- CTCs and tdEVs is understudied.

Methods: This study retrospectively analyzed 258 pts with HER2- MBC enrolled at Northwestern University (Chicago, IL) between 2016 and 2021 (NU16B06 trial). Baseline blood samples were processed for CTCs with the CellSearch® system using an anti-HER2 antibody. CTCs were manually counted and classified according to HER2 staining intensity. The ACCEPT software was applied to evaluate HER2 status on CK- CTCs and tdEVs.

Results: 122 pts (47%) had ≥ 5 CTCs/7.5 mL of blood. HER2 status of CTCs was assessed in 198 pts: 92 (47%) had ≥1 CTCs with moderate or strong staining (i.e. HER2+ CTCs). CK- HER2+ CTCs were detected in 220 pts (85%); CK+ HER2+ tdEVs were detected in 51 pts (20%). The distribution according to CTCs is shown in the table. CTCs and tdEVs were significantly associated with overall survival (OS). Overall, detection of ≥1 HER2+ CTC was associated with shorter OS (19 vs 47 months, p<0.001). In pts with ≥ 5 CTCs, HER2+ CTCs were associated with a numerical decrease in OS (25 vs 15 months; p=0.069). Pts with ≥1 CK- HER2+ CTCs had worse outcome (23 vs 33 months; p=0.029) whereas HER2+ tdEVs were not significantly associated with OS. In multivariate analysis, hormone receptor status, therapy line, CTC count, CTC-HER2 status, and tdEV count independently predicted OS.

Table: 431P

	CTC < 5	CTC ≥ 5	p value
CTC CK+ HER2+	0 [0-0]	3 [1-9]	<0.001
tdEV CK+	4 [1-13]	153 [51-464]	<0.001
CTC CK- HER2+	3 [1-6]	4 [2-10]	<0.001
tdEV CK+ HER2+	0 [0-0]	0 [0-0]	0.461
tdEV CK- HER2+	31 [10-83]	40 [14-98]	0.131

Conclusions: HER2 expression can be detected in CTCs from HER2- MBC pts representing a prognostic factor and a possible therapeutic target. The prognostic role of CK- HER2+ CTCs suggests their tumor origin as cells with mixed epithelial-mesenchymal phenotype; additional studies on these CTCs are needed. HER2 expression on tdEVs was not associated with outcome.

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432P Ki67 and progesterone receptor status could be predict sensitivity to cyclin-dependent kinase inhibitor

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Background: Cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) combined with endocrine therapy has been approved as first-line treatment for hormone receptor-positive(HR+) advanced breast cancer (ABC). A challenge is finding biomarkers to identify patients who respond to treatment with CDK4/6i.

Methods: We identified all patients in treatment with CDK4/6i for ABC in our centre. Restrospectively, we analyzed the values of Ki 67 and progesterone receptor(PR) detected by inmunohistochemistry and their impact on CDK4/6i duration and progression-free survival(PFS). PFS was evaluated by Kaplan Meier method and survival curves were compared using the longrank test. Results were considered statistically significant with a p value <0'05. Analyses were realized with SPSS.

Results: Between January 2018 and January 2023, 210 patients received CDK4/6i treatment at our institution, 68'6% (144) received palbociclib, 24'3%(51) ribociclib and 7'1%(15) abemaciclib. The media age was 52 years (36-91). The median follow up time was 21 months (range 1-69 months). Ki 67 and PR expression were analyzed both as continuos and dichotomized variables and PR was classified as positive or negative. In the total population, patients with Ki67 >30% had significant shorter CDK4/6i treatment duration versus Ki 67<30% (16'80 months vs not reached, p=0'04). In regard to PR expression, we observed patients with PR positive had longer CDK4/6i treatment duration compared with PR negative (17'54 vs 7'55 months, p=0'027). Also, if we analyzed PFS, we observed patients PR positive had longer PFS versus PR negative (45'50 months vs 17'71 months, p=0'02), we recorded

PFS as the duration from the beginning of treatment to disease progression or death, whichever happened first.

Conclusions: In clinical practical, there is a high individual variability in clinical response in patient with CDK4/6i treatment. Actually, there are not biomarkers that predict which patients respond to treatment. In this study, we investigated the impact of Ki67 and PR values on CD4/6i treatment in HR-positive ABC patients. Also, we revealed that PFS seemed to be negatively influenced by elevated Ki 67 values (>30%) and negative PR expression. We have to corroborate these data in prospective studies.

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433P Effectiveness and safety of vinorelbine + inetetamab + pyrotinib in ≥second-line treatment of HER2-positive metastatic breast cancer

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Background: In real-world settings, patients with HER2-positive metastatic breast cancer (MBC) who cannot receive antibody-drug conjugates (ADCs) as standard second-line regimen and who have no preferred regimen in ≥third line by NCCN guidelines, require new regimens to meet their clinical needs. This study aimed to explore the effectiveness and safety of vinorelbine + inetetamab + pyrotinib (VIP) for ≥second-line treatment of HER2-positive MBC.

Methods: Patients with HER2-positive MBC who received ≥second-line treatment at our hospital from June 2020 to December 2022 were enrolled. Progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR) and adverse reactions were assessed. Patients received VIP regimen until disease progression or unacceptable toxicity and were evaluated every two cycles according to the RECIST 1.1 criteria.

Results: Eight-nine patients were included based on the inclusion and exclusion criteria. Among them, 45 patients received second-line treatment who couldn't use T-DM1 or T-DXd, and 44 patients received ≥third-line treatment. The median PFS of the second-line treatment subgroup was 17months, the ORR and CBR were 60.0% and 86.7%, respectively, which were significantly higher than those in the ≥third-line treatment subgroup and numerically superior to T-DM1 as a second-line treatment option. Additionally, the median PFS of patients with baseline brain metastasis who did not receive radiotherapy was 7 months, and ORR and CBR were 27.3% and 72.7%, respectively. The most common adverse events observed were leukopenia (37.1%), neutropenia (42.7%), anemia (34.8%) and diarrhea (67.4%). The incidence of grade 3-4 leukopenia, neutropenia, anemia and diarrhea were 11.2%, 15.7%, 5.6% and 27.0%, respectively. A total of 8 patients (8.9%) discontinued medication due to adverse reactions.

Conclusions: The VIP regimen demonstrated good efficacy and controllable toxicity as a second-line treatment for HER2-positive MBC. This therapeutic regimen provides a viable alternative option for patients who are unable to receive ADCs as the second-line treatment.

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434P Incidence and prognostic value of HER2-low expression metastatic breast cancer in Asian population: A 10-year retrospective study

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Background: The natural disease across each molecular subtype of breast cancer are variable. Although novel drugs for the treatment of human epidermal growth receptor (HER2) overexpression subtype metastatic breast cancer have been widely utilized, the treatment options for HER2 low expression is limited. The epidemiology and clinical outcome of metastatic HER2-low expression breast cancer among the Asian population have not been thoroughly described.

Methods: A 10-year retrospective cohort study was conducted from the Ramathibodi Cancer Registry database during 2011-2021. We aimed to investigate the incidence and compare the overall survival (OS) of non-HER2 expression and HER2-low metastatic breast cancer. Prognostic factors for survival were analyzed by logistic regression analysis.

Results: Out of 8,633 patients, 491 met the study criteria. Of those, 104 (21.2%) had HER2-low expression tumors, while 247 (50.3%) had HER2-negative expression tumors. When stratified by hormonal receptor status, 85 patients (81.7%) were hormonal receptor (HR)-positive and 19 patients (18.3%) were HR-negative. The median OS (IQR) was significantly longer in patients with HER2-low expression tumors compared to those with HER2-negative expression tumors (median OS 41 (26-56) months vs. 23 (19-27) months; HR, 0.66, 95% CI (0.49-0.88), p = 0.004). Among the HR-positive tumors, patients with HER2-low expression also had a significantly longer OS than those without HER2 expression (median OS 54 (42-66) months vs. 30 (26-34) months; HR, 0.65, 95% CI (0.46−0.92), p= 0.014). In the HR-negative group, the survival in patients with HER2-low expression tumors was comparable to those without HER2 expression tumors (median OS 13 (8-18) months vs. 14 (11-17) months; HR, 1.09, 95% CI (0.64−1.86), p=0.76).

Conclusions: One in five Asian patients with metastatic breast cancer could develop HER2 low-expression tumors. Those with HER2 low-expression tumors, particularly in the HR-positive subtype, tend to have longer survival than those without HER2 expression tumors among patients with metastatic breast cancer.

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435P Phase II single arm study of durvalumab and olaparib (D+O) in heavily pretreated triple-negative breast cancer (TNBC) with or without germline BRCA mutation (gBRCAm)

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Background: PARP inhibitors (PARPis) induce STING-cGAS activation and increase tumor mutational load in TNBC preclinical models, making TNBC sensitive to immune checkpoint blockade. The MEDIOLA phase II study demonstrated a 63.3% overall response rate (ORR) defined as CR+PR with D+O in PARPi naïve gBRCAm BC (1 median number of prior therapies [range 0-4]). We evaluated D+O activity in heavily pretreated TNBC.

Methods: Key eligibility criteria include metastatic TNBC, adequate performance status and organ function. Patients (pts) with prior use of D or PARPi, and active CNS or leptomeningeal disease were not eligible. No limit on the number of prior systemic therapies. For germline BRCA wild type (gBRCAwt), Simon's 2-stage design with a target of 30% ORR with α=0.1 and β=0.1 was used. If ≥ 2 responses in the first stage (16 pts), 9 additional pts were planned to enroll. 5 ≥ of 25 responses warrant a further later stage study. For gBRCAm, a pilot single stage design was used with a stopping rule. If 1≥ response in the first 5 pts, another 5 pts were planned to enroll. RP2D determined in our earlier phase I study; D 1500 mg iv q4w and O 300 mg BID po (28-day cycle) was administered until PD or intolerable toxicity. The primary endpoint was ORR by RECIST v1.1 (CT q2mo). Secondary objectives were safety by CTCAE v4.03, clinical benefit rate (CBR) defined by CR+PR+SD≥4mo, and PFS.

Results: 14 of 15 pts were RECIST evaluable (11 gBRCAwt and 3 gBRCAm). The median number of prior therapies are 3 (range 0-9). A majority of pts (78.6%; 11/14) had ≥ 3 prior systemic therapies and 64.3% (9/14) had previous platinum. Of note, 4 pts had either HR+/HER2-BC (n=3) or HR+/HER2+BC (n=1) at diagnosis which converted to TNBC at recurrence. ORR was 28.5% (3/3 gBRCAm [3 PR] and 1/11 gBRCAwt [PR for 10.3 mo]). One pt with gBRCAm remains on the study with PR >4 yr (96% reduction at best). CBR was 42.9% (3/3 gBRCAm and 3/11 gBRCAwt). Median PFS was 3.7 mo (IQR 1.9-10.3). There were no new safety signals. Accrual is ongoing.

Conclusions: D+O exhibited modest clinical activity in heavily pretreated TNBC pts with or without gBRCAm. Comprehensive biomarker and pharmacodynamic studies are ongoing for the exceptional responder with gBRCAm.

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Legal entity responsible for the study: J-M. Lee.

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436P Preliminary results from a prospective study of inetetamab in combination with pyrotinib and utidelone for HER2-positive metastatic breast cancer (IPUtrial)

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Background: Anti-HER2 therapy combined with chemotherapy is the standard therapy for HER2-positive metastatic breast cancer (MBC). Efficacy and safety of inetetamab and pyrotinib in advanced first-line and second-line treatment of HER2-positive breast cancer have been confirmed. Utidelone, a genetically engineered epothilone analogue, has demonstrated antitumor activity in MBC. This study aimed to explore efficacy and safety of the new regimen combined with these three drugs.

Methods: IPUtrial is a prospective, multicenter, single arm, phase 2 study. The study enrolled HER2-positive MBC patients (pts) with first/second line therapy. Pts received inetetamab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles, day 1, IV), pyrotinib (400 mg/d, qd, po) and utidelone (30mg/m^2, days 1-5, IV) of each 21-day cycle until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) per investigator (INV). The secondary endpoints included INV-assessed progression-free survival (PFS), overall survival (OS) and safety.

Results: At date cutoff (1 Apr 2023), we enrolled 47 pts (29 patients were evaluable for response with median cycles of 8 (4-20) and still undergoing treatment, 19 (65.5%) for the first-line therapy and 10 (34.5%) for the second-line therapy). We reported the efficacy and safety from 29 pts. Partial response (PR) was achieved in 23 pts and stable disease (SD) in 4 pts, the ORR was 79.3% and DCR was 93.1%. The median PFS was not reached. Most of the treatment-related adverse events (TRAEs) were grade 1 or 2 and were considered manageable and reversible. The most common TRAEs was diarrhea (29[100%]). Grade 3 diarrhea was reported in 24 pts (82.8%) with the combination therapy. No treatment-related discontinuation or deaths occurred.

Conclusions: Inetetamab plus pyrotinib and utidelone may be an excellent scheme for HER2-positive metastatic breast cancer. This trial is still ongoing and needs long-term follow-up.

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437P Improving safety and convenience for breast cancer patients receiving CDK 4/6 inhibitor treatment via a telemedicine app

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Background: CDK 4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, have become an essential component of breast cancer treatment. These targeted therapies require monitoring of blood counts, biochemistry, drug interactions, and synergic side effects like QTc prolongation. Post-COVID-19, a telemedicine app was developed for a more convenient and safe patient management approach.

Methods: A prospective pilot study enrolled breast cancer patients on CDK 4/6 inhibitors to use a telemedicine app, allowing them to return home after blood collection, receive results and recommendations, register adverse reactions, and, in ribociclib cases, monitor ECG with automatic QTc evaluation. The app offered comprehensive information on drug interactions and synergic side effects with concomitant medications. App performance was assessed using EORTC QLQ-C30 and FACT-B questionnaires at baseline and after app usage.

Results: 20 patients participated in the study. According to the EORTC QLQ-C30 global health status and FACT-B scores, the patients' quality of life was effectively maintained. The app reduced waiting room time by an average of 127 minutes per visit ($p<0.01$). In addition, the physicians involved in the study reported increased confidence in patient safety due to the comprehensive information provided by the app.

Conclusions: The telemedicine app offers a valuable tool for optimizing the management of patients on targeted therapies. It not only maintains patients' quality of life but also enhances overall healthcare efficiency by reducing waiting times and strengthening physicians' perception of patient safety. Future studies should explore the long-term impacts of the app, particularly on patient adherence, survival rates, and cost-effectiveness. With an enlarged patient cohort, there is substantial potential for notable enhancements in quality of life. This expanded investigation could offer deeper insights, enabling us to tailor our telemedicine approach more effectively, thus promoting a higher standard of patient care.

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438P Phase I study of ZV0203, a first in class pertuzumab ADC, in patients with HER2+ advanced solid tumors

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Background: ZV0203, a first in class pertuzumab antibody-drug conjugate (ADC), targets HER2+ tumor cells with tubulin inhibitor duostatin-5 (DUO5) as its payload via a stable and protease-cleavable valine-citrulline linker. In preclinical studies, ZV0203 demonstrated superior antitumor activity compared to Kadcyla in multiple tumor cell line xenograft models with no noticeable toxicity. GLP toxicity studies indicated that ZV0203 was well tolerated with an estimated therapeutic index of 35.

Methods: This was an open-label, multicenter, phase 1, dose-escalation study in patients (pts) with HER2+ advanced solid tumors. Primary objectives were safety, tolerability and recommended phase 2 dose. Secondary objectives included pharmacokinetics (PK), immunogenicity and preliminary clinical efficacy. ZV0203 was administered intravenously Q3W on a 21-day cycle. An accelerated titration design was used for the 0.3 and 0.6 mg/kg doses, followed by a 3+3 design for 1.2, 1.8, 2.7 and 3.6 mg/kg dose levels.

Results: As of August 23, 2023, 15 pts with solid tumors (breast [11], colorectal [2], gastric [1], lung [1]) were enrolled across doses of 0.3-3.6 mg/kg with a median age of 52 years (range 35-65), of which 9 pts received prior HER2-targeted therapy (trastuzumab $\pm$ pertuzumab) and 11 pts completed 21-day DLT assessment (0.3 mg/kg and 0.6 mg/kg [1 each], 1.2 mg/kg, 1.8 mg/kg and 2.7 mg/kg [3 each]) with no DLT incidence. Treatment-related adverse events (TRAE) occurred in 11 (73.3%) pts. The most frequent TRAEs were elevated liver enzymes [6], corneal epitheliopathy [5], dry eyes [4], leukopenia, neutropenia, proteinuria and anemia [3 each], and most were grade 1-2 in severity. 2 pts experienced grade 3 TRAEs: lymphocytopenia (1.8mg/kg [1]) and blurred vision (2.7 mg/kg [1]), which were manageable during treatment. TRAEs led to 6.7% (1/15) treatment discontinuation. Among 11 pts evaluated, 2 pts achieved a best tumor response of PR; 5 pts had SD; 1 pt had Non-CR/Non-PD per RECIST v1.1. Thus, disease control rate was 73% (8/11). Interim PK results demonstrated that the PK profile of total antibody was similar to that of ZV0203 ADC, whose systematic exposure increased in a dose-dependent manner. Concentration of DUO5 remained scarce, suggesting good stability of ZV0203.

Conclusions: ZV0203 has a manageable safety profile with preliminary antitumor activity in heavily pretreated pts with HER2+ cancer. Further evaluation at higher doses is underway.

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439P Testing HR+ / HER2- patients with advanced or metastatic breast cancer for identification of tissue mutations in the PIK3CA gene: Results of a national program by the Hellenic Society of Medical Oncology (HeSMO)

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Background: PIK3CA mutations have been identified in approximately up to 40% of breast cancer cases and PIK3CA targeting has already been incorporated in treatment algorithms, especially in the second line of ER+/HER2- patients. HeSMO launched a national program to provide PIK3CA mutation testing, which is officially not reimbursed, with the aim to identify mutations in the PIK3CA gene, and, therefore, lead to more therapeutic options.

Methods: All HR+/HER2- patients with a diagnosis of metastatic breast cancer were eligible to participate in this program. The result of the test was obtained using the COBAS® PIK3CA method, a diagnostic test specifically designed to detect mutations in the PIK3CA gene in tumor tissue samples (FFPE) attained by biopsy or surgically, which detects 17 different mutations in the PIK3CA gene, including the most commonly occurring in Exons 9 and 20.

Results: From June 2022 to March 2023, 149 patients from across the country were tested within this program. Sixty one (61) patients (40.94%) were detected with mutation in PIK3CA gene and 88 (59.06%) without mutation (Table). 23 patients had Exon 9 mutations (37.70%), 33 in Exon 20 (54.10%), and 8 had mutations in the remaining Exons 1, 4 and 7 (13.11%). In 1 sample 4 mutations were detected: (Exon 7/9/20), and 2 mutations in another 2 samples (Exon 9: E545X, Q546X and Exons 1/20), while in all other samples just 1 mutation was detected in each.

Table: 439P PIK3CA mutation results of HeSMO's program

Exon	Mutation	Samples	Mutation percentage in all patients detected with PIK3CA gene mutation (61)	Mutation percentage in all patients tested (149)
Exon 1	R88Q	2	3,28%	1,34%
Exon 4	N345K	3	4,92%	2,01%
Exon 7	C420R	3	4,92%	2,01%
Exon 9	E542K	7	11,48%	4,70%
Exon 9	E545X	12	19,67%	8,05%
Exon 9	Q546X	2	3,28%	1,34%
Exon 9	E545X, Q546X	1	1,64%	0,67%
Exon 9	E542K, E545X	1	1,64%	0,67%
Exon 20	H1047X	32	52,46%	21,48%
Exon 20	G1049R	1	1,64%	0,67%

Conclusions: In our series, 40.94% of the patients tested, were detected with mutations in PIK3CA gene, in accordance with published data. Apart from the significant implications for treatment possibilities in a substantial patients' population, these results provide valuable epidemiological data and strengthen our efforts for reimbursement of PIK3CA mutation testing in Greece.

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440P Palliative radiotherapy in metastatic breast cancer: Does molecular subtype predict patient response to radiotherapy?

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Background: This study aimed to determine whether molecular subtype does impact patient response to palliative radiotherapy in metastatic breast cancer.

Methods: All metastatic breast cancer patients referred for palliative radiotherapy (either for pain-relief or spinal cord/nerve decompression), between 2017 and 2022, were included in this study. Patient response to radiotherapy was evaluated at 3 weeks from radiotherapy. Re-irradiation need was assessed. Radiotherapy outcomes were statistically analyzed with regards to breast cancer molecular subtypes.

Results: Data of 137 metastatic breast cancer patients were evaluated. Ductal cell carcinoma was the most common histological type. Patients' distribution according to molecular subtype was as follow: 17% of luminal A tumors, 72% of luminal B tumors, 6% of Her2 tumors and 5% of triple-negative tumors. All patients received single fraction palliative radiotherapy with a prescription dose of 8 Gy and 6 Gy respectively in 77 % and 13 % of cases. Forty-six patients were lost to follow-up and one patient didn't complete treatment. Complete response to radiotherapy was reported in 21%, 54% and 50% of cases, respectively for luminal A, luminal B and Her2 tumors. No complete response was found in the triple-negative breast cancer subgroup. The "no response to radiotherapy" rate for luminal A and luminal B tumors, was 21% and 20% respectively. Re-irradiation of the same metastatic subsite was performed in 8 patients, all with luminal B molecular subtype. Although not statistically significant, luminal tumors tended to respond better to palliative radiotherapy when compared to non-luminal tumors, with a complete response rate of 48% versus 30% respectively ($p=0.3$). No statistically significant correlation was found between breast cancer molecular subtype and radiotherapy outcomes.

Conclusions: This study suggests that breast cancer subtypes do exhibit differential responses to palliative radiotherapy. Yet molecular subtype failed to reliably predict radiotherapy outcomes and identify patients who would derive greater than average benefit from palliative radiotherapy. Further studies are needed to identify reliable biomarkers predictive of likely radiotherapy sensitivity.

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441P Real-world efficacy of ribociclib (RIB) + aromatase inhibitor (AI)/fulvestrant (FUL) in subgroups of special interest: 5th interim analysis (IA) of the RIBANNA study

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Background: RIBANNA (CLEE011ADE03) is a prospective, noninterventional study assessing the efficacy and safety of RIB+AI/FUL, or endocrine therapy (ET) or chemotherapy (CT) in pre-, peri- and postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) in a broad patient population. Real-world data on the efficacy of RIB in subgroups of special interest resulting from the 5th IA from the RIBANNA study will be presented at the conference.

Methods: Efficacy outcomes in subgroups of special interest will be determined. Adjusted progression-free survival (PFS) for 1L RIB will be separately analyzed for patients with visceral vs. non-visceral metastases (lung, liver, central nervous system), pre- vs postmenopausal patients, patients receiving AI vs FUL as Ribociclib combination partner, de novo vs. recurrent and endocrine-resistant vs. -sensitive disease. In addition, conditional PFS (this is, the probability of survival without progression for further months given a previous survival for a defined number of months) will be analyzed for patients without progression at 6, 12, and 24 months in the overall study population.

Results: At data cutoff Sep 6, 2022, 2581 patients were enrolled in the study (RIB+AI/FUL, n = 2163; ET, n = 237; CT, n = 181). At baseline there were 189 pre/peri and 1605 postmenopausal patients and 750 patients with visceral metastases in the RIB cohort included in the study. 1566 patients received AI and 415 received FUL in the RIB cohort at baseline. At study start 381 de novo and 1765 recurrent patients were included over all treatment cohorts. The unadjusted KM estimate for median PFS was 32.2 months (95% CI, 29.3—34.8) in the RIB + AI/FUL cohort. Herein, efficacy data (PFS, conditional PFS) in the specified patient subgroups will be presented.

Conclusions: The RIBANNA study analyses the use of RIB in a diverse patient population in the clinical routine. RIB showed efficacy superiority over ET and CT in the overall patient population. Data on the real-world efficacy of specific patient subgroups will be presented at the conference.

Clinical trial identification: CLEE011ADE03.

Legal entity responsible for the study: Novartis Pharma GmbH.

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442P Menopausal status may derive in different second-line treatment benefits in breast cancer patients that experienced disease progression with CDK4/6 inhibitors (SUMA-001)

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Background: CDK4/6 inhibitors added to hormone therapy (CDKi-HT) is the standard first-line (1L) treatment for patients with HR+/HER2- advanced breast cancer (ABC). After CDKi-HT, treatment strategies are associated with shorter progression-free survival (PFS), and therapeutic strategies are usually tailored to clinical factors and predictive biomarkers. Our aim was to explore prognostic factors in the second-line (2L) treatment setting and determine clinical factors associated with treatment efficacy.

Methods: Retrospective cohort of HR+/HER2- ABC patients, from 17 public and private facilities in Argentina. Patients were included if started 2L treatment between November 2015 and October 2022. Clinical factors associated with treatment decisions were evaluated with t and chi-square tests. Kaplan-Meier method was used for survival analysis. Cox regression tests were applied to explore prognostic factors. $p<0,05$ was considered statistically significant.

Results: 280 patients were analyzed (Mean age 52.4+/-14, 57% postmenopausal). 98.5% received CDKi-HT in the 1L setting (med. PFS 17.8m, CI95% 8.1-28.4). Among the 240 patients with evaluable data, 39.2% received chemotherapy (CT) for the 2L setting and 53.7% received hormone therapy with or without other agents. With a median follow-up of 26 months, med. 2L-PFS was 6.6 months (CI 95% 5.8-7.6). After applying multivariate analysis, menopausal status (adj. HR 0.65 CI95% 0.44-0.98; p=0.038) and primary sample Ki67 (adj. HR 2.37 CI95% 1.14-4.9, p=0.02) were associated with 2L-PFS. An interaction was observed between selected treatment agents and menopausal status (p=0.015). In patients that did not receive CT, Median 2L-PFS was 4.66 (CI95% 4.06-6.03) and 8.7 (CI95 7-11.16) months for premenopausal and postmenopausal patients respectively (p=0.0006).

Conclusions: Real-world evidence is relevant to obtain further information regarding prognostic and predictive factors. Treatment selection should be carefully individualized in patients that experienced disease progression after CDKi-HT. The implications of our results should be carefully analyzed incorporating the experiences of other collaborative efforts.

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443P Efficacy and safety of CDK 4/6 inhibitors in patients with bone marrow-involved metastatic breast cancer

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Background: No data on the efficacy of cyclin-dependent kinase 4/6 inhibitors (CDKi) were presented in randomized clinical trials in patients with metastatic breast cancer (mBC) with bone marrow involvement. This study aimed to investigate the efficacy and safety of CDKi in patients with mBC with bone marrow involvement.

Methods: The data of patients with bone marrow-involved hormone receptor-positive (HR+) Her2-negative mBC between 2019- 2022 who received ribociclib or palbociclib in combination with endocrine therapy (ET) were retrospectively analyzed within the thirteen centers.

Results: The median age of 23 patients included in the study was 48 (range: 29-75). Eleven (48.8%) of the patients were denovo metastatic. Eight of the patients (34.8%) received CDKi treatment in the first line, 5 (21.7%) in the second line, and 10 (43.5%) in $\geq$ the 3rd line. In addition to bone marrow metastasis, 39.1% of the patients had bone +/- lymph nodes, and 56.5% had bone + visceral organ metastasis. Of the patients, 15 (65.2%) received ribociclib and 8 (34.8%) received palbociclib. When the CDKi response was evaluated, 2 (8.7%) of the patients had a complete response, 11 (47.8%) had a partial response, 8 (34.8%) had stable disease, and 2 (8.7%) had progressive disease. Median follow-up was 15.1 (95% CI: 5.8-24.5) months. The progression-free survival (PFS) of patients who received CDKi in first-line was 21.3 (95% CI: 0.8-41.9) months, those who received CDKi in second-line 13.1 (95% CI: 6.9-19.3) months, and those who received CDKi in $\geq$3rd line 5.3 (95% CI: 3.9-6.7) months (p=0.004). CDKi dose reduction was required in 60.9% of patients. CDKi was discontinued in 2 (8.7%) patients due to cytopenias and 56.5% due to disease progression. Eleven (47.8%) patients had grade $\geq$3 neutropenia, and 5 (21.7%) patients had grade $\geq$3 thrombocytopenia. No treatment-related death was detected.

Conclusions: It has been shown that PFS similar to those in randomized clinical studies can be achieved with CDK 4/6 inhibitors combined with ET in treating hormone receptor-positive Her2-negative bone marrow-involved metastatic breast cancer. The CDKi discontinuation associated with cytopenia was also meager showed that CDKi treatment could be safe in this patient group.

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444P Efficacy and safety of sintilimab in combination with anlotinib plus metronomic chemotherapy in advanced triple-negative breast cancer (SPACE): Preliminary results of a single-arm, multicenter phase II trial

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Background: Antiangiogenic drugs have demonstrated synergistic effect with anti-PD-1 antibody in advanced triple-negative breast cancer (TNBC). Anlotinib is an oral multi-target tyrosine kinase inhibitor (TKI) that strongly inhibits VEGFR, PDGFR, FGFR, and c-kit. Preclinical studies showed that metronomic chemotherapy inhibited angiogenesis and enhanced the efficacy of immunotherapy in TNBC via modulation of the tumor immune microenvironment. We hereby conducted a trial to investigate the efficacy and safety of sintilimab (anti-PD-1 antibody) plus anlotinib and metronomic chemotherapy as a potential novel therapeutic strategy in advanced TNBC and explore potential biomarkers.

Methods: 43 cases were planning to be included in this trial. The eligible patients who had received no more than two lines of chemotherapy for metastatic disease were enrolled and received sintilimab (200 mg iv q3w) and anlotinib (12 mg po d1-14 q3w) plus capecitabine (500 mg po, tid) or vinorelbine (40 mg po, tiw) until disease progression or intolerable toxicity. The primary endpoint is objective response rate (ORR).

Results: As of April 2023, a total of 38 patients were enrolled, and 36 patients were evaluable for efficacy. 3 patients (8.3%) achieved complete response (CR). 6 patients (16.7%) achieved partial response (PR). 21 patients (58.3%) achieved stable disease (SD). The ORR is 25.0% (95%CI 0.12-0.42) and DCR is 83.3% (95%CI 0.67-0.94). The median PFS was 6.6 months (95%CI 2.12-11.08). The most common grade 1 or 2 adverse events (AEs) include elevated thyroid stimulating hormone (58.33%, 21/36), elevated bilirubin (27.78%, 10/36) , hand-foot syndrome (22.22%, 8/36), leukopenia (19.44%,7/36) and nausea (16.67%, 6/36) . Grade 3 AEs include elevated bilirubin (2.78%, 1/36), hypertension (2.78%, 1/36) and herpes zoster (2.78%, 1/36). No grade 4 or 5 AEs occurred.

Conclusions: Our date showed that sintilimab in combination with anlotinib plus metronomic chemotherapy have shown favorable efficacy and acceptable safety profile in patients with advanced TNBC.

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Legal entity responsible for the study: H. Li.

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445P Tyrosine kinase inhibitors (TKIs) in HER2-positive metastatic breast cancer after trastuzumab emtansine (T-DM1) failure: A multicenter real-world study

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Background: Trastuzumab emtansine (T-DM1) is recommended as the standard treatment of second-line therapy of HER2-positive metastatic breast cancer (MBC) previously treated with trastuzumab. However, subsequent therapeutics after T-DM1 failure remain controversial. This study investigated the effectiveness and safety of tyrosine kinase inhibitors (TKIs)-based therapy in HER2-positive MBC with T-DM1 resistance.

Methods: From September 2018 to October 2021, 53 patients with HER2-positive MBC who received TKIs-based therapy after T-DM1 failure were enrolled in this multicenter real-world study. The primary endpoint was progression free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR) and safety.

Results: 53 patients received TKIs-based therapy in 2 or later line treatment. The median PFS of TKIs-based therapy was 11.9 months (95% CI 7.9-15.9). ORR and CBR were 19.6% and 72.5%, respectively. A median PFS of 10.5 months (95% CI 7.5-13.5) and an intracranial ORR of 33.3% were observed among patients with brain metastasis (n=12). A better PFS was observed among patients with pyrotinib (n=21) compared with lapatinib (n=30), and patients who derived favorable benefit from T-DM1 (PFS $\geq$ 6 months). Hormone receptor status (HR) and T-DM1 response were independent indicators for curative effect of TKIs-based therapy. The most commonly adverse events were thrombocytopenia (23.6%), diarrhea (15.7%), leucopenia (15.7%), and hand-foot syndrome (15.7%).

Conclusions: TKIs-based therapy showed promising efficacy and safety in patients with HER2-positive MBC after T-DM1 failure, including those with brain metastases. Patients who benefited from prior T-DM1 achieved a significantly longer PFS in subsequent TKIs-based therapy.

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446P CDK4/6 inhibitors in the first-line treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer: An updated network meta-analysis and cost-effectiveness analysis

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Background: Recently updated results of clinical trials have confirmed that palbociclib, ribociclib and abemaciclib plus letrozole/anastrozole significantly prolonged survival compared to placebo plus letrozole/anastrozole in the first-line treatment for postmenopausal women with HR+/HER2- metastatic breast cancer. However, the high cost of CDK4/6 inhibitors imposes a huge financial burden on patients and healthcare systems.

Methods: Studies estimating CDK4/6 inhibitors plus NSAI for HR+/HER2- ABC were searched. A network meta-analysis was made with the main outcomes HRs of OS and PFS. The costs and efficacy of four first-line therapies for HR+/HER2- ABC were evaluated by Markov model. The main outcomes in the cost-effectiveness analysis were incremental cost-utility ratios (ICURs), incremental monetary benefit (INMB), and incremental net-health benefit (INHB). The robustness of the model was assessed by one-way, three-way, and probabilistic sensitivity analyses.

Results: Seven studies involving 5347 patients were included in the NMA. The three first-line CDK4/6 inhibitors plus NSAI groups provided significant PFS and OS superiority to NSAI alone. Abem+NSAI represented a significant statistical advantage on PFS and indicated a trend in best OS benefit compared to the Placebo+NSAI group. Abem+NSAI, Palbo+NSAI, and Ribo+NSAI groups resulted in additional costs of $12,602, $20,391, and $81,258, with additional effects of 0.38, 0.31, and 0.30 QALYs, respectively, leading to an ICUR of $33,163/QALY, $65,777/QALY, and $270,860/QALY. Additional pairwise comparisons showed Abem+NSAI was the only cost-effective option in three CDK4/6 inhibitors plus NSAI groups. The sensitivity analyses showed that the proportion of receiving subsequent CDK4/6 inhibitors and the cost of abemaciclib significantly influenced the results of Abem+NSAI.

Conclusions: From the Chinese payers'perspective, Abem+NSAI was a cost-effective treatment compared with Placebo+NSAI at the willingness-to-pay of $38,029/QALY. The Palbo+NSAI and Ribo+NSAI groups were cost-effective unless adjusting drug prices to 50% or 10% of current prices is probably cost-effective.

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447P Efficacy and safety of trastuzumab with or without a tyrosine kinase inhibitor for HER2-positive breast cancer: A systematic review and meta-analysis

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Background: This study aimed to explore whether the combination of trastuzumab and small molecule tyrosine kinase inhibitor (TKI) can further improve the efficacy of HER2-positive breast cancer without adding additional adverse events.

Methods: PubMed, Embase, Cochrane, and Web of Science were systematically searched for relevant articles from inception until Nov 2022. Overall survival (OS) and progression-free survival (PFS) were the primary outcomes. Subgroup analyses were performed based on disease status and TKI types.

Results: A total of 10,623 patients from 16 studies were included in this meta-analysis. Trastuzumab combined with TKI dual-target blockade showed significant improvement in PFS and OS compared with trastuzumab single-targeted therapy. A random-effects model was applied and the pooled HR was 0.52 (95% CI: 0.41—0.66, $P<0.001$), suggesting that trastuzumab plus TKI was highly associated with better PFS. Further subgroup analysis of the different TKI agents (including lapatinib, pyrotinib, and tucatinib) showed that combination therapy was related to better PFS in all subgroups. In the metastatic setting, patients receiving trastuzumab combined with TKI had significantly longer OS than those receiving trastuzumab monotherapy (HR=0.71, 95% CI: 0.58—0.87, P=0.001). Besides, higher objective response rate was observed with trastuzumab plus TKI (OR=2.17, 95% CI: 1.34—3.50, P=0.002). Patients receiving combination therapy had a higher incidence of discontinuation, and grade $\geq$3 diarrhea.

Table: 447P Subgroup analysis for the OS and PFS

Subgroup	OS			PFS		
	No. of patients	Pooled HR (95% CI)	*P* -value	No. of patients	Pooled HR (95% CI)	*P* -value
All patients	5,660	0.77 (0.67—0.88)	<0.001	1,439	0.52 (0.41—0.66)	<0.001
Treatment						
tucatinib+ trastuzumab	612	0.73 (0.59-0.90)	0.003	612	0.57 (0.47-0.70)	<0.001
lapatinib+ trastuzumab	5,048	0.78 (0.64-0.96)	0.022	237	0.62 (0.44-0.88)	<0.001
pyrotinib+ trastuzumab	-	-	-	590	0.41 (0.32-0.53)	<0.001

Conclusions: In summary, combining TKI with trastuzumab confers a significant improvement in clinical outcomes with tolerable toxicity for individuals with HER2-positive breast cancer, especially in advanced settings. The different efficacies of TKIs combined with trastuzumab may be related to the mechanism of action of the different TKIs.

Legal entity responsible for the study: L. Li.

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448P Real-world experience with CDK4/6 inhibitors for HR+/HER2- metastatic breast cancer (MBC)

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Background: Metastatic hormone receptor-positive (HR+)/human epidermal growth factor receptor-2-negative (HER2-) breast cancer remains a significant cause of cancer-related mortality. First-line treatment with endocrine therapy (ET) with a cyclin-dependent kinases 4 and 6 inhibitor (CDK4/6i) has become the standard of care. Data on populations that have been treated in the real-world setting may provide an insight into changes of patient characteristics and prognosis over time.

Methods: Retrospective data of patients (pts) who received CDK4/6i with ET between 2017 and 2022 at University Hospitals of Leicester NHS Trust were analysed. Patient characteristics, efficacy and toxicity outcomes were examined. Kaplan-Meier survival curves were determined using SPSS program.

Results: In all, 235 pts who were on ET in combination with Palbociclib 51% (n=119), Ribociclib 41% (n=97) and Abemaciclib 8% (n=19) were included. The median age was 62 years (33-90). De novo MBC accounted for 33% (n=78) of pts. Most (n=180, 70%) were post-menopausal. The majority 74% (n=175) had visceral disease (lung, liver, peritoneum) vs 26% (n=60) with bone-only disease. The CDK4/6i was discontinued in 48% (n=113) due to disease progression. Over half (n=135, 57%) required at least one dose reduction (DR). The most common reason for DR was neutropenia. Sixty (26%) pts remain on treatment at the time of analysis. Thirteen pts had CDK4/6i switched within 3 months of starting treatment due to toxicities. Median duration on Palbociclib (P), Ribociclbib (R), and Abemaciclib (A) was 20 months; 95%

CI= 16.4-23.6, 18; 95% CI= 12.6-23.4 and 8; 95% CI= 0.7-15.3 months respectively. Median PFS between different CDK4/6i were P (24 months; 95% CI= 19.5-28.7), R (27 months; 95% CI= 20.5-33.3) and A (13 months; 95% CI= 6.8-18.9), p=0.22. The difference in median OS was statistically significant (p=0.004) between CDK4/6i; P (54 months; 95% CI= 42.4-58.8), R (46 months; 95% CI= 32.8-60.1) and A (26 months; 95% CI= 4.2-47.8).

Conclusions: CDK4/6i is safe and effective in this population with extensive burden of disease. Dose reduction did not appear to have an impact on efficacy. Survival outcomes observed were similar to randomised phase 3 clinical trials.

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449P Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) treatment in metastatic lobular breast cancer (mLBC): A retrospective cohort study

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Background: CDK4/6i plus ET is the standard of care for HR-positive HER2-negative mBC. The trials that led to this combination approval included mainly patients (pts) with ductal breast cancer, while limited data are reported on LBC. However, LBC are characterised by a unique pattern of metastatic recurrence and different degrees of endocrine sensitivity. This study aims to analyse CDK4/6i combinations on mLBC pts survival outcomes.

Methods: In this retrospective cohort study, we analysed outcome data of pts with mLBC who received CDK4/6i plus ET as first-line treatment between January 2017 and December 2022. Kaplan-Meier method was used to estimate median progression-free survival (mPFS). Long-rank Mantel-Cox test was used to evaluate differences in outcomes between different subgroups and between drugs.

Results: The study included 30 pts with a median age at mBC diagnosis of 63.1 years. 8/30 (27%) pts had de-novo metastasis, and 22/30 (73%) had recurrent disease. As CDK4/6i, 13/30 (43%) pts received Palbociclib (P), 14/30 (47%) Ribociclib (R) and 3/30 (10%) Abemaciclib. As ET, 13/30 (43%) pts received Fulvestrant (F) and 17/30 (57%) Letrozole (L). The overall mPFS was 28.7 months (mos). There were no statistically significant differences in mPFS between pts treated with R vs P (29.5 vs 23.7 mos, HR 0.82 [0.31-2.21], p=0.7). Similarly, no significant differences were observed in pts with de-novo metastasis vs recurrent disease (29.5 vs 23.8 mos, HR 0.59 [0.20-1.74], p=0.3), and in pts with only-bone vs visceral metastasis (23.9 vs 28.7 mos, HR 0.92 [0.33-2.54], p=0.9). In line with the different endocrine sensitivity of the two groups, a much longer mPFS, even if not statistically different, was observed in pts treated with L vs F (35.1 vs 15.1 mos, HR 0.56 [0.20-1.57], p=0.2). A statistically significant difference was observed in mPFS of HER2-0 vs HER2-low LBC pts (29.5 vs 5.9 mos, HR 0.20 [0.05-0.79], p=0.02).

Conclusions: CDK4/6i plus ET is an effective treatment in pts with mLBC. However, there is a significant difference in clinical outcomes of pts with a HER2-0 vs HER2-low mLBC. This suggests that further research is needed to identify new biomarkers for a more tailored treatment choice in pts with LBC.

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450P A prospective, single-arm, single-center, exploratory clinical study of anlotinib combined with irinotecan in second-line and above treatment of HER-2-negative advanced breast cancer

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Background: The group of HER2-negative accounts for 70-80% of breast cancer and effective treatments for heavily pretreated patients with HER2-negative metastatic breast cancer are urgently needed. Irinotecan is a semi-synthetic water-soluble camptothecin derivative which can be used as a chemotherapeutic agent for HER2-negative breast cancer after failure of anthracycline and taxanes treatments. Anlotinib is a novel multitarget tyrosine kinase inhibitor targeting VEGFR, PDGFR, FGFR, and c-Kit. This study aimed to evaluate the efficacy and safety of irinotecan combined with anlotinib in second-line and above treatment of HER-2-negative advanced breast cancer.

Methods: This open-label, single-arm, phase II study enrolled women $\geq$ 18 years with HER2-negative breast cancer who underwent $\geq$1 line chemotherapy, All patients were treated with intravenous irinotecan (60mg/m^2 on days 1 and 8) and oral anlotinib (12 mg once daily on days 1-14). The combination regimen repeated every 21 days. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), disease control rate (DCR), overall survival (OS) and safety.

Results: From November 2020 to April 2023, 20 patients were enrolled in this study. Median follow-up was 10.8 months (95% CI 0-21.8). Median PFS was 4.8 months (95% CI 3.0-6.6). Of all the patients whose efficacy could be evaluated (15/20), no patient achieved complete response (CR); 4(26.7%) and 9(60%) patients got partial response (PR) and stable disease (SD), respectively. ORR was 26.7% (95% CI 7.8-55.1) and DCR was 86.7% (95% CI 59.5-98.3). OS has not reached. The major treatment-related adverse events were hypertension (30%), fatigue (25%), neutropenia(20%), hand foot syndrome (15%) and myelosuppression (10%). There was one case of grade 3 nausea, and no grade 3/4 adverse events occurred . 20% (4/20) of patients had dose reductions.

Conclusions: The combination of irinotecan and anlotinib showed better treatment response and tolerable toxicity in the treatment of second-line and above patients with HER2-negative metastatic breast cancer. Further studies enrolling more patients are still needed.

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451P Breast Cancer Lighthouse study: 1 year follow-up results of ribociclib treatment patterns and clinical outcomes in a real-world Portuguese cohort

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Background: CDK4/6 inhibitor treatment in advanced breast cancer (ABC) has shown benefit in progression-free survival (PFS) and another clinical endpoints in landmark clinical trials. This study aims to comprehend real-world use of ribociclib, effectiveness and safety in the Portuguese population.

Methods: Retrospective-prospective study of Portuguese cohort adult women with HR+/HER2- ABC treated with ribociclib through 3 years. Ribociclib treatment patterns, PFS at 1 year follow-up after ribociclib initiation and others secondary endpoints are reported. Data collection began in January 2019 with analysis cut-off in March 2023. Confidence intervals and survival analyses were performed using R® software.

Results: Of the 270 patients included, 64 (23.7%) were pre/peri-menopausal and 206 (76.3%) were post-menopausal patients. Median follow-up duration was 11.9 months. Baseline characteristics were described previously. Regarding treatment patterns, 207 (76.7%) received ribociclib as first-line [61 (22.6%) *de novo* patients and 146 (54.1%) after prior therapy], 40 (14.8%) as a second line and 23 (8.5%) after second line. During first year's follow-up, mean ribociclib dose was of 488.4 [468.6; 508.2] and 114 (42.4%) patients reported dose adjustments. Of these 85 (74.6%) had a single dose adjustment. Patients had an average number of 12.1±5.3 clinical appointments, a mean of 3.4±2.5 imaging exams and 178 patients (65.9%) performed ECGs. Disease progression/death was experienced by 88 in 261 patients at a median of 407 days after ribociclib initiation, with a survival rate at 12 months of 0.782±0.027. At 12 months, complete response was achieved in 15 patients (5.6%), 80 patients (29.6%) had partial response and 52 (19.3%) remained stable. At cut-off, 175 (64.8%) patients were still being treated with ribociclib. Most common reasons for ribociclib discontinuation: disease progression (64, 67.4%) and AEs (21, 22.1%). Most common AEs were neutropenia (320, 42.3%), anemia (50, 6.6%), fatigue/asthenia (44, 5.8%), and leukopenia (42, 5.5%).

Conclusions: This is the first cohort of Portuguese patients to provide efficacy and safety data in a real-world setting, demonstrating similar clinical trial outcomes.

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452P A phase II trial of anlotinib and fulvestrant in patients with metastatic breast cancer previously treated with an aromatase inhibitor

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Background: Fulvestrant is used after aromatase inhibitor (AI) failure in metastatic breast cancer but resistance develops quickly. We hypothesized that using anlotinib, a novel multi-target tyrosine kinase inhibitor, may delay fulvestrant resistance in patients (pts) and thus improve its efficacy. This single-arm, phase II trial aims to evaluate the efficacy and safety of the combined regimen in pts with HR-positive and HER2-negative, previously AI treated, locally advanced or metastatic breast cancer.

Methods: The key enrolled criteria were women aged 18 years or older of any menopausal status (premenopausal or perimenopausal women received ovarian function suppression), ECOG PS 0-1, histologically confirmed HR-positive and HER2-negative breast cancer, and disease relapse within 12 months after a more than 24 months AI adjuvant setting or disease progress after a more than 6 months AI metastatic setting. Eligible pts received 500 mg fulvestrant by intramuscular injection on days 1 and 15 of cycle one and then on day one of each subsequent cycle (28 days). Pts were also given 12 mg oral anlotinib once daily for 2 weeks, followed by a week off in a 21-day cycle. The primary endpoints is progression-free survival (PFS) and the secondary endpoints include overall response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

Results: 22 pts have been enrolled from Aug 25, 2021, to Apr 7, 2023. After a median follow-up time of 5.5 months (95% CI, 3.4-7.6), 21 pts had the confirmed best overall response assessments which inferred the ORR of 19.0% (PR in 4 pts. 95% CI, 5.4-41.9) and the DCR of 81.0% (PR in 4 pts and SD in 13 pts. 95% CI, 58.1-94.6). The median PFS was 7.6 months (95% CI 4.2-11.0) and the mOS has not reached. Any adverse events (AEs) were observed in 95.2% of pts, and the frequent AEs (incidence $\geq$ 10%) included hypertension (57.1%), proteinuria (23.8%), increased TSH (23.8%), hand-foot syndrome (19.0%), wight loss (19.0%), and thrombocytopenia (14.3%).

Conclusions: Anlotinib combined with fulvestrant showed a promising efficacy with an acceptable safety profile for patients with metastatic breast cancer previously treated with AI. Further results are expected.

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453P Clinical outcomes of pyrotinib-based therapy after prior trastuzumab and pertuzumab in HER2-positive metastatic breast cancer

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Background: At present, trastuzumab and pertuzumab has become the standard treatment for HER2-positive early breast cancer at high risk of recurrence and metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. There is currently no clinical trials exploring the efficacy of pyrotinib for HER2-positive advanced breast cancer after prior trastuzumab and pertuzumab. The aim of this study is to analyze the efficacy and safety of pyrotinib-based therapy in patients after prior trastuzumab and pertuzumab.

Methods: The pathological and clinical data of 77 HER2-positive advanced breast cancer patients treated with pyrotinib after prior trastuzumab and pertuzumab were retrospectively analyzed. Observation indexes included PFS, CBR, ORRand adverse events.

Results: A total of 77 patients were enrolled in this study at the Breast Oncology Department of the Fifth Medical Center of the PLA General Hospital from February 2019 to March 2023. Median age of the patients was 52 years (28-73 years), 64.9% were HR positive, 63.6% had visceral metastases, and 27.3% had brain metastases. 50(64.9%) of the patients received pyrotinib combined with capecitabine, 8(10.4%) received pyrotinib combined with vinorelbine, 3(3.9%) received pyrotinib combined with nab-paclitaxel, and 16(20.8%) received pyrotinib combined with endocrine therapy. The median line of pyrotinib was 2 (1-7), the median number of anti-HER 2 targeted therapy was 2 (2-6). Median follow-up was 17.8 months (1.6-51.4months) by the data cutoff date (May 2023). The median PFS was 13.6 months (95%CI: 8.3-18.9). The ORR was 50.0% in the 56 patients with evaluable lesions,the CBR was 54.5%, and the mPFS was 10.8 months (95%CI: 7.7-13.9). 46 patients who progressed on prior trastuzumab and pertuzumab had evaluable lesions, the ORR was 43.5%, CBR was 69.6%, and the mPFS was 9.2 months (95%CI: 6.4-12.0). The most common adverse events was diarrhea in the study.

Conclusions: This study first retrospectively analyze the value of pyrotinib in the era of dual anti-HER2 therapy, preliminarily showing good efficacy and safety of pyrotinib in patients after prior trastuzumab and pertuzumab.

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454P Real-world genomic profiling of patients with advanced or metastatic triple-negative breast cancer in the UK and EU4: A systematic literature review

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Background: Advanced or metastatic triple-negative breast cancer (A/M TNBC) is a detrimental disease with limited treatment options. Molecular subtyping of A/M TNBC has the potential to enhance diagnostic accuracy and further enable targeted therapies, given its high degree of heterogeneity. This systematic literature review (SLR) aimed to identify real-world evidence for genetic alterations among A/M TNBC patients.

Methods: Key biomedical databases (EMBASE®, MEDLINE®, MEDLINE-in-process) were searched to identify real-world studies assessing genomic alterations among A/M TNBC patients in the UK and EU4. The current review followed a standard HTA compliant two review process methodology for screening and data extraction.

Results: A total of three of 203 studies fulfilled the inclusion criteria. All three studies were conference proceedings, with one study each conducted in Spain, Italy, and the UK. A total of 399 A/M TNBC patients were analyzed for genetic profiling across these studies, using either digital droplet PCR (ddPCR), error-corrected 73-gene targeted panel (Guardant360), or AVENIO Expanded ctDNA Analysis Kit. In the Gruppo Italiano Mammella 14 BIOMETA study, BRCAmu+ was detected among 8% of 195 mTNBC patients. Further, in the RegistEM study, 50% of 32 Spanish mTNBC patients had TP53mu+, followed by MAP2K1mu+ and APCmu+ (25% each). In the UK plasmaMATCH study, PIK3CA mutation was more prevalent (9.3% and 14.7% by ddPCR and targeted ctDNA panel, respectively), while ESR1mu+ was the least prevalent (0% and 0.7% by ddPCR and targeted ctDNA panel, respectively). The targeted ctDNA sequencing identified definite genomic profiles compared to ddPCR.

Conclusions: The current SLR highlights the scarcity of real-world evidence on genetic alterations in A/M TNBC. Molecular subtyping exhibits a significant potential in identifying specific genetic alterations, emphasizing the need for further research and larger-scale studies.

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455P Post progression treatments after endocrine therapy (ET) plus palbociclib in patients with HR+/HER2- metastatic breast cancer (MBC): A prospective, real-world study

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Background: The association of ET and CDK 4/6 inhibitors (CDK 4/6i) is the gold standard of treatment in women with HR+/HER2- MBC. The optimal therapeutic strategy after CDK 4/6i progression is still a matter of debate. The present study aimed to evaluate the benefit of the different treatments adopted in a real-world context.

Methods: In this prospective study we included women with HR+/HER2- MBC progressing to ET plus palbociclib (P). Either ET or chemotherapy (CT) were prescribed taking into account:1) site and burden of disease (visceral/plurimetastatic *vs* bone only/oligometastatic); 2) median PFS1 ($<$4 months *vs* $\geq$4 months); 3) tolerability profile; 4) patient's preferences. Primary objective was median progression-free survival 2 (PFS2). Secondary aims: analysis of the determinants of physician's choice, clinical benefit rate (CBR), impact of neutrophil-to lymphocyte ratio (NLR), monocyte-to lymphocyte ratio (MLR), platelet-to lymphocyte ratio (PLR) and body mass index (BMI) on PFS2.

Results: From May 2017 to October 2021, 78 pre- and postmenopausal patients were enrolled and 56 were evaluable for the final analysis: 18 had received ET plus P as 1st line, 38 in $\geq$2nd line; 22 patients were excluded because they were still on therapy at the time of the last follow-up. At progression 15 patients (26.7%) received ET (everolimus+exemestane 8, fulvestrant 7) and 41 (73.2%) were treated with CT (eribulin, capecitabine, nab-paclitaxel, vinorelbine). In the whole population mPFS1 was 17.5 months; mPFS2 was 5 months in the overall cohort (95% CI = 4-48 months) with a significant difference between ET and CT (10 months *vs* 5 months, p=0.035); CBR was 50% and 55.2%, in ET and CT, respectively. At multivariate analysis CT prescription was associated to a higher visceral burden and a shorter mPFS1. Elevated NLR and PLR were correlated with worse PFS2 in both treatment groups, while no impact of MLR and BMI was observed.

Conclusions: In this real life experience, treatments beyond ET plus P failure provided limited but comparable clinical benefit. The physician's choice was clearly driven by visceral burden of disease; the inflammatory status seems to have a detrimental effect on PFS2.

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456P Quality of life (QOL) analysis from the phase II RIGHT choice study of first-line ribociclib (RIB) + endocrine therapy (ET) vs combination chemotherapy (combo CT) in aggressive HR+/HER2− advanced breast cancer (ABC)

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Background: RIGHT Choice showed a statistically significant median progression-free survival benefit of $\approx$1 yr with first-line RIB + ET vs combo CT (HR, 0.54; P=0.0007) in patients (pts) with aggressive HR+/HER2− ABC. As QOL data provide information on real-life treatment (tx) benefit as well as impact tx choice and duration, a QOL analysis was performed.

Methods: Pre/perimenopausal pts with no prior systemic therapy for aggressive HR+/HER2− ABC were randomized 1:1 to RIB + ET or combo CT. The FACT-B scores were determined by a questionnaire administered at protocol-defined time points. The median time to deterioration (mTTD) in overall health status, nausea or pain was defined as a composite endpoint of time from randomization to either first occurrence of $\geq$10% deterioration in FACT-B scores with no later improvement or date of discontinuation due to progressive disease, death, or adverse events. Only pts with baseline and at least one post-baseline pt reported outcome assessment were included. Pts without events were censored at the last evaluation prior to the earliest of cutoff date, end of tx, start of new tx, or when lost to follow-up, or at consent withdrawal. Descriptive summary of change from baseline in FACT-B total score was also summarized.

Results: The composite endpoint of mTTD in overall health status was delayed with RIB + ET (N=111) vs combo CT (N=96;16.8 vs 10.6 mo; HR, 0.63; Table). The mTTD in subdomains of nausea (18.4 vs 10.4 mo; HR, 0.56) and pain (13.0 vs 10.4 mo; HR, 0.70) was also delayed in pts on RIB + ET vs combo CT. A numerical trend in change from baseline in FACT-B total scores during tx favoring RIB + ET over combo CT was observed.

Table: 456P

End Points	Outcomes	RIB + ET (N=111)	Combo CT (N=96)
TTD in overall health status	**Deterioration events, n**	67	66
	FACT-B score decrease, n_1/n (%)	24/67 (35.8)	22/66 (33.3)
	Tx discontinuation, n_2/n (%)	43/67 (64.2)	44/66 (66.7)
	mTTD, mo	16.8	10.6
	HR; 95% CI	0.63; 0.44-0.90	
TTD in nausea	**Deterioration events, n**	67	69
	FACT-B score decrease, n_1/n (%)	29/67 (43.2)	30/69 (43.5)
	Tx discontinuation, n_2/n (%)	38/67 (56.7)	39/69 (56.5)
	mTTD, mo	18.4	10.4
	HR; 95% CI	0.56; 0.39-0.79	
TTD in pain	**Deterioration events, n**	72	65
	FACT-B score decrease, n_1/n (%)	34/72 (47.2)	22/65 (33.8)
	Tx discontinuation, n_2/n (%)	38/72 (52.8)	43/65 (66.2)
	mTTD, mo	13.0	10.4
	HR; 95% CI	0.70; 0.49-0.99	

Conclusions: This analysis suggests that first-line RIB + ET is associated with better QOL than combo CT for pts with aggressive HR+/HER2− ABC, providing supportive evidence for RIB + ET use in this pt population.

Clinical trial identification: NCT03839823.

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457P Disparities in receipt of CDK4/6 inhibitors with endocrine therapy as therapy for hormone receptor-positive, HER2-negative metastatic breast cancer in the real-world setting

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Background: This retrospective study, using real-world evidence (RWE), compared outcomes for patients receiving treatment for hormone receptor-positive (ER+), HER2-negative, metastatic breast cancer (MBC) with CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) versus ET alone and explored disparities in use of CDK4/6i.

Methods: We used the nationwide electronic health record-derived Flatiron Health de-identified database to examine real-world impacts of CDK4/6i and ET. A total of 3,917 patients received CDK 4/6i+ET (n=2170) or ET alone (n=1747) in the first-line setting between February 2015, and November 2021. Characteristics of patients receiving CDK4/6i+ET versus ET alone were compared using statistical tests. Baseline characteristics were balanced using inverse probability weighting (IPW). Kaplan-Meier method and Cox proportional hazards were used to test the impact of CDK4/6 treatment on rwPFS and rwOS.

Results: Compared to patients receiving ET alone, those received CDK4/6i+ET were younger, more likely to have presented with de novo MBC (36% vs. 29%, p<0.001), had better performance status (50% vs. 40% patients with ECOG value 0, p=0.001), and more likely to have lower number of comorbidities (30% vs. 27% with at least 1 comorbidity, p=0.04). After IPW adjustment, CDK4/6i+ET treatment was associated with significantly longer median PFS compared to ET alone (27 vs 17 months; hazard ratio [HR]=0.61, p<0.001). Median OS was 52 months in the CDK4/6i+ET group and was 42 months with ET alone (HR=0.74, p<0.001).

Conclusions: RWE confirms the added PFS and OS benefit of adding CDK4/6i to endocrine therapy in patients with ER+, HER2-negative MBC. We found disparities in CDK4/6i use by age, stage at diagnosis, baseline Ecog value, and number of comorbidities. Future work is needed to improve access to this important class of drugs.

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458P Metastatic breast cancer: How and how often do we communicate? Results from an Italian national survey

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Background: Communication is a complex process; an effective communication requires a two-way relationship between patients (pts) and healthcare providers (hp). The areas of communication concern diagnosis, prognosis and treatment. In this context, a tailored communication approach is suggested to keep pts involved in the clinical decision-making process.

Methods: Between 21 June and 4 October 2022, a 38-question web survey, promoted by the IncontraDonna Foundation and carried out in collaboration with both the Italian Society of Psycho-Oncology (SIPO) and the Italian Association of Medical Oncology (AIOM), was sent to oncologists members of AIOM. The aim of this study was both to investigate how and how much oncologists communicate with metastatic breast cancer pts (mBCp) and to probe clinicians' opinions and needs.

Results: 140 oncologists from 19 Italian regions participated in the survey. Responders reported discussing prognosis with their mBCp both in terms of residual life (96%), goals of care (98%) and likelihood of treatment response (94%), in the last two cases especially at the time of the first oncological visit (67% and 60%, respectively). As many as 93% of responders stated that they investigate the degree of understanding of the information provided. In communicating the prognosis, 49% of responders considered the presence of a caregiver "very useful" and 61% considered her/his absence "very disadvantageous". About the organization of one's department, the time dedicated to doctor-patient communication was considered "quite sufficient" in 16%", "little but sufficient" in 44%, "scarce" in 31% and "insufficient " in 10% of cases. In 89% of cases the presence of a psycho-oncology service was reported, to which mBCp would be referred regularly in only 14% of cases. Specific training courses for hp (69%) and periodic meetings with expert psycho-oncologists (59%) are the improvement actions most requested by clinicians.

Conclusions: The results of this survey highlighted heterogeneity in the management of communication in mBCp across the Italian country. Although the figure of the psycho-oncologist is considered important, its integration into the therapeutic process still appears complex.

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459P Progression-free survival (PFS) assessment by local investigators versus blinded independent central review (BICR) in randomized clinical trials (RCTs) in metastatic breast cancer (MBC): Is it really needed?

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Background: In RCTs, BICR is used to minimize the heterogeneity and risk of bias associated with radiological response evaluation by local investigators. However, BICR adds costs and complexity in trial management, which questions its practical utility. We aimed to assess the discrepancy index between PFS assessment by local investigators and by BICR in RCTs of MBC.

Methods: A systematic search of PubMed, Embase, Cochrane databases and conference proceedings (ASCO, SABCS and ESMO meetings) was performed up to January 4, 2023. All RCTs published from 2000 to 2022, including MBC patients treated in first or second-line, and reporting PFS assessed by local investigators and BICR were included (PROSPERO - CRD42021229865). The agreement between hazard ratios (HRs) of PFS assessed by local investigators and BICR was measured using intraclass correlation coefficient (ICC). A discrepancy index, defined as the ratio of BICR-assessed HR by the corresponding investigator-assessed HR, was calculated for each trial to quantify the level of agreement in the estimated effect.

Results: A total of 24 studies with 13,338 patients were included in the analysis. Among them, 19 (79%) were in first line, 18 (75%) were phase III trials and 23 (96%) had PFS as primary endpoint. The overall combined discrepancy index was 0.97 (95% CI 0.85-1.10; ICC = 0.831, p-value <0.001) suggesting no statistically significant difference in PFS assessment by local investigators vs BICR. This result was consistent across all subgroups analyzed (the table).

Table: 459P Discrepancy index and 95% confidence intervals in the overall population and in subgroups

	Discrepancy index (95% CI)
Overall	0.97 (0.85-1.10)
Line of treatment	
First line	0.98 (0.84-1.15)
Second line	0.94 (0.75-1.17)
Study phase	
Phase II	1.05 (0.66-1.66)
Phase III	0.96 (0.84-1.10)
Study design	
Double blind	0.97 (0.83-1.13)
Open label	0.97 (0.78-1.21)
BC subtype	
HER2+	0.96 (0.70-1.28)
Luminal	0.94 (0.67-1.30)
TNBC	0.96 (0.67-1.39)
Study start year	
Before 2010	0.97 (0.83-1.13)
After 2011	0.97 (0.77-1.21)
RECIST	
1.0	0.97 (0.82-1.14)
1.1	0.96 (0.78-1.18)
PFS primary endpoint	
Yes	0.97 (0.85-1.10)
No	0.87 (0.25-3.07)

Conclusions: The good concordance between local investigator and BICR assessments supports the reliability of local investigator-assessed PFS as primary endpoint for RCTs in MBC. The resources used for BICR might be reallocated to other areas, such as translational research, decreasing the burden of clinical trial conduction.

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460P Impact of fulvestrant utilization on prognostic outcome among patients with HR+ve/HER2-ve metastatic breast cancer: Results from a real-world dataset

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Background: Overall survival (OS) of pts with HR+ve/HER2-ve MBC has improved with the use of CDK4/6i and sequential use of endocrine therapy. The selective estrogen receptor modulator (SERM) Fulvestrant has been shown to work well post progression on aromatase inhibitors (AI) in an endocrine resistant cohort. Clinical trials have shown no difference in progression free survival with the use of an AI or fulvestrant in combination with a CDK4/6i in the first-line setting. The objective of this retrospective analysis was to look at trends in use of and associated prognostic outcome associated with fulvestrant among pts with HR+ve /HER2-ve MBC in the real-world setting.

Methods: We utilized a federated network of de-identified health data representing approximately 107 million pt lives available through the TriNetX Research Network. We identified 47,999 pts with HR+ve /HER2-ve MBC treated with endocrine therapy. OS was computed using the Kaplan Meier product limit method.

Results: Mean age was 60 yrs. 17.5% (n=8390) received fulvestrant at any time of whom 24% received it in the first-line setting. Use of fulvestrant increased from 1.04% in the period 2005-2009 to 9.03% in the period of 2015-2019. 20.6% (n=9,908) received CDK4/6i at any time of whom 39.7% received it in the first-line setting. 2-year OS among pts who did and did not use fulvestrant was 80.3% and 77.5% respectively (HR 0.8, p<0.01). 2-yr OS among pts who did and did not use fulvestrant as first-line therapy was 69.9% and72.6% respectively(HR 1.05, p = 0.41). 2-year OS among pts who did and did not use CDK4/6i was 84.6% and 78.3% (HR 0.64, p < 0.01). 2-yr OS among pts who did and did not receive CDK4/6i as first-line therapy was 78.3% and 73.8% respectively (HR 0.74, p < 0.01). 2-yr OS among pts receiving CDK4/6i with or with out fulvestrant in the first-line setting was 74.7% and 79.1% respectively (HR 1.27, p = 0.06).

Conclusions: Fulvestrant use has increased over time. Real world data indicate OS benefit to use of fulvestrant at some time point in the therapy of pts with HR +ve/ HER2-ve MBC. Use of fulvestrant with CDK4/6i in the first-line setting does not improve prognostic outcome compared to use of CDK4/6i + AI in the first-line setting in keeping with the results of clinical trials.

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461P Impact of comorbidities on real-world patient-reported outcomes of patients (pts) with hormone receptor-positive human epidermal growth factor 2-negative (HR+/HER2-) advanced breast cancer (ABC) enrolled in the POLARIS trial

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Background: POLARIS is a prospective, observational real-world study of pts with HR+/HER2− ABC receiving palbociclib in routine clinical practice. As part of this study, we evaluated the impact of comorbidities on pt quality of life (QoL) using the EORTC-QLQ-C30 questionnaire.

Methods: EORTC data were collected at baseline, monthly for the first 3 months, and every 3 months thereafter until palbociclib discontinuation; here we report absolute global QoL and functional/symptom subscales scores according to pt baseline Charlson comorbidity index (CCI) score (grouped 0, 1−2, and 3+) at study baseline, month 6, 12 and 18. EORTC differences of ≥10 between CCI groups at each timepoint and within a CCI group over time were considered clinically meaningful. Differences in global QoL/subscale scores between CCI groups at each timepoint were compared using a two-sample t-test.

Results: Between January 2017 and December 2018, 1285 pts were enrolled, and 1250 received ≥1 dose of palbociclib. At baseline, pts had a median of 2 (range 0−9) comorbidities. 30.2%, 54.6% and 15.3% of pts had a CCI score 0, 1−2, and 3+, respectively. The most frequent comorbidities were vascular (54.3%), psychiatric (26.6%), blood/lymphatic system (18.4%), and metabolic/nutritional (18.2%) disorders. Generally, absolute mean global QoL and functional/symptom subscale scores (range: 0 to 100) were preserved from baseline to Month 18 within each CCI group (Table). Overall, differences in mean global QoL scores (and functional/symptom subscale scores) between the CCI 0 and CCI 1−2 were similar at each timepoint; while notably lower scores (less favorable) were observed for the smaller CCI 3+ group.

Table: 461P Global QoL in pts with HR+/HER2− ABC by CCI

*Absolute mean**	Time point	CCI score 0		1−2		3+	
	Baseline	69.89 (n=336)		62.95 (n=651)		56.90 (n=180)	
	Month 6	73.29 (n=219)		69.69 (n=400)		60.40 (n=113)	
	Month 12	74.23 (n=151)		70.42 (n=262)		59.98 (n=71)	
	Month 18	75.08 (n=103)		69.28 (n=198)		62.02 (n=52)	
Diff in means		CCI 0 vs 1-2		CCI 0 vs 3+		CCI 1-2 vs 3+	
		Diff	p-value	Diff	p-value	Diff	p-value
	Baseline	6.94	<0.0001	12.99	<0.0001	6.06	0.0028
	Month 6	3.60	0.0401	12.89	<0.0001	9.29	<0.0001
	Month 12	3.81	0.0546	14.25	<0.0001	10.44	0.0002
	Month 18	5.80	0.0225	13.06	0.0004	7.26	0.0314

*Higher scores more favorable. Subscales were consistent with global QoL.
Data cut off January 2023.
CCI, Charlson comorbidity index; Diff, difference; QoL, quality of life.

Conclusions: QoL of pts with HR+/HER2- ABC treated with palbociclib differed by comorbidity level, with a general preservation in their relationship over 18 months.

Clinical trial identification: NCT03280303.

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462P Health outcomes of treatment sequences with eribulin or other single agents' chemotherapy for treating relapsed metastatic HER2-negative breast cancer

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Background: Treatment of HER2- metastatic breast cancer (MBC) is driven by biomarker status (HR+ vs. triple negative [TNBC]). Single agent chemotherapy (ChT) is recommended for patients relapsing on targeted therapies including endocrine therapy or immunotherapies, with ChTs optimal sequence not yet established. The study objective was to compare the health outcomes (life years [LYs], quality adjusted LYs [QALYs]) in sequences starting ChT with eribulin (ERI), capecitabine (CAP) or treatment of physician choice (TPC), in second-line (2L) to fourth-line (4L) settings.

Methods: A stochastic microsimulation was developed tracking a MBC cohort through 2L-4L, with patients starting the next line of therapy due to progression or serious adverse events (SAEs) discontinuation. After each line, patients could receive another active therapy or best supportive care. Treatment sequences across three treatment pathways, capturing ChT initiation in 2L, 3L or 4L (the table), were based on clinical guidelines, real-world data and clinical interviews. Clinical inputs were stratified by biomarker and treatment line, with QALYs driven by progression status, response rates and SAEs. The analysis time horizon was 20 years, with outcomes discounted at 3.5%.

Results: In the HR+ subgroup, sequences with ERI used earlier than CAP/TPC led to higher LYs (1.62 - 2.24 vs. 1.57 - 2.22) and QALYs (0.75 -1.28 vs. 0.69 − 1.27), across the three pathways, driven by improved ERI efficacy and safety profile vs. CAP/TPC. Similarly, in the TNBC subgroup, earlier use of ERI vs. CAP/TPC led to higher LYs (1.19 - 1.64 vs. 1.16 - 1.63) and QALYs (0.55 - 0.86 vs. 0.49 - 0.85) when used in 2L or 4L, while 3L ERI vs. 3L TPC led to higher QALYs (0.70 vs. 0.67 - 0.68), but comparable LYs (1.40). The results were consistent across the sensitivity analyses conducted.

Table: 462P

Pathway	2L HR+	3L	4L	2L TNBC	3L	4L
ChT post taxane/anthracycline in 1L or post adjuvant settings	CAP	TPC	ERI	CAP	TPC	ERI
	CAP	ERI	TPC	CAP	ERI	TPC
	ERI	CAP	TPC	ERI	CAP	TPC
	ERI	TPC	CAP	ERI	TPC	CAP
ChT post 2L taxane	PAC	CAP	TPC	PAC	CAP	TPC
	PAC	CAP	ERI	PAC	CAP	ERI
	PAC	TPC	CAP	PAC	TPC	CAP
	PAC	TPC	ERI	PAC	TPC	ERI
	PAC	ERI	CAP	PAC	ERI	CAP
	PAC	ERI	TPC	PAC	ERI	TPC
HR+: ChT post 2L CDK4/6 inhibitors and 3L taxane **TNBC:** ChT post 2L taxane and 3L SAC	FUL + PAL	PAC	CAP	PAC	SAC	ERI
	FUL + PAL	PAC	ERI	PAC	SAC	CAP
	FUL + PAL	PAC	TPC	PAC	SAC	TPC

CDK = cyclin-dependent kinase; FUL = fulvestrant; PAC = paclitaxel; PAL = palbociclib; SAC = sacituzumab. Note: TPC includes vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines and hormonal therapy.

Conclusions: Starting single agent ChT with ERI vs. CAP or TPC is associated with improved health outcomes for 2L-4L HER2- MBC management.

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463P Impact of two waves of Sars-Cov-2 outbreak on the clinical presentation and outcomes of newly referred breast cancer cases at AP-HP: A retrospective multicenter cohort study

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Background: The Sars Cov-2 pandemic and the national lockdowns disrupted healthcare systems in 2020. We assessed the impact on care pathways and clinical outcomes for new breast cancers (BCs) in Paris area.

Methods: We performed a retrospective multicenter cohort study on the data warehouse of Greater Paris University Hospitals (APHP). We identified pts newly referred with BC between Jan 2019, and Dec 2020. We assessed the delays of care management, the initial tumor stage from pathology and baseline PET/CT and CT-scan reports, and the trt categories: breast surgery, exclusive systemic therapy, exclusive radiation therapy, or exclusive best supportive care (BSC). We calculated pts' 1-year overall survival (OS) and compared indicators for 2019 and 2020.

Results: In 2019 and 2020, 2,303 and 2,258 patients were newly referred with a BC diag among whom 2,055 and 1,988 female patients underwent a BC treatment, respectively. During the 1st and the 2nd lockdowns, the number of BC diag varied by -18% and by +23% compared to the same periods of 2019. Between 2019 and 2020, the rate of *de novo* metastatic disease (respectively 15% and 15%, p=0.95) did not differ, neither did the pTNM and the ypTNM distributions (p=0.37 and p=0.31). The time from 1st multidisciplinary meeting to trt did not differ (p=0.23). Pts' access to reconstructive surgery (15% and 17%, p=0.08) and distribution across trt categories did not vary: tumor resection (73% and 72%), exclusive systemic trt (13% and 14%), exclusive radiation trt (9% and 9%), and exclusive BSC (5% and 5%) (p=0.8), respectively. Age-based subgroup analyses yielded to similar results (p=0,95). The rate of neoadjuvant trt for resected pts was lower in 2019 (16%) compared to 2020 (20%) (p=0.02), especially in patients aged < 50 years (15% vs 21%, p=0,01), respectively. The 1-year OS rates in 2019 vs. 2020 were 99.3% vs. 98.9% (HR=0.96; 95% CI, 0.77-1.2), 72.6% vs. 76.6% (HR=1.28; 95% CI, 0.95-1.72), 96.6% vs. 97.8% (HR=1.09; 95% CI, 0.61-1.94), and 15.5% vs. 15.1% (HR=0.99; 95% CI, 0.72-1.37), in the trt groups, respectively.

Conclusions: Despite an initial decrease in new BCs, we did not observe any tumor stage shift, and OS did not vary significantly during Sars-Cov-2.

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464P Developing a prognostic risk stratification model and treatment options for HER2-positive breast cancer brain metastasis

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Background: Brain metastasis occurs in about 50% of advanced HER2-positive BC patients. Moreover, there are still a lot of unresolved clinical issues, such as how to classify patients and adapt targeted therapy to better prolong survival.

Methods: The study recruited HER2-positive BCBM patients who attended the Fifth Medical Center of PLA General Hospital from 2003 to 2022. 32 HER2-positive BCBM patients treated between 2008 and 2022 at the First Hospital of Peking University and 43 HER2-positive BCBM patients from 2012 to 2022 at Xi'an Jiaotong University First Affiliated Hospital were included as an independent test set. All statistical methods and survival analyses were performed in SPSS 22.0 and R version 4.2.1.

Results: This study included 300 patients with HER2-positive BCBM. According to multi-factor analysis, the age, the number of brain metastases, radiotherapy after BCBM, and anti-HER2 therapy after BCBM were all independent factors influencing survival after diagnosis of BCBM. Different independent prognostic factors comprised the patient hierarchical evaluation model. Patients' warning scores range from 0 to 7. We divided the patients into three groups with obvious differences in prognosis: Low-risk (score≥1), median-risk group (score≥3), and high-risk group (score≥6). The patient prognosis was worse when the warning score was high. The results of the survival analysis showed significant differences between the three groups of patients ($P<0.0001$). The mean AUC values for 1-year, 2-year prognosis prediction was 0.69, 0.71, respectively. We acquired clinical data from 75 patients from other centers to further assess our model's generalization capabilities. Patients are categorized using the prognostic grading evaluation model, and prognostic analysis is performed ($P<0.0001$). The AUC values for 1-year, 2-year prognostic forecasts were 0.94. Patients in the median-risk group who received drug therapy combined with radiotherapy had significantly prolonged BMOS compared with the patients who received only drug therapy or radiotherapy ($P=0.01$).

Conclusions: A survival and prognostic stratification model was constructed based on the clinicopathological characteristics of a large cohort of HER2-positive BCBM patients.

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465P Reporting of older subgroups enrolled to registration breast cancer trials, 2012-2021

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Background: Although older women comprise a large and rapidly growing proportion of patients diagnosed with breast cancer, the trial-level evidence base for treating this population is limited. This study assessed the completeness of reporting of older subgroups enrolled to registration trials in breast cancer between 2012-2021.

Methods: Trials which supported novel FDA approvals of systemic therapies in breast cancer between 01/2012 and 12/2021 were included. Individual trial-level PUBMED searches according trial/drug name, and trial registration number, were conducted on 31/08/22. Following title/abstract review, relevant publications and supplementary material were retrieved. Clinicaltrials.gov registry data was also retrieved. Non-efficacy (n = 1), site-agnostic (n = 1) biosimilar (n = 4), and trials conducted exclusively among premenopausal women (n = 1), were excluded. Immature endpoints (n = 5), for which no interim data were available in the full cohort, and studies which did not collect HRQOL data (n = 3), were excluded from relevant analyses. The availability and completeness of data for baseline characteristics, protocol-defined (co-)primary and secondary efficacy endpoints, toxicity, and HRQOL among older subgroups, was assessed systematically by two reviewers according to methods adapted from Chan & Altman (JAMA, 2004).

Results: 27 trials were included. 785 unique publications were identified, of which 569 were excluded. 216 publications (median: 6 per trial, IQR: 4), and registry data, were assessed in full. 20.3% of enrolled patients were aged ≥65. 70.0% of patients were ECOG 0; 29.8% ECOG 1, and 0.2% ECOG 2. The completeness of data across efficacy endpoints, baseline characteristics, toxicity and HRQOL domains are reported in the table.

Table: 465P Completeness of reporting of geriatric subgroups enrolled to registration trials in breast cancer 2012-2022

		n	Complete	Partial	Qualitative	Unreported
Efficacy endpoints						
	All efficacy endpoints	133	37 (27.8%)	3 (2.3%)	8 (6.0%)	95 (71.4%)
	Primary endpoints	33	24 (72.7%)	3 (9.1%)	1 (3.0%)	5 (15.2%)
	Secondary endpoints	110	13 (11.8%)	0 (0.0%)	7 (6.4%)	90 (81.8%)
	Overall survival	22	11 (50.0%)	1 (4.5%)	2 (9.1%)	8 (36.4%)
Baseline Characteristics		27	6 (22.2%)	2 (7.4%)	0 (0.0%)	19 (70.4%)
Toxicity		27	12 (44.4%)	0 (0.0%)	0 (0.0%)	15 (55.6%)
HRQOL		24	1 (4.2%)	0 (0.0%)	2 (8.3%)	21 (87.5%)

Rows 1-4: n Endpoints (%) Rows 5-7: n Trials (%).

Conclusions: This study identified significant gaps in the reporting of older subgroups enrolled to registration breast cancer trials. Improved reporting practices are required to support evidence-based decision making in this population.

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466P Integrated analysis of potential prognosis and differential expression between primary and metastatic foci for COL12A1 in breast cancer

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Background: Extracellular matrix (ECM) plays a key role in tumorigenesis and progression. Collagen XII, expressed by the COL12A1 gene, is an important component of the ECM. COL12A1 is associated with tumorigenesis and poor prognosis in several cancers, but its role in breast cancer (BC) is unclear, especially the different expression between primary and metastasic foci of BC has not been reported.

Methods: We analyzed the expression of COL12A1 in tumor tissue and normal tissue, plotted a Kaplan-Meier curve by GEPIA, and analyzed mutation by COSMIC and cBioPortal in BC. PPI, GGI and pathway and process enrichment analysis were performed by STRING and Metascape. GeneMANIA was used to map gene interaction networks. BC cases with paired primary and metastatic foci were found out from TCGA database for analyzing different expression of COL12A1 in primary and metastatic foci. Immunohistochemical (IHC) staining was performed in paraffin tissue samples of paired primary lesion and lung metastases from triple-negative breast cancer (TNBC) patients.

Results: The results showed that COL12A1 in BC tissues was upregulated and was associated with poor prognosis of BC and the Luminal A+Luminal B subgroup. 3.04% of BC patients had COL12A1 gene alteration. Missense substitution (37.59%) was the most frequent mutation type. Among the 10 related genes, COL3A1, COL5A2, MMP12, P4HA1, P4HA2, P4HA3 and SERPINH1 were significantly upregulated in tumor tissue. The 20 most relevant genes in the GGI network are COL11A1, ID1, COL8A1, MMP9, COL5A1, MMP2, ISLR, LUM, COL7A1, COL3A1, COL1A2, MMP3, COL10A1, COL6A1, COL11A2, COL8A2, MMP8, MMP12. SERPINH1 and MMP13, which are enriched in several pathways including collagen degradation, collagen formation, collagen metabolic process, endodermal cell differentiation, collagen fibril organization and so on. Furthermore, analysis of paired cases from the TCGA-BRCA database revealed that COL12A1 was expressed with higher level in primary foci than metastatic foci. IHC staining revealed that the expression of COL12A1 was upregulated in primary foci of TNBC.

Conclusions: In conclusion, COL12A1 may be a poor prognostic predictor and a specific therapeutic target for primary foci in BC, especially in TNBC.

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467P Initial results from the Canarian registry of luminal breast cancer patients treated with first-line CDK 4/6 inhibitors

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Background: CDK 4/6 inhibitors have revolutionized the treatment of HER2-negative luminal breast cancer, with median progression-free survival (PFS) of over 25 months and overall survival (OS) of over 60 months. After more than five years since their commercialization in our country, the Canarian Breast Cancer Group decided to analyze the results obtained in our region.

Methods: We collected data on the characteristics of patients treated with cyclin inhibitors in the first line, including their diagnosis, treatment, and evolution, in the 7 oncology centers across the archipelago.

Results: From January 2017 to December 2022, 583 patients were registered, median age of 60 y. Of these, 65% had relapsed, with 30% relapsing more than one year after completing adjuvant hormonal therapy (HT) and the remaining 35% relapsing during the HT. The median PFS was 15 months, in de novo patients and in those who had completed HT more than one year before was 20 months. The OS was 52 months, in de novo patients having a higher OS of 58 months. Patients treated with abemaciclib

tended to have higher PFS and OS rates in cases of hormone resistance and visceral disease. No differences were found in patients diagnosed under 50 years of age.

Conclusions: Our patients experienced lower PFS and OS rates than those reported in clinical trials, which may be due to a higher number of patients exposed to HT and up to 46% of patients presenting with visceral disease at diagnosis. Further follow-up is required to confirm differences between cyclin inhibitors.

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468P Impact of low HER2 status on CDK4/6 inhibitor and endocrine therapy in metastatic HR+ breast cancer: A retrospective multicenter study

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Background: CDK4/6 inhibitors combined with endocrine therapy have revolutionized the treatment of metastatic HR+ breast cancer. However, the influence of low HER2 expression on treatment response and progression-free survival (PFS) remains unclear.

Methods: We conducted a multicenter retrospective study including 204 HR+ breast cancer patients who received a combination of CDK4/6 inhibitor and endocrine therapy. Among them, 138 (68%) patients exhibited HER2-zero disease, while 66 (32%) patients had HER2-low disease. We analyzed treatment-related characteristics and clinical outcomes, with a median follow-up of 22 months.

Results: In the HER2-low group, the objective response rate (ORR) was 72.7%, compared to 66.6% in the HER2-zero group (p=0.54). Median PFS did not significantly differ between the HER2-low and HER2-zero groups (19 months vs. 18 months, p=0.89). Notably, a trend towards longer PFS was observed in the HER2-low group for first-line treatment (24 months progression-free survival rate: 63% vs. 49%). For recurrent disease, the median PFS was 25 months in the HER2-low group and 12 months in the HER2-zero group (p=0.08), while in de novo metastatic disease, the median PFS was 18 months in the HER2-low group and 27 months in the HER2-zero group (p=0.16). Independent variables affecting PFS were identified as the order of CDK4/6 inhibitor use and the presence of visceral metastasis.

Conclusions: Low HER2 expression did not significantly impact treatment response or PFS in HR+ breast cancer patients treated with a CDK4/6 inhibitor and endocrine therapy. Because of the conflicting results in the literature, further prospective studies are needed to evaluate the clinical significance of HER2 expression in HR+ breast cancer.

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469P Metastasic breast cancer: Differences in motor activity and sleep patterns by kind of treatment

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Background: Improving the quality of life, in addition to survival, is one of the main objectives of treating metastatic breast cancer. Among the primary treatments for most of these patients are hormonal therapies + CDK inhibitors or chemotherapy, which have varying toxicity profiles and impacts on quality of life. Hormonal therapies have been associated with improvements in quality of life based on questionnaires, but we have limited objective parameters to assess quality of life.

Methods: We analysed circadian rhythms in 55 metastasic breast cancer patients who were compared to healthy controls (digital twin) matched by age, weight, and height. The healthy controls were recruited from the Kronohealth database, which includes more than 10,000 subjects. The patients were divided in two groups by kind of treatment. Group 1 patients with first or second chemotherapy line and Group 2 patients with cyclin dependant kinasa inhibitor plus hormonal therapy All participants had Performance status 0 or 1. EUROQOL-5D 5L quality of life test was performed.

Results: The EQ-5D-5L scale did not show significant differences in any of the five aspects analyzed: pain, anxiety, mobility, usual activities, and self-care were evaluated as either without problems or with mild problems regardless of the treatments received. However, patients in group 1 exhibited patterns of aged rhythms compared to healthy controls, with decreased time and amplitude of movements (motor activity) and increased hours of sleep. Patients in group 2 maintained levels of physical activity similar to those of the control group, and there were no differences in sleep patterns. Body temperature was decreased in both groups of patients, and the recovery of temperature after the initiation of activity was slowed down compared to controls.

Conclusions: CDK Inhibitors plus hormonotherapy have a lesser impact on the quality of life compared to chemotherapy treatments in patients with metastatic breast cancer, as these patients maintain better levels of physical activity and less disrupted sleep patterns. We have observed a significant decrease in body temperature in oncology patients, which will be the subject of future investigations.

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470P Increased risk of vertebral fractures in healthy bone in metastatic breast cancer patients treated with CDK4/6 inhibitors combined with endocrine therapy

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Background: CDK4/6 inhibitors (CDK4/6-i) combined with endocrine therapy (ET) have become the standard of care for ER-positive HER2-negative metastatic breast cancer (mBC) and have significantly improved clinical outcomes. In long-term survivors, bone health is a crucial issue. The risk of fragility fractures associated to ET is well established. Preclinical data suggest that CDK4/6-i could have an effect on the bone microenvironment, however no clinical data are available. The aim of this study is to evaluate vertebral fractures (VFs) progression in mBC patients (pts) treated with CDK4/6-i combined with ET.

Methods: A series of 211 ER-positive HER2-negative mBC pts treated with CDK4/6-i combined with ET and referred to Medical Oncology and Breast Unit of ASST Spedali Civili, Brescia, from 2017 to 2023 were enrolled. VFs were evaluated through CT scan at baseline and at subsequent CT restaging and were classified as mild, moderate and severe based on Genant classification.

Results: All pts were female, with a median age of 55.5 years (32-79). CDK4/6-i were administered as first, second and third line of treatment in 113 (53.6%), 65 (30.8%) and 6 (2.9%) pts, respectively. ETs were aromatase inhibitor and fulvestrant in 104 (49.3%) and 107 (50.7%) pts, respectively. At baseline, 141 patients (66.8%) had bone metastases. 102 (48.3%) pts were treated with bone-targeted agents (BTAs). VFs in healthy bone were detected in 22 (10.4%) pts at baseline and in 37 (17.5%) pts after a mFU of 24 months ($p<0.001$), with 21 (10.1%) pts experiencing VFs progression, defined as the onset of a new VF of the worsening of pre-existing VFs. Among pts receiving BTAs, VFs in healthy bone were detected in 6 (5.9%) pts at baseline and in 16 (15.7%) pts after a mFU of 24 months ($p = 0.006$). Correlations between fracture risk factors and VFs progression as well as the comparison between patients receiving and patients not receiving BTAs will be presented at the meeting.

Conclusions: These data suggest a detrimental effect of CDK4/6-i and ET combination on bone health. Studies with a prospective design, a control arm with ET alone and longer follow-up are needed to better explore this issue.

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471P Liver toxicities during cyclin-dependent kinase inhibitors (CDKi) in patients affected by hormone receptor-positive breast cancer (BC)

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Background: CDKi are standard of care for patients (pts) with advanced hormone-positive (HR+) BC, with recent results even in the adjuvant setting. Nevertheless, management and clinical implication of hepatotoxicity during CDKi are not well described in literature, even if it is reported in a non-negligible rate within trials.

Methods: A multicenter Italian retrospective study was conducted in 2023, collecting and pooling data of pts affected by HR+ HER2- BC, treated with CDKi and aromatase inhibitors (AI) or fulvestrant (FULV). This study aims to describe the incidence and the management of liver adverse events (AEs) during CDKi in a real-world setting. A descriptive analysis was performed as pivotal evaluation for designing an observational study.

Results: 256 pts were included across 5 centres: 96% of pts received CDKi in the metastatic setting. Pts were treated with ribociclib (42%), abemaciclib (25%) and palbociclib (33%) associated with AI or FULV. Liver AEs occurred in 16% of pts, with a median time of onset of 90 days. 19 pts (46%) experienced grade $\geq$3 (G$\geq$3) liver AEs: mostly with elevated liver enzymes (95%). No acute liver failure was reported. The rate of liver AEs was 20% for ribociclib, 17% for abemaciclib and 11% for palbociclib. Ribociclib and abemaciclib were associated with 79% and 21% of G$\geq$3 liver AEs. Diagnostic assessments were performed in 37% of pts with liver AEs: hepatotropic viruses screening (68%), autoimmunity screening (28%) and radiological exams (4%). Only one liver biopsy was performed with a diagnosis of drug induced liver injury. Recovery of normal liver function after CDKi discontinuation was achieved in 68% of pts, with a median time of 30 days. After resolution of G$\geq$3 liver AEs, 26% of pts discontinued any treatment, 5% continued only AI or FULV, 48% resumed CDKi with dose reduction and 21% shifted to another CDKi without any further G$\geq$3 liver AEs.

Conclusions: In our cohort the incidence of liver AEs was significant, with a relevant number of G$\geq$3 AEs. Since hepatotoxicity is defined by diagnosis of exclusion, a prompt screening for differential causes is crucial in case of abnormal liver function. After non serious liver AEs, resumption of lower dose or shift to another CDKi may be a safe therapeutic option.

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472P Prevention of metastasis formation by combination therapy targeting Her2 and PD-L1 in Her2-expressing tumors based on observed efficacious vaccination against Her2-positive tumors

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Background: The overexpression of human epidermal growth factor receptor Her2 is associated with a more aggressive cancer phenotype. We have formulated a Her2 vaccine (HER-Vaxx), comprising B-cell peptide from the trastuzumab binding site, inducing anti-tumor immune responses and immunological memory in pre-clinical and clinical investigations. In the phase 1b evaluation (NCT02795988) of the vaccine, one patient had progressed with a new metastatic lesion with no Her2 expression. The vaccine's pre-clinical evaluation was shown to significantly reduce Her2 lung metastases size in a murine model, and was associated with Her2 loss and upregulation of tumoral PD-L1 expression. In light of the preclinical observation, the patient's primary tumor at the pre- and post-treatment time points was evaluated with regard to expression levels of Her2 and PD-L1.

Methods: Biopsies of the patient's primary tumor from the pre- and post-treatment time points were evaluated by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for Her2, and combined positive score (CPS) for PD-L1 expression. The murine Her2 lung metastases model was employed to further investigate the proteins' expression association.

Results: The assessment of the patient's primary tumor biopsies indicated Her2 3+ (IHC), Her2 /CEP17 ratio of 4.98 (FISH) and 0% PD-L1 CPS at the pre-treatment time point. At the post-treatment time point, the primary tumor's assessment showed a loss of Her2 expression: 0 (IHC) and Her2 /CEP17 ratio of 1.63 (FISH), with 5% PD-L1 (CPS) expression. In the mouse model, vaccination with HER-Vaxx resulted in a significant reduction of Her2 and upregulation of PD-L1 expression 6 weeks or longer after tumor cell implantation, at transcriptional and translational levels in the same tumors of the metastasized lungs of the vaccinated mice.

Conclusions: These results strongly suggest an immune evasive tumor cell response with an upregulation of PD-L1 expression in both, the clinical and preclinical settings. A combination therapy targeting both Her2 and PD-L1 in Her2-overexpressing tumors might efficiently prevent metastasis formation and immune evasion.

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473P Predictive factors for drug-induced liver injury in patients with ER-positive HER2-negative metastatic breast cancer treated with first-line cyclin-dependent kinase 4/6 inhibitors

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Background: The combination of endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitors (CDKi) for ER+HER2neg metastatic breast cancer has been associated with 13% of drug-induced liver injury (DILI). In a previous work (Vega et al, ESMO Breast 2023), we identified 26 cases of DILI (5.5%), defined as AST/ALT elevation $\geq$G2, among 472 patients (pts) treated. Here, we present a case-control study to evaluate the clinical factors associated with DILI.

Methods: The case-control study includes i) 89 pts without DILI randomly selected and retrospectively analyzed (control group) and ii) 26 cases with DILI previously reported. 15 potential predictive factors were evaluated either individually or in combination. Baseline liver steatosis was based on computed tomography reports. To study the association with DILI, odds ratios (ORs) were calculated using logistic regression.

Results: The main characteristics of the 115 pts are shown in the table. In the univariate analysis, no baseline risk factor alone was statistically associated with DILI, steatosis and AST/ALT baseline elevation had the best results ($p<0.15$). However, the combination of steatosis and pre-menopause status (n=9, 7.8%) significantly increased the risk to 66.7% vs 19% (20/105) (OR=8.6, 95% CI 2.1-43.6; p=0.004). No other variables, including cardiovascular risk factors, ET partner or liver metastasis predicted DILI development.

Table: 473P Baseline characteristics of cases and control

	Cases n=26	Controls n=89
Palbociclib	8	32
Abemaciclib	9	29
Ribociclib	9	28
Age (median)	61	60
Overweight	33%	36%
Obesity	26%	28%
Pre-Menopause	54%	35%
Hypertension	27%	27%
Diabetes mellitus	4%	11%
Dyslipidemia	31%	29%
Aromatase inhibitor	65%	57%
Fulvestrant	35%	43%
Liver metastasis	27%	30%
Steatosis	31%	15%
Baseline ALT or AST >35 IU/mL	36%	17%

Conclusions: In our case-control series, the combination of premenopausal status and steatosis was the strongest predictor for CDKi-related DILI. Our findings suggest that metabolic changes due to ovarian factor suppression cooperate with CDKi to induce DILI in pts with underlying steatosis. A prospective study is needed to validate these findings.

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474P ctDNA-based copy number dynamics during anti-PD1 treatment in patients with metastatic triple-negative breast cancer

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Background: Circulating tumor DNA (ctDNA) is an emerging technology to predict outcome in cancer patients and monitor treatment response including immune checkpoint blockade (ICB). So far, data on ctDNA dynamics during ICB in breast cancer are lacking. Moreover, in the context of ICB, most of the ctDNA assays focus on detection of mutations, while many cancer types including breast cancer are mainly driven by copy number alterations (CNA). Here we present ctDNA-based CNA dynamics in patients with metastatic triple-negative breast cancer (mTNBC) treated with anti-PD1 in the TONIC-trial.

Methods: Low-coverage (0.5x) whole genome sequencing was performed on plasma samples taken at baseline and after 8 weeks of treatment for a subset (n=30) of patients with mTNBC treated with nivolumab in the TONIC trial (Voorwerk et al., Nat Med 2019). 16 patients had progressive disease; 14 patients ('responders') responded to nivolumab or had stable disease for at least 24 weeks. CNA profiles were generated with QDNASeq, NoWaves and CGHcall, followed by calculating copy number profile abnormality (CPA) scores.

Results: ctDNA CNA profiles were significantly correlated with tumor CNA profiles with an average correlation of 0.5 (range 0.21 - 0.86). Baseline ctDNA levels and ctDNA-based CPA scores were not associated with response to anti-PD1. While in non-responders ctDNA levels increased during ICB ($p = 0.008$), in responders CPA scores decreased ($p = 0.0004$). Higher on-treatment CPA scores were negatively correlated with overall survival (OS) and progression-free survival (PFS) ($p = 0.000005$, $p = 0.0008$, respectively).

Conclusions: ctDNA-based copy number alterations dynamics in patients with mTNBC was highly correlated with anti-PD1 response. This pilot study is the first report on the potential utility of low coverage ctDNA-based surveillance during ICB treatment and warrants further validation in TNBC and other tumor types.

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475P Dynamics of TROP2 expression in triple-negative breast cancer

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Background: With the approval of antibody drug conjugates (ADC) for metastatic TNBC (mTNBC), understanding prevalence and changes in ADC target expression from early-stage to metastatic breast cancer is key. Here we report TROP2 expression in a cohort of patients (pts) diagnosed with TNBC with collection of matched tumor samples over time.

Methods: Pts were identified from an institutional database of pts who underwent surgery for stage I-III TNBC at Dana-Farber/Brigham Cancer Center between 2015-2018, and a prospective biopsy protocol for pts who developed mTNBC. TROP2 immunohistochemistry (IHC), RNA and exome sequencing were performed in samples at diagnosis (DX), residual disease (RD) post-neoadjuvant therapy (if applicable), and recurrence (MR). TROP2 IHC (tumor cell membrane expression) was scored by a trained pathologist and classified: low, L (H score <100); medium, M (100-<200); high, H (200-300). RNA expression was quantified using log2p1-transformed and normalized transcripts per million.

Results: TROP2 IHC was performed in 161 samples (62 DX, 54 RD, 45 MR) from 94 pts (Table). TROP2 H/M distribution was similar at DX (90.3%; 56/62) vs MR (88.9%; 40/45). In samples with available TROP2 and HER2 IHC, TROP2 H/M distribution was 88.8% (71/80) in HER2-0 and 91.3% (42/46) in HER2-low TNBC. In 20 pts with paired DX and RD, TROP2 IHC was discordant (H/M vs L) in 15% (3/20). Of 17 TROP2 H/M DX tumors, 2 (11.8%) were L at RD. In 15 pts with paired DX and MR, TROP2 IHC was discordant in 26.7% (4/15). Of 14 TROP2 H/M DX tumors, 3 (21.4%) were L at MR. Correlation between TROP2 IHC and *TACSTD2* expression was observed (n=53; Pearson r=0.38; p=0.005). *TACSTD2* expression was numerically higher in TROP2 H/M vs L (p=0.09). Increased gene expression was also observed for L vs H (p=0.06) and M vs H (p=0.047). No *TACSTD2* mutations were identified.

Table: 475P Distribution and changes in TROP2 IHC (n samples) in pts diagnosed with TNBC. A) TROP2 IHC by sample type. B) From DX to RD; C) From DX to MR. Discordant cases (H/M vs L) are highlighted in grey

A)		TROP2 (DX, RD, MR)			
		Low	Med	High	TOTAL
Sample type	DX	6	11	45	62
	RD	4	13	37	54
	MR	5	8	32	45
	TOTAL	15	32	114	161
B)		**TROP2 (RD)**			
		Low	Med	High	TOTAL
TROP2 (DX)	Low	**2**	**0**	**1**	3
	Med	**0**	1	1	2
	High	**2**	4	9	15
	TOTAL	4	5	11	20
C)		**TROP2 (MR)**			
		Low	Med	High	TOTAL
TROP2 (DX)	Low	0	**1**	**0**	1
	Med	**0**	**1**	1	2
	High	**3**	1	8	12
	TOTAL	3	3	9	15

Conclusions: TROP2 IHC was H/M in the majority of samples, with similar distribution at DX and MR, and between HER2-0 and HER2-low TNBC. In paired DX/RD or DX/MR, discordance between TROP2 H/M and L groups was low.

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476P Allosteric PI3K-alpha inhibition reverses on-target resistance to orthosteric inhibitors mediated by secondary PIK3CA mutations

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Late withdrawal

477P Do ESR1-related mutations generate neoantigens in hormone-receptor-positive HER2-negative metastatic breast cancer?

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Background: Breast Cancer (BC) is the most common type of cancer in women and 80% of cases are hormone-receptor positive. In 20 % a key mechanism of endocrine resistance to the standard first line is mutation of the ligand-binding domain of Estrogen Receptor 1 (ESR1) encoding estrogen receptor a. These mutations are clustered in a "hotspot" within the LBD. Four mutations are known in positions 537 and 538 (D538G, Y537C, Y537N, and Y537S), and lead to cell proliferation and potentially enhanced metastatic capacity. This project aims to identify if ESR1 receptor mutations are neoantigens in patients with HR+ HER2- metastatic BC, and thus resistant to endocrine therapy.

Methods: We identified candidate ESR1-derived-peptides, to evaluate the immunogenicity of these peptides we conducted a vaccination assay on a humanized mouse model. We administered 100 µg of each peptides and 50 µg of CpG on day 0 (D0). We achieved three boosts with 50 µg of each peptides and 30 µg of CpG on D7, D14 and D21. Spleen and lymph nodes were isolated on D23 and immunogenicity tests were conducted. We also evaluated the immunogenicity of ESR1-derived peptides in PBMC on 30 healthy donors (HD) and 25 patients with mBC HR+ BC by ELISpot assay. Furthermore, we cloned T-cells with 2 stimulations in 30 days, to demonstrate that T-cells can lyse tumour cells.

Results: Preliminary results validated the HLA-A2 ESR1 peptide immunogenicity in humanized mice. In the same way, we demonstrated the ESR1 peptide immunogenicity in HD and patients with BC. Our results showed that 40% of patients had specific immune responses. and these patients presented secondary hormone-resistance. These data allow the selection of the most relevant peptides which are either weakly or not observed at all with HD. These results support that the ESR1 mutation generates neoantigens in hormone-receptor-positive metastatic breast cancer.

Conclusions: From the perspective of those results, we will try to demonstrate the natural ESR1-specificity T cell clones to recognize and kill transduced ESR1 tumour cells. Additionally, we will analyze HLA Class I expression in mutated/non-mutated ESR1 patients by bioinformatics in order to understand if tumour resistance may be linked to the loss of HLA expression.

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478P Germline BRCA1/2 pathogenetic variants (gBRCA1/2 PV) affect outcome of hormone (HR)-positive HER2-negative metastatic breast cancer (MBC) patients (pts) treated with cyclin-dependent kinase 4/6 inhibitor (CDK 4/6i) plus endocrine therapy (ET): The BREAK study

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Background: Although available evidence establishing the impact of germline PV of DNA-repair genes in patients with luminal MBC is conflicting, the standard treatment is represented by CDK 4/6i plus ET.

Methods: In this retrospective multicenter study, HR+ HER2- MBC pts tested for gBRCA1/2 genes and who received CDK 4/6i plus ET from 1st Jan 2017 to 31th December 2021, were included. The objectives were the evaluation of outcome (primary/secondary end-points: progression free survival [PFS]/overall survival [OS]) according to gBRCA1/2 status (PV *versus* wild type [wt]/variants of uncertain significance [VUS]), estimated by Kaplan-Meier method. Cox model was used to assess the correlation between baseline variables and outcomes.

Results: 249 pts in 13 centers were included in the study: 40 (16.1%) pts carried gBRCA1/2 PV (N=31 with gBRCA2 PV), 20 (8.0%) pts had VUS BRCA1/2, 189 (75.9%) pts were wt. Baseline charateristics were: median age 52 years (range: 26 − 83 yrs); male 2.8% (N=7; with 3 gBRCA2 PV); premenopausal 46.6% (N=116); visceral metastases 78% (N=194); ECOG PS 0 80% (N=199); 1st line CDK4/6i plus aromatase inhibitor (AI) 53% (N=132); chemotherapy (CT) before CDK4/6i plus ET 16.5% (N=41). The two groups differed for ECOG PS $\geq$ 1 (32.5 vs. 17.7%; p= 0.032) and previous CT (32.5% vs. 13.4%; p= 0.003). With a median follow up of 37.5 months (95%CI 31.4 − 43.5) the mPFS was 10.7 vs. 26.7 months for pts with gBRCA1/2 PV and wt, respectively (p< 0.001). Similarly, mOS was shorter for gBRCA1/2 PV pts (40.1 vs. 69.0 months; p= 0.013). After adjusting survivals for ECOG PS status and use of previous CT for MBC, the worse outcome was confirmed for pts with gBRCA1/2 PV (HR for PFS, 1.61; 95%CI: 1.09 − 2.44; p= 0.017 and HR for OS, 1.72; 95%CI: 1.01 − 2.94; p= 0.047). Among gBRCA1/2 PV pts, PARP inhibitor and CT were the treatments after CDK4/6i progression in 15.6% (N=5) and 62.5 % (N=20; 8 pts had platinum based treatment), respectively.

Conclusions: These data reported gBRCA1/2 PV as a negative prognostic factor for HR+ HER2- MBC pts treated with CDK4/6i plus ET. Different strategies are urgently needed for this subgroup of pts.

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479P Radiomics to predict HER2 status in breast cancer brain metastases

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Background: Significant discordance rates in HER2 status between primary breast cancer (BC) and brain metastases (BCBM) have been reported, potentially affecting clinical decision-making. Biological recharacterization of BCBMs is difficult due to inherent neurosurgery risks. We here assess the potential of radiomics to non-invasively assess HER2 status of BCBMs.

Methods: We retrospectively identified BC patients from 2 centers, for which HER2 status evaluated on BCBMs (HER2-positive versus HER2-negative by ASCO-CAP) and preoperative brain MRI were available. A total of 218 radiomics features, complying with Imaging Biomarker Standardization Initiative feature definition, were extracted from manually segmented BCBMs using Python. Robust features (selected using LASSO) associated with HER2 status in univariate analysis (p<0.05) were tested in multivariate analysis. Linear regression model (LRM) and non-linear logistic regression model (NLRM) were constructed. Machine learning (ML) algorithms

(decision tree, k-nearest neighbor, and support vector machine [SVM]), were tested, by spliting the dataset into 70% for training, 20% for testing, and 10% for validation. Classifiers were trained and tested using the cross-validation approach 10 times; median values for AUC, accuracy, sensitivity and specificity were obtained. The performance of the best classifiers was evaluated on the validation dataset. Analyses were performed using MATLAB R2021b Statistics and Machine Toolbox (MathWorks).

Results: We identified 54 BC patients, for which HER2 status evaluated on 56 BCBMs (HER2+ N=27, HER2- N=29) and preoperative brain MRI was available. At univariate analysis, 9 features were significantly associated with HER2 status, but diagnostic accuracy was low (maximum 67%). Using LRM and NLRM, including the 9 significant features at univariate analysis, accuracy increased to 79%. Using the ML approach, the best classifier among the pattern recognition approaches tested was a SVM including the 9 significant features, which reached an AUC of 0.97 and an accuracy of 91% and 86% on test and validation set, respectively.

Conclusions: Radiomics using machine learning approach shows potential to non-invasively predict HER2 status of BCBMs.

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480P Prognostic significance of somatic DNA gene rearrangement and structural atypia in metastatic breast cancer

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Background: Comprehensive genomic profiling (CGP) testing for breast cancer has become widely used to identify genetic alterations, including somatic DNA gene rearrangement and structural atypia. The prognostic impact of somatic DNA gene rearrangement/structural atypia in metastatic breast cancer (MBC) is unclear. In this study, we aimed to clarify the prognostic significance of DNA gene rearrangement and structural atypia.

Methods: We evaluated 1790 cases of MBC who received cancer gene panel tests under the national health insurance system using FoundationOne CDx(R) between June 2019 and October 2022. Genomic and clinical data were collected from the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) Research-Use Portal in Japan. Patients were divided into two groups based on the presence or absence of somatic DNA gene rearrangement/structural atypia described in the reports: the rearrangement group (with at least one DNA gene rearrangement/structural atypia) and the others (without). Genomic alterations and overall survival from the date of diagnosis were evaluated.

Results: One hundred sixty-four patients (9.2%) had one or more DNA gene rearrangements or structural atypia. Overall, 285 DNA gene rearrangements/structural variants were found, with FGFR1 rearrangement being the most common (n=10), followed by MTOR rearrangement (n=7), FGFR2 rearrangement (n=6), NOTCH2 rearrangement (n =5). The rearrangement group had significantly better overall survival than the others (rearrangement group, NA, the others, 162.3m; log-rank P-value = 0.0006; hazard ratio, 0. 43; 95% confidence interval, 0.26-0.71).

Conclusions: MBC patients with one or more DNA gene rearrangements and structural atypia had a significantly better prognosis. Further investigations of the prognostic and biological significance of these alterations in MBC patients are warranted.

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481P Second generation oral selective estrogen receptor degraders (SERDs) in breast cancer: A systematic review and meta-analysis of clinical trials

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Background: SERDs are effective treatment options for breast cancer (BC) patients (pts) after progression on first-line therapy, especially for those harboring estrogen-receptor 1 (*ESR*1) mutations (mut). Several studies have explored the potential of SERDs to overcome endocrine resistance, yielding promising results.

Methods: We conducted a systematic review and meta-analysis to assess oral SERDs in hormone receptor-positive, HER-2-negative BC pts. Efficacy was evaluated by tumor response according to *ESR1*mut, and the number of pts with variant allele frequency (VAF) decreased with SERD therapy. We searched Pubmed, Scopus, and Cochrane Library databases and congress websites for randomized and non-randomized clinical trials. We used a random effects model for data pooling; heterogeneity was assessed with I^2 statistics.

Results: We included 19 studies with 1,798pts. Of 855 pts tested, 387 (45%) had *ESR1*mut. *ESR1*mut frequency and respective overall response rate (ORR) are described in the table. We found 80% of pts(95%CI 0.72-0.88 $I^2$56%) had a decrease in VAF with SERD therapy. The estimated risk of all-causality adverse events (AE) was 86% (95% CI 0.80-0.92), and grades 3 or 4 AE were 19% (95% CI 0.11-0.28). SERD plus Palbociclib resulted in higher rates of AEs (p<0.01). Elacestrant had numerically higher G3-4 AEs compared to the other SERD (p=0.05). The most common AEs were nausea (35%), diarrhea (30%), and fatigue (23%). Arthralgia was reported in 15%, and only 1% of pts had to discontinue treatment due to AE.

Table: 481P Characterization of *ESR1*mut and response to SERD (Amcenestrant, Elacestrant, and Camizestrant)

*ESR1*mut	Prevalence of *ESR1*mut(%)	Patients assessed for response(n)	ORR(%)
D538G	34	25	44
Y537S	28	23	61
E380Q	8	8	25
Y537N	7	11	45
L536H	6	4	75
Others	16	13	15

Conclusions: Our study supports the favorable safety profile of the new generation oral SERD and presents its efficacy according to *ESR1*mut. Further studies shall assess the potential biomarker role of individual *ESR1*mut.

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482P Precision imaging with human epidermal growth factor receptor 2-positron emission tomography (HER2-PET) for refined treatment selection in patients with HER2-low breast cancer

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Background: HER2-low metastatic breast cancer (mBC) is a clinically relevant subgroup with promising treatment options. Challenges relate to establishing HER2-low status when biopsies are not feasible, and little is known about disease heterogeneity. PET-imaging with a HER2-specific tracer could shed light on these issues.

Methods: At the Karolinska Comprehensive Cancer Center in Stockholm, Sweden we conducted a proof-of-concept prospective imaging study with the [^{68}Ga]Ga-ABY-025 tracer in patients with mBC with a previous HER2-low tumor biopsy, who were scheduled for a new line of systemic therapy. A HER2-PET and tumor biopsy (immunohistochemistry [IHC] and in situ hybridization [ISH]) were performed. The study was funded by the Swedish Breast Cancer Society and Stockholm's Region.

Results: Seventeen patients were informed, ten patients provided written consent and in ten, paired PET and biopsy results are available (Table). No unexpected side effects were noted. In all, HER2-PET revealed areas with [^{68}Ga]Ga-ABY-025 maximal Standardized Uptake Value (SUV_{max}) higher than background ratio. HER2-low status was confirmed in tumor biopsies in eight, whereas two patients had HER2 0 in a tumor lesion that was avid on HER2-PET. Substantial heterogeneity was observed in [^{68}Ga]Ga-ABY-025 uptake between different lesions within the same patient.

Conclusions: The visualization of HER2-expressing mBC with [^{68}Ga]Ga-ABY-025 PET/CT is feasible and safe. An intriguing finding is the fact that we noted tracer uptake in lesions that are HER2 0. A continued study is planned where patients with HER2-low mBC are selected for HER2-antibody drug conjugate based on HER2-status on PET and/or IHC.

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Legal entity responsible for the study: Karolinska University Hospital/Region Stockholm.

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483P Prognostic value of androgen receptor expression in patients with advanced triple-negative metastatic breast cancer treated with sacituzumab govitecan: A French multicentre retrospective study

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Background: Androgen receptor (AR) is expressed in around 30% of triple-negative breast cancer (TNBC) tumors, and presents with different clinical evolution and resistance to standard chemotherapy. Sacituzumab govitecan (SG) is an antibody-drug conjugate recently approved in TNBC advanced tumors.

Methods: We conducted a retrospective study in 8 French University Hospitals and cancer centers. All patients with TNBC MBC treated with SG were included. The primary endpoint was progression-free survival (PFS) as per AR expression (cut-off 10%). Secondary endpoints included overall survival (OS). Univariable and multivariable analyses were performed.

Results: A total of 127 patients were included, of which 88 (69%) were AR-. The median age was 51yo (range 25 - 77), with younger patients in AR- (47yo) vs. AR+ (55.5yo; p=0.02). AR- tumors were mostly ductal subtype (95.5% vs. 82.1%; p=0.005) and higher grade III (79.8% vs. 58.3%; p=0.021). No differences were observed between AR- and AR+ in the median number of prior treatments at SG start: 2 (0 - 11) and the median number of SG cycles: 6 (1 - 28) with 27 patients (21.3%) still on SG at the time of analyses. With a median FU of 10.4m [95%CI 8.3-11.2], median PFS was 4.1m [3.7-4.7] with no differences based on AR expression (4.1m vs. 4.3 m, AR- vs. AR+, respectively; HR 0.83 [95%CI: 0.53-1.32], p=0.432). In univariable analysis, age at SG treatment (HR 0.98 [0.97-1.00]; p=0.028), adjuvant capecitabine (HR 1.65 [1.06-2.56]; p=0.025), and metastasis-free interval (MFI) (HR 2.39 [1.38-4.14] and 1.09 [0.63-1.91] for 6-24m and > 24m respectively vs. < 6m) were associated with PFS. Short MFI remained significant for worse prognosis in a multivariable analysis (HR (6-24m vs. <6m) 2.0 [1.04-3.88]; p=0.039). The mOS was 9.7m [7.1-12.2] with 67 (52.8%) patients still alive. AR was not associated with OS in the univariable (HR 0.66 [0.37-1.19]; p=0.165] or multivariable analyses (HR=0.69 [0.34-1.38]; p=0.290].

Conclusions: Despite AR+ tumors being described as lesser chemo-sensitive, in this large retrospective cohort, AR expression was not associated with benefit in terms of PFS and OS from SG in patients with advanced TNBC.

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Table: 482P

Pat ID	HER2-PET					Biopsy			
	Metastases	SUV_{max} tumor	SUV_{max} spleen	SUV_{max} liver *	SUV_{max} myocardium (left chamber)	Site	ER/PR/Ki67	HER2 IHC biopsy	HER2/C17 gene amplification quote
1	Liver	12.9	2.6	9.1	3.1	Liver	100/100/19	IHC 1+	2.85/1.0 2.85
2	Bone and lymph nodes	6.1	3.9	13.7	4.4	Lymph node	0/0/95	IHC 1+	-
3	Liver	28.7	3.0	n.a.	4.1	Liver	80/70/x	IHC 2+	3.3/2.3 1.4
4	Bone and liver	10.7	5.0	n.a.	3.2	Liver	80/70/78	IHC 1+	4.4/2.5 1.76
5	Bone and liver	24.9	3.9	13.4	4.1	Liver	30/0/60	IHC 0	-
6	Bone, skin, liver	3.7	2.8	n.a.	3.1	Skin	0/0/39	IHC 0	-
7	Breast, brain	10.3	2.3	13.8	3.8	Breast	60/0/40	IHC 2+	3.6/1.45 2.48
8	Liver	33.4	2.7	13.3	4.1	Liver	95/0/3	IHC 2+	1.3/1.8 0.7
9	Bone, liver	19.0	3.0	n.a.	3.7	Liver	95/95/13	IHC 2+	2.25/1.55 1.45
10	Liver, bone	12.0	2.7	n.a	2.7	Liver	0/0/33	IHC 2+	2.65/1.35 1.96

* measured on healthy liver tissue

484P Multi-platform characterization of HER2 expression in triple-negative breast cancer

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Background: To improve quantification methods of antibody drug conjugate (ADC) targets, it is critical to understand differences in expression across assays. Here we report HER2 expression per local (L-IHC) and central (C-IHC) IHC, RNA sequencing (seq), and copy number amplification (CNA) by exome seq in patients (pts) with TNBC using matched tumor samples over time.

Methods: Pts were identified from an institutional database of pts who underwent surgery for stage I-III TNBC, and a prospective biopsy protocol for pts who developed metastatic TNBC. Samples were collected at diagnosis (DX), residual disease (RD) post-neoadjuvant therapy (if applicable) and recurrence (M). Clinical pathology records were reviewed for L-IHC; slides were blindly reviewed by a pathologist for C-IHC. HER2 IHC was classified as HER2-0 if IHC 0, and HER2-low if 1+ or 2+/ISH non-amplified. RNA expression was quantified using log2p1-transformed and normalized transcripts per million. Normal subtype samples were excluded.

Results: L-IHC and C-IHC were available in 96 samples (28 DX, 11 RD, 57 M) from 61 pts (Table). HER2-low prevalence was 25.0% (24/96) per L-IHC and 35.4% (34/96) per C-IHC. Discrepant HER2 category was observed in 16.7% of samples (16/96). In 67 samples with L-IHC and RNA seq, *ERBB2* expression was higher in HER2-low (n=21) vs HER2-0 (n=46) groups (p=0.03). A similar trend in *ERBB2* expression was observed with C-IHC (p=0.32). HER2-enriched (HER2E) subtype was present in 23.8% (5/21) of HER2-low vs 6.5% (3/46) of HER2-0 tumors (p=0.10). Basal subtype was 71.4% (15/21) in HER2-low vs 89.1% (41/46) in HER2-0 tumors (p=0.09). Among 17 paired DX/RD and M, 6 pairs had change in L-IHC with no difference in *ERBB2* expression (p=0.83). Of 90 samples with L-IHC and exome seq, none had *ERBB2* CNA.

Table: 484P Distribution of HER2 C-IHC and intrinsic subtype (research-based PAM50) according to HER2 L-IHC in samples from pts with TNBC. Discordant HER2-low and HER2-0 cases are highlighted in grey

A)		L-IHC			
		IHC 0	IHC 1+	IHC 2+	TOTAL
C-IHC	IHC 0	59	**2**	**1**	62
	IHC 1+	**13**	11	4	28
	IHC 2+	**0**	0	6	6
	TOTAL	72	13	11	96

B)		L-IHC			
		IHC 0	IHC 1+	IHC 2+	TOTAL
Intrinsic subtype	Basal	41	11	4	56
	HER2-E	3	3	2	8
	Luminal A	0	0	1	1
	Luminal B	1	0	0	1
	Non-classified	1	0	0	1
	Normal	6	3	1	10
	TOTAL	52	17	8	77

Conclusions: Most discrepant cases between L-IHC and C-IHC resulted in change from HER2-0 to HER2-low. Correlation between HER2 IHC and gene expression was observed in TNBC pts. HER2E subtype was numerically more prevalent in HER2-low vs HER2-0 tumors.

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485P A novel approach to identify subpopulation of CTCs with metastatic potential using sc-RNA-seq

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Background: Integrins are known to play a crucial role in the adhesion, invasion and migration of tumor cells. Recent studies revealed the association of certain integrin subunits in organotropic metastasis of breast cancer. In this study, we investigated the biological properties associated with different integrin subunits gene expression in CTCs.

Methods: The study included 81 patients with non-metastatic invasive breast carcinoma of no special type (T1-4N0-3M0, all molecular subtypes). Single-cell cDNA libraries were prepared using the Single Cell 3′ Reagent Kit v3.1 and a 10x Genomics Chromium Controller. The ready cDNA libraries were sequenced on NextSeq 500 and NextSeq 2000 (Illumina, USA).

Results: CTCs were identified based on the expression of one or more epithelial markers: *KRT5, 7, 8, 14, 18, EPCAM, MUC1* and *CDH1* (E-cadherin). In total, expression of 14 integrin subunits was detected in CTCs: nine α-subunits and five β-subunits. In each cell, the combination of different integrin subunits was evaluated, and if complementary α and β-subunits gene expression detected in one cell, we suggested that CTCs potentially could synthesize functionally complete integrin heterodimers. Depending on the combinations of different subunits in CTCs, 455 cells were divided into nine groups. In each group, we assessed the proportion of cells with expression of genes relevant to the most important functions that determine the malignant potential of tumor cells: stemness, EMT, invasion. The most differences were observed in the group of CTCs potentially capable to express the $\alpha6\beta4$ heterodimer. Namely, integrins $\alpha6$- and $\beta4$-positive CTCs more frequent expressed stemness (*ALDH1A1, CD133, KLF4, MYC*) and invasion markers (*RAC1, RHOC, ROCK, MMP1,2*). A combination of epithelial (*KRT 8, 10, 18, 19* and *MUC1*) with mesenchymal features (absence of *EPCAM* expression, expression of *CDH2, VIM, ZEB1)* indicates a hybrid state of EMT.

Conclusions: A novel approach to scRNA sequence analysis has identified subpopulations of CTCs with pronounced biological properties which can play role of

"seeds". The simultaneously presence of integrin α6 and β4-subunits in CTCs was associated with stemness, EMT and invasiveness of CTCs in breast cancer patients.

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486P The influence of NF1 germline and somatic mutations on breast cancer patient survival

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Background: Somatic inactivation of the *NF1* gene is frequent in breast cancer, particularly in advanced stages, and it has been suggested as a potential mechanism of resistance to endocrine therapy. Pathogenic germline variants of the *NF1* gene cause neurofibromatosis 1 (NF1) syndrome that is associated with an increased risk for breast cancer and reduced estrogen receptor expression in breast cancer. The present study aims to explore the consequences of somatic and germline *NF1* mutations in hormone receptor positive and negative breast cancer.

Methods: In order to study germline *NF1* alterations, a Finnish cohort of 1,811 individuals with verified NF1 syndrome (926 women) and a ten-fold control cohort were cross-referenced with the Finnish Cancer Registry. The process identified 49 women with NF1 and 226 controls who had been diagnosed with breast cancer between 1996 and 2020. The analysis was limited to non-localized disease. Register-based information on endocrine therapy was used as a proxy for hormone receptor status. Survival after breast cancer with or without somatic *NF1* deficiency was analyzed using the METABRIC dataset, which contained 582 breast cancers harboring somatic alterations of the *NF1* gene, and 1,392 tumors where the *NF1* gene was intact. Cox proportional hazards models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CI).

Results: Somatic *NF1* alterations were associated with worse prognosis compared to tumors with normal *NF1* after estrogen receptor positive breast cancer (HR 1.53, 95% CI 1.16-2.02) while the *NF1* alteration status had no effect on survival after the diagnosis of an estrogen receptor negative breast cancer (HR 1.10, 95% CI 0.80-1.52). In contrast, pathogenic germline variants of the *NF1* gene were not associated with decreased survival in patients with or without endocrine therapy (HR 0.76, 95% CI 0.28-2.04; and HR 1.04, 95% CI 0.40-2.70, respectively).

Conclusions: Only somatic alterations of the *NF1* gene modify endocrine therapy outcomes in breast cancer. This suggests that estrogen receptor-positive breast cancer employs a different pathway for estrogen receptor signaling in women with pathogenic germline *NF1* variants than in the setting of somatic *NF1* inactivation.

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487P Induction of an inflammatory tumor microenvironment with oncolytic virus CF33-hNIS-antiPD-L1 intratumoral injection in patients with metastatic triple-negative breast cancer (mTNBC)

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Background: CF33-hNIS-anti-PD-L1 (CHECKvacc) is a novel chimeric orthopoxvirus with robust anti-cancer activity in TNBC xenografts. CHECKvacc increased CD8+ T cell infiltration and favorably modulated the tumor microenvironment (TME) in xenograft models. Here we report data from the ongoing first-in-human clinical trial of CHECKvacc intratumoral (IT) injections in patients with mTNBC.

Methods: This is a phase I, single center, single arm trial of CHECKvacc IT. Eligibility criteria include patients with mTNBC that progressed on $\geq$ 2 chemotherapy regimens and have at least 1 tumor amenable to IT injections. Patients receive CHECKvacc IT at 1 of 8 assigned escalating dose levels on Days 1 and 15 of each 28-day cycle for 3 cycles. Primary objective is to evaluate safety and tolerability. Secondary objectives are to determine recommended phase II dose and efficacy. Exploratory objectives include assessment of TME immune modulation. Formalin fixed tissue biopsies were assessed by multiplex immunofluorescence for CD3, CD8, PD-L1, and pan-cytokeratin and digitally quantified for densities of immune phenotypes. PD-L1 expression was also assessed by a pathologist for a combined positive score (CPS).

Results: From October 2021 to December 2022, 8 patients were enrolled in this ongoing study and received $\geq$1 dose of CHECKvacc at 1 of the first 3 dose levels (1x105, 3x105, 1x106 PFU). There were no dose limiting toxicities. Six patients had evaluable baseline and post-treatment tissues for immune quantification. From baseline to cycle 1 day 2, CD8+ T cells in the TME increased in 5 of 6 patients (median increase: 34%; range: 9-251%). CD4+ T cells increased in 4 of 6 patients (median increase: 39%; range: 23-73%). PD-L1 expression by CPS increased in 5 of 6 patients (range of increase: 4-50%; p=0.063 by Wilcoxon signed-rank test).

Conclusions: CHECKvacc induces tumor infiltration of CD4+ and CD8+ T cells. Upregulation of PD-L1 within the TME further suggests immune activation by CHECKvacc. The clinical trial is ongoing to further assess dose escalation, tumor response, and the potential for future combination trials with systemic therapies, such as checkpoint blockade and chemotherapy.

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488P Comprehensive genomic profiling to identify actionable alterations for breast cancer brain metastases in the Chinese population

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Background: Breast cancer brain metastasis (BCBM) is an significant issue in the treatment of breast cancer and always leads to poor prognosis. Novel therapeutic targets are needed in clinical practice. In this study, we aimed to identify potential actionable targets in brain metastases utilizing the FoundationOne® CDx (F1CDx).

Methods: Formalin-fixed paraffin-embedded (FFPE) specimens including 17 primary tumors, 49 BCBMs and 7 extra-cranial metastases from 54 patients who underwent surgery for BCBM were tested by F1CDx. Tumor infiltrated lymphocytes (TILs) of BCBM were also tested by hematoxylin-eosin staining.

Results: The median tumor mutation burden (TMB) and TILs were 5.0 (range: 0- 29) Muts/Mb and 1.0 (range: 0- 5) respectively in BCBMs. High TMB (>10 Muts/MB) were detected in 3 BCBMs. Genomic alterations(GAs) were detected in all samples. The top-ranked mutated genes in BCBMs were TP53(81.6%), PIK3CA(34.7%), MLL2(22.4%), BRCA2(14.3%) and ATM(14.3%); and the most prevalent copy number alterations (CNAs) were ERBB2(57.1%), CDK12(36.7%), CCND1(28.6%),FGF19 (26.5%), and MYC (22.4%). ATM mutation was detected in 7 BCBMs while none in primary tumors, although without statistically significant difference. The most prevalent GAs were relatively consistent between paired primary and BCBMs. Actionable GAs were detected in 93.9% of all BCBMs and consistent rate were 54.5% (6/11) between paired primary and BCBMs. Compared to matched primary tumors, reduced actionable GAs were found in 4 BCBMs and additional actionable GAs were discovered in only one BCBM.

Conclusions: TMB and TILs was relatively low in BCBMs. Comparable consistency of actionable GAs was identified between primary and BCBMs. It was reasonable to treat BCBM according to genomic profiling of primary tumors if BCBM specimens were unavailable since possibility to find additional therapeutic targets was relatively low.

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489P Liquid biopsy with combination of cell & cell-free analysis identifies HER2-expression in patients with metastatic breast cancer

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Background: Circulating Tumor Cells (CTCs) are non-invasive diagnostic approaches that can inform treatment decisions for patients with metastatic breast cancer (MBC) when a conventional tissue biopsy is not feasible. Recently, the novel anti-HER2 antibody-drug conjugate, T-DXd, has shown effectiveness against MBCs with low HER2 expression detected by tissue biopsy. In this report, we present data from a comprehensive liquid biopsy platform that includes immunofluorescent HER2 protein expression in CTCs (ctcIF), determination of *ERBB2* amplification by single-cell CTC genomics (ctcDNA), and ctDNA alterations in plasma.

Methods: Blood samples were collected from 531 patients with MBC and patient's HER2 status was determined by the ordering healthcare provider based on previous tissue biopsy results, which were documented on the DefineMBC test requisition form. After isolation, nucleated cells were plated, and slides and plasma were stored in a biobank. CTCs were identified using Epic Sciences digital imaging and machine learning algorithms, and ctcIF allowed for HER2 low determination. ctcDNA was analyzed by low-pass whole-genome sequencing in individual CTCs, and ctDNA alterations were analyzed using a validated NGS panel.

Results: Among the 531 patients, 51% (n=276) were reported HER2 negative but did not have documented HER2 IHC expression, and 15% (n=80) were reported as 0 by IHC from the most recent tissue biopsy. Therefore, 67% (n=356) may not be eligible for T-DXd treatment. Among the 356 patients with unknown IHC status or IHC 0, 93% (331/356) had DefineMBC test results reported to clinicians. DefineMBC identified HER2 expression by ctcIF with no ERBB2 amplification by ctcDNA or ctDNA, which is consistent with HER2-low in 29% (74/258) of patients with unknown IHC status, and 27% (20/73) in patients with HER2 0 by IHC and may indicate for T-DXd treatment.

Conclusions: A liquid biopsy platform combining ctcIF, ctcDNA, and ctDNA with high sensitivity and specificity can determine clinically actionable HER2 expression in MBC that can impact therapeutic decision-making for patients with MBC who do not have documented HER2 IHC expression or HER2 0 by IHC from a previous tissue biopsy.

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490P Metastatic breast cancer is associated with increased levels of soluble forms of TIM-3 and LAG-3 and decreased levels of soluble forms of GITR, GITR-L, CD27, CD28, CD40, CD86, ICOS, PD-L1, CTLA-4 and BTLA

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Background: Breast cancer (BC) cells exploit the up-regulation or down-regulation of immune checkpoint molecules (ICM) to evade anti-tumor immune responses.ICMs can be measured in human plasma; however, their biological and clinical significance remains essentially unknown. The present analysis aimed to measure plasma ICMs in metastatic BC patients (pts) and compare them to healthy controls.

Methods: Soluble forms of ICM and RANTES, arginase, TGF-b1, CD163, and CD206 were measured using Multiplex® bead array and ELISA technologies. Plasma samples from 20 metastatic breast cancer (MBC) pts and 45 healthy controls were analyzed for each protein, and compared between MBC pts and healthy controls using a non-parametric test (Mann-Whitney).

Results: The median age of the cohort was 53 years (range 34-79 years). The performance status was as follows; PS=0 (11 pts), PS=1 (7 pts) and PS=2 (2 pts). The soluble co-stimulatory molecules, GITR ($p<0.0011$), GITRL ($p< 0.0000$), CD27 ($p< 0.0039$), CD28 ($p<0.0069$), CD40 ($p< 0.0022$), CD86 ($p< 0.0000$) and ICOS ($p< 0.0157$), as well as the co-inhibitory molecules, PD-L1 ($p< 0.0002$), CTLA-4 ($p< 0.0002$) and BTLA ($p<0.0145$) levels were significantly lower in MBC pts compared to healthy controls. Conversely, the co-inhibitory molecules, TIM-3 ($p< 0.0001$) and LAG-3 ($p<0.0000$ were significantly higher than those of healthy controls. Other biomarkers with raised plasma concentrations included TLR ($p<0.0039$). Plasma CD80 ($p<0.0992$), PD-1 ($p<0.2325$), HVEM ($p<0.062,6$), RANTES ($p<0.4861$) CD163 ($p<0,8565$) and CD206 ($p<0,2454$) levels were not significantly different between the MBC pts and the healthy controls.

Conclusions: We identified lower levels of CD27, CD28, CD40, ICOS, GITR, GITRL, CD86, PD-L1, CTLA-4, BTLA, arginase, and TGF-β1, and higher levels of TIM-3 and LAG-3 immune checkpoint molecules in MBC pts compared to healthy controls. These results indicate that a down-regulation of soluble ICM pathways and an up-regulation of some inhibitory ICM pathways are associated with MBC patients. To our knowledge, this is the first study to describe soluble immune checkpoint molecules in MBC pts.

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491P Comparison of ctDNA profiles from HR+/HER2-low and HR+/HER2-0 advanced breast cancer patients

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Background: Despite the substantial progress in systemic treatment of hormone receptor-positive (HR+) breast cancer, a significant proportion of patients has dismal prognosis. A meaningful proportion of these patients has HER2-low disease. Circulating tumor DNA (ctDNA) profiles between HER2-low and HER2-0 have not yet been comprehensively investigated.

Methods: 67 plasma samples from 59 metastatic breast cancer patients (HR+/HER2-low, n=53; HR+/HER2-0, n=14) were collected either before starting 1st line or 2nd line treatment. Tumor fractions were assessed using an untargeted aneuploidy screening and expressed as z-scores (mFAST-SeqS). The mutational landscape of ctDNA was established using a 77-gene panel (AVENIO ctDNA Expanded). Tumor fractions, the number of somatic variants and variant allele frequencies (VAF) were compared between HER2-low and HER2-0 patients.

Results: HER2-low patients had significantly higher z-scores compared to HER2-0 patients (median 3.22 vs. 1.65, rank-sum p-value 0.025). In contrast, neither the highest nor the average VAF differed significantly between the two groups. HER2-low patients had a median of 3 detected variants (range 1-20), with a median of 2 clonal (range 0-9) and 1 subclonal (range 0-19) variants. HER2-0 patients presented with a median of 5 variants (range 1-12), including a median of 3 clonal (range 1-4) and 1 subclonal (range 0-8) variants. In contrast to previous reports, *PIK3CA* mutations were more prevalent in HER2-0 patients (57.1%) compared to HER2-low patients (35.8%), whereas *TP53* mutations were identified at the same extent with 28.6% in HER2-0 and 22.6% in HER2-low patients.

Conclusions: Our results suggest a significant difference in the tumor fractions in plasma between HER2-0 and HER2-low patients. Moreover, the mutational landscape of our cohort revealed differences from previous reports, indicating that further investigations are needed to elucidate and establish the distinct features of HER2-low breast tumors.

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492P Wound stress stimulation promotes lung metastasis of breast cancer by regulating CXCL12/CXCR4 axis through MDSC exosome miR-126a-5p

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Background: Surgery is one of the necessary treatment methods for breast cancer patients. However, wound caused by surgery is the main source of clinically related stress stimulation, and can promote tumor metastasis. Currently, as an important component of the tumor microenvironment, myeloid-derived suppressor cells (MDSC) have become a hotspot in the study of tumor metastasis.

Methods: We comprehensively explored the influence of wound stress on tumor growth, EMT related metastasis, and the recruitment of MDSC in the tumor microenvironment in a subcutaneous 4T1 tumor model.

Results: We found that wound stress stimulation promoted breast cancer growth and lung metastasis in mice, and enhanced the recruitment of stressed MDSC in the tumor microenvironment. The expression of Vimentin increased, suggesting EMT transformation. In vitro, bone marrow MDSC cells from mice undertaking stress stimulation promoted the EMT transformation in 4T1. The exosomes were extracted and the expression of mmu-miR-126a-5p was low in stressed MDSC exosomes. Mmu-miR-126a-5p overexpression suppressed tumor growth, lung metastasis and EMT transformation. Through the database screening of the target gene of mmu-miR-126a-5p combined with the results of sequencing analysis, CXCL12 was predicted to be the target gene of mmu-miR-126a-5p, which was verified by double luciferase reporting assay. CXCL12 and CXCR4 were highly expressed in the wound stress stimulation model, indicating mmu-miR-126a-5p induces breast cancer EMT transformation by targeting CXCL12/CXCR4 axis.

Conclusions: Here, we found that surgical stress stimulation can elicit the recruitment of stressed MDSC in the tumor microenvironment. Reduced exosome miR-126a-5p released by stressed MDSC leads to EMT transformation of tumor cells by attenuating the inhibition of CXCL12/CXCR4 axis in 4T1 cells and ultimately promotes increased lung metastasis. From the perspective of tumor microenvironment, these findings explain the phenomenon of increased lung metastasis caused by surgical stress stimulation and optimize new targets for MDSC, thus providing new ideas for breast cancer treatment.

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493P Identifying genomic changes in breast tumours that metastasise to the brain

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Background: The development of metastatic tumours after what appears to be a successful treatment of breast cancer remains a major problem. Many of these late-developing, secondary metastatic tumours occur specifically in the brain and metastatic brain tumours have very poor prognoses. Identifying genomic alterations in breast-to-brain metastatic tumours may provide new opportunities for treatment and prognosis.

Methods: Whole Exome Sequencing of 26 breasts to brain metastases was carried out on a high output V2 150 cycle flowcell (Illumina) as a 75 paired. Bioinformatic analysis was performed to identify recurrent mutations. Confirmation of mutated variants by Sanger sequencing. Functional analysis was conducted on a CRISPR_Cas9 knockout candidate gene in the MCF7 breast cancer cell line.

Results: Following analysis of Whole Exome Sequencing data, we identified $>$ 13000 nonsynonymous variants. To eliminate potential germline polymorphisms, variants with a MAF $\leq$1% were maintained. All variants were screened for their consequence on the protein product (via SIFT and Polyphen2), and the variants with scores related to pathogenicity were retained. This screening generated a list of 286 variants found across the 26 tumours analyzed. Protein domain analysis showed that most mutated variants are found within conserved protein domains. This sequencing identified frequent mutations in a gene encoding a member of the ARFGEF family of proteins. Furthermore, Following CRISPR_Cas9 knockout of this ARFGEF protein, the expression of neurotransmitter subunits was observed. This suggests that this protein may be implicated in the regulation of neuronal signalling, presenting a rationale for brain colonization by breast to brain metastatic tumour cells.

Conclusions: We expect that the identification of these commonly mutated genes may lead to the development of prognostic biomarkers that could be used to predict the risk of brain metastases from breast tumours and provide essential molecular information relating to the existing metastatic tumour. Additionally, these genes can contribute to the development of novel therapeutic approaches.

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494P Proviral insertion in murine 1 (PIM1) kinase expression and clinical outcomes in advanced breast cancer (ABC)

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Background: Prior and current data has shown PIM1 Kinase Expression (PIM1) in renal cell carcinoma (RCC) is associated with a poor prognosis.[1] CDK4/6 inhibitor (CDK4/6i) abemaciclib (A), but not palbociclib (P) may specifically target PIM1.[2] Given the differential efficacy of CDK4/6i in ABC without a biomarker beyond hormone receptor (HR+), we explored the relationship between PIM1 and patient outcomes. 1 An Analysis of PIM1 Kinase Expression and Clinical Outcomes in Renal Cell Carcinoma (RCC) Holder SL, et al. ESMO Congress 2023 Submission #2301 2 Small J, et al. Addition of abemaciclib to sunitinib induces regression of renal cell carcinoma xenograft tumors. Oncotarget. 2017 Jul 27;8(56):95116-95134.

Methods: Whole transcriptome sequencing (WTS) data in Caris Life Sciences real-world database breast cancer (BC) patient tumors were stratified by PIM1 expression quartiles and BC subtypes (HR+ and triple negative (TN]). Overall survival (OS; defined as time from diagnosis to last contact or death) and time on treatment (TOT) were obtained from insurance claims data.

Results: In 8,104 BC tumors, high PIM1 (Q4) had worse OS (27.3 mos) compared to low PIM1 (Q1, 41.9 mos). Median PIM1 transcripts were higher in TNBC vs HR+ (7.93 vs 4.46). In HR+ ABC, PIM1 Q4 was associated with different co-mutation frequencies (Table) and worse OS (Q1 57.7 vs Q4 45.3 mos, HR 1.28 95%CI=1.03-1.58 p=0.023). In TN ABC, PIM1 quartiles had similar co-mutation profiles, and no OS difference was noted (Q1 23.8 vs Q4 26.1 mos, HR=1.06 95%CI: 0.83-1.35 p=0.67). In HR+, PIM1 Q4 had significantly shorter TOT for A only (5.6 vs 2.6 mos, HR=1.68 95%CI: 0.99-2.82 p=0.049), no difference with P or R.

Table: 494P Co-mutation frequencies in hormone receptor-positive advanced breast cancer by PIM1 expression

HR+ BC WTS	PIM1-low (Q1), %	PIM1-high (Q4), %	p-value	q-value
TP53	31.7	47.0	0.0011	0.0017
PIK3CA	46.1	41.4	0.2952	0.3384
CDH1	18.5	11.4	0.0301	0.0402
CHEK2	0.4	4.3	0.0073	0.0105
ARID1A	15.7	4.2	0.0025	0.0037
PTEN	7.6	3.4	0.046	0.06
ESR1	4.6	2.9	0.3503	0.3946
MEN1	0.0	2.5	0.0141	0.0196
CDKN2A	0.0	2.1	0.0246	0.0332
BRCA2	3.4	1.7	0.2482	0.2893
BRCA1	1.3	1.7	0.7117	0.7454
Macrophage M2	4.9	5.8	0.0021	0.0031
Macrophage M1	2.7	4.1	0	0
PD-L1 (SP142) IC	20.9	34.6	9.00E-04	0.0014

Conclusions: Real-world data shows PIM1 correlates with high-risk phenotype in HR+ ABC. In contrast to the data reported in RCC, no CDK4/6i showed improved TOT among patients with Q4 PIM1, and other real-world variables may TOT limit analysis.

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495P Prognostic value of PIK3CA mutational status in tissue & plasma in HR+/HER2- breast cancer (BC)

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Background: *PIK3CA* mutations are described in about 30-40% of BC. They confer resistance to endocrine therapy and overall worse prognosis. Concordance between testing methods (tissue & plasma) are not widely studied. We aim to correlate tissue & plasma assays and to analyze the prognostic value of *PIK3CA* mutations in HR+/HER2- BC.

Methods: Retrospective and unicentric analysis of *PIK3CA* mutational status in tissue & plasma samples in patients (p) with HR+/HER2- BC from Feb/21 to Mar/23. *PIK3CA* test: Cobas®PIK3CA Mutation Kit. We correlated both diagnostic methods and analysed progression-free survival (PFS) in *PIK3CA* mutated (*PIK3CAm*) vs wild-type (wt).

Results: We analyzed 225 samples in 161p with HR+/HER2- BC (149 in tissue & 76 in plasma). *PIK3CA* mutations were detected in 62p (38.5%), of which 39.6% (59p) in tissue and 11.8% (9p) in plasma. *Hotspot* mutations: H1047X (45.7%), E545X (20%) and E542K (12.8%). Tissue & plasma correlation was conducted in 64p (M1 stage), with overall correlation rate of 70.3%. 19 cases (29.7%) were positive in tissue but not in plasma. 80p received treatment with CDK4/6 inhibitors + endocrine therapy. PFS was shorter in *PIK3CAm* vs wt (24m vs 30m; HR=1.39 [95%CI,0.7-2.4], p=0.25). A sub-analysis was performed based on exons 9 & 20, showing a significantly lower PFS in *PIK3CAm* exon 9 vs 20 population (9.7m vs 30.3m; HR=2.84 [95%CI,1.1-7.4], p=0.02). Although we observed a poorer PFS in p with visceral involvement in *PIK3CAm* (21.9m vs 30.1m; HR=2.82 [95%CI,0.6-12.3], p=0.14), in a multivariate analysis, mutations in exon 9 were an independent poor prognostic factor regardless visceral involvement; p=0.027.

Table: 495P

		Tissue		
		Mutated	Wild-type	**Total**
Plasma	**Mutated**	**9 (32.1%)**	0 (0%)	9 (14.1%)
	Wild-type	19 (67.8%)	**36 (100%)**	55 (85.9%)
	Total	28 (100%)	36 (100%)	64 (100%)
		Positive agreement: 9/28 (32.1%)		
		Negative agreement: 36/36 (100%)		
		Overall agreement: 45/64 (70.3%)		

Conclusions: Our results support the determination of *PIK3CA* in tissue as the diagnostic method of choice, although further studies are needed to assess the role of liquid biopsy in the detection of *PIK3CAm*. In our population, the presence of *PIK3CAm* confers worse prognosis in luminal BC, being significantly worse in mutation carriers in exon 9 regardless visceral involvement.

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496P Comprehensive genomic profiling of advanced HR+/HER2- breast cancer patients using liquid biopsy

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Background: Breast cancer is the most common cancer among women, and HR+/HER2- is the most frequent subtype. This type of cancer is characterized by a complex genomic landscape. However, obtaining tissue biopsies from patients with recurrent metastasis can be challenging. Moreover, previous liquid biopsy studies had limited success in detecting gene copy number loss. In this study, we present a comprehensive genomic profiling analysis of advanced HR+/HER2- breast cancer patients using liquid biopsy.

Methods: 76 patients with advanced HR+/HER2- breast cancer were retrospectively recruited, and blood samples were collected prior to receiving chemotherapy or CDK4/6 inhibitor treatment. The study applied PredicineCARE, a targeted NGS liquid biopsy assay, to detect somatic alterations in ctDNA of blood.

Results: In total, 370 somatic mutations and 85 copy number variants were identified in 76 patients. The most commonly altered genes included TP53 (38%), PIK3CA (37%), ATM (24%), ESR1 (22%), FAT1 (22%), RAD50 (22%), and BRCA2 (17%). Among all patients, 27 were Ki67 negative, 43 were Ki67 positive, and the Ki67 status of 6 patients was unknown. The prevalence of NBN gene variations was significantly higher in the Ki67 positive group than in the Ki67 negative group (Ki67+: 8/43 vs. Ki67-: 0/27, $p<0.05$). Seventeen patients had metastasis at the time of initial diagnosis, among which the prevalence of FAT1 variations was significantly higher than that of non-metastasis patients (metastasis+ 10/17 vs. metastasis- 7/59, $p<0.05$). Of all 76 patients, 39 were treated with CDK4/6 inhibitors, and 37 were treated with chemotherapies. Patients treated with CDK4/6 inhibitors had a prolonged overall survival time compared to those treated with chemotherapies. The median overall survival time of the two groups was 38.7 months (chemotherapy) vs. not reached after 34.2 months (CDK4/6 inhibitors), $p<0.001$.

Conclusions: This study presents a comprehensive analysis of the mutational landscape of advanced HR+/HER2- breast cancer patients using liquid biopsy. Additionally, it compares the molecular profiles of patients with different clinical features receiving diverse treatments, thus identifying potential biomarkers for prognosis and targeted therapies.

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497P Metastatic potential of the somatic alteration associated with TCA-cycle in breast cancer

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Background: Cancer metastasis is considered to occur through a complicated process in which cancer cells from the primary tumor migrate via the vascular and lymphatic systems. The mechanism of metastasis has previously been focused on the expression of molecules; however, their ability to form metastasis, and metastatic potential to target organs remains unknown. Because glucose metabolism is essentially active in brain tissue, FDG is substantially accumulated even in normal tissue. As a consequence, it is absolutely necessary for cancer cells to have the ability to survive in the brain microenvironment, in which glucose is unavailable. In this study, we investigated whether metabolic reprogramming of the TCA cycle, which enables energy production from sources other than glucose, plays a pivotal role in forming brain metastases (BM).

Methods: The genomic information was obtained from the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) Research-Use Portal. 2,629 cases of MBC who received cancer gene panel testing (Foundation One CDx (R)) between June 2019 and October 2022 were subjected to this analysis. The relationship between the somatic alteration associated with the TCA-cycle (TCA-alteration) and overall survival (OS) or BM incidence was examined.

Results: 221 patients (8.4%) had TCA-alteration. The median of OS was 6,217 days in TCA-alteration and 5,050 days in others (log-rank p=0.8377, n.s). TCA-alteration was discovered in 27 of 243 BM patients (11.1%) and 194 of 2,386 non-BM cases (8.1%) (p=0.11, n.s).

Conclusions: Despite the fact that metabolic reprogramming is necessary for metastatic potential, there was no significant difference in survival or the incidence of BM and TCA-alterations. In addition to genetic profiling, a metabolic approach will be necessary to understand the metabolic tumor microenvironment.

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CNS TUMOURS

498O INDIGO: A randomized, double-blinded, phase III study of vorasidenib versus placebo in IDH1 or IDH2 low-grade glioma

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Background: Grade 2 gliomas are slowly progressive brain tumours with poor long-term prognosis. Current treatments are not curative and can be associated with toxicities. Mutations in isocitrate dehydrogenase (IDH) 1 or 2 occur in nearly all grade 2 gliomas and are a disease-defining characteristic in the World Health Organization 2021 definition. Vorasidenib (VOR) is an oral, brain-penetrant, dual inhibitor of mutant (m)IDH1/2 enzymes.

Methods: In this double-blind phase 3 study, patients (pts) were randomized 1:1 to receive VOR 40 mg daily or placebo (PBO) daily in 28-day cycles, stratified by 1p19q status and baseline tumour size. Key eligibility criteria: age ≥12 y; Karnofsky performance scale (KPS) >80; residual or recurrent grade 2 mIDH1/2 oligodendroglioma or astrocytoma; measurable non-enhancing disease; no prior treatment for glioma with most recent surgery 1–5 years from randomization; and not in immediate need of chemotherapy/radiation. Primary endpoint: radiographic progression-free survival (PFS) by blinded independent review committee (BIRC). Key secondary endpoint: time to next intervention (TTNI).

Results: As of 6 Sep 2022 (2nd planned interim analysis data cut-off date), 168 pts were randomized to VOR and 163 to PBO (median age, 40.4 y; KPS=100, 53.5%; oligodendroglioma, 172; astrocytoma, 159; median time from last surgery to randomization, 2.4 y). Median follow-up was 14.2 mo. PFS by BIRC was significantly improved with VOR vs PBO (hazard ratio [HR] 0.39, 95% CI 0.27–0.56; 1-sided P=0.000000067). Median PFS: VOR, 27.7 mo; PBO, 11.1 mo. TTNI was significantly improved with VOR vs PBO (HR 0.26, 95% CI 0.15–0.43; 1-sided P=0.000000019). Median TTNI: VOR, not reached; PBO, 17.8 mo. In pts with IDH1-R132H variant (n=284, 85.8%) the HR for PFS by BIRC was 0.33 (95% CI 0.22–0.50). Adverse event of grade ≥3 elevated alanine aminotransferase was seen in 9.6% of pts with VOR (and 0% with PBO).

Conclusions: In the first randomized phase 3 study of a targeted therapy in grade 2 mIDH1/2 glioma, VOR significantly improved PFS by BIRC compared with PBO, with a manageable safety profile. Findings show the clinical benefit of VOR in pts for whom chemotherapy and radiotherapy are being delayed. (NCT04164901 funded by Servier Pharmaceuticals LLC).

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499O A phase II study to explore the efficacy and safety of FCN-159 in recurrent or progressive pediatric low-grade glioma (pLGG) with MAPK pathway-activated

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Background: The MAPK pathway over-activation is the primary driver in most of pLGG, mainly including $BRAF^{V600E}$, KIAA1549-BRAF fusion and $NF1^{mut}$ with limited therapeutic options available. FCN-159 is an oral inhibitor of MEK1/2 with highly potent selectivity, and is expected to be an efficacious targeted therapy of pLGG. A multi-center, single-arm phase II study was designed to evaluate safety and efficacy of FCN-159 in pediatric patients (pts) with recurrent or progressive LGG.

Methods: Pediatric pts with recurrent or progressive LGG were enrolled and received FCN-159 monotherapy continuously 5mg/m^2 once daily based on body surface area

(BSA). The primary endpoint was to assess preliminary efficacy of FCN-159 by RANO criteria.

Results: As the cut-off date of July 31th, 2023, 23 subjects have been enrolled. Median age is 8 years (range: 3-17) at study entry, 56.5% were female. All pts were identified as *BRAF* or *NF1* alterations (*BRAF*^{V600E} 12/23, 52.2%, *KIAA1549-BRAF* fusion 8/23, 34.8% and *NF1*^{mut} 3/23, 13.0%). At a median follow-up of 7.79 months, 22 pts were evaluated for efficacy: 6 partial response (PR, 27.3%, unconfirmed PR 3), 9 minor response (MR, 40.9%, unconfirmed MR 2), and 7 stable disease (SD, 31.8%). Among 23 pts, 22 pts (95.7%) experienced treatment-emergent adverse events (TEAEs), which were reported to be drug-related. Most common TEAEs (incidence $\geq$ 20%) included blood lactate dehydrogenase increased, α-hydroxybutyrate dehydrogenase increased, blood creatine phosphokinase increased, upper respiratory tract infection, paronychia and rash. Majority were grade 1 or 2, and 2 pts reported grade 3, no grade 4 or above reported. One pt experienced serious adverse event as liver function test abnormal. TEAEs leading to drug interruption were reported in 16 pts, and 10 pts were related to study drug. No TEAEs leading to drug dose reduction, discontinuation or death were reported.

Conclusions: The preliminary study results showed that treatment of FCN-159 was remarkably efficacious for pLGG pts. FCN-159 is well tolerated and easily manageable, without new safety signal observed. Long-term efficacy and safety follow-up are ongoing.

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500O Trotabresib (CC-90010) combined with concomitant temozolomide (TMZ) plus radiotherapy (RT) and adjuvant TMZ in patients (pts) with newly diagnosed primary glioblastoma (ndGBM): Updated results from a phase Ib/II study

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Background: Trotabresib (TROTA) is a novel bromodomain and extraterminal protein inhibitor that has shown brain tumor tissue penetration, encouraging tolerability and preliminary efficacy in combination with standard of care (SOC) concomitant TMZ + RT and adjuvant TMZ in pts with ndGBM. We present long-term follow-up for part A (dose escalation) and an update on part B (expansion) of the ph 1b/2 CC-90010-GBM-002 study (NCT04324840).

Methods: Study design has been previously described (Vieito et al. SNO 2022 . Abstr CTNI-21). Part B enrolled pts with IDH wild-type ndGBM; pts were randomized 2:1 to TROTA + SOC then maintenance TROTA (arm A) vs SOC alone (arm B).

Results: As of 20 Jan 2023, part A has closed with 32 pts enrolled (concomitant, n = 14; adjuvant, n = 18); part B has enrolled 136 pts (arm A, n = 91; arm B, n = 45). In part A, no new safety events were observed with longer follow-up; median follow-up was 21.6 mo (range 3.4—27.6). The most frequent grade (G) 3/4 treatment-related adverse event (TRAE) was thrombocytopenia (8/14 pts [57%] in the concomitant group and 9/18 pts [50%] in the adjuvant group). Efficacy in part A is shown in the table. At last follow-up, 8 pts (4 per group) remained on treatment, including 1 pt with ongoing complete response at cycle 24. In part B, the most common all-cause G 3/4 AE was thrombocytopenia occurring in 21/88 (24%) and 5/43 (12%) patients in arms A and B, respectively. TRAEs related to TROTA led to treatment discontinuation in 3 pts (arm A), and TRAEs related to TMZ led to discontinuation in 4 pts (2 in each arm); no treatment-related deaths reported. Enrollment of part B was recently completed; efficacy data are not yet mature.

Conclusions: Addition of TROTA to SOC followed by maintenance TROTA in pts with ndGBM was well tolerated with no new safety signals in parts A and B, and promising efficacy in part A. Follow-up is ongoing.

Table: 500O

Outcome	Concomitant TROTA: 15 or 30 mg/day* (n = 14)	Adjuvant TROTA: 15, 30 or 45 mg/day* (n = 18)
Median duration of treatment, weeks (range)	43 (10—102)	37 (6—121)
Median PFS, months (95% CI) Range	14.0 (5.8—NE) 2.1—22.3	10.3 (5.0—24.8) 0.03—26.5
Median OS, months (95% CI) Range	21.3 (11.1—NE) 3.4—22.7	21.6 (10.7—NE) 5.9—27.6
12-month OS rate, % (95% CI)	77 (44—92)	72 (46—87)

*Administered on days 1—4 of each 28-day cycle. 30 mg/day is the recommended phase 2 dose. NE, not estimable; OS, overall survival; PFS, progression-free survival.

Clinical trial identification: NCT04324840.

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501O Glasdegib in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Phase Ib/II GEINO 1602 trial

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Background: Glioblastoma (GB) resistance against anticancer therapies is enhanced by Smoothened (SMO) signaling. Glasdegib (GLG), a SMO inhibitor, may lead to improved efficacy of the Stupp scheme.

Methods: Newly diagnosed GB patients (pts) received GLG with standard radiotherapy (RT)/ temozolomide (TMZ) followed by maintenance with GLG monotherapy. The study was carried out in two phases. In phase Ib the primary objective was the recommended phase 2 dose (RP2D) in a 3+3 dose escalation strategy. The dose of 75 mg/QD of GLG was declared the RP2D. The primary objective in phase II was 15-m overall survival (OS) rate. The study established a futility threshold of 60% for 15-m OS to consider the trial positive; accrual required: 70 evaluable pts in phase II. Secondary objectives included progression-free survival (PFS) according to RANO criteria, safety, changes in performance status, pharmacokinetic and exploratory biomarker analysis.

Results: Between 2018 and 2020, 79 GB pts were enrolled, and 74 (98.7%) pts received GLG at 75mg/QD. The median age was 55 years (range: 28-78), 54% were male, 58.1% were ECOG 1, 39.2% were MGMT methylated, and 1 pts had an IDH1/2 mutation. Complete surgical resection was achieved in 35 (47.3%) pts. GLG treatment lasted a median of 6.9 m (range 0.7-24). 68 (91.9%) finalized concomitant period with RT/TMZ, 64 (86.5%) started adjuvant therapy with TMZ, 33 (51.6%) finalized adjuvant period, and 28 (37.8%) continued GLG monotherapy. 53 pts (71.6%) presented stable disease. After a median follow up of 14.8 m (range 0.7-36.4), mPFS was 7 m (95% CI: 6.1-8.6), and the 12-m PFS rate was 22.2% (95% CI: 14.4-34.2). The mPFS based on MGMT status was 8.4 m (95% CI: 6.5-16.9) and 7.3 m (95% CI: 4.9-9.1) for MGMT methylated and unmethylated respectively ($p = 0.044$). The mOS was 15.3 m (95% CI: 14-21.2). At data cut-off, 22 (29.7%) pts alive. The mOS was 25.6 m (95% CI: 16-NR) and 14.3 m (95% CI: 11.7-19) for MGMT methylated and unmethylated respectively ($p = 0.005$).

Conclusions: The addition of GLG to standard RT and TMZ showed preliminary efficacy for newly diagnosed GBM, with almost 30% pts still alive at data cutoff. Long-term survival will be updated. No new safety alerts were reported.

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502MO Target therapy matched to genomic alterations in patients with recurrent IDH wildtype glioblastoma: A real-life cohort analysis from Veneto Institute of Oncology, Padua (Italy)

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Background: Next-generation sequencing (NGS) allows to identify patients (pts) that may respond to target therapies (TT). Only a few data are available regarding TT for recurrent glioblastoma (rGBM).

Methods: We retrospectively analyzed a cohort of pts with rGBM treated with TT based on NGS profile obtained on formalin-fixed paraffin-embedded tissue samples. We identified 7 druggable alterations, classified according to ESCAT: BRAFV600E (IB), NTRK fusions (IC), FGFR1-3 alterations (IIB), ROS1 fusions, MET amplification/fusions, PIK3CA mutations and PTEN loss/mutations (IIIA).

Results: Between 03/20 and 03/23, 37 pts received TT. All pts received radiotherapy and temozolomide as first-line. Median line of TT was 3 (range 2-7). TT was dabrafenib/trametinib (9 pts), larotrectinib (2 pts), erdafitinib (4 pts), entrectinib (1 pt), vebreltinib (2 pts), capmatinib (1 pt), alpelisib (6 pts), ipatasertib+/-atezolizumab (12 pts). At data cut-off (05/23), 24 patients had died. In the entire cohort, median overall survival and progression-free survival (PFS) after starting TT was 8.19 and 2.11 months (mo), respectively. The dabrafenib/trametinib (D/T) subgroup had the longest median PFS (5.23 mo), a disease control rate (DCR) of 77%, an objective response rate of 22%, and a median duration of response of 22.5 mo. 7/9 pt had died and 2 are continuing D/T. The pt with ROS1-GOCP fusion maintained a complete response for 12 mo with entrectinib. A multifocal rGBM patient with PTPRZ1-MET fusion, identified by Caris MI-Transcriptome, had impressive PR after 8 weeks of vebreltinib in third-line during participation in APL-101-01 study (NCT03175224): duration of response is pending as TT is ongoing. Among the others, no complete/partial responses were detected. DCR was 67% in MET-inhibitors, 50% in larotrectinib and erdafitinib, 8% in ipatasertib+/-atezolizumab subgroups. No toxicities were reported with D/T. Among all pts, no grade 4 adverse events were observed and in any case, TT was interrupted for toxicity.

Conclusions: Our results confirm the activity of D/T in BRAFV600E mutant rGBM. We had a dramatic response to a MET inhibitor. Deeper explorations are needed in targeting FGFR e ROS1.

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503MO Real-world clinical and genomic characterization of gliomas: Predictive and prognostic insights

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Background: Based on our proposal for the first ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) classification for brain tumors [Mirallas et al. ESMO 2022] and the descriptive analysis of real-world data in gliomas [Mirallas et al. ASCO 2023], we aim to define the clinical actionability of molecular alterations (MA) detected by next-generation sequencing (NGS) in a multicentric glioma cohort.

Methods: Patients (pts) with glioma who had NGS at seven Spanish institutions were included between Jan 2018 and Dec 2022. For predictive associations, pts were classified into Tier1/2, Tier3/4 or wild type (WT) group according to their ESCAT score. Groups were compared using Kruskal-Wallis or Chi-squared tests. To explore prognostic markers, pts with grade 4 glioblastoma (GBM) IDH WT tested within 1 year from diagnosis who had TERT or TP53 genomic results were analyzed. Overall survival (OS) was estimated using the Kaplan-Meier method and Cox hazard ratio were fitted.

Results: Of 580 pts included, 567 pts (98%) underwent NGS testing. A total of 395/567 (71%) had a diagnosis of GBM and 165 (29%) harbored a Tier 1/2 MA. Median age was 51y (IQR: 39-61), 381 (67%) had ECOG $\geq$1, 223 (40%) were women, and 148 (26%) were 40 or younger. Most common MAs in the entire cohort were PI3KCA (29%), CDKN2A/B loss (28%), EGFR gain (26%), IDH1 (22.4%), EGFRvIII and ATRX (both 17%). Tier 1/2 MAs were more prevalent in younger pts (56% vs 10% in $<$40y vs $>$40y), non-GBM (65% vs 9% in non-GBM vs GBM), and TP53 mut (52% vs 24% in mutant vs WT) [all $p<0.001$]. Meanwhile, Tier 3/4 MAs were more typical for grade 4 gliomas with EGFR MAs (57% vs 2% in WT), TERT mut (55% vs 33% in WT) and CDKN2A/B loss (43% vs 13% in WT) [all $p<0.001$]. Among pts with grade 4 GBM-IDH WT, 53% had TERT mut and 26% had TP53 mut. In this subset of pts, median OS in case of incomplete resection (R1) was 29.5 months [95%CI 20-40.3] for those with

TERT WT and 17 months [95% CI 14-22] in TERT mut pts (p=0.01), but no differences in OS were found in TP53 mut vs WT pts.

Conclusions: Most common actionable MA were IDH, PIK3CA, EGFR, ATRX, suggesting NGS value for identifying potential candidates for targeted treatment. TERT mut was prognostic of worse OS in pts with grade 4 GBM-IDH WT after incomplete tumor resection.

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504MO Validation of a spectroscopic liquid biopsy for the earlier detection of brain cancer

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Background: Brain cancer has a very high fatality rate with only one third of patients surviving five years or more after a diagnosis. Early referral for brain imaging is crucial, but existing symptom-based referral guidelines inadequately stratify patients for brain imaging. Delayed detection leads to 62% of brain tumor patients receiving a diagnosis when they present to the emergency department (ED). A liquid biopsy could rapidly triage the symptomatic population in primary care. The most at-risk patients would be fast-tracked for urgent brain imaging, whereas those with a negative result can be monitored with routine follow-up.

Methods: We initially recruited 988 patients prospectively with non-specific symptoms associated with a brain tumor in NHS Lothian (Edinburgh, UK). Patient blood serum samples were analyzed using the Dxcover® Brain Cancer liquid biopsy. This technology utilizes infrared spectroscopy combined with a diagnostic algorithm to predict the presence of intracranial disease. Sensitivity analysis explored cost-effectiveness across possible combinations of sensitivity and specificity defined by the receiver operating characteristic (ROC) curve. Thereafter, an additional 500 patients were recruited for a verification study, in preparation for an EU-IVDR Performance Evaluation trial. In this clinical performance study, multiple sites across the UK and Europe will collect and analyze patient samples for clinical validation of the test.

Results: In our initial feasibility studies, the liquid biopsy reported an area under the ROC curve of 0.8. The algorithm detected 96% of the patients with brain tumors, and the diagnostic models can be tailored towards higher sensitivity (or specificity) depending on clinical priorities. We will also present the results of our verification study, the cost-effectiveness analysis and an interim analysis of the EU-IVDR trial at the meeting.

Conclusions: This simple, non-invasive blood test facilitates the triage and radiographic diagnosis of brain tumor patients, while providing reassurance to healthy patients. By decreasing the time to diagnosis, the morbidity from treatment can be reduced, which in turn would improve the quality of life of brain cancer patients.

Legal entity responsible for the study: Dxcover Limited.

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Disclosure: J.M. Cameron, A. Sala, J.J.A. Conn, G. Antoniou: Financial Interests, Personal, Full or part-time Employment: Dxcover Limited. D.S. Palmer: Financial Interests, Personal, Full or part-time Employment: Dxcover Limited; Financial Interests, Personal, Leadership Role: Dxcover Limited; Financial Interests, Personal, Stocks or ownership: Dxcover Limited; Financial Interests, Personal, Advisory Role: Dxcover Limited; Financial Interests, Personal, Research Funding, Dxcover Ltd, GSK, Endophotonics: Dxcover Limited. M.J. Baker: Financial Interests, Personal, Leadership Role: Dxcover Limited; Financial Interests, Personal, Full or part-time Employment: Dxcover Limited; Financial Interests, Personal, Stocks or ownership: Dxcover Limited.

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505MO A phase 0/Ib study of AZD1390 plus radiotherapy in recurrent glioblastoma patients

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Background: ATM inhibition has been hypothesized to potentiate the effects of radiation by preventing acute phase DNA damage repair, and a phase 1 trial of this combination in patients with GBM is ongoing (NCT03423628). To test this hypothesis, this phase 0/1b study aimed to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of AZD1390, an ATM inhibitor with BBB penetration, in combination with ex vivo radiation in patients with GBM (NCT05182905).

Methods: Recurrent GBM patients received 3 days of AZD1390 prior to planned resection at 2-4, 4-6 or 23-25 hours following the final dose. Tumor tissue, cerebrospinal fluid (CSF), and plasma were collected. Total and unbound drug concentrations were measured using validated LC-MS/MS methods. A PK 'trigger' determined eligibility for the therapeutic expansion phase. ATM inhibition was assessed via *ex vivo* radiation and quantification of pRAD50 levels compared to non-radiated control. Patients exceeding the PK threshold were eligible for an expansion phase of study drug plus radiotherapy followed by maintenance regimen.

Results: In 12 patients treated to date, AZD1390 was consistently measured in the Gd-non-enhancing tumor region. All patients (n=12) exceeded the PK threshold to qualify for the expansion phase of the study. With 5Gy ex-vivo radiation of surgical specimen, pRAD50 expression was significantly suppressed in AZD1390 treated patients compared to untreated controls (median 2.1% vs 34.8%, average 94% reduction, $p<0.01$). Median 6-month progression-free survival has not been reached at a median clinical follow-up of 4.4 months.

Conclusions: AZD1390 is well-tolerated in recurrent GBM patients, achieving pharmacologically relevant concentrations in non-enhancing tumor tissue, and substantially suppressing induction of pRAD50 levels *ex vivo* post-radiation. This is the first pharmacodynamic evidence that AZD1390 may be a potent radio-potentiator in patients with GBM.

Clinical trial identification: NCT05182905.

Legal entity responsible for the study: Neurotrials.

Funding: Barrow Neurological Foundation, Ben and Catherine Ivy Foundation.

Disclosure: A. Tovmasyan: Financial Interests, Personal, Royalties: Biomimetix. All other authors have declared no conflicts of interest.

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506MO A phase I dose-expansion cohort of SYHA1813, a vascular endothelial growth factor receptor (VEGFR) 1-3 /colony-stimulating factor 1 receptor (CSF1R) inhibitor, in patients (pts) with recurrent meningioma

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Background: SYHA1813 is a highly potent inhibitor, mainly against VEGFR1-3/CSF1R, and exerts synergistic anti-tumor effects by blocking tumor angiogenesis and modulating tumor microenvironment. Here, we report early findings from pts treated with SYHA1813 in the recurrent meningioma cohort.

Methods: Adult pts (Karnofsky performance status $\geq$ 60) with recurrent histologically confirmed meningioma not amenable to surgery or radiotherapy were enrolled and treated with 15mg or 20mg SYHA1813 once daily. The primary endpoints were objective response rate (ORR) and the 6-month progression-free survival rate (PFS-6) per Response Assessment in Neuro-Oncology Criteria for meningioma. The secondary endpoints included incidence, type, and severity of adverse events, graded by Common Terminology Criteria for Adverse Events (Version 5.0).

Results: As of Apr. 12, 2023, 11 eligible pts (5 males) with a median age of 50 (range 34-76) were enrolled, including 1 with World Health Organization (WHO) grade I tumor, 6 WHO grade II, and 4 WHO grade III. The median number of prior surgeries were 2 (range 1-4). With a median treatment duration of 1.45 months (range 0.23-6.24), ORR was 45.5% [95% confidence interval (CI) 16.8%—76.6%], with 1 partial response (PR), 2 minor response (MR), 1 unconfirmed PR and 1 unconfirmed MR. Tumor regression in target lesions was observed in 10 out of 11 pts, of which 6 reached $\geq$ 25% reductions in tumor size. PFS-6 was 75.8% (95% CI 30.5%-93.7%). All

pts experienced treatment-emergent adverse events (TEAEs), of which 6 (54.5%) were ≥ grade 3, and all of them were recovered within 7 days. Of these ≥ grade-3 TEAEs, hypertension occurred in ≥ 2 patients. One patient with a complex surgery history developed a serious TEAE, grade-4 intracranial hemorrhage, which was resolved quickly after interventions. No grade-5 TEAEs were reported.

Conclusions: SYHA1813 showed encouraging objective responses with a well-tolerated safety profile in pts with recurrent meningioma.

Clinical trial identification: ChiCTR2100045380.

Legal entity responsible for the study: CSPC Pharmaceutical Group Limited.

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507MO REGOMA-OS: A large Italian multicenter, prospective, observational study analyzing regorafenib efficacy and safety in recurrent glioblastoma patients

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Background: In the randomized phase 2 REGOMA trial, regorafenib (REG) showed promising activity in recurrent glioblastoma (GBM) patients (PTS); subsequently, in Italy the National Health System has permitted the reimbursement of the REG as second-line treatment. We performed a large multicenter, prospective and observational study to confirm REGOMA data in a real-world setting.

Methods: Major inclusion criteria were: histologically confirmed diagnosis of GBM according to WHO 2016 and relapse after Stupp treatment, good performance status (ECOG PS 0-1), good liver function. REG was administered at the standard dose of 160mg/die for 3 weeks on/1 week off. Brain MRI was performed within 14 days before starting REG and every 8-12 weeks, subsequently. The primary endpoint was overall survival. RANO criteria were used for response evaluation, CTACAE v. 5 for adverse events.

Results: From Sept 2020 to Oct 2022, 192 recurrent GBM PTS were enrolled from 29 Cancer Centres in Italy: median age was 58ys (IQR 52.8-67.0), 68% male, ECOG PS was 0 in 85 (44%), 115 PTS (60%) undertook steroids at baseline. MGMT was methylated in 43%, IDHwt in 92%. Median follow-up was 16.6 months (IQR 12.6-19.6). Median OS was 8.2ms (95% CI 6.5-9.6), 12ms-OS was 34.7% (95%CI 27.2-42.4); median PFS was 2.6ms (95%CI 2.3-2.9), 6ms-PFS was 14.3%. The radiological response was PR and SD in 12 (8%) and 25 (16%) PTS. 77 (44%) PTS received third-line therapy. The median of REG cycles per patient was 3 (IQR 2.0-4.0). Grade 3-4 adverse events (AE) were reported in 53 (28%) PTS; reduction/delay and permanent discontinuation due to AE in 36% and 8% of PTS. No death was considered as treatment-related AE.

Conclusions: Compared to the REGOMA trial, this large Italian multicenter, prospective and observational real-world trial confirmed the results in terms of overall survival with a good toxicity profile of REG in recurrent GBM PTS.

Clinical trial identification: NCT04810182.

Legal entity responsible for the study: Veneto Institute of Oncology IOV-IRCCS.

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508MO Spatial remodeling of the immune tumor microenvironment after radiotherapy and CXCL12 inhibition in glioblastoma in the phase I/II GLORIA trial

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Background: Radiotherapy (RT) causes upregulation of CXCL12, a chemokine facilitating recruitment of tumor-associated macrophage (TAM) precursors promoting neovasculogenesis and the formation of an immunosuppressive tumor microenvironment (TME). Here, we report an in-depth analysis of the immune TME (iTME) in patients of the multicentric phase 1/2 GLORIA trial (NCT04121455) which combines RT and CXCL12 inhibition with the RNA-Spiegelmer NOX-A12.

Methods: We analyzed tumor tissue of 10 GLORIA patients with newly diagnosed, incompletely resected (n=8) or biopsied (n=2) GBM with ECOG≤2 lacking MGMT promoter methylation. All patients received standard RT and escalating dose levels of continuous (24/7) i.v. infusions of NOX-A12. Two patients underwent re-surgery, whereas one was diagnosed with pseudoprogression (PsP) and one with recurrence. To characterize the iTME, we used highly multiplexed immunofluorescence (mIF) imaging. As a comparison to the GLORIA cohort, we investigated the pre/post-therapeutic iTME of reference patients receiving standard-of-care (n=7) treatment.

Results: In all samples analyzed, CXCL12 co-localized with endothelial cells. Unlike in the reference cohort, matched pre-/post-treatment tissue analysis of the patient with PsP revealed endothelial and gliomal CXCL12 depletion following treatment with NOX-A12, confirming the mode of action of the drug. Both post-treatment GLORIA samples showed intralesional clustering of activated $CD8^+$ T cells. In the non-responder diagnosed with recurrence, a pro-tumorigenic spatial rearrangement of the iTME was observed, characterized by a presence of M2-like TAMs in the proximity of the perivascular T cell clusters, confirmed by nearest neighbor analysis. None of the reference patients showed similar alterations of the iTME.

Conclusions: m IF of matched pre-/post-therapy tissue samples from the ongoing GLORIA trial supports the proposed modes of action of RT and NOX-A12 counteracting vasculogenesis and modulating the iTME reflected through its spatial rearrangement. This opens up the question of a targetable, compartment-specific role of CXCL12 to be further assessed.

Clinical trial identification: NCT04121455.

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509P Spatial analysis of tumor-associated macrophages within the tumor microenvironment of primary tumors and matched brain metastases

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Background: Novel immunotherapies (IO) show mixed responses, particular in context of brain metastases (BM). We therefore aimed to investigate the density of tumor-associated macrophages (TAM) in primary tumors (PT) and matched BM tissue samples.

Methods: We retrospectively identified patients who received resection of PT and BM between 01/1990 and 10/2022. Immunohistochemical staining and density quantification (positive cells/mm^2) of TAMs (CD68$^+$ & CD163$^+$) was performed. Generated heatmaps were analyzed for heterogeneity as quantified by Shannon Entropy.

Results: We included 62 patients (61.3% male, 38.7% female) with matched samples: 46/62 non-small cell lung cancer, 8/62 breast cancer (BC), 8/62 renal cell carcinoma. Median CD163$^+$ TAM density was 733 cells/mm^2 (range 105-5110 cells/mm^2) in BM and 407 cells/mm^2 (range 52-1786 cells/mm^2) in PT. Median CD68$^+$ TAM density was 924 cells/mm^2 (range 119-5521 cells/mm^2) in BM and 744 cells/mm^2 (range 99-2164 cells/mm^2) in PT. CD163$^+$ TAM density was significantly higher in BM compared to PT over all entities ($p<.05$). For CD68$^+$ TAM, a significant difference was only observed in BC with higher density in BM than in PT ($p=.016$). Median difference in CD163$^+$ TAM density between PT and BM was 163 cells/mm^2 (range -1258-3602 cells/mm^2) and 348 cells/mm^2 (range -1390-4390 cells/mm^2) in CD68$^+$ TAM. No correlation between TAM density difference and clinical outcome (time to BM and OS from BM) was observed ($p>.05$). Median entropy for CD163$^+$ TAM in BM was 15.8 (range 1.5-76.2) and 14.3 (range 0.5-45.2) in PT. Concerning CD68$^+$ TAM, median entropy was 19.9 (range 1.8-88.7) in BM and 23.9 (range 1.9-54.9) in PT. A significant difference in entropy was only observed in BC as primary breast cancer CD68$^+$ TAM showed lower entropy indices ($p=.02$). Median difference in entropy between PT and BM was 3.4 (range -34.8-41.3) in CD163$^+$ TAM and 1.41 (range -34.4-39.9) in CD68$^+$ TAM. No correlation of TAM entropy and clinical outcome (time to BM and OS from BM) was observed ($p>.05$).

Conclusions: TAM density is significantly higher in BM compared to PT. In BC, higher CD68$^+$ TAM entropy was observed in BM, indicating higher herterogeneity. Further analyses with enlarged cohort and additional immune cell markers are ongoing.

Legal entity responsible for the study: The authors.

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510P CD47 regulates cellular and metabolic plasticity in glioblastoma

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Background: Glioblastoma (GBM) is the most common and aggressive form of primary brain tumor with poor survival rates. While conventional therapies including surgery, chemotherapy, and radiotherapy extend patient survival, recurrence within 6-9 months is common with no effective therapy. Thus, novel treatment strategies that have greater specificity and efficacy are warranted. Analyzing the Ivy Glioblastoma Atlas Project's transcriptomics data based on anatomic structures (http://www.brain-map.org/), we identified that CD47, a ubiquitously expressed receptor known to block phagocytosis by interacting with SIRPα on myeloid cells, is abundantly expressed on the leading invasive edge of GBM patient tumors. Increased expression of CD47 is also associated with poorer survival in GBM patients. Importantly, the role of CD47 in GBM besides promoting immune escape is not well understood. Therefore, we propose to identify cell-intrinsic mechanisms that CD47 regulates in GBM.

Methods: To identify intracellular mechanisms regulated by CD47 in GBM, we created a CD47 CRISPR knock-out (KO) cell line using U87 GBM cells. Using the control and CD47 KO cells, we performed a clonogenic assay and transwell migration assay to assess changes in cellular phenotype. Subsequently, we performed bulk RNA-seq followed by gene set enrichment analysis to identify pathways regulated by CD47. To address changes in cell metabolism, a seahorse assay followed by non-targeted metabolomics and metabolic flux analysis was also conducted.

Results: We have found that loss of CD47 in GBM cells reduces cell migration and proliferation in the absence of myeloid cells, suggesting a cell-autonomous function of CD47. Consistently, gene set enrichment analysis in control and CD47 KO GBM cells indicates that cell polarity, axonal guidance, cell differentiation, and cell proliferation pathways are driven by CD47 signaling. Furthermore, our data shows that CD47 regulates metabolic plasticity. We found that CD47 KO cells exhibit elevated levels of several glycolytic metabolites which correlates with increased mitochondrial spare respiratory capacity and mitochondrial biogenesis.

Conclusions: We have identified a novel immune-independent function of CD47 in linking cellular and metabolic plasticity in GBM.

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511P Immunodisruptive conditions and glioma diagnosis: 24-year retrospective study of an under-recognized scenario

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Background: Disruption of the immune system is known to favor carcinogenesis and cancer breakthrough. Gliomas constitute de most prevalent primary malignant brain tumors. We aimed to study the occurrence of immune disruptive conditions (IDC) in patients with gliomas at our institution.

Methods: Retrospective study of patients (pts) diagnosed with a glioma at Hospital Clínico Universitario San Carlos, Madrid (Spain). IDCs included autoimmune diseases (AID), organ transplantation (OT) requiring chronic immunosuppressive therapy (IST), and hematological malignancies (HM). A descriptive study, as well as time since IDC, time under IST, and progression-free survival (PFS) and overall survival (OS) since glioma diagnosis were analyzed.

Results: Within the period January 1999 – April 2023, among 481 patients diagnosed with a glioma, 30 (6.2%) patients harbored IDCs. Male/Female: 14/16. Age: 63y (32-83). WHO 5th Ed.: IDH-WT GB: n=26 (MGMTmeth: 50%, MGMTunmeth: 50%), IDH-MUT Astro: n=3, Pleomorphic xanthoastro: n=1. Frontal: n=14, Temporal: n=8, Parietal: n=6. Unilobar: n=23, Bilobar: n=4, Trilobar: n=1. Right: n=8, Left: n=19, Bilateral: n=3. Resection: GTR=8, STR=1, Partial=3, Biopsy=14. RTx=20 pts, CRTx=18, Adj CTx=13. Median PFS and OS since diax were 9 and 10 months (m), respectively. No. of IDCs: 1 (n=21 pts), $\geq$ 2 (n=9 pts). IDC type: AID (n=27 pts) among which: endocrine (4: Addison, Hypothyroidism, Hashimoto's thyroiditis), respiratory (7: asthma, sarcoidosis, alergic rinoconjunctivitis), cutaneous (7: chronic eccema, psoriasis), neurological (4: multiple sclerosis, Guillain-Barré), digestive system (2: inflammatory bowel disease), rheumatological (13: Horton's disease, Sjöegren's syndrome, systemic lupus erithematosus, uveitis, vasculitis); HM (1: chronic lymphocytic leukaemia); OT (2: renal). IST for IDCs used in 20 pts (systemic IST in 17). Median time since IDC: 101 m (10-411). Median time under IST: 108 m (0-283).

Conclusions: Within a large 24-year long retrospective series, a minority of pts with glioma harbored an IDC, most commonly rheumatological, respiratory, or cutaneous. Studies should be conducted to unveil if gliomas occurring in pts with IDCs are biologically and immunologically distinct.

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512P Heterozygous germline Fanconi anemia-related gene mutations increase susceptibility to central nervous system germ cell tumors

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Background: Central nervous system germ cell tumors (CNS GCTs) are a group of rare heterogeneous CNS tumors. CNS GCTs are usually in midline location and mainly affect children and adolescents. The incidence of CNS GCTs is higher in Asia (11%) than that in Western Europe (4%) with a male predominance. The different tumor distribution demographically and high incidence in East Asia suggests a probable genetic background.

Methods: We collected samples including tissue and blood leukocyte control from 17 patients with CNS GCTs. All samples were tested using a 551-cancer related gene profiling, and somatic mutations, TMB, MSI and germline mutations were analyzed. The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics guidelines. We screened out the pathogenic and likely pathogenic (P/LP) mutations of germline mutations and calculated the relative risk (RR) in our cohort compared to that in a control population (gnomAD). Then the relationship between mutation characteristics and clinical features were further analyzed, as well as the correlation with patient prognosis.

Results: In 17 patients with CNS GCTs, 4 patients (4/17) were found harboring germline pathogenic or likely-pathogenic mutations, respectively, in *FANCA, FANCD2, FANCE, SDHA*. All the four genes are Fanconi anemia (FA)-related genes. The RR of total FA mutations in patients with CNS GCTs was 21.589 (95% CI, 28.934-257.728; P value, 3.22E-07) compared to gnomAD controls. Then the 17 patients were divided into two groups, the FA group (with FA-related gene heterozygous germline P/LP mutations) and the non-FA group (without P/LP mutation). The results showed that pathological classification (P=0.00588) and site of lesion (P=0.00714) were significantly different in the two groups. There was no significant difference in gender, age and TMB between the two groups. The 4 recurrent patients were all in the non-FA group, but there was no statistical difference in prognosis between the two groups.

Conclusions: FA-related gene germline P/LP mutations increase the susceptibility to CNS GCTs. Moreover, the germline FA mutation may be related to the pathological subtype, site of lesion and prognosis, which needs to be verified with a large sample.

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513P Cyclin pathway in oligodendrogliomas IDH mut and 1p/19q codeleted

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Background: Oligodendrogliomas (OLIG), are rare tumors of the central nervous system. The current WHO classification requires the presence of IDH mutation and 1p/19q codeletion. Grade 3 OLIG presents a higher number of chromosomal alterations than grade 2, indicating that progression to malignancy is associated with the acquisition of multiple genetic abnormalities. An increased incidence of deletions in the short arm of chromosome 9 has been found. CDKN2A is located on chromosome 9 and encodes for 2 proteins p16 (or p16INK4a) and p14arf. Previous studies have found CDKN2A involvement at 9p21 with homozygous deletion in 25% of grade 3 oligodendrogliomas. Many of these studies were performed in a series of patients with OLIG diagnosed by histopathological criteria, but not by current molecular criteria. This study analyzed the cyclin pathway in a series of oligodendrogliomas with IDH mutation and 1p/19q codeletion.

Methods: Cases with a morphological diagnosis of oligodendroglioma were identified (182 cases). This same cohort was subsequently reclassified according to current WHO criteria (91 cases). The median follow-up of this case series was 9 years. In the reclassified cohort, p16, pRb and D1 cyclin were studied by immunohistochemistry.

Results: There was no p16 expression in 16 of 71 cases (22.5%). The absence of expression was significantly associated with a worse prognosis. Median OS in the absence of p16 of 9 years (95%IC 9.36-17.35) vs 13.35 years when there was p16 expression (95%IC 9.36-17.35) p=0.023 HR 0.41. In grade 2 oligodendrogliomas, the median OS was 10.86 vs 13.35 p=0.754, and in grade 3, 4.76 vs 17.49 p=0.010. According to a multivariate analysis including data on the extent of surgery, tumor grade, adjuvant treatment, and p16, only the absence of p16 showed a statistically significant prognostic value (p=0.034). There was no correlation between the loss of p16 and the presence of microvascular proliferation, necrosis, or uptake on MRI. In grade 2 oligodendrogliomas, high cyclin D1 expression was associated with worse survival; 12.3 vs 0.78 years (p=0.001).

Conclusions: Loss of p16 is more frequent in grade 3 than in grade 2 oligodendrogliomas and is associated with worse survival.

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514P Immunophenotypic profile of glioblastoma microenvironment: A cohort study

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Background: Glioblastoma (GBM) is the most aggressive brain tumor in adults and is characterized by an immunosuppressive microenvironment. Different factors shaping its tumor microenvironment (TME) regulate tumor initiation, progression, and treatment response. The aim of this study was to characterize the TME and the expression of immunomodulatory targets in patients (pts) with GBM.

Methods: Immunohistochemistry for CD3, CD4, CD8, programed death ligand 1 (PD-L1) and programed death 1 (PD1) was performed on surgical tumor specimens from pts diagnosed with GBM, according to the CNS WHO 2021 criteria. A descriptive statistic was applied to the data set. OS and PFS were estimated through the Kaplan-Meier method and analyzed by the means of a log-rang test.

Results: We included 30 pts, with median age of 59.8 years [range 40.2-69.1 years]. All pts were treated with surgery followed by temozolomide concurrent with and adjuvant to radiotherapy. MGMT was methylated in 46.7% of pts and unmethylated in 53.3% of pts. Overall CD4+ lymphocytes, both intratumoral and perivascular, were significantly more represented than CD8+ lymphocytes in the GBM TME (p= 0.01). A lower density of CD4+ lymphocytes (<10%) was found to be a favorable prognostic factor for GBM outcome (p= 0.02). Pts with MGMT methylated and unmethylated tumors exhibited a distinct TME composition, with a significant higher number of perivascular CD8+ lymphocytes (p= 0.002), intratumoral CD8+ lymphocytes (p= 0.0024) and perivascular CD4+ lymphocytes (p=0.014) in MGMT unmethylated compared to MGMT methylated tumors. PD-L1 expression in GBM cell surface was 13.3% (n=4) and PD1 was expressed in 30% (N=9) of the GBM-infiltrating T cells, with predominantly perivascular distribution.

Conclusions: CD4+ lymphocytes lower density (<10%) correlates with improved survival. Given the small numbers of our cohort, the prognostic value of CD4+ lymphocytes density needs to be validated in large-scale studies. MGMT methylated and unmethylated tumors exhibit different immune profiles, reflecting the different biology of these tumors. The expression of PD-L1 and PD1 in GBM patients is confined to a small subpopulation.

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515P A MRI-based radiomics model for predicting the response to anlotinb combined with temozolomide in recurrent malignant glioma patients

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Background: Anlotinib is a multitarget anti-angiogenic drug that combined with temozolomide (TMZ) can effectively prolongs the overall survival (OS) of recurrent malignant glioma(rMG), but some patients do not respond to anlotinib combined with TMZ. These patients were associated with a worse prognosis and lack effective identification methods. Therefore, there is a great need to differentiate patients who are likely to have a good response to anlotinb in combination with TMZ from those who are not, so as to provide more personalized targeted therapy and free patients who might have a poor treatment response from risk of those severe side effects and high cost.

Methods: A total of 53 rMG patients (42 in training cohort and 11 in validation cohort) receiving anlotinib combined with TMZ were enrolled. A total of 3668 radiomics features were extracted from the recurrent MRI images. Radiomics features are reduced and filtered by hypothesis testing and LASSO regression. Eight machine learning models construct the radiomics model, and then screen out the optimal model. The performance of the model was assessed by its discrimination, calibration, and clinical usefulness with validation.

Results: 53 patients with rMG were enrolled in our study. 34 patients displayed effective treatment response, showed a higher survival benefits than non-response group, the median PFS was 8.53 months versus 5.33 months(P=0.06) and the median OS was 19.9 months and 7.33 months (P=0.029), respectively. Three radiomics features were incorporated into the model construction as final variables after LASSO regression analysis. Compared with other models, LR model has the best performance with an AUC of 0.929 in validation cohort, which can effectively predict the response of rMG patients to anlotinib in combination with TMZ. The calibration curve confirmed the agreement between the observed actual and prediction probability. Within the reasonable threshold probability range (0.38-0.88), the radiomics model shows good clinical utility.

Conclusions: The above-described radiomics modle performed well, which can serve as a clinical tool for individualized prediction of the response to anlotinb combined with TMZ in rMG patients.

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516P Building a new prognostic score for patients with central nervous system (CNS) tumors enrolled in early phase clinical trials

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Background: Patients (pts) with primary CNS tumors are often excluded from early phase clinical trials because of doubts regarding the blood brain penetration, adherence to study treatment and use of corticosteroids in immunotherapy clinical trials. Scores built to help selectection of pts that would be good candidates for early phase clinical trials such as the Royal Marsden Score (RMH) or the Gustave Roussy Immune Score (GRIm) are not relevant to pts with primary CNS. We aimed to determine factors associated with prognosis to help physicians referring pts.

Methods: We conducted a retrospective analysis of all pts treated for a CNS tumor and enrolled in an early phase clinical trials at the Drug Development Department at Gustave Roussy between January 2013 and December 2022. Descriptive statistics were used to present the population and a multivariate Cox regression was used to determine prognostic factors in uni and multivariate analysis on overall survival (OS).

Results: A total of 108 pts were included in the study. Median age was 47 (18-82), most males (F/M=35/73), 44% were symptomatic in the three months before study entry, 46% had a multifocal disease at C1D1. The ratio between low grade glioma (LGG) and high grade glioma (HGG) according to the new molecular classification of 2021 were 24/84. Molecular alterations were: IDH mutation (59%), MGMT methylation (14.2%, 94 unknown), 1p19q codeletion (19.7%, 53 unkown). Targeted therapies were the most common drug used (44%), followed by immunotherapy (33.%) and epigenetic drugs (8.4%). Pts harbouring a BRAF mutation treated with a specific target therapy were 12; pts with an FGFR mutation or fusion treated in the same setting were 18. Median progression free survival (PFS) was 9.7 months, 40% of pts were progressing at 3 months. Altogether, 34% of pts were alive at 6 months. In multivariate analysis, lymphocyte counts ≥900/mm3 (HR=0.7 95% CI 0.46 - 1.07), absence of steroids at baseline (HR=2.3 95% CI 1.5 - 3.5), absence of antiepileptic drugs at baseline (HR=2.06 95%CI 1.2 - 3.7) were associated with a better overall survival.

Conclusions: Corticosteroid use, lymphocyte count and use of antiepileptics will be used to build a new score that will be presented at the conference.

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517P Differentiating IDH-wildtype and IDH-mutant high grade gliomas with deep learning

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Background: Glioblastomas (GBM) are the most frequent primary malignant brain tumours affecting adults. Over 85% of GBM cases are *IDH-wildtype (IDHwt)*, which carry an expected survival of around 1 year. A small number of cases have the morphological features of GBM but harbour an *IDH-mutation (IDHmut)*. These cases, designated grade 4 *IDH-mutant* astrocytoma under the 5th edition WHO CNS classification, are important to identify due to superior prognosis and implications for clinical management. In practice, most neuropathology departments use immunohistochemistry (IHC) to determine *IDH* status. IHC is not infallible, however, and requires additional tissue and laboratory work. Multiple studies have demonstrated that Deep Learning (DL) can predict molecular alteration status directly from routine pathology whole slide images (WSI). Validating the use of AI for such applications has the potential to improve diagnostic precision and add further value to a digital pathology workflow. We hypothesise that DL can accurately differentiate *IDHwt* and *IDHmut* high-grade gliomas directly from WSI.

Methods: We used an attention-based multiple-instance learning (attMIL) approach and applied it to an international biorepository of digitised neuropathology images. Our primary cohort was obtained from University College London (UCL), through collaboration with BRAIN UK and comprised 774 WSIs. The Cancer Genome Atlas (TCGA) was used as a secondary cohort for external validation and comprised 332 WSIs.

Results: We found that DL was able to predict *IDH* status in high-grade glioma images. On internal cross validation in the UCL dataset, this gave an area under the receiver operating characteristic curve (AUROC) of 0.92. These findings were sustained on external validation in the TCGA dataset, with an AUROC of 0.79.

Conclusions: In the future, DL-based image analysis could be used as a screening tool in the setting of a digital pathology diagnostic environment to guide Pathologists on the targeted use of IHC.

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518P Artificial intelligence real-world applications in pediatric neuro-oncology: The AICCELERATE project

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Background: Artificial Intelligence (AI) holds the promise to transform medicine during diagnosis, management and therapy of diseases. The AICCELERATE project will introduce an operational approach to develop AI-enabled digital solutions to improve medical processes by creating a digital twin. In our study, we performed the first pilot application of the AICCELERATE project at Bambino Gesù Children's Hospital in Rome (OPBG). The aim of our study is to design a supervised machine learning (ML) model to predict time to surgery and time to diagnosis based (outputs) on time from admission to first consultation and imaging (inputs) in newly diagnosed pediatric patients.

Methods: We included pediatric patients with new diagnoses of brain tumors, treated in OPBG from December 2017 to December 2022. We collected from EHR the following data: age and sex, start and end date of the first admission, department of hospitalization, consultations and radiological imaging date, diagnosis, and surgery date.

Results: We included 48 patients with a pediatric brain tumor, with a mean age of 8.6 years. We used a multiple linear regression model, which does not require large datasets such as more complex models. Our analysis showed that delayed consulting and imaging led to a delayed diagnosis, with the consulting presenting a higher importance than the imaging. This result was validated by the model's estimated regressors coefficients, with the consulting factor being assigned a larger weight β_C=1.81 than the imaging factor β_I=-0.33. Similarly, we observed that delayed consulting and imaging led to a delayed surgery, estimating a higher coefficient for the consulting β_C=0.71 than the one estimated for the imaging β_I=-0.06. While the ML model achieved a reasonable performance in both frameworks, the time to surgery was predicted with a lower MAE 4.45±0.87 compared to the diagnosis MAE of 6.74±0.95.

Conclusions: This preliminary study conducted in a small number of patients, suggests that decreasing time to consultation can shorten time to surgery in children with brain cancer. As the AICCELERATE is ongoing, more accurate models will be developed and will help to better understand how to optimize the journey of children with brain cancer.

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519P The landscape of PDGFRA mutation in Chinese patients with glioma

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Background: Glioma originated from the intracranial glial cells, represents the most aggressive subtype of brain tumors, with few treatments available. Platelet-derived growth factor receptor alpha (*PDGFRA*) is the second most frequently mutated tyrosine kinase receptor in glioblastoma (GBM). Mutations in *PDGFRA* are potential therapeutic targets. Here, we explore the *PDGFRA* mutation profile in Chinese adult glioma patients.

Methods: Next-generation sequencing (NGS) with 131-gene profiling was performed to analyze postoperative tissue from 4294 Chinese adult glioma patients from 2019 to 2023. Somatic mutations and copy number variations in tumor samples were detected using the NGS method according to standard operating procedures (SOP). We screened for *PDGFRA* mutations and calculated mutation frequencies and evaluated other co-mutations.

Results: *PDGFRA* mutations were observed in 185 of 4294 tumor samples (4.3%). The extracellular domain accounted for the majority of mutations (62.78%), followed by the tyrosine kinase domain (27.82%) and the transmembrane domain (9.40%). The main mutation hotspot was found to be in exon 5/6/7, accounting for 42.48% of the mutations. The most common mutations identified were p.C235Y (5.26%), p.Y288C (4.51%), and p.E229K (4.14%). The most common tyrosine kinase domain mutation is p.D842Y (1.82%) of exon 18 (9.39%), while p.D842V (1.12%) is also frequently observed, which should be noted that the *PDGFRA* mutation pattern in gliomas differs from that observed in solid tumors. The majority of the samples analyzed exhibited both *PDGFRA* mutation and *PDGFRA* amplification, with a small percentage (3.28%) showing *PDGFRA* fusion, specifically *KIT-PDGFRA* fusion.

Conclusions: The incidence of *PDGFRA* mutation in glioma patients is 4.3%. This type of mutation is mostly found in the non-tyrosine kinase domain. Investigating the *PDGFRA* map and *PDGFRA* inhibitors has significant exploratory value.

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520P Copy number variation spectrum analysis of primary glioblastoma

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Background: Glioblastoma, IDH-wildtype (GBM) is the most common malignant tumor of the human central nervous systemwith a poor prognosis. The distribution of copy number variations and the molecular targeted therapy are unknown. Therefore, it is important to understand the somatic copy number genome profile of Chinese adult glioblastoma patients.

Methods: Next-generation sequencing of 131 genes was performed in postoperative tissues of 4294 Chinese adult glioma patients from 2019 to 2023. Standard operating procedures (SOP) were used to detect somatic mutations and copy number variations. We screened out copy number variants in glioblastoma and calculated mutation frequency and evaluated other co-mutations.

Results: Copy number variations was observed in 1871of 2839 glioblastoma samples (65.9%). The six most common genes with copy number variation were *CDKN2A* (48.8%), *CDKN2B* (47.1%), *EGFR* (24.3%), *PTEN* (17.1%), *CDK4* (11.3%), *PDGFRA* (9.3%). Patients with *EGFR* amplification often carried *CDKN2A* (16.2%), *CDKN2B* (15.4) and *PTEN* (7.0%), while patients with *PDGFRA* amplification often carried *KIT* (7.54%), *CDKN2A* (6.1%) and *KDR* (5.9%). *MDM2* (7.0%), *CDKN2A* (6.0%) and *CDKN2B* (6.2%) were common copy number variants in the *CDK4*-amplification group.

Conclusions: In our GBM patients, 65.9% present copy number variations *RB1* cell-cycle, *TP53*, and *RTK* pathways are common signaling pathway alterations. CDKN2A/B deletion had the highest incidence and were enriched in EGFR-amplified patient. The high frequency of copy number variations in *RB1* cell-cycle pathways in glioblastoma suggests that it may be a direction for targeted therapy.

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521P Deciphering a three-miRNA signature as a prognostic biomarker in glioma patients: Correlation with DFS and OS

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Background: Gliomas are diffusely growing brain tumors and challenging cancers for diagnosis and treatment. The identification of genetic/epigenetic markers has changed glioma classification. Among the key genetic events, IDH mutations are noteworthy from a diagnostic and a prognostic point of view. MiRNAs are important players in glioma modulating cancer-related processes, including invasion and progression. We recently identified a serum diagnostic/prognostic miR-1, miR-26a-1 and miR-487b signature deregulated in glioma patients according to IDH mutation profile. We also found that this signature displays oncosuppressive functions with a marked inhibitory effect on migration and invasion by the direct targeting of crucial genes for invadopodia activity such as SH3PXD2B (miR-1), SH3PXD2A (miR-26a-1) and EFHD2 (miR-487b).

Methods: TCGA and CGGA databases were used to evaluate the correlation of the gene expression with glioma recurrence and Overall survival (OS). GSEA tool was used to identify pathways. Digital PCR and qRT-PCR were used to analyze miRNA and gene expression, respectively.

Results: *In silico* analyses show that the three-miRNA signature target genes were significantly downregulated in primary respect to recurrent patients. We also found that the combination of 2 out of 3 target genes is a strong prognostic biomarker. Median OS was 94.5 months in the Low-expression group *versus* 27.1 months in the High-expression group (HR=2.82[2.26-3.52], p=7.8e-20). These data were confirmed in a validation cohort. We also identified potential pathways deregulated in patients overexpressing the two genes and interestingly we found enriched pathways related to the immune system, angiogenesis and cell cycle. Our on-going experiments aim to validate experimentally the *in silico* data using a cohort of 80 glioma patients, including paired primary and recurrent tumor tissues.

Conclusions: The identification of a prognostic/predictive miRNA signature and its target genes, with a potential key role in glioma progression/recurrence through the regulation of important biological processes, could represent a step forward for the development of novel complementary therapies useful for patients management.

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522P Galectin 3 binding protein as potential biomarker in glioma diagnosis

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Background: Gliomas, or malignant brain tumors that grow from glial cells, are the most prevalent form. They account for roughly 40% of all primary brain tumors and 70% of all primary malignant brain tumors. The only procedures available for diagnosing different stages of glioma are surgical incision and biopsy; however, our work focuses on finding a minimally invasive way for early glioma diagnosis. Identification of proteins released by cancer cells is of particular interest in this area, as it could lead to a better understanding of tumor growth.

Methods: Extracellular vesicles (EVs) were extracted from pooled plasma of healthy individuals (n=03) and glioma patients of various grades (Grade I, II, or III). The size and concentration of Plasma derived-EVs marker were determined using nanoparticle tracking analysis, immunohistochemistry, western blot, and flow cytometry. In furthermore, an iTRAQ-based LC-MS/MS analysis of EVs protein was performed. The candidate protein galectin-3 binding protein was validated using ELISA and other methods (LGALS3BP).

Results: Total 123 proteins were identified from plasma derived pooled EVs and 34, 12 and 14 proteins were found to be differentially abundant by more than 1.3 in the different grades of glioma grade I, pilocytic astrocytoma; grade II, diffuse astrocytoma; grade III, anaplastic astrocytoma, respectively, in comparison with the control samples. A total of seven proteins-namely, CRP, SAA2, SERPINA3, SAA1, C4A, LV211, and LGALS3BP-showed differential abundance in all the three grades. LGALS3BP is the only protein which found to be strikingly high in all three grades in a progressive manner. Further ELISA and immunohistochemistry technique implemented to verify LGALS3BP in cohort of samples.

Conclusions: LGALS3BP was shown to be elevated across all grades, and ELISA analysis of individual blood plasma and plasma-derived extracellular vesicles validated the enhanced expression of LGALS3BP in glioma patients. That shows the possible biomarker for early diagnosis of glioma and improved patient survival. This study would further provides the information of progression and monitoring the tumor grades (grade I, grade II, grade III).

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523P Analysis of DNA damage response (DDR) gene expression as a prognostic factor for glioblastoma patient mortality

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Background: Glioblastoma (GBM) is associated with an exceptionally poor prognosis with a median survival of 15 months. At present, standard of care involves initial maximal surgical resection, followed by radiotherapy as well as concomitant and adjuvant temozolomide chemotherapy. However, as current therapeutic strategies are insufficient in sterilising tumour cells, GBM represents an area of vital unmet clinical need. Upregulation of DNA damage response (DDR) gene expression in cancer is implicated in tumorigenesis and disease recurrence through the acquisition of driver mutations, evasion of cell death, and reversal of chemotherapy and radiotherapy cytotoxicity. However, DDR gene expression in GBM has not been widely studied. This bioinformatics study aimed to identify DDR genes with expression that is significantly associated with GBM patient survival.

Methods: Clinical and transcriptomic (RNAseq) data from 155 GBM and 4 non-tumour samples using the TCGA-GBM database were subjected to analysis. Kaplan-Meier stratified survival analysis following fitting of the Cox proportional hazard model was conducted on clinical data after stratification based on the median expression of each gene. Multivariate analysis considering the known prognostic significance of age, sex and O6-methylguanine- DNA-methyltransferase *(MGMT)* promoter methylation status was conducted on gene expression with significant p and q values.

Results: Only 1 out of 298 DDR genes subjected to analysis was significantly associated with patient prognosis after correction for multiple comparisons. This study identified that upregulation of *RDM1* gene expression is an independent predictor for detrimental patient prognosis after multivariate analysis in GBM (multivariate HR 1.61, 95% CI 1.03 to 2.51, p = 0.035).

Conclusions: Due to the small proportion of DDR genes with expression significantly associated with prognosis, DDR gene expression is unlikely to be a significant prognostic indicator in GBM patient survival. Further investigation into *RDM1* function is warranted to determine the mechanism by which this gene might influence patient outcomes and explore the potential development of novel *RDM1*-targeted therapies.

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524P Cell line study of nucleosome-based biomarkers in the diagnosis and detection of relapses in glioblastoma

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Background: Currently, glioblastoma (GBM) diagnosis and monitoring rely on neuroimaging and histopathological confirmation. However, overall survival has not improved in last decades due to therapeutic failure and to a lack of biomarkers for relapses' detection. Liquid biopsies (i.e. blood or CSF) using nucleosomes-containing-histone post-translational modifications (PTMs) have the potential to become valuable biomarkers for diagnosis and monitoring GBM.

Methods: Four glioblastoma cell lines (SF-126, U-87MG, U-118MG, and U-138MG) compared to a healthy microglia cell line (HMC3) and other solid cancer cell lines including pancreas (MIA PaCa-2), liver (HepG2), and cervix/uterus (HeLa) have been analyzed to identify their epigenetic profile. Nucleosomes were extracted and analyzed with the Nu.Q® Discover immunoassays platform addressing 13 histone-PTMs. Quantitative results of PTMs expression were normalized on quantification of total nucleosomes (H3.1-nucleosomes). Moreover, to demonstrate the capacity of the Nu.Q® assays to quantitatively monitor PTMs, GBM cell line SF-126 (n=3) was treated with an EZH2 inhibitor (responsible of H3K27 methylation) (iEZH2) for 4-, 24-, and 48 hours.

Results: The immunoassay identified three candidate biomarkers compared to control cell lines (n=4): citrullinated-histone H3 (H3R8Cit) (control=4.68% ; GBM=13.88% ; $p<0.05$), phosphorylation of H3S10 (H3S10Ph) (control=2.31% ; GBM=5.57% ; $p<0.05$), and a trend in H3K4Me2 elevation (control=0.43% ; GBM=1.07% ; p=0.066) in GBM cell lines(n=4). These results were confirmed by western blot. In addition, PCA revealed a segregation between GBM and control cells, mainly driven by these three PTMs. Moreover, the monitoring assay revealed that, after 24 hours and 48 hours of exposure, the level of H3K27Me3 – expressed as ratio of total nucleosomes was decreased by 32% (control=14.67%±0.58% ; iEZH2=10.00%±1.73% ; $p<0.05$) and 41% (control=15.33%±1.53% ; iEZH2=9.00%±0.00% ; $p<0.05$), respectively. Those results were also confirmed by western blot analysis.

Conclusions: In conclusion, we identified three specific *in vitro* epigenetic-based marks of GBM and demonstrated that the Nu. Q® technology is a valuable tool to monitor the degree of PTMs expression.

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525P Immuno markers in newly glioblastoma patients underwent Stupp protocol after neurosurgery

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Background: Glioblastoma (GBM) is characterized by an "immune-deserted" tumor microenvironment (TME) consisting of tumor-associated macrophages (TAMs) and tumor infiltrating lymphocytes (TILs). We aimed to investigate the prognostic role of tumor tissue markers correlating with overall survival (OS) and progression-free survival (PFS).

Methods: By immunohistochemistry (IHC), we analyzed on 31 archival formalin-fixed paraffin embedded (FFPE) tissue specimens: CD3, CD4, CD8, CD20, CD45, CD68, CD163, CD66b and PDL-1. Expression values were classified according to density score from 0 to 4 (0=no expression; 1=1-25%; 2=26-50%, 3=51-74%; 4=75%-100%) in two areas: Vascular/perivascular (V) and diffuse in tumor parenchyma (D). Percentage of infiltrating immune system cell was calculated by the rate of absolute number of positive stained cells/total number of cells multiplied by 100.

Results: All tissues were negative for PDL1 and only two positive for CD20. We observed that CD68+ macrophage and CD66b+ neutrophils expressed in V showed a statistically significant prognostic role (p-value of 0.027 and 0.029 respectively) (Table). CD68-V showed a prognostic role for PFS (p-value 0.032), while CD66b-V expression did not. CD3, CD4, CD8, CD45 and CD163 were not associated with OS and PFS.

Conclusions: Despite having a smaller cohort of tissues, we showed a different expression of immune markers. In particular, CD68-V was associated with a significant positive impact on both OS and PFS. This relation could be partially explained because TAM do not raise only from peripheral blood, but also from resident microglia. Moreover, we observed high density of CD66b+ cells in V related to OS probably for growth factors overproduced by tumor cells with their recruitment from blood. Further studies are needed in large series to explore the prognostic role of selected TME immune molecules to develop therapeutic strategies that aim to hit different components of GBM.

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526P In silico evaluation of the mutational profile of glioblastomas with high expression of PD1, CTLA4 and LAG3 identifies the ERBB-PI3K pathway as a druggable vulnerability target

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Background: Glioblastoma (GBM) is a major therapeutic challenge. Genomic studies have helped to decipher the molecular landscape of commonly deregulated genes in GBM. Unfortunately, approved immune checkpoint inhibitors, such as anti PD1, anti LAG3 and antiCTLA4 agents, have not shown clinical activity in GBM. In this study we explore the mutational profile of tumors with high expression of PD1, LAG3 and CTLA-4, to identify potential druggable vulnerabilities.

Methods: We interrogated TCGA with data from 528 patients. We explored the mutational profile of tumors with high expression of PD1, LAG3 and CTLA4 to explore the associations between the selected mutated genes and immune infiltration using TIMER2.0. Gene Ontology Biological processes related to each gene were explored with the EnrichR platform. Protein expression was evaluated using the Human Surfaceome Atlas.

Results: We selected 82 (15,53%) patients that had high hPDCD1 expression, 84 (15,9%) with elevated hLAG3 levels, and 70 (13,25%) with high hCTLA4. Among the total number of mutated genes in each subgroup we selected only those expressed in > 5% of the patients. As a result, we identified 23 mutated genes in the hPDCD1 subgroup, 66 in the hLAG3 and 69 in the hCTLA4 group. Genes highly mutated in the three subgroups included: TP53 24-30%, EGFR 20-37%, PTEN 15-30%, TTN 24-28% and MUC16 17-20%. This set of genes represented 21% of patients in the hPDCD1 group, 7,57% in hLAG3 and 7,24% in the hCTLA4 group. 21 mutated genes in the hPDCD1 group were shared with the other groups, 13 genes in the hCTLA4 and hLAG3 groups, and only one gene was commonly mutated between hPDCD1 and hLAG3, and between hPDCD1 and hCTLA4 tumors. These frequently mutated genes correlated with the expression of gamma-delta T cells (30% in hPDCD1, 35% in hLAG3 and up to 26% in hCTLA4). Gene set enrichment analysis included: PIK3 and ERBB2 signaling pathway, ion channel activity, protease/phosphatase binding, or C-X3-C chemokine binding.

Conclusions: GBM with high expression of PD1, CTLA4 and LAG3 display frequent mutations in the ERBB-PI3K signaling pathway including EGFR and PTEN. These genes correlated with presence of gamma-delta T cells in tumor infiltrates.

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527P Targetable gene fusions and other alterations in central nervous system tumors assessed by RNA and DNA-based next-generation sequencing

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Background: Central nervous system (CNS) tumors may have an underlying genetic mechanism, where oncogenic fusion proteins play an important role in tumorigenesis. This provides an opportunity to develop specific and effective therapies. Here, we used RNA and DNA- based next-generation sequencing (NGS) to identify actionable or potentially actionable oncogenic fusions and other molecular alterations in our patients with CNS tumors.

Methods: Pediatric and adult patients with CNS tumors treated in our hospital between 2018 and 2022 undergoing surgery were enrolled. Fusion transcript detection and mutation analysis in FFPE tumor samples were assessed by both DNA-based next-generation sequencing (NGS) assay (520-gene panel) (Burning Rock OncoScreen Plus, Burning Rock Biotech, China) and RNA-based NGS assay (115 fusion-related-gene panel) (OncoRNA, Burning Rock Biotech, China) to identify molecular alterations.

Results: NA-based NGS detected 50 tissue samples from 50 enrolled patients. RNA-based NGS successfully detected 49 samples, excluding 1 RNA degraded sample. Oncogenic fusions were identified in 63.2% (31/49) of patients by RNA-based NGS. At least 2 kinds of fusion transcripts were detected in 7 patients. Actionable fusions were KIAA1549::BRAF in 13 patients with pilocytic astrocytoma, FGFR1::TACC1 fusion in 2 patients with pilocytic astrocytoma and PTPRZ1-MET fusion in a patient with high-grade glioma. ZFTA::RELA fusions were found in 13 patients with ependymoma. A total of 31 patients (62.0%) were identified with at least an actionable or potentially actionable alteration by RNA- or DNA-based NGS. Besides targetable fusions, actionable alterations were most often located in SETD2 mutation (n=8), CDKN2A deletion (n=4) and CDKN2B deletion (n=4).

Conclusions: The combination of RNA- and DNA-based NGS provides information about molecular alterations for the management of patients with CNS tumors. Those with actionable gene fusions or other alterations may benefit from target therapy, especially in the setting of limited choice of treatments.

Table: 525P

Characteristics	Univariable models OS		Multivarible model OS		Univariable models PFS		Multivarible model PFS	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
CD68V								
0-1	1.00	-	1.00	-	1.00	-	1.00	-
2-4	0.42 (0.19-0.91)	0.027	0.46 (0.21-0.99)	0.049	0.41 (0.18-0.92)	0.032	0.45 (0.20-1.01)	0.054
CD66bV								
0-1	1.00	-	1.00	-	1.00	-	1.00	-
2-4	0.38 (0.16-0.90)	0.029	0.41 (0.17-0.98)	0.046	0.45 (0.17-1.12)	0.087	0.49 (0.19-1.24)	0.136

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528P Progression risk after pregnancy in patients with glioma

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Background: A significant proportion of women with diffuse gliomas are diagnosed in childbearing-age, resulting in the desire of patients to fulfil their family dream. However, data on glioma progression after and during pregnancy are sparse and controversial.

Methods: Female adult patients in their reproductive years (≥18 years and <46 years) with histopathological diagnosis of WHO grade 2 or 3 glioma from 2 academic centres between 01/01/2000 and 01/01/2019 have been included in the study. Diagnosis was updated according to WHO classification of CNS Tumours 2021 by a board-certified neuropathologist. Association of pregnancy and glioma progression was assessed in a time-dependent manner. The following parameters were included in the multivariate analysis: ECOG, extent of resection, WHO grading, adjuvant therapy after surgery, pregnancy after diagnosis.

Results: Of 159 women after a median follow up (FU) of 127.4 months (mo), 47 (29.6 %) were identified as nullipara, 89 (56 %) as primi-/multipara before glioma diagnosis and 23 (14.5 %) as primi-/multipara after diagnosis. Updated diagnosis according to latest WHO classification revealed 92 (57.8 %) astrocytomas (isocitrate dehydrogenase [IDH]-mutant) CNS WHO grade 2 and 3, 54 (33.9 %) oligodendrogliomas (IDH-mutant, 1p/19q codeleted) CNS WHO grade 2 and 3, 11 (7.1 %) glioblastomas (IDH-wildtype) CNS WHO grade 4, and 2 (1.3 %) diffuse midline gliomas (H3-K27-altered). Median overall survival (OS) and progression free survival (PFS) was 247.6 mo (95 % CI 155.7 − 339.5) and 67.9 mo (95 % CI 60.1 − 75.7), respectively. Among 23 patients with glioma diagnosis prior to pregnancy, mean time between diagnosis and conception was 54.6 mo (0.6 − 116 mo). Tumor progression happened in 17 (73.9 %) cases and death occurred in 4 (17.4 %) patients. Mean time from start of pregnancy to date of tumor progression/last-FU or death/last-FU was 35.3 mo (9 − 229.2 mo) and 107.2 mo (17.7 − 229.2 mo), respectively. In multivariate time-dependent analysis, pregnancy after diagnosis in comparison to nullipara or pregnancy before diagnosis was associated with shorter PFS ($p \leq 0.05$), but not with shorter OS ($p > 0.05$).

Conclusions: Pregnancy after glioma diagnosis is associated with shorter PFS. Longer follow up as well as larger cohorts are needed to investigate a potential impact on OS.

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529P Post-marketing surveillance data from patients ≥70 years of age with central nervous system malignancies treated with Tumor Treating Fields (TTFields) therapy between 2011 −2022

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Background: Glioblastoma (GBM) is among the most aggressive central nervous system (CNS) malignancies. Furthermore, older age is associated with increased risk of treatment-related systemic toxicity. TTFields are electric fields that exert physical forces to disrupt cellular processes critical for cancer cell viability. TTFields therapy is approved for recurrent and newly diagnosed GBM, following the pivotal phase 3 EF-11 (TTFields 200 kHz) and EF-14 studies (TTFields 200 kHz + temozolomide), respectively, which demonstrated clinical benefit without additional systemic adverse events (AEs). We report safety data from patients (pts) ≥70 years of age with CNS malignancies receiving TTFields from a global post-marketing surveillance (PMS) analysis.

Methods: Unsolicited PMS data were collected from pts receiving TTFields globally (October 2011—March 2022). Data from pts ≥70 years old are reported here. AEs were categorized using MedDRA version 25.1.

Results: Overall, 25,898 pts from the US, Europe and Israel, and Japan were included. Of these, 4,071 (16%) were ≥70 years old. Overall, 75% of patients ≥70 years old experienced ≥1 AE, with 56% being related to TTFields, which is comparable to the overall population (73% and 56%, respectively). The most common TTFields-related AEs in the ≥70-year-old population were skin reaction (45%; overall population: 43%), heat (warmth) sensation (11%; overall population: 14%), and electric (tingling) sensation (10%; overall population: 14%). Serious AEs for the ≥70-year-old and overall group were 27% and 22%, respectively. No systemic toxicities were reported, regardless of age.

Conclusions: These long-term, real-world PMS data demonstrate that TTFields has a tolerable safety profile in pts ≥70 years old with CNS malignancies, with no new safety signals. Most AEs were localized skin reactions which can be easily managed. Real-world data of TTFields therapy in elderly subgroups provides clinicians with insights on adapting strategies to optimize treatment management.

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530P Ultra low bevacizumab (BEVULTRA-100) as a novel approach in symptomatic management of high grade glioma: Can minimal dose make a difference?

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Background: High grade gliomas are primary malignant brain tumors where surgery followed by radiotherapy and chemotherapy remains the standard of care. Majority of patients manifest with post treatment changes like necrosis, edema or pseudoprogression for which the management is challenging. Currently steroids remain the treatment of choice in such scenarios but have many dose limiting toxicities. Bevacizumab (BEV) is approved in recurrent HGG. Fewer studies with dose de escalation up to 50% of standard dose have attained similar results in control. However it's anti angiogenic/anti edema effect is quite unexplored in management of post treatment changes. In our study, we analyzed the role of BEVULTRA-100 in symptomatic/asymptomatic HGG as an alternative to steroids.

Methods: In this prospective, interventional single arm study, 117 patients of HGG treated with chemotherapy and radiotherapy as primary modality from July 2013 till April 2023 were included. All patients received Ultra-Low Dose Bevacizumab - 100 mg once in every month along with oral temozolomide. Complete blood counts and vitals were monitored before each cycle. All patients were assessed at regular intervals for clinical and imaging parameters-DOPA PETCT & MRI in regards with post treatment changes.

Results: Median age was 44.5 years Range: 9 to 70. M:F ratio of 1.54 :1. A Median of 12 cycles UltraBEV (Range:1 to 62) were received (1514 cycles in total). All patients tolerated well without any significant toxicities. None of the patients had intracranial/tumoral bleed. Use of steroids was markedly reduced in more than 90% patients with BEVULTRA-100 resulting in substantial improvement in the QOL. Similar pattern was observed in imaging parameters including reduction of post treatment edema.

Conclusions: This pilot study aims at providing a proof of concept for BEVUltra100 in management of post treatment changes in HGGs. This is a feasible, cost effective option with better compliance compared to steroids with improved survival. This study also paves a trailblazing path for exploring the field of radiation dose escalation and reirradiation with adequate control over toxicities improving the QOL, which might translate into improved survival.

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531P Tumor treating fields therapy for glioblastoma: Identifying needs and satisfaction of new and long-term users

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Background: Tumor Treating Fields (TTFields) therapy uses electric fields to disrupt processes critical for cancer cell survival. TTFields therapy delivered by a wearable, portable device is approved in several counties for the treatment of newly diagnosed and recurrent glioblastoma (GBM), including Germany, Austria, Switzerland (DACH) and the US, and is under investigation for other tumour types.

Methods: Two surveys (independently developed and administered) were distributed (mail and online) in DACH and the US to patients/caregivers using TTFields (Optune(R); Novocure(R) GmbH, device manufacturer) as therapy for GBM.

Results: Between 1 January—31 December 2022, 545 (DACH) and 1282 (US) patients/caregivers returned surveys (response rates of 43% and 27%, respectively). In DACH, 43% had recently initiated therapy ("new starters"; 66% were male, 55% were ≥60 yrs of age). In the US, 31% of responses were from new starters; 69% were male and 63% were ≥60 yrs. Respondents with TTFields usage of >6 months (long-term users) accounted for 21% of DACH and 29% of US surveys; most were male (59% in DACH; 65% in US), and around half were ≥60 yrs of age (40% in DACH; 55% in US). Overall satisfaction (*very satisfied*, *satisfied*, *mixed*, *less satisfied* or *dissatisfied*) with TTFields was high; most respondents indicated they were very satisfied or satisfied (82% and 61% of new starters, and 67% and 74% of long-term users, in DACH and the US, respectively). Amongst long-term users, most noted that using TTFields required changes to daily life (63% DACH; 57% US). Frequently mentioned changes related to skin irritation, device handling, and impact of weight/portability on lifestyle. Despite this, the majority (74% in DACH; 73% in US) of long-term TTFields users/caregivers would recommend the treatment for GBM.

Conclusions: Surveys returned in DACH and the US showed the population of TTFields therapy users was representative of patients with GBM. Users from both surveys had a high level of satisfaction with the therapy and mostwould recommend it to others. Any potential concerns regarding device handling/portability can perhaps be mitigated by increased educational and communication efforts.

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532P Nitric oxide is a target by a combo-drug for glioblastoma treatment

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Background: Glioblastoma is the most common and aggressive type of primary brain tumor, with a high morbidity and mortality rate. Nitric oxide (NO) has been shown to have diverse effects on various cancers, including glioblastoma. Nitric oxide synthase (NOS) activation has been implicated in the growth and progression of glioblastoma. In this study, we investigated the effects of our novel two drugs HU-53 and HU-54, on the U87-MG cell line and a xenograft model of glioblastoma. Both drugs attenuate nitrative stress through different mechanisms.

Methods: NOD.CB17-Prkdc-scid/NCrHsd mice were used for the xenograft subcutaneous tumor model to evaluate the ability of HU-53 and HU-54 treatment regimens. Both treatments were given intraperitoneally. Tumor weight and volume were measured during the study. The experiments were also carried out on the human-derived U87-MG cells. Nitrite content was measured biochemically by Griess assay. Immunofluorescence and immunoblotting assessed nitrosative stress.

Results: We found that treatment with the combo-drug resulted in a significant decrease ($P<0.0001$) in cell viability and proliferation as compared to vehicle in the U87-MG cell line. The combo-drug also induced apoptosis as evidenced by increased caspase-3 activity. In addition, treatment with HU-53 and HU-54 resulted in a significant reduction ($p<0.0001$) in tumor growth in the xenograft model of glioblastoma, as demonstrated by decreased tumor volume and weight. Furthermore, we observed that the combo treatment resulted in a significant decrease in the level of nitrite content ($p<0.02$) and 3-Nitrotyrosine (a marker of nitrosative stress) which are important mediators of glioblastoma growth.

Conclusions: Our results suggest that targeting the nitrosative stress with HU-53 and HU-54 may be a promising therapeutic strategy for glioblastoma treatment.

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533P Oligodendrogliomas: What is the impact after the introduction of the WHO molecular classification?

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Background: Oligodendrogliomas are rare tumors and affect young people. In 2016, the new WHO classification was introduced that includes molecular features (IDH mutation and 1p/19q codeletion) that were not present in previous classifications. Currently, there is no data indicating the impact of this new classification on our clinical practice. The objective of this study is to review the clinical evolution of a cohort of patients, before and after reclassification, using molecular criteria.

Methods: Cases with a diagnosis of grade 2 and grade 3 oligodendroglioma and oligoastrocytoma were identified in the registries of two tertiary hospitals. A total of 182 cases, corresponding to a period of 37 years (between 1977 and 2014), were identified and termed initial cohort. Subsequently, IDH mutation and codeletion of 1p/19q analysis were performed in this cohort. A total of 91 patients fulfilled these characteristics and were termed the reclassified cohort. The clinical evolution of both cohorts was analyzed.

Results: The mean age of the cohort was 45 years (14-75), with a Males: Female ratio of 61%/39%. Frontal lobe location 60%, 65% grade 2 and 22% oligoastrocytomas. Complete resection 47% (subtotal 22%, partial 20%, biopsy 7%). After surgery, 50% received radiotherapy, 30% chemotherapy, 36% did not receive adjuvant therapy. The median follow-up was 9 years. Unlike what was observed in the initial cohort, there were no statistical differences in median overall survival (OS) in the reclassified cohort regardless of grade; grade 2, 13.3y (95%CI 8.2-18.4), grade3, 12 years (95%CI 5.6-18.3), therefore, grade loses its prognostic impact with the new molecular classification. OS in the excluded cohort was 7.52years (95%CI 4.67-10.38). The OS in those cases without adjuvant treatment was 12 years. 30% of oligoastrocytomas in the initial cohort were reclassified to oligos.

Conclusions: Molecular classification allows a more accurate selection of oligodendrogliomas and implies that cases have a better prognosis, regardless of grade and treatment received. These data should be taken into account in clinical practice for a better selection of the risks and benefits of adjuvant treatment.

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534P Glioblastoma treatment in patients older than 60 years: Hypofractionated radiotherapy and temozolomide versus conventional radiotherapy and temozolomide

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Background: Treatment of glioblastoma patients under 70 years and with good Karnofski performance status (KPS>70) associates standard radiation therapy (SRT, 60 Gy in 30 fractions) with concomitant and adjuvant temozolomide for 6 monthly cycles (SRT-TMZ). Clinical trials of glioblastoma radiation treatment in patients older than 60 years (≥60-ys) showed no significant difference in survival comparing SRT to hypofractionated radiotherapy (HRT, 40.05 Gy in 15 fractions). Adding TMZ to HRT (HRT-TMZ) in patients ≥65-ys have translated into increased median overall survival (mOS) and progression-free survival (mPFS). In daily clinical practice, as in previous retrospective studies, older patients and/or those with KPS ≤70 may still be treated with radiation and temozolomide regardless of the MGMT tumor status, often opting for HRT-TMZ.

Methods: We retrospectively included all glioblastoma patients older than 60 years treated from 2017 to 2021 in our hospital with SRT-TMZ or HRT-TMZ. The primary endpoint was OS. The secondary endpoints were PFS, survival at 12 months (mo) and toxicity profile. Comparisons were made using Fisher's exact test and Mann-Whitney test. Survival curves were estimated using the Kaplan-Meyer method and compared using the log-rank test.

Results: 69 patients were treated, 33 with SRT-TMZ and 36 with HRT-TMZ. Median age was significantly different between these two groups (64 ys [range 60-70]) vs. 71 ys [range 62-85]), p<0.0001). KPS, extent of surgery, MGMT and IDH status did not show significant differences between groups. mPFS was 9 mo for SRT-TMZ vs. 10.2 mo for HRT-TMZ (p=0.57) and mOS was 14.8 mo vs. 13.8 mo (p=0.99), respectively. Treatment with SRT-TMZ was associated with increased thrombocytopenia events at the end of the first phase (p=0.01).

Conclusions: In real world, elderly glioblastoma patients pragmatically oriented to HRT-TMZ still had similar OS and PFS as younger patients treated with standard and potentially more toxic SRT-TMZ. This may support the extended use of HRT-TMZ in patients above 60 years.

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535P Hypofractionated radiotherapy in fit elderly patients with glioblastoma: Relevant or detrimental?

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Background: Glioblastoma (GBM) is the most common malignant primary brain tumor in adults. It remains a relatively rare disease with an incidence of 3/100.000 in France, and an age-related peak in incidence at 70 years of age, which corresponds to the age limit inclusion criteria of the Stupp Trial on 2005, cornerstone of the GBM strategy. Therefore, treatment of GBM in elderly patients is not standardized and depends on several clinical and biological factors. The aim of this study is to compare survival outcome of elderly patients with glioblastoma treated with standard radiotherapy (SRT) versus hypofractionated radiotherapy (HRT) versus no radiotherapy (RT), with or without Temozolomide.

Methods: A single-center retrospective case series analysis was conducted, including newly diagnosed GB patients older than 70 from January 2010 to December 2021. The Log-Rank test was used to compare the PFS and OS of patients treated with SRT versus HRT versus no RT. Furthermore, a Cox regression analysis was performed to identify risk factors associated with OS. Statistical significance was considered when p<0.05.

Results: A total of 304 patients were included with a median age of 74.36 years [71.63, 78.62], among whom, 142 were women. Most patients had a performans status of 0 or 1. Median OS was 11.4 months [95% CI 10.4 − 12.3] while median PFS was 8.1 months [95% CI 7.4 − 9.1]. Overall, 231 patients (76%) were treated with RT, 94 (30.9%) with SRT, 129 (42.4%) with HRT and 73 (24%) did not receive RT. On univariate analysis, the SRT group showed a better OS compared to the HRT and no RT groups (23.1 months, 11.1 months and 4.7 months, respectively, p<0.01). Same trend was observed for median PFS (SRT 13.6 months, 8.08 months and 3.7 months respectively, p<0.05).

Conclusions: While previous randomized trials showed a benefit or non-inferiority of HRT over SRT in elderly glioblastoma patients, this large retrospective "real-life" cohort shows on the contrary a benefit in terms of OS of the standard normo fractionated RT regimen. Standard treatment should not always be degraded in elderly patient, and a proportion of them may still benefit from standard RT if their clinical status allows it.

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536P Safety and efficacy of silibinin in patients with brain metastases after stereotactic radiosurgery (SRS): The SUSTAIN trial

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Background: Brain metastases (BMs) account for more than one-half of all intracranial tumors. In recent years, stereotactic radiosurgery (SRS) has become the mainstay of BMs treatment, providing high rates of local tumor control. Nevertheless, SRS alone is associated with a 30-50% risk of distant brain failure (DBF), consequently requiring careful follow-up and possible rescue treatments. Silibinin or silybin, a natural polyphenolic flavonoid, has shown promising antitumor activity, leading to improvement of BMs in patients with progressive non-small cell lung cancer. Therefore, our exploratory study aims to evaluate whether the use of a silibinin-based nutraceutical (SILLBRAIN, HEALTH4U S.r.l.) can significantly reduce DBF rate at 6 months in patients with first-diagnosed BMs treated with SRS with or without surgery.

Methods: SUSTAIN is an interventional, prospective, single-arm, phase II study. A total of 80 patients treated in our institution are planned to be enrolled. Patients receive 2 capsules of SILLBRAIN per day for the first month after SRS and 1 capsule per day thereafter. Primary endpoints are 6-month distant brain failure (DBF) rate and safety.

Results: Thirty patients have been enrolled at the time of the primary analysis. NSCLC and breast cancer were the prevalent histologies. Overall, the number of treated lesions was 73, with a median of 1 lesion (range 1-9). All patients underwent SRS,

with a median prescription dose and a median prescription isodose line of 24 Gy and 80%, respectively. After a 14-month enrollment period, with a median follow-up of 9 months, 6 patients reported DBF according to RANO-BM criteria, with a 6-month DBF rate of 20%. Only 1 treated lesion met the criteria for progression, accounting for a 6-month local control (LC) rate of 98%. Six patients died, with a 6-month OS rate of 80%. Two patients discontinued SILLBRAIN assumption due to G1 nausea. No other adverse events were reported.

Conclusions: At about half of our enrollment target, the results show a favorable trend towards 6-month DBF rate reduction. Toxicity proved manageable, consistent with the literature and limited to gastrointestinal effects. A larger sample and longer follow-up are needed to confirm our hypothesis.

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537P S100A9 serum levels are associated with survival prognosis in patients with brain metastases

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Background: Brain metastases (BM) are a clinical challenge in oncology. Further insight on pathobiology is the basis for new treatment approaches. Recently, S100A9 has been postulated as a novel potential biomarker for therapy resistance to radiotherapy in preclinical BM models. Therefore, we aimed to explore S100A9 levels in a real-life BM patient cohort.

Methods: S100A9 protein expression was measured in the serum of patients treated at the Medical University of Vienna between 2019-2023 using an enzyme-linked immunosorbent assay (ELISA) to correlate its levels with clinicopathological parameters. Sample concentrations below the lower limit of quantification (LOQ) were treated as 50% of LOQ's concentration and considered as non-quantifiable. Samples with a concentration above the upper limit of quantification were remeasured in dilutions.

Results: 80 patients (39% male; 61% female) with BM (n=69) and without BM (n=11) were included in this pre-liminary analysis. Median serum level of S100A9 was 23 pg/mL (IQR 16-97 pg/mL). No difference in median S100A9 levels were observed between patients with BM (23 pg/mL, IQR 16-114) and without BM (23 pg/mL, IQR 15-41) at time of blood sampling (p=0.7). Furthermore, no difference was found in median S100A9 levels in BM patients according to primary tumor's origin (lung cancer 23 pg/mL vs. breast cancer 16 pg/mL, p=0.6) or radiated versus non-radiated BM (37 pg/mL vs. 23 pg/mL, p=0.3). Median overall survival of patients with quantifiable S100A9 levels were significantly longer than patients with non-quantifiable S100A9 serum levels (HR 2.05; p=0.05).

Conclusions: Based on the results of these pre-liminary data, S100A9 levels did neither correlate with BM diagnosis, primary tumor's origin nor previously applied radiotherapy. However, detected S100A9 levels correlated with survival analysis in this real-life BM patients. Further studies are currently ongoing to further evaluate S100A9 as a diagnostic and predictive biomarker in larger real-world patient cohorts.

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538P Single-center retrospective analysis of patients with brain metastases included in early phase clinical trials

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Background: Historically patients (pts) with brain metastases (BM) were excluded from early phase clinical trials due to concerns over prognosis, risk of toxicity or lack of brain penetrance. Recent trials allow the inclusion of pts with stable (asymptomatic and/or treated) BM, as recommended by the ASCO and Friends of Cancer Research Brain Metastases Working Group. We aimed to describe the outcomes of patients with BM enrolled in early phase clinical trials.

Methods: Retrospective cohort analysis of clinical and treatment (trt) response data of pts included in early phase clinical trials at Vall d'Hebron Institute of Oncology between January 2012 and April 2023. Objective response rate (ORR) and disease control rate (DCR) were calculated. Median progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, survival between groups was compared using log-rank test and cox regression.

Results: A total of 815 pts treated at our center were analyzed; 51 pts had stable BM at inclusion, 28 (54.9%) male and 23 (45.1%) female. Most frequent types: lung (51.0%), melanoma/skin (23.5%). Forty-one pts (80.4%) received prior brain trt: 37 radiotherapy, 3 surgery and 1 both. Ten pts (19.6%) were included with asymptomatic untreated BM. Type of experimental trt: immunotherapy 72.5%, targeted therapy 21.6%, antibody-drug conjugates 5.9%. Phase of clinical trial in which pts were included: phase 1 dose escalation 23.5%, phase 1 expansion cohorts 70.6%, and phase 2 basket studies 5.6%. Median OS in pts without BM was comparable to those with: 9.1 months vs 6.3 (p=not significant); median PFS was superior in BM pts: 1.8 vs 2.6 (HR 0.52, $p<0.0001$). The rate of OS<3 months was 31.4% in BM pts and 33.3% had PFS>4 months. ORR and DCR were respectively 19.6% and 54.9%, intracranial ORR and DCR were 7.8% and 72.7%. Only 4 pts discontinued treatment due to isolated intracranial progression (iPD), and 2 had iPD as best response. There were no statistically significant differences in PFS and OS of pts with treated BM and asymptomatic untreated BM.

Conclusions: The trt response and survival data for pts with BM in our cohort support the recommendations of ASCO and Friends of Cancer Research on the inclusion of pts with BM in clinical trials.

Legal entity responsible for the study: The authors.

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539P Epidemiology and prognostic factors of lung cancer and brain metastases: A 10-year retrospective population cohort study in Girona, Spain

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Background: Lung cancer (LC) has the highest rate of brain metastases (BM). The aim of this study is to analyze the incidence, survival, and prognostic factors of LC patients with BM from a retrospective cohort.

Methods: Population-based study of LC patients with BM diagnosed in the province of Girona, Spain between 2010-2019. Clinical records were searched for BM in June 2021 and the end follow-up was 31 December 2022. The age-standardized rates (ASR) (2013 European) were calculated. Kaplan-Meier method and Cox regression model were used for analysis of survival and prognostic factors.

Results: 3,952 LC cases were identified, 15.8% (n=625) developed BM. According to histology, BM were more common in adenocarcinoma (ADC) (21.1% [306/1450]), followed by small cell lung cancer (SCLC) (20.3% [108/533]), not otherwise specified (NOS) (14.2% [133/936]), and squamous (SQ) (7.6% [78/1033]). Among the 625 patients with LC and BM, 72.6% were male and the median age was 63 years [IQR: 56-70]. Histologically, 49.0% had ADC, 21.3% had NOS, 17.3% had SQ, and 12.5% had SCLC. Most were diagnosed at stage IV (79.8%) and 68.7% had synchronous BM. The ASR of LC and BM was 9.3 cases per 100,000 p-y (95%CI: 8.6-10.1). During follow-up, 602 patients died; median survival was 2.8 months (95%CI: 2.5-3.2). However, median survival increased from was 2.4 months in 2010-2014, to 3.3 months in 2015-2019 (p=0.009). In multivariate analysis, histology, targetable mutant status, extra-cranial disease, number of BM, BM size, BM surgery, radiotherapy, and systemic treatment were statistically significant independent prognostic factors (Table).

Table: 539P Prognostic factors

	Multivariate analysis	
	HR (95%CI)	p-value
BM size	1.01 (1.00-1.02)	0.006
Histology		
Adenocarcinoma	1	0.005
Squamous	1.61 (1.18-2.21)	0.003
Small cell	1.45 (1.05-1.98)	0.022
NOS	1.45 (1.07-1.95)	0.015
Targetable mutations	0.60 (0.42-0.86)	0.006
Extra brain disease	1.28 (1.01-1.62)	0.045
Number of BM		
≥4	1.26 (1.00-1.59)	0.049
ECOG at diagnosis of BM		
≥2	1.73 (1.32-2.27)	<0.001
Brain surgery	0.49 (0.33-0.73)	<0.001
Brain radiotherapy	0.67 (0.52-0.85)	0.001
Systemic treatment BM	0.41 (0.31-0.53)	<0.001

Conclusions: There is a high rate of BM in patients with LC, especially in ADC and SCLC. Our data suggest that many factors may have an impact on the survival of patients. Although the prognosis for patients with LC and BM remains a major challenge, data show an improving trend.

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540P Impact of adjuvant radiotherapy (ART) on survival time in patients with hemangiopericytoma (HPC): A population study

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Background: HPC is a rare solitary fibrous tumor of the central nervous system (CNS), accounting for only 1% of all vascular tumors. Surgery is the standard treatment. However, the role of ART remains controversial. Therefore, we conducted this study to evaluate the impact of ART on the overall survival (OS) and cancer-specific survival (CSS) of patients with HPC.

Methods: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2019. Patients with a history of cancer or concurrent malignancies, lacking pathologic diagnosis, tumor not arising from the CNS, and those with unknown data were excluded. T-tests and chi-square tests were used to compare variables, while the Kaplan-Meier estimator, log-rank tests, and Cox proportional hazard regression were used to identify prognostic factors of OS and CSS.

Results: The study population comprised 395 patients. Among them 121 patients with "Surgery," 246 patients with "Surgery + ART", 10 patients with "Surgery + Chemotherapy" and 18 patients received "Surgery + ART + Chemotherapy". Of the patients, 55.2% were females, and 60.5% were over 50 years old. The average tumor size was 5 cm. The white group was the largest racial group (N=315). Most cases (51.9%) had a tumor size greater than 5 cm, with a median tumor size of 5 cm. Most cases were localized (65.8%), and a few had distant metastasis (8.6%, n=34). "Surgery + ART" had the best survival outcome 5-year OS of 81.5%, followed by "Surgery + ART + Chemotherapy" and "Surgery + Chemotherapy" both 80%, and "Surgery" at 61.1%. The therapeutic groups showed significant differences in the OS and CSS ($p<0.022$ and $p<0.017$, respectively). Localized stage positively impacted OS and CSS, while age and metastasis had a negative impact. Multivariable analysis confirmed that "Surgery + ART" improved both 5-year OS and CSS (HR=0.6, 95%CI:0.42-0.87 and HR=0.33, 95%CI:0.14-0.77, respectively).

Conclusions: Our results showed that ART may improve the OS and CSS in patients with HPC. These findings provide valuable insights into HPC treatment and may inform future clinical decisions. However, further research is needed to validate these results and investigate any potential confounding factors that may have affected the outcomes.

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541P A multicenter study evaluating the clinical and molecular characteristics of adult patients with diffuse midline and non-midline K27M altered gliomas

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Background: Diffuse midline high grade glioma (DMG), H3 K27-altered previously known as DMG H3 K27M-mutant can appear both in childhood and in adulthood and the presence of this mutation is a well-known marker for poor prognosis with a median survival of around 9 months regardless of the histologic appearance. The goal of this retrospective study is to describe our multi-institutional experience with the clinical and molecular characteristics of these tumors in adults.

Methods: We retrospectively reviewed the electronic medical records (EMR) of all consecutive adult patients that underwent a surgical procedure for glioma excision and whose tissue was tested for the K27M mutation either by next generation sequencing (NGS) or immunohistochemistry (IHC) at the three main sites of our institution (Florida, Minnesota, and Arizona) from inception of the EMR to date.

Results: A total of 245 adult patients were included in this study, 138 (56.32%) male and 107 (43.68%) female with a median age of 48.50 years. Of these, n=72 (29.39%) had a K27M alteration and n= 173 were K27M wt. The most frequent location for the K27M altered and the K27M wt was the thalamus (n=30, 41.67% and n=45, 22.5%). In the H3K27M-altered group, the main 3 treatments were TMZ + RT in n= 36 (13.2%), RT alone in n= 19 (7%) and TMZ + RT + Optune device in n= 3 (1.1%). In the H3K27M-wt group, n= 122 received TMZ + RT (80.26%), n= 13 received RT alone (8.55%), and palliative care in n= 17 (11.18%). When comparing K27M altered vs GBM, both groups had similar OS with 18 months (95% CI 14.24-21.76) and 16 months (95% CI 10.29-21.70, p=0.57). In a subanalysis according to the tumor localization, the midlines showed an OS of 19 months (95% CI 15.041-22.96) vs. 13 months for the non-midline group ([95% CI 15.04-22.96], p=0.56).NGS was done in 93 patients (38%). The most frequent gene alterations were the TERT promoter mutation n= 61 (65.59%), TP53 gene mutation n= 34 (33.34%), and NF1 mutation n=31 (30.39%) and PIK3CA gene mutation n= 26 (34.67%).

Conclusions: Our study shows similar results in terms of survival to those reported in the literature, however the molecular alterations found in NGS show a small proportion of possible molecular targets that could help in the treatment of patients.

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542P Drug screening in Li-Fraumeni syndrome brain tumor models

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Background: Li-Fraumeni Syndrome (LFS) is a genetic disorder characterized by constitutional pathogenic *TP53* mutation. The affected individuals are predisposed to develop various types of cancer, frequently brain tumors. Radiation and DNA damaging agents tend to show decreased efficacy and increased toxicity in LFS patients. This study aims to find an efficacious and safe therapeutic approach for LFS-associated brain tumors.

Methods: A custom library consisting of 345 compounds was designed to target a total of 61 proteins. *In vitro* drug screening was carried out in two TP53^{mut} brain cancer cell lines (SJ-GBM2 and UW228-2) and primary fibroblasts obtained from a LFS patient. The performance of each drug was evaluated based on the efficacy (cell viability assay) and genotoxicity (micronucleus assay). Subsequently, selected compounds were tested in combinations using cancerous cell lines and *in vitro* patient-derived xenograft (PDX) organoid cultures.

Results: As a result of in vitro screening, we found 42 compounds that showed favorable toxicity in cancer cell lines compared to primary LFS fibroblasts. From these drugs, 26 caused little to no genotoxic effect measured by DNA damage in primary LFS fibroblasts. Inhibitors of ATM/ATR, CHK1/CHK2, and WEE1, as well as microtubule-associated compounds passed a validation step and were selected for combination testing. The combination of WEE1 inhibitor adavosertib and vinca alkaloid vincristine demonstrated the highest efficiency in cancer cell lines, which was later confirmed in in vitro PDX cultures of LFS-associated brain tumors.

Conclusions: Adavosertib and vincristine were identified as a drug combination that eradicates TP53mut cancer cells without inducing DNA damage in normal tissues. This qualifies them as a novel and promising therapeutic approach for LFS patients diagnosed with brain tumors. The further steps include confirming the efficacy and safety of adavosertib and vincristine in vivo using brain tumor PDXs and LFS mouse models.

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543P Bevacizumab and hydroxyurea treatment in grade 2 and 3 meningioma: A monocentric experience

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Background: Various systemic treatments for recurrent meningiomas (MEN) have been investigated with controversial results. We analyzed and compared the role of bevacizumab (BEV) and hydroxyurea (HYD).

Methods: Retrospectively, we analyzed recurrent grade 2 and 3 MEN PTS receiving BEV or HYD at the Veneto Institute of Oncology (Padua, Italy) from Nov 2011 to March 2023. All pts were not more amenable for surgery or RT. NGS data (Foundation One) were also collected. Kaplan-Meier curves were for survival rate; RANO criteria were used for radiological assessment.

Results: 31 pts in the BEV cohort were included. Baseline data for the BEV cohort were: 13 (41.9%) female pts; 17 (54.8%) below 65 years old; 16 (51.6%) PS ECOG <2; ≤ 2 previous surgeries in 17 (54%); 28 (90.3%) with less than 2 previous treatments. BEV was administered at 5 or 10 mg/Kg q2w or 7.5 mg/Kg q3w schedule. 13 pts were included in the HYD cohort. Baseline data for the HYD cohort were: 9 (69%) female pts; 5 (38%) $<$ 65 years old; 6 (46%) ECOG PS <2; ≤ 2 previous surgeries in 8 (61%); 1 (8%) previously treated. HYD was administered at 1000 mg/day. Pts affected by NF2 were 1 (8%) in HYD cohort and 2 (6%) in the BEV cohort. Pts treated with BEV achieved a DCR of 86.7%; mPFS was 19.6ms [95%CI: 10.6-NA]; 6m-PFS rate was 84.6% [95% CI 71.6-99.8]; mOS was 16.1ms [95%CI: 11.4-NA]; median follow up was 17.5ms. Pts treated with HYD achieved a DCR of 53.8 %; mPFS 5.6ms [95%CI: 2.9-NA]; 6m PFS 49.4% [95% CI 27.4-88.9]; mOS 22.6ms [95%CI: 12.3-NA]; median follow up was 117,1ms. Difference in OS was not statistically significant (p-value 0.8256), but difference in PFS was statistically significant (p-value 0.0026). NGS data were available for 22 pts (71%) of the BEV cohort; NF2 mutations were detected in 14 (63.63%); PTEN loss/mutation in 3 (9.67%); FGFR, JAK, ALK each in 1 case (3.2%).

Conclusions: BEV can be considered a useful therapeutic option to control disease in recurrent MEN pts although it appears not to impact survival compared to HYD. Further analyses on predictive biomarkers of efficacy is needed.

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544P Clinical and molecular features of primary central nervous system tumor with Lynch syndrome

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Background: Central nervous system tumour (CNST) is a heterogeneous group of human tumors that vary significantly in incidence by age, sex, and race/ethnicity. Lynch syndrome (LS), caused by germline pathogenic variants (PVs) in mismatch

repair (MMR) genes, leads to 2-8% lifetime risk to CNST. We aimed to identify clinical features of CNST with MMR PVs.

Methods: Germline mutations of MMR genes (including *MLH1*, *MSH2*, *MSH6*, *PMS2*) and microsatellite instability (MSI) were detected by next-generation sequencing (NGS) in CNST patients(pts). The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines.

Results: There were 47 of 4787 (0.98%) CNST pts identified with LS. The median age of LS CNST pts was 36 years (range: 3-77 years), and the detection rate of MMR PVs was higher in CNST pts< 40 years (n=28, p<0.05). Of 47 LS CNST included IDH-wildtype glioma (n=34, predominantly high-grade glioma), astrocytoma IDH-mutant(n=7), medulloblastoma(n=2), meningeal melanoma(n=1), pilocytic astrocytoma(n=1), diffuse hemispheric glioma H3 G34-mutant(n=1), ependymoma(n=1). This was the first report a pt with LS with meningeal melanoma. Unlike the conventional glioblastoma IDH-wildtype, LS-related high grade IDH-wildtype glioma did not have TERT promoter mutation, EGFR gene amplification, +7/−10 chromosome copy-number changes. In contrast, LS-associated high grade IDH-wildtype gliomas commonly harbor TP53, ATRX mutations. In addition, MSI-H was found in 31.9% (15/47) of LS CNST pts, MSI-L was found in 17.0% pts (8/47), and 51.1% (24/47) pts exhibited MSS.

Conclusions: MMR germline gene pathogenic mutations were carried by 1% of CNST pts, predominantly high-grade gliomas, and developed at an early age. Genetic profile of LS related high grade glioma was different from that of conventional GBMs, which suggested that the importance of adding MMR genes test to CNST.

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545P Antibody-fragment based immunotherapeutic approaches for medulloblastoma and rhabdomyosarcoma

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Background: Medulloblastoma (MB) with SHH-MB as most frequent subtyp is the most common pediatric brain tumor. Conventional therapy can result in severe brain damage and high relapse rates. Thus, targeted less immunogenic immunotherapy is needed. Neo-antigens are rare in pediatric cancers due to their low mutational load. But, SHH-MB overexpresses the EGF-receptor, a well-characterized immunotherapeutic target. Even though it is also expressed at low levels in healthy tissue, it was our immunotherapeutic-target of choice. We established a platform in order to test the target specificity in SHH-MB using EGFR-specific antibody fragments (scFv) as part of fusion proteins with a SNAP-tag. Then, the scFvs were used as part of immunotoxins (ITs) and bispecific T-Cell engagers (BiTEs). Apart from EGFR, *PIK3CA* mutations occur in SHH-MB and may also serve as therapeutic target. Besides MB the pediatric tumor rhabdomyosarcoma (RMS) also shows EGFR overexpression and abnormal signaling in the PI3-kinase pathway. RMS, the most common pediatric soft tissue sarcoma, shows brain metastasis. The Pi3-kinase inhibitor BKM-120, can therefore tested in combination with EGFR-specific immunotherapy.

Methods: ScFv-SNAP fusions were coupled to Benzylguanin-modified fluorophores under nucleophilic substituent reaction. Specific binding of all constructs was proved with flow cytometry, internalization with confocal microscopy. Impact on cell viability was tested in cell viability assays, luminescent cytotoxicity assays and AnnexinV-apoptosis assays. *In vitro*- Blood Brain Barrier (BBB) models were generated from hiPSCs (human inducible pluripotent stem cells).

Results: The EGFR-specific scFv shows specific binding and internalization to target cells. The IT demonstrates IC_{50}-values in the low nanomolar range and specific apoptotic effects. In combination with BKM-120 the IC_{50} decreases. BiTEs influence the cell viability with an effector to target cell ratio of 5:1 and show apoptotic effects. The IT and BKM-120 were used in the BBB-model showing preliminary results of permeability.

Conclusions: Targeted innovative scFv-based immunotherapy as highly specific and less immunogenic therapy for MB or RMS was established, also as combination therapy approach.

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546P Early urinary potassium level is predictive of delayed methotrexate (MTX) elimination in patients with primary central nervous system lymphoma (PCNSL)

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Background: First-line treatment of PCNSL includes high dose MTX. Nevertheless, MTX is associated with renal toxicity, requiring prolonged hospitalization and potentially compromising chemotherapy completion and so prognosis. Our objective was to identify early predictive factors of MTX delayed elimination.

Methods: We prospectively included all patients referred to our department for newly-diagnosed PCNSL. Daily serum and urinary creatinine and ionogram were collected from the day before MTX administration until elimination. Standard elimination delay of MTX was defined by plasmatic MTX level $\leq$ 0.05 µg/L before 72 hours. We conducted 2 independent training (TC) and confirmation (CC) cohorts.

Results: We included 64 cures (20 patients) in the TC and 59 cures (22 patients) in the CC between November 2020 to May 2021 and January 2022 to May 2022, respectively. At inclusion, median ages were 71 years (range 33-86) and 74 years (range 47-87), median KPS were 70% (range 40-80%) and 80% (range 40-100%) and median elimination delay of MTX was 95 hours (range 47-205) and 96 hours (range 62-264) in the TC and the CC respectively. In the TC, median urinary potassium level at day 1 (uK+D1) was 23.9 mmol/L (range 5.5-64.1). In multivariate analysis, older age (p=0.004), low KPS (p=0.036) and high uK+D1 (p=0.001) were associated with delayed MTX elimination. Using a ROC analysis (p=0.008, AUC=0.712), an optimal cutoff for uK+D1 was defined at 17.1 mmol/L with a specificity of 81% and a positive predictive value of 84%. In the CC, we confirmed in multivariate analysis that older age (p=0.002), low KPS (p=0.007) and high uK+D1 (p=0.004) remained associated with delayed MTX elimination. After merging the cohorts, we were able to predict a standard MTX elimination probability based on age and uK+D1. Patients younger than 70 years had a standard MTX elimination probability of 84% versus 33%, depending on low and high uK+D1, respectively. Conversely, older patients had a probability of 26% and 14%, respectively.

Conclusions: uK+D1 may be predictive of delayed MTX elimination, opening personalized perspectives for young patient management. Its relevance as an element of decision making need to be validated in a larger prospective cohort.

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547P Clinicopathological and molecular study of embryonal tumours with multilayered rosettes

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Background: To analyze clinicopathological features of ETMRs.

Methods: A total of 14 cases of ETMRs from 2016 to 2021 in Xuanwu Hospital of Capital Medical University were retrospectively summarized. The clinical and imaging characteristics, pathological and molecular characteristics were analyzed, and the related literature was reviewed.

Results: All 14 patients (6 males and 8 females) aged from 9 months old to 3 years old (mean 2 years) mainly had a history of headache or/and vomiting. Twelve tumors were supratentorial and two infratentorial, seven of which occurred in the frontal lobe. The MRI findings showed that the lesions were located in the third ventricle, and the enhanced MRI showed abnormal enhancement signals. The MRI enhancement all showed an abnormal enhancement signal. Pathological finding showed that 12 cases had displaying the morphological characteristics of ETMR. The distribution of tumor cells is sparse and uneven, and some cells arrange in multiple layers and grow around blood vessels, partially forming a "Homm-rett group" structure, island-like structure can be seen. IHC showed Syn and Lin28a were immunopositive in all 14 cases (14/14). GFAP and Olig-2 were partially immunopositive in 3 cases (3/14). EMA was dot-and/or-ring immunopositivity in 2 cases (90%, 2/14). At the same time, there was a case immunopositive for H3K27M, with the loss of H3K27me3. 12 ETMRs were available to detect C19MC and Dicer1 gene mutation. 11 in 12 (88.9%) were found to have C19MC amplification, and one have Dicer1 mutation as well as H3K27M mutation. Among the 14 patients after surgery, All 10 patients received adjuvant radiotherapy/chemotherapy,Progression-free survival was 6.2 months, and overall survival was 11 months.

Conclusions: ETMRs have relatively distinguishing clinical and histopathological features. C19MC alteration and Dicer1 gene mutation, can be considered as useful biomarkers for the diagnosis and differential diagnosis, and provide a direction for targeted therapy in the future.

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548P Diffuse midline gliomas H3K27-altered in adults, the experience of an oncology center

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Background: Midline gliomas H3K27-altered (GLM-H3K27) are a rare and very aggressive oncologic entity. Although the clinical, imaging, and prognostic characteristics are better characterized in childhood, studies of this pathology in the adult population are scarce.

Methods: Demographic, clinical, treatment, and survival characterization of adult patients with GLM-H3K27, followed at an Oncology Hospital between 2012-2022, through a retrospective review of clinical processes. The data cut-off was 31 December 2022.

Results: Cohort consisting of 17 patients, 53% male, mean age at diagnosis 38 years (18-63 years). The mean time from symptomatology to diagnosis was 3.9 months. The most common initial symptoms are related to cranial nerve dysfunction (6), headache (6) or motor defect (3). The most frequent anatomical locations were thalamus and trunk, 41% and 35%, respectively. Surgical samples were mostly obtained by biopsy (58%), the remainder by partial excision. The initial histological diagnosis varied, including grade 2 to 4 gliomas. In 88% of the cases (N=15) it was possible to identify the presence of the H3F3A K27M mutation by immunohistochemistry and/or mutational analysis of the gene, with 2 of the cases the diagnosis was made only by the loss of expression of H3K27me3. Most patients (82%) were treated with radiotherapy and chemotherapy; in 11.7%, isolated radiotherapy was performed, and only palliative care was given in one case. So far, 14 patients (70.1%) have died; 3 are alive and 1 patient was lost to follow-up. The median disease-free survival was 11 months (95%CI 8.6-13.4 months) and the median overall survival was 20 months (95%CI 12-28 months).

Conclusions: Our study highlights the clinical, anatomical and histological heterogeneity of this new and rare entity, particularly in adulthood. We emphasize the importance of the integrated diagnosis of this population, with the expectation that in the future an effective therapeutic approach can be implemented.

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COLORECTAL CANCER

549O Adagrasib with or without cetuximab in patients with KRASG12C-mutated colorectal cancer (CRC): Analysis of tumor biomarkers and genomic alterations

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Background: Adagrasib (ada) is a $KRAS^{G12C}$ inhibitor with favorable properties including 23 hr half-life, dose-dependent PK, and CNS penetration. $KRAS^{G12C}$ inhibitor resistance may occur in CRC via EGFR reactivation, and a dual EGFR/$KRAS^{G12C}$ blockade may be necessary to effectively treat $KRAS^{G12C}$-mutated CRC. In phase 1/2 cohorts of KRYSTAL-1 (NCT03785249), ada was well tolerated as monotherapy (mono) and in combination with cetuximab (cetux) in patients (pts) with $KRAS^{G12C}$-mutated CRC who were previously treated with chemotherapy, with a higher response (46%) and longer median progression-free survival (6.9 months) for ada + cetux.

Methods: Pts with previously treated $KRAS^{G12C}$-mutated CRC received ada mono (600 mg BID) or ada (600 mg BID) + cetux (400 mg/m^2 then 250 mg/m^2 QW or 500 mg/m^2 Q2W). Exploratory analyses in both cohorts included mechanisms of acquired $KRAS^{G12C}$ resistance and correlation of plasma ctDNA clearance and baseline tumor IHC-assessed EGFR expression with response. Plasma was collected at baseline, cycle (C) 2 day (D) 1, C4D1, and end of treatment (EOT). Acquired genomic alterations were characterized for pathogenicity and defined as absent at baseline and present at EOT.

Results: At data cutoff (16 June 2022), 44 pts had received ada and 32 ada + cetux. A total of 27 pts in the ada cohort and 11 in the ada + cetux cohort had paired plasma samples at baseline and EOT. Acquired genomic alterations were observed in 81% (22/27) and 73% (8/11) of pts on ada and ada + cetux, respectively, and included mutations, copy number changes, and fusions. Mutant allele frequency clearance of >95% by C2 occurred in 55% (16/29) and 88% (14/16) of pts on ada and ada + cetux, respectively. Preliminary data suggest a relationship between tumor EGFR expression and response to ada + cetux.

Conclusions: Exploratory analyses suggest diverse mechanisms of acquired resistance in pts treated with ada mono and in combination with cetux, and a greater depth of ctDNA response in pts treated with ada + cetux. Ada + cetux is being investigated in 2L CRC in the phase 3 KRYSTAL-10 trial (NCT04793958).

Clinical trial identification: NCT03785249.

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550O Safety and efficacy of D-1553 in combination with cetuximab in KRAS G12C mutated colorectal cancer (CRC): A phase II study

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Background: As a highly selective and potent $KRAS^{G12C}$ inhibitor, D-1553 has shown encouraging antitumor activity in patients (pts) with KRAS G12C mutated CRC. Targeting KRAS and EGFR pathways at the same time may enhance the antitumor activity of D-1553. An ongoing multi-country phase II study (NCT04585035) is evaluating the safety and efficacy of D-1553 combined with cetuximab, an EGFR antibody, in KRAS G12C mutated CRC.

Methods: Pts with metastatic CRC progressed after standard treatment were enrolled. Pts were required to have KRAS G12C mutations, and no prior KRAS G12C directed treatment. Enrolled pts received D-1553 600 mg BID combined with

cetuximab (standard dose). Study endpoints included efficacy (RECIST, v1.1), safety, and pharmacokinetics (PK).

Results: As of April 17, 2023, 29 pts (37.9% female, median age 56.0 [range 32-76] years, 65.5% with ≥3 prior therapies [median 3; range 1-6], 100% stage IV disease at baseline, and 24.1%/75.9% ECOG PS 0/1) were enrolled. At data cutoff, 20 (69.0%) pts remained on treatment. The median treatment duration was 5.95 (range 1.35-9.13) months with a median follow-up of 6.24 (range 2.33-9.13) months. A preliminary overall response rate of 51.7% (15/29) was observed and 9 out of 15 responders had confirmed response, with 5 still on treatment and their responses to be confirmed. The disease control rate was 93.1% (27/29). Median progression-free survival (PFS) was 7.56 months (95% CI: 5.49, NA). Treatment-related adverse events (TRAEs) of any grade occurred in 29 (100%) pts, with the most common (≥ 20%) being rash, increased AST, increased ALT, and paronychia, predominantly ≤ grade 2. Grade 3-4 TRAEs occurred in 3 (10.3%) pts, all of which were related to cetuximab. No grade 5 TRAEs were reported. TRAEs led to D-1553 dose interruption in 2/29 (6.9%) pts, to cetuximab dose reduction and interruption in 1/29 (3.4%) and 5/29 (17.2%) pts respectively, and cetuximab discontinuation in 1/29 (3.4%) pt.

Conclusions: Combination of D-1553 and cetuximab showed an acceptable safety profile and achieved a higher response rate than D-1553 monotherapy and a promising PFS in heavily pretreated pts with KRAS G12C mutated CRC. More data will be presented at the meeting.

Clinical trial identification: NCT04585035.

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551O Impact of baseline molecular alterations on the efficacy of tucatinib (TUC) plus trastuzumab (Tras) for HER2+, RAS WT metastatic CRC (mCRC) in MOUNTAINEER

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Background: HER2 is an actionable biomarker for mCRC, though the impact of concomitant genomic alterations is unknown. On the basis of the MOUNTAINEER study, TUC + Tras was approved by the FDA for use in pts with chemo-refractory HER2+, RAS-WT mCRC. Here we present the impact of concomitant baseline genomic alterations on the clinical activity of TUC + Tras.

Methods: MOUNTAINEER enrolled pts w/ locally assessed HER2+ mCRC by tissue immunohistochemistry (IHC), in situ hybridization (ISH), and/or next-generation sequencing (NGS). Baseline tissue and blood samples were retrospectively analyzed by IHC/FISH, PGDx tissue NGS and Guardant 360 blood NGS. cORRs (proportion of pts w/ CR or PR per RECIST v1.1 by BICR) and DoR were calculated for selected genomic alterations (SNVs and CNVs) occurring in ≥5 pts treated with TUC + Tras. This analysis was descriptive; no statistical comparisons were made.

Results: From 84 pts treated with TUC+Tras, 65 samples were available for FISH testing. cORR was numerically higher w/ greater HER2 amplification as measured by either HER2/CEP17 ratio (>5, n=50: cORR [95%CI] = 44.0% [30.0, 58.7]; ≤5, n=15: cORR [95%CI] = 26.7% [7.8, 55.1]) or HER2 copy number (>9.45, n=57: cORR [95%CI] = 42.1% [29.1, 55.9]; ≤9.45, n=8: cORR [95%CI] = 25.0% [3.2, 65.1]). NGS testing of tissue (n=45) and blood (n=66) samples from pts w/ a central HER2+ test result identified concomitant mutations and/or genomic amplifications in key genes including ERBB2, PIK3CA, APC, and TP53. In these pts, cORR and DOR were generally similar to those observed overall (Table).

Conclusions: This exploratory analysis of the MOUNTAINEER trial found generally consistent clinical efficacy of TUC + Tras to the primary analysis across subsets of pts w/ HER2+ RAS-WT mCRC and other clinically relevant genomic alterations.

Table: 551O

	cORR			DOR		
	n	%	95% CI	n	Months	95% CI
	Mutations					
Tissue NGS	45	46.7	31.7 – 62.1	21	15.3	8.9 – 25.5
ERBB2	6	66.7	22.3 – 95.7	-		
APC	36	44.4	27.9 – 61.9	16	16.6	6.1 – NE
TP53	40	45.0	29.3 – 61.5	18	16.6	8.9 – NE
ctDNA NGS	66	39.4	27.6 – 52.2	26	12.4	8.3 – 20.5
PIK3CA	7	28.6	3.7 – 71.0	-		
ERBB2	15	46.7	21.3 – 73.4	7	11.4	6.1 – NE
APC	37	45.9	29.5 – 63.1	17	15.3	6.2 – NE
	Amplifications					
Tissue NGS	45	46.7	31.7 – 62.1	21	15.3	8.9 – 25.5
ERBB2	44	47.7	32.5 – 63.3	21	15.3	8.9 – 25.5
BRCA2	5	80.0	28.4 – 99.5	-		
ctDNA NGS	66	39.4	27.6 – 52.2	26	12.4	8.3 – 20.5
BRAF	7	14.3	0.4 – 57.9	-		
CCND1	7	14.3	0.4 – 57.9	-		
CDK6	10	30.0	6.7 – 65.2	-		
EGFR	19	36.8	16.3 – 61.6	7	12.5	4.2 – NE
ERBB2	57	40.4	27.6 – 54.2	23	12.4	6.2 – 38.3
PIK3CA	5	40.0	5.3 – 85.3	-		

*cORR and DOR were not calculated for sample sizes <5.

Clinical trial identification: EudraCT Number 2020-000540-60.

Legal entity responsible for the study: Seagen Inc.

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Disclosure: J.H. Strickler: Financial Interests, Personal, Advisory Board: SeaGen, AstraZeneca, Amgen, Pfizer, Bayer, AbbVie, Natera, Viatris, Inivata, Silverback Therapeutics; Financial Interests, Personal, Other, Consulting: Mereo, GSK, Pionyr Immunotherapeutics; Financial Interests, Institutional, Invited Speaker: SeaGen, Roche Genentech, AbbVie, AstraZeneca, Amgen, Astar D3, Sanofi, Curegenix, Nektar, Leap Therapeutics, Daiichi Sankyo, Erasca, Gossamer Bio, Silverback Therapeutics. A. Cercek: Financial Interests, Personal, Advisory Board: Bayer, GSK, Janssen, Merck, Seagen, Pfizer; Financial Interests, Personal, Stocks/Shares: Haystack; Financial Interests, Personal, Royalties, Pending patent neoadjuvant PD1 blocked in mismatch repair deficient solid tumors: Memorial Sloan Kettering; Financial Interests, Personal, Royalties, Pending patent for HAI FUDR in DPD metastatic colorectal cancer: Memorial Sloan Kettering Cancer Center; Financial Interests, Institutional, Invited Speaker, Clinical trial funding: Seattle Genetics; Financial Interests, Institutional, Invited Speaker, Clinical trial: GSK. K. Ng: Financial Interests, Personal, Advisory Board, Was also a paid speaker as well for colorectal cancer awareness in March 2022: Bayer; Financial Interests, Personal, Advisory Board: Bicara Therapeutics, GSK, Pfizer, Redesign Health; Financial Interests, Institutional, Funding: Evergrande Group; Financial Interests, Institutional, Research Grant: Janssen, Revolution Medicines; Non-Financial Interests, Leadership Role, Chair of Scientific Program Committee for 2023 Annual Meeting: ASCO; Non-Financial Interests, ,Advisory Role: Colorectal Cancer Alliance, Colon Cancer Foundation, Fight CRC, Prevent Cancer Foundation; Non-Financial Interests, Principal Investigator: Alliance for Clinical Trials in Oncology; Non-Financial Interests, Institutional, Product Samples, Provides product for an NCI cooperative group phase III trial for which I am National Study Chair: Pharmavite. S. Siena: Financial Interests, Personal, Advisory Board, Advisory Board Member: Agenus, AstraZeneca, Bristol Myers Squibb, Checkmab, Daiichi Sankyo, GSK, Novartis, Seagen, T-One-Therapeutics. T. André: Financial Interests, Personal, Advisory Board, Advosiry Board on February 12, 2021: Astellas Pharma; Financial Interests, Personal, Advisory Board, Advisory Board on February 2021: Kaleido Biosciences; Financial Interests, Personal, Invited Speaker, and advisory board 2021: Amgen; Financial Interests, Personal, Invited Speaker, Invited speaker in a symposuim december 2020: AstraZeneca; Financial Interests, Personal, Advisory Board, and consultant fees and consultant contract 2021 and 2022: Bristol Myers Squibb; Financial Interests, Personal, Advisory Board, Advisory board in Janaury 2020 : Clovis; Financial Interests, Personal, Advisory Board, Advisory board in January 2020: Gritstone Oncology; Financial Interests, Personal, Advisory Board, Advisory board 2020: Haliodx; Financial Interests, Personal, Advisory Board, and consultant fees/consultant contract and invited speaker: MSD Oncology; Financial Interests, Personal, Invited Speaker, and other: Pierre Fabre; Financial Interests, Personal, Invited Speaker, in an symposuim in 2020: Roche; Financial Interests, Personal, Invited Speaker, in a meeting in 2019: Ventana; Financial Interests, Personal, Invited Speaker, In a educational meeting in 2019: Sanofi; Financial Interests, Personal, Advisory Board, in a symposuim in 2020: Servier; Financial Interests, Personal, Expert Testimony, Consultant with personnal fees and invited speaker: Servier; Financial Interests, Personal, Advisory Board, in 2019: GSK; Financial Interests, Personal, Invited Speaker, in 2020 and 2021: GSK; Financial Interests, Personal, Invited Speaker, Virtual symposuimLecture: 1 MSI-H CRC: Implementation of Immunotherapy in clinical practice (30 minutes) – (this will be pre-recorded) Q&A – Live Q&A – (10 minutes) (on July 2, 2021): MSD Oncology; Financial Interests, Personal, Invited Speaker, June 2022 : Sanofi; Financial Interests, Personal, Advisory Board, Contract 2021, 2022, 2023: Merck & Co., Inc; Financial Interests, Personal, Advisory Board, Contrat 2019, 2020, 2021, 2022: Bristol Myers Squibb; Financial Interests, Personal, Advisory Board, Contract 2021: Gritstone Oncologie; Financial Interests, Personal, Invited

Speaker, June 2022 and June 2023 during ESMO GI meeting: Seagen; Financial Interests, Personal, Invited Speaker, Contract of consulting 2021 and 2022 and 2023: MSD Oncology; Financial Interests, Personal, Advisory Board, September 2022 : GSK, Seagen; Financial Interests, Personal, Invited Speaker, Contract of consulting 2022 and 2023: GSK; Financial Interests, Personal, Invited Speaker, Contract of consulting 2022: Nordic Pharma; Financial Interests, Personal, Invited Speaker, October 2022: Merck Serono; Financial Interests, Personal, Other, Educationnal in 2022: Roche; Financial Interests, Personal, Other, Contract of consulting 2020, 2021, 2022,2023: Servier; Financial Interests, Personal, Advisory Board, 2023: Aptide Health, Glilead; Financial Interests, Institutional, Other, Investigator and scientific committee president: Gercor Academic group; Financial Interests, Institutional, Invited Speaker, PI Garnet study: GSK; Financial Interests, Institutional, Invited Speaker, Keynote 164 and 171 and 811 and C08: MSD; Financial Interests, Institutional, Invited Speaker, Bristol Myers Squibb CA209-8HW, Bristol Myers Squibb CA209-142, Bristol Myers Squibb CA209-577: Bristol Myers Squibb; Financial Interests, Institutional, Invited Speaker, SPOTLIGHT study: Astellas; Financial Interests, Personal, Invited Speaker, and International PI (trial chair Solstice study): Servier; Financial Interests, Personal, Invited Speaker, MOUNTAINEER and MOUNTAINEER-03 study (PI for France) 2022, 2023: Seagen; Non-Financial Interests, Invited Speaker, Investigator: Gercor group; Non-Financial Interests, Invited Speaker, President since October 2022: ARCAD Foundation . 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Hubbard: Financial Interests, Personal, Advisory Board: Merck; Financial Interests, Institutional, Advisory Board: Incyte, Bayer, BeiGene; Financial Interests, Institutional, Invited Speaker: Boston Biomedical, Senhwa Biosciences, Bayer, Merck, Taiho Pharmaceutical, TreoBio, Hutchison MediPharma, Seattle Genetics, Tovogene, Trioncology, Incyte, Pionyr, G1 Therapeutics, Effector Therapeutics, Roche. A.L. Coveler: Financial Interests, Institutional, Invited Speaker: Seagen, AbGenomics, Novocure, Amgen, Actuate Therapeutics, Surface Oncology, Nucana, Nextrast. C. 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552O FOxTROT: Results of embedded phase II evaluating the addition of panitumumab (pan) to neo-adjuvant FOLFOX for patients (pts) with KRAS-wt colon cancer (CC) with extended biomarker panel

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Background: The FOxTROT trial has reported advantages of neoadjuvant chemotherapy (NAC) in locally advanced CC and also reported the embedded phase II which tested the addition of panitumumab (pan) to NAC in KRAS-wt pts. Here we present detailed results of neoadjuvant FOLFOX +/- pan with extended hypothesis-led biomarker testing, to reflect current pan use.

Methods: Pts had operable CC; CT-predicted stage T3-4, N0-2, M0, and KRAS-wt. *KRAS*-wt pts who had been allocated to NAC could optionally be sub-randomized 1:1 to 6 weeks FOLFOX ± pan during the NAC phase. All pts received FOLFOX post-op. RAS/RAF were tested by NGS; EREG/AREG (EGFR receptor ligands) by RNAseq. Primary endpoint of this exploratory analysis is RFS in RAS/BRAF-wt pts; secondary endpoints include safety, histological downstaging, DFS, CC specific survival, and test impact of primary tumor location (PTL) and EREG/AREG expression on pan effect.

Results: Biomarker data was available for 232(83%) pts randomised; 22(9.5%) were RAS mut; 41/210(19.5%) BRAF-mut. In 169 RAS/BRAF-wt pts with a median 42 month follow up, RFS was 88.1% in pts treated with FOLFOX+pan compared with 79.2% with FOLFOX (HR=0.51,p=0.09). Effect size was stronger in pts with high EREG/AREG (RFS HR=0.29,p=0.04), and for CC-specific survival (see table). Pan did not result in greater pathological response (TRG 1-3 16.4% vs 22.4%,p=0.27) or downstaging compared with FOLFOX. Pan was associated with higher rates of grade 3 diarrhoea (8% vs 3%) and rash (22% vs 2%), and trend towards more post-operative complications than FOLFOX alone.

Table: 552O

RAS/BRAF-wt population		Events	FOLFOX + pan vs FOLFOX HR	p-value
RFS	Overall	27/169	0.51 (0.24-1.10)	0.09
	Left PTL	16/102	0.45 (0.16-1.23)	0.12
	Right PTL	11/67	0.67 (0.20-2.21)	0.51
	High EREG/AREG	13/74	0.29 (0.09-0.99)	0.04
	Low EREG/AREG	13/83	0.75 (0.25-2.22)	0.60
DFS	Overall	39/169	0.51(0.27-0.97)	0.04
CC-specific death	Overall	13/169	0.23 (0.06-0.83)	0.03

Conclusions: In this exploratory analysis, neoadjuvant FOLFOX+ pan showed promising activity in RAS/BRAF-wt pts compared with FOLFOX alone in pts with operable CC. Further pt selection with EREG/AREG appears beneficial. No impact on tumour regression was seen with pan. Further testing and safety assessment is warranted.

Clinical trial identification: ISRCTN 87163246.

Legal entity responsible for the study: The authors.

Funding: Amgen.

Disclosure: J. Seligmann: Financial Interests, Personal, Other, Travel: Bristol Myers Squibb; Financial Interests, Personal, Other, CME activities: GI Connect; Financial Interests, Personal, Invited Speaker: Merck Serono, Pierre Fabre, Servier; Financial Interests, Personal, Advisory Board: Pierre Fabre, Seagan, Ventana, Zentalis, AstraZeneca, Elevate Oncology, Merck Serono; Financial Interests, Institutional, Other, Research Funding: Pierre Fabre Medicament; Financial Interests, Personal, Other, Review of guidelines, consultancy: Roche Diagnostics; Financial Interests, Personal, Other, travel: Servier. All other authors have declared no conflicts of interest.

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553O Prognostic value of KRAS and BRAF mutations in microsatellite stable (MSS) and unstable (MSI) stage III colon cancer: An ACCENT/IDEA pooled analysis of 7 trials

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Background: Whether *KRAS* and *BRAFV600E* mutations are prognostic in stage III CC remains controversial and has never been clearly analyzed in the subgroup of MSI-H patients (pts) due to sample size limitations. The prognostic value of individual KRAS mutations has also not been widely studied.

Methods: We studied the prognostic impact of individual *KRAS* exon 2 and *BRAFV600E* mutations in pts with surgically resected stage III CC who participated in 7 clinical trials from the ACCENT/IDEA databases. Associations between mutations and time to recurrence (TTR), overall survival (OS) and survival after recurrence (SAR) were assessed by Cox model, stratified by study and adjusted for sex, age, performance status, T and N stage, disease grade, and primary tumor location. The prognostic value of individual KRAS exon 2 submutations (G12A, G12C, G12D, G12R, G12S, G12V, G13D and others) was also analyzed.

Results: 8286 pts were included, 11.6% were MSI-H (N=967) with 5 yr recurrence rates of 24.1% for MSI-H and 30.3% for MSS subgroups. *BRAFV600E*, *KRAS* exon 2 mutants or double wild type represented 40.6%, 18.1% and 41.3% of the MSI-H group and 7.8%, 38.6% and 53.7% of the MSS group, respectively. In the MSS group, 5y TTR rates of 61.7%, 66.4% and 73.2% emerged in pts with *BRAFV600E, KRAS* exon 2 mutants and in double wild-type pts, respectively, (adjHR: 1.34 and 1.32, both $p<0.001$), while in the MSI group shorter TTR in mutated subgroups was not seen with 5y TTR rates of 76.1%, 75.8% and 75.6%, respectively (adjHR: 1.01 and 0.98, both $p>0.05$). Similar results were found for OS. However, SAR was significantly shorter for pts with tumors harboring a *KRAS* exon 2 or *BRAFV600E* mutation in both MSS (adjHR: 1.16 and 2.05; both $p<0.0001$) and MSI (adjHR: 1.76 and 2.00; both $p<0.05$) pts. No major differences were noted in the prognostic value of *KRAS* exon 2 submutations.

Conclusions: In the largest analysis of the association of *KRAS* exon 2 and *BRAFV600E* mutations and disease outcome in resected stage III CC, either mutation was associated with significantly shorter DFS, OS and SAR in MSS tumors, but only with shorter SAR in MSI-H tumors. In addition, all *KRAS* codon 12 and 13 mutations had similar prognostic value.

Clinical trial identification: IDEA France: NCT00958737 PMID: 29620995 C07: NCT00004931 PMID: 17470851 C89803: PMID: 17687149 PETACC3: PMID: 19451425 C08: PMID: 20940184 PETACC8: EudraCT 2005-003463-23 PMID: 24928083 N0147: NCT00079274 PMID: 22474202

Legal entity responsible for the study: ACCENT group.

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P. Laurent-Puig: Financial Interests, Personal, Invited Speaker: Amgen, Roche, Sanofi; Financial Interests, Personal, Advisory Board: Biocartis, Pierre Fabre; Financial Interests, Personal, Ownership Interest: Methys DX; Financial Interests, Institutional, Research Grant: Federation Francophone de Cancerologie Digestive; Non-Financial Interests, Leadership Role: President of Canceropole Ile de France. Q. Shi: Financial Interests, Personal, Advisory Board: Regeneron Pharmaceuticals, Inc., Kronos Bio; Financial Interests, Personal, Advisory Board, DSMB: Hoosier Cancer Research Network, Yiviva Inc., Mirati Therapeutics Inc; Financial Interests, Institutional, Research Grant: Genentech, Bristol Myers Squibb, Novartis, Johnson & Johnson. All other authors have declared no conflicts of interest.

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554MO Cetuximab plus FOLFOXIRI versus cetuximab plus FOLFOX in *RAS* wild-type patients with initially unresectable colorectal liver metastases: The TRICE randomized clinical trial

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Background: The TRICE study was designed to determine whether intensifying the chemotherapy backbone in cetuximab-containing regimens could confer additional clinical benefits to RAS wild-type colorectal cancer (CRC) patients with initially unresectable liver metastases.

Methods: Patients were randomly assigned to receive either cetuximab plus FOLFOXIRI (triplet arm) or cetuximab plus FOLFOX (doublet arm) every 2 weeks. Primary efficacy analyses were conducted based on the intention-to-treat population, while

safety analyses were performed on patients who received at least one line of chemotherapy. The primary end point was the objective response rate (ORR). Secondary end points included the median depth of tumor response (DpR), early tumor shrinkage (ETS), R0 resection rate, progression-free survival (PFS), overall survival (OS), and treatment-related adverse events.

Results: From January 2018 to December 2022, 146 patients were randomized to the cetuximab plus FOLFOXIRI (n = 72) or the cetuximab plus FOLFOX (n = 74) treatment arms. The ORR was comparable with 84.7% versus 79.7% in the triplet and doublet arms, respectively (OR = 0.71, 95% CI 0.30 to 1.67; P = .43). Although intensifying the chemotherapy backbone led to a higher median DpR (59.6% vs. 55.0%; P = .039), other secondary outcomes remained comparable between the two arms. At a median follow-up of 26.2 months, the median PFS was 11.7 months in the triplet arm vs. 13.4 months in the doublet arm (HR = 1.37, 95% CI 0.91 to 2.07; P = .13). Additionally, the triplet arm was associated with a higher incidence of grade 3-4 neutropenia (44.1% vs. 27.0%; P = .03) and diarrhea (5.9% vs. 0%; P = .03).

Conclusions: Although intensifying upfront systemic chemotherapy in RAS wild-type metastatic CRC patients offered a better depth of tumor response, there was an increase in neutropenia and diarrhea incidence with no significant difference in ORR, PFS, and R0 resection rate.

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555MO Modified (m)-FOLFOXIRI plus cetuximab treatment and predictive clinical factors for RAS/BRAF wild-type and left-sided metastatic colorectal cancer (mCRC): The DEEPER trial (JACCRO CC-13)

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Background: The DEEPER trial, which evaluated m-FOLFOXIRI (irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU 2400 mg/m^2) plus cetuximab (cet) vs. bevacizumab (bev) as initial treatment in terms of depth of response (DpR) as the primary endpoint in *RAS* wild-type mCRC, has demonstrated a significantly better DpR of the cet arm (Tsuji A, et al. ASCO 2021). Moreover, longer PFS and OS in the cet arm were observed in *RAS*/*BRAF* wild-type and left-sided tumors although *BRAF* status was available for only half of the patients (pts) (JSMO 2023). An updated survival analysis was performed using *BRAF* status added by tumor tissue biomarker analysis.

Methods: The DpR and other clinical outcomes were evaluated in per protocol set (PPS) consisted of pts evaluable for the DpR at external review board. Survival analysis was performed according to clinical factors including primary tumor sidedness which was one of the stratification factors using a log-rank test. In 359 enrolled pts, *BRAF* status was available in 255 pts with biomarker analysis for 71 pts. All statistical tests were two-sided, and *P* values $\leq$ 0.05 were deemed significant.

Results: 321 pts were defined as PPS (median age 65y, 64% male, PS0/1: 91%/9%, left/right primary: 84%/16%). In 178 pts with *RAS*/*BRAF* wild-type and left-sided tumors, DpR and PFS both were significantly better in the cet compared to the bev arm (DpR, median 59.2% vs. 47.5%, *P*=0.0017; PFS, median 14.5 vs. 11.9 months, HR 0.71, *P*=0.032). A sub-group analysis by clinical factors showed that PFS was better in the cet arm among pts without surgical resection of R0/1 (HR 0.66, *P*=0.029), and it was significantly longer in pts with extra-hepatic metastases (HR 0.63, *P*=0.015) but not liver-limited disease. In addition, in the cet arm, male had a better PFS compared to female. Median PFS was longer in the cet compared to the bev arm among male (18.0 vs. 13.1 months, HR 0.72, *P*=0.096) but not female.

Conclusions: m-FOLFOXIRI plus cet regimen could be a good option for upfront chemotherapy with high DpR and longer PFS in mCRC pts with *RAS*/*BRAF* wild-type and left-sided tumors. The benefit may be relevant for pts with extra-hepatic metastases or male.

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556MO A phase II clinical trial of sintilimab plus chidamide combined with or without bevacizumab in patients with MSS/pMMR metastatic colorectal cancer

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Background: Immune checkpoint inhibitors(ICI) have shown significant clinical benefit for MSI-H/dMMR metastatic colorectal cancer (mCRC) patients. However, the majority of MSS/pMMR mCRC patients show no response to immunotherapy and better combinations are currently lacking. Based on our preclinical research, we designed a study to explore whether an ICI sintilimab combined with an HDAC inhibitor chidamide, with or without bevacizumab would show efficacy in MSS/pMMR mCRC patients.

Methods: This open-label, multicenter trial (NCT04724239) recruited patients with MSS/pMMR mCRC that had failed or were intolerant to at least two lines of systemic therapies. The patients were randomly assigned to two arms, sintilimab plus chidamide (doublet) group, and sintilimab plus chidamide combined with bevacizumab (triplet) group. Patients in the doublet group received sintilimab 200 mg IV q3w plus chidamide 30 mg PO biw. Patients in the triplet group received sintilimab 200 mg IV q3w plus chidamide 30 mg PO biw and bevacizumab 7.5 mg/kg IV q3w. The primary endpoint was progression-free survival rate achieved at 18 weeks (18wPFS). The secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety.

Results: Between March 2021 and April 2022, 23 and 25 patients were randomly allocated to the doublets group and triplets group. 18wPFS was 17.4% in the doublets group and 66.7% in the triplets group (P = 0.0012). ORR was 13.0% and 44.0%, and DCR was 39.1% and 72.0% in the doublets and triplets group. The median PFS was 1.5 months with doublets and 7.3 months with triplets (P = 0.008). The median OS for the triplet arm had not been reached, while the median overall survival for the doublet arm was 18.9 months (P = 0.41). The most common treatment-emergent adverse events (TEAEs) were proteinuria (60.9%), thrombocytopenia (43.5%), and animea (39.1%) with doublets and thrombocytopenia (72.0%), proteinuria (72.0%), and neutropenia (60.0%) with triplets. Grade 3 and above TEAEs occurred in 7 (30.4%) patients in the doublet arm and 13 (42.0%) patients in the triplet arm.

Conclusions: Sintilimab combined with chidamide and bevacizumab had promising efficacy and tolerable toxicity in MSS mCRC patients.

Clinical trial identification: NCT04724239.

Legal entity responsible for the study: The authors.

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557MO Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic anal squamous cell carcinoma: Subgroup analysis of the PEVOsq basket trial

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Background: No standard therapies beyond first line are established for advanced squamous cell anal carcinoma (SCAC). Although PD-1 blockade demonstrated activity in patients (pts) with advanced SCAC, response rate is modest. Preclinical data suggests that vorinostat (V), an HDAC inhibitor, might improve immunotherapy efficacy by modulating the epigenome.

Methods: PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of pembrolizumab (P) in combination with V in pts with recurrent and/or metastatic squamous carcinomas. Pts had to be PD1/PD-L1 antagonist-naïve with no restriction in terms of prior lines of treatments. P dose was 200 mg Q3W IV, and V 400 mg QD PO. Sample size was determined using an A'Hern design with the following hypotheses (alpha=5%, power=90%, p0=15%, p1=40%). Primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

Results: Among 112 included pts, 29pts with SCAC were evaluable for safety and efficacy. Median age was 63 years old [range: 49-84], 23 were female and the median number of prior lines of therapies was 2 [range: 0-4]. Nine pts (31.0%) had an objective response [95%CI: 17.2; 47.9] and median DOR was not reached [95%CI: 5.6-NR]. Median PFS and OS were 5.8 [95%CI: 2.7-11.0] and 18.8 months [12.8-NR] respectively. Among the 22 pts with p16 evaluated, all were positive. Eighteen (62.1%) pts developed G3/4 treatment related adverse events. P and V were stopped for toxicity in 13.0% and 44.4% of pts, respectively. 79.3% of pts had a dose-reduced of V for toxicity including hematotoxicity, gastrointestinal disorders, asthenia and creatinine increase. Results according to PDL1, MSI, TMB and HPV will be presented at the meeting.

Conclusions: PEVOsq study met its primary endpoint, documenting promising antitumoral activity of the association of P+V in heavily pretreated SCAC pts. However, the high rate of toxicities requires a special attention in future trials.

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558MO Circulating tumor (ct)DNA as a prognostic biomarker in patients (pts) with resected colorectal cancer (CRC): An updated 24 months (mos) disease free survival (DFS) analysis from GALAXY study (CIRCULATE-Japan)

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Background: Postoperative ctDNA-based molecular residual disease (MRD) is reported to be associated with a high risk of recurrence. Here, we present an updated analysis on the prospective, observational GALAXY study.

Methods: Serial ctDNA was analyzed using tumor-informed assay (Signatera™) at 1 (4-week (wk)), 3, 6, 9, 12, 18, and 24 mos after surgery until recurrence in pts with resectable CRC. The primary endpoint was disease-free survival (DFS).

Results: Among 3,034 pts with clinical stage II-IV CRC enrolled between May 2020 and Nov 2022, 2,280 pts were included in this study. The median follow-up period was 16.5 mos (range: 0.1 - 31.9). Pts with ctDNA-positivity at 4-wk timepoint demonstrated a significantly inferior DFS compared to ctDNA-negative pts (HR: 16.9, $p<0.0001$). We further explored the benefit of adjuvant chemotherapy (ACT) amongst pts with stage II-III (N=1,555), in MRD-negative pts (N=1,333), 24-mo DFS was 95% in ACT group and 92.5% in no ACT group with no significant difference (HR: 1.4, p=0.2), whereas MRD-positive pts (N=222) showed significant benefit from ACT (HR: 0.4, $p<0.0001$) with a 24-mo DFS of 51.9% vs Not Reached. Additionally, within all stage pts who received ACT for either 3 mos or 6 mos, MRD-negative pts (N=606, HR: 1.1, p=0.89) showed no significant survival difference between the 2 cohorts while MRD-positive pts showed a significant benefit from 6 mos of ACT (N=154, HR: 0.4, p=0.002). On ctDNA dynamics analysis between 4 -12 wks, compared to pts who remained ctDNA-negative (N=941), a significantly shorter DFS was observed for pts who converted (N=22, HR: 11, $p<0.001$) or remained positive (N=81, HR: 20, $p<0.001$), respectively. Multivariate analysis in pts with stage II-III for DFS revealed that ctDNA-positivity was the most prognostic factor associated with poor outcomes (HR: 11.33, $p<0.001$).

Conclusions: Here we present an updated analysis on the GALAXY cohort with >2,000 pts analyzed. Our results indicate that pts with MRD-positivity showed benefit from ACT, possibly 6-mos ACT. Overall ctDNA status remains the most significant prognostic factor and predictive of pt outcomes.

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559MO Rechallenge with EGFR inhibitors in ctDNA RAS/BRAF wild type refractory metastatic colorectal cancer: Individual patients' data pooled analysis from 4 phase II trials

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Background: Rechallenge with anti-EGFR inhibitors demonstrated clinical activity in patients (pts) with refractory circulating tumor DNA (ctDNA) *RAS/BRAF* wild type (wt) metastatic colorectal cancer (mCRC) and it is included as an option in clinical guidelines. However, the available evidence (III C) is derived from small retrospective/prospective studies.

Methods: We conducted an individualized patients' data pooled analysis of pts enrolled in the CAVE, VELO, CRICKET and CHRONOS trials treated with anti-EGFR rechallenge with *RAS/BRAF* wt ctDNA. Overall survival (OS), progression free survival (PFS), overall response rate (ORR) and disease control rate (DCR) were calculated. Safety was reported.

Results: Overall, 114/194 pts that received anti-EGFR rechallenge as experimental therapy (48 cetuximab plus avelumab, 26 trifluridine/tipiracil plus panitumumab, 13 irinotecan plus cetuximab and 27 panitumumab) had *RAS/BRAF* wt baseline plasma ctDNA and were included in the current analysis. The study population included heavily pre-treated pts: 83/114 (72.8%) and 31/114 (27.2%) pts received rechallenge with EGFR inhibitors as third- or later lines of treatment, respectively. Median PFS (mPFS) and median OS (mOS) were 4.0 months (95% CI, 3.2-4.7) and 13.1 months (95% CI, 9.5-16.7). One patient achieved complete response (CR), 19 pts displayed partial response (PR), while 65 and 29 had stable disease (SD) and progressive disease as best response, respectively. The ORR (CR+PR) was 17.5% (20/114); DCR (CR+PR+SD) was 74.6% (85/114). Almost one of three pts significantly benefited from anti-EGFR rechallenge therapy (6-months PFS rate, 32.5%; 18-months OS rate, 31.6%). Treatments showed manageable toxicity, in lines with previous findings.

Conclusions: Results of this individual patients' pooled analysis demonstrate promising clinical activity of rechallenge with EGFR inhibitors with nearly one-third of the pts experiencing long PFS that lead to prolonged survival. Thus, rechallenge with anti-EGFR-based strategies might be considered as a therapeutic option in the continuum of care of pts with refractory ctDNA *RAS/BRAF* wt mCRC.

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560MO Maintenance with 5FU/LV-Aflibercept after induction with FOLFIRI-Aflibercept vs FOLFIRI-Aflibercept until progression in older patients (pts) in 2nd line metastatic colorectal cancer (mCRC): The randomized AFEMA trial

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Background: FOLFIRI-Aflibercept (A) is one of the 2nd-line standard treatments for mCRC. We evaluated the efficacy and safety of induction with FOLFIRI-A (6 cycles) followed by maintenance with 5FU/LV-A or FOLFIRI-A until progression in older pts with mCRC.

Methods: This was a multicenter, randomized, open-label, non-inferiority phase II trial. Pts aged $\geq$70 years who failed a prior oxaliplatin-based regimen, were randomly assigned (1:1) to induction with 6 cycles FOLFIRI-A followed by maintenance with 5FU/LV-A until progression (arm A, experimental) or FOLFIRI-A until progression (arm B, control). Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), and safety. To claim non inferiority with 95% CI, the upper limit of the boundary could not exceed HR=1.5, with one-sided α=0.075 and 80% power.

Results: Between November 2017 and February 2022, 170 pts were randomized to arm A (n=85) or arm B (n=85). Both arms were comparable at baseline (median age 74 years). Over a median follow-up time of 12.2 months (m) in arm A vs 10.9 m in arm B, most pts had died (arm A 83.5%, arm B 88.2%) mainly from disease progression. Arm A was non inferior to arm B in terms of PFS (HR=0.781 [95% CI 0.566-1.076]). There were also no significant differences in OS and ORR between arms (Table). Grade $\geq$3 adverse events related to treatment occurred in 58.8% of pts in arm A vs 62.4% in arm B (p=0.754). Severe asthenia was significantly higher in arm B during the maintenance phase (4.5% vs 21.6%, p=0.038).

Conclusions: Primary endpoint was met: induction with 6 cycles FOLIRI-A followed by maintenance with 5FU/LV-A was non-inferior to FOLFIRI-A until progression, in terms of PFS. OS and ORR did not either differ between arms. In older pts, severe asthenia was significantly reduced with 5FU/LV-A maintenance.

Table: 560MO

Efficacy	Arm A Experimental	Arm B Control	p-value
	FOLFIRI q2w + A 4 mg/kg IV 6 cycles 5FU/LV q2w + A 4mg/kg IV	FOLFIRI q2w + A 4 mg/kg IV	
PFS (m), median (95%CI)	6.1 (5.3-6.9)	5.5 (4.8-6.2)	0.128[a]
OS (m), median (95%CI)	12.2 (10.6-13.9)	11.5 (8.7-14.4)	0.466[a]
ORR, % (95%CI)	20 (12.1-30.1)	9.4 (4.2-17.8)	0.082[b]

[a]Log-rank [b]Fisher test

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561P Risk of colorectal cancer and premalignant lesions after kidney transplantation

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Background: Improved survival of kidney transplant recipients has led to an increased cancer risk, including colorectal cancer (CRC). We hypothesize that impaired immunosurveillance allows progression of sessile serrated lesions (SSL), leading to a higher incidence of immunogenic mismatch repair deficient (dMMR), but not mismatch repair proficient (pMMR) CRC.

Methods: The nationwide Dutch transplant, pathology, and cancer registries were linked by probabilistic matching to retrieve clinical data of all transplant patients between 2000-2022. A standardized incidence ratio (SIR) was calculated for CRC adjusted for age, sex, and incidence year. Mismatch repair (MMR) status was determined through immunohistochemistry and risk ratios (RR) were estimated. Premalignant lesions were identified within the Dutch CRC screening program. Kidney transplant patients were 1:4 matched to controls based on age, sex, and year of screening.

Results: 20 181 kidney transplant patients were identified between 2000-2022 (Table). The mean recipient age was 48 years and 60% were male. 218 tumors were observed, resulting in a SIR of 1.11 (95% CI: 0.96-1.26). In the 162 transplant patients in which MMR status was determined, dMMR occurred more frequently compared to the general population, RR 2.1 (95% CI: 1.6-2.7). Polyps were identified in 488 kidney transplant patients and matched to 1952 patients without kidney transplantation. SSL with dysplasia occurred more often in the transplantation cohort, RR 2.3 (95% CI: 1.3-3.9).

Table: 561P Incidence of CRC

	CRC	
	Transplantation cohort	Control
Total no. of people	20 181	Population (16.6 mln.)
Observed and expected tumors	218 (observed)	197 (expected)
dMMR/total tumors	45/162 (28%)	5640/42 982 (13%)
Stage I	9/37 (24%)	1214/9405 (13%)
Stage II	14/36 (39%)	2138/9635 (22%)
Stage III	10/35 (29%)	1839/15 370 (12%)
Stage IV	12/45 (27%)	449/8572 (5%)
Stage unknown	0/9	-
	Premalignant lesions (2015-2022)	
Total no. of people	488	1965
Total no. of findings	1336	5181
Adenoma	1099	4050
Serrated polyps	237	1131
Type of serrated polyps		
Hyperplastic	172 (73%)	748 (66%)
SSL	61 (26%)	351 (31%)
Traditional serrated adenoma	4 (1.6%)	32 (2.8%)
Dysplasia		
SSL with dysplasia	15 (25%)	38 (8%)
SSL without dysplasia	46 (75%)	313 (92%)

Conclusions: This population-wide study suggests an increased risk to develop dMMR CRC, in all stages, after kidney transplantation but not pMMR CRC. Furthermore, we show an increased incidence of dysplasia in SSL, in which dMMR frequently occurs. This illustrates that unchecked immunosurveillance in transplant patients is clinically apparent in precancerous and cancerous lesions. These findings could change the manner of CRC screening and management of kidney transplant patients.

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562P Quantifying the effect of colonoscopy and polypectomy rates in stage shift of colorectal cancer and reduced need for adjuvant chemotherapy

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Background: Existing literature supports the principle of early detection of colorectal cancer (CRC) via screening but has not definitively demonstrated an association between colonoscopy or polypectomy rates and CRC stage over time.

Methods: A longitudinal study was performed using the Australian national health database to obtain colonoscopy and polypectomy rates between 1998-2017. A second prospective database of CRC resection specimens was analysed for this period. The cohort was divided into three based on time intervals related to the national bowel cancer screening program: pre-commencement 1998-2006 (Period A), immediately post-commencement 2007-2011 (Period B), and subsequent years 2012-2017 (Period C).

Results: Annual colonoscopy rates doubled, and polypectomy rates tripled during the study ($p<0.001$). A total of 4506 patients underwent colorectal cancer resections. Annual colonoscopy rate correlated to a lower T-stage ($p=0.038$) and lower N-stage ($p=0.026$) leading to a 7% absolute (13.4% relative) increase in early CRC (stage I-II) in Period C ($p<0.001$). Across the study there was also a significant increase in right-sided tumours, and concurrent MMR deficiency and BRAF mutation.

Conclusions: Polypectomy and colonoscopy rates increased after the introduction of a national screening program which correlated to a clinically relevant shift to earlier CRC stages, a reduction in CRC incidence which manifested five years after implementation, and a reduced need for adjuvant chemotherapy.

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563P The impact of participation in colorectal cancer screening: A population-based results from Lithuania

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Background: Around 1.9 million new cancer cases and around 930,000 deaths were attributed to colorectal cancer (CRC) worldwide in 2020. The European Union recommends population-based CRC screening. Reported long'term results from various CRC screening programs are quite controversial as some of them report no survival gains. In June 2009 the CRC screening program was initiated in Lithuania. The aim of the study is to report the impact of CRC screening program on long-term mortality.

Methods: The anonymous data of the population aged 50-74 from the years 2013 to 2019, who participated in the CRC screening program were extracted from the statistical database of the National Health Insurance Fund, which provided both, the participation in different services of screening indicated by specific codes, and the mortality and survival marked in the database. For statistical analysis we divided patients in three groups: Negative fecal immunochemical test (FIT); positive FIT and screening colonoscopy performed; positive FIT and screening colonoscopy was not performed. The statistical analysis was performed using the R statistical software package v4.2.2.

Results: From the year 2013 to 2019 a total of 1,521551 people participated in the screening program. During the observation period 66920 (4.4%) patients died. The highest mortality was seen in patients that were diagnosed with cancer (19%). High mortality was seen in patients that did not proceed with further colonoscopy after a positive FIT. These patients had a significantly higher mortality rate: Negative FIT (4.2%) vs. Positive FIT + colonoscopy (4.9%) vs. Positive FIT - colonoscopy (8.6%); $p<0.001$. A univariate logistic regression analysis revealed that positive FIT + colonoscopy (OR 1.19 95% CI 1.15-1.24; $p<0.001$) and positive FIT - colonoscopy (OR 2.18 95% CI 2.12-2.24; $p<0.001$) groups had significantly increased mortality risks when compared to the negative FIT group.

Conclusions: Fully completed screening after a positive FIT result is associated with significantly reduced mortality.

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564P A large-scale real-world study for colorectal cancer screening

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Background: Colorectal cancer (CRC) is a major public health concern worldwide. CRC screening is recommended for average-risk population starting at age 45 to 50. However, the participation rate of CRC screening is often low due to lack of awareness or limited access to screening. Fecal DNA tests have shown promising performance in detecting CRC, but large-scale, prospective, population-based evidence for screening effectiveness has been lacking.

Methods: A community-based CRC screening program was implemented in Wuhan, Hubei Province, China, from 2021 to 2022. Residents aged between 45 and 60 were eligible. Stool samples were self-collected and returned to the community health centers. A fecal DNA test (ColoTect®) which detected methylation status of *SDC2*, *ADHFE1*, and *PPP2R5C* was used, with a sensitivity of 88% for detecting CRC and a sensitivity of 46% for detecting advanced adenoma, at a specificity of 92%. Participants who tested positive were advised to receive diagnostic colonoscopy. All participants provided written informed consent.

Results: 105,537 subjects were invited, 102,348 subjects returned stool samples and 101,217 passed quality control. 4,483 (4.4%) subjects tested positive for fecal DNA test, and 3,200 (71.3%) underwent colonoscopy. Among these, 2347 (73.3%) had abnormal colonoscopy findings, of which 1,330 (56.7%) subjects received pathological diagnosis. Positive predictive values (PPVs, number of cases/number of colonoscopies) for CRC, adenomas, polyps were 1.3%, 16.3%, and 21.6%, respectively; 28.0% of all colonoscopies showed colorectal neoplasm but lack pathological diagnosis. 6.1% showed other abnormalities such as enteritis. Compared to a national CRC program implemented in Hubei Province between 2018 and 2019 using fecal immunochemical tests and CRC risk assessment questionnaires, current program showed a lower initial positive rate (4.4% vs. 17.4%), higher PPVs for CRC (1.3% vs. 0.08%) in the age-matched group, and a higher adherence rate for colonoscopy (71.3% vs. 18.2%).

Conclusions: Preliminary prospective evidence suggested that fecal DNA tests had promising diagnostic yield in population-based CRC screening, outperforming FIT/risk assessment questionnaire-based screening strategy.

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565P Real-world data of early-onset colon cancer (early-onset CC) from the AIO colopredict plus (CPP) registry: Clinical and molecular characteristics, treatment and outcome

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Background: The incidence of early-onset colon cancer (early-onset CC, age <50 years (yrs)) is rising with limited data on its clinical and molecular characteristics. We analyzed a real-world cohort of the AIO ColoPredict Plus (CPP) Registry.

Methods: CPP collects data and tissue from patients (pts) with CC UICC stage I-III. Clinical and molecular characteristics were assessed comparing pts <50yrs with pts 50+ using student's Test and Fishers exact test. Disease-free survival (DFS) rate at 3 yrs was reported. Comorbidity was assessed by Charlson comorbidity index (CCI). Median follow-up was 28.1 months.

Results: Out of 9215 pts 479 (5%) had early-onset CC (median age 44 yrs (22-49) vs. 72 yrs (50-100) in late-onset CC). There were no significant differences regarding sex or BMI. Younger pts had less comorbidities (CCI 0: 91%) than older pts. (CCI 0: 60%, p <0.001). Interestingly, younger patients had larger tumors (p=0.045), more often lymph node metastases (p=0.002) and thus higher UICC stages (p<0,001). Tumor localization was predominantly left-sided in early- (53%) and right-sided in late-onset CC (61%, p<0,001). Younger pts more often received adjuvant chemotherapy (p<0,001) and more frequently oxaliplatin combinations (p<0,001). Mutational analysis was available in 5045 pts, 5% (264 pts) with early-onset CC. No significant difference in K- or N-RAS mutations or MSI were detected. The KRAS subtype p.G12C and BRAF mutations were significantly less prevalent in early-onset compared to late-onset CC (p=0,03 and p<0,01). Younger pts had a better 3 yrs DFS rate.

Conclusions: Pts with early-onset CC in our unique real-world cohort are more often UICC stage III with left primary tumors and better DFS. They also display distinct molecular features which should be considered when making treatment decisions.

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566P Long-term survivorship outcomes of adolescents and young adults (AYA) with cancer of the lower gastrointestinal tract

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Background: The incidence of lower gastrointestinal tract (GI) cancers among adolescents and young adults (AYAs) is rising. A cancer diagnosis and treatment(s) can lead to long-term morbidity and disrupt physical, cognitive, and psychosocial development, which can result in a reduced health-related quality of life (HRQOL) in this young population. The aim of this study was to describe the long-term survivorship outcomes of AYA with lower GI cancer.

Methods: The Netherlands Cancer Registry identified AYA cancer survivors (aged 18-39 years at initial cancer diagnosis, 5-20 years past diagnosis). They were invited to participate in a population-based, cross-sectional questionnaire study (SURVAYA). Survivorship issues (EORTC QLQ-SURV111) and HRQOL (EORTC QLQ-C30) were assessed. For this secondary analysis, we used data of all participating AYA colorectal and anal cancer patients.

Results: 82 SURVAYA participants were selected (43% colon, 47% rectal and 8% anal cancer; 59% male sex; mean age 34 years at study participation; 11.3 years after diagnosis). Primary treatment consisted of surgery (18%); surgery and chemotherapy (23%); surgery and radiotherapy (10%); radiotherapy and chemotherapy (10%); surgery, radiotherapy and chemotherapy (39%); 35% of patients had a stoma. AYA cancer survivors reported to some extent issues related to body image (41%), sexual intimacy (41%), fertility (49%), social isolation (43%), uncertainty about future (71%), reduced career opportunities (55%), reduced income (41%), and getting a mortgage/insurance (49%). Compared to the normative population, AYA cancer survivors experienced higher levels of fatigue (31.9 vs. 19.4), pain (15.4 vs. 11.4), insomnia (22.4 vs 17.3) and diarrhea (16.2 vs. 5.5); and reported lower physical (89.7 vs. 94.8), role (81.1 vs. 91.7), emotional (77.7 vs. 85.4), cognitive (80.0 vs. 92.0) and social functioning (85.3 vs. 93.6). Overall HRQOL was lower for AYAs compared to the norm (72.1 vs. 75.9; all p<0.05).

Conclusions: A substantial proportion of AYA lower GI cancer survivors reports long-term psychosocial and physical survivorship issues. Access to tailored age-specific healthcare resources is needed to maximize their HRQOL.

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567P Impact of concomitant medication on recurrence, survival and tolerability of chemotherapy in early colon cancer patients: Results from the PETACC 8 study

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Background: Few information is available about the impact of concomitant medication (CM) on the tolerability of chemotherapy as well as on the outcome of cancer patients. Therefore, we evaluated the impact of CM on disease-free survival (DFS), overall survival (OS) as well as side effects under adjuvant chemotherapy in a large cohort of early colon cancer (CC) patients.

Methods: Patients of the phase III randomized trial PETACC8 had resection with curative intent of a stage II or III CC and were treated with standard adjuvant fluoropyrimidine and oxaliplatin (+/- cetuximab) over 6 months.Information on CM intake has been gathered by study visits at inclusion and during chemotherapy. We investigated the association between number of CM as well as the 5 most frequently applied CM categories according to the WHO ATC classification system (gastroesophageal reflux disease (GERD) treatment, anticoagulants, aggregation inhibitors, cardiovascular sphere (CVS) treatment and antidiabetic drugs) with DFS, OS and grade 3/4 adverse events (AEs).

Results: Within 2537 patients eligible for this analysis, median number of CM intake was 8 (range 0 to 25), with only 22 patients (0.9%) without any CM. 1328 (51.9%) reported a GERD treatment, 452 (17.7%) an anticoagulant, 279 (10.9%) an anti-aggregant therapy, 1028 (40.2%) a CVS treatment and 236 (9.2%) an antidiabetic drug. Anticoagulation was the only CM category significantly and independently associated with a shorter DFS (HR 1.29, 95%CI 1.07-1.56, *p=0.009*) as well as OS (HR 1.29, 95%CI 1.03-1.61, *p=0.027*). No association of number of CM (<5, 5-10, >10) has been observed neither with DFS (ref.; HR 0.98; HR 1.17) nor OS (ref.; HR 0.98; HR 1.15) (*p>0.05*). Grade 3/4 AEs directly correlated with number of CM (*p<0.001*) and occurred significantly more frequently in patients with GERD treatment (78.8 vs 66.6%, *p<0.001*), anticoagulation (81.4 vs 71.1%, *p<0.001*) and anti-aggregants (79.2 vs 72.1%, *p=0.001*).

Conclusions: Early CC patients with a high CM intake did not generally exhibit an impaired outcome, even though tolerability of adjuvant chemotherapy was reduced. Anticoagulation was the only CM category associated with a shorter DFS and OS.

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568P Single cell AI-based detection of DNA mismatch repair deficiency in 1,988 colorectal cancers reveals prognostic and predictive value in the SCOT trial

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Background: Testing for DNA mismatch repair deficiency (MMRd) is recommended for all colorectal cancers (CRC). Automation of this would facilitate precision medicine, particularly if it provided information on likely aetiology.

Methods: We developed AIMMer, an AI-based method for determination of MMR protein expression at single cell level from IHC-stained routine pathology samples. We applied it to over 2,000 cases from the SCOT clinical trial, which compared 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy (mFOLFOX6 or CAPOX) for stage II/III CRC. AIMMer performance was evaluated against ground truth established by blinded review by two expert pathologists, and MMRd prognostic and predictive value was determined by Cox proportional hazards models.

Results: Benchmarking of AIMMeR against pathologist ground truth MMR calls revealed AUROC of 0.98 (bootstrap 95% CI = 0.97−0.99) and Youden index (sensitivity plus specificity) of 1.87 at cutpoint of 10.7% MMR positive cells. This cutpoint gave positive predictive value (PPV) of >95% for both the commonest pattern of somatic MMRd (MLH1 and PMS2 loss) and for MMR proficient (MMRp) status, and agreement with pathologist calls approaching that between individual pathologists (k = 0.79−0.82 vs 0.88). Analysis of CRC recurrence-free interval (RFI) confirmed MMRd prognostic value in oxaliplatin-treated patients (multivariable-adjusted HR (aHR) = 0.62, 95% CI = 0.44−0.88, P=0.007), with effect size larger in those <70 years and those with right-sided tumours. MMRd did not predict differential benefit from chemotherapy duration. Patients with MMRp tumors had similar RFI whether treated with CAPOX or FOLFOX (aHR = 0.95, 95% CI= 0.77-1.16, P=0.6), while those with MMRd tumours treated with FOLFOX had shorter RFI (aHR = 2.08, 95% CI= 1.09-3.97, P=0.027, $P_{\text{INTERACTION}}$=0.04).

Conclusions: AIMMeR holds promise to reduce pathologist workflow and streamline clinical diagnostics in CRC. The possible predictive value of MMRd for chemotherapy regimen should be investigated in additional cohorts.

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569P Artificial intelligence for detection of mismatch repair deficiency in colon carcinomas (alliance)

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Background: Artificial intelligence (AI) algorithms have been developed to distinguish MMR-D from MMR-P (proficient) tumors, yet they lack biological interpretability. To address this shortcoming, we used validated AI algorithms to detect and quantify well described morphological features in colon cancers from whole slide images.

Methods: Digital images of stage III colon carcinomas from participants in a phase III trial of FOLFOX-based adjuvant chemotherapy (NCCTG N0147; Alliance) were utilized. Available MMR-D (n=191) and randomly selected MMR-P (n=188) cancers were analyzed. QuantCRC quantifies the amount of stroma and stromal subtypes (immature, mature, inflammatory) and tumor/stroma ratio in addition to grade, mucin, signet ring cells, budding/poorly differentiated clusters (TB/PDC) and tumor-infiltrating lymphocytes (TILs). We also distinguished TILs in epithelium vs stromal using another AI algorithm (Lunit SCOPE IO). Area under the curve (AUC), i.e., discrimination threshold, was measured for each feature to predict MMR status.

Results: Among AI-derived morphological features, significant differences were found by MMR status whereby dMMR cancers had lower immature stroma but higher inflammatory stroma, higher tumor grade, and increased mucin, signet ring cells, tumor size, TB/PDCs, and TILs (all Kruskal-Wallis p<0.05). Univariately, AUC (95% CI) values for prediction of MMR status above 0.6 were as follows: TILs 0.72 (0.67-0.77), immature stroma 0.67 (0.62-0.73); inflammatory stroma 0.67 (0.62-0.73); tumor grade 0.65 (0.60-0.71); signet ring cells 0.65 (0.60-0.71); mucin 0.64 (0.59-0.70). Given that TILs in the overall tumor was most discriminant, we then utilized a TIL-specific AI algorithm measuring TILs in epithelium and stroma and found that epithelial TILs had a significantly higher AUC [0.79 (0.74-0.84) compared to stromal TILs 0.58 (0.52-0.63) p<0.0001].

Conclusions: Among morphological tumor features quantified by AI, tumor immature desmoplastic stroma and TILs, particularly epithelial TIL densities, were best able to distinguish MMR-D from MMR-P tumors. These findings have implications for prognosis and subtype-based interventions and can guide spatial molecular interrogation.

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570P Subclasses of microsatellite-instability colorectal cancer with unique molecular features and immune cell infiltration patterns

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Background: Mismatch repair deficient or microsatellite instable (MSI) tumors are often characterized by high mutational burdens and strong immune infiltration and have shown higher sensitivity to immune checkpoint inhibitors (ICIs) compared to microsatellite stable (MSS) tumors. However, only a portion of the patients with MSI colorectal cancer (CRC) gain survival benefits from ICIs treatment, suggesting unclear heterogeneity in MSI tumors.

Methods: We analyzed the whole-genomes and transcriptomes of 223 ICIs treatment-naïve MSI CRC tumors from U-CAN project. Immune cell infiltration and cancer-relevant pathways were evaluated by CIBERSORT and PROGENy, respectively. An MSI subtyping model was developed based on ResNet50.

Results: Unsupervised classification based on gene expression data divided MSI tumors into two distinct classes (class1 and 2), with MSI class1 characterized by a lower level of chromosomal instability, a higher level of hypoxia, and more activated EGFR, JAK-STAT, TNFa, and NFkB pathways than class2. However, two MSI classes showed no differences in 5-year survival. Further investigation of the immune cell population showed that class1 had considerably higher immune cell infiltration compared to class2, specifically in M0, M1 and M2 macrophages, CD4 and CD8 T-cells, naïve B-cells, resting NK-cells, and neutrophiles. Class2 exhibited significantly higher loss in 10q23.31 (containing *PTEN*) and reduced expression of *PTEN*, which may lead to an immunosuppressive tumor microenvironment and partially explain the higher activation in PI3K and VEGF pathways in class2 compared to class1. Importantly, ICIs targets, such as *CTLA4, PD-1,* and *PD-L1* all had higher expressions in calss1. We further developed an MSI subtyping model based on refined pathway features of normal tissue, tumors with MSS, class1 or 2. Ongoing analyses include validation of MSI classification in the TCGA dataset.

Conclusions: We illustrated the heterogeneity in MSI CRCs and revealed two subclasses of MSI with distinct molecular features, which may be informative for immune-based treatments. The MSI subtyping model may further facilitate precision immunotherapy and allow patients to derive clinical benefits.

Legal entity responsible for the study: Uppsala University Umeå University BGI-Shenzhen.

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571P Artificial intelligence-powered analysis of tumor lymphocytes infiltration: A translational analysis of AtezoTRIBE trial

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Background: Adding atezolizumab (atezo) to FOLFOXIRI/bev prolongs PFS of mCRC patients (pts) in AtezoTRIBE trial. We explored the predictive role of immune phenotypes (IPs) and Inflamed Score (IS), as assessed by means of Lunit SCOPE IO, an artificial intelligence (AI)-powered whole-slide images (WSI) analyzer of tumor infiltrating lymphocytes (TILs).

Methods: In AtezoTRIBE study mCRC pts were randomized 1:2 to upfront FOLFOXIRI/bev -/+ atezo. AI-powered spatial and quantitative analyses of TILs were conducted on pre-treatment hematoxylin & eosin-stained WSI from 173 (79%) enrolled pts. Three IPs (inflamed, excluded, desert) were defined according to TILs density in tumor epithelium and stroma, and IS was calculated as the proportion of grids classified as inflamed within a WSI. IPs and IS were correlated with immune-related biomarkers (MMR, TMB, Immunoscore IC, Immunoscore, TPS PD-L1, TILs by optical microscope) and clinical outcome.

Results: AI-powered analyses were successfully performed in 154 (84%) cases. 67 (44%) and 87 (56%) cases were classified as excluded and desert, respectively, while no inflamed cases (IS $\geq$ 33.3%) were detected. Pts with excluded and desert tumors had similar baseline features, except for a higher percentage of pts with Immunoscore IC-high (p= .006), Immunoscore-high (p= .008), and TILs-high (p= .006) tumors in the excluded *vs* desert group. A similar PFS benefit from adding atezo was reported in the excluded (HR 0.70, 95% CI 0.40-1.23) and desert (HR 0.73, 95% CI 0.45-1.17) groups (p_{int}=0.817). Tumors with high ($\geq$3rd quartile, 1.01%) IS (n=39) were more frequently dMMR (p= .031) and TMB-high (p= .020) than those with low (<3rd quartile) IS (n=115). The PFS benefit from adding atezo was homogeneous between tumors with high IS (HR 0.80, 95% CI 0.38-1.67) and low IS (HR 0.69, 95% CI 0.44-1.07) (p_{int}=0.791). Similar results were found in the pMMR cohort.

Conclusions: IPs and IS by Lunit SCOPE IO provide a characterization of tumor microenvironment, being associated with Immunoscore, Immunoscore IC and TILs. Further development of AI-powered TILs analyses taking into account their densities may help identifying biomarkers of immunogenicity in mCRC.

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572P Neoantigen heterogeneity among subtypes in colorectal cancer

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Background: Colorectal cancer (CRC) is a heterogeneous disease with multiple subtypes that differ in their clinical and molecular features. The presence of neoantigens derived from somatic mutations is a promising avenue for immunotherapy in CRC. However, the heterogeneity of the neoantigen landscape among CRC subtypes remains unclear.

Methods: We analyzed the whole-genomes and transcriptomes of 1063 CRC patients from a Swedish large cohort. HLA alleles were called by at least two HLA callers including HLA-HD, HLA-LA, Kourami, OptiType, PHLAT, Polysolver, xHLA for each patient. Neoantigens were predicted by pVACseq pipeline using the default settings.

Results: In total, 83,630 MHC class I neoantigens derived from 29,106 mutations (511,159 mutations were inputted) were predicted in 979 patients. Average 6.1 neoantigens were from 4,480 frameshift INDELs while only average 2.3 neoantigens were from 24,276 SNVs. Patients older than 80 years carried more neoantigens than those under 65 years, and women tended to have more neoantigens than men (Wilcoxon test, P<0.01). Tumor neoantigen burden was significantly higher in right-colon, stage II, and hypermutated (HM) tumors (P<0.0001). In total, 850 mutations were predicted to generate neoantigens in at least two patients, including *KRAS* G12D (6.3%), *RNF43* G659X (6.1%), *KRAS* G12V (5.2%), *TBC1D23* K647X (2.9%), and *MSH3* K381X (2.8%). Neoantigen numbers from *PODXL2* and *CRAT* mutations were significantly higher in consensus molecular subtype (CMS) 3 tumors, whereas neoantigens from *JAG2* mutations were more common in CMS2 (chi-square test, P <0.05). Neoantigens derived from *DNAH3*, *KRAS* and *ERBB2* mutations (37%, 47% and 52% respectively) in non-HM patients were significantly more than those (5%, 14% and 13% respectively) in HM patients. Furthermore, in stage I-III, nHM patients (n=11) with *DNAH3* neoantigens have significantly longer overall survival than patients (n=24) with only *DNAH3* mutations.

Conclusions: Our study constitutes the largest neoantigen dataset from integrated genome and transcriptome of CRC to date and illustrates the heterogeneity of the neoantigen landscape among CRC subtypes. The identified neoantigens may contribute to future individualized CRC immunotherapies.

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573P Multiparameter immunoprofiling reveals independent prognostic value of intraepithelial CD8 and intrastromal FoxP3 infiltrate in stage II/III colorectal cancer: Analysis of 3,409 cases from the SCOT and QUASAR2 trials

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Background: Tumour infiltrating CD8$^+$ cytotoxic T cells confer favourable prognosis in colorectal cancer (CRC). The added prognostic value of other immune cells is unclear.

Methods: We used multiparameter co-immunofluorescence to determine the density of CD8$^+$, CD20$^+$, FoxP3$^+$ and CD68$^+$ cells in the intraepithelial (IE) and intrastromal (IS) compartments in stage II/III CRCs from the SCOT and QUASAR2 trials. We determined

marker prognostic and predictive value by Cox regression of SCOT cases, with validation in the QUASAR2 cohort.

Results: Our study included 2,340 SCOT and 1,069 QUASAR2 cases. Univariable analysis of recurrence-free interval (RFI) in SCOT revealed expected prognostic value of intraepithelial CD8 ($CD8^{IE}$) (continuous variable: HR for cases at 75th vs 25th percentile (HR^{75vs25})= 0.73, 95% CI=0.68-0.79, P=2.5e-16) and, less expectedly FoxP3 within tumour stroma ($FoxP3^{IS}$) (HR^{75vs25})= 0.71, 95% CI=0.64-0.78, P=1.5e-13), but not epithelium. $CD8^{IE}$ and $FoxP3^{IS}$ were independently prognostic in multivariable analysis, and a composite marker including both ($CD8^{IE}$-$Foxp3^{IS}$) was superior to either alone as a continuous variable ($adjHR^{75vs25}$= 0.70; 95%CI=0.63−0.78; P=5.1e-11), and when categorised into three groups (Low/Int/High) using sample medians (Int vs High HR = 1.60, 95%CI=1.24−2.05, P=2.5e-04; Low vs High HR = 2.30, 95%CI=1.80−2.95; P=3.6e-11). These results were validated in the QUASAR2 trial. Pooled analysis of both studies revealed interactions between $CD8^{IE}$-$FoxP3^{IS}$ and tumour sidedness ($adjP_{INT}$=0.010), stromal proportion ($adjP_{INT}$=0.018), and MMR status ($adjP_{INT}$=0.079). $CD8^{IE}$-$FoxP3^{IS}$ refined stage III risk groups, with clinical low risk (T1-3, N1), $CD8^{IE}$-$FoxP3^{IS}$ low cases demonstrating similar 3-year recurrence-free probability to clinical high risk (T4 and/or N2), $CD8^{IE}$-$FoxP3^{IS}$ high cases (79.2 vs 76.4%, adj log-rank P=0.16).

Conclusions: Combined evaluation of $CD8^{IE}$ and $FoxP3^{IS}$ is superior to single markers and refines CRC risk stratification. $FoxP3^{IS}$ prognostic value is inconsistent with an immunosuppressive role; further investigation of these cells as an immunotherapy target is merited.

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574P Comparative analysis of the tumor immune microenvironment (TIME) in primary and metastatic sites of microsatellite stable (MSS) and microsatellite instability-high (MSI) colorectal cancer

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Background: We have previously reported significant differences between the tumor immune microenvironment (TIME) of primary colorectal cancer (CRC-P) and different metastatic sites. Increased immune cell infiltration, B-cells, and CD8 cells and decreased macrophages were noted in CRC-P and lung metastatic (LuM) lesions compared to liver (LM) and peritoneum (PM) metastases. We expanded our work to MSI CRC and compared their TIME to respective MSS tumor sites.

Methods: De-identified cases of MSS and MSI metastatic CRC that underwent next-generation sequencing with the Tempus xT assay were selected from the Tempus Database. Gene expression patterns of immune cells, including B, T (CD4+, CD8+), NK cells, and macrophages, were used to predict relative intra-tumor abundance. MSI and MSS cohorts included CRC-P, LM, and PM. LuM was analyzed only in MSS tumors due to the limited number of MSI LuM. Tumor mutational burden (TMB), neoantigen burden, and proportion of immune cells in CRC-P, LM, and PM were compared across MSI and MSS patients. Chi-squared/Fischer's exact tests or Kruskal-Wallis tests were used to assess statistical significance.

Results: A total of 208 MSI and 6,732 MSS tumors were subject of analysis. No differences were noted in TMB, neoantigen load, or PD-L1 expression between MSI CRC-P, LM, or PM. Across the 3 tissue groups, the median TMB and neoantigen tumor burden were significantly higher in MSI cohorts when compared to MSS cohorts ($p<0.001$). Compared to MSS LM, MSI LM exhibited a higher percentage of CD8 cells ($p=0.002$) and NK cells ($p<0.001$), with a trend towards a lower percentage of macrophages ($p=0.14$). Similar differences were noted for MSI PM compared to MSS PM (CD8 cells $p=0.018$, NK cells $p=0.044$ and macrophages $p=0.023$). The TIME of MSS LuM lesions shared more similarities with that of MSI LM/PM than MSS LM/PM.

Conclusions: MSI LM and PM have a more favorable TIME than respective MSS metastases, explaining the discordance in response to checkpoint inhibitors (CPI) and reported CPI benefits in MSI cases across all metastatic sites. MSS LuM have a comparable TIME to MSI metastatic sites, explaining the recently reported benefits from CPI therapy in this group.

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575P Impact of immunological alterations and post-operative biomarkers on long-term outcomes in patients with locally advanced rectal cancer: Results from the STAR-01 study cohort

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Background: Preoperative chemoradiotherapy (CRT) may enhance antitumor immunity by increasing T-cell activation and tumor infiltration. These effects could possibly sensitize tumour cells to immunecheckpoint inhibitors and other immunotherapies. We investigated the immunologic alterations occurring after preoperative CRT for locally advanced rectal cancer (LARC).

Methods: The multicenter randomized STAR-01 study compared the preoperative CRT regimen with 50.4 Gy in 28 daily fractions with concomitant infused fluorouracil at the dose of 225 $mg/m^2/d$ with the same regimen plus oxaliplatin given weekly at the dose of 60 mg/m^2 in patients with LARC. Pre- and/or postoperative specimens were available for 305 patients from this trial (109 paired pre- and post-treatment samples). The immunoistochemical evaluation was performed with a panel of immune cells and associated factors such as CD3, CD20, CD4/CD8, PD-1. The pattern of tumor infiltrating lymphocytes (TILs) and related infiltrating lymphocytes (RILs) were also assessed. Microsatellite instability (MSI)/mismatch repair deficiency (dMMR) was evaluated on pre-treatment tumour biopsies.

Results: After therapy we observed a decreased CD4/CD8 ratio ($P<.0001$) and reduced expression levels of CD20 ($P<.0001$). The expression level of CD3+ and PD-1+ cells after therapy did not change significantly. The relative increase of lymphocytes CD8+ within the CD4/CD8 ratio evaluated on post-operative samples was significantly associated with pathological complete response after CRT ($P<.0001$), event-free survival (EFS) [hazard ratio (HR)=1.77, 95% confidence interval (CI)=1.08 to 2.89, $P=.0227$] and overall survival (OS) [HR=2.01, 95% CI=1.19 to 3.4, $P=.0087$] adjusted for treatment arm and adjuvant chemotherapy.

Conclusions: Our data indicate that CRT may induce an enrichment of CD8+ T lymphocytes and this translates in a better response to CRT and survival. Data on MSI status will be presented at the meeting.

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576P Prognostic values of a modified diagnostic biopsy-adapted immunoscore based on double immunohistochemical staining in patients with locally advanced rectal cancer

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Background: Tumor immune contexture plays a crucial role in the outcome of cancer patients. The aim of this study was to evaluate the prognostic value of the modified diagnostic biopsy-adapted immunoscore (mIS_b) for patients with locally advanced rectal cancer (LARC).

Methods: We included 181 LARC patients from a single sub-center of a prospective study (NCT02533271), with 151 (83.4%) receiving surgical treatment and 30 (16.6%) following a watch-and-wait (W&W) strategy. Tumor biopsy tissues were stained using dual immunohistochemistry for CD8+ and CD3+ T cell densities, and the CD8/CD3 ratio was calculated. mISb was developed using mean percentile values of CD8+ T cell density and CD8/CD3 ratio, and patients were classified into low (0%-25%), intermediate (>25%-70%), and high (>70%-100%) mIS_b groups. Spearman correlation analysis was performed. Kaplan-Meier survival analysis, multivariate Cox regression models were used to assess the prognostic value of mIS_b for disease-free survival (DFS), and the role of mIS_b in the W&W strategy was further investigated.

Results: A strong correlation was found between CD8+ and CD3+ T cell densities (R=0.86, $P<0.001$), and a weaker correlation with the CD8/CD3 ratio (R=0.45). In the low, intermediate, and high mIS_b groups, there were 35 (23.2%), 84 (55.6%), and 32 (21.2%) patients, respectively. The respective 3-year DFS rates for these groups were 59.0%, 69.5%, and 80.1% (P=0.01). Multivariate analysis in surgically treated patients revealed mIS_b as an independent prognostic factor for DFS (intermediate vs. high: HR=2.38, 95% CI: 0.92-6.16, P=0.08; low vs. high: HR=3.69, 95% CI: 1.35-10.07, P=0.01). Among W&W patients, 6 (37.5%) in the $mIS_b \leq 50\%$ group experienced local-region or distant metastases, while only 1 (7.1%) in the $mIS_b > 50\%$ group had local-region recurrence.

Conclusions: mIS_b, as a potentially valuable prognostic indicator, demonstrates significant importance in assessing the prognosis of LARC patients. Future research is needed to further investigate the clinical application of mIS_b in rectal cancer prognosis, particularly in the context of the W&W strategy.

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577P Systematically assessing the intratissue microbiota in 937 patients with colorectal cancer

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Background: Dysbiosis of the fecal microbiota has been closely related to colorectal cancer (CRC) and has increasingly proven to be associated with CRC prognosis. However, a significant knowledge gap still exists regarding intestinal tissue-resident microbes and their associations with host genetic alterations, gene expressions and prognosis in CRC.

Methods: We undertook a comprehensive analysis of the tissue-resident microbes in CRC patients from the U-CAN cohort, a large prospective longitudinal study of adult cancer patients in Sweden, using treatment-naïve whole-genome (average 53x coverage) and whole-transcriptome sequencing data of tumors (n=937) and their adjacent normal tissues (n=475).

Results: In total, 301 genera and 420 species were identified as common tissue-resident taxa. We showed for the first-time distinct enrichment patterns of tissue-resident microbiome in the right- and left-sided colons. Importantly, these patterns were highly consistent between tumor and normal tissues, with right-sided colons enriched with *Clostridium spp* and left-sided colons enriched with *Akkermansia muciniphila* and *Bifidobacterium spp*. We identified 94 tumor-enriched bacteria, and 38 were significantly associated with host hypermutation (HM) status. Previously known CRC-enriched bacteria, such as *Fusobacterium* groups and *Campylobacter*, were more prevalent in right-sided and HM tumors, and strongly correlated with mutations in host drivers and DNA damage repair genes. CRC driver genes that correlated with identified intratissue bacteria including *CASP8, TP53* and *SMAD2,* with *CASP8* significantly associated with multiple CRC-enriched taxa in all and in HM samples. Finally, risk scores derived from tumor or normal-resident taxa could both predict CRC prognosis and significantly improve the prognosis performance of the consensus molecular subtypes (CMS).

Conclusions: Our study provides new insights into the interactions between tumor-enriched microbiota with CRC and identifies potential bacteria markers that could improve the accuracy of CRC prognosis prediction. These findings can guide future efforts to exploit the performance of intratissue bacteria on CRC prognosis prediction.

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578P Tissue-resident microbiota characterization in colorectal cancer metastases

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Background: Early evidence suggested a role of tissue-resident microbiota (TRM) in the development of colorectal cancer. However, its presence in colorectal cancer metastases (CRCM) is poorly reported. Here, we aim to explore and characterize the TRM in CRCM.

Methods: From several biobanks in Belgium, we retrospectively collected 237 frozen samples, including 104 CRC primary tumor (PT) and 133 patient-matched CRCM (liver CRCM=98). Hepatocellular carcinoma (HCC, n=50), cholangiocarcinoma (CGC, n=23) and breast liver metastases (BLM, n = 16) were also collected. 82 CRCM were collected prospectively. The V4 region 16S rRNA gene was amplified and sequenced. We strictly applied sterile conditions from sample collection to sequencing, with the integration of negative controls (n=253). Additionally, 257 duplicated random samples were processed twice by independent experimenters. Sequencing results were processed with DADA2 to identify bacterial amplicon sequence variants (ASVs).

Results: ASVs were identified in all tissues. Microbial composition was significantly different between tumor samples and negative controls (PERMANOVA, p=0.0001). PT presented the highest bacterial biomass. ASV sharing frequency between PT and CRCM was significantly higher within than between patients (Wilcoxon test, p=0.007), suggesting potential bacterial translocation from PT to CRCM. The most prevalent PT bacteria were also the most shared in matched CRCM. No difference was observed between CRCM locations (liver, others). TRM of HCC, CGC and BLM were characterized by an ultra-low bacterial biomass, and distinct phyla compared to CRCM. In CRCM, the presence of Ruminoccocus gnavus (Rg) was associated with overall survival after CRCM resection (median 83.6 vs 41.6 months, HR: 0.35 IC95:0.13-0.90, p=0.024).

Conclusions: We observe a specific TRM in CRCM, shared with matched PT and suggesting bacterial translocation from PT to CRCM. In this cohort, the presence of Rg in CRCM seems prognostic after CRCM resection. Further experiments are needed to confirm and detail these results.

Legal entity responsible for the study: M. van den Eynde.

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579P A clinico-imaging predictive artificial intelligence model of relapse in colon cancer using baseline CT scans

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Background: Up to 35% of patients with localized colon cancer (CC) have a relapse, even after receiving optimal initial treatment. New prognostic biomarkers are required to more accurately identify patients who benefit from receiving adjuvant treatment and more personalized care. We propose an artificial intelligence (AI) model combining clinical data with fractals, radiomics and deep features extracted from baseline computed tomography (CT) exams for the prediction of CC relapse.

Methods: This multi-center retrospective observational study includes real-world clinical data from CC patients and CT examinations from 2015 to 2021. Manual segmentation of the tumor was performed by an experienced abdominal radiologist. A total of 2158 radiomics, deep features and fractal dimension features were extracted using Quibim Precision® software (Quibim, Valencia, ES). Harmonization techniques were applied to address image quality variability. ResNet152V2 deep convolutional network was applied as a transfer learning framework for deep features extraction and logistic regression model to estimate probability of relapse. 80% of the cases (136 studies) were used to train and validate the model following a nested cross-validation strategy to handle overfitting problem while 20% (34) were used for independent test set to analyze model generalization.

Results: Baseline CT exams from 170 localized CC patients (69 relapsed and 101 non-relapsed patients) with stages I (4%), II (20%) and III (76%) were included. Ten features were finally selected (2 radiomics, 8 deep features) by mRMR algorithm, providing an increased area under the curve (AUC) of 0.70 (95% CI: 0.52-0.88) in the independent set higher than that obtained with the model trained with clinical variables alone (0.50, 95% CI: 0.35-0.65). Using the DeLong test to probe the difference between the AUC of models, it can be conclude that model including radiomic information has a statistically different AUC from model with only clinical features with p-value < 0.05 ($p = 0.023$).

Conclusions: This AI approach, by identifying a panel of imaging biomarkers and in combination with clinicopathological features, will help improve clinical decision-making and patient outcomes using standard-of-care data.

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580P Prognosis in stage II colorectal cancer: The effect of the primary tumor location and biomarkers

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Background: Primary tumor location (PTL) is a well-established prognostic factor in stage III and IV colorectal cancer (CRC), with right-sided CRC (RSCC) showing a worse prognosis compared to left-sided CRC (LSCC). However, the impact of PTL on stage II CRC remains uncertain. One explanation for these inconsistencies is the potential confounding effect of molecular biomarkers, such as MMR status. Therefore, there is a need to elucidate the prognostic value of PTL, as well as the role of biomarkers in this effect.

Methods: This study utilized observational data from a retrospective cohort obtained from the Belgian Cancer Registry (BCR). The study population comprised all patients diagnosed with pathologically confirmed stage II CRC in Belgium from January 1st, 2015, to December 31st, 2016 (n= 3,278). Information on PTL, demographics, pathologic T category (pT category), and molecular biomarkers (including MMR status, BRAF and KRAS mutations) was collected from the registry, along with vital status to calculate overall survival (OS). The primary aim of this study was to investigate the independent prognostic value of PTL in stage II CRC. Additionally, we assessed whether potential confounding factors, such as biomarkers and demographics, influenced the prognostic effect of PTL.

Results: In the univariate analysis, patients with stage II RSCC had a significantly worse OS compared to those with LSCC (including rectal cancer; p-value=0.0055 and excluding rectal cancer; p-value=0.0035). Higher age and pT4 were also significantly associated with worse OS. However, in the multivariable analysis, only gender, age, and pathologic T-stage were found to be significant predictors of OS. PTL was not a significant factor in multivariable analysis. Furthermore, biomarkers such as MMR-status, BRAF-, and KRAS mutations did not show a significant effect on OS in either analysis.

Conclusions: Our analysis led us to the conclusion that PTL is not an independent prognostic factor in stage II. Notably, we observed confounding effects between patient characteristics and the prognostic impact of PTL, such as older age at diagnosis and shorter OS in patients with RSCC. Furthermore, molecular biomarkers did not have a statistically significant effect on OS in stage II CRC.

Legal entity responsible for the study: University of Antwerp.

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581P The effect of exercise intervention on defecation related symptoms of colorectal cancer patients a randomized controlled trial

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Background: Although colorectal cancer (CRC) survivors often suffer from defecation related symptoms (DRS), there are very few treatment options to improve DRS. Strengthening of abdominal muscles to increase intra-abdominal pressure and pelvic floor exercises to improve pelvic floor dyssynergia may improve DRS in colorectal cancer patients. However, the effects of exercise on DRS have not been studied fully. Therefore, the purpose of this study is to investigate the efficacy of exercise on DRS in CRC.

Methods: A total of 120 CRC who completed surgery and adjuvants therapy were recruited out of 441 approached. 120 participants were randomly assigned to either exercise (EG) or usual care group (CG). The combined weekly supervised and home-based exercise program (12 weeks) includes increase in physical activity (PA) levels to meet the ACSM guideline as well as daily calisthenics exercises. Calisthenics exercises include a total of 12 movements aimed to increase whole body muscle strengths which focused on core and pelvic floor muscles. The primary outcome was DRS score assessed the sum of blood and mucus in stool, stool frequency, abdominal pain, buttock pain, bloating, flatulence, fecal incontinence and embarrassment in EOTRC-QLQ-CR29. A two-way ANOVA repeated measures were used determine group and time interaction.

Table: 581P Effects of exercise on defecatory symptoms

	Control		Exercise		*p*-value
	Pre	Post	Pre	Post	
Blood in stool	4.7 ± 9.7	4.4 ± 9.1	7.2 ± 15.5	3.1 ± 8.9	0.05
Stool frequency	26.3 ± 27.0	20.1 ± 20.5	28.7 ± 25.1	23.4 ± 23.8	0.91
Abdominal pain	14.4 ± 22.4	11.7 ± 19.2	18.3 ± 24.9	10.0 ± 16.6	0.21
Buttock pain	12.2 ± 21.2	12.8 ± 25.4	18.9 ± 30.3	12.8 ± 26.1	0.08
Bloating	22.8 ± 22.5	25.0 ± 25.8	34.4 ± 30.7	22.8 ± 27.1	0.01
Flatulence	21.0 ± 26.0	17.7 ± 23.3	28.3 ± 33.5	21.5 ± 25.1	0.42
Fecal incontinence	13.5 ± 20.5	13.1 ± 20.5	16.9 ± 24.8	12.9 ± 25.3	0.26
Embarrassment	20.4 ± 26.8	16.7 ± 20.8	27.6 ± 32.0	18.0 ± 25.5	0.16

Bolds were statistically significant different between pre and post (p<.05), *p*= Difference between control vs. exercise

Results: Among the 120 participants enrolled, 100 (96.6%) completed the trial with supervised exercise compliance rate of 95%. PA levels increased and fitness levels improved only in the exercise group. Exercise significantly decreased DRS score (6 week - 0 week: CG= -14.0 ± 54.7 vs. EG= - 56.1 ± 99.5, *p* for group and time interaction = 0.02). Symptom scores in EG include blood and mucus in stool, abdominal pain, buttock pain, bloating, flatulence and embarrassment were improved.

Conclusions: It is concluded that both combined supervised and home-based exercise significantly reduced bowel and defecatory problems in colorectal cancer patients.

Clinical trial identification: This study was approved by The Institutional Review Board of Severance Hospital (IRB No. 4-2018-0841).

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582P High accuracy of a blood-based multimodal ctDNA test to detect advanced neoplasms in a FIT-positive screening population

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Background: Current colorectal cancer (CRC) screening assays decrease CRC-related incidence and mortality. However, effectiveness of screening programs is limited by the very low adherence of the population to screening recommendations. Development of less invasive, more accessible, and more convenient tests is an unmet clinical need.

Methods: A circulating tumor (ct)DNA blood-based assay that integrates genomics, epigenomics and fragmentomics was tested in blood samples from two cohorts: (1) consecutive FIT-positive individuals from the CRC Barcelona stool-based screening program; (2) patients diagnosed with CRC. Colonoscopy was performed in all individuals. Primary endpoint was to establish the accuracy of the assay to detect CRC and advanced adenomas (AA) compared to colonoscopy. A secondary exploratory endpoint analyzed the accuracy of a refined version of the assay (including protein and updating bioinformatic thresholding) to detect AA in a cohort of random FIT-positive individuals from the CRC screening program.

Results: A total of 623 blood samples were analyzed in the primary analysis. Sensitivity and specificity of the assay to detect CRC was 93% and 90%, respectively. The sensitivity of CRC detection was high in all TNM stages (84% stage I, 94% stage II, 96% stage III, 100% stage IV). The test detected advanced neoplasms (AA or serrated lesion or CRC) with a sensitivity of 85% and a specificity of 90%. Sensitivity to detect AA was 23% when using a refined version of the test, with a specificity of 86%.

Conclusions: A blood-based multimodal ctDNA assay detected advanced neoplasms with high accuracy. This non-invasive, accessible, and convenient test is key to increase the population compliance to screening recommendations.

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583P A rapid blood test for the earlier detection of colorectal cancer

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Background: The detection of colorectal cancer (CRC) in early stages can enable the removal of pre-cancerous lesions and allow earlier treatment. Most CRCs develop from adenomas, with "advanced" adenoma (AA) considered to be clinically relevant precursor of CRC. Screening for CRC is recommended for average-risk adults using faecal immunochemical testing (FIT), but the performance of FIT is limited. FIT reportedly has false positive rate of ∼93%, and ∼10% of CRC diagnoses have a negative FIT result. Moreover, the sensitivity for detecting AA is only 24%, highlighting the need for alternative strategies.

Methods: The Dxcover® Colorectal Cancer Liquid Biopsy is a spectroscopic test that interrogates a blood sample with infrared light and generates a distinctive signature that represents the whole biomolecular profile of the sample. Patient samples (n=296) were retrospectively collected for this discovery study, and the full cohort consisted of 100 CRC, 99 adenoma (A) and 97 colonoscopy screening controls with a non-cancer (NC) diagnosis. Machine learning algorithms have been developed with the resultant spectral profiles to predict CRC and AA. Feature importance analysis has also been carried out to identify the spectral regions found to be most significant for each classification.

Results: The CRC v NC model achieved an area under the receiver operating characteristic curve (AUROC) of 0.93. At 90% specificity, the overall CRC sensitivity was 80%, and the detection rates were consistent across stages: 83% (I), 73% (II), 76% (III), and 100% (IV). The CRC+A v NC model reported an AUROC of 0.88, and at 90% specificity, the overall CRC sensitivity was 78%. The test successfully detected 83% of stage I, 73% of stage II, 76% of stage III and 87% of stage IV CRC. Furthermore, 59% of AA patients were identified with this classifier, which is greater than the current performance levels of FIT.

Conclusions: A rapid blood test that is sensitive to AA and early-stage CRC could substantially improve patient outcomes. This liquid biopsy can be fine-tuned to give a different balance of sensitivity and specificity depending on international healthcare markets. Current screening programmes have addressable shortcomings, and the emergence of new technologies is essential to support earlier CRC detection.

Legal entity responsible for the study: Dxcover Limited.

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584P Two-year update of the prospective evaluation of ColonAiQ (PreC) study

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Background: PreC study supported ColonAiQ® (a blood-based assay targeting circulating tumor DNA methylation) as a robust noninvasive option for colorectal cancer (CRC) and advanced adenoma (AA) screening to efficiently stratify individuals with a higher risk based on the first year's real-world data reported in 2022 World Congress on Gastrointestinal Cancer (LBA SO-23). Here, the update CRC screening outcome was reported.

Methods: 105,285 participants living in the local community, aging from 40 to 80, were recruited from Jan 2021 to Dec 2022. ColonAiQ® test was used as the primary screening method for all participants and a follow-up colonoscopy was recommended after a positive primary test. Numbers of positive ColonAiQ® test, colonoscopy compliance rate and positive predictive values (PPV) for AA and/or CRC were determined.

Results: Overall, a total of 6,759 participants (6.42%) were tested positive via ColonAiQ® test. In the positive test population, 3,282 (48.56%) participants performed colonoscopy with pathological confirmation. Overall, there were 1,773 (54.02%) participants confirmed with colonoscopy findings, including 63 (1.92%) CRC, 441 (13.44%) AA, 754 (22.97%) non-advanced adenoma, 327 (9.96%) polyps, and 188 (5.73%) non-neoplastic GI disorders. Particularly, early colorectal neoplasm diagnosis rate reached 90.28%. Therefore, The predictive value (PPV) was 1.92% for CRC and 36.41% for adenoma (13.44% for AA).

Conclusions: The 2-year real world study confirms the initial findings that population compliance rate of colonoscopy is obviously higher than the average rate in Cancer Screening Program in Urban China (48.56% VS 17.25%). ColonAiQ® test could help to identify the asymptomatic patients with neoplasm who need endoscopic resection or surgery excision. These results warrant the cost-effectiveness of the two-step screening pattern in community populations from the ongoing PreC study.

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Legal entity responsible for the study: The authors.

Funding: Singlera Genomics Inc.

Disclosure: Y. Li, Q. Yuan, H. Luo, C. Wang, Y. Li, W. Pan, H. Yang, H. Jia, B. li, Y. Zhang, R. Liu: Financial Interests, Institutional, Full or part-time Employment: Singlera Genomics Inc. All other authors have declared no conflicts of interest.

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585P Fragmentomics early detection assay leading to potential clinical benefits in colorectal cancer

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Background: Colorectal adenocarcinoma (CRC) patients often experience delayed diagnosis, making liquid biopsy-based early detection a promising approach. Yet, its clinical usage has been restricted due to its insufficient sensitivity. We aimed to develop an integrated model using fragmentomic profiles of plasma cell-free DNA (cfDNA) for the accurately and cost-effectively detection of early-stage CRC.

Methods: 360 participants were enrolled as the training cohort, consisting of 176 CRC patients and 184 healthy controls. Plasma cfDNA were extracted and prepared for subsequent whole genome sequencing. To differentiate healthy controls from CRC patients, an ensemble stacked model was built upon five machine learning models couple with five cfDNA fragmentomic features. The model was subsequently validated in a cohort of 236 individuals, comprising 117 CRC patients and 119 healthy controls.

Results: The contracted ensemble stacked model demonstrated remarkable ability in distinguish between CRC patients and healthy controls as evidence in multiple facets. In the validation cohort, the ensemble stacked model demonstrated superior performance compared to all other base models constructed using feature-algorithm pairs, achieving a high AUC of 0.986. At 97% specificity, the sensitivity for detecting CRC patients in validation cohort reached 93%. Additionally, the sensitivity of our model increases alongside the progression of cancer stage. Our model consistently maintained high levels of accuracy during both within-run and between-run tests, successfully predicting cancer status at different clinical settings. Through a real-world simulation, the model's effectiveness was confirmed showing a potential increase of 17.47% in the 5-year survival rate.

Conclusions: Our ensemble stacked model, which leverages the multiplex nature of cfDNA, exhibited exceptional performance in terms of sensitivity and stability for detecting CRC risk. This model has the potential to facilitate early diagnosis and benefit a larger number of patients.

Legal entity responsible for the study: The authors.

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586P Minimal residual disease (MRD) detection using a tumour naïve circulating tumour DNA (ctDNA) assay in patients (pts) with resected colorectal cancer (CRC) in the phase III ASCOLT trial

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Background: Although ctDNA is associated with MRD and recurrence in curatively treated CRC, implementation in clinical practice remains to be optimised. We evaluated the utility of a tumour naive ctDNA assay using serial prospectively collected plasma samples from the ASpirin for Dukes C and high risk Dukes B COLorecTal cancer trial (ASCOLT, NCT00565708), a large randomised phase III study of adjuvant aspirin.

Methods: Plasma samples were collected at baseline, 6 and 12 m in the Australian/New Zealand cohort (n= 452). In a cohort of 118 pts matched by follow-up time (59 with recurrence [cases] and 59 non-recurrent [controls]), we used an ultra-sensitive ctDNA assay (SafeSEQ, Sysmex Inostics) for MRD detection. Cell pellets were analysed for mutations related to clonal haematopoiesis of indeterminate potential (CHIP). Results were correlated with recurrence and CEA.

Results: 291 plasma samples (median 4.0 mL, median DNA 71.0 gen equiv/uL) were analysed (54/118 F; median age 68; 48 high risk stage II, 70 stage III; all had adjuvant chemotherapy; median follow-up 53.1 m). 59 pts recurred at median 12.4 m, of whom 32 had detectable ctDNA (sens 54%, Table). CEA sensitivity for detecting recurrence was 26%. Of the 27 pts with recurrence but no detectable ctDNA, 13 (48%) recurred >12 m after final sample collection. 8 pts without recorded recurrence had plasma mutations (CHIP analysis not available n = 3, all TP53). In multivariate analysis adjusting for known risk factors, ctDNA positivity was independently associated with recurrence (OR, 6.5; 95% CI, 2.2 — 18.9; p<0.001). Median time from 1st positive ctDNA to imaging detected recurrence was 7.9 m (range 0.2 — 40.2). ctDNA change over time and correlation with tumour sequencing will be presented.

Table: 586P Summary of ctDNA Data

	Recurrence	No recurrence	Total
Positive ctDNA* at any time point	32	8	40
Negative ctDNA	27	51	78
Total	59	59	
	Sensitivity 54%	Specificity 86%	

*SafeSEQ 14 gene CRC MRD assay: AKT1, APC, BRAF, CTNNB1, ERBB3, FBXW7, KRAS, NRAS, PIK3CA, POLE, PPP2R1A, RNF43, SMAD4 and TP53

Conclusions: Tumour naïve, serial ctDNA detection within 1 year of adjuvant chemotherapy is independently associated with recurrence, noting limitations in sensitivity and specificity.

Legal entity responsible for the study: The authors.

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587P Short lead time and high rates of concomitant radiographic recurrences for ctDNA-based minimal residual disease assays colorectal cancer (CRC) during surveillance: Results from the MD Anderson INTERCEPT program

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Background: Although observational cohorts have shown that detection of circulating tumor DNA (ctDNA)-defined minimal residual disease (MRD) following curative intent therapy has a lead time of over 9 months (m) prior to radiographic recurrence, real world data (RWD) where results are returned to patients and providers are lacking. This is especially important since these studies have not incorporated rigorous clinical evaluation for concomitant recurrence.

Methods: In the INTERECEPT program, pts with stages II-IV CRC treated with curative intent at MD Anderson Cancer Center between 1/1/2022 and 31/12/2022 were evaluated with a tumor-informed MRD assay (Signatera, Natera) with an overarching goal to generate RWD and to integrate MRD-based testing into CRC pt care. Surveillance evaluations were per established guidelines; ctDNA was recommended post-operatively and q3m with each surveillance visit. Pts and providers were informed of the results; subsequent clinical decisions and courses were tracked.

Results: Of 847 pts (median 57y, [21-93], 55% were male; stage% I-III/IV were 69/31; colon/rectum% were 61/39. 20.5% (n=174) of pts had a positive ctDNA assay during surveillance, prompting imaging tests in 99% of cases (CT scan in 157 pts, PET/CT in 13 pts, MRI in 3 pts). These radiological investigations demonstrated definitive disease in 48% of cases, indeterminate findings in 11% and no evidence of disease in 41% of cases. Of those with indeterminate findings, 17/19 had a recurrence confirmation with a 2nd imaging modality. The median time to radiologic recurrence after a positive ctDNA result was less than 2 months. For those patients without radiologic recurrence identify concurrently with ctDNA+, the median time to recurrence was 3 months.

Conclusions: CRC pts on surveillance who are ctDNA+ are likely to have radiographic recurrence identify upon further investigation. The potential clinical benefit of this earlier radiographic identification of recurrent disease remains to be determined. True MRD pts (ctDNA+ but radiographically -ve) have a lead time providing a potential opportunity for therapeutic intervention.

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588P PLCRC-PROVENC3 study: Prognostic value of post-surgery liquid biopsy circulating tumor DNA in stage III colon cancer patients

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Background: Surgery followed by adjuvant chemotherapy (ACT) is standard of care in stage III colon cancer. However, only 15-20% of the patients truly benefit from ACT because 55% was cured by surgery alone and 25-30% develop recurrences despite ACT. Post-surgery circulating tumor DNA (ctDNA) is a biomarker for minimal residual disease, which may facilitate stratification of stage III colon cancer patients for ACT treatment decisions. The aim of this study is to determine the prognostic value and clinical validity of post-surgery ctDNA-testing in stage III colon cancer patients.

Methods: 236 stage III colon cancer patients treated with ACT were included in the PROVENC3 study. Blood was collected pre-surgery, post-surgery and post-ACT. Tumor-informed detection of plasma ctDNA was performed through integrated whole genome sequencing (WGS) analyses of formalin-fixed paraffin-embedded tumor tissue DNA (80x), germline DNA (40x), and plasma cell-free DNA (30x). Outcome measurement is time to recurrence (TTR).

Results: From 124 patients (median follow up: 31 months) show a worse TTR of ctDNA-positive patients [HR: 4.7, 95%CI: (2,37-9,3), $p<0.001$]. 64% of the ctDNA positive, and 21% of the ctDNA negative patients experienced a recurrence. 40% of the patients who experienced a recurrence were ctDNA positive post-surgery. TTR was significantly different per ctDNA status, with a shorter median TTR for ctDNA-positive compared to ctDNA-negative patients (7.7 vs 13.1 months). Final results from the complete cohort with median follow up of 41 months will be presented in October 2023.

Conclusions: Post-surgery ctDNA detection by WGS is a strong prognostic biomarker in stage III colon cancer patients. Importantly, part of the ctDNA-positive patients did not experience a recurrence and were likely cured by ACT. Approximately 60% of the recurrences were not detected by post-surgery ctDNA-testing. Ultimately, the results of this study will be used to model and design a ctDNA-guided interventional trial in stage III colon cancer patients, to reduce futile ACT and its associated negative side-effects.

Legal entity responsible for the study: Prospective Dutch Colorectal Cancer Cohort (PLCRC).

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589P Impact of landmark point selection on molecular residual disease detection in stage I-IV resectable colorectal cancer

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Background: Circulating tumor DNA (ctDNA) based molecular residual disease (MRD) detection has been shown to predict prognosis and guide individualized management of colorectal cancer (CRC). The landmark point is usually set at 4-12 weeks post resection in consideration of the disturbance to cell-free DNA (cfDNA) by surgery. This study aimed to evaluate the feasibility of moving the landmark point to 1-week post resection.

Methods: The study prospectively and consecutively enrolled stage I-IV CRC patients who received R0 resection. Blood samples at baseline, post-operative day (POD) 7, POD30 and subsequent every 3-6 months surveillance were collected. The MRD status of all the samples were evaluated by the Burning Rock Patient-specific pROgnostic and Potential tHErapeutic marker Tracking (brPROPHET™) approach. The cfDNA level, mean tumor mutant (MTM), positive predictive value (PPV) and negative predictive value (NPV) were compared between POD7 and POD30.

Results: In total, 164 eligible patients were enrolled. The median follow-up duration was 311 days (95% CI, 296-351) up to date. The brPROPHET displayed a high sensitivity of 95.1% (155/163) for detecting ctDNA preoperatively, with 88.5%, 96.1%, 96.2%, 100% in stage I to IV, respectively. Post-resection ctDNA positive rates were decreased to 15.2% (25/164) at POD7 and 12.8% (21/164) at POD30. The cfDNA levels of POD7 were significantly higher than those of baseline and POD30 ($P<0.001$). However, the MTMs were similar between POD7 and POD30 ($P = 0.55$). The accordance between POD7 and POD30 was 91.5% (150/164). For 6-month recurrence, the PPV was 13.6% vs 15.8% for POD7 and POD30, respectively, with NPV of 100% vs 98.2%. Of the 25 ctDNA positive patients at POD7, 9 turned negative at POD30 and had significantly lower ctDNA levels at POD7 than those who didn't ($P<0.001$). Patients with decreased ctDNA from POD7 to POD30 had a higher ctDNA clearance rate during surveillance than those without decreased ctDNA (100% vs 30%, $P = 0.02$).

Conclusions: The performance of ctDNA detection in POD7 and POD30 was similar. Shift of the landmark time to 1-week post resection may provide an easier way to evaluate MRD status for prognostic stratification.

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590P Assessment of circulating tumor (ct)DNA in patients (pts) with locally advanced rectal cancer (LARC) pts treated with neoadjuvant therapy (NAT)

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Background: Approximately 30% of colorectal cancers arise from the rectum with surgical resection being the mainstay of treatment. For rectal cancers with high-risk pathological features or cases of LARC, preoperative NAT followed by total mesorectal excision +/- adjuvant therapy is recommended. However, this paradigm is associated with questionable survival benefits and high morbidity. Post-NAT and post-surgical risk stratification using ctDNA may help predict outcomes in LARC pts.

Methods: Plasma samples (n=90) from pts with LARC (N=30, median age: 67 years) were analyzed retrospectively. A tumor-informed assay (Signatera™) was used to quantify ctDNA pre-NAT, post-NAT, and post-surgery. Neoadjuvant rectal (NAR) score was calculated and compared to ctDNA status to predict recurrence risk and survival outcomes.

Results: At the pre-NAT time point, ctDNA detection rate was 90% (27/30). Pts who were ctDNA-positive either post-NAT (N=5) or post-surgery (N=3) had worse recurrence-free survival (RFS) (HR 8.4, 95%CI: 2.3-30, $p<0.001$ and HR 14, 95%CI: 3.1-66, $p<0.001$, respectively), when compared to ctDNA-negative pts. Similarly, pts with a high NAR score exhibited an inferior RFS when compared to those with a low-risk score (HR: 21, 95%CI: 2.6-2731, $p=0.001$). When utilized in combination with ctDNA status in the post-NAT setting, ctDNA-positive with an intermediate-high NAR score exhibited an inferior RFS compared to ctDNA-negative pts with a low NAR score (HR 33.5, 95%CI: 3.7-4419, $p<0.001$) with 100% recurrence rate. Likewise, post-surgery, ctDNA-positive pts with an intermediate-high NAR score exhibited an inferior RFS, with a recurrence rate of 37.5%, when compared to ctDNA-negative pts with a low NAR score, none of whom recurred (HR 75, 95%CI: 2.6-4916, $p<0.001$). In multivariate analysis, ctDNA status post-surgery ($p=0.039$) and pathological nodal status ($p=0.033$) were the most significant risk factors associated with recurrence.

Conclusions: Post-treatment ctDNA status either as a sole surrogate outcome measure or as an adjunct to the NAR score may predict NAT response, improve risk stratification and potentially improve outcomes in LARC pts.

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591P Survival and benefit of adjuvant chemotherapy (ACT) by circulating tumor DNA (ctDNA)-based genomic profile and molecular residual disease (MRD) in resectable colorectal oligometastases (CRM): PRECISION, a prospective multicenter study

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Background: The utility of ctDNA analysis in guiding personalized ACT for resectable CRM remains unclear.

Methods: Patients (pts) with previously untreated resectable CRM scheduled for curative resection were prospectively enrolled between March 2021 and October 2022. Pretreatment genomic alterations were detected using Guardant360, a 74-gene ctDNA profiling assay, while postoperative 4-week MRD was assessed using Guardant Reveal, a methylation-based ctDNA MRD assay.

Results: Of 118 eligible pts enrolled, pretreatment ctDNA was detected in 99 pts (84%), 62 (53%) of whom had poor genomic profile, predetermined to have at least one of BRAF, RAS, PIK3CA, or SMAD4 mutations. Of 110 pts who underwent surgery for CRM, postoperative 4-week MRD was detected in 26 (22%) pts. Eighteen patients (16%) had both pretreatment poor genomic profile and positive MRD. With a median follow-up time of 11.0 months (m), median recurrence-free survival (RFS) was 15.2 m. Poor genomic profile (hazard ratio [HR], 2.26 [95% CI, 1.00−5.10]) and MRD positivity (HR, 3.85 [95% CI, 1.79−8.30]) were significantly associated with shorter RFS in

multivariate analysis. Positive MRD was associated with shorter RFS (HR, 5.04 [95% CI, 2.30—11.05]) in the poor genomic profile group but not in those without poor genomic profile. Patients with poor genomic profile and positive MRD derived significant benefit from ACT (median RFS, 8.0 m vs. 2.0 m; HR, 0.25 [95% CI, 0.07—0.82]), while no significant benefit was observed in other groups.

Conclusions: Pretreatment genomic profile and postoperative MRD by ctDNA analysis accurately stratify the prognosis and may guide personalized ACT in pts with resectable CRM.

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Legal entity responsible for the study: The authors.

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592P The role of early change in circulating tumor DNA as a potential predictor of response to chemotherapy in patients with metastatic colorectal cancer

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Background: There remains a need to improve the method to predict the therapeutic effect of metastatic colorectal cancer (mCRC). The aim of this study is to explore the value of early change in circulating tumor DNA (ctDNA) as a biomarker for prediction of the drug efficacy of chemotherapy in mCRC (NCT04555369).

Methods: Patients with mCRC treated with first-line chemotherapy (including clnical routine regimens such as XELOX, FOLFIRI, mFOLFOX6 with or without cetuximab or bevacizumab) were enrolled in this study. Plasma ctDNA was detected at baseline and before the second cycle of chemotherapy, and the mutation of 25 tumor-related genes in ctDNA were detected by next generation screen technology. The primary endpoint of this study is to evaluate the role of early change of ctDNA in predicting ORR (objective response rate).

Results: From Sep. 2020 to Sep.2022, 209 mCRC patients treated with first-line chemotherapy were enrolled in this study.The median follow-up time was 331 days. Among these 209 patients, the ctDNA mutations were detected in 84.21% of patients at baseline. The most frequently mutated genes were TP53 (60.29%), APC (56.94%) and KRAS (34.93%) gene. The value of MSAF (maximum somatic allele frequency) change after the first cycle of chemotherapy was significantly different between tumor remission and non-remission groups (P=0.001). The cut-off value of MSAF change for predicting tumor remission was 6.27% (AUC 0.637,95%CI:0.556-0.719, P=0.002). The ORR were 54.2% and 31.4% in patients with MSAF change $\geq$ 6.27% group and < 6.27% group (P=0.003), while DCR (disease control rate) were 95.3% and 91.4% (P = 0.347) in these two groups, respectively. In addition, the K-M survival curve and log-rank test showed that PFS (progression free survival) were significantly different in the two groups (median PFS of MSAF change $\geq$ 6.27% group vs. MSAF change < 6.27% group: 317 days vs. 217 days; HR:1.598, 95%CI:1.016-2.514, P=0.03).

Conclusions: The early changes in ctDNA levels after initiation of first-line chemotherapy in mCRC would enable early prediction of response prior to radiological assessment.

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593P Role of circulating tumor DNA (ctDNA) in assessing primary anti—epidermal growth factor receptor (EGFR) resistance in untreated RAS/BRAF wild-type (WT) metastatic colorectal cancer (mCRC) patients (pts)

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Background: Current guidelines recommend anti-EGFR—based first-line therapy after evaluation of *RAS, BRAF* mutational status and primary tumor sidedness in mCRC pts. However, knowledge gaps about primary resistance to EGFR inhibition exist and more negative predictive biomarkers are required to identify pts who can be spared toxicities from anti-EGFR therapy and benefit from alternative biologic agents. With limited prospective data available, this study was conducted to explore the clinical utility of ctDNA NGS (Guardant360) in assessing alterations of primary EGFR resistance.

Methods: This is a prospective study looking to identify 40 newly-diagnosed, untreated mCRC pts who are RAS/BRAF WT by routine tumor profiling and planned for chemotherapy in combination with anti-EGFR therapy. Prior to treatment initiation, all pts underwent ctDNA testing to assess presence of at least one of the following alterations associated with resistance to anti-EGFR: mutations (mt) (*RAS*, *BRAF, PTEN, AKT, PI3KCA, SMAD4, EGFR)*, amplifications (amp) (*ERBB2, MET)*, and fusions (*NTRK/ROS1/ALK/RET)*. Pt characteristics, treatment information and outcomes were analyzed.

Results: With 21 pts consented thus far, sequencing success rate was 95.2% (20/21). Median age was 62 years, 100% left-sided tumors, 53% male and 90% (18/20) had at least 1 cycle of anti-EGFR therapy. Average turnaround time for ctDNA was 7.2 days. 6 pts (30%) had alterations of primary EGFR resistance including mt in *ERBB2* (N=1) and *SMAD4* (N=3); *ERBB2* amp (N=1) and *RAF* amp (N=1). Treatment response to anti-EGFR was observed in 10 of 13 pts (76.9%) without resistant alterations vs. 2 of 5 pts (40%) with alterations (odds ratio=1.92; p=0.27). With a median follow-up of 4.7 months(m), there was a trend towards improved median progression-free survival of pts without vs. with alterations (7.0 vs. 2.8m; HR=0.88; p=0.88).

Conclusions: ctDNA testing detects primary resistance to EGFR inhibition in a subgroup of untreated, RAS/BRAF WT mCRC pts, thus serving as a prognostic classifier and providing additional value above routine tumour profiling. Updated results will be presented.

Legal entity responsible for the study: The authors.

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594P The efficacy of anti-EGFR therapy for RAS mutant metastatic colorectal cancer (mCRC) patients with RAS mutation negative in circulating-tumor DNA (ctDNA) after 1st- or 2nd-line chemotherapy

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Background: Liquid biopsy studies have shown the change of *RAS* status in ctDNA after chemotherapy in *RAS* wild-type mCRC. Our prospective observational study (RASMEX study) showed that the rate of *RAS* mutant mCRC patients (pts) with *RAS* mutations (mts) negative in ctDNA after standard chemotherapy was 22.8% (*Izawa*, et al, JSMO annual meeting 2023). Here, we present the efficacy of anti-epidermal growth factor receptor (EGFR) therapy for these pts.

Methods: *RAS* mutant mCRC pts with refractory or intolerable after response to prior fluoropyrimidine-containing regimen were enrolled. OncoBEAM™ RAS CRC kit was used to measure *RAS* mts in ctDNA just after 1st- or 2nd-line treatment. For pts with *RAS* mts negative in ctDNA who received anti-EGFR therapy after enrollment, the overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) were prospectively evaluated. In *RAS* mts negative pts in ctDNA, blood samples were also collected before anti-EGFR therapy and *RAS/BRAF/PIK3CA* mts were measured by Plasma-SeqSensei ™ CRC RUO Kit.

Results: Of 55 (22.8%) had *RAS* mts negative in ctDNA among 241 pts who filled the eligibility criteria, 29 received chemotherapy including anti-EGFR antibody: median age, 66 years; left-sided primary tumor, 79.3%; 11 pts for 2nd-line setting and 18 pts for 3rd- or later-line setting. In 11 pts receiving 2nd-line combination chemotherapy, ORR and DCR were 0% and 54.5% (95% confidence interval [CI]: 25.1—84.0), respectively. The median PFS was 4.9 months (95%CI: 1.9—6.5). In 8 pts without any mts in ctDNA before treatment, DCR was 62.5% and median PFS was 5.6 months. While, ORR and DCR were 5.6% (95%CI: 0—16.1) and 55.6% (95%CI: 32.6—78.5), respectively, in 18 pts receiving 3rd- or later-line treatment with combo- or monotherapy. The median PFS was 3.3 months (95%CI: 1.6—4.8). In 12 pts without any mts in ctDNA before treatment, ORR and DCR both were better (8.3% and 58.3%, respectively).

Conclusions: Our prospective observational study revealed the efficacy of anti-EGFR therapy for *RAS* mutant mCRC pts with *RAS* mts negative in ctDNA after 1st- or 2nd-line treatment. Further prospective studies need to be conducted for these pts.

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Legal entity responsible for the study: Japan Clinical Cancer Research Organization.

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595P The DUREC trial: Durvalumab plus total neoadjuvant therapy in locally advanced rectal cancer - a multicenter, single-arm, phase II study (GEMCAD-1703)

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Background: Total neoadjuvant therapy (TNT) is a new standard of care for locally advanced rectal cancer (LARC). However, the activity of immunotherapy in combination with chemoradiotherapy (CRT) in microsatellite-stable (MSS) rectal cancer has been limited. We explored the efficacy and safety of TNT in combination with the anti-PD-L1 durvalumab (D) in LARC pts with MSS rectal adenocarcinoma.

Methods: The DUREC study is a multicenter, single-arm, phase II trial that recruited pts with stage II and III MSS rectal adenocarcinoma with MRI-defined high-risk T3 (extramural vascular invasion (EMVI), >5mm of perirectal fat infiltration, mesorectal fascia involvement), T4, N2, or distal third tumors (T3/4). Pts received 6 cycles of FOLFOX with D at 1500 mg q4W, followed by CRT with capecitabine and D, continuing D until surgery. The first 6 pts underwent a safety run-in phase. Primary endpoint was pathological complete response (pCR) rate. Assuming a minimum efficacy for pCR of 16% and an optimum of 30%, with an α error of 0.1 and a β error of 0.1 (90% power), the study aimed to recruit 58 pts.

Results: 61 pts were enrolled (median age, 61.3 years; 70% male). Clinical staging was T3/T4 tumors (78/22%), N2 (53%), and 60% had EMVI positivity. Mean number of administered cycles of mFOLFOX6 and durvalumab were 5.8 and 6.2, respectively, with 41 patients (67.2%) receiving 7 cycles of durvalumab before surgery. Among the 56 (92%) pts who underwent surgery, 22 (39%) achieved a pCR and 18 (32%) achieved a major response (71% of major pathological responses). pCR rate for the intention-to-treat population was 36% (95% CI 24.2%-49.4%). Reasons for not performing surgery were metastatic disease progression during therapy (n=3), toxicity (n=1) and major protocol deviation (n=1). Eight pts (13%) had treatment-related serious adverse events, with diarrhea being the most common (3.3%).

Conclusions: The DUREC trial is the first prospective clinical study evaluating the combination of immunotherapy throughout the TNT process for treating MSS LARC. The study met its primary endpoint, demonstrating promising activity and safety, and deserving further development in a phase III study.

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Legal entity responsible for the study: Spanish Group of Digestive Cancer (GEMCAD).

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596P Comparison of neoadjuvant chemoradiotherapy with CAPEOX versus single-agent capecitabine in high-risk locally advanced rectal cancer: Long-term results from a multicenter randomized controlled trial (MONT-R)

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Background: The benefit of adding oxaliplatin to neoadjuvant chemoradiotherapy (nCRT) for locally advanced rectal cancer (LARC) remains controversial. We conducted a multicenter randomized trial aimed at evaluating the value of adding oxaliplatin to nCRT in high-risk LARC patients.

Methods: LARC patients with high-risk factors (cT4 or cN2, high pathological grade, neurovascular invasion, or anal sphincter involvement) were randomized in a 1:1 ratio to receive long-course radiotherapy plus three cycles of concurrent CAPEOX or single-agent capecitabine. The primary endpoint was 3-year disease-free survival (3y-DFS). Secondary endpoints included pathological complete response (pCR) rate, CAP tumor regression grade, and treatment-related adverse reactions.

Results: From August 2017 to April 2022, 505 patients were randomized to the CAPEOX group (n=248) or the Capecitabine group (n=257). 91.5% of the CAPEOX group and 92.2% of the Capecitabine group underwent radical surgery after nCRT. Pathological examination showed no significant difference in pCR rate between the two groups (25.6% for the CAPEOX and 25.3% for the Capecitabine group, $P > 0.05$). However, compared with the single-agent group, a higher proportion of patients in the CAPEOX group achieved significant tumor regression (CAP 0-1) (59.0% *vs*. 46.8%, $P=0.009$). There was no significant difference in the incidence of grade 3-4 treatment-related toxicity between the CAPEOX and the Capecitabine group (46.5% *vs*. 39.9%, $P > 0.05$). After a median follow-up of 37 months, there was no significant difference in 3y-DFS between the two groups (81.7% in the CAPEOX *vs*. 83.5% in the Capecitabine group, $P > 0.05$). In the overall analysis, patients achieving CAP 0-1 had significantly better 3y-DFS than those achieving CAP 2-3 (89.0% *vs*. 80.9%, $P=0.018$).

Conclusions: We showed that adding oxaliplatin to nCRT in high-risk LARC patients may improve tumor regression with acceptable toxicities, although this may not translate into long-term oncological benefits.

Clinical trial identification: NCT 03042000.

Legal entity responsible for the study: The authors.

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597P Surgical quality for patients (pts) treated with neoadjuvant chemotherapy vs chemoradiation for locally advanced rectal cancer (LARC): PROSPECT (NCCTG N1048, alliance)

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Background: Radiation with sensitizing fluoropyrimidine (5FUCRT) is a standard curative intent treatment for LARC. The PROSPECT trial compared FOLFOX chemotherapy with selective use of 5FUCRT (intervention) to 5FUCRT (control) for neoadjuvant treatment prior to total mesorectal excision (TME) for LARC and the primary endpoint of non-inferiority disease-free survival was met. Analyzing quality of surgery is key to interpreting the results of PROSPECT.

Methods: Trial eligibility included cT2N+, cT3N-, cT3N+ rectal cancers deemed appropriate for neoadjuvant therapy prior to TME. Exclusions included tumors not amenable to sphincter preservation, T4 disease, threatened radial margins, or $\geq$ 4 enlarged lymph nodes. Pts were randomized 1:1 to 5FUCRT with 5040 cGy over 5.5 weeks with capecitabine or 5FU (control) or 6 cycles of mFOLFOX6 (intervention) followed by restaging. Secondary and post hoc surgical quality endpoints included: rate of sphincter preservation, completeness of TME, number of lymph nodes examined, radial margin status, length of hospital stay, reoperation, readmission, and rate of ostomy formation.

Results: From 6/2012 to 12/2018, 1194 pts were randomized, 1128 initiated protocol-assigned treatment, and 1045 completed surgery. Median age was 57 years, 34.4% were women, 61.9% had clinically positive nodes, 78.9% of tumors were <10 cm from the anal verge with a median tumor height of 8 cm. The table shows surgical quality outcomes.

Table: 597P

Surgical Quality	5FUCRT n(%)	FOLFOX with selective 5FUCRT n(%)	p-value
Completed Surgery	510	535	
Minimally invasive surgery	399 (78.2)	428 (80.0)	0.483[1]
Low anterior resection	485 (95.1)	508 (95.0)	0.914[1]
Ostomy performed	465 (91.2)	416 (77.8)	<0.0001[1]
Lymph nodes examined (median)	16	20	<0.0001[2]
Positive radial margin (≤1mm)	7 (1.4)	6 (1.1)	0.669[1]
Complete/near complete TME	499 (97.7)	527 (98.5)	0.718[1]
Length of hospital stay (median)	5.0	5.0	0.625[2]
Reoperation within 30 days	44 (8.6)	35 (6.5)	0.202[1]
Readmission within 30 days	99 (19.4)	77 (14.4)	0.030[1]

[1]Chi-Square; [2]Kruskal-Wallis

Conclusions: Low rate of positive radial margin along with high rate of complete/near complete TME and number of lymph nodes examined demonstrate a high quality of surgery in this multicenter trial. More pts treated with 5FUCRT (relative to the FOLFOX arm) required an ostomy and readmission within 30 days of surgery.

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Legal entity responsible for the study: Alliance.

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BilliontoOne. E.M. O'Reilly: Financial Interests, Personal, Advisory Board: Boehringer Ingelheim, BioNTech, Merck, AstraZeneca, Novartis, Fibrogen, Astellas, Tempus, Merus, Bristol Myers Squibb, Berry Genomics, Exelixis, Incyte, Helio, Neogene, Newbridge, QED, Sevier, Thetis, Vector, Yiviva; Financial Interests, Personal, Advisory Board, +Spouse: Ipsen; Financial Interests, Personal, Advisory Board, Spouse: Genentech/Roche, Eisai; Financial Interests, Personal, Advisory Board, + spouse: Autem; Financial Interests, Institutional, Local PI: Genentech/Roche, Arcus, Elicio; Financial Interests, Personal and Institutional, Coordinating PI: BioNTech; Financial Interests, Institutional, Coordinating PI: AstraZeneca, Pertzye; Financial Interests, Institutional, Research Grant: Parker Institute for Cancer Immunotherapy; Non-Financial Interests, Other, Scientific and Medical Advisory Board: Pancreas Cancer Action Network; Non-Financial Interests, Member of Board of Directors: National Pancreas Foundation; Other, Editor: American Society of Clinical Oncology, American Association of Cancer Research (AACR); Other, Advisor/no compensation: Thetis, BioSapien. J. Meyerhardt, H. Mamon: Financial Interests, Personal, Advisory Board: Merck. D. Schrag: Financial Interests, Personal, Research Funding: GRAIL; Financial Interests, Personal, Stocks or ownership: Merck; Financial Interests, Personal, Royalties: JAMAA. All other authors have declared no conflicts of interest.

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598P Influence of the early stoma closure after low rectal cancer resection on completeness of adjuvant chemotherapy (CoCStom): A randomized, controlled multicentre trial of the AIO (AIO KRK 0113)

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Background: There is uncertainty whether early closure (EC) of a defunctioning stoma influences the complete administration of the adjuvant chemotherapy (CoC) after low anterior rectal resection (LAR) for rectal cancer. CoC was previously shown in retrospective analyses to improve the five-year OS and DFS.

Methods: CoCStom trial was a prospective randomized multicenter investigator-initiated study. Patients undergoing neoadjuvant therapy (chemoradiation or 5x5 Gy radiotherapy) followed by LAR for locally advanced rectal cancer were randomized in two arms. Experimental - EC, 8 to 10 days after LAR; and control - late closure of the stoma (LC), after completion of the adjuvant chemotherapy (26 weeks) which included both 5-FU- and oxaliplatin-based regimens according to local practice and tumor stage. The primary endpoint was CoC. The study was designed to show an CoC improvement of 20 % (power 80%, alpha-value 0.05). Secondary endpoints: oncological and surgical outcomes as well as quality of life.

Results: A total of 257 patients with comparable baseline characteristics and pathohistological (UICC) stages were randomized between 2013 and 2018. Of these, 233 (EC: 116 vs. LC: 117) were eligible for analysis. Median follow up was 24 months. Surgical morbidity after stoma closure was comparable (Clavien Dindo III-IV: EC vs. LC: 15.8 vs. 18.9%). The median hospitalization after LAR was 17 days in both groups. CoC was similar EC [62.9% (95% CI: 53.5 - 71.7%] and LC [65.8% (56.5 -74.3%]. Patients in the EC group started adjuvant chemotherapy (median 38 vs. 27 days after randomization) significantly later and received less oxaliplatin-based regimens (8.5 vs. 15%). DFS was numerically better in the EC group (HR 1.6; 95% CI: 0.83 − 3.06).

Conclusions: EC of the stoma was feasible and did not lead to increased surgical morbidity. CoC was not improved, however, a trend towards better DFS was observed within the EC group despite similar CoC, a later start of adjuvant therapy as well as less use of oxaliplatin-based regimens. Thus, EC of the stoma appears to be a valid option for patients undergoing LAR.

Clinical trial identification: DRKS00005113.

Legal entity responsible for the study: Flavius Sandra-Petrescu, MD, on behalf of the CoCStom Study Group.

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599P R-IMMUNE: A phase Ib/II study to evaluate safety and efficacy of atezolizumab combined with radio-chemotherapy in a preoperative setting for patients with locally advanced rectal cancer (LARC)

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Background: There is a strong rationale to combine radiotherapy with immune checkpoint inhibitors (ICIs). This study evaluates this combination before surgery in locally advanced rectal cancer (LARC).

Methods: R-IMMUNE, a multicentric phase Ib/II trial, included patients with stage II/III LARC treated with a preoperative combination of radio-chemotherapy (45-50 Gy/25 fractions, 5FU 225 mg/m2/d, 5d/w from week 1 to 5) + atezolizumab 1200 mg/infusion (ATZ). The phase Ib evaluated a single infusion of ATZ at week 3. Phase II evaluated 4 infusions of ATZ at weeks 3, 6, 9 and 12. Surgery was planned for week 15. Safety and efficacy based on the pathological complete response (pCR) rate are primary objectives. Based on a two-stage Simon design, 33 patients (+3 for the replacement of non-evaluable patients) were required in phase II to detect an increase in pCR rate from 15% to 35% ($\alpha = 0.1$, $\beta = 0.1$), with at least 8 pCRs to reject the null hypothesis.

Results: Six patients were included in phase Ib and 34 in phase II. This analysis covered 39 patients (median age 63 years, 56% male, 82% stage III, 12% MSI-H), excluding 1 phase II patient who is still undergoing treatment. A total of 193 adverse events (AEs) were reported, of which 29 (15%) were grade 3-4 and involved 19/39 (49%) of patients. Among gade 3-4 AEs, most frequent were urinary tract infections (6/29), blood disorders (5/29), post-operative anastomotic leaks/infections (4/29) and gastrointestinal disorders (4/29). Five patients presented immune-related AEs: 1 immune thrombocytopenia (grade 4), 2 endocrine disorders (grade 2) and 2 skin disorders (grade 1). So far, efficacy was assessed in 6 phase Ib patients and in 31 patients from the phase II (2 were excluded for protocol deviation). Respectively, 2/6 and 8/31 patients had a pCR. Overall, 10/37 (27%) patients had a pCR (including 2 MSI-H).

Conclusions: An analysis of the nearly complete R-immune cohort confirmed an acceptable safety profile and met study efficacy objectives. The results warrant further investigations of ICIs combined with radiotherapy in LARC eventually within a total neoadjuvant treatment and organ preservation based strategies.

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Legal entity responsible for the study: Grand Hôpital de Charleroi − Belgium.

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600P Effectiveness and safety of rectal arterial infusion chemotherapy combined with anti-PD1 antibody for microsatellite stable locally advanced rectal cancer: Early outcome report of a two-stage, single armed, phase II study (RAIC)

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Background: The standard neoadjuvant therapy for locally advanced rectal cancer (LARC) is chemoradiotherapy (CRT) which increases perioperative complications. Chemotherapy alone has approximately 60% objective response rate and lower pathological complete response pCR rate compare with CRT. We propose a new strategy (induction chemotherapy followed by arterial infusion chemotherapy and anti-PD1 antibody) to achieve high pCR rate for microsatellite stable (MSS) LARC without radiotherapy.

Methods: Two cycles of Capox were given to eligible LARC patients (tumor located 5-12cm from anal verge). Patients who achieved more than 20% regression of maximum tumor diameter receive 2 cycles of rectal arterial infusion oxaliplatin (50mg, D1) + intravenous anti-PD1 inhibitor (Sintilimab, 200mg, D2) + capecitabine (1000mg/m2, po, twice daily, D1-D14) with 6 weeks before operation. Patients with tumor regression less than 20% were suggested to receive CRT. The primary endpoint is pCR rate. A total of 38 patients (10 in the first stage, 28 in the second) stage are planned to be recruited by Simon's two-stage design. The second stage will be conducted if more than 2 patients achieve pCR in the first stage, otherwise the trial will be terminated.

Results: A total of 20 patients had been enrolled and 13/20 reached 20% regression criterion after induction chemotherapy and received arterial infusion chemotherapy combined with intravenous anti-PD1 antibody. One patient achieved clinical complete response and refused surgery. Other 12 patients received operation and 4/12 (33.3%) achieved pCR (3/10 in the first stage). According to the tumor regression grading TRGstandard of the eighth edition of AJCC, the patients number of TRG0/1/2/3 was 4/4/2/2, respectively. Among the 12 patients 5 had grade 3 adverse event (abdominal pain and readmission), including one grade 3 immune-related adverse event (dermatitis).

Conclusions: Rectal arterial infusion chemotherapy combined with intravenous anti-PD1 antibody for MSS LARC achieved high pCR rate. The RAIC trial is now progressed to the second stage.

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Legal entity responsible for the study: The Second Affiliated Hospital Zhejiang University School of Medicine.

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601P Short-course radiotherapy based total neoadjuvant therapy combined with PD-1 inhibitor for locally advanced rectal cancer: Preliminary findings of TORCH

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Background: For locally advanced rectal cancer (LARC), total neoadjuvant therapy (TNT) increases the rates of complete response and organ preservation. Hypofractionated radiotherapy shows better synergistic effects in combination with PD-1 inhibitor. The combination of short-course radiotherapy (SCRT) based TNT and PD-1 inhibitor is likely to improve tumor response and prognosis.

Methods: TORCH is a prospective, multicentre, randomized phase II trial. 130 LARC (T3-4/N+M0, distance from anal verge $\leq$10cm) patients will be treated with TNT and assigned to consolidation arm (A) and induction arm (B). Arm A receives SCRT (25Gy/5Fx) followed by 6 cycles of Toripalimab combined with CAPOX (ToriCAPOX). Arm B receives 2 cycles of ToriCAPOX followed by SCRT and 4 cycles of ToriCAPOX. TME surgery is scheduled 2 weeks after TNT while a watch and wait (W&W) option can be applied to patients achieving clinical complete response (cCR). The primary endpoint is complete response (CR, pathological complete response [pCR] plus cCR) rate. The secondary endpoints include the grade 3-4 acute adverse effects (AE) rate, 3-year DFS rate, etc.

Results: Up to 2023/4/1, 130 patients were recruited and 104 patients have completed the treatment (Arm A 54, Arm B 50). The median age was 55 and 91 patients were stage III. 82.7% (86/104) of them showed one of the following features: lower location ($\leq$5cm), cT4, cN2, MRF+ and EMVI+. 59 patients underwent TME, of which 29 cases achieved pCR (49.2%, 29/59), and the major pathologic response rate (TRG0-1) was 62.7% (37/59). 29 patients achieved cCR and adopted W&W. The total CR rate was 55.8% (58/104), with 57.4% (31/54) in Arm A and 54.0% (27/50) in Arm B. The remaining 16 non-cCR patients refused surgery and went on with close follow-up. Among 53 patients who were assessed N+ on baseline MR and underwent surgery, 48 were pathologically confirmed N0 (90.6%, 48/53). The main grade 3-4 AE was thrombocytopenia (42.3%, 44/104), with 4 cases of grade 4 thrombocytopenia.

Conclusions: For LARC, SCRT based TNT combined with PD-1 inhibitor has achieved a high CR rate, which could provide new choice to achieve organ preservation for MSS and low rectal cancer patients and worth to be further validated in phase III trial.

Clinical trial identification: NCT04518280.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

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602P Brazil-TNT: A randomized phase II trial of neo-adjuvant chemoradiation followed by FOLFIRINOX vs chemoradiation for stage II/III rectal cancer

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Background: Neoadjuvant radiation and oxaliplatin-based systemic therapy (Total Neoadjuvant Therapy — TNT) has been shown to increase response and organ-preservation rates in localized rectal cancer. However, trials have been heterogeneous regarding treatment protocols and few have used a watch-and-wait (WW) approach for complete responders. This trial evaluates if conventional long-term chemoradiation followed by consolidation FOLFIRINOX increases complete response rates and number of patients managed by WW.

Methods: Thiswas apragmatic randomized phase II trial conducted in 2 Cancer Centers in Brazil that included patients with T3+ or N+ rectal adenocarcioma. After completing long-course 54Gy chemoradiation with capecitabine patients were randomized 1:1 to observation or 4 cycles of mFOLFIRINOX (Oxaliplatin 85, irinotecan 135, 5-FU 2400). All patients were re-staged with dedicated pelvic MRI and sigmoidoscopy 12 weeks after the end of radiation. Patients with a clinical complete response were followed using a WW protocol. Primary enpoint was complete response: complete clinical response (cCR) or pathological response(pCR).

Results: Between Feb 2020 and April 2023, 46 patients were randomized to TNT and 42 to standard of care. Median age was 59 and 64% were male. Tumors were 68% stage 3, median distance from anal verge was 5cm, 43% had at-risk circumferential margin and 21% involved sphincter. The rates of cCR+pCR were 9/46 (19%) for TNT vs 5/42 (11%) for controls (OR 1.79, CI95% 0.54-6.3 p=0.16) and rates of WW were 5/46 (10.8%) and 2/45 (4%) (ns). Median follow-up was 16.9 months and recurrence rates were 8/46 (17%) and 11/42 (26%) for TNT and controls (ns).

Conclusions: TNT with consolidation FOLFIRINOX is feasible and has high response rates. Complete data from 96 patients will be presented at the meeting. This trial was supported by a grant from the Brazilian Ministry of Health (PROADI-SUS) - NUP 25000.164382/2020-81.

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Legal entity responsible for the study: The authors.

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603P Updated results of a prospective phase II study of total neoadjuvant therapy for locally advanced rectal cancer

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Late withdrawal

604P Overall and progression-free survival of patients with metastatic colorectal cancer: A real-world prospective, longitudinal cohort study on the continuum of care (PROMETCO)

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Background: Advances in metastatic colorectal cancer (mCRC) treatment have improved overall survival (OS) in clinical trials, but real-world survival data, in particular in later lines of treatment, are scarce. PROMETCO (NCT03935763) is the first international, prospective, real-world study to investigate the continuum of care in all patients (pts) with mCRC after two disease progressions since diagnosis.

Methods: Adult mCRC pts who were willing to receive subsequent treatment were included. Endpoint data presented include OS, progression-free survival (PFS; defined as start of treatment until progressive disease, death or start of new treatment), patient characteristics and treatment patterns.

Results: As of April 2023, 738 pts from 18 countries were enrolled (Table). 49% of pts were RAS mutant; 32% RAS/BRAF wild type; 5% BRAF mutant. 40% of pts had unknown microsatellite instability (MSI) status; 2% were MSI high; 3% were MSI low; 55% were microsatellite stable. Median time from mCRC diagnosis to PROMETCO inclusion was 22.0 mo. During the course of their disease, most pts had received fluoropyrimidine (99%), oxaliplatin (88%), irinotecan (96%), an anti-VEGF (79%) or an anti-EGFR antibody (40%), FTD/TPI (75%) or regorafenib (25%). 64% and 23% of pts had colorectal or liver surgery, respectively. For 628 pts who completed the study, mOS from mCRC diagnosis was 35.4 mo; mOS from inclusion in PROMETCO (i.e., after second disease progression) was 6.8 mo; and mOS from start of third-line treatment was 6.4 mo. Median PFS was 9.5 mo in first-; 4.8 mo in second-; 2.6 mo in third- and 2.4 mo in fourth-line.

Conclusions: These data provide key insights on pts characteristics, survival (which reflects observations from clinical trials) and treatment patterns in the real-world, which are generally consistent with ESMO guidelines. Table: Patient characteristics at enrollment.

Table: 604P

Characteristic	
Mean age (range), years	66 (31-87)
Male sex, %	59
ECOG PS, % 0 1	39.5 52.8
<3 metastatic sites, %	89.8
Synchronous metastases, %	65.3
Metastasis site, % Liver Lung Other Peritoneal carcinomatosis	73.3 38.8 21.4 14.2
Disease sidedness, % Right Left	28.2 42.1

Clinical trial identification: NCT03935763.

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(Kanker.nl); Non-Financial Interests, , Leadership Role, chair of RWD & DH working group: ESMO; Other, PI of the Dutch Prospective Colorectal Cancer Cohort study: PLCRC project. R. Garcia-Carbonero: Financial Interests, Personal, Advisory Board: AAA, Advanz Pharma, Amgen, Bayer, Bristol Myers Squibb, HMP, Ipsen, Merck, Midatech, MSD, Novartis, PharmaMar, Pierre Fabre, Servier; Financial Interests, Institutional, Research Grant: Bristol Myers Squibb, MSD, Pfizer; Non-Financial Interests, Leadership Role, Global PI of investigator-initiated clinical trials (AXINET, NICENEC, PEMBROLA): Bristol Myers Squibb, MSD, Pfizer; Other, Honoraria received by spouse for advisory board or invited speaker roles: AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Genomica, Lilly, MSD, Merck, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Servier, Takeda. C. Pinto: Financial Interests, Personal, Advisory Board: Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Lilly, Merck Serono, MSD, Novartis, Roche, Sanofi, Servier; Financial Interests, Personal, Invited Speaker: Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Lilly, Merck Serono, MSD, Novartis, Roche, Sanofi, Servier. A. Mitroshkin: Financial Interests, Personal, Other: Servier, Bayer, Pierre Fabre, Merck; Financial Interests, Personal, Funding: Servier, Bayer, Pierre Fabre, Merck. G. Bodoky: Financial Interests, Personal, Advisory Board: Roche, Bayer, Janssen, Novartis, Pfizer, Bristol Myers Squibb , Merck; Financial Interests, Personal, Invited Speaker: Roche, Bayer, Janssen, Novartis, Pfizer, Bristol Myers Squibb, Merck. V. Bourgeois: Financial Interests, Personal, Research Funding: Servier; Financial Interests, Personal, Advisory Board: Servier, Pierre Fabre, AstraZeneca; Financial Interests, Personal, Advisory Role: Servier, AstraZeneca; Financial Interests, Personal, Invited Speaker: Pierre Fabre, MSD; Financial Interests, Personal, Speaker's Bureau: Merck. A. Ruiz-Casado: Financial Interests, Personal, Invited Speaker: Servier, Abbott, Nestle, Medtronic; Financial Interests, Personal, Advisory Board: Pierre Fabre, Amgen. A. Fernandez Montes: Financial Interests, Personal, Invited Speaker: Lilly, Pierre Fabre, Amgen, Servier, Eisai, AstraZeneca, MSD. A. Sullivan, E. Choucair, M. Sicaire: Other, Personal, Full or part-time Employment, Employee of Servier: Servier. F.E. Marti: Financial Interests, Personal, Other, Has received honoraria from Servier: Servier. J. Bachet: Financial Interests, Personal, Other: Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, GSK, MSD, Merck Serono, Pierre Fabre, Roche, Sanofi, Servier; Non-Financial Interests, Personal, Other: Amgen, Merck Serono, Roche, Servier. All other authors have declared no conflicts of interest.

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605P First-line chemotherapy with or without targeted therapies in metastatic colorectal cancer: The GEMCAD 14-01 prospective cohort

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Background: First-line randomized clinical trials in metastatic colorectal cancer (mCRC) comparing chemotherapy with doublets (CT) plus targeted therapies (bevacizumab, cetuximab and panitumumab) (TT), have shown substantial benefit in progression free survival but modest benefit in overall survival over CT alone. In addition, elderly patients (pts) and pts with ECOG performance status (PS) of 2 are usually under-represented. GEMCAD 1401 is a prospective observational, multicenter study (GEMCAD 1401. ClinicalTrials.gov identifier: NCT02254941), that compared overall survival benefit in treatment naïve mCRC pts, treated with or without first-line TT.

Methods: Between June 2014 and June 2018, 1107, mCRC pts were included and 1020 were eligible (640 pts treated with CT plus TT and 380 pts treated with CT alone). Baseline pts characteristics that would influence initial treatment strategy decision and efficacy (age, gender, tumor stage at diagnoses, primary tumor side, surgery of primary tumor, *RAS* and *BRAF* status, ECOG PS, Charlson score, number and type of affected organs, leucocyte, alkaline phosphatase, lactate dehydrogenase and CEA level) and postbaseline variables (time-varying covariates; ECOG PS, Charlson score, lactate dehydrogenase and grade 3-4 toxicities), were balanced using Inverse Probability Treatment Weighting (IPTW).

Results: After IPTW application, standardized differences of all basal variables between groups were $<$10%. The median overall survival was 21.2 months 95% confidence interval (CI) (18.9-23.6) in the CT plus TT group and 21.4 months (95% CI 18.2-25.3) in the CT group (hazard ratio (HR) for death, 0.93; 95% CI 0.8-1.08). The median progression free survival was 9.9 months (95% CI 9.3-10.7) in the CT plus TT and 8.9 months in the CT alone (95% CI 8.1-9.7). HR 0.87 (95% CI 0.76- 0.99).

Conclusions: First-line treatment with CT alone compared with CT plus TT, show no detrimental effect in overall survival.

Clinical trial identification: NCT02254941.

Legal entity responsible for the study: Grupo Español Multidisciplinar en Cáncer digestivo.

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606P Regional lymph nodes (N+ vs N0) in metastatic colorectal cancer

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Background: Regional lymph node metastases are negative prognostic factors in localized disease and after liver resection, but little is known in metastatic colorectal cancer (mCRC). We studied demographics, treatments, and outcomes for mCRC with (N+) and without (N0) regional lymph node metastases in population-based and real-world settings.

Methods: Patients from three Nordic mCRC cohorts were combined; the population based PRCRC-study, the likewise Uppsala Region cohort and the real-world RAXO study. The dataset included 1764 patients with resected primary tumours, of which 1710 had pathologic N-stage reported. Characteristics and treatments were compared using Chi-square. Overall survival (OS) was estimated with Kaplan-Meier and compared using log-rank.

Results: N+ were seen in 1242 (73%) and N0 in 468 (27%). N+ patients associated with female sex, right-sided primaries, higher tumour grade, synchronous metastases, more metastatic sites, more liver, distant lymph node, and peritoneal metastases, and fewer lung metastases compared with N0 (Table). No differences were seen for ECOG and age $>$70 years. *BRAF*-V600E mutations (mt) were more common in N+, as was deficient mismatch repair, whereas *RAS*mt were seen less often.

Table: 606P

		N0		N+		p-value
Age (years)	</=70	241	51%	689	55%	0.141
	>70	227	49%	553	45%	
Sex	Male	276	59%	662	53%	0.036
	Female	192	41%	580	47%	
Primary sidedness	Right	131	28%	473	39%	<0.001
(15 unknown/multiple)	Left	334	72%	757	62%	
Tumour stage	1-2	87	19%	52	4%	<0.001
(11 missing)	3	284	62%	777	63%	
	4	91	20%	408	33%	
Tumour grade	Low	359	90%	829	77%	<0.001
(23 missing)	High	41	10%	254	23%	
Presentation of metastases	Synchronous	167	36%	682	55%	<0.001
	Metachronous	301	64%	560	45%	
Metastatic sites	Liver	285	61%	823	66%	0.038
	Lung	154	33%	323	26%	0.005
	Distant nodes	62	13%	350	28%	<0.001
	Peritoneum	73	16%	269	22%	0.005
Mutation groups	RAS&BRAFwt	116	31%	311	32%	0.001
(357 not adequately tested)	RASmt	224	60%	503	51%	
	BRAF-V600Emt	34	9%	165	17%	

N+ patients had less metastasectomies (31% vs 39%, p=0.001) and more systemic therapy only (51% vs 43 %, p=0.001), with no difference for best supportive care. Median OS was shorter in the N+ vs N0 group (23 vs 34 months, p <0.001); likewise for metastasectomy patients (64 vs 96 months, p=0.001), and systemic therapy only (20 vs 27 months, p=0.001). N+ did worse than N0 with non-liver metastasectomy (77 vs 45 months, p=0.018), with similar trends for synchronous (77 vs 39 months, p=0.060) and metachronous presentation (not reached vs 58 months, p=0.172) subgroups.

Conclusions: Regional lymph node metastases (N+) were associated with several other negative prognostic factors. This resulted in fewer metastasectomies and impaired outcome in all and non-liver metastasectomy and systemic therapy only.

Clinical trial identification: NCT01531595; EudraCT 2011-003137-33.

Legal entity responsible for the study: The authors.

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607P Impact of primary tumour sidedness (PTS) on demographics, resectability, and outcome after metastasectomy +/- local ablative therapy (LAT), or systemic therapy in metastatic colorectal cancer patients (a RAXO substudy)

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Background: Primary tumour sidedness (PTS) in mCRC is prognostic and predictive for anti-EGFR efficacy, progression-free (PFS) and overall survival (OS). We aimed to investigate the impact of (PTS) on demographics, resectability, and outcomes of metastasectomy, local ablative therapy (LAT) and systemic therapy.

Methods: The prospective Finnish real-life RAXO study (NCT01531621) included 1086 patients 2012-2018 (Osterlund, TLRHE 2021). Bonferroni corrected $\chi 2$ <0.05, Kaplan-Meier estimates, and Cox regression were analysed. P-value <0.05 denoted with*.

Results: PTS was right in 310 (29%) and left (colon/rectum) in 770 (61%), with multiple primaries excluded. Patients with right-sided tumours more often had female sex, age >70 years, unresectable metastases upfront, mucinous & signet cell histology, high-grade differentiation, *RAS* and *BRAF* mutations, dMMR, regional and distant lymph node metastases, peritoneal and less typical metastases. Patients with left-sided tumours had more liver and lung metastases. There was no difference in ECOG, synchronous presentation, T-stage, or number of metastatic sites. Right vs left PTS was associated with less upfront resectable (26% vs 30%*) and borderline resectable (14% vs 18%*) metastases. Final resectability (upfront + converted resectable) was also lower (32% vs 45%*), and fewer patients had metastasectomy/LAT (33% vs 41%*). Median OS from mCRC diagnosis for right and left was 21 vs 35 months (HR 0.59, CI95% 0.51-0.69); after R0-1 metastasectomy 80 vs 86 months, after R2/LAT 24 vs 50* months, and 18 vs 23* months for systemic therapy only., PFS in systemic therapy only was 8.9 vs 10.0* months (HR 0.82, 0.69-0.94). In multivariable analysis for OS right PTS, *RAS* and *BRAF* status, N-stage, and unresectable metastases upfront remained significant but not female sex, age >70 or dMMR status.

Conclusions: Right-sided PTS associates with several negative prognostic and predictive factors but is an independent negative prognostic factor in multivariable analysis. Resectability and metastasectomy/LAT rates are slightly lower in right primaries and outcomes slightly worse but still "excellent".

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608P Resectability of colorectal liver metastases (CLM) with aflibercept plus FOLFIRI: Results from a prospective French cohort

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Background: Liver resection is the only treatment offering a chance of long-term overall survival (OS) to patients (pts) with CLM.This prospective cohort evaluates the R0/R1 resection rate in pts with predominant CLM who were treated with aflibercept (AFL)+FOLFIRI after failure of an oxaliplatin-based regimen.

Methods: All pts with predominant CLM initiating AFL (4 mg/kg q2w) + FOLFIRI per physician choice were eligible. Primary endpoint was R0/R1 resection rate. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), OS and safety. Assuming a resection rate of 10-20% and 10% of follow-up loss, 140 patients were needed to determine R0/R1 resection rate with good precision.

Results: From July 2017 to July 2020, 136 consecutive pts with CLM [median age 65 years; 64.7% males; 28.7% right-sided; 55.1/8.1% RAS/BRAFmt; 80.1% synchronous; 46.3% extrahepatic sites and median of 4 CLM] were enrolled at 21 French sites. All pts received a prior oxaliplatin-based regimen, 77.4% prior anti-VEGF and 19.0% prior anti-EGFR agents. A median of 7 cycles of AFL+FOLFIRI was given. Overall, 16.2% of pts had R0/R1 liver resections (19.2% for liver only disease): 4/11 (36.4%) after failure of adjuvant oxaliplatin, 17/99 (17.2%) in 2nd line and 1/26 (3.8%) in 3rd line mCRC. Of 22 pts resected, 4 were judged resectable upfront, 15 potentially resectable and 3 unresectable before treatment by the investigator. Median duration of follow-up was 10.7 months (Table). Four pts (18.2%) had post-operative complications (all Dindo-Clavien grade I-II); 34.3% had grade $\geq$3 adverse events with AFL+FOLFIRI, mainly general health deterioration (8.0%) and diarrhoea (3.6%).

Table: 608P Secondary efficacy endpoints

	All (n=136)	Resected (n=22)	Not resected (n=114)
Best ORR*, %	30.1%	68.2%	22.8%
Median PFS, mo [95% CI]	5.4 [4.4-5.9]	11.1 [5.9-13.8]	5.1 [3.7-5.7]
Median OS from AFL initiation, mo [95% CI]	11.2 [9.4-14.1]	NR [20.4-NR]	9.4 [8.2-11.2]
Median OS from mCRC diagnosis, mo [95% CI]	28.1 [24.1-30.8]	55.0 [54.4-NR]	26.5 [21.7-29.0]
2-year OS rate from AFL initiation	19.9%	62.6%	11.1%

*Complete + partial responses; mCRC: metastatic colorectal cancer; CI: confidence interval; mo: months; NR, not reported

Conclusions: This prospective cohort suggests that AFL+FOLFIRI allows a clinically relevant rate of conversion from potentially resectable/unresectable to resectable CLM.

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609P The impact of surgical invasiveness on the efficacy of mFOLFOX6 in resected colorectal liver metastasis: An exploratory analysis of JCOG0603

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Background: In JCOG0603, the addition of mFOLFOX6 to hepatectomy provided no clear survival benefit over hepatectomy alone in patients with colorectal liver metastasis (CLM). Therefore, this study examined the impact of surgical invasiveness on the tolerability of chemotherapy and survival.

Methods: Among patients registered in JCOG0603, those who received mFOLFOX6 after hepatectomy were analyzed in this subgroup analysis. The associations of factors related to surgical invasion (e.g., extent of hepatectomy, operative time, blood loss, postoperative complications) with factors related to the tolerability to mFOLFOX6 (completion of nine cycles, dose intensity, and adverse events) and disease-free survival (DFS) were assessed. The Hx ratio (resected liver weight/body weight) was calculated to evaluate the relative resected liver wight for each patient.

Results: One hundred forty-one patients treated with mFOLFOX6 were analyzed. The Hx ratio was identified as a predictor of the completion of nine cycles of mFOLFOX6 (≥median vs. <median: 50.8% vs. 74.2%, p = 0.0096), oxaliplatin dose intensity (72.9% vs. 86.1%, p = 0.0002), and occurrence of grade 2–4 hematological adverse events (90.5% vs. 75.8%, p = 0.0033). The Hx ratio [≥median/<median: hazard ratio (HR) = 1.94, 95% CI = 1.16–3.22], resected liver weight (≥300 g/<300 g: HR = 2.27. 95% CI = 1.36–3.78), and operative time (≥median/<median: HR = 1.71, 95% CI = 1.06–2.75) were identified as poor prognostic factors for DFS in univariate analysis. There were some interactions of the effect of mFOLFOX6 compared to hepatectomy alone with these factors.

Table: 609P

Surgical invasiveness		mFOLFOX6 vs. hepatectomy alone	
		HR (95% CI)	p
Hx ratio	≥Median	0.73 (0.48–1.10)	0.12
	<Median	0.55 (0.31–0.950)	0.03
Extent of hepatectomy	Major hepatectomy	0.93 (0.45–1.90),	0.84
	Minor hepatectomy	0.65 (0.46–0.92)	0.015
Liver weight	≥300 g	0.81 (0.47–1.40)	0.44
	<300 g	0.55 (0.37–0.83)	0.038

Conclusions: Surgical invasiveness, especially the relative resected liver weight, might affect both the tolerability and cytotoxic effect of mFOLFOX6. Adjuvant mFOLFOX6 should be cautiously administered when the extent of hepatectomy is large.

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610P Predicting benefit from FOLFOXIRI plus bevacizumab versus FOLFOX/FOLFIRI plus bevacizumab in patients with metastatic colorectal cancer

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Background: Individual patient outcomes may substantially differ from average treatment effects obtained in randomised controlled trials (RCT) due to patient heterogeneity. We aimed to predict which patients with metastatic colorectal cancer (mCRC) will benefit from first-line FOLFOXIRI versus FOLFOX/FOLFIRI, both plus bevacizumab.

Methods: Data from 639 patients (434 deaths) included in the phase III TRIBE2 RCT were used for developing a Cox regression model based on prespecified clinical, molecular, and laboratory variables for predicting 2-year mortality. Data from 232 patients (199 deaths) included in the phase II CHARTA RCT were used for external validation and heterogeneity in treatment effects analysis. Missing data was handled by multiple imputation. The C-index and calibration plots were used for performance assessment. C-for-benefit was calculated to assess evidence for treatment heterogeneity. The hazard ratio and absolute risk reduction were plotted as a function of the predicted mortality risk to explore treatment heterogeneity.

Results: In TRIBE2, the C-index was 0.68 (95%CI 0.65 – 0.71). At external validation, the C-index was 0.70 (95%CI 0.64 – 0.75), and the calibration plot indicated slight underestimation of mortality in high-risk patients. The c-for-benefit was 0.56 (95%CI 0.47 – 0.65). On the relative scale, there was no evidence of treatment heterogeneity (p for interaction = 0.16). On the absolute scale, the risk reduction in the lowest risk to highest risk quarter was 18% (95%CI 0 – 37%), 24% (95%CI 2 – 45%), -4% (95%CI -3 – 18%) and 0% (95%CI -16 – 16%), respectively.

Conclusions: Although our data suggest that patients with a low mortality risk have greater benefit of intensified treatment on an absolute scale, the predictions lack sufficient certainty to be used in clinical practice for individualised decision making. Larger samples are required to draw final conclusions on whether benefit from FOLFOXIRI could be predicted in patients with mCRC.

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611P SHR-1701 in combination with BP102 and XELOX as first-line (1L) treatment for patients (pts) with unresectable metastatic colorectal cancer (mCRC): Data from a phase II/III study

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Background: The standard 1L therapies for mCRC involve a fluoropyrimidine with oxaliplatin and/or irinotecan, and a biologic agent. SHR-1701, a novel bifunctional fusion protein targeting PD-L1 and TGFβ, may enhance antitumor activity in combination with 1L standard therapies in mCRC pts. This phase 2/3 trial was designed to evaluate the safety and efficacy of SHR-1701 in combination with BP102 (a biosimilar of bevacizumab) and XELOX as 1L treatment in this pt population.

Methods: In the phase 2 part, eligible pts with previously untreated, unresectable mCRC were given SHR-1701 (30 mg/kg, iv, d1, q3w) + BP102 (7.5 mg/kg, iv, d1, q3w) + XELOX (capecitabine 1000 mg/m^2, po bid, d1-14, and oxaliplatin 130 mg/m^2, iv, d1) of 21-day cycles. Primary endpoints were safety and objective response rate (ORR) per investigator according to RECIST v1.1. Secondary endpoints were duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Results: From June 22 2021 to February 28 2023, 62 pts were enrolled. Median age was 56 years (range, 23-73). The main characteristics of the pts were as follows: 22 (35.5%) right-sided mCRC, 43 (69.4%) had liver metastases, 62 (100.0%) had MSS/pMMR, 36 (58.1%) had *RAS* mutation, and 4 (6.5%) had *BRAF* mutations. As of February 28, 2023, the median follow up time was 12.5 months (range, 1.4-18.8). Grade $\geq$3 TRAEs were reported in 37 (59.7%) pts, with the most common being anemia (8.1%), decreased neutrophil count (6.5%), and anaphylactic reaction (4.8%). TRAEs led to discontinuation of any study agent in 12 (19.4%) pts; of these, 6 (9.7%) discontinued SHR-1701 due to TRAEs (1 in grade 1, 3 in grade 3 and 2 in grade 4). This combination regimen resulted in an ORR of 59.7% and a DCR of 83.9%. Median DoR was 10.7 months (95% CI, 8.4-13.0). Median PFS was 10.3 months (95% CI, 8.3-13.7), and median OS was immature.

Conclusions: SHR-1701 in combination with BP102 and XELOX as 1L treatment provided a manageable safety profile and potent antitumor activity in pts with unresectable mCRC.

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612P Updated results from the multicenter phase II study of fruquintinib plus mFOLFOX6/FOLFIRI as first-line therapy in advanced metastatic colorectal cancer (mCRC)

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Background: The fruquintinib (a highly selective, and potent oral inhibitor of VEGF receptor 1, 2, 3) plus mFOLFOX6/FOLFIRI (standard chemotherapy) in patients (pts) with advanced mCRC study was a prospective, open-label, multi-center, single-arm phase 2 study (NCT05004441). The results of this study have been previously reported at the 2023 ASCO GI (152 Poster Session) and here we updated the efficacy and safety results with more enrolled pts and longer follow-up duration.

Methods: Pts aged 18-75 years with unresectable or metastatic CRC, without prior systemic threatment were recruited. RAS/BRAF status should be detected to exclude BRAF mutations before enrollment. Pts received fruquintinib (3mg, QD, PO, Q4W) in combination with mFOLFOX6/FOLFIRI (Q2W) for up to 8 cycles. Pts with SD or above were followed by maintenance therapy (fruquintinib 3mg, QD, PO, Q4W, capecitabine 850mg/m^2, BID, PO, D1-7, D15-21, Q4W) until disease progression or intolerable toxicity. The primary endpoint was ORR, secondary endpoints included DCR, PFS, OS and safety.

Results: At updated analysis (cutoff: April 20, 2023), 37 pts were enrolled (median age 56, 18 males, 6 with right half colon cancer, 15 harboring RAS mutations, 18 with liver metastases). For 30 pts who were in efficacy analysis, 23 achieved PR (76.67%), 6 achieved SD (20%), resulting in an ORR of 76.67% and a DCR of 96.67%. At a median follow-up of 7.49 mo, 2 pts underwent surgical resection, 21 pts were still in treatment, and median PFS had not yet reached. Safety profile exhibited that the regimen was tolerable and mainly grade 1/2. Grade 3 TRAEs were neutrophil count decreased (23.33%), leukopenia (10%), GGT increased and hypertension accounted for 6.67% respectively, AST increased (3.33%). No pts have serious adverse events.

Conclusions: Updated analysis of this study data further support current combination therapy with fruquintinib plus mFOLFOX6/FOLFIRI as the first-line therapy followed by fruquintinib plus capecitabine maintenance for advanced mCRC pts, which shows durable response and a favorable long-term safety profile. The study is still ongoing.

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613P Effect of prior use of anti-VEGF agents on overall survival in patients with refractory metastatic colorectal cancer: A post-hoc analysis of the phase III SUNLIGHT trial

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Background: SUNLIGHT, an international, open-label, randomized, phase 3 study comparing trifluridine/tipiracil (FTD/TPI) + bevacizumab (FTD/TPI + bev) vs FTD/TPI monotherapy in patients (pts) with metastatic colorectal cancer (mCRC), demonstrated a 3.3-month increase in overall survival (OS) from 7.5 months with FTD/TPI monotherapy to 10.8 months with FTD/TPI + bev (HR, 0.61; 95% CI: 0.49 - 0.77; P$<$0.001). Here discussed are data on the effects of prior anti-VEGF use on OS.

Methods: A post-hoc analysis of SUNLIGHT was conducted in ptns with anti-VEGF treatment during prior regimens to assess the effect of prior anti-VEGF use on OS in a subgroup analysis and evaluate the treatment benefit associated with FTD/TPI + bev vs FTD/TPI monotherapy in each subgroup. Of note, the trial was not powered to detect statistical significance in this analysis.

Results: In the subgroup analysis (no anti-VEGF [group 1], anti-VEGF in first regimen only [group 2], anti-VEGF in second regimen only [group 3], and anti-VEGF in both first and second regimens [group 4]), ptns treated with FTD/TPI + bev had a higher OS than those treated with FTD/TPI monotherapy in each prespecified subgroup. In group 1, mOS was 16.36 months (95% CI: 11.86 - NA) with FTD/TPI + bev vs 7.39 months (95% CI: 5.52 - 9.3) with FTD/TPI monotherapy (HR, 0.42; 95% CI: 0.25 - 0.69).

In group 2, mOS was 10.41 months (95% CI: 8.54 - 15.31) with FTD/TPI + bev vs 7.23 months (95% CI: 5.55 - 12.52) with FTD/TPI monotherapy (HR, 0.65; 95% CI: 0.38 - 1.1). In group 3, mOS was 9 months (95% CI: 8.15 - 15.14) with FTD/TPI + bev vs 8.15 months (95% CI: 6.21 - 10.18) with FTD/TPI monotherapy (HR, 0.66; 95% CI: 0.44 - 1). In group 4, mOS was 9.36 months (95% CI: 7.49 - 10.97) with FTD/TPI + bev vs 6.9 months (95% CI: 5.98 - 8.51) with FTD/TPI monotherapy (HR, 0.76; 95% CI: 0.52 - 1.1). In group 2, the OS was similar to the other subgroups, suggesting that an anti-VEGF break did not have any impact on the efficacy.

Conclusions: All subgroups showed a comparable OS benefit. The benefit of FTD/TPI + bev vs FTD/TPI on OS is observed independently of the use or not of anti-VEGF during prior regimens. For ptns who had prior anti-VEGF, this benefit is observed independently of whether they had anti-VEGF breaks or not.

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614P Effect of KRASG12 mutations on overall survival in patients with refractory metastatic colorectal cancer: A post-hoc analysis of the phase III SUNLIGHT trial

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Background: SUNLIGHT, a randomized phase 3 study comparing trifluridine/tipiracil (FTD/TPI) + bevacizumab (FTD/TPI + bev) vs FTD/TPI monotherapy in patients (pts) with metastatic colorectal cancer (mCRC), demonstrated a 3.3-month increase in overall survival (OS) from 7.5 months with FTD/TPI monotherapy to 10.8 months with FTD/TPI + bev (HR, 0.61; 95% CI, 0.49 — 0.77; $P<0.001$). Here reported are data on the effects of $KRAS^{G12}$ mutational status on OS.

Methods: A post-hoc analysis of the SUNLIGHT trial was conducted in pts with a $KRAS^{G12}$ mutation to assess the effect of the mutation on OS in the overall population treated with FTD/TPI monotherapy and FTD/TPI + bev. In addition, a subgroup analysis according to the $KRAS^{G12}$ mutational status was conducted to assess the treatment benefit associated with FTD/TPI + bev vs FTD/TPI monotherapy on OS.

Results: In the overall population, a similar OS trend was observed regardless of $KRAS^{G12}$ mutational status. In pts with a $KRAS^{G12}$ mutation, mOS was 8.34 months (95% CI: 7.49 — 9.59); whereas, in pts with no $KRAS^{G12}$ mutation, mOS was 9.17 months (95% CI: 8.15 — 10.94). A non-detrimental effect on OS was observed in pts with a $KRAS^{G12}$ mutation vs in pts with no $KRAS^{G12}$ mutation (HR, 1.09; 95% CI: 0.87 — 1.36) in the overall population treated with both FTD/TPI monotherapy and FTD/TPI + bev. Similar results were observed when the analysis was restricted to the RAS mutant subgroup. In the subgroup analysis, pts treated with FTD/TPI + bev were more likely to benefit with a higher OS than those treated with FTD/TPI monotherapy in

each subgroup ($KRAS^{G12}$ mutated or not). In the $KRAS^{G12}$ mutant subgroup, mOS was 9.36 months (95% CI: 8.15 − 10.94) with FTD/TPI + bev vs 7.23 months (95% CI: 6.31 − 9.13) with FTD/TPI monotherapy (HR, 0.67; 95% CI: 0.48 − 0.93). In the subgroup with no $KRAS^{G12}$ mutation, mOS was 11.27 months (95% CI: 9.56 − 14.19) with FTD/TPI + bev vs 7.13 months (95% CI: 5.88 − 8.87) with FTD/TPI monotherapy (HR, 0.59; 95% CI: 0.43 − 0.81).

Conclusions: The presence of a $KRAS^{G12}$ mutation had no detrimental effect on OS, with a similar OS trend regardless of whether the pts had a $KRAS^{G12}$ mutation or not. The benefit of FTD/TPI + bev vs FTD/TPI on OS was confirmed independently of the $KRAS^{G12}$ mutational status.

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615P The impacts of starting regorafenib dose on treatment outcomes in metastatic colorectal cancer

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Background: Based on the results of the ReDOS study, starting a reduced dose of regorafenib (REG) is considered a treatment option for patients with metastatic colorectal cancer (mCRC). However, the effect of starting REG at a reduced dose on treatment outcomes in a real-world setting has not been fully investigated.

Methods: Clinical data ofpatients who received REG for mCRC between May 2013 and December 2020 were retrospectively collected from four institutions in Japan. These patients were divided into two groups: those who received a standard starting dose of REG (Group S) and those who received a reduced starting dose of REG (Group R). Treatment outcomes were compared between the two groups using Cox proportional hazards models based on propensity score adjustment for baseline characteristics.

Results: A total of 573 patients were enrolled (299 in Group S and 274 in Group R). After propensity score matching, 151 patients each in Group S and R were analyzed. The median overall survival was 6.4 months [95% C.I. 5.5-7.4] in Group S, and 6.1 month [95% C.I. 5.1-7.1] in Group R, respectively (HR 1.018, p=0.882). The median progression free survival was 2.1 months [95% C.I. 1.8-2.4] in Group S and 2.1 months [95%C.I. 1.8-2.3] in Group R, respectively (HR 1.077, p=0.522). The median time to the first dose reduction was 33.0 days [95% C.I. 29.1-36.9] in Group S and 74.0 days [95% C.I. 30.6-117.4] in Group R (HR 0.613, p=0.002). The median time to the first dose interruption was 14.0 days [95% C.I. 13.3-14.7] in Group S and 16.0 days [95% C.I. 11.9-20.1] in Group R (HR 0.757, p=0.033). Both any grades and ≥grade 3 proteinuria were significantly less frequent in Group R than in Group S (any grades: 68.7% vs 53.8%, p=0.027, ≥grade 3: 11.3% vs. 3.8%, p=0.045). The median time to onset of any grades and ≥grade 3 proteinuria was significantly longer in Group R (any grades: HR 0.711, p=0.042, ≥grade 3: HR 0.338, p=0.045). No significant difference was observed in the frequency of hand foot skin reaction and hypertension between the two groups.

Conclusions: Our results suggest that starting a reduced dose of REG contributes to a reduction in the frequency and delay in the onset of proteinuria without any impact on efficacy.

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616P Sequential treatment with regorafenib (REG) and trifluridine/tipiracil (TAS) +/- bevacizumab (Bev) in refractory metastatic colorectal cancer (mCRC) in community clinical practice in the USA

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Background: REG and TAS are approved for the treatment of refractory mCRC. However, data on their sequential use in any setting is limited. The aim of this study was to describe the characteristics and clinical outcomes of patients (pts) with mCRC treated sequentially in community clinical practice in the USA.

Methods: This was a retrospective cohort study using the nationwide de-identified Flatiron Health electronic health record-derived database. Pts aged ≥18 years at mCRC diagnosis treated sequentially with REG and TAS±Bev from Jan 2015 to Sep 2022 were divided into two cohorts: R-T (REG followed by TAS±Bev) and T-R (TAS±Bev followed by REG). Index date was the initiation of the first therapy in a sequence. Minimum follow up was 3 months (mos). Clinical outcomes included overall survival (OS), time to treatment discontinuation (TTD), neutropenia, and use of granulocyte-colony stimulating factor (G-CSF).

Results: A total of 818 pts were included (n=393 R-T; n=425 T-R). Most pts received index therapy in 3L (41.9%) or 4L (23.7%). Baseline characteristics were similar between cohorts (Table). Median OS improved with R-T vs T-R in both 3L and 4L (13.1 vs 11.5 mos in 3L; 11.6 vs 10.3 mos in 4L), though the differences were not statistically significant (HR [95% CI]: 0.94 [0.74, 1.19] 3L; 0.86 [0.63, 1.18] 4L). TTD was slightly longer with R-T vs T-R in 3L (8.7 vs 8.1 mos, HR 0.91 [0.73, 1.14]) and 4L (8.5 vs 7.9 mos, HR 0.86 [0.63, 1.16]). Frequency of neutropenia and use of G-CSF were lower with R-T vs T-R (38.9% vs 48.0% neutropenia; 14.0% vs 17.9% G-CSF).

Table: 616P

n (%)	R-T n = 393	T-R n = 425
Median age (IQR), years	63 (56, 70)	63 (56, 72)
Male gender	233 (59.3)	227 (53.4)
Race White Black or African American Asian	241 (61.3) 64 (16.3) 19 (4.8)	270 (63.5) 54 (12.7) 16 (3.8)
Stage IV mCRC at diagnosis	217 (55.2)	237 (55.8)
ECOG PS 0/1	278 (70.7)	300 (70.6)
KRAS mut	183 (46.6)	194 (45.6)
BRAF mut	5 (1.3)	19 (4.5)
Line of index treatment 1 2 3 4 ≥5	26 (6.6) 67 (17.0) 167 (42.5) 87 (22.1) 46 (11.7)	27 (6.4) 67 (15.8) 176 (41.4) 107 (25.2) 48 (11.3)
Median months since mCRC diagnosis (IQR)	24.6 (16.6, 35.7)	24.5 (17.3, 36.0)
Prior anti-EGFR	131 (33.3)	153 (36.0)
Prior bevacizumab	308 (78.4)	337 (79.3)
TAS+Bev	45 (11.5)	63 (14.8)
Neutropenia	15 (3.8)	9 (2.1)
Prior G-CSF	198 (50.4)	227 (53.4)

Conclusions: This real-world study showed that pts treated with sequential R-T vs T-R appeared to have longer OS and TTD, and less neutropenia and G-CSF use. Sequential therapy starting with REG may provide a chemotherapy break to improve tolerability and reduce myelosuppression in pts with refractory mCRC.

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617P Predictive and prognostic impact of primary tumor location on sequential treatment with regorafenib and trifluridine/tipiracil at third line and beyond in metastatic colorectal cancer: A real-world multicenter retrospective analysis

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Background: Primary tumor location (PTL) has a confirmed prognostic and predictive effect in colorectal cancer first-line therapy, but its effect during the refractory stage is uncertain.

Methods: Clinical data of patients diagnosed with mCRC who received regorafenib (R) and/or trifluridine/tipiracil (T) between July 2012 and March 2022, were collected from 13 Italian cancer institutes retrospectively. Patients were divided into two groups based on whether they presented right (RCC) or left colon cancer (LCC). Our aim was to evaluate the impact of PTL on overall survival (OS), progression-free survival (PFS), and disease control rate (DCR) in R or T treatment groups in a real-world setting.

Results: 866 patients were included. Of these, 146 (16.8%) received T followed by R (T/R), 116 (13.3%) the reverse sequence (R/T), 325 (37.5%) received T alone, and 279 (32.5%) R alone. M/F=504/362; median age was 68 (30-87); median duration of follow-up was 7.2 months. We focused on patients who were sequentially treated with T and R and with the reverse sequence. Among 262 patients, we identified 52 RCC and 94 LCC in the T/R group, compared to 34 RCC and 82 LCC of the reverse sequence. In LCC patients, we found an OS advantage, with a median of 16.8 months in the R/T group vs. 14.7 months in the T/R group (p=0,0569). PFS was statistically significantly longer for the LCC patients who received the R/T sequence (11.7 vs. 9.1 months of the reverse sequence) (p=0,0022). PTL had no effect on disease control rate: we identified the best DCR (34.8%) in LCC patients in both T/R and R/T sequences (p=0.4904).

Conclusions: In our real-world analysis, PTL appears to have a prognostic impact in patients with refractory metastatic colorectal cancer who have received R and T in a sequential way. In fact, treatment with the sequence R/T seemed to us significantly correlated with better outcomes in terms of OS and PFS in patients with left-sided primary cancer. In terms of DCR, we cannot state that PTL is a predictive factor. We advise conducting additional research with sequential R and T treatment. Prospective clinical investigations, we believe, are required in this context.

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618P Efficacy and safety of vactosertib and pembrolizumab combination in patients with previously treated microsatellite stable metastatic colorectal cancer

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Background: Vactosertib (TEW-7197), a highly selective and potent inhibitor of TGF-β receptor type 1, combined with PD-1 inhibition could induce immune restoration and enhance anti-tumor responses in patients with microsatellite stable metastatic colorectal cancer (mCRC). MP-VAC-204 is a phase 1b/2a study evaluating the combination of vactosertib with pembrolizumab in previously treated MSS mCRC. Here we report the updated safety and efficacy data of this phase 1b/2a study (NCT03724851).

Methods: Eligible patients were >18 years old with ECOG performance status 0-1 and who had disease progression after treatment with all available therapies including fluoropyrimidine and oxaliplatin or irinotecan. The MSI testing was conducted by local or central tests. Tumor biomarkers including granzyme B+ CD8+T cells were measured in serial tumor samples by multiplex immunofluorescence staining and deconvolution-based immune cell analysis. Circulating proteins, TGF-b, CTGF, PAI-1 and PDGF-AB were evaluated from serial blood samples.

Results: A total of 105 patients (36 in 200mg BID, 30 in 200mg QD, 7 in 200mg TID and 32 in 300mg BID) were enrolled. In all patients (N=105), the overall objective response rate was 13.3% [95% confidence interval (CI), 7.5- 21.4] and median duration of response was 6.0 months (95% CI, 2.9-Not Reached [NR]). Median PFS and OS were 1.3 months (95% CI, 1.2-1.4) and 15.8 months (95% CI, 7.9-NR) respectively. Overall PFS rate at 6 months was 17.1% (95% CI, 10.5-25.7) and overall survival rate at 12 months was 61.0% (95% CI, 51.0-70.3). Rash, headache and decreased appetite were the most frequent treatment emergent adverse events (TEAEs), but all were manageable. No fatal serious TEAEs were observed in any cohort. The levels of TGF-β signaling related circulating cytokines, TGF-b, CTGF, PAI-1, and PDGF-AB/BB were significantly decreased after treatment. Tumor-infiltrating and microenvironmental granzyme B secretion by CD8+ cells were significantly increased after treatment.

Conclusions: Vactosertib combined with pembrolizumab showed anti-tumor activity, prolonged overall survival and manageable safety profiles in patients with MSS mCRC. The phase 2 part is still ongoing.

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619P Pelareorep + atezolizumab and chemotherapy in third-line (3L) metastatic colorectal cancer (mCRC) patients: Interim results from the GOBLET study

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Background: Pelareorep (pela) is an intravenously administered, non-genetically modified oncolytic reovirus that selectively kills tumor cells and activates innate and adaptive immune responses. Pela primes tumors for checkpoint inhibition by enhancing tumor infiltrating lymphocytes and PD-L1 expression. The GOBLET study is assessing safety and efficacy of pela + atezolizumab (atezo) +/- chemotherapy in multiple gastrointestinal cancers. Here we report the interim results for 3L mCRC with microsatellite stable (MSS) disease.

Methods: GOBLET is a phase 1/2 Simon two-stage basket study. Eligible patients must have mCRC failing 2 prior lines of chemotherapy. Patients receive pela, atezo and trifluridine/tipiracil. The first stage enrolled 15 evaluable patients (patients with at least one post-baseline tumor assessment). Primary objectives are safety and efficacy (per tumor response/disease stabilization). The Stage 1 success criterion for 3L CRC is $\geq$4 patients with stable disease at Week 16. Blood samples were collected for T cell receptor sequencing (TCR-seq) to assess treatment effects on the T cell repertoire.

Results: No safety signals were observed in treated patients. Five of 15 evaluable patients had stable disease (SD) as their best response, including 4 with SD at week 16. 10 patients had progressive disease (PD). The overall clinical benefit rate was 33%. Translational research, including TCR-seq, supported findings: an expansion of new and preexisting T-cell clones was demonstrated. Updated efficacy (PFS and OS) and TCR-seq results will be presented.

Conclusions: Consistent with previous clinical trials of pela, the investigational combination therapy was well-tolerated. The primary efficacy success criterion was met. Given pela's immunologic mechanism of action and the significant changes seen in the T cell repertoire by C2D1, we hypothesize that potentially protective immune responses may have been initiated. However, these heavily pretreated patients may have been too immunocompromised or have insufficient time before progressing to benefit fully from the immunotherapy.

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620P A phase II trial evaluating the activity of cabozantinib in pre-treated patients with metastatic colorectal cancer (mCRC): ABACO trial initial molecular data

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Background: Angiogenesis is a crucial mechanism in colorectal cancer (CRC) development and progression, and anti-angiogenic drugs are a mainstay of CRC systemic treatment.

Methods: We conducted, according to Simon's "minimax" two stage design, an open-label, single arm phase II trial to evaluate the antitumor activity of cabozantinib in pretreated metastatic CRC (mCRC) patients (pts), that progressed after at least 2 lines of prior therapy for metastatic disease. The primary endpoint was the Progression Free Survival (PFS) rate at 16 weeks; secondary endpoints include PFS, Overall Survival (OS), Response Rate (RR), Disease Control Rate, safety. Here we present the initial exploratory biomarkers analysis.

Results: From October 2019 to January 2023 a total of 33 (19 male and 14 female) pts, median age of 58 years (30-79), were treated with cabozantinib 60 mg/daily per os. A comprehensive genomic profiling by next generation sequencing (NGS) was performed with FoundationOne CDx and FoundationOne Liquid CDx (324 genes) on tumor tissue (20/33) and plasma circulating tumor DNA (ctDNA) (15/33) both in 8/33 pts. 11 out of 33 patients were free of progression at 16 weeks and were considered responders and among these the NGS analysis was available at the time of abstract submission in 10 pts. No specific genetic feature was identified in responders, only 1 patient had *AXL* amplification (that represents a potential target of cabozantinib). Of note *MET* amplification found in 2/25 pts did not correlate with response to cabozantinib. In not responding pts *SMAD4* mutation as well as genetic alteration defying a "BRCAness" phenotype were most reported. RNASeq analysis is currently ongoing in 26/33 (78.8%) patient samples.

Conclusions: The ABACO study showed clinical activity of cabozantinib in a subset of refractory mCRC, to the date of the analysis no predictive markers were identified so far. Further analysis are ongoing.

Clinical trial identification: EudraCT 2019-000674-28.

Legal entity responsible for the study: Department of Precision Medicine.

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621P The systemic proteome of consensus molecular subtypes from patients with RAS wild-type metastatic colorectal cancer: Analysis from the randomized phase II PanaMa (AIO KRK0212) trial

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Background: Consensus molecular subtypes (CMSs) are used to classify metastatic colorectal cancer (mCRC) based on gene expression patterns and may provide insights into the biology of the disease and guide treatment decisions. Here, we describe the systemic proteome of CMSs from patients with *RAS* wild-type (wt) mCRC receiving fluorouracil and folinic acid with or without panitumumab (Pmab) after Pmab + mFOLFOX6 induction within the randomized phase II PanaMa trial.

Methods: Serum samples were collected at baseline (prior to first cycle of chemotherapy) from 271 *RAS* wt mCRC patients within the PanaMa trial, and the CMS classification was determined by RNA sequencing of the primary tumor. The systemic proteome was analyzed from serum using liquid chromatography-mass spectrometry. Differential protein abundance analysis was performed to identify potential biomarkers and pathways associated with CMSs.

Results: A total of 6 differentially abundant proteins (DAPs) were identified among CMS subtypes. For CMS1, no significant DAPs were detected. CMS2 showed significant downregulation of C-reactive protein (CRP, 1.47-fold decrease; $P=0.011$). CMS3 showed significant upregulation of immunoglobulin-related proteins. In contrast to CMS2, CMS4 presented significant downregulation of peptidoglycan recognition protein 2 (PGLYRP2, 0.72-fold decrease; $P=0.027$) and upregulation of CRP (1.46-fold increase; $P=0.027$) and SERPINA1 (0.65-fold increase; $P=0.048$) and SERPINA3 (0.66-fold increase; $P=0.048$).

Conclusions: The identification of CMS-specific proteomic signatures helps elucidate the systemic setting of CMS-based tumor classification and ultimately may help inform the development of personalized treatment strategies for patients with mCRC.

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Legal entity responsible for the study: AIO-Studien-gGmbH.

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Sanofi, Taiho, Takeda; Financial Interests, Personal, Invited Speaker: Leo Pharma, AstraZeneca; Financial Interests, Institutional, Research Grant: Merck KGaA, Pierre Fabre, Roche. T. Trarbach: Financial Interests, Personal, Other, Travel, Accommodations, Expenses: Ipsen, Takeda, OMT, AbbVie, Novartis, MSD, Sanofi/Aventis, Amgen, Johnson & Johnson/Janssen; Financial Interests, Personal, Research Funding: Amgen. D.P. Modest: Financial Interests, Personal, Invited Speaker: Amgen, Servier, Merck, Onkowissen, MSD, Bristol Myers Squibb, AstraZeneca, Pierre Fabre, Lilly, Cureteq, GSK, Seagen, Medison, COR2ED, JE, 21up; Financial Interests, Personal, Advisory Board: Amgen, Servier, Merck, MSD, Bristol Myers Squibb, Incyte, Takeda, G1, Onkowissen, Pierre Fabre, AstraZeneca; Financial Interests, Institutional, Research Grant: Amgen; Financial Interests, Institutional, Coordinating PI: Servier. All other authors have declared no conflicts of interest.

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622P Evaluation of the metastatic colorectal cancer score (mCCS) in predicting outcome for patients with RAS wild type metastatic colorectal cancer (mCRC) treated with first-line (1L) panitumumab (PAN) plus FOLFIRI/FOLFOX: Updated interim results of the non-interventional study VALIDATE

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Background: The modified mCCS intends to predict overall survival (OS) of mCRC patients (pts) at start of 1L therapy. Five clinical routine parameters assign pts into three prognostic risk groups from low to intermediate and high risk: tumor stage, tumor grading, lymph node ratio, primary tumor resection status and number of metastatic sites at start of 1L treatment (Marschner N, et al. Colorectal Dis. 2019). VALIDATE (NCT03043950) prospectively validates the mCCS in a large patient cohort with RAS WT mCRC.

Methods: VALIDATE is a multicenter, non-interventional study evaluating real-world effectiveness, safety and quality of life in pts with RAS WT mCRC receiving 1L PAN plus FOLFIRI/FOLFOX. Pts were allocated to three mCCS risk groups. This second interim analysis (IA2) was performed 24 months after last patient in. Data were analyzed descriptively for effectiveness, response rates and secondary resection rates.

Results: At data-base cut (Nov 17, 2022), 611 pts from 108 German and 5 Austrian sites were evaluable. Median age was 66.1 years, 68.9% of pts were male and 83.3% had an ECOG performance status 0/1. 59.4% of pts were diagnosed with a colon tumor. 84.3% of these pts had a left-sided tumor.

Table: 622P

	Total N=611	mCCS		
		Low risk N=202	Intermediate risk N=198	High risk N=211
Overall response rate n (%)	381 (62.4%)	121 (59.9%)	128 (64.6%)	132 (62.6%)
Secondary resections n (%)	115 (18.8%)	43 (21.3%)	47 (23.7%)	25 (11.8%)
24-month OS rate [95%-CI]	54.2% [50.0, 58.3]	60.0% [52.4, 66.8]	61.3% [53.8, 67.9]	42.3% [35.3, 49.0]

Most common grade 3/4 (MedDRA v20.0) treatment-emergent adverse drug reactions (TEADR) were dermatitis acneiform (5.8%), rash (2.9%) and diarrhea (3.2%). One investigator assessed fatal TEADR (arterial embolism) occurred.

Conclusions: The IA2 showed favorable effectiveness for PAN plus FOLFIRI/FOLFOX in the total population and in all mCCS risk groups in clinical routine in Germany and Austria. Interestingly, rates of secondary resections were >20% for low and intermediate risk pts. mCCS predicting OS will be validated in the final analysis. No new safety signals emerged.

Clinical trial identification: NCT03043950.

Legal entity responsible for the study: iOMEDICO AG.

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623P VIC regimen (vemurafenib/irinotecan/cetuximab) versus bevacizumab plus chemotherapy as first-line treatment for BRAF V600E-mutated advanced colorectal cancer

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Background: The need for safe and effective therapies for untreated, BRAF *V600E*-mutated, unresectable locally advanced or metastatic colorectal cancer remains unmet. The purpose of this study was to compare the efficacy and safety of the VIC (Vemurafenib/Irinotecan/Cetuximab) regimen versus bevacizumab plus chemotherapy as first-line setting in Asian patients.

Methods: In the single-center prospective cohort study, 78 untreated, BRAF V600E-mutant, locally advanced or metastatic CRC patients were enrolled. Every two weeks, the VIC regimen and bevacizumab plus doublet or triplet chemotherapy are administered. We evaluated the objective response rate (ORR), the disease control rate (DCR), and the conversion resection rate. In progression-free survival (PFS) and overall survival, the Kaplan-Meier method was utilized (OS).

Results: In the evaluable population, 32 patients received VIC regimen and 35 patients received bevacizumab plus chemotherapy. The ORR and DCR in the VIC group were significantly higher than in the bevacizumab-therapy group (ORR: 68.8% versus 40.0%, P=0.018; DCR: 100.0% versus 80.0%, P=0.023). The VIC regimen was significantly superior to bevacizumab plus chemotherapy for PFS (median, 11.9 vs 7.9 months; hazard ratio [HR]=0.48, 95% CI, 0.27-0.87; P=0.012) and OS (median, 24.5 vs 14.4 months; HR=0.36, 95% CI, 0.16-0.78; P=0.007). In the VIC group, the conversion resection rate for liver metastases was 42.1% (8 of 19 patients), and for local CRC it was 66.7% (6 of 9 patients with initially unresectable local CRC). Rates of treatment-related adverse events of Grade 3 to 4 were 32.4% and 31.1% for the VIC regimen and bevacizumab plus chemotherapy, respectively.

Conclusions: Among Asian patients with BRAF *V600E*-mutated advanced CRC, the VIC regimen was superior to bevacizumab plus chemotherapy in terms of tumor response and oncological survival, with a tolerable and manageable toxicity profile in the first-line setting.

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624P Tolerability and safety of vemurafenib, cetuximab combined with camrelizumab for BRAF V600E-mutated /MSS metastatic colorectal cancer

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Background: The doublet combination of the BRAF inhibitor and the EGFR antibody showed unsatisfactory effect for patients with BRAF V600E-mutated metastatic colorectal cancer (mCRC). Furthermore, multiple immune escape mechanisms exist in BARF V600E mutated/MSS tumors. Combining targeted therapy with PD-1 antibody is a promising treatment option.

Methods: We enrolled previously treated patients with BRAF V600E-mutated/MSS mCRC. Eligible patients had received at least one systemic treatment for metastatic disease, not include EGFR inhibitor, BRAF inhibitor, and PD-1 inhibitor (ECOG PS 0-1) and had at least one measurable disease according to RECIST 1.1. All enrolled patients received cetuximab (500mg/m2, iv, q14 days), camrelizumab (200mg, iv, q14 days) and vemurafenib (two dose levels of 960mg, po, daily or twice daily). The primary endpoints were safety, tolerability per CTCAE.5 The second endpoints included ORR, DCR, PFS per RECIST1.1 and OS.

Results: 12 patients were enrolled and received trial regimen. Median age is 51 years, and 50% were male. Because of the high incidence of AEs in first 3 patients, all patients finally treated with lower dose of vemurafenib (960mg, po, daily). With a median follow-up of 13.68 months, grade 1-2 treatment-related AEs occurred in 12 patients (100.0%). Grade 1-2 AEs included drug-related rash (75.0%), articular pain (75.0%), reactive capillary proliferation disease (66.7%), anemia (53.3%), muscular pain (41.7%), mucosal hemorrhage (41.7%), fatigue (25.0%), and mouth ulcers (16.7%).6 patients (50.0%) had grade 3 treatment-related AEs, included fever (25%), drug-related rash (16.7%), mucosal hemorrhage (8.3%), diarrhea (8.3%), immune myocarditis (8.3%), anemia (8.3%), thrombocytopenia (8.3%), mucosal hemorrhage (8.3%), and immunological myocarditis (8.3%). Finally, 10 patients received response evaluation. ORR is 40.0%, and DCR is 80.0%. 1 patient achieved CR with duration of response of 24.83 months. 3 patients achieved PR and 4 patients were evaluated as SD. Median PFS is 3.37 months (95%CI, 1.28-5.26). Median OS is 11.47 months (95% CI, 4.67-18.27).

Conclusions: The VCC regimen is effective and moderate-tolerated for patients with BRAF V600E-mutated /MSS mCRC.

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625P Efficacy and safety of the combination of encorafenib and cetuximab in patients with BRAF V600E mutated metastatic colorectal cancer: An AGEO real-world multicentre study

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Background: The combination of encorafenib with cetuximab has become the standard of care in patients with *BRAF* V600E mutated metastatic colorectal cancer (mCRC), after a prior systemic therapy. This retrospective study aims to describe the efficacy and safety of encorafenib with cetuximab combination in the real-world setting.

Methods: All consecutive patients with *BRAF* V600E-mutated mCRC who received the combination encorafenib + cetuximab +/- binimetinib (e/c+/-b) from January 2020 to June 2022 in 24 French centers and 8 non-French centers were included.

Results: Overall, 201 patients were included, with 55% of women, a median age of 62 years and an ECOG-PS $\geq$2 in 20% of cases. Other main patients' tumor characteristics were 60% of right-sided primary tumor, 11% of MSI/dMMR phenotype and liver and peritoneum being the 2 main metastatic sites (57% and 51%). The e/c+/-b combination was prescribed in 1st line (L1) for 8 patients (4%), in 2nd line (L2) for 113 patients (56%), in 3rd line (L3) for 58 patients (29%), beyond L3 for 22 patients (11.3%), with an addition of binimetinib for 21 patients (10%). With e/c treatment, 21% of patients experienced grade $\geq$3 adverse events (AEs), with each type of grade $\geq$3 AE observed in less than 5% of patients The most frequent grade 1-2 AEs were acneiform dermatitis/rash (43%), dry skin (29%), arthralgia (21%), and anemia (22%). The objective response rate under e/c+/-b was 32% and the disease control rate was 71%, all lines combined. Median PFS under e/c+/-b was 4.4 months (95% CI 3.9-5.6) and median OS was 9.1 months (95% CI 7.8-10.8). In multivariate analysis, the factors associated with a shorter PFS under e/c+/-b were the presence of liver metastases (HR: 1.6, p=0.02) and ECOG-PS$\geq$2 (HR: 1.9, p=0.002) but not the line of treatment.

Conclusions: This real-world study showed that in patients with *BRAF* V600E mutated mCRC treated with encorafenib + cetuximab +/- binimetinib, efficacy data are very similar to those reported in the BEACON CRC registration trial. In this series, the main prognostic factors for this treatment are ECOG-PS$\geq$2 and liver metastases. The safety profile was favorable with only 21% of patients experiencing a grade 3 or more AE.

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626P Mucinous differentiation (MD) as predictor of response in BRAF-V600E mutated metastatic colorectal cancer (mCRC) treated with BRAF inhibitors (BRAFi) combinations

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Background: In *BRAF*-V600E mutated metastatic colorectal cancer (mCRC), 40% of tumors present with MD. This feature has been associated with poor prognostic and resistance to chemotherapy. However, the clinical impact of the presence of MD in patients treated with BRAFi remains unclear. Aim: The aim of this study is to evaluate the clinical impact of MD in a cohort of patients with *BRAF*-V600E mutated mCRC treated with BRAFi.

Methods: Patients with *BRAF*-V600E mCRC treated at Vall d'Hebron Hospital from 2019 to 2021 were included. MD was determined baseline based on the percentage of neoplasic mucinous component (FFPE). Data were collected prospectively. Survival analysis were calculated using K-M curves.

Results: A total of 54 patients were included, with a median age of 62 years, and 61% were females. Of these patients, 65% had right-sided tumors, 11% had MSI. 68% of patients received BRAFi-antiEGFR, while 32% received BRAFi-antiEGFR-MEKi. Initially, a dichotomic MD was established based on the presence or absence of tumoral mucin, with 36 and 17 patients, respectively. ORR was 41% and 25% for mucinous and non-mucinous tumors, respectively. PFS was 8.43 months (HR 0.49, 95%CI 4.83-11.1, p 0.02) for mucinous tumors, compared to 3.84 months for non-mucinous tumors. Mucinous tumors tended to have better overall survival (OS) (14 vs 10.2 months, HR 1.3, 95%CI 0.4-1.4, p 0.4). Then, we evaluated whether the percentage of tumor mucin impacted outcomes. Three groups were established based on an arbitrary cut-off of 20%: high-mucin -HM- (>20% of mucin, n:17), low-mucin -LM- (<20% of mucin, n:11), and non-mucinous -NM- (n:17). ORR was 68%, 33%, and 25%, respectively. Patients with high-mucin had better PFS compared to non-mucinous tumors, 9.4 months vs 3.84 months (HR 0.87, 95%CI 0.17-0.9, p 0.02). Patients with low-mucin tended to have better PFS than non-mucinous tumors (5.62 months, HR 1.2, 95%CI 4.60-12.9, p 0.08). Tumors with MD tended to have better OS in both groups (15 months in the HM group, 16.6 months in the LM group vs 10.2 months in the NM group).

Conclusions: Tumor mucin may be a potential predictive biomarker in *BRAF*-V600E mutated mCRC patients treated with BRAF inhibitors. Further validation is required.

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628P Immunotherapy in mismatch repair-deficient metastatic colorectal cancer: Long-term outcome and novel predictive markers

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Background: PD-1 with or without CTLA-4 blockade is the treatment of choice in dMMR/MSI-H metastatic colorectal cancer (mCRC) patients. However, there are currently no validated predictors for treatment response, and there is a paucity of real-world data on treatment efficacy. Our aim was to assess predictive markers for response to immunotherapy in this patient population.

Methods: A study using two prospective cohorts from the University of Texas MD Anderson Cancer Center and Sheba Medical Center of consecutive patients with dMMR/MSI-H mCRC that were treated with immunotherapy between 2014-2022. Primary outcomes were progression-free survival (PFS) and overall response rate (ORR). Evaluated predictors included ECOG-PS score, *RAS*/*BRAF* status, single-agent versus nivolumab plus ipilimumab immunotherapy, metastatic sites, disease burden, and CEA levels prior to treatment initiation. Kaplan-Meier analysis and univariate Cox proportional hazard regression model were used to analyze the effect of all exposure variables on PFS.

Results: The study cohort included 153 patients with a median age of 60 (IQR 45-71), of them 51.6% (n=79) were males. First-line immunotherapy with anti-PD-1 or anti-PD-1 plus anti-CTLA-4 was used in 77.8% (n=119) and 22.2% (n=34) of patients, respectively. Median follow-up time was 26 months (IQR 11-48). Median PFS was 51.6 months (95%CI 38.1-NR) and ORR was 58.1% (n=89). ECOG-PS score ≥2 and ≥3 metastatic sites were associated with worse PFS with a HR of 2.09 (95%CI 0.98-4.47) and 3.11 (95%CI 1.61-6.03), respectively. The presence of liver or lung metastasis, either solitary or mixed sites, were associated with worse PFS with HRs of 2.35 (95%CI 1.43-3.88) and 2.30 (95%CI 1.31-4.04), respectively. Right-sided tumors were associated with improved PFS with a HR of 0.56 (95% CI 0.32-0.97). CEA levels >5 μg/L prior to treatment initiation were associated with worse PFS with a HR of 2.23 (95%CI 1.30-3.81).

Conclusions: Liver or lung metastasis, and high CEA levels predict poor response to immunotherapy in dMMR/MSI-H mCRC. Conversely, right-sided tumor predicts improved response.

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629P First results of the french prospective cohort of colorectal cancers with microsatellite instability (COLOMIN2)

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Background: Colorectal cancers with microsatellite instability/deficient mismatch repair (dMMR/MSI CRC) are associated with particular outcome and treatment, especially in the recent context of immune checkpoint inhibitors (ICI). There is no large prospective real-life cohort evaluating outcome and prognostic factors in dMMR/MSI CRC.

Methods: COLOMIN2 is a prospective, multicenter cohort designed to assess treatment and prognosis of dMMR/MSI CRC. Key eligibility criteria included histologically proven CRC with a MSI (molecular biology) and/or dMMR (immunohistochemistry, IHC) status. The primary endpoint is time to recurrence (TTR) for non-metastatic tumors and progression-free survival (PFS) for metastatic tumors.

Results: Between January 2016 and December 2021, 637 patients were included by 37 centers with stage I (8.2%), II (36.4%), III (35.5%) or IV (18.7%) dMMR/MSI CRC. The mean age was 69.6 years, 59.8% were women and 62.6% were ECOG PS 0 or 1. Most tumors had a MMR IHC (76.1%) and 23.9% a MSI test alone. *BRAF* and *RAS* mutations were identified in 44.9% and 25.0%, respectively; with no difference according to tumor stage. One third of patients had a Lynch syndrome with proven MMR gene mutation (32.5%). Most tumors are located in ascending colon (69.5%) and well/moderately differentiated (55.3%). Among stage II and stage III CRC patients 16.9% and 61.7% had adjuvant chemotherapy (CT), respectively; mostly with oxaliplatin-based CT (82.6%) whatever the tumor stage. After a median follow-up of 23 months, TTR at 3 years were 97.0% in stage I, 88.6% in stage II and 68.9% in stage III. Most patients with stage IV disease had one metastatic site (74.5%), mostly in liver (48.1%) and peritoneum (36.8%). Most patients were treated by first-line CT +/- targeted therapy (79.8%) and few by ICI (12.9%). Median PFS were 11.8 [95%CI: 7.1-28.0] months and 28.0 [95%CI: 2.1-NA] months for patients treated with CT and IO, respectively.

Conclusions: This real-life cohort confirms the good prognosis of non-metastatic dMMR/MSI CRC by contrast to metastatic patients treated by chemotherapy +/- targeted therapy. Clinical and biological prognostic factors are currently explored, and will be presented during ESMO meeting.

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630P Determining a prognostic score using imaging to assess the benefit of combo anti-PD1 + anti-CTL4 vs anti-PD1 in patients with metastatic MSI/dMMR colorectal cancer (mCRC MSI)

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Background: The aim is to determine, using quantitative imaging features from baseline CT-scans and clinical factors, the response to mono vs combo immunotherapy for metastatic patients with mCRC MSI.

Methods: This retrospective study included 105 patients treated either with a single anti-PD1 (mono) or a combination of anti-PD1 and anti-CLA4 (combo). Baseline scanners were annotated manually in 2D on the axial plane slice with the largest diameter for each visible lesion by 6 expert radiologists. Tumor volume was computed by summing the volume of each lesion, and reproducibility was assessed using Intercorrelation coefficient (ICC2k). Cox models were used to predict overall survival (OS) on bootstrap samples, and the concordance index was used to assess its performance on out-of-bag samples. Progression free survival (PFS) was evaluated. Recursive feature elimination (RFE) was used to reduce the number of variables. Cutoffs were determined using maximally selected rank statistics and were used to binarize features, and a risk score was built using weights derived from the Hazard ratios. The final model was modified to exclude the type of treatment, and the cutoff was adjusted.

Results: In total, 1633 lesions were annotated. ICC2k was equal to 0.95 for total tumor volume. Of the 13 variables studied, 5 were selected after the RFE: age, type of treatment, presence of peritoneal carcinomatosis (PC), number of lesions and total tumor volume. The cutoffs for total tumor volume, number of lesions and age were 73 cm3, 20 lesions and 60 years old. The weights for total tumor volume, number of lesions, age and PC were 1.13, 0.96, 0.91 and 0.38 and the cutoff of the risk score was 1.51. Patients with a low risk score had similar OS and PFS independently of treatment, while those with a high score had significantly worse OS and PFS if treated with monotherapy ($p=0.004$ and $p=0.0001$).

Conclusions: Total tumor volume had the highest weight amongst other quantitative imaging measures and age, emphasizing the need to compute tumor burden before initiating treatment. This score could allow oncologists to identify mCRC MSI patients who need combo therapy, limiting its unnecessary side effects compared to monotherapy.

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631P Using the unique somatic mutation profile of POLE loss of proof-reading mutation helps in selection of patients who may benefit from immunotherapy

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Background: It has been reported that POLE mutant tumors are likely to respond to immune therapy, however, most POLE mutations are passenger mutations and do not induce a hypermutated phenotype. Current methods to classify POLE mutations are limited in both accuracy and completeness complicating the selection of patients (pts) most likely to benefit from immunotherapy.

Methods: A curated list of 13 known loss of proof-reading (LOP) *POLE* mutations was used to identify 66 tumors with *POLE* LOP mutation from which we extracted somatic mutation signatures, these averaged together defined a positive control *POLE* LOP signature. POLE mutant tumors with mutational signatures highly correlated with the positive control (> 0.7) were determined to be LOP.

Results: A total of 1467 *POLE* mutations (mut) were identified from 50962 tumors accessed from cBioPortal. Correlation with the positive control *POLE* LOP signature was sensitive (all tumors with known *POLE* LOP mutation from literature were recovered) and specific ($92/97 = 94.8\%$ had high TMB, a hallmark feature of *POLE* LOP). In addition to recovering known LOP mut found in the exonuclease region, several new LOP were discovered including R705W mut, which is in the DNA

polymerase domain and positioned to interface with the binding to DNA. To evaluate *POLE* LOP as a predictive biomarker a cohort of pts with *POLE* mutant mCRC treated with immunotherapy (IO) (n=29) was identified from institutional databases. All 7 pts with *POLE* LOP achieved clinical benefit (3 CR, 3 PR, 1 SD) and remain on immunotherapy at the time of submission (median follow up time = 36 months). In contrast, none of the 7 MSS pts with Non-LOP *POLE* mut achieved an objective response to IO therapy (2 SD, 5 PD), and had disease progression with median PFS of 3.6 months (log-rank p<0.0003). For the other 15 pts with Non-LOP *POLE* mut response was supported by MSI-H status.

Conclusions: Identifying of the subset of *POLE* mut that cause LOP is critical in order to correctly identify pts most likely to benefit from immune therapy. CRC tumors with LOP *POLE* mutation were found to have deep, sustained response to IO therapy, in contrast to those with non-LOP *POLE* mutations.

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632P Predictive value of C-reactive protein (CRP) in microsatellite-stable (MSS) metastatic colorectal cancer (mCRC) patients given first-line alternating short-course oxaliplatin-based chemotherapy (FLOX) and nivolumab

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Background: Tumour-associated systemic inflammation impedes immune checkpoint blockade (ICB) efficacy. We explored whether the initial two FLOX cycles of alternating short-course FLOX and nivolumab may affect circulating CRP and outcome (progression-free survival; PFS) in first-line treatment of MSS-mCRC.

Methods: In the METIMMOX randomised trial, patients were assigned to FLOX (oxaliplatin 85 mg/m^2 day 1, bolus 5-fluorouracil 500 mg/m^2 and folinic acid 100 mg day 1-2) Q2W (control arm) or alternating two cycles each of FLOX and nivolumab (240 mg) Q2W (experimental arm) with PFS as the primary endpoint. CRP was measured at baseline and every treatment visit. In this *post hoc* analysis, patients were categorised based on CRP ≥5.0 mg/L and <5.0 mg/L after the initial two FLOX cycles, immediately before the third FLOX (control arm) or first nivolumab (experimental arm) cycle was started.

Results: Patients were randomly assigned 2018/05-2021/10. At censoring 2023/01, median PFS was 9.3 months in both study arms. For the entire cohort, CRP was median 13.0 mg/L (range 0.70-112) at baseline (n=76) and 6.0 mg/L (range 0.50-60.0) after two FLOX cycles (n=73); p=0.014 (Mann-Whitney U-test). For experimental-arm patients, CRP <5.0 mg/L immediately before commencing nivolumab (n=17) was associated with significantly improved median PFS 15.7 months (range 2.6-41.6) compared to patients with CRP ≥5.0 mg/L (n=19) with median PFS 4.4 months (range 1.9-17.1); p=0.0004 (log-rank). No such difference was seen in the control arm; p=0.82 (log-rank). Experimental-arm patients with CRP <5.0 mg/L after the first two FLOX cycles had longer PFS compared to the corresponding control group; p=0.0082 (log-rank).

Conclusions: In MSS-mCRC patients receiving first-line therapy, CRP <5.0 mg/L after initial two FLOX cycles identified patients responding to sequential nivolumab with improved PFS compared to patients continuing FLOX. As a rapid, cost-effective analysis, and if early oxaliplatin-based chemotherapy counteracts tumour-associated systemic inflammation, CRP may predict ICB efficacy in MSS-mCRC.

Clinical trial identification: NCT03388190.

Legal entity responsible for the study: A. H. Ree.

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633P Genomic alterations in SPEN predict outcome of immune checkpoint therapy in gastrointestinal cancer

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Background: Application of Immune Checkpoint Inhibitors (ICIs) has become important therapy for gastrointestinal cancer (GC). *SPEN* gene encodes Msx2-interacting protein which can block the differentiation of precursor B-cells into marginal zone B-cells and represses transcription. However, the correlation between *SPEN* mutation and immune efficacy is unclear.

Methods: We retrospectively analyzed the genomic and survival data from 236 patients with GC derived from MSKCC cohort (Nat Genet 2019) to evaluate the relationship between *SPEN* mutation status and efficacy of immunotherapy. Then we explored the prognostic value of *SPEN* mutation in 914 GC patients from The Cancer Genome Atlas (TCGA) database. TMB was calculated as the total count of non-synonymous mutations in coding sequence. The CIBERSORT analysis relied on RNA-seq data in TCGA database to evaluate 22 types immune cell infiltration status.

Results: The TMB level of *SPEN*-mutant patients was higher than *SPEN*-wildtype patients in both MSKCC (Median [IQR]: 64.94[2.63-203.64] vs 6.14[0.00-153.47], P < 0.001) and TCGA (Median [IQR]: 31.20[0.96-296.91] vs 2.70[0.05-194.70], P < 0.001) cohort. In MSKCC cohort, compared to *SPEN*-wildtype patients, *SPEN*-mutant patients achieved prolonged OS (median OS: 34 vs 13 months, P=0.009). Moreover, a multivariable analysis across the MSKCC cohort demonstrated that *SPEN*-mutant was associated with better OS (HR=0.30; 95%CI, 0.11-0.82; P=0.019), after adjusting for age, gender, metastasis and treatment. In TCGA cohort, there was no significant difference in OS between *SPEN*-wildtype group and *SPEN*-mutant group (median OS: 67.3 vs 60.8 months, P = 0.33). The CIBERSORT analysis revealed that CD8+ T cell infiltration and activated CD4 memory T cell were significantly higher in *SPEN*-mutant group than *SPEN*-wildtype group (p < 0.05).

Conclusions: *SPEN* mutation is associated with higher TMB in ICI-treated gastrointestinal cancer patients. Survival analysis suggests that *SPEN* mutation may serve as a novel predictive biomarker in GC patients with ICIs, but not a prognostic factor. The significantly higher CD8+ T cell infiltration and activated CD4 memory T cell in *SPEN*-mutant group may be the potential mechanism.

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634P The ave-rec phase II trial of PD-L1/PD-1 blockade with avelumab plus chemoradiotherapy for resectable ESMO high risk rectal cancers

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Background: Long course chemoradiotherapy (LCCRT) for locally advanced rectal cancer (LARC) results in a complete pathological CR in 10-30% of patients (pts). Radiotherapy (RT) is immuno-stimulatory by enhancing tumour cell death, but also immunosuppressive stimulating PDL1 production and myeloid-derived suppressor cells. PDL1 inhibition may be required to enhance RT immuno-stimulatory effects. *Hypothesis:* In pts with resectable LARC, Avelumab given post LCCRT may enhance tumour response rates whilst reducing relapses.

Methods: Phase II single arm trial. Pts had LCCRT (50.4Gy + 5FU [225mg/m^2/day/CI] or Capecitabine [825mg/m^2 BID]/5.5 weeks). Post LCCRT pts received 4 cycles Avelumab (AV) (10mg/kg, q2 weeks), then resection 10-12 weeks post LCCRT. Fresh tumour biopsy/ctDNA sampling taken at pre LCCRT, pre AV and at surgery. Response by FDG PET and pelvic MRI. *Inclusion Criteria*: pts with MRI stage T3b-4/N1-2/M0 LARC , tumoural lower border <12cm from anal verge, measurable disease, ECOG 0-1, adequate organ function. *Endpoints:* (a) *Primary*; Complete pathological response rate (Target $\geq$ 35%) reported centrally, (b) *Secondary*; Imaging responses, Toxicity. (c) *Exploratory;* Tumoural immune cell subsets/checkpoint expression and ctDNA analysis, Distant relapse-free survival and the sites of relapse.

Results: 37 pts entered. Baseline TNM: T3b-d 75%, T4a-b 25%. 33 pts completed LCCRT, 31 pts (83%) had all 4 cycles of AV and 32 pts (86%) had surgery. ORR Pelvic MRI (N=33): 2 CR, 14 PR, 31 DCR. FDG PET: 10 CMR, 18 PMR.. 10 pts Grade 3 AEs, 3 pts with treatment-related G3 and no G4 AEs. No immune-related G3 AEs. Post-operative complications as expected. Pathological response (Modified Ryan Score) (N=32): Complete pathCR (18.7%), near CR (15.7%), in MSI-H (N=4), 50% and 25% resp. Median followup 3.1 yrs: 3 yr est. time to progression 82%, distant relapse free survival 80%, disease free survival 80%.

Conclusions: The Ave-Rec phase II study has shown Avelumab post LCCRT is safe with significant imaging responses and complete/near-complete path response rate of 34.3% in pts with ESMO high risk rectal cancers. Parallel translational studies are ongoing. The addition of immune checkpoint inhibitors warrants further evaluation in LARC.

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635P Avelumab (AVE) combined with cetuximab (CET) and irinotecan (IRI) for the treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): The AVETUXIRI phase II study

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Background: Cetuximab could mediate, independently from RAS mutation, an immunogenic tumor cell death and antitumor immune response. This trial explores the efficacy and safety of AVE, CET and IRI for the treatment of refractory MSS mCRC.

Methods: Chemo-refractory (+anti-EGFR refractory if RAS wt) MSS, mCRC patients (pts) were enrolled in 3 cohorts (A: RAS wt, B & C: RAS mut) and treated with CET (500 mg/m^2/Q2W), IRI (150 mg/m^2/Q2W) and AVE (10 mg/kg/Q2W). Primary endpoints were safety, overall response rate (ORR) (cohorts A-B) and 6 months progression-free survival rate (6m-PFSR) (cohort C). Secondary and exploratory endpoints included disease control rate (DCR), PFS, OS and immunoscore (IS) biomarker. Based on a Simon 2-stage design (α=0.1; β=0.2) for ORR (cohorts A: P0/P1=0.15/0.33 – B: P0/P1=0.09/0.25) and 6m-PFSR (cohort C: P0/P1=0.15/0.31), 10+18 (A); 13+15 (B) and 14+25 (C) pts were needed. At least 2+5 (A); 2+3 (B) and 3+6 (C) pts must reach ORR (A-B) or 6m-PFSR (C) for efficacy objectives. Immunofluorescence (CD3, CD8 densities) was performed on baseline metastasis biopsies to generate IS.

Results: 57 pts (median 62 yrs, 73.7% male, 84.2% left-sided, 86.0% synchr. mCRC) were included and 55 pts treated. Any treatment-emergent adverse event (AE) grade >=3 occurred in 35 pts (63.6%; diarrhea in 11 pts, 20.0%). Immune-related AEs grade >=3 appeared in 2 pts (3.6%; 1 acute kidney injury, 1 cholangitis). Efficacy results are summarized.

Table: 635P

Characteristics	Cohort A (n=28)	Cohort B (n=13)	Cohort C (n=14)
ORR, % (pts)	21.4% (6/28)	0.0% (0/13)	0.0% (0/14)
DCR, % (pts)	50.0% (14/28)	61.5% (8/13)	42.9% (6/14)
6m-PFSR, % (pts)	25.0% (7/28)	38.5% (5/13)	7.1% (1/14)
Median PFS, months (95%CI)	3.6 (2.5-5.6)	3.7 (2.7-6.4)	2.8 (2.4-3.8)
Median OS, months (95%CI)	11.4 (5.3-15.6)	10.1 (6.0-22.8)	6.8 (5.3-9.7)

Independently of RAS mutation, high IS was associated with greater tumor shrinkage (OR=8.3, p<0.01), DCR (OR=8.0, p=0.05), PFS (median 7.1 vs 3.1 months; HR=0.29, p<0.01) and OS (median 12.9 vs 7.2 months; HR=0.62, p=0.19).

Conclusions: Despite good tolerability, AVETUXIRI trial did not reach its efficacy endpoint. IS could be a predictive biomarker for selecting patients with potential treatment benefits.

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636P Combination therapy of envafolimab, suvemcitug, and FOLFIRI in patients with metastatic microsatellite stable (MSS) or mismatch-repair proficient (pMMR) colorectal cancer: Results from a phase II clinical trial

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Background: Envafolimab is a humanized single-domain anti- PD-L1 antibody which is administered subcutaneously (SC). Suvemcitug is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). This study aims to assess the efficacy and safety of the combination of envafolimab and suvemcitug with chemotherapy as second-line or later therapy in patients (pts) with advanced or recurrent MSS/ pMMR mCRC.

Methods: This was an open-label, multi-cohort, multicenter, phase II trial conducted in China. Eligible pts had received at least one prior line of treatment for MSS/pMMR mCRC and were treated with envafolimab plus suvemcitug and FOLFIRI (Irinotecan, Leucovorin, and 5-Fluorouracil). The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of overall response (DoR), disease control rate (DCR), and progression-free survival (PFS) and safety.

Results: As of March 31,2023, 20 pts with MSS/pMMR mCRC were enrolled. 25.0% pts (5/20) received two prior therapies and 50.0% pts (10/20) were prior treated with antiangiogenic agents. The confirmed ORR was 25.0% (95% CI 8.7%-49.1%). DCR was 90.0% (95% CI 68.3%-98.8%). With a median follow-up time of 8.0 months (IQR 6.9-9.8), the median PFS was 5.6 months (95% CI 4.01-7.59) and DoR was 4.1 months (95% CI 3.02-NE). The most common grade $\geq$ 3 TRAEs were neutrophil count decreased (60.0%) and leucopenia (25.0%). No death was reported. Both envafolimab and suvemcitug showed similar pharmacokinetic profile to monotherapy. Biomarker analysis suggested APC wild type or TP53 mutation were associated with poor efficacy, while KRAS, PI3KCA, BRAC2, SMAD4 and AR mutations, which reported with poor response to immunotherapies, had no effect on the response.

Conclusions: To the best of our knowledge, this is the first study demonstrated promising antitumor activity and a manageable safety profile of immunotherapy plus anti-angiogenic agent and chemotherapy in pts with MSS/ pMMR mCRC who had failed at least one line of therapy. The results support further evaluation of the therapy in a larger population.

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637P A phase II study to evaluate the efficacy and safety of fruquintinib combined with tislelizumab and Hepatic Artery Infusion Chemotherapy (HAIC) for advanced Colorectal Cancer Liver Metastases (CRLM)

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Background: Metastases to the liver remain the primary driver of disease-specific mortality for colorectal cancer (CRC). The FRESCO study has shown that fruquintinib significantly prolongs the survival of CRLM patients (pts). Meanwhile the combination of fruquintinib and PD-1 inhibitors has shown promising efficacy in advanced CRC. HAIC is an unique and effective option for CRLM pts. So we carried out a study to assess the efficacy and safety of fruquintinib combined with tislelizumab and HAIC for advanced CRLM pts.

Methods: We enrolled CRLM pts who had failed standard therapy in this phase II study (NCT05435313). Eligible pts received fruquintinib (3mg, qd, po, D2-21, Q3W) in combination with tislelizumab (200mg, ivgtt, D2,Q3W) and HAIC (TOMOX: raltitrexed 2mg/m^2, D1, oxaliplatin 85mg/m^2, D1, Q3W; or TOMIRI: raltitrexed 2mg/m^2, D1, irinotecan 120mg/m^2, D1, Q3W) for 4-6 cycles, followed by maintenance therapy with fruquintinib and tislelizumab until disease progression, death or unacceptable toxicity. The primary endpoint was ORR. The secondary endpoints were DCR, PFS, 6mo-PFS%, OS and safety.

Results: Between July 17, 2022 and April 27, 2022, 38 pts were enrolled. Median age was 59 (range: 35-73) years and 24 were male, MSS accounted for 37 pts and 18 pts harboring RAS mutation. 22 and 4 pts had previously received bevacizumab and regorafenib, respectively. At data cut off, 29 pts with MSS had efficacy evaluation data, the combination therapy provided an ORR of 27.59% (1 CR, 7 PR) and a DCR of 93.10% (19 SD). ORRs of RAS mutation and wild type were 14.29% (2/14) and 40% (4/10), respectively. 19 (65.52%) of 29 pts showed evidence of a reduction in tumour volume. Neither median PFS nor median OS were reached. TEAEs were mainly grade 1/2, Grade 3/4 TEAEs occurred in 5 pts, including hypertension, hand-foot-skin reactions, GGT increased, neutrophil decreased and AST increased. No treatment related death.

Conclusions: Fruquintinib combined with tislelizumab and HAIC showed promising efficacy and acceptable safety for CRLM pts who had failed standard therapy in this interim analysis. Updated data will be presented in the future.

Clinical trial identification: NCT05435313.

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638P Stereotactic ablative radiotherapy combined with fruquintinib and tislelizumab in metastatic colorectal cancer: Preliminary findings from a single-arm, prospective phase II trial (RIFLE)

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Background: Stereotactic ablative radiotherapy (SABR) has been shown to sensitize immunotherapy through inducing immunogenic death and remodeling the tumor immune microenvironment. Anti-angiogenic therapy exhibits synergistic antitumor effects with PD-1/PD-L1 antibodies through its immunomodulatory effects for $\geq$ 3L metastatic colorectal cancer (mCRC) patients. Here, we report the preliminary results from RIFLE trial: the efficacy and safety of the combination of fruquintinib, PD-1 inhibitor tislelizumab and SABR in mCRC patients.

Methods: This is a single-center, single-arm, prospective phase II clinical trial (NCT04948034). mCRC patients with at least 2 measurable lesions who have failed $\geq$ 1L standard therapy will receive SABR followed by fruquintinib (5 mg, d1-14, qd) and tislelizumab (200 mg, d1, q3w) within two weeks from completion of radiation. The primary endpoint is the objective response rate (ORR). The secondary endpoints include disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) rate, overall survival (OS) rate and toxicity.

Results: From August 2021 to April 2023, 27 patients were included in the trial and 24 in the efficacy analysis. Median age was 64 years, 17 (70.8%) patients were male, 21(87.5%) had $\geq$ 3 metastases, and 12(50%) had received $\geq$ 3 prior lines of systemic therapy. The biological effective dose (BED) for irradiated lesions ranged from 37.5 to 105 Gy. Median study follow-up was 12.6 months, 20 patients were alive and 11 remained on treatment. 7 patients achieved partial response (PR) for target lesions, 10 stable disease (SD), illustrating an ORR of 29.2% and a DCR of 70.8%. Median PFS was not reached. The most common treatment-related adverse events (TRAEs) were proteinuria (45.8%), hypertension (25%) and rash (16.7%). Grade 3-4 AEs occurred in 8 patients, including proteinuria and hypertension, and there were no treatment-related deaths.

Conclusions: SABR combined with tislelizumab and fruquintinib shows promising effects and good safety in the treatment of metastatic colorectal cancer, which is expected to provide new therapeutic strategies and improve the prognosis for mCRC patients.

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639P First report of the safety/tolerability and preliminary antitumor activity of fruquintinib plus capecitabine versus capecitabine as maintenance treatment for metastatic colorectal cancer: An open-label, randomized phase Ib/II study

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Background: Maintenance therapy with fluoropyrimidines (such as capecitabine [Cap]) following induction therapy is wildly recommended to unresectable mCRC patients. Fruquintinib (Fru) is a highly selective inhibitor of VEGFR1/2/3 with conspicuous safety and efficacy in mCRC. We sought to evaluate and compare the therapeutic potential of Fru plus Cap (FC) versus Cap as maintenance therapy for mCRC.

Methods: Eligibility criteria included: histologically confirmed mCRC (stage IV), age $\geq$ 18 years, ECOG PS 0-2, achieved disease control (including CR/PR and SD) after $\geq$ 6 cycles of first-line standard chemotherapy and still unresectable. In safety lead-in phase (SP), patients (pts) were orally administered with Fru (4 mg, QD, d1-21, Q4W) plus Cap (850 mg/m^2, BID, d1-7 and d15-21, Q4W). In expansion phase, pts were randomized in a 1:1 ratio between FC (Arm A) and Cap (Arm B) only. The primary objectives were to characterize safety, confirm the recommended phase 2 dose (RP2D; in phase SP), and evaluate the efficacy (in phase EP).

Results: As of April 24, 2023, 22 pts were enrolled (SP: n = 6; EP: Arm A/B n/n = 7/7). In phase SP, 1 pt experienced DLT of grade 3 oral mucositis. The treatment emergent AEs (TEAEs, Grade $\geq$3) were hypertension (1/6), oral mucositis (1/6), voice alteration (1/6), small intestinal obstruction (1/6) and blood bilirubin increased (1/6). After full consideration about patient's tolerance and safety, the RP2D of Fru was adjusted from 4mg to 3mg through charrette. In Arm A, the most common TEAEs (Grade $\geq$3) were merely hypertension and leukopenia. Intriguingly, these results provided further evidence that reducing RP2D from 4 mg to 3mg can ensure the safety and tolerance. In 6 evaluable pts of phase SP, the DCR was 100% while the mPFS was immaturity, but 3 pts showed the PFS of $\geq$ 6 months (7.5, 8.6, 8.9 mon, respectively).

Conclusions: The combination of fruquintinib plus capecitabine demonstrated an acceptable tolerability profile. Preliminary antitumor activity was observed in pts with mCRC that revealed promising efficacy and safety as a first-line maintenance therapy. Dose expansion is ongoing at the RP2D in dedicated mCRC.

Clinical trial identification: NCT05451719.

Legal entity responsible for the study: The authors.

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640P A phase II, multicenter, open-label study of PolyPEPI1018 in combination with atezolizumab in participants with relapsed or refractory microsatellite-stable metastatic colorectal (MSS mCRC) cancer (Oberto-301): Initial results

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Background: The efficacy of checkpoint inhibitor immunotherapy in MSI-H mCRC has not been replicated in MSS mCRC. Therefore, additional interventions are needed to convert immunologically "cold" MSS CRC to "hot" tumors resembling MSI-H tumors. PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine containing 12 immunogenic epitopes derived from 7 cancer testis antigens which demonstrated early evidence of clinical activity, in first-line MSS mCRC.

Methods: Patients with MSS mCRC who have progressed on 2-3 lines of prior chemotherapy regimen received PolyPEPI1018 (1.2 mg, sc) and atezolizumab (1,200 mg, iv) Q3W. The primary endpoint was safety. A Simon 2-stage design was applied; data from the stage 1 of the study will be presented.

Results: 18 patients (77% female) were enrolled for stage 1 of the study. At baseline, median age was 55 years (range 38—79), 50% had liver metastases and 61% received at least 3 lines of prior therapies. PD-L1 expression was <1% for 85% of patients. The median number of doses received was 4 (range 2-10). A formal review of safety was performed after the initial 6 participants received 2 cycles of study therapy. The combination was well-tolerated; most common side effect related to treatment was Grade (Gr) 1-2 local skin reaction (n=12). Gr 3 events (n=2) at least possibly related to treatment were nausea and vomiting. There were no Gr 4-5 events or study discontinuation due to treatment AE. The ORR was 0% and the DCR was 68% (n=18). Post-treatment, vaccine-specific T cell responses were detected in the PBMC of 3/4 subjects tested and 3/5 patients had increased density of CD3+ and CD8+ TILs by up to 10-fold. The average PD-L1 expression (IC %) increased significantly after treatment (n=5; p=0.04), consequently 2/5 patients' tumor converted to high Immunoscore (Veracyte).

Conclusions: PolyPEPI1018 in combination with atezolizumab has a manageable safety profile. PolyPEPI1018 induced immunological responses at both peripheral and tumor level, converted "cold" tumor into "hot", although to date no responses per RECIST have been noted. The study is on-going.

Clinical trial identification: NCT05243862.

Legal entity responsible for the study: Treos Bio Ltd.

Funding: Treos Bio Ltd, Roche.

Disclosure: J. Hubbard: Financial Interests, Personal, Advisory Board: Merck; Financial Interests, Institutional, Advisory Board: Incyte, Bayer, BeiGene; Financial Interests, Institutional, Local PI: Boston Biomedical, Senhwa Biosciences, Bayer, Merck, Hutchison MediPharma, Seattle Genetics, Tovogene, Trioncology, Incyte, Pionyr, G1 Therapeutics, Effector Therapeutics, Roche; Financial Interests, Institutional, Coordinating PI: Taiho Pharmaceutical, TreoBio. M. Kremlitzka: Financial Interests, Personal, Full or part-time Employment, I am an employee of Treos Bio Ltd., working as a Senior Immunologist: Treos Bio Limited. Z. Csiszovszki: Financial Interests, Personal, Full or part-time Employment: Treos Bio Zrt; Financial Interests, Personal, Stocks/Shares: Treos Bio Ltd. E. Somogyi: Financial Interests, Personal, Full or part-time Employment, I am senior researcher at Treos Bio Zrt.: Treos Bio Zrt.; Financial Interests, Personal, Stocks/Shares, I hold shares at Treos Bio Ltd.: Treos Bio Ltd.. O. Lorincz: Financial Interests, Personal, Full or part-time Employment: Treos Bio; Financial Interests, Personal, Stocks/Shares: Treos Bio. L. Molnar: Financial Interests, Personal, Full or part-time Employment: Treos Bio. J. Toth: Financial Interests, Personal, Full or part-time Employment, Bioinformatician: Treos Bio Zrt.; Financial Interests, Personal, Stocks/Shares: Teos Bio Limited. H. Youssoufian: Financial Interests, Personal, Advisory Board: Flamingo, Verastem Oncology, C4 Therapeutics, Treos Bio; Financial Interests, Personal, Ownership Interest: Solid Therapeutics. E.R. Toke: Financial Interests, Personal, Full or part-time Employment: Treos Bio Zrt; Financial Interests, Personal, Member of Board of Directors: Treos Bio Ltd; Financial Interests, Personal, Stocks/Shares: Treos Bio Ltd. All other authors have declared no conflicts of interest.

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641P Phase I/II study of the EP4 antagonist CR6086 combined with the anti-PD-1 balstilimab in mismatch-repair-proficient and microsatellite stable (pMMR/MSS) chemorefractory metastatic colorectal cancer (mCRC)

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Background: Approved immune checkpoint inhibitors (ICI) have little to no benefit in patients (pts) with pMMR/MSS mCRC. Several combination strategies to overcome intrinsic resistance have failed. Prostaglandin E2, through its receptor 4 (EP4), is a major contributor to immunosuppression in the tumor microenvironment and blockade of this pathway may sensitize cold tumors to ICI. In preclinical models, the EP4 antagonist CR6086 significantly enhanced the activity of PD-1 blockade, prompting this ongoing phase I/II study of CR6086 added to the anti-PD-1 balstilimab in pMMR/MSS chemorefractory mCRC.

Methods: Adult pts with pMMR/MSS mCRC, ECOG PS $\leq$1 and previous exposure to fluoropyrimidines, oxaliplatin and irinotecan, received oral CR6086 (30, 90 or 180 mg twice daily) plus balstilimab (3 mg/kg every 2 weeks) until disease progression, unacceptable toxicity or death. Primary endpoints are safety and disease control rate (DCR) per RECIST 1.1. Secondary endpoints include objective response rate (ORR), duration of response, progression-free and overall survival (PFS, OS). Exploratory endpoints include tissue and blood biomarkers.

Results: Twenty-eight pts were treated and 8 are still ongoing. Median age was 59 (interquartile range [IQR]: 54-68) years and 54% were men; median prior treatment lines was 4 (IQR: 3-5). No dose-limiting toxicities were observed. CR6086-related AEs were grade 1 (G1), except for a serious G4 duodenal ulcer which led to consideration of proton pump inhibitors prophylaxis in all pts. Balstilimab-related AEs were $\leq$G2 and one was serious (pneumonitis). Three pts had partial response (all ongoing at 15, 8, and 6 months) and 11 had stable disease, with an ORR of 11% and a DCR of 50% (8% and 25% in the 12 pts with liver metastases). At a median follow-up of 6.4 months (IQR 5.3-8.4), median PFS and OS were 2 (95% CI, 1.7—3.6) and 11.3 (95% CI, 8.8—not reached) months, respectively. Translational analyses are ongoing.

Conclusions: CR6086 combined with balstilimab was well tolerated and achieved durable responses in pMMR/MSS mCRC. Expansion in other gastrointestinal tumours and further clinical development in pMMR/MSS mCRC are ongoing.

Clinical trial identification: NCT05205330.

Legal entity responsible for the study: Rottapharm Biotech Srl, Italy.

Funding: Rottapharm Biotech Srl, Italy.

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642P A phase I dose escalation study of GCC19CART: A novel CoupledCAR therapy for subjects with metastatic colorectal cancer

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Background: GCC19CART, the first clinical candidate from the CoupledCAR® solid tumor platform, targets guanylate cyclase-C (GCC) which is expressed in colorectal cancers. CoupledCAR utilizes multiple vectors to make both solid tumor targeting CAR-T and CD19 CAR-T in a single manufacturing step. An investigator-initiated dose escalation trial in China for patients with relapsed or refractory metastatic colorectal cancer (R/R mCRC) is reported here.

Methods: Based on a data cutoff of October 20, 2022, 21 subjects have been enrolled and treated, with all subjects completing $\geq$1 evaluation of response and being evaluable. Eligible subjects undergo leukapheresis, a single dose of lymphodepleting chemotherapy (fludarabine 30mg/m^2 and cyclophosphamide 300mg/m^2) 3 days prior to infusion, and then administration of a single infusion of GCC19CART at one of two preassigned doses: Dose 1 (1x10^6) or Dose 2 (2x10^6) CAR T-cells/kg. Endpoints are safety and preliminary evidence of efficacy.

Results: 13 subjects have been enrolled to dose level 1 (1x10^6 cells/kg) and 8 subjects have been enrolled to dose level 2 (2x10^6 cells/kg). The most common adverse events were cytokine release syndrome (CRS) in 21/21 subjects (Grade 1 19/21 (90.48%) or Grade 2 2/21 (9.52%)) and diarrhea in 21/21 subjects (Grade 1 6/21 (28.57%) Grade 2 5/21 (23.81%) Grade 3 9/21 (42.86%) or Grade 4 1/21 (4.76%)). All patients with grade 3 and higher side effects were well managed. Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 2/21 (9.52%) subjects at Grade 3 or 4 and resolved with corticosteroids. For dose level 1, the overall response rate (ORR) per RECIST 1.1 was 15.4% (2/13). The median PFS was 2.0 months and the median overall survival was also 13.3 months. For dose level 2, The ORR per RECIST 1.1 was 50% (4/8). The median PFS was 6.3 months and the median follow-up was also 21.3 months.

Conclusions: Preliminary results demonstrate that GCC19CART has meaningful dose-dependent clinical activity and an acceptable safety profile in relapsed or refractory metastatic colorectal cancer. This trial is ongoing and updated data will be presented. A phase 1 trial of GCC19CART in the US has opened for accrual and is expected to enroll patients in mid-2022.

Legal entity responsible for the study: Innovative Cellular Therapeutics.

Funding: Innovative Cellular Therapeutics.

Disclosure: L. Xiao: Financial Interests, Personal and Institutional, Other, Stock holders: Innovative Cellular Therapeutics. All other authors have declared no conflicts of interest.

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643P A phase Ib/IIa study to assess the safety, tolerability, pharmacokinetics, and antitumor activity of YYB101, hepatocyte growth factor neutralizing humanized monoclonal antibody, in combination with irinotecan in metastatic or recurrent colorectal cancer patients (NOV110501-201)

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Background: The hepatocyte growth factor (HGF)/MET pathway is implicated in tumorigenesis and treatment resistance of colorectal cancer (CRC). This report presents final results of a multi-center phase Ib/IIa study investigating biweekly YYB101, an anti-HGF monoclonal antibody, combined with irinotecan in refractory metastatic/recurrent CRC.

Methods: Eligible patients had metastatic/recurrent CRC with disease progression <6 months from the last irinotecan dose. phase Ib determined the recommended phase II dose (RP2D) of YYB101 with irinotecan (150 mg/m2), starting at 20 mg/kg, focusing on dose-limiting toxicities (DLT) incidence. Phase IIa assessed objective response rate (ORR) as the primary endpoint, with secondary endpoints including progression-free survival (PFS), overall survival (OS), disease control rate (DCR), safety, and pharmacokinetics. Archival tissue specimens and serial blood samples were collected for exploratory analysis.

Results: Thirty-five patients, aged 42-73 (median: 56), were enrolled. All had received $\geq$3 prior therapy lines (42.9% $\geq$4 lines). No DLTs were reported in phase Ib, with 20 mg/kg YYB101 selected as RP2D. In phase IIa, ORR was 5.7% (2/35) [95% confidence interval (CI), 0.70—19.16], and DCR was 82.9% (95% CI, 66.4—99.4). Median PFS was 4.80 months (95% CI, 3.15-8.84), and median OS was 14.9 months (95% CI, 9.30—not reached). Adverse events were generally manageable, mostly grades 1-2. During the COVID-19 pandemic, 54.3% of patients skipped one or two YYB101 doses but maintained serum concentrations above the predicted minimum effective concentration (100 μg/ml).

Conclusions: The YYB101 and irinotecan combination showed modest efficacy and tolerable adverse events in refractory metastatic/recurrent CRC. Ongoing biomarker analyses aim to identify genomic and transcriptomic variables associated with long-term disease control.

Clinical trial identification: NCT04368507.

Legal entity responsible for the study: National OncoVenture, National Cancer Center, Goyang, Korea; CellabMED Inc, Seoul, Korea.

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644P Phase Ib/II open-label study to evaluate the safety, tolerability, and efficacy of rivoceranib plus trifluridine/tipiracil in patients with previously treated metastatic colorectal cancer

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Background: Rivoceranib (Rivo) is a novel oral TKI that potently and selectively inhibits vascular endothelial growth factor receptor-2 (VEGFR2). Selective inhibition of VEGFR2 has been shown to enhance the efficacy of chemotherapy. Herein, we present safety and efficacy results of the phase 1b portion of this study evaluating Rivo in patients (pts) with previously treated metastatic colorectal cancer.

Methods: In phase 1b of the study, a 3+3+3 dose-escalation was conducted to identify the recommended phase 2 dose (RP2D) of Rivo to be used in combination

trifluridine/tipiracil. The phase 2 portion will evaluate the RP2D of Rivo PO QD (Days 1-28) in combination with trifluridine/tipiracil 35 mg/m^2 PO BID (Days 1-5, 8-12 Q28 days).

Results: As of September 2022, 29 pts received treatment with Rivo. The median age was 54 yrs (range, 30-80), most pts were male (55.2%) and White (86.2%), ECOG PS was 0 (55.2%) or 1 (44.8%), and most pts received 3 (24.1%) or 4 (24.1%) prior lines of systemic therapy. Efficacy results at each dose level are summarized in the table. Dose limiting toxicities included myelosuppression, nausea, diarrhea, fatigue, asthenia, anorexia, proteinuria and arrythmia. No treatment-related deaths occurred. The patient who received the longest duration of treatment (>26 cycles) continues to receive treatment with rivoceranib.

Table: 644P Efficacy Results (Intent-to-Treat Population)

	300 mg (n=7)	400 mg (n=7)	500 mg (n=8)	600 mg (n=7)
ORR, n (%)	0	0	1 (12.5)	0
BOR per RECIST v1.1				
PR, n (%)	0	0	1 (12.5)	0
SD, n (%)	4 (57.1)	5 (71.4)	4 (50.0)	1 (14.3)
PD, n (%)	2 (28.6)	1 (14.3)	3 (37.5)	4 (57.1)
NE, n (%)	1 (14.3)	1 (14.3)	0	2 (28.6)
mPFS, mo (95% CI)	3.9 (0.9,8.3)	4.2 (1.8,NE)	3.6 (1.8,14.6)	2.1 (1.2, NE)
mOS, mo (95% CI)	13.4 (1.9, 26.9)	6.7 (3.1, NE)	11.3 (3.3, NE)	7.6 (5.2, NE)
OS at 12 mo (95% CI)	57.1 (17.2,83.7)	42.9 (9.8,73.4)	50.0 (15.2,77.5)	33.3 (4.6,67.6)

Conclusions: Rivo 400 mg PO QD is the RP2D to be used in combination with trifluridine/tipiracil 35 mg/m^2 PO BID.

Clinical trial identification: NCT04073615.

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Funding: Elevar Therapeutics.

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645P A phase Ib dose escalation study of binimetinib plus mFOLFIRI in patients with metastatic RAS mutated colorectal cancer

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Background: MEK inhibition (MEKi) may act synergistically when combined with cytotoxics in RAS mutated (mt) metastatic colorectal tumours (mCRC). We investigated the safety and clinical activity of MEKi, binimetinib, and mFOLFIRI in patients (pts) with *RAS* mt mCRC.

Methods: Eligibility criteria: Pts >18 years with *RAS* mt mCRC, ECOG 0-1, acceptable organ function, measurable disease, and progression or ineligibility to oxaliplatin. Pts received binimetinib plus mFOLFIRI, in a dose-escalated standard 3+3 design, to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). A 6-day lead-in period with binimetinib alone was required prior to combination therapy. Two levels of binimetinib were evaluated - 30mg BID and 45mg BID - and given on days 1-12/14-day cycle po with mFOLFIRI every 14 days iv. An additional 12 patients enrolled in the dose expansion phase to assess preliminary efficacy. The study completed accrual and herein we report the updated results.

Results: 13 pts enrolled in the dose escalation phase (7 pts on the first binimetinib dose level and 6 on the second) and 12 pts in the expansion phase. Median age was 49 yrs (35-71), and 13 were male. All pts in expansion and 9 in escalation, had received irinotecan prior. All pts in the expansion cohort had irinotecan refractory disease. The MTD of binimetinib was 45mg BID. The most common grade 1-2 adverse effects (AEs) (%) were diarrhoea (64), fatigue (64), nausea (48), vomiting (44), rash (24). Grade 3-4 AEs included fatigue (12), rash (4), heart failure (4), and pneumonitis (4). 1 pt with pre-existing heart disease had a DLT of decreased cardiac ejection fraction on dose level 1. 17 pts discontinued therapy due to progression, 5 due to AEs and 3 for other reasons. The mean number of FOLFIRI and MEK cycles received was 6.7 (0-29) and 7.5 (1-30), respectively. Of the 25 pts, 24 were evaluable for response. Best response included 1 PR and 12 SD (all had received prior irinotecan and 10 had progressed on it). 4 pts remained on study for >6 months (7-15). The median PFS was 3.35 months (95% CI 2-8.61) and the median OS was 8.41 months (95% CI 4.7-12.8).

Conclusions: MEKi plus mFOLFIRI has acceptable toxicity and showed activity even in patients with prior progression on irinotecan.

Clinical trial identification: NCT02613650.

Legal entity responsible for the study: Huntsman Cancer Institute.

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646P Phase Ib/II study of ompenaclid (RGX-202-01), afirst-in-class oral inhibitor of the creatine transporter SLC6A8, in combination with FOLFIRI and bevacizumab (BEV) in RAS mutated (RASm) second-line (2L) advanced/metastatic colorectal cancer (mCRC)

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Background: Creatine Kinase B (CKB) was identified as a driver of RASm mCRC. CKB generates ATP from phosphocreatine (PCr), which is imported by SLC6A8. Ompenaclid depletes PCr and ATP resulting in tumor cell apoptosis. In a phase 1a study, ompenaclid monotherapy showed objective anti-tumor activity in RASm mCRC without dose-limiting toxicities (DLTs).

Methods: Objectives of this ongoing phase 1b/2 study are evaluation of safety, PK/PD and efficacy of ompenaclid + FOLFIRI/BEV in 2L mCRC. Eligible pts had disease progression after a 1L oxaliplatin-containing regimen.

Results: Enrollment as of 28Apr2023, 35 pts (22 KRASm, 3 NRASm, 10 RAS-wt) in the Dose Escalation/Expansion cohorts receiving 2400mg BID (n=14) or 3000mg BID (n=21); all pts received FOLFIRI/BEV. No DLTs were observed in Dose Escalation and a MTD was not reached. Across safety-evaluable pts (n=33), the most common treatment emergent AEs Gr≤2 were nausea (50%), diarrhea (44%); Gr≥3 were neutropenia (15%), abdominal pain (11%), diarrhea (11%), fatigue (11%). The AE profile is similar to FOLFIRI/BEV alone, demonstrating good combinability. At both ompenaclid doses, systemic exposure was comparable and resulted in up to a 48X increase in urine creatine, suggesting robust target inhibition. The ORR in 17 RASm and 10 RAS-wt evaluable pts was 41% (6 confirmed PRs, 1 unconfirmed PR) and 20% (2 unconfirmed PRs), respectively. Five RASm pts are pending 1st scan and not yet evaluable. PRs were observed in pts with diverse KRASm (G13D [2 pts], G12V [2 pts], G12D, G12S and pG10dup). For RASm pts, mPFS was 11.8M and mOS was 19.1M, and for RAS-wt pts, mPFS was 7.5M and mOS was 14.5M.

Conclusions: At the evaluated dose levels, ompenaclid + FOLFIRI/BEV was well tolerated and induced potent inhibition of the target SLC6A8. Encouraging efficacy was observed in pts with RASm mCRC, with a response rate exceeding that expected with SOC. This preferential RASm activity is consistent with preclinical and phase 1a data. There is a high unmet need for a safe and combinable oral pan-RASm therapy in mCRC. Recruitment of RASm pts continues and a randomized controlled trial in 2L RASm mCRC is planned.

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647P Patient-derived xenograft approach to explore differential responses to diet dependent on genotypic or phenotypic characteristics of colorectal cancer

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Background: Colorectal cancer (CRC) results from the combination of genetic alterations and environmental risk factors. Several evidences indicate that the diet may have a role in prevention and progression of CRC, but more research is needed to clarify the heterogeneity of dietary associations with CRC.

Methods: Patient-derived xenografts (PDXs) were generated implanting subcutaneously human CRCs at different staging into immunodeficient mice, and feeding with control normal diet (ND) and classical western diet (WD). Tumor phenotype, transcriptomic, genetic and metabolomic were analyzed.

Results: The response to WD was heterogeneous among all generated PDXs. Only one out of three showed a greater growth in mice fed with WD. Particularly, WD induced transcriptomic perturbations of several genes related to epigenetic regulations and tumor progression, remodeling tumor microenvironment, promoting mucin secretion, mitochondria dysfunction and metabolic reprogramming. Interestingly, the three PDXs responded to the same WD with a distinct metabolomic profile that was validated through the machine learning. With whole exome sequencing, PDXs did not share the same somatic cancer mutations that could play a key role in conditioning response to a specific diet. Consistently, the same heterogeneous response to WD in tumor growth was observed in xenografts generated with CRC cell lines. To strictly mimics human diet, we tested in comparison to classic WD, humanized WD diet that displayed a different tumor behavior. The analysis of patient derived organoids developed from PDX fed with humanized diets revealed that the altered metabolic reprogramming acquired *in vivo* is also maintained *in vitro* in absence of any stimulus, suggesting a metabolic memory of cancer cells.

Conclusions: Specific CRC somatic mutations, modifying several signaling pathway and tumor metabolism promote tumor growth and progression, and could be predictive of a response to a specific diet. In this scenario, PDX could be considered as a suitable approach to study the response to the diet and to provide a screening of different diets in order to create a dietary guidance for CRC patients.

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648P Medium to long-term effects of the COVID-19 pandemic on colorectal cancer diagnosis and management in Italy: Preliminary findings from an updated analysis of the real-world multicenter COVID-DELAY study

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Background: As extended analysis of the COVID-DELAY study, we aimed to assess COVID-19 impact on diagnosis, staging and treatment outcomes of CRC patients in 2021 and 2022 compared to 2019 and 2020.

Methods: All consecutive newly diagnosed CRC patients referred to 8 Italian Oncology Departments between March and December 2019, 2020, 2021, and 2022 were evaluated. Access rate (number of patients/year), demographic characteristics, diagnostic and therapeutic temporal intervals (between date of symptoms onset, radiological and cytohistological diagnosis, treatment start, and first radiological evaluation), as well as PFS and OS were assessed and compared.

Results: Compared to 2019 (n=485), a reduction in new CRC cases was found in 2020 (n=390, -19.6%). On the other hand, a progressive increase in new CRC diagnosis was found in 2021 (n= 461, +18.2%) and 2022 (n= 509, +30.5%), compared to 2020. A higher rate of stage IV tumours was diagnosed in 2020 (31.3%) and 2021 (29.6%) compared to 2019 (20.8%), with a normalization in 2022 (22.8%) ($p<0.001$); a lower number of patients has been discussed in multidisciplinary tumor boards in 2020 (22.1%) compared to 2019 (34.9%), 2021 (37.0%), and 2022 (47.6%) ($p<0.001$). A significant difference in terms of temporal interval between histological diagnosis and first oncological examination (median of 31 vs. 38 days, respectively, p=0.004), cytohistological diagnosis and systemic treatment start (median of 52 vs. 58 day, $p<0.001$), first oncological appointment and systemic treatment start (median of 52 compared to 58 days, p=0.034), was found between 2020 and 2021-2022 years, respectively. At multivariate analysis, the 2021-2022 years confirmed to be associated with a reduction in the risk of disease progression compared to 2020 (HR=0.71 (0.53-0-97); p=0.031).

Conclusions: A worsening drop in CRC diagnosis in 2020, with a progressive increase in 2021 and 2022, in parallel with a higher incidence of late-stage CRC diagnosed in 2020 and 2021. This might have affected some diagnostic-therapeutic time intervals in 2021-2022 years compared to 2020.

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649P The genomic landscape of appendiceal adenocarcinoma (AA) revealed by 855 whole exome sequences (WES)

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Background: AA is a rare malignancy with a predilection for peritoneal metastases without hematogenous or lymphatic metastases. Despite this, AA is treated with chemotherapy similar to colorectal cancer. Studies suggest inefficacy of these regimens for many AA patients supporting the likelihood of a unique genomic landscape.

Methods: WES of tumor tissue was performed as part of personalized circulating tumor DNA (ctDNA) testing (Signatera™) in 855 patients with AA. Tumor mutational burden (TMB) and microsatellite instability (MSI) were assessed; Kyoto Encyclopedia of Genes and Genomes (KEGG) network analysis was performed. WES data on stage-

matched colon (CC, N=833) and rectal cancer tissues (RC, N=841) were compared with AA.

Results: A total of 98,310 variants were identified from 855 AA tumor tissues (median 132.5 variants/tumor). AA had lower TMB (median: 2.14 Muts/Mb) than RC or CC (median: 3.55 and 4.31 Muts/Mb, respectively). Only 1.3% (11/855) of the AA were MSI-high, compared to RC (2.5%) and CC (16.76%). Comparison of frequently mutated genes highlighted that AA has much less frequent APC and TP53 and more frequent GNAS mutations. Despite differences in driver mutations and overall lower TMB, the mutational signatures for AA, CC, and RC were similar with SBS1 (clock-like) and SBS6 (MMR-deficient) being predominant in each tumor type. Co-mutation analysis identified a dense interaction network of 805 co-occurring or mutually exclusive interactions highlighted by connections between Wnt, Ras-MAPK, and DNA repair pathways. Copy number analysis identified that AA has less aneuploidy relative to CC or RC, however, within AA, TP53 mutation was associated with significantly higher aneuploidy relative to wildtype. Interestingly, TP53 mutations were also associated with detectable ctDNA in AA (44.6% vs. 24.9%, p<0.001), but not in CC or RC.

Conclusions: WES data on AA reveals important differences in driver somatic mutations, CNV, and co-mutational networks compared to CC and RC. This is the first large-scale genomic profiling of AA, establishing the genetic landscape of this rare and orphan disease. Future studies should focus on AA-specific treatments rather than the extrapolated CC/RC experience.

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650P Genomic profiling of small bowel adenocarcinoma: A pooled analysis

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Background: Several genomic alterations have been described in small bowel adenocarcinoma (SBA) but the prognostic value of these alterations remains unclear. The aim of this multicentre study was to determine the genomic profile of SBA and its impact on the prognosis.

Methods: Three cohorts in France and Italy were pooled. A common dataset of genomic analysis have been performed on 35 genes of interest. MSI (MicroSatellite Instable) and MMR (MisMatch Repair) status were also assessed.

Results: A total of 188 tumour samples had conclusive results for mutation analysis. The patients (pts) were male (55.3%), with duodenum primary (58.5%), stage I-II (39.6%), III (40.6%) and IV (18.8%). with a predisposing disease (21%) mainly Lynch syndrome (LS) (n=19) and Crohn disease (CD) (n=11). The most frequent mutation were *KRAS* (42.0%) of which 7/79 G12C, *TP53* (40.4%), *APC* (19.1%), *PIK3CA* (18.6%), *SMAD4* (12.8%) and *ERBB2* (9.6%). *TP53* mutations were more frequent in CD (81.8%) but less frequent in LS (15.8%) than in no predisposing disease (39%). *ERBB2* mutations were more frequent in LS (26.3%) than in no predisposing disease (7.5%). No *APC* mutation was observed in CD. *KRAS* and *SMAD4* mutations were more frequent in tumour than in localized tumour (59.4% vs 37.7%, p=0.0164) and (24.3% vs 9.9%, p=0.0187). *ERBB2* mutations were less frequent in metastatic than in localized tumour (0% vs 11.9%, p=0.0272). For localized tumour univariate analysis revealed that: age ≥65 (p=0.0327), T4 (p=0.570), high grade (p=0.0028) stage III (p=0.0390) and wild type *APC* (p=0.395) were associated with a poor overall survival (OS). In multivariate analysis: high grade (p=0.023), age ≥65 (p=0.0123) and wild type *APC* (p=0.0254) were associated with a poor OS. For metastatic tumour a trend for a better OS was observed in case of a mutated *KRAS* tumour (HR=0.6 (0.34-1.06), p=0.0797) in univariate analysis. dMMR/MSI status was available in 238 pts. Overall, dMMR/MSI was reported in 29.8%, 31.8% in localized and 11.3% in metastatic tumour. dMMR/MSI was associated with a better OS (HR=0.61 [0.39-0.96], p=0.0333).

Conclusions: There is different genomic profile according to the predisposing disease. MSI/dMMR predict a better prognosis. *APC* mutation in localized and *KRAS* mutation in metastatic tumour are associate with a better prognosis.

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651P DCF versus doublet chemotherapy as first-line treatment of advanced squamous anal cell carcinoma: A multicenter propensity score matching study

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Background: Triplet DCF (docetaxel, cisplatin and 5-fluorouracil) and doublet CP/CF (carboplatin and paclitaxel/cisplatin and 5-fluorouracil) regimens were prospectively evaluated in advanced squamous anal cell carcinoma (SCCA), and validated as standard treatments. Even though the high efficacy and good tolerance of DCF regimen were confirmed in 3 independent prospective trials, doublet CP regimen is still recommended in several guidelines based in its better safety profile with similar efficacy compared to CF regimen.

Methods: We performed a propensity score-adjusted method with inverse probability of treatment weighted (IPTW) and matched case control (MCC) comparison among patients with metastatic or non-resectable locally advanced recurrent SCCA, treated with chemotherapy as first-line regimen. The primary endpoint was the overall survival (OS), and the secondary endpoint was the progression-free survival (PFS).

Results: 247 patients were included for analysis. 154 patients received DCF and 93 patients received a doublet regimen. Patients' characteristics and outcomes in both groups were comparable to published data. The median OS was 32.3 months with DCF and 18.3 months with doublet regimens (HR 0.53, 95%CI 0.38-0.74; p=0.0001), and the median PFS was 11.2 months with DCF versus 7.6 months with doublet regimens (HR 0.53, 95%CI 0.39-0.73; p<0.0001). The hazard ratios by IPTW and MCC analyses were 0.411 and 0.406 for OS, and 0.466 and 0.438 for PFS (Table).

Table: 651P Multivariate Cox analyses for OS and PFS in propensity score matched population and with IPTW weighted method

	Matched analysis (n=154)			IPTW analysis (n=247)		
	HR	95%CI	P	HR	95%CI	P
OS	0.406	0.261-0.632	<0.0001	0.411	0.324-0.521	<0.0001
PFS	0.438	0.298-0.644	<0.0001	0.466	0.376-0.576	<0.0001

Conclusions: The triplet DCF regimen provides a high and significant benefit in OS and PFS over doublet regimens, and can be considered as upfront treatment for eligible patients with advanced SCCA.

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DEVELOPMENTAL THERAPEUTICS

652O Preliminary clinical activity of RMC-6236, a first-in-class, RAS-selective, tri-complex RAS-MULTI(ON) inhibitor in patients with KRAS mutant pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC)

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Background: RMC-6236 is a novel, oral RAS^{MULTI}(ON) inhibitor that is selective for the active, GTP-bound state of both mutant and wild-type variants of the canonical RAS isoforms. Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly PDAC and NSCLC harboring KRAS glycine-12 substitutions ($KRAS^{G12X}$).

Methods: Patients with previously treated, advanced $KRAS^{G12X}$ mutant solid tumors were enrolled at escalating doses (10mg to 160mg once daily (QD)) of single agent RMC-6236. Additional patients with PDAC or NSCLC were enrolled at dose levels that cleared dose-limiting toxicity evaluation.

Results: As of April 24, 2023, 22 patients with $KRAS^{G12X}$ PDAC (13 G12D, 7 G12V, 2 G12R) and 11 with $KRAS^{G12X}$ NSCLC (5 G12D, 4 G12V, 2 G12A) were enrolled, and 14 patients with PDAC and 9 patients with NSCLC continue treatment with RMC-6236. Median prior therapies was 3 (range, 1-7). Treatment-related adverse events (TRAEs) occurring in $\geq$10% of patients were rash (52%), diarrhea (21%), nausea (21%), and vomiting (15%). The only Grade $\geq$3 TRAE was in a patient with PDAC who had a Grade 4 large intestine perforation at the site of an invasive tumor that reduced in size on treatment. Preclinical modeling predicts tumor regressions at 80mg QD or higher in humans. Preliminary clinical activity in PDAC and NSCLC was assessed at 80mg and 120mg QD. Among 14 patients (10 PDAC, 4 NSCLC) dosed at least 8 weeks prior to the data cut-off date, the objective response rate was 36% (2 confirmed and 3 unconfirmed; 2/10 PDAC and 3/4 NSCLC). Median time to onset of initial response was 6 weeks (range, 5-11). Disease control rate was 86% (12/14; 8/10 PDAC and 4/4 NSCLC). Tumor reduction was observed in 4 patients with stable disease (range, -2% to -21% by RECIST v1.1). Of the 12 patients with partial response or stable disease, 11 continue on treatment.

Conclusions: RMC-6236 exhibits promising anti-tumor activity in patients with $KRAS^{G12X}$ PDAC and NSCLC at doses that are well tolerated. Dose escalation is ongoing and data from additional patients will be available at the time of the meeting.

Clinical trial identification: NCT05379985.

Legal entity responsible for the study: Revolution Medicines, Inc.

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653O Glecirasib (KRAS G12C inhibitor) in combination with JAB-3312 (SHP2 inhibitor) in patients with KRAS p.G12C mutated solid tumors

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Background: Glecirasib is a direct oral KRAS G12C inhibitor (KRAS G12Ci) with favorable tolerability and promising efficacy. JAB-3312 is a potent oral SHP2 inhibitor that may overcome KRAS G12Ci resistance. Together these compounds were shown to exert synergistic anti-tumor effect when combined with glecirasib in multiple animal models. Here we present the preliminary clinical data from the dose escalation phase.

Methods: The phase 1/2a study [NCT05288205] evaluated glecirasib plus JAB-3312 in patients (pts) with *KRAS p.G12C* mutated solid tumors. The primary endpoint of the dose escalation part was safety and tolerability. The secondary endpoints included objective response rate (ORR), disease control rate (DCR) per RECIST 1.1 and pharmacokinetics (PK) profile. Glecirasib 400 mg or 800 mg daily was combined with various JAB-3312 doses and schedules.

Results: As of April 7th, 2023, 60 pts (50 non-small cell lung cancer [NSCLC], 9 colorectal cancer, and 1 pancreatic cancer) were enrolled in six dose levels. About 40% had $\geq$ 2 prior lines of therapy, and 26.7% had received prior KRAS G12Ci treatment. Dose escalation concluded with one dose-limiting toxicity (grade 3 pneumonitis) at a higher dose level. The most common (>20%) treatment-related adverse events (TRAE) included anemia, ALT/AST increased, hypertriglyceridemia, bilirubin increased, neutropenia/leukopenia, creatine kinase increased, and edema. TRAE $\geq$ grade 3 occurred in 36.7% of pts. No TRAE led to discontinuation of both glecirasib and JAB-3312. PK of JAB-3312 of the combination was generally comparable with historical monotherapy, suggesting low risk of drug-drug interaction. Amongst the 50 pts with NSCLC, 35 were efficacy evaluable, 14 have not reached the first scan and one withdrew due to COVID-19. Out of 28 evaluable pts with KRAS G12Ci naïve NSCLC, ORR was 50% (14/28) and DCR was 100%. In pts with KRAS G12Ci treated NSCLC, ORR was 14.3% (1/7), and DCR was 57.1%. Additional safety, efficacy and PK data will be presented at this meeting.

Conclusions: Glecirasib plus JAB-3312 was well tolerated with promising efficacy in *KRAS p.G12C* NSCLC. Currently, dose expansion is underway to further evaluate efficacy and safety.

Clinical trial identification: NCT05288205.

Legal entity responsible for the study: Jacobio Pharmaceuticals Group Co., Ltd.

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654O Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with solid tumors harboring specific HER2-activating mutations (HER2m): Primary results from the international phase II DESTINY-PanTumor01 (DPT-01) study

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Background: T-DXd is an antibody—drug conjugate targeting HER2 approved in HER2-expressing breast cancer (BC), HER2-positive gastric cancer (GC), and *HER2*-mutant non-small cell lung cancer (NSCLC) in the US. Treatment (Tx) options are limited for pts with other solid tumors harboring *HER2*m.

Methods: In an open-label, multicenter, phase 2 study (NCT04639219) in pts with advanced solid tumors harboring prespecified *HER2*m (excluding HER2-overexpressing BC and GC, and *HER2*-mutant NSCLC), and who failed previous systemic Tx received T-DXd 5.4 mg/kg q3w. The primary endpoint was confirmed objective response rate (ORR) by RECIST 1.1 according to independent central review (ICR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), and safety.

Results: 102 pts were assigned to T-DXd (data cutoff Jan 25 2023; median follow-up, 8.61 [range 1.5—22.1] months [mo]) with median 3 [range 1—13] prior lines of systemic therapy. The ORR was 29.4% (95% CI 20.8, 39.3); median DoR was not reached (54.2% of responders remained in response by ICR at 18 mo); median PFS was 5.4 mo (95% CI 2.7, 7.1). Responses were observed across HER2 expression levels, including HER2 IHC 0 tumors. The table shows ORR by tumor type and *HER2*m domain. Grade

Table: 654O

	N	ORR by ICR	
		n	%
All pts	102	30	29.4
Tumor type			
Breast	20	10	50.0
Colorectal	20	4	20.0
Biliary tract	19	2	10.5
Esophageal/esophagogastric	11	1	9.1
Urothelial	7	2	28.6
Salivary gland/head and neck AC	6	4	66.7
Small intestinal AC	5	0	-
Cervical	3	2	66.7
Endometrial	2	2	100
Other neuroendocrine	2	1	50.0
Pancreatic	2	0	-
AC of unknown primary	1	1	100
Extramammary Paget's disease	1	1	100
Melanoma	1	0	0
Ovarian	1	0	0
Urachal	1	0	0
***HER2*m domain**[a]			
Tyrosine kinase[b]	52	19	36.5
Extracellular[c]	34	10	29.4
Transmembrane/juxtamembrane[d]	17	1	5.9

AC, adenocarcinoma

[a]By local testing;[b]L755S, D769H, Y772_A775dup/A775_G776insYVMA, V777L, G778_P780dup/P780_Y781insGSP, V842I, T862A; [c]S310F, S310Y; [d]R678Q

(G) ≥3 adverse events (AEs) occurred in 51.0% of pts; 9.8% discontinued Tx due to AEs. Adjudicated drug-related interstitial lung disease/pneumonitis occurred in 11 pts (10.8% [G3, n=1; G5, n=2]).

Conclusions: DPT-01 is the first tumor-agnostic global study of T-DXd in a range of solid tumors with prespecified *HER2*m. In heavily pretreated pts with limited Tx options, T-DXd demonstrated encouraging anticancer activity and long DoR across multiple tumor types with *HER2*m and a range of HER2 expression levels, with a known safety profile. Translational research will help characterize pts who may derive greatest benefit from T-DXd.

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655O Phase Ib study of cofetuzumab pelidotin, an anti-PTK7 antibody-drug conjugate, in patients with PTK7-expressing recurrent non-small cell lung cancer (rNSCLC)

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Background: Cofetuzumab pelidotin (Cofe-P), a protein tyrosine kinase 7 (PTK7)–targeting antibody-drug conjugate, was tolerable and had preliminary antitumor activity in patients (pts) with advanced solid tumors (Phase 1; NCT02222922). Results are presented from an ongoing Phase 1b, open-label, single-arm, multicenter study (NCT04189614) of Cofe-P in pts with PTK7-expressing rNSCLC.

Methods: Eligible pts were ≥18 yrs with PTK7-expressing (central immunohistochemistry [IHC]) rNSCLC and prior platinum doublet and immune checkpoint inhibitor (tumors w/o actionable genetic alterations [AGA−]) or platinum doublet and targeted agent(s) (AGA+ tumors). Pts received 2.8 mg/kg Cofe-P IV Q3W until PD/unacceptable toxicity.

Results: As of August 9, 2022, 56 pts received Cofe-P (median age, 64 years; male, 63%; Asian, 50%, White, 46%); 27 pts (48%) were nonsquamous (NSQ) EGFR WT, 13 (23%) were NSQ EGFR mutant, and 16 (29%) were squamous (SQ). PTK7 IHC enrollment cutoff was refined during study; 42 pts (75%) had PTK7 expression above

Table: 655O

Parameter	NSQ EGFR WT, PTK7 ≥90%/≥2+ N=21	Overall N=56
ORR, % (95% CI)	30.0 (11.9, 54.3)[a]	19.6 (10.2, 32.4)
CBR (CR + PR + SD), % (95% CI)	90.0 (68.3, 98.8)[a]	78.6 (65.6, 88.4)
mDOR, mo (95% CI)	5.8 (2.8, −)	7.2 (2.8, 9.7)
mPFS, mo (95% CI)	5.5 (2.6, 8.5)	5.3 (3.6, 5.9)

[a]Response-evaluable pts (N=20) (≥1 postbaseline measurement).
CI, confidence intervals; CBR, clinical benefit rate; CR, complete response; EGFR, epidermal growth factor; mDOR, median duration of response; mPFS, median progression free survival; NSQ, nonsquamous; ORR, objective response rate; PR, partial response; PTK7, protein tyrosine kinase 7; pts, patients; SD, stable disease; WT, wild type.

final ≥90%/≥2+ cutoff; of these, 21 (50%) were NSQ EGFR WT. Enrollment of SQ and NSQ EGFR mutant pts was halted to prioritize NSQ EGFR WT accrual due to response rates in each subgroup. Efficacy results are shown in the table. TEAEs were reported in all pts, most common (≥30%): alopecia (52%), neutropenia (45%), headache (36%), pruritis (36%), and decreased appetite (30%). Grade ≥3 TEAEs were reported in 68% of pts, most common (≥5%): neutropenia (39%), leukopenia (9%), pneumonia (7%), anemia (5%), fatigue (5%). Peripheral neuropathy was reported in 18% of pts; 2% had Grade 3. No deaths related to Cofe-P were reported. PK was similar to previous phase 1 study with Cofe-P conjugate elimination half-life ∼3 days.

Conclusions: Cofe-P was well-tolerated with encouraging antitumor activity observed in rNSCLC and 30% ORR in the subpopulation with NSQ EGFR WT NSCLC and PTK7 ≥90%/≥2+.

Clinical trial identification: NCT02222922.

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656MO The HER2-targeting ADC SHR-A1811 in HER2-expressing/mutated advanced non-breast solid tumors (STs): Results from the global phase I study

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Background: SHR-A1811 is a novel ADC composed of trastuzumab (anti-HER2), a cleavable linker, and a topoisomerase I inhibitor payload, with optimized drug-antibody ratio of 6 and strong bystander killing effect. We initiated this global, dose escalation, PK expansion, and indication expansion phase 1 study in HER2-expressing/mutated advanced STs. The primary analysis showed that SHR-A1811 was well-tolerated and had promising antitumor activity, especially in HER2-positive or low-expressing breast cancer (AACR 2023 , CT175). Here we report the findings focusing on non-breast STs.

Methods: Patients (pts) with advanced, unresectable, or metastatic HER2-expressing/mutated STs that were refractory or intolerant to standard therapies were treated with SHR-A1811 at 1.0−8.0 mg/kg Q3W (IV).

Results: As of Feb 28, 2023, 98 pts with non-breast STs were enrolled. Pts had a median 2 prior lines of therapy (range 1−9), and 66.3% had ≥2. ORR was 45.9% (39/85 evaluable pts; 95% CI 35.0−57.0); DCR was 88.2% (75/85; 95% CI 79.4−94.2); and median TTR was 1.4 mo (range 0.7−5.8). ORR was 54.1% (20/37) in pts with HER2 IHC3+, 41.7% (10/24) with IHC2+, and 50.0% (7/14) with IHC1+. For individual tumor type, ORR was 56.3% (9/16) in BTC pts, 59.1% (13/22) in UC, 50.0% (6/12) in GC/GEJA, and 36.4% (4/11) in CRC (data by HER2 status for each tumor type are shown in table). Overall, 38 (38.8%) of 98 pts had disease progression or died; the 6-mo PFS rate was 52.1%. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 50

Table: 656MO ORR by tumor type and HER2 status

	BTC (N=22)	UC (N=23)	GC/GEJA (N=13)	CRC (N=14)	Other tumors (N=26)
ORR*, n/N (%) (95% CI)	9/15 (60.0%) (32.3–83.7)	13/22 (59.1%) (36.4–79.3)	6/12 (50.0%) (21.1–78.9)	4/11 (36.4%) (10.9–69.2)	7/25 (28.0%) (12.1–49.4)
HER2 IHC 3+	7/10 (70.0%) (34.8–93.3)	2/6 (33.3%) (4.3–77.7)	4/10 (40.0%) (12.2–73.8)	3/3 (100.0%) (29.2–100.0)	4/8 (50.0%) (15.7–84.3)
HER2 IHC 2+	0/1	7/10 (70.0%) (34.8–93.3)	2/2 (100.0%) (15.8–100.0)	0/3	1/8 (12.5%) (0.3–52.7)
HER2 IHC 1+	1/2 (50.0%) (1.3–98.7)	4/5 (80.0%) (28.4–99.5)	0	0/1	2/6 (33.3%) (4.3–77.7)
HER2 mutation and/or amplification	1/2 (50.0%) (1.3–98.7)	0/1	0	1/4 (25.0%) (0.6–80.6)	0/3

*tumor response evaluable set.

(51.0%) of pts; the most common (≥10%) were decreased neutrophil count and anemia. Serious TRAEs were reported in 15 (15.3%) pts. Of note, only 1 (1.0%) pt had interstitial lung disease.

Conclusions: SHR-A1811 had favorable antitumor activity and acceptable safety profile in heavily pretreated HER2-expressing/mutated advanced non-breast STs, including BTC, UC, GC/GEJA, and CRC.

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657MO Recommended phase II dose (RP2D) selection and pharmacodynamic (PD) data of the first-in-human immune-stimulating antibody conjugate (ISAC) BDC-1001 in patients (pts) with advanced HER2-expressing solid tumors

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Background: BDC-1001 is an ISAC consisting of a trastuzumab biosimilar conjugated to a proprietary cell membrane impermeable TLR7/8 agonist via a non-cleavable linker. It is designed to trigger the innate immune system and generate a durable tumor-targeted adaptive immune response. We present new results from the recently completed dose-escalation study (NCT04278144).

Methods: Pts with HER2+ (protein or gene) or HER2-low solid tumors progressing after standard therapies (Txs) were enrolled. BDC-1001 was given IV q3w, q2w, or q1w as monotherapy (mono; n=94) and q2w or q1w with nivolumab 240mg q2w (combo; n=37).

Results: As of 24 March 2023, 131 pts with 16 different tumor types received 0.15 to 20mg/kg of BDC-1001. Mean age 60 yrs, median 4 prior lines of Txs (range 0-13; prior anti-HER2 67%, immune 29%). The RP2D of 20mg/kg q2w (mono/combo) was determined based on safety, efficacy, pharmacokinetic, and PD data. BDC-1001 was well tolerated as mono/combo. Grade 1/2 infusion-related reactions were the most common adverse events (30%). Clinical activity observed in multiple tumor types and doses improved as targeted Cmin ≥10mg/mL was reached, particularly at the RP2D. 6 pts (3 mono) had partial response (PR), 11 pts (9 mono) achieved stable disease (SD) ≥24 wks. Clinical benefit rate in 15 pts with HER2+ tumors at the RP2D was 47% (27% confirmed PR, additional 20% SD ≥24wks), 60% tumor shrinkage and 33% pts still on active Tx. Comprehensive plasma and fresh biopsies (bx) studies performed. PD responses in plasma and paired tumor bx (protein/gene analyses) demonstrated immune activation with BDC-1001 (e.g., IFNg, antigen processing, macrophage activation), not observed by trastuzumab treatment, and subsequent T cell recruitment in tumor tissue.

Conclusions: Our novel ISAC BDC-1001 (mono/combo) led to tolerable, encouraging efficacy, translational biomarker data consistent with novel MOA in pts with pretreated HER2+ tumors, particularly at the 20mg/kg q2w RP2D. International phase 2 expansions in HER2+ colorectal, gastroesophageal, and endometrial cancers and a new phase 2 in breast cancer (BDC-1001 ± pertuzumab) have been initiated.

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658MO Phase I study of SHR-A2009, a HER3-targeted ADC, in advanced solid tumors

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Background: HER3 is widely expressed in solid tumors and associated with tumor growth/spread, drug resistance and poor prognosis. SHR-A2009 is a novel ADC composed of a fully human anti-HER3 IgG1 mAb, cleavable peptide linker and DNA topoisomerase I inhibitor. We report preliminary results from the first-in-human, multinational phase 1 trial of SHR-A2009 in patients (pts) with advanced solid tumors refractory to standard therapy.

Methods: SHR-A2009 was given at doses of 1.5-10.5 mg/kg (Q3W, iv) in an i3+3 dose escalation scheme, followed by cohort expansion at selected doses. The primary endpoints were MTD/MAD, RP2D and safety.

Results: At data cutoff (Apr 24, 2023), 42 pts were enrolled (ECOG 1, 83.3%; stage IV, 100%; NSCLC, 85.7%; brain metastasis, 31.0%); median prior lines of systemic therapy was 3 (range, 1-11). Among 36 NSCLC pts, 34 (94.4%) had *EGFR* mutations; all were resistant to EGFR-TKI, with 85.3% (29/34) previously treated with 3rd generation agents. Up to 10.5 mg/kg, no DLT was observed; dose-escalation is ongoing. Grade≥3 TRAEs were reported in 13 (31.0%) pts, with all occurring in ≥5% being hematotoxicities. TRAEs led to drug discontinuation in 3 (7.1%) pts. Interstitial lung disease occurred in 2 (4.8%) pts. In evaluable pts, ORR was 25.0% (9/36; 95% CI 12.1-42.2) across all tumor types and 30.0% (9/30; 95% CI 14.7-49.4) in NSCLC; median DoR was 7.0 mo (range, 2.8-8.5) in both pt sets. Tumor response by dose is shown in the table. 1. 6-mo PFS rate was 46.4% (95% CI 27.0-63.8) across all tumors and 49.8% (95% CI 28.8-67.8) in NSCLC. Systemic exposure of SHR-A2009, total antibody and free toxin increased approximately dose proportionally after single/multiple doses at 1.5-9.0 mg/kg; plasma toxin exposure was low across all levels (data not available for 10.5 mg/kg).

Conclusions: SHR-A2009 showed a tolerable safety profile and encouraging anti-tumor activity in pts with heavily pretreated advanced solid tumors. The trial is ongoing to assess SHR-A2009 at higher doses and in selected cancer types (NSCLC and other solid tumors).

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Table: 658MO Tumor response by dose

	1.5 mg/kg	3.0 mg/kg	4.5 mg/kg	6.0 mg/kg	7.5 mg/kg	9.0 mg/kg	10.5 mg/kg	Total
All tumors, n	3	3	3	11	3	13	0	36
ORR*, n (%)	0	1 (33.3)	1 (33.3)	3 (27.3)	1 (33.3)	3 (23.1)	0	9 (25.0)
DCR, n (%)	2 (66.7)	2 (66.7)	3 (100)	6 (54.5)	2 (66.7)	11 (84.6)	0	26 (72.2)
Median DoR (range), mo	NE	NE	7.0 (7.0-7.0)	5.7 (2.8-8.5)	NE	NE	NE	7.0 (2.8-8.5)
NSCLC†, n	3	3	3	8	3	10	0	30
ORR*, n (%)	0	1 (33.3)	1 (33.3)	3 (37.5)	1 (33.3)	3 (30.0)	0	9 (30.0)
DCR, n (%)	2 (66.7)	2 (66.7)	3 (100)	5 (62.5)	2 (66.7)	9 (90.0)	0	23 (76.7)
Median DoR (range), mo	NE	NE	7.0 (7.0-7.0)	5.7 (2.8-8.5)	NE	NE	NE	7.0 (2.8-8.5)

Analyzed in pts with post-baseline assessment. *Including unconfirmed response. †*EGFR*-WT, n=2 (PR, n=1; SD, n=1). NE, not evaluable.

659MO Preliminary results from a phase I/II study of 9MW2821, an antibody-drug conjugate targeting nectin-4, in patients with advanced solid tumors

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Background: Nectin-4 is an adhesion molecule that highly expressed in variety of solid tumors and could be a potent therapeutic target. 9MW2821 is a monoclonal antibody-drug conjugate (ADC) that delivers monomethyl auristatin E to cells expressing Nectin-4. Here we report the first-in-human, multicenter, phase I/II study designed to explore the safety, pharmacokinetics and efficacy of 9MW2821 in advanced solid tumors.

Methods: 9MW2821 was administered by intravenous infusion on days 1, 8 and 15 of each 28-day cycle. The study included dose escalation, dose expansion and cohort expansion period which included urothelial cancer (UC) and other Nectin-4 positive solid tumors. Primary objectives were assessment of safety and preliminary efficacy.

Results: As of April 27, 2023, 97 patients (pts) were enrolled with doses ranging from 0.33 to 1.5mg/kg. Median age was 57 years (range, 32-78). Only 1 dose limiting toxicity of grade 4 neutropenia lasted more than 5 days was observed at 1.5mg/kg group. Maximum tolerated dose was not yet reached. Treatment related adverse events (TRAEs) of any grade occurred in 64.9% pts. The most common TRAEs were white blood cell (WBC) count decreased (36.1%), neutropenia (35.1%), nausea (22.7%), aspartate aminotransferase increased (22.7%), rash (19.6%), alopecia (19.6%), fatigue (18.6%), decreased appetite (18.6%), anemia (17.5%), vomiting (16.5%), peripheral sensory neuropathy (16.5%). Grade 3/4 TRAEs occurred in 35.1% pts. The most common grade 3/4 TRAEs were WBC count decreased (18.6%) and neutropenia (18.6%). Treatment related death was not observed. Among 39 pts treated with 9MW2821 at 1.25mg/kg or above and evaluable for tumor assessment, objective response rate (ORR) and disease control rate (DCR) was 38.5% and 84.6%, respectively. In 18 pts with UC who progressed after platinum-based chemotherapy and immune checkpoint inhibitors and dosed at 1.25mg/kg, ORR and DCR was 55.6% and 94.4%, respectively. Objective responses were also observed in pts with breast cancer and cervical cancer.

Conclusions: The results showed that 9MW2821 had manageable safety profile and promising antitumor activity. Enrollment continues to determine efficacy of 9MW2821 in certain solid tumors.

Clinical trial identification: NCT05216965.

Legal entity responsible for the study: Mabwell (Shanghai) Bioscience Co., Ltd.

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660MO First-in-human study of SGN-B7H4V, a B7-H4-directed vedotin ADC, in patients with advanced solid tumors: Preliminary results of a phase I study (SGNB7H4V-001)

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Background: B7-H4 is a B7 immune checkpoint ligand expressed at low levels in normal tissue and is upregulated in solid tumors, including breast, ovarian, and endometrial cancers. SGN-B7H4V is an investigational vedotin ADC comprising a B7-H4-directed monoclonal antibody conjugated to monomethyl auristatin E via a protease-cleavable linker. We report first results from dose escalation (Part A) of this ongoing phase 1 study.

Methods: SGNB7H4V-001 is a first-in-human, multicenter study evaluating the safety, tolerability, pharmacokinetics, and antitumor activity (objective response rate per RECIST v1.1) of SGN-B7H4V in patients with advanced solid tumors. Part A enrolled patients with histologically or cytologically confirmed locally advanced unresectable or metastatic solid tumors irrespective of B7-H4 expression. Patients received SGN-B7H4V on Days 1 and 8 of a 21-day cycle (2Q3W, 0.75, 1.0, 1.25, or 1.5 mg/kg), or on Days 1 and 15 of a 28-day cycle (2Q4W, 1.25, 1.5, 1.75, or 2.0 mg/kg).

Results: As of 10 March 2023, 75 patients were enrolled and received SGN-B7H4V. In 2Q3W (n=35), 3 patients (8.6%) had dose-limiting toxicities (DLTs) of hyperglycemia (1.25 mg/kg), arterial embolism (1.5 mg/kg), and neutropenia (1.5 mg/kg). The most common TEAEs across doses were fatigue (20.0%), peripheral sensory neuropathy (20.0%), and neutropenia (17.1%). The most common grade ≥3 TEAE was neutropenia (14.3%). In 2Q4W (n=40), 2 of 39 DLT-evaluable patients (5.1%) had DLTs of peripheral sensory neuropathy (1.5 mg/kg) and transaminitis (2.0 mg/kg). The most common TEAEs were fatigue (27.5%), peripheral sensory neuropathy (27.5%), and nausea (22.5%). The most common grade ≥3 TEAEs were anemia, dyspnea, hypotension, and pneumonia (5.0% each). Confirmed objective responses (starting at 0.75 mg/kg) were observed in evaluable patients with breast (7/25 patients), ovarian (2/15 patients), endometrial (1 [complete response]/16 patients), and biliary tract cancers (2/9 patients).

Conclusions: SGN-B7H4V showed a manageable safety profile in patients with advanced solid tumors. Responses were observed at all tested dose levels and across various tumor types. Dose expansion in select tumor types is planned.

Clinical trial identification: EudraCT 2021-002107-35, NCT05194072; Release date: 03 April 2023.

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Legal entity responsible for the study: Seagen Inc.

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661MO Anti-tumor activity of belvarafenib in combination with cobimetinib in patients with metastatic solid tumors harboring BRAF fusions or BRAF class II/III mutation

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Background: Belvarafenib (Belva) is a type II selective RAF dimer inhibitor that, in combination with Cobimetinib (Cobi) has shown clinical activity in patients with NRAS-mutant melanoma (ASCO 2021 , ESMO 2021). One cohort in this phase I trial evaluated BRAF fusions (including indel/rearrangement) or class II/III point mutations, which are considered potential therapeutic targets for Belva +/- Cobi. Here, we present findings on activity and safety of Belva and Cobi in patients with BRAF fusion including indel/rearrangement.

Methods: A total of 23 patients harboring BRAF non-canonical aberration were enrolled and treated with Belva 300mg PO BID and Cobi 20mg PO TIW (3 times a week) in the HM-RAFI-103 study (NCT03284502). Sub-cohort A (SC-A) enrolled patients with BRAF fusions and sub-cohort B (SC-B) enrolled patients with BRAF class II/III point mutations. Safety results were updated based on 133 patients who were treated with Belva and Cobi as of Jan 31, 2023.

Results: In SC-A, a total of 15 patients harboring BRAF fusions (Melanoma (10), NSCLC (3), CRC (1), Pancreatic cancer (1)) and 8 patients with BRAF class II/III point mutation were in SC-B (Biliary tract cancer (3), CRC (3), SCLC (1), Glioblastoma (1)) were enrolled. The confirmed objective response rate (ORR), assessed by investigators' assessment, for SC-A was 60.0%, median progression-free survival (mPFS) was 13.7 months, and median duration of response was 12.0 months (95% CI: 7.43 to 22.34) with median follow-up time 12.9 months, while patients in SC-B showed best response of stable disease. As of cut-off date, the most common treatment related adverse events from 133 patients is dermatitis acneiform (54.1%), rash (28.6%), and blood creatine phosphokinase increased (24.1%). No new safety signals were found.

Table: 661MO

		SC-A: BRAF fusion (N=15)	SC-B: Point mutation (N=8)
Best overall response	CR	0	0
	PR	9 (60.0)	0
	SD	5 (33.3)	4 (50.0)
	PD	1 (6.7)	4 (50.0)
ORR	n (%)	9 (60.0)	0
	95% CI	32.29, 83.66	0, 36.94
Disease control rate (PR+SD)	n (%)	14 (93.3)	4 (50.0)
	95% CI	68.05, 99.83	13.70, 78.80
mPFS	month	13.7	2.1
	95% CI	7.36, 18.23	1.61, 7.16

Conclusions: The combination of Belva with Cobi showed promising anti-tumor activity as well as durable responses in patients with BRAF fusions regardless of cancer type.

Clinical trial identification: NCT03284502.

Legal entity responsible for the study: Hanmi Pharmaceutical.

Funding: Hanmi Pharmaceurical.

Disclosure: T.W. Kim: Financial Interests, Institutional, Research Grant: Genentech. J. Lee: Financial Interests, Steering Committee Member: Seattle Genetics, AZ; Non-Financial Interests, Principal Investigator: AstraZeneca, Daiichi Sankyo, Merck MSD, BMS, Leaptherapeutics; Non-Financial Interests, Project Lead: Samsung Bioepis, Genome and Company, Oncxerna; Non-Financial Interests, Advisory Role: Mirati Therapeutics; Non-Financial Interests, Member: KSMO; Non-Financial Interests, Other, AP Council: ASCO. S. Han: Financial Interests, Institutional, Local PI: Hanmi, Genentech, Roche, Loxo, Mirati, MSD, Janssen, Lilly, Seagen, Arcus. J. Kim: Financial Interests, Personal, Invited Speaker: CJ Healthcare, AstraZeneca, GeneCKer, Sanofi/Aventis, Gencurix, Boryung; Financial Interests, Personal, Advisory Board: ABION, CJ Healthcare; Financial Interests, Personal, Member of Board of Directors: IMBdx; Financial Interests, Local PI: AstraZeneca, Boehringer Ingelheim, Sanofi, Lilly, CJ Healthcare, Hanmi, Ono Pharmaceutical, Pfizer, Novotech, Astellas Pharma, Merck, Alpha Biopharma, Yuhan, MSD, IL-Yang Pharm, AbbVie, Boryung, ChongKeunDang Healthcare, Daiichi Sankyo, BeiGene. D.H. Lee: Financial Interests, Personal, Advisory Board, honoraria for lectures and

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662MO Phase I, multi-center, dose-escalation and dose-expansion study of IMP7068, a WEE1 inhibitor, in patients with advanced solid tumors

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Background: IMP7068 is a potent and highly selective WEE1 inhibitor. Ongoing phase 1 study showed preliminary antitumor activity with a manageable safety profile in patients (pts) with advanced solid tumors.

Methods: Eligible pts were enrolled in escalation cohorts starting with 30mg (administered orally, once [QD] or twice daily [BID] for 3 days, followed by 4 days off [3/4] every week for 21-day cycles).

Results: As of April 12, 2023, 50 pts were enrolled across 10 dose cohorts (Table). Additional schedules including 2 days of dosing followed by 5 days off (2/5) and 5 days of dosing followed by 2 days off (5/2) every week were suggested by SMC after the notice of grade 3 ECG QT prolongation. The most common (>10%) treatment related adverse events were QT prolongation (28%), vomiting (16%), diarrhea (14%) and nausea (14%). 9 dose-limiting toxicities (DLTs) of grade 3 QT prolongation and pulmonary embolism were observed in 8 pts (Table). The mean QT interval prolongation in 80mg BID is lower than that in 160mg QD in schedule 3/4. 35 pts were efficacy evaluable, 1 patient with uterine serous cancer in cohort 4 has maintained complete response for 30 weeks, 18 pts had stable disease (SD), of which 1 patient with ovarian cancer in cohort 7 has maintained SD for 24 weeks. 5 pts are still on treatment. The pharmacokinetic (PK) analysis showed the exposure of IMP7068 in cohort 7 was comparable to that in cohort 4. The phosphorylated cyclin-dependent kinase 1 level in cohorts 4, 7 and 9 was reduced by ≥50% after treatment. Based on safety, PK and pharmacodynamic data, 80mg BID can be considered as a recommended phase 2 dose (PR2D) of 3/4 schedule.

Table: 662MO DLT by escalating cohorts

Cohorts	Dose (mg)	Schedules	Subject number/DLT evaluable	DLT, Subject number
1	30 QD	3/4	1/1	No
2	60 QD	3/4	1/1	No
3	120 QD	3/4	3/3	No
4	160 QD	3/4	9/9	1
5	200 QD	3/4	10/9	2
6	300 QD	3/4	3/3	3
7	80 BID	3/4	9/9	1
8	240 QD	2/5	3/3	1
9	50 BID	5/2	8/7	No
10	60 BID	5/2	3/2	No

Conclusions: IMP7068 conferred promising antitumor activity and good tolerability as QT prolongation has been mitigated by altering schedule. 80mg was defined as a potential PR2D in 3/4 schedule, and a second potential RP2D is being explored in 5/2 schedule. RP2D for IMP7068 will be determined soon.

Clinical trial identification: NCT04768868.

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663P Safety and preliminary efficacy of the KRAS G12C Inhibitor MK-1084 in solid tumors and in combination with pembrolizumab in NSCLC

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Background: We present preliminary results from a phase 1, open-label, global, dose-escalation study (NCT05067283) of MK-1084, a selective *KRAS* G12C inhibitor, as monotherapy in advanced solid tumors and in combination with pembrolizumab (pembro) for first-line metastatic NSCLC.

Methods: Eligible pts aged ≥18 y had locally advanced unresectable or metastatic solid tumors and ≥1 line of prior therapy (Arm 1), or previously untreated metastatic NSCLC with PD-L1 TPS ≥1% (Arm 2), with histologic or blood-based confirmation of *KRAS* G12C mutation, measurable disease per RECIST v1.1 and ECOG PS of 0 or 1. Pts received MK-1084 PO QD or BID (25—800 mg) as monotherapy (Arm 1) or with pembro 200 mg Q3W (Arm 2) using a modified toxicity probability dose-escalation design. Treatment continued until PD, unacceptable toxicity, withdrawal, or maximum permitted cycles (≤35 cycles for pembro; no limit for MK-1084). Primary endpoints were dose-limiting toxicities (DLTs), AEs and discontinuations due to AEs. AEs were graded per NCI CTCAE v5.0. ORR per RECIST v1.1 by investigator review was a secondary endpoint.

Results: As of Apr 5, 2023, 43 pts received MK-1084 in Arm 1 and 15 received MK-1084 plus pembro in Arm 2. Median (range) follow-up was 6.0 (0.03—14.47) mo in Arm 1 and 4.4 (0.07—10.17) mo in Arm 2. Arm 1 included 28 pts (65%) with CRC and 9 (21%) with NSCLC; 31 pts (72%) had ≥2 lines of prior therapy. No DLTs have been reported to date. AEs of any cause occurred in 36 pts (84%) in Arm 1 and 13 (87%) in

Arm 2; none led to discontinuation. Treatment-related AEs occurred in 22 pts (51%) in Arm 1 (all grade 1 or 2 except 1 pt [2%] with grade 3 increased blood alkaline phosphatase) and 11 (73%) in Arm 2 (all grade 1 or 2 except 2 pts [13%] with grade 3 pruritus, rash, and papular rash); none were grade 4 or 5. There were no grade ≥3 transaminases elevations. ORR was 19% (8/42 pts, all PR; 4 in CRC, 4 in NSCLC) in Arm 1 and 47% (7/15 pts, all PR) in Arm 2; 7 and 3 pts not yet assessed, respectively.

Conclusions: MK-1084 as monotherapy and in combination with pembro showed manageable safety and preliminary antitumor activity in pts with previously treated solid malignancies and previously untreated NSCLC whose tumors harbored *KRAS* G12C mutations. Study is ongoing; updated data will be presented.

Clinical trial identification: NCT05067283.

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664P Final results of a phase I/II study of combined BCL-xL and MEK inhibition with navitoclax and trametinib in KRAS or NRAS mutant advanced solid tumors

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Background: MEK inhibitors (MEKi) lack clinical monotherapy efficacy in most RAS-mutant cancers and typically produce only a cytostatic response in preclinical RAS-mutant cancer models. BCL-XL is an anti-apoptotic BCL2 family protein identified by a synthetic lethal shRNA screen as a key suppressor of apoptotic response to MEKi. Combined BCL-XL/MEK inhibition led to tumor regressions in mouse models of RAS-mutant cancers.

Methods: We conducted a dose escalation study (NCT02079740) of the BCL2, BCL-xL and BCL-w inhibitor navitoclax and the MEK inhibitor trametinib in patients with RAS-mutant tumors with dose expansion cohorts for (1) pancreatic cancer, (2) gynecologic (GYN) cancers, (3) non-small cell lung cancer (NSCLC), and (4) other cancers harboring NRAS mutation. Paired pre-treatment and day 15 tumor biopsies and serial cell-free (cf)DNA were analyzed.

Results: 91 patients initiated study treatment, 38 in dose escalation. Overall 58.2% had 3 or more prior therapies. 15 patients (16.5%) had colorectal cancer (CRC), 19 (10.9%) pancreatic, 15 (16.5% NSCLC, and 32 (35.2%) GYN cancers. The recommended phase 2 dose (RP2D) was established as trametinib 2mg daily days 1-14 and navitoclax 250mg daily days 1-28 of each cycle after a 7-day lead-in of navitoclax at 150 mg daily during cycle 1. The most common adverse events included diarrhea, thrombocytopenia, increased AST and ALT, and acneiform rash. At RP2D, 8/49 (16.3%) evaluable pts had a partial response (PR) with disease control rate (DCR) 59.2%. Disease-specific differences in efficacy were noted. In GYN patients at the RP2D, 7/21 (33.3%) achieved a confirmed PR, with DCR 85.7% and median duration of response of 8.2 months. By contrast, no PRs were observed in any CRC, NSCLC, or pancreatic patients. Evidence of MAPK pathway inhibition was observed in paired pre- and on-treatment tumor biopsies, and reductions in KRAS or NRAS mutation levels in cfDNA correlated with clinical benefit.

Conclusions: Navitoclax in combination with trametinib was tolerable, and the R2PD was established. Durable clinical responses were observed in patients with RAS-mutant GYN cancers, warranting further evaluation of combined BCL-XL/MEK inhibition in this population.

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665P First-in-human, phase Ia/b, dose-escalation/expansion study of KRAS G12C inhibitor BI 1823911, as monotherapy and combined with anticancer therapies, in patients (pts) with advanced or metastatic solid tumours harbouring a KRAS G12C mutation

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Background: BI 1823911, a mutant-selective KRAS G12C inhibitor, covalently binds to G12C mutant KRAS, irreversibly locking it in its inactive GDP form, interfering with cell signalling, causing tumour cell apoptosis and blocking cell proliferation. NCT04973163 is assessing BI 1823911 monotherapy and is designed to evaluate combinations with other anticancer therapies in pts with locally advanced/metastatic solid tumours with a KRAS G12C mutation.

Methods: The study has two arms (monotherapy; combination with anticancer therapies) and three parts (dose escalation, A; confirmation, B; expansion, C). Primary endpoint in Part A is number of pts with dose-limiting toxicities (DLTs) during the maximum tolerated dose (MTD) evaluation period. Primary endpoint in Parts B and C is objective response (confirmed complete or partial response [PR]). Primary objective is to ascertain the MTD/recommended phase II dose of BI 1823911, alone and in combination.

Results: As of 23rd Jan 2023, 17 pts received monotherapy in Part A (50/100/200/400/600/900/1200 mg QD, n=1/1/1/3/3/3/5); 9 male, 8 female; median age 58 years. 8 discontinued treatment (progressive disease, n=4; adverse event [AE], n=2). 3 pts had DLTs in the MTD evaluation period: G3 gastrointestinal stoma complication (n=1; 900 mg) and G3 diarrhoea (n=2; 1200 mg; 1 serious AE [SAE]). All pts experienced AEs (G3, n=8), most commonly diarrhoea (n=14) and nausea (n=14). 16 had drug-related AEs (G3, n=3; G4, n=0), most commonly diarrhoea (n=12; G3, n=3), nausea (n=12; G3 n=0) and vomiting (n=10; G3 n=0). 1 had a DLT outside the MTD evaluation period (G3 diarrhoea; 600mg; SAE). 2 had AEs leading to discontinuation; 6 had AEs leading to dose reduction. During early dose escalation (≥100 mg), 11 pts had disease control, including 8 with stable disease and 3 with confirmed PR (600 mg, n=2, lung and unknown cancer, Day 53 and 55; 900 mg, n=1, small intestine, Day 50).

Conclusions: Preliminary data suggest BI 1823911 monotherapy is generally well tolerated and offers clinical activity. Recruitment is ongoing; updated data will be presented.

Clinical trial identification: NCT04973163.

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666P Updated efficacy and safety data of entrectinib in patients (pts) with locally advanced/metastatic NTRK fusion-positive (fp) solid tumours

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Background: *NTRK* gene fusions are oncogenic drivers of various solid tumour types. Entrectinib, a potent CNS-active TRK inhibitor, yielded systemic and intracranial responses in pts with *NTRK*-fp solid tumours in previous integrated analyses of three phase I/II trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]). We present updated data with ∼30% more pts and longer follow-up (data cut-off: 2 Aug 2022).

Methods: Adults with measurable, locally advanced/metastatic *NTRK*-fp solid tumours and ≥12 months' follow-up from first on-study scan, who received ≥1 dose of entrectinib, were efficacy evaluable. The safety population comprised all pts who received ≥1 dose of entrectinib. Eligible pts from TAPISTRY (NCT04589845) were also included. Tumour responses were assessed by blinded independent central review per RECIST v1.1 at Week 4 and then every 8 weeks. Primary endpoints: objective response rate (ORR); duration of response (DoR). Key secondary endpoints: progression-free survival (PFS); overall survival (OS); safety.

Results: The efficacy-evaluable population comprised 194 pts with 17 types of solid tumours. Median age: 58 years (range 19−92); 63 (32.5%) pts received ≥2 prior lines of therapy. Median survival follow-up was 38.7 months. ORR was 62.4% (95% CI 55.2−69.2); the table shows responses in histologies with n>10. Median DoR was 29.4 months (95% CI 17.2−36.8). Median PFS and OS were 15.7 months (95% CI 13.7−22.9) and 38.2 months (95% CI 28.6−56.5), respectively. In the safety cohort (N=296), median treatment duration was 8.3 months (range 0.0−72.0). Of all pts with treatment-related adverse events (TRAEs; n=265), 57% had grade 1−2 TRAEs; dose reduction, interruption and discontinuation occurred in 24%, 34% and 6% of all pts, respectively.

Table: 666P

NTRK-fp tumour types* (n>10)	Objective response rate, n/N (%)
Total	121/194 (62.4)
CNS metastases at baseline	22/36 (61.1)
No CNS metastases at baseline	99/158 (62.7)
Non-small cell lung cancer	32/51 (62.7)
Sarcoma	23/38 (60.5)
Salivary (mammary analogue secretory carcinoma)	27/31 (87.1)
Thyroid	14/21 (66.7)
Breast	8/13 (61.5)
Colorectal cancer	4/13 (30.8)

*Other tumour types in the efficacy-evaluable cohort: neuroendocrine (n=7); head and neck (n=5); pancreatic (n=4); cancer of unknown primary (n=3); gynaecological (n=2); adrenal (n=1); cholangiocarcinoma (n=1); gastrointestinal (n=1); neuroblastoma (n=1); penile (n=1); prostate (n=1).

Conclusions: In this updated analysis, entrectinib was well tolerated and continued to induce clinically meaningful responses in pts with *NTRK*-fp solid tumours.

Clinical trial identification: EudraCT 2012-000148-88; NCT02097810; NCT02568267; NCT04589845.

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667P Efficacy and safety of larotrectinib (laro) as first-line treatment for patients (pts) with tropomyosin receptor kinase (TRK) fusion cancer

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Background: Laro is a highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumour-agnostic use in pts with TRK fusion cancer based on a rapid, robust and durable objective response rate (ORR) in both adult and paediatric pts. We report data on laro-treated pts without prior systemic therapy.

Methods: Pts with treatment-naïve non-primary CNS TRK fusion cancer from three laro clinical trials were included. Laro was administered at 100 mg twice daily in most pts. Responses were assessed per independent review committee (IRC) using RECIST v1.1.

Results: As of July 2022, 84 pts were eligible for efficacy analyses by IRC; three pts (all adults) had known brain metastases at baseline. There were 12 different tumour types; the most common were soft tissue sarcoma (n=24; 29%), infantile fibrosarcoma (n=18; 21%), thyroid (n=15; 18%) and salivary gland (n=14; 17%). Median age was 31.5 years (range 0–90). The gene fusions involved were *NTRK1* (n=30; 36%), *NTRK2* (n=3; 4%) and *NTRK3* (n=51; 61%). ORR was 80% (95% confidence interval [CI] 70–88): 42 (50%) complete response (CR; including six pathologic CR), 25 (30%) partial response, 10 (12%) stable disease, six (7%) progressive disease and one (1%) not evaluable. Median time to response was 1.8 months. Median duration of response was 44.5 months (95% CI 31.4–not estimable [NE]) at a median follow-up of 26.7 months. Medians for progression-free survival and overall survival (OS) were 46.2 months (95% CI 32.0–NE) and not reached, respectively, at median follow-ups of 30.4 and 41.3 months. The 48-month OS rate was 82% (95% CI 71–92). Treatment duration was 0–64+ months. Treatment-related adverse events (TRAEs) were mainly Grade 1/2. Grade 3/4 TRAEs occurred in 20 (24%) pts. Two pts discontinued due to a TRAE (malaise and hypoventilation occurred in one pt each).

Conclusions: Laro demonstrated rapid and durable responses, extended survival and a favourable safety profile in pts without prior systemic therapy. This supports the use of laro in a first-line setting and the wider adoption of next-generation sequencing panels that include *NTRK* gene fusions to identify pts who may benefit from treatment.

Clinical trial identification: NCT02576431, NCT02122913, NCT02637687.

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668P Efficacy and safety of larotrectinib in a pooled analysis of patients (Pts) with tropomyosin receptor kinase (TRK) fusion cancer

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Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumour types. Larotrectinib is a highly selective, central nervous system-active TRK inhibitor, approved to treat pts with TRK fusion cancer. We report updated efficacy and safety data in an expanded dataset of pts with longer follow-up.

Methods: Data were pooled from 3 clinical trials (NCT02576431, NCT02122913, NCT02637687) of pts with TRK fusion cancer treated with larotrectinib. Responses were assessed by independent review committee (IRC) per RECIST v1.1.

Results: As of 20 July 2022, a total of 289 pts (median age 44 years [range 0—90]) were included. There were 26 different tumour types, including soft tissue sarcoma (24%), infantile fibrosarcoma (17%), thyroid (10%), and lung (10%). Pts received a median of 1 prior line of systemic therapy, with 124 (43%) pts receiving ≥2. Among 274 IRC-eligible pts, the objective response rate was 66% (95% CI 60—72): 75 (27%) complete response (CR), including 13 (5%) pathological CR (pCR); 107 (39%) partial response (PR); 49 (18%) stable disease; 26 (9%) progressive disease; and 17 (6%) not evaluable. Median duration of response was 43.3 months (mo; 95% CI 31.4—54.7) at a median follow-up of 31.5 mo. Median progression-free survival was 30.8 mo (95% CI 22.5—36.1) at a median follow-up of 31.3 mo. Median overall survival (OS) was not reached; 48-mo OS rate was 65%. Pts were treated for up to 75+ mo. At data cut-off, 108 pts had progressed; 46 continued treatment post-progression for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were mainly Grade 1/2; 59 (20%) pts had Grade 3/4 TRAEs. Five (2%) pts discontinued due to TRAEs. In a 5-year long-term follow-up analysis of the original 55 pts from the July 2018 primary data cut-off, 8 pts had an improved best overall response from PR to CR (or pCR), with a total CR rate of 27%.

Conclusions: Larotrectinib continued to demonstrate rapid and durable responses, extended survival benefit, and a favourable safety profile. This supports the wider adoption of next-generation sequencing panels that include *NTRK* gene fusions to identify pts who may benefit from treatment.

Clinical trial identification: NCT02576431, NCT02122913, NCT02637687.

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669P Patient-reported outcomes with selpercatinib in patients with RET-driven cancers in the phase I/II LIBRETTO-001 trial

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Background: Selpercatinib, a first-in-class highly selective and potent rearranged during transfection (*RET*)-inhibitor, demonstrated efficacy in treatment of *RET*-driven cancers in the phase 1/2 LIBRETTO-001 trial. We report patient-reported outcomes for non-small cell lung cancer (NSCLC), medullary thyroid cancer (MTC), non-MTC thyroid cancer (TC) (15 Jun 2021, data cut-off date) and tumor agnostic (TA) cohorts (24 Sep 2021, data cut-off date).

Methods: Patients completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (QLQ-C30) at baseline (BL), approximately every 8 weeks until cycle 13, and then every 12 weeks until end of treatment (EoT). Subscales were scored 0—100; higher scores indicate better functioning or more severe symptoms based on the subscale. Proportion of patients with improved, stable, or worsened status post-BL was assessed. For symptom subscales improved is 10-point decrease from BL, worsened is 10-point increase from BL, and stable is being within 10 points from BL. For other subscales improved is 10-point increase from BL, worsened is 10-point decrease from BL, and stable is being within 10 points from BL.

Results: For patients with NSCLC, MTC, TC, and TA, respectively, 200 (63%), 208 (71%), 32 (70%), and 28 (68%) patients completed BL assessment; compliance rate was 85%,

87%, 72%, and 86%. BL functional domain subscale scores were >65 points across cohorts. Mean (SD) BL global health status (GHS) scores were: NSCLC — 62 (24), MTC — 65 (24), TC — 73 (20), and TA — 59 (26). The highest BL symptom scores (mean [SD]) were: NSCLC — fatigue (37 [26]) and dyspnea (30 [29]), MTC — diarrhea (42 [38]) and fatigue (36 [27]), TC — insomnia (28 [27]) and fatigue (27 [24]), and TA — fatigue (40 [29]) and appetite loss (37 [36]). Change in post-BL status varied across cohorts (Table).

Table: 669P

		Proportion of patients with post-BL response (Cycle 3 to EoT), mean (SD)
NSCLC		
GHS	Improved	42 (9)
	Stable	42 (10)
	Worsened	17 (8)
Fatigue	Improved	44 (7)
	Stable	27 (5)
	Worsened	29 (9)
Dyspnea	Improved	34 (6)
	Stable	57 (5)
	Worsened	9 (4)
MTC		
GHS	Improved	37 (7)
	Stable	45 (4)
	Worsened	19 (7)
Fatigue	Improved	46 (6)
	Stable	28 (5)
	Worsened	26 (8)
Diarrhea	Improved	53 (5)
	Stable	35 (3)
	Worsened	12 (4)
TC		
GHS	Improved	21 (9)
	Stable	54 (8)
	Worsened	25 (6)
Fatigue	Improved	39 (10)
	Stable	32 (14)
	Worsened	30 (11)
Insomnia	Improved	24 (14)
	Stable	56 (7)
	Worsened	21 (13)
TA		
GHS	Improved	39 (10)
	Stable	44 (8)
	Worsened	17 (4)
Fatigue	Improved	49 (12)
	Stable	19 (9)
	Worsened	33 (11)
Appetite loss	Improved	44 (9)
	Stable	51 (13)
	Worsened	5 (6)

Conclusions: The majority of patients with *RET*-driven cancers remained stable or improved on most QLQ-C30 domains during treatment with selpercatinib.

Clinical trial identification: NCT03157128.

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670P Preliminary efficacy and safety of tinengotinib (TT-00420) monotherapy in Chinese patients (pts) with advanced solid tumors: Results from a phase Ib/II study

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Background: Tinengotinib is a spectrum-selective multi-kinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting Aurora kinases A/B, Janus kinases and receptor tyrosine kinases (FGFRs and VEGFRs). Tinengotinib has shown promising clinical signal in solid tumors from several studies globally. Here we present the interim data from a phase Ib/II trial in China.

Methods: Pts with advanced/metastatic solid tumors were enrolled and treated with tinengotinib in 21-day cycle. Monotherapy and combination therapy with dose escalation (phase Ib) and dose expansion (phase II) were designed.

Results: As of 5-Mar-2023, thirty-three (33) pts have received tinengotinib monotherapy. Median age was 58.0 years (29-81), 66.7% were male, 81.8% had ECOG of 1, 87.9% had stage IV disease, 69.7% had ≥3 lines of prior therapies. No DLT was observed in phase Ib (3 pts in each group of 8, 10, 12 mg QD). 10 mg QD was selected as RP2D. Treatment-related AEs (TRAEs) were reported in 30 (90.9%) pts, Gr 3 in 14 (42.4%), Gr 4 in 1 (3.0%), and no Gr 5. The most common TRAEs (≥30%) included abnormal laboratory parameters (blood thyroid stimulating hormone increased, white blood cell count decreased, neutrophil count decreased, aspartate aminotransferase increased, alanine aminotransferase increased), palmar-plantar erythrodysaesthesia syndrome and anaemia. Among 22 efficacy-evaluable pts, the median Progression-free survival (PFS) have reached 6.70 (95% CI, 3.22-NA) months. For 19 pts with measurable target lesions, the overall response rate (ORR) and disease control rate (DCR) were 15.8% and 89.5%, respectively. For 4 CCA pts harboring FGFR2 alteration, ORR was 50%, DCR was 100%. One responder with prior treatment of erdafitinib achieved tumor reduction of 44%, the other with no prior FGFR inhibitor treatment achieved 69% reduction.

Conclusions: Tinengotinib monotherapy was well-tolerated in Chinese pts and 10 mg QD was selected as RP2D. Promising efficacy has been observed, especially in CCA with FGFR2 alteration. The ongoing study is to further evaluate the safety and efficacy of monotherapy and combination therapy.

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671P Safety and efficacy of PM060184 plus gemcitabine in advanced solid tumors

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Background: PM060184 (PM) induces depolymerization of tubulin fibers with disorganization and fragmentation of the microtubule network leading to mitosis. PM combined with gemcitabine (GEM) showed synergistic antitumor activity in preclinical studies.

Methods: This dose-ranging, phase I trial evaluated the safety, pharmacokinetics (PK) and efficacy of PM 10-min infusion plus GEM 30-min infusion, both on Day 1 and 8 in 3-week cycles, in eligible patients (pts) with advanced pretreated solid tumors. Tumors were assessed every 6 weeks until Cycle 4, and every 9 weeks thereafter. Adverse events (AEs) were graded per NCI-CTCAE v.4.

Results: 57 pts were enrolled into 8 dose levels (DLs). 74% were females, 74% had ECOG PS1; median age was 62 years; median number of prior lines of therapy was 3 (range, 1-7). Dose-limiting toxicities in Cycle 1 were grade (G) 3 peripheral sensory neuropathy, G3 abdominal pain, G3 intestinal obstruction (at the MTD), and G4 thrombocytopenia (1 pt each). The highest DL (DL8: PM 10.5 mg/m^2 + GEM 1000 mg/m^2) was the MTD. Accrual into DL7 (PM 10.0 mg/m^2 + GEM 1000 mg/m^2) was stopped before it was formally defined as the RD. Most common treatment-related non-hematological AEs at all DLs were fatigue (56%), nausea (55%), diarrhea (31%), decreased appetite and vomiting (27% each). Most of these AEs were G1/2 and none reached G4; most common G3 AEs were fatigue (3 pts), nausea, vomiting and abdominal pain (2 pts each). G3/4 hematological toxicities comprised anemia (35%), neutropenia (27%) and thrombocytopenia (17%). No treatment-related deaths occurred. Mean PK parameters for PM at DL7 in Cycle 1 were maximum concentration 665 μg/L, area under curve 430 h*mg/L and half-life 4 h. PK parameters for GEM or dFdU at all DLs were in line with reference values from the literature. 6/46 evaluable pts were responders (overall response rate [ORR]: 13%) and 12/46 pts had stable disease (SD) >4 months (disease control rate: 39%) at all DLs and tumor types. Of note, 2 partial responses and 2 SD >4 months occurred among 13 pts with ovarian cancer.

Conclusions: The combination of PM and GEM is well tolerated. The MTD was PM 10.5 mg/m^2 + GEM 1000 mg/m^2. No PK drug-drug interaction was found. While ORR was modest overall, the most encouraging outcome occurred in ovarian cancer pts.

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672P Phase I/II trial of RVU120 (SEL120), CDK8/CDK19 inhibitor in patients with relapsed/refractory metastatic or advanced solid tumors

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Background: CDK8 and its paralog CDK19 are part of the mediator complex connecting enhancers and core promoters and regulating genes responsible for oncogenic transformation and differentiation. RVU120 is a selective CDK8/19 inhibitor, currently in phase 1 clinical development. RVU120 showed strong anticancer activity in non-clinical cancer models.

Methods: In the ongoing phase I/II study (NCT05052255), patients with metastatic or locally advanced solid tumors receive RVU120 until disease progression or unacceptable toxicity. Primary objectives are safety, tolerability, and determination of the recommended phase 2 dose. Secondary objectives include ORR, pharmacokinetic and pharmacodynamics. Molecular response to RVU120 is assessed by genetic profiling of tumor biopsies and ctDNA. NanoString technology is used for transcriptional profiling of tumor biopsies.

Results: As of 01 May 2023, there were 30 patients treated across 7 cohorts (75 - 375 mg). The most frequent AEs were nausea and vomiting, all were G1 or 2. No patient experienced a DLT, 10 SAEs were reported in 6 patients (worsening of tumoral pain, urinary tract infection, medullary compression, lower GI bleeding, worsening of basal ataxia/dizziness, renal calculi, stroke). One patient died following an SAE of general physical health deterioration due to PD. No SAE was considered IMP related. A total of 15 patients had at least 1 RECIST assessment: 2 PD (21% and 26% increase in TL size), 13 radiologic SD (between -4% and +11% change in TL size). Out of these, a patient with refractory pancreatic cancer achieved a reduction of CA19.9 on 3 consecutive time points and radiologic SD after cycle 3. Pharmacodynamic profiling of all patients revealed target engagement of >70% at doses up to 375 mg. Data from genetic and transcriptomic profiling will be presented.

Conclusions: After 7 dose levels with single agent RVU120 (up to 375 mg), a favorable safety profile was observed. Most TEAEs were mild/moderate, no DLTs nor IMP related SAEs were reported. RECIST assessments of 15 patients demonstrated radiologic SD in 13 patients. Dose escalation is currently ongoing with PK modeling indicating high target engagement.

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673P A phase I dose-escalation and expansion study evaluating the safety and efficacy of the MDM2−p53 antagonist brigimadlin (BI 907828) in patients (pts) with solid tumours

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Background: BI 907828, a highly potent mouse double minute-2 (MDM2)-p53 antagonist, has shown potent preclinical antitumour activity. This phase I study is evaluating BI 907828 in pts with advanced solid tumours. Here we report safety and efficacy for all pts who received BI 907828 once every 3 weeks (Q3W).

Methods: During dose escalation (phase Ia), pts received escalating doses of BI 907828 on day 1 of 21-day cycles (Q3W) or days 1 and 8 of 28-day cycles; recommended dose for expansion (RDE) was 45 mg Q3W (Gounder et al, ESMO 2021). During dose expansion (phase Ib), pts were enrolled in Cohort 1 (*TP53*wt, *MDM2*-amplified liposarcoma) or Cohort 2 (other *TP53*wt, *MDM2*-amplified solid tumours). Primary endpoint was progression-free survival (PFS); secondary endpoints included objective response and the number of pts with grade ≥3 treatment-related adverse events (TRAEs).

Results: At data cut off (April 2023), 140 pts had been enrolled to receive BI 907828 Q3W (29 in phase Ia; 111 in phase Ib); 78 (55.7%) were male, 77/62 (55.0%/44.3%) had ECOG PS 0/1, the median number of prior systemic therapies was 2. Of the 140 pts who received BI 907828 Q3W, 130 (92.9%) and 65 (46.4%) had any-grade and grade ≥3 TRAEs, respectively. The most common any-grade TRAEs were nausea (73.6%) and fatigue (57.9%). The most common grade ≥3 TRAEs were neutropenia (26.4%), thrombocytopenia (22.9%) and anemia (12.1%). Forty pts had serious AEs; the most common were thrombocytopenia (n=5), nausea, pulmonary embolism and neutropenia (n=4 each). At data cut off, 16/140 pts (11.4%) had a confirmed partial response (PR), and 89 pts had stable disease (SD), giving a disease control rate (DCR; at least SD) of 75.0%. Preliminary median PFS was 7.8 months; 36 pts (25.7%) had PFS >6 months. A total of 10 pts with advanced biliary tract cancer (BTC) received BI 907828 Q3W; of these, 3 (30%) had a confirmed PR and 5 had SD (DCR 80%). Two pts with BTC achieved PFS >12 months.

Conclusions: BI 907828 demonstrated antitumour activity and a manageable safety profile in pts with advanced solid tumours, including those with BTC; dose expansion is ongoing. BI 907828 is being further assessed in pts with BTC in the phase IIa/IIb open-label Brightline-2 trial (NCT05512377).

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674P Response of thrombopoietin receptor agonists in MDM2 inhibitor induced thrombocytopenia

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Background: MDM2 targets p53 for proteasomal degradation and has been exploited as a therapeutic target. Clinical trials have evaluated the efficacy and safety of MDM2 inhibitors (MDM2i), with thrombocytopenia being recognized as a class effect. Thrombopoietin Receptor Agonists (TPO-RAs) have been shown to improve thrombocytopenia secondary to chemotherapy, but their role in thrombocytopenia induced by MDM2 inhibition remains unclear.

Methods: Patients who were enrolled in any MDM2i clinical trial were identified from February 2014 to March 2023 at MSKCC. Patient characteristics and safety outcomes were collected from medical record. Statistical analysis consisted of the Mann-Whitney test.

Results: 113 Patients treated with 4 MDM2i using 8 different dosing schedules were evaluated. The median age was 59 years (range 19-89) and patients received a median of 2 (range 0-12) prior lines of therapy. Forty eight percent of patients had liposarcoma, with the remaining 52% having other solid tumors. Thrombocytopenia of any grade were present in 50% of patients, and of these, 26% were grade 3-4. Thirteen patients who experienced grade 3-4 thrombocytopenia were evaluated for response to any TPO-RA. Among these patients, the median time to platelet recovery, defined as achieving a platelet count of 75 k/mcl or higher, was 36 days (95% CI: 11-37) in 11 patients who received a TPO-RA vs. 16 days (95% CI: 9-21) in 14 patients who did not receive a TPO-RA (p=0.085). Dose reductions occurred in approximately 45% of patients who experienced grade 3-4 thrombocytopenia, 24% of whom received a TPO-RA vs. 21% who did not receive a TPO-RA. Dose interruptions occurred in 97% of all patients who experienced grade 3-4 thrombocytopenia. Two patients in the TPO-RA cohort and one patient in the non-TPO-RA cohort never achieved a platelet count above 75 k/mcl. No reports of severe bleeding or thromboembolism were observed in the TPO-RA cohort.

Conclusions: In this retrospective study with a heterogenous patient population, no significant difference in days to resolution of grade 3-4 thrombocytopenia secondary to an MDM2i was observed in those who received TPO-RAs. The role of TPO-RAs in this setting warrants further investigation.

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675P A phase I study of safety, pharmacokinetics, and pharmacodynamics of SCR-6920, a protein arginine methyltransferase 5 (PRMT5) inhibitor, in patients with advanced malignant tumors

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Background: SCR-6920, a highly potent and selective PRMT5 inhibitor, demonstrates anti-tumor effect in multiple tumor models. SCR-6920 observed a better anti-tumor effect and lower target-related hematological toxicity in pre-clinical studies. Evaluation on pharmacokinetics (PK), pharmacodynamics (PD) and safety in clinic were ongoing in the phase I study.

Methods: Patients with advanced malignant tumors were enrolled in this phase I study (NCT05528055) with the guidance of the Bayesian Optimal Interval (BOIN) design for dose escalation. Patients received oral SCR-6920 once daily (QD) on a 21-day cycle. Safety, PK, PD, and preliminary efficacy were evaluated to identify the recommended phase II doses (RP2D).

Results: As of 25 February 2023, twenty-one patients were enrolled and dosed from 10 to 160 mg QD. The most common tumor types were non-small cell lung cancer (NSCLC) (28.6%), ovarian cancer (OC) (23.8%), cervical cancer (23.8%). Seventeen patients (81%) experienced treatment-related adverse events (TRAEs). Most common ($\geq$10%) TRAEs included anaemia (47.6%), white blood cell count decreased (23.8%), hypoalbuminaemia (23.8%), and neutrophil count decreased (23.8%). Grade 3 TRAEs included anaemia (9.5%), alanine transaminas increased (4.8%), aspartate aminotransferase increased (4.8%), lymphocyte count decreased (4.8%), and chronic colitis (4.8%). No dose-limiting toxicity (DLT) and grade 4 or 5 TRAE were reported. Six patients had serious adverse events (SAEs), and only chronic colitis was treatment related. Available PK indicated fast absorption with median T_{max} less than 1 hour. Concentration-dependent blood-to-plasma partition was observed in clinical led to a non-linear blood and plasma PK from 10 to 160 mg QD. The terminal half-life was $<$1 day and $>$ 3 days in plasma and blood respectively. The major metabolite SCR-6959 accounted for 30$\sim$80% from SCR-6920. Plasma symmetric dimethyl arginine (SDMA), the enzymatic product of PRMT5 was significantly reduced (inhibitory rate: 52.8%$\sim$77.4%) at steady state.

Conclusions: SCR-6920 had a manageable safety profile and further assessments are ongoing to determine the RP2Ds.

Clinical trial identification: NCT05528055.

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676P Preclinical characterization of novel peptide binders for EphA2-targeted radiopharmaceutical therapy

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Background: EphA2 is a transmembrane glycoprotein, primarily involved in tissue patterning during embryonic development, and its expression levels are low or absent in normal adult tissues. EphA2 overexpression has been observed in multiple cancers, and is often associated with poor prognosis. The broad overexpression in solid tumors and relatively low expression in normal adult tissues make EphA2 attractive for targeted radiopharmaceutical therapy.

Methods: RAYZ-6114 is comprised of a peptide binder to EphA2, a linker, and DOTA chelator that can be complexed with different isotopes. RAYZ-6283 differs from RAYZ-6114 only in the linker. The binding affinity, selectivity and cross-species reactivity to EphA2 and other Ephrin proteins were determined by SPR. Internalization was measured using flow cytometry. In vivo biodistribution and anti-tumor efficacy studies were performed in nude mice. For tumor type identification, EphA2 IHC was performed on tumor microarrays representing diverse tumor types.

Results: IHC analyses confirmed EphA2 expression in a multitude of tumors, with the highest positivity rates in cervical, pancreatic, bladder, colorectal, esophageal and lung cancers. RAYZ-6114 showed potent binding to human EphA2 (K_D=0.03 nM), which was conserved across mouse and cynomolgus monkey EphA2. No binding to other Ephrin type-A or Ephrin type-B proteins was detected. The binder internalized in EphA2+ H1299 cells, with $\sim$75% internalized by 1 hour. In PC3 xenograft mice, ^{177}Lu-RAYZ-6283 showed sustained tumor uptake ($\sim$25% ID/g) for up to 48 hours and tumor/kidney ratios of 2.7, 3.3, and 5.9 at 24h, 48h, and day 7, respectively. Low uptake was seen in other normal tissues. Both ^{177}Lu- and ^{225}Ac- labelled RAYZ-6114 significantly inhibited tumor growth. Particularly, durable tumor regression and survival benefit were achieved by a single dose of ^{225}Ac-RAYZ-6114 (3 uCi), out-performing ^{177}Lu-RAYZ-6114 dosed at 3 mCi. All treatments were well tolerated.

Conclusions: RAYZ-6114 and RAYZ-6283 are first-in-class, highly potent and selective macrocyclic peptide binders. Preclinical pharmacodynamic, pharmacokinetic, biodistribution and efficacy data demonstrated their potential for treatment of patients with EphA2-positive tumors.

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677P Preliminary findings from a phase I, open-label, dose-finding study of SNB-101 in patients with advanced solid tumors

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Background: SNB-101 is a nanoparticle lyophilized injection of SN-38 (active metabolite of irinotecan), using polymer micelle technology, that is being developed to treat advanced solid tumors. The aim of this phase 1, dose-escalation study (SNB-101 101; NCT04640480) is to determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SNB-101 in patients (pts) with advanced solid tumors.

Methods: SNB-101 101 is a 6-cohort, open-label, dose-escalation study with an estimated enrollment of up to 36 pts. Key eligibility criteria: age $\geq$18y; histologically/cytologically confirmed, locally advanced/metastatic disease progressing after standard systemic treatment; not suitable for complete surgical resection; measurable/evaluable disease (RECIST 1.1); ECOG PS 0/1. Pts receive SNB-101 i.v. (5/8 to 50/80 mg/m^2 SN-38/irinotecan HCl) d1&15 q28d, until progressive disease, unacceptable toxicity, death or consent withdrawal. An independent safety review committee determines dose escalation/de-escalation/modification and MTD/RP2D. Key efficacy outcomes: objective response rate (ORR); disease control rate (DCR); progression-free survival (PFS); overall survival (OS). Pharmacokinetic (PK) analysis of SN-38 and irinotecan is also performed.

Results: As of April 28, 2023, 21 pts have been enrolled/are evaluable. Most common treatment-related AEs: neutropenia (61.9%); white blood cell decreased (28.6%); nausea (23.8%); anemia (19.0%); platelet count decreased (19.0%). Most frequent grade 3/4 AEs: neutropenia (33.3%); white blood cell decreased (14.3%); platelet count decreased (9.5%). MTD was not reached after dose escalation at all planned doses. ORR is 14.3% and DCR is 42.9%, with 3 partial responses (SCLC, NSCLC, rectal) and 6 pts with stable disease (NSCLC, SCLC, tonsil, gastric x2, rectal). Median PFS and OS are 1.9 and 6.1 months, respectively. PK of SN-38 and irinotecan appears dose dependent.

Conclusions: SNB-101 was well tolerated; despite relatively high rates of hematological AEs, neutropenia was manageable. SNB-101 demonstrated antitumor efficacy, which appeared to be dose dependent. A phase 1b/2a trial combining SNB-101 with immunotherapy is planned.

Clinical trial identification: NCT04640480.

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678P ExoDS: A bioengineered exosome-based capsule for targeted delivery of chemotherapy drugs to cancer cells and cancer stem cells

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Background: Cancer stem cells (CSCs) are the major cause of therapy failure. CSCs are responsible for cancer relapse, metastasis, chemo-resistance, and radiation resistance. Therefore, targeting CSCs is imperative for better therapy outcomes. To date, there is no therapy precisely targeting CSCs. To fill these lacunae we have developed ExoDS a bioengineered exosome-based platform to precisely deliver chemotherapy drugs directly to CSCs effectively eliminating them.

Methods: ExoDS is an exosome-based platform that has been isolated and purified from immune cells that have been treated with a patented bioformulation and the specific drug to be incorporated within exosomes. To test the efficacy of ExoDS in targeting CSCs, we first generated and isolated CSCs from breast cancer cell lines, MCF7, MDA-MB-231, and MDA-MB-468. We next isolated CSCs from chemo-naïve breast tumor tissue samples to test the efficacy of ExoDS in targeting breast CSCs. We extensively used flow cytometric dependent analysis of AnnexinV to determine apoptosis in CSCs.

Results: Our results have shown that ExoDS can specifically identify and target CSCs with a 12-fold higher efficiency as compared to free drugs. At a cellular level, we established that ExoDS gets internalized inside CSCs within 6hrs of treatment. ExoDS was also found to target CTCs isolated from patient blood (n=5). Further analysis revealed that ExoDS spared healthy PBMCs isolated from healthy donors (n=9) as well as breast cancer patients (n=7). Our data confirmed that ExoDS can reduce chemotoxicity by more than 30%. Broadly, our results highlight the benefits of using ExoDS as compared to free chemotherapy drugs. ExoDS is a potential chemotherapy alternative.

Conclusions: Collectively, ExoDS efficiently targeted CSC in-vitro and also ex-vivo. Its specificity towards CSCs was established by the inability of ExoDS to target PBMCs derived from healthy individuals as well as patients. ExoDS can potentially target CSCs in a clinical setting making it a first-of-its-kind therapy vehicle. Targeting CSCs will revolutionize cancer treatments and will lead to better therapy outcomes. Currently, we are testing ExoDS in murine models to test it's in vivo efficacy and efficiency.

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679P Lurbinectedin (LRB) pharmacokinetics (PK) and safety when co-administered with itraconazole (ITZ) in patients with advanced solid tumor

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Background: LRB is a highly selective inhibitor of oncogenic transcription primarily metabolized by CYP3A4. This study investigated whether the PK and safety profile of LRB is affected by co-administration with ITZ, a strong CYP3A4 inhibitor, in adult patients with advanced solid tumors.

Methods: This was a 2-part crossover, open-label, phase Ib drug-drug interaction study (NCT05063318). In Part A, 3 patients were assigned to sequence 1 (TR) receiving a cycle (C) 1 of LRB (0.8 mg/m^2, 1 hour [h], iv) co-administered with ITZ (200 mg/day oral; 12-days), followed by a C2 of LRB alone (3.2 mg/m^2, 1 h, iv). In Part B, 11 patients were randomized (1:1) to receive either sequence 1 (TR) or 2 (RT). Plasma samples for LRB and ITZ PK were collected.

Results: 11 patients were evaluable for the primary objective of the study: 3 patients in Part A and 8 patients in Part B (4 in each of sequences 1 and 2). The systemic exposure of LRB was increased [15% for C_{max}, 2.4-fold for AUC_{0-t} and 2.7-fold for $AUC_{0-\infty}$] with ITZ co-administration. This correlated with reduced clearance (CL) by 63% and prolonged elimination half-life ($t_{1/2}$) by 2.2-fold. Co-administration with ITZ produced statistically significant modifications in the unbound plasma LRB PK parameters of similar extent than in total plasma with a 2.2-fold and 2.4-fold increase in AUC_{0-t} and $AUC_{0-\infty}$, respectively compared to LRB alone. Unbound LRB CL decreased by 58% and $t_{1/2}$ was 2-fold longer. Consistent with previous studies, the most common treatment-related adverse events of LRB alone at dose of 3.2 mg/m^2 were neutropenia, nausea, vomiting and fatigue. Safety profile of LRB at a dose of 0.9 mg/m^2 when co-administered with ITZ was no worse than that of LRB administered alone at 3.2 mg/m^2.

Conclusions: In comparison with LRB alone, the co-administration with multiple doses of ITZ, significantly altered LRB systemic exposure reducing total plasma (by 63%) and unbound (by 58%) LRB CL. The magnitude of these changes showed a clinically relevant effect of ITZ co-administration on LRB PKs. To avoid LRB overexposure and a worst safety profile when co-administered with strong CYP3A4 inhibitors a LRB dose reduction proportional to CL reduction should be applied.

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Legal entity responsible for the study: PharmaMar.

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680P First results from the phase I trial of the ATR inhibitor, ART0380, in advanced solid tumors

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Background: Ataxia telangiectasia and Rad3-related (ATR) is a critical protein in sensing DNA damage and activating the DNA damage checkpoint. ART0380 is a potent and selective, orally administered ATR inhibitor. This is the first report of the ongoing phase I trial (NCT04657068).

Methods: Patients (pts) with advanced solid cancers received escalating doses of ART0380 on a continuous daily (QD) or intermittent (3 days on, 4 days off) schedule. Investigators were guided to enroll pts with cancers that harbored DNA damage response deficiencies as identified by the Artios DcoDeR platform. Key study objectives included evaluation of safety and tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics.

Results: 49 pts were dosed with ART0380 monotherapy: 39 pts on intermittent doses between 100mg and 1200mg, and 10 pts on QD doses of 200mg and 400mg. PK data show ART0380 is rapidly absorbed followed by immediate decline to a low level succeeded by a longer mean elimination half-life of 8.3 hours. ART0380 exposure is dose proportional with increasing dose from 100mg to 1200mg in terms of Cmax and AUC0-24ss. The recommended phase II doses have been established as 600mg intermittent and 200mg QD. Approximately 36% of pts experienced the only Grade 3 treatment-related adverse event of anemia. Pts on QD dosing experienced fewer unplanned dose interruptions due to adverse events compared to intermittent dosing. Confirmed partial responses were observed in 3 pts with endometrial adenocarcinoma and 1 pt with anal cancer. One pt with cholangiocarcinoma had a profound reduction in their tumor marker associated with a reduction in non-measurable disease. There was a 25% confirmed objective response rate in pts with measurable disease treated on the QD regimens. Target engagement was

demonstrated via γH2AX modulation in circulating tumor cells. Exploratory biomarker analysis is underway.

Conclusions: These early data demonstrate that ART0380 dosed both continuously and intermittently is well tolerated and clinically active. ART0380 has a PK profile conducive with both intermittent and continuous dosing. The DcoDeR platform enabled the successful identification of pts with cancers sensitive to ATR inhibition.

Clinical trial identification: NCT04657068.

Legal entity responsible for the study: Artios Pharma Limited.

Funding: Artios Pharma Limited.

Disclosure: K.N. Moore: Financial Interests, Personal, Advisory Board: Aadi, AstraZeneca, Alkemeres, Blueprint Pharma, Clovis, Caris, Duality, Eisai, GSK, Genentech/Roche, Immunogen, IMab, Merck, Mersana, Mereo, OncXerna, OncoNova, Novartis, Pannavance, VBL Therapeutics, Verastem, Zentalis; Financial Interests, Institutional, Research Funding: PTC Therapeutics, Eli Lilly and Company, Verastem, Merck, GSK, Genentech; Financial Interests, Institutional, Member of Board of Directors: GOG Foundation , ASCO. M.R. Patel: Financial Interests, Personal, Advisory Board: Daiichi Sankyo, Janssen, Accutar; Financial Interests, Institutional, Local PI, Institution Received Research Funding: Daiichi Sankyo. G.S. Falchook: Financial Interests, Institutional, Advisory Board, 2018 : FujiFilm; Financial Interests, Institutional, Advisory Board, 7/24/2020, 9/17/2021: Silicon; Financial Interests, Institutional, Advisory Board, 3/10/21: Navire; Financial Interests, Institutional, Advisory Board, 4/22/21: Turning Point; Financial Interests, Institutional, Advisory Board, 10/2/21: Predicine; Financial Interests, Institutional, Advisory Board, 10/26/21: Inspirna; Financial Interests, Institutional, Advisory Board, 10/28/21: Regeneron; Financial Interests, Personal, Advisory Board, 6/2010, 3/2011: EMD Serono; Financial Interests, Institutional, Advisory Board, 1/18/22 and 8/17/22: Jubilant; Financial Interests, Institutional, Advisory Board, 6/4/22: BostonGene; Financial Interests, Institutional, Advisory Board, 9/30/22: AbbVie; Financial Interests, Personal, Invited Speaker, 2019 : Total Health Conferencing; Financial Interests, Personal, Invited Speaker, 2020 : Rocky Mountain Oncology Society; Financial Interests, Personal, Other, Travel, for work and/or research related to institution, 2015: Bristol Myers Squibb; Financial Interests, Personal, Other, Travel, for work and/or research related to institution, 2011, 2012, 2013: EMD Serono; Financial Interests, Personal, Other, Travel, to present research at a conference (Cholangiocarcinoma Foundation meeting), 2018: Fujifilm; Financial Interests, Personal, Other, Travel, to present research at a conference (ESGO), 2013: Millennium; Financial Interests, Personal, Other, Travel, for work and/or research related to institution, at least once yearly: Sarah Cannon Research Institute (employer); Financial Interests, Personal, Other, Travel, to present research at a conference (WCLC), 2022: Amgen; Financial Interests, Personal, Other, Travel, to present research at a conference (ESMO), 2022: Synthorx / Sanofi; Financial Interests, Institutional, Advisory Board, Scientific advisory board 11/18/22: Teon Therapeutics; Financial Interests, Institutional, Advisory Board, 12/8/22: Merck; Financial Interests, Personal, Royalties: Wolters Kluwer; Financial Interests, Institutional, Local PI: 3-V Biosciences, Abbisko, AbbVie, ABL Bio ADC Therapeutics, Accutar, Aileron, American Society of Clinical Oncology, Amgen, ARMO/Eli Lilly, Artios, AstraZeneca, BeiGene, Bioatla, Bioinvent, Biothera, Bicycle, Boehringer Ingelheim, Celldex, Celgene, Ciclomed, Curegenix, Curis, Cyteir, Daiichi Sankyo, DelMar, eFFECTOR, Eli Lilly, EMD Serono, Epizyme, Erasca, Exelixis, GSK, Freenome, Fujifilm, Genmab, Hutchison MediPharma, IGM Biosciences, Ignyta, ImmunoGen/MarcoGenics, Incyte, Jacobio, Jounce, Kolltan, Loxo/Bayer, MedImmune, Millennium, Merck, miRNA Therapeutics, Molecular Templates, National Institutes of Health, Navire, NiKang, Novartis, OncoMed, Oncorus, Oncothyreon, Poseida, Precision Oncology, Prelude, PureTech, Pyramid, RasCal, Regeneron, Rgenix, Ribon, Samumed, Sapience, Silicon, Simcha, Strategia, Syndax, Synthorx/Sanofi, Taiho, Takeda, Tarveda, Teneobio, Tesaro, Tocagen, Turning Point, U.T. 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681P First-in-human study of ATR inhibitor IMP9064 monotherapy and in combination with PARP inhibitor senaparib in patients with advanced solid tumors

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Background: IMP9064 is a potent oral ataxia telangiectasia and rad3-related (ATR) inhibitor with anti-tumor activity demonstrated in vitro and in vivo. This ongoing first-in-human study (NCT05269316) explores IMP9064 monotherapy and in combination with senaparib (IMP4297) in patients with advanced solid tumors.

Methods: This phase I/II, open-label study aims to evaluate the safety, pharmacokinetics, anti-tumor activity, maximum tolerated dose, recommended phase 2 dose for IMP9064 monotherapy and combination with senaparib. Here, we report the preliminary results in dose escalation of monotherapy stage. Patients received IMP9064 once daily, 3 days on and 4 days off per 21-day cycle using an i3+3 dose escalation design.

Results: As of Feb 14th,2023, 16 patients were enrolled: Cohort 1 (n=1, 7.5 mg); Cohort 2 (n=1,15 mg); Cohort 3 (n=4, 30 mg); Cohort 4 (n=3, 45 mg); Cohort 5 (n=4, 80 mg); Cohort 6 (n=3, 120 mg). No dose-limiting toxicities were observed in the dose range of 7.5 to 80 mg. 10 (62.5%) patients experienced at least one treatment emergent adverse event (TEAE). TEAEs reported in 3 or more patients included nausea (25.0%), diarrhea (18.8%), fatigue (18.8%). Grade $\geq$3 TEAEs occurred in 4 (25.0%) patients. The only grade $\geq$ 3 AE related to IMP9064 was grade 3 diarrhea, which led to dose interruption and resolved within 48 hours. No drug-related death was reported. 9 of 13 evaluable patients had stable disease as their best response. A patient with advanced renal tumor from cohort 4 experienced stable disease and remains on trial with more than 7 cycles to date. In Cohort 3, a non-small cell lung cancer patient displayed a 158% ctDNA increase on C2D1, followed by a 58.2% decrease on C4D1 and an 84% decrease on C6D1 relative to C2D1. In the dose range of 7.5 to 80 mg investigated, the IMP9064 exposure increased as the dose increased; the median Tmax ranged from 1 to 3 hours, the mean elimination half-life ranged from 4 to 6 hours, and with minimal accumulation.

Conclusions: These results indicate that IMP9064 monotherapy appears to be well-tolerated and support further dose escalation. More MRD and biomarker analyses are underway.

Clinical trial identification: NCT05269316.

Legal entity responsible for the study: IMPACT Therapeutics Inc.

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Disclosure: C. Lin: Financial Interests, Personal, Other, Travel support: BeiGene, Daiichi Sankyo; Financial Interests, Personal, Advisory Board: Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo, Novartis, AbbVie, PharmaEngine, Merck KGaA, Boehringer Ingelheim; Financial Interests, Personal, Invited Speaker: Eli Lilly, Novartis, Roche; Financial Interests, Personal, Other, Travel Support: IMPACT Therapeutics. R.E. Schneider: Financial Interests, Institutional, Principal Investigator: IMPACT Therapeutics Inc. M. Gutierrez: Financial Interests, Personal, Invited Speaker: Guardant Health; Financial Interests, Personal, Stocks/Shares: COTA Healthcare; Financial Interests, Institutional, Invited Speaker: Merck, BMS, Incyte, NexCure, Pfizer, Roche/Genentech, Boehringer Ingelheim, GSB Pharma, Moderna, Eisai, Silenseed, Seattle Genetics, Regeneron, Sanofi, Johnson & Johnson, MedImmune, Checkpoint Therapeutics, Acerta Pharmaceuticals, Arcus Biosciences, Array BioPharma, Bayer, Celgene, Compass Therapeutics, Constellation Pharmaceuticals, Cyter, EMD Sereno, Fate Therapeutics, GSK, Infinity, Pharmacyclics, Synlogic, Tesaro, Vedanta. L. Shen, B. Gao, K. Chung, D.B. Doroshow, M. Millward: Financial Interests, Institutional, Principal Investigator: IMPACT Therapeutics Inc. C. Hsieh, S.X. Cai, Y.E. Tian: Financial Interests, Institutional, Leadership Role: IMPACT Therapeutics Inc. C. Xu: Financial Interests, Institutional, Member of Board of Directors: IMPACT Therapeutics Inc. L. Liu, C. Shen, B. Li, Y. Tan, C. Zhang, M. Ma, X. Chen: Financial Interests, Institutional, Member: IMPACT Therapeutics Inc. L. Li: Financial Interests, Institutional, Other: IMPACT Therapeutics Inc.

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682P Preclinical and ongoing phase I study data of the CHK1 inhibitor BBI-355 in development for patients with oncogene amplification on extrachromosomal DNA (ecDNA)

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Background: Focal high-copy number gene amplifications of oncogenes (e.g., *MYC, EGFR*) frequently occur on extrachromosomal DNA (ecDNA), highly transcribed units of circular non-chromosomal DNA. While targeted therapies have improved survival for patients with oncogene mutations, they have limited activity in most oncogene amplified cancers. We validated several drug targets essential for ecDNA function; tumor cells with oncogene amplification on ecDNA exhibit increased DNA replication stress and are hypersensitive to inactivation of checkpoint kinase 1 (CHK1). Thus, we developed BBI-355, a potential best-in-class orally available, potent (IC50 16nM), selective small molecule inhibitor of CHK1, which is in phase 1 development.

Methods: BBI-355-101 is a first-in-human, dose-escalation and dose-expansion, phase 1/2 study of BBI-355 alone or in combination with targeted therapies directed against a relevant amplified oncogene (e.g., EGFR inhibitor targeting amplified wildtype EGFR) in patients with solid tumors with oncogene amplification on ecDNA (NCT05827614).

Results: *Preclinical: In-vivo* anti-tumor activity of single agent BBI-355 was demonstrated in multiple ecDNA+ tumor models. Applying targeted therapy pressure to tumors with oncogene amplification on ecDNA induced tumor cells to evade such pressure via ecDNA-based resistance mechanisms, further increasing reliance on CHK1. Synergistic anti-tumor activity of BBI-355 in combination with agents targeting the amplified oncogenes was demonstrated in multiple *in-vivo* tumor models including: FGFR inhibitors in ecDNA+ *FGFR2* amplified gastric cancer (TGI: ∼120%) and CDK4/6 inhibitors in ecDNA+ *CDK4* amplified sarcoma models (TGI: ∼80%). *Clinical:* Safety, pharmacokinetic, predicitive biomarker, and efficacy data of the first dose levels of single agent BBI-355 will be presented for the first time at the conference.

Conclusions: The first ecDNA directed therapy, BBI-355, demonstrated significant anti-tumor activity as a single agent and in combination with targeted therapies in multiple ecDNA+ oncogene amplified tumor models. Clinical testing in patients with oncogene amplification is ongoing.

Clinical trial identification: NCT05827614.

Legal entity responsible for the study: Boundless Bio, Inc.

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Disclosure: A. Drilon: Financial Interests, Personal, Advisory Board: 14ner/Elevation Oncology, AbbVie, Amgen, ArcherDX, AstraZeneca, BeiGene, BerGenBio, Blueprint Medicines, EcoR1, Exelixis, Helsinn, Hengrui Therapeutics, Ignyta/Genentech/Roche, Janssen, Liberum, Loxo/Bayer/Lilly, Melendi, Monopteros, Monte Rosa, Novartis, Pfizer, Remedica Ltd., TP Therapeutics, Takeda/Ariad/Millennium, Tyra Biosciences, Verastem Oncology; Financial Interests, Personal, Other, CME: AiCME, Clinical Care Options, MJH Life Sciences, Med Learning, Medscape, Medscape, Onclive, Paradigm Medical Communications, PeerView Institute, PeerVoice, Physicians Education Resources, Targeted Oncology, WebMD; Financial Interests, Personal, Other, Consulting: Applied Pharmaceutical Science, Inc., EPG Health, Entos, Harborside Nexus, Merus, Nuvalent, Ology, Prelude, TouchIME, Treeline Bio, mBrace; Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical, RV More, Remedica Ltd.; Financial Interests, Personal, Stocks/Shares: Treeline Biosciences; Financial Interests, Personal, Royalties: Wolters Kluwer; Financial Interests, Personal, Other, stocks: mBrace; Financial Interests, Institutional, Funding, Research funding: Pfizer, Exelixis, PharmaMar, GSK, Teva, Taiho; Financial Interests, Personal, Funding, Research: Foundation Medicine; Non-Financial Interests, Member: ASCO, AACR, IASLC; Other, Food/Beverage: Merck, PUMA, Merus; Other, Other: Boehringer Ingelheim. 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683P Preclinical evaluation of HLX42, a novel EGFR-targeting ADC, for cetuximab or TKI resistant cancer

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Background: EGFR is highly expressed in various tumour types and is a driving force in tumourigenesis and progression. Although anti-EGFR and EGFR TKIs have demonstrated success in cancer treatment, a considerable medical need remains for patients who do not respond to or experience relapse following standard care. EGFR ADCs in clinical evaluation displayed preliminary efficacy, but conventional EGFR ADCs could pose considerable toxicity risks due to the universal expression of EGFR in normal epithelial tissues.

Methods: HLX42, a next-generation EGFR ADC, is comprised of a highly specific humanized IgG1 anti-EGFR connected to a novel topoisomerase-I inhibitor payload, whose cleavage and release are tumour microenvironment dependent and do not necessitate internalisation of ADC. This distinct mechanism of payload release grants HLX42 a superior therapeutic index compared to its predecessors. HLX42 was examined in antigen binding, internalisation, and plasma stability assays; efficacy analyses were also performed in multiple CDX and PDX models.

Results: *In vitro* evaluations verified that HLX42 possessed a similar binding affinity and internalisation rate as its parental antibody. Additionally, the ADC remained stable in rat and cynomolgus monkey plasma. HLX42 exhibited robust tumour suppression in several CDX and PDX models that were resistant to anti-EGFR or TKIs. In comparison to conventional ADC technologies such as vc-MMAE and GGFG-Dxd, HLX42 displayed superior efficacy and elicited more durable antitumour responses. In the NCI-H1993 model, weekly administration of HLX42 at 8 mg/kg for three times resulted in a 91.5% TGI compared to 79.8% TGI induced by anti-EGFR-GGFG-Dxd. Furthermore, the combination of HLX42 and osimertinib exhibited strong synergy in the LU3075 PDX model which poorly responded to osimertinib alone. In our pilot toxicity studies, HLX42 was well tolerated in rats and non-human primates (severely

Table: 684P Efficacy outcomes

	All GC/GEJ* (N=55)	HER2-positive GC/GEJ† 6.4 mg/kg (N=32)	All CRC* (N=43)	HER2-positive CRC† 6.4 mg/kg (N=32)
ORR‡, % (n/N; 95% CI)	38.2% (21/55; 25.4-52.3)	43.8% (14/32; 26.4-62.3)	44.2% (19/43; 29.1-60.1)	46.9% (15/32; 29.1-65.3)
DCR, % (n/N; 95% CI)	83.6% (46/55; 71.2-92.2)	84.4% (27/32; 67.2-94.7)	86.1% (37/43; 72.1-94.7)	93.8% (30/32; 79.2-99.2)
TTR‡, median (range), mo	1.5 (1.3-4.6)	1.4 (1.3-3.0)	2.8 (1.2-7.1)	2.9 (1.5-7.1)
6-mo PFS, % (95% CI)	71.0% (54.0-82.7)	73.9% (52.1-86.9)	75.6% (57.9-86.6)	85.5% (65.6-94.3)

*HER2-expressing, IHC1+, 2+, or 3+ or ISH+. †HER2-positive, IHC3+ or IHC2+/ISH+. ‡Unconfirmed response.

toxic dose in 10% of animals = 50 mpk in rats; highest non-severely toxic dose = 20 mpk in non-human primates).

Conclusions: Taken together, these preclinical data strongly suggest that HLX42 is a potential best-in-class EGFR-targeting ADC which is worth further clinical investigations.

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684P Phase I trial of SHR-A1811 in HER2-expressing advanced gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJ) and colorectal cancer (CRC)

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Background: SHR-A1811 is a novel ADC consisting of a humanized, anti-HER2 IgG1 mAb bound to a DNA topoisomerase I inhibitor payload via a cleavable, tetrapeptide-based linker. We conducted a phase 1 trial to assess SHR-A1811 in HER2-expressing locally advanced or metastatic GC/GEJ and CRC.

Methods: Patient (pts) who had failed or had no available/applicable standard treatment were enrolled. Pts were given SHR-A1811 at 3.2, 4.8, 6.4 and 8.0 mg/kg (Q3W, iv) in an i3+3 dose-escalation (DE) scheme, followed by PK expansion at selected tolerable doses and then clinical expansion at RP2D. The primary endpoints were DLT, safety and RP2D.

Results: As of data cutoff (Apr. 21, 2023), 98 pts were enrolled, including 55 GC/GEJ and 43 CRC pts (HER2-positive, 72.7%/86.0%; ≥2 lines of prior therapy, 29.1%/67.4%). During DE, 1 DLT (grade 4 decreased platelet count) occurred at 8.0 mg/kg. Combined with dose-proportional systemic exposure of SHR-A1811, total antibody, and payload at 3.2-8.0 mg/kg, and general treatment tolerability and an ORR of 50.0% (6/12) at 6.4 mg/kg during DE and PK expansion, 6.4 mg/kg was established as RP2D. Overall, the respective ORR in GC/GEJ and in HER2-positve GC/GEJ at RP2D were 38.2% (21/55; 95% CI 25.4-52.3) and 43.8% (14/32; 95% CI 26.4-62.3); the corresponding ORR in CRC were 44.2% (19/43; 95% CI 29.1-60.1) and 46.9% (15/32; 95% CI 29.1-65.3). Additional tumor response data are shown in the table. The respective 6-mo PFS rates in GC/GEJ and in HER2-positve GC/GEJ at RP2D were 71.0% (95% CI 54.0-82.7) and 73.9% (95% CI 52.1-86.9); the corresponding rates in CRC were 75.6% (95% CI 57.9-86.6) and 85.5% (95% CI 65.6-94.3). Grade ≥3 TRAEs occurred in 67 of 98 pts (68.4%), with all events occurring in ≥10% being hematotoxicities. No interstitial lung disease was reported.

Conclusions: SHR-A1811 showed an acceptable safety profile and promising clinical activity in pts with HER2-expressing GC/GEJ and CRC. Further investigation was warranted.

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Legal entity responsible for the study: Jiangsu Hengrui Pharmaceuticals, Co., Ltd.

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685P BL-M07D1, a HER2 antibody-drug conjugate in subjects with locally advanced or metastatic HER2 expressing breast cancer and other solid tumors

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Background: BL-M07D1 is an anti-HER2 antibody drug conjugate (ADC). It consists of a humanized anti-HER2 antibody, a cathepsin B cleavable linker, and a novel topoisomerase I inhibitor (Ed-04).

Methods: This study included subjects with locally advanced or metastatic HER2 expressing (positive/low) breast cancer (BC) and other solid tumors. For dose escalation (D-ESC), BL-M07D1 is planned to be administered at doses of 1.0mg/kg D1D8 Q3W or 2.6, 3.2, 3.8, 4.4, 5.0, 5.6, 6.2 mg/kg D1 Q3W. A subset of subjects were enrolled in the dose-expansion phase (D-EXP) at D1 Q3W regimens.

Results: As of May 1st, D-ESC has reached a dose of 5.0 mg/kg, with no observed dose limiting toxicities (DLTs).The maximum tolerated dose (MTD) was not reached. A total of 50 pts were treated with at least one dose, 19 pts in D-ESC and 31 in the D-EXP phase. The dose levels for expansion included 3.8, 4.4 and 5.0 mg/kg D1 Q3W. Among 50 pts,one received BL-M07D1 at 1.0 mg/kg on Day 1 and Day 8 every 3 weeks (D1D8 Q3W), while the remaining 49 subjects were treated with the drug on a Day 1 every 3 weeks (D1Q3W) schedule. The study enrolled 41 BC, 5 gastric cancer, 2 rectal cancer and 2 non-small cell lung cancer patients. The most common TRAEs (>10%, all grade /≥G3) were leukopenia (60%/13%), neutropenia (58%/21%), nausea (44%/0%), anemia (44%/0%), vomiting (25%/2%), lymphocyte count decreased (23%/8%),

Table: 685P

	ALL (n=26)	BC (n=23)	HER2+BC (n=15)
Median prior treatment lines (range)	3 (1-13)	3 (1-13)	3 (1-13)
Best overall response			
PR (cPR)	11 (6)	10 (6)	9 (6)
SD (with shrinkage)	12 (8)	11 (8)	6 (4)
PD	3	2	0
ORR, % (95% CI)	42.3 (23-63.1)	43.5 (23.2-65.5)	60 (32.3-83.7)
DCR, % (95% CI)	88.5 (69.9-97.6)	91.3 (72-98.9)	100%

gamma-glutamyltransferase increased (21%/2%), asthenia (19%/0%), thrombocytopenia (19%/0%), decreased appetite (17%/0%), alopecia (17%/0%), aspartate aminotransferase increased (15%/0%). No ILD was observed. Twenty six subjects were evaluated for efficacy (i.e., at least one post-baseline tumor assessment). Updated efficacy and pharmacokinetic (PK) results will be presented at the conference.

Conclusions: BL-M07D1 demonstrated encouraging efficacy in heavily pretreated HER2 expressing cancers, especially in HER2-positive BC. The safety profile showed adequate safety and tolerability.

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Legal entity responsible for the study: SystImmune Inc.

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686P Phase I study of HRS8807, an oral selective ER covalent antagonist (SERCA), in ER+/HER2- locally advanced (LA) or metastatic (M) breast cancer (BC)

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Background: HRS8807 exerts strong antitumor effect in wild-type and mutant ER+ BC cells and mouse xenograft models. Here we report the preliminary results of HRS8807, the second SERCA to enter clinical development, in patients (pts) with ER+/HER2- LA/M BC.

Methods: In this phase 1 study, eligible pts were women of any menopausal status who had received $\geq$1 line of endocrine therapy and/or $\leq$2 lines of chemo with radiologically confirmed disease progression from the most recent anticancer regimen. Dose escalation was started at 25 mg with 1 pt and then switched to i3+3 design at doses of 75 to 600 mg. 3 d after a single dose, HRS8807 was given continuously qd in 28-d cycles. Dose-limiting toxicities (DLTs) were observed from the first dose to end of the first cycle (ie, 31 d).

Results: As of Apr 12, 2023, 7 pts were recruited (1 at 25 mg, 3 at 75 mg, and 3 at 150 mg). Median age was 53 yr. All had ECOG PS of 1. 71.4% were PR+. Median time from diagnosis to enrollment was 44.6 mo. For the LA/M disease, 57.1% had $\geq$2 lines of prior anticancer therapies; 71.4% had prior selective ER modulator degrader (SERD) and 85.7% had prior CDK4/6i. No DLTs were observed. Treatment-related adverse events (TRAEs) were reported in all pts, with the most common being hypertriglyceridemia, increased AST, hyperuricemia, increased ALT, increased blood creatinine, and anemia. No grade $\geq$3 TRAEs occurred, and no TRAEs led to treatment discontinuation. 3 pts achieved PR (1 at 75 mg and 2 at 150 mg; in which 2 had prior SERD [fulvestrant] and all had prior CDK4/6i in the M setting; treatment duration was 8.4, 8.6+, and 7.0+ mo). Impressively, ORR reached 42.9% (95% CI 9.9-81.6) in overall population, and 66.6% (95% CI 9.4-99.2) at 150 mg and 33.3% (95% CI 0.8-90.6) at 75 mg. The active metabolite SHR180451, a reversible ER inhibitor slightly more potent than HRS8807 in prohibiting BC cell proliferation *in vitro*, had longer terminal elimination half-life than and comparable systemic exposure to the parent. ^{18}F-FES PET-CT SUV_{max} decreased significantly after treatment.

Conclusions: HRS8807 was well-tolerated and showed early signs of robust antitumor activity, favorable PK properties (both parent and active metabolite), and high ER occupancy in pretreated ER+/HER2- LA/M BC.

Clinical trial identification: NCT04993430, Release date: 6 August 2021.

Legal entity responsible for the study: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

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687P A CRUK phase I/IIA, first in human dose-escalation and expansion trial of HMBD-001 (an anti-HER3 antibody) in patients with advanced HER3 positive solid tumours

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Background: Human epidermal growth factor receptor (HER)3 is a HER family transmembrane protein. Overexpression of HER3 is observed in multiple solid tumour types and are associated with poor clinical outcome. HMBD-001 is an IgG1 humanized monoclonal antibody specifically targeting HER3 with a unique mechanism of action, inhibiting both ligand-dependent and independent activation.

Methods: HMBD-001 is being evaluated in a first in human, multi-centre, open-label, non-randomised phase 1/IIA trial: Part A dose-escalation, with an initial intra-patient dose escalation, followed by inter-patient dose escalation utilising a one-stage Bayesian continuous reassessment design in advanced solid tumours commonly overexpressing HER3; and Part B, a dose-expansion phase in combination in metastatic castration-resistant prostate cancer (mCRPC) (NCT05057013). The primary objectives of Part A are to determine safety and tolerability and the recommended dose and schedule for phase 2 evaluation (RP2D). The pharmacokinetic profile, clinical and pharmacodynamic activity of HMBD-001 as a single agent and potential predictive and pharmacodynamic biomarkers are being evaluated.

Results: As of 11 April 2023, 17 patients with advanced solid tumours have received weekly infusions of HMBD-001 monotherapy across 6 cohorts (150mg-3000mg). In total, 70 HMBD-001 treatment related adverse events (TRAEs) have been reported. 14 (82.4%) patients have had $\geq$1 TRAE. No grade $\geq$3 TRAEs nor DLTs have been observed. More TRAEs have been observed at higher doses. Gastrointestinal disorder TRAEs are the most frequently reported (45.7%, 32/70); 13 patients (76.5%) experienced grade $\leq$ 2 diarrhoea. 4 patients (23.6%) have experienced trial-specific events of special interest; grade $\leq$2 infusion related reactions. Stable disease has been recorded in 4/12 evaluable heavily pre-treated patients.

Conclusions: Preliminary data supports a highly tolerable safety profile, supporting combination therapy. HMBD-001 will next be evaluated in Part B in biomarker selected mCRPC with Enzalutamide. Trials of HMBD-001 in squamous NSCLC and NRG1 fusions are also planned for Q3/4 2023.

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688P Pharmacokinetics of HMBD-001, a human monoclonal antibody targeting HER3, a CRUK first-in-human phase I trial in patients with advanced solid tumours

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Background: HMBD-001 is an IgG1 humanised monoclonal antibody that directly blocks the dimerisation of HER3 to HER2 and EGFR. The ongoing first-in-human trial is an open-label, multi-centre, phase I/IIa adaptive study design (CRUKD/22/002) of HMBD-001 in patients with tumour types known to overexpress HER3. We report the pharmacokinetic profile of HMBD-001 from the initial dose escalation cohorts.

Methods: Patients (n = 17) were allocated to dose-escalating cohorts and administered an IV once weekly infusion dose (150, 300, 600, 1200, 1800 and 3000 mg) over 2 hours. The pharmacokinetics of HMBD-001 were evaluated over 7 days following administration on days 1 and 15 of cycle one. Concentrations of HMBD-001 in serum samples were determined by a validated bridging enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification of 250 ng/mL. Pharmacokinetic parameters, including maximum concentration (C_{max}), T_{max}, area under curve (AUC), terminal half-life ($t_{1/2}$), and clearance (CL), were calculated by non-compartmental analysis using Certara WinNonlin software (version 8.3). A population pharmacokinetic approach was explored using Lixsoft Monolix Suite (version 2023R1).

Results: HMBD-001 C_{max} and AUC values increased linearly with dose on days 1 and 15 of treatment and a $T_{1/2}$ of 12.2 +/- 3.4 days was calculated at a dose of 3000mg. Drug clearance values observed on day 15 (dose 3) were significantly lower than those on day 1 (dose 1) (p = 0.017). Preliminary population pharmacokinetic suggest that the data are best described by a one compartmental model, with sex and weight as covariates for clearance and volume of distribution, respectively.

Table: 688P Pharmacokinetics of HMBD-001 on day 1 of dosing

Cohort	n	Dose (mg)	C_{max} (µg/mL)	T_{max} (h)	C_{trough} (µg/mL)	CL (mL/h)	AUC (µg/mL.h)	$T_{1/2}$ (days)
1	1	150	33	2.7	11	33.3	4499	4.5
2	1	300	98.3	2.1	25.6	25.4	11822	5.8
3	3	600	137.0 ± 34.9	4.1 - 25.1	62.7 ± 17.7	21.8 ± 6.4	29251 ± 9062	6.4 ± 0.6
4	3	1200	296.2 ± 60.2	2.2 - 7.4	148.4 ± 6.4	15.6 ± 1.6	77099 ± 7548	8.6 ± 2.2
5	6	1800	412.1 ± 57.8	2.4 - 4.9	158.6 ± 41.2	23.7 ± 5.0	79966 ± 23210	6.5 ± 1.6
6	3	3000	841.2 ± 209.3	2.2 - 2.8	368.3 ± 92.4	13.4 ± 1.9	227419 ± 32461	12.2 ± 3.4

Conclusions: The pharmacokinetic data generated to date are consistent with dose-dependent increases in drug exposure for HMBD-001. A $T_{1/2}$ of approximately 12 days is predicted.

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689P DB-1305 (a Trop-2 targeted antibody-drug-conjugate [ADC]) in patients (pts) with advanced solid tumors: Preliminary clinical results from the phase (Ph) I/IIa study

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Background: DB-1305 is a novel ADC composed of a humanized anti-trophoblast cell-surface antigen 2 (Trop-2) IgG1 monoclonal antibody attached to a DNA topoisomerase I inhibitor (P1021) via a cleavable linker. Here, we present the initial results of the first-in-human (FIH) study.

Methods: This multi-center, open-label Ph 1/2a study includes dose escalation and expansion. Pts with advanced solid tumors who had failed standard therapy were enrolled. In Ph1, DB-1305 was planned to be administered from 2 mg/kg to 8 mg/kg (Q3W, iv) in a 3+3 design with accelerated titration for the starting dose; additional pts were enrolled to determine the recommended phase 2 dose (RP2D). Ph 2a will enroll approximately 10-40 pts per cohort at the RP2D to assess efficacy.

Results: As of 07 Apr 2023, 44 pts (2 mg/kg, n=1; 4 mg/kg, n=20; 5 mg/kg, n=17; 6 mg/kg, n=6) were enrolled in the Ph1. The median treatment duration was 1.5 (range, 0.7-6.1) months with 25 pts (56.8%) remaining on treatment. Pts had 3 median prior lines of therapy (range, 1-6). Three patients dosed at 6 mg/kg experienced dose-limiting toxicities (i.e., stomatitis, febrile neutropenia, and white blood cell decreased), and the maximum tolerated dose was established as 5 mg/kg. The most common (≥30%) treatment-related adverse event (TRAE) was stomatitis (75.0%). The most common (≥10%) Gr≥3 TRAE was stomatitis (22.7%), while all other events were reported in ≤2 pts. No TRAE led to death. The initial PK results suggest that exposure of DB-1305 increased with dose. The half-life of DB-1305 is approximately 3-4.5 days at the dose range of 4-6 mg/kg. The average systemic ADC/payload molar ratio is approximately 80, indicating ADC stability in systemic circulation. As of cut-off date, 7 pts (non-small cell lung cancer [NSCLC], n=6; fallopian tube cancer, n=1) had partial responses, 4 confirmed, and 3 requiring further confirmation. The objective response rate (ORR) was 30.4% (7/23), and disease control rate (DCR) was 87.0% (20/23). Thirteen NSCLC pts had an ORR of 46.2% (6/13), with a DCR of 92.3% (12/13).

Conclusions: DB-1305 has a manageable toxicity profile. Encouraging efficacy signals were observed in the NSCLC. Study continues to identify dose(s) of DB-1305.

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690P Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase I/II study

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Background: I-DXd is a novel B7-H3—directed antibody—drug conjugate that leverages the clinically validated deruxtecan (DXd) technology with a plasma-stable linker and potent topoisomerase I inhibitor payload. Here we present a follow-up analysis (7 mo since last report) of an ongoing phase 1/2 trial that includes heavily pretreated patients with castration-resistant prostate cancer (CRPC), esophageal squamous cell carcinoma (ESCC), squamous non-small cell lung cancer (sqNSCLC), and small cell lung cancer (SCLC). DOR, OS, and B7-H3 correlations with response are reported for the first time for CRPC, ESCC, and sqNSCLC.

Methods: Efficacy and safety were analyzed in patients treated with I-DXd at 4.8 to 16.0 mg/kg. Response was evaluated in patients with ≥2 postbaseline scans or discontinuation for any reason. Fourteen patients with CRPC lacked measurable target lesions at baseline (BL) and were excluded from ORR analysis. B7-H3 level was evaluated retrospectively as patients were not pre-selected by BL expression.

Results: As of 31 Jan 2023, 8 patients remained on treatment. Safety data were consistent with previous reports. I-DXd still demonstrated promising ORR results, including in an updated sample size for sqNSCLC (Table). Even in this heavily pretreated population, I-DXd exhibited durable response and encouraging early OS (Table), although further follow-up is needed. B7-H3 expression was moderate to high in most patients; no correlation was observed between response and B7-H3 level, and an update will be presented at the congress.

Table: 690P Efficacy

	CRPC	ESCC	sqNSCLC	SCLC
No. of prior lines, median (range)	6 (1 − 11)	4 (1 − 7)	3 (1 − 12)	2 (1 − 9)
ORR by RECIST v1.1 (confirmed)	n = 59	n = 28	n = 13	n = 21
n (%)	15 (25)	6 (21)	4 (31)	11 (52)
DOR by RECIST v1.1	n = 59	n = 28	n = 13	n = 21
Median, mo (95% CI)	6.4 (2.8 − 10.6)	3.5 (2.4 − NE)	4.1 (2.8 − NE)	5.9 (2.8 − 7.5)
PFS by RECIST v1.1	n = 73	n = 28	NR	n = 21
Median, mo (95% CI)	4.8 (3.9 − 5.9)	2.8 (1.6 − 4.2)		5.8 (3.9 − 8.1)
OS	n = 73	n = 28	NR	n = 21
Median, mo (95% CI)	13.5 (10.3 − 16.6)	7.0 (4.8 − 12.2)		9.9 (5.8 − NE)

DOR, duration of response; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

Conclusions: I-DXd continues to demonstrate a manageable safety profile and promising antitumor activity with encouraging DOR and OS in these heavily pretreated patients, which warrants further clinical evaluation across multiple indications.

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691P Efficacy of ABBV-400 monotherapy in patients with MET gene amplified advanced solid tumors

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Background: Anti−c-Met (MET protein) antibody-drug conjugate ABBV-400 comprises monoclonal antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor via a stable, cleavable linker. *MET* gene amplification (amp) occurs at low frequency in primary tumors (<5%) but has increased frequency in recurrent/refractory disease. ABBV-400 showed deep, durable responses in preclinical patient (pt)-derived xenograft models of *MET* amp, c-MET−overexpressing advanced solid tumors. A first-in-human phase I study (NCT05029882) is evaluating safety, pharmacokinetics, and preliminary efficacy of ABBV-400 in pts with advanced solid tumors; we present results of an ad hoc analysis of efficacy in pts with *MET* amp.

Methods: Analyzed pts had measurable disease per RECIST v1.1 and history of advanced solid tumors that progressed/were not amenable to any available therapies/surgery. Pts had *MET* amp per local NGS reports of tissue/blood samples from various approved labs. ABBV-400 administered intravenously once every 3 weeks.

Results: As of 3 Apr 2023, 11 pts with *MET* amp advanced solid tumors were treated with ABBV-400 at 2.4 (N=4), 3 (N=6), or 4 (N=1) mg/kg; median follow-up 6.7 months. Enrolled tumor types included NSCLC, intrahepatic cholangiocarcinoma, gastroesophageal, ovarian, urachal, colorectal, and breast cancers. Median age 65 (range 41−73) years, 64% male, 64% Asian, 27% White, 9% Black, 6 (55%)/5(45%) had ECOG PS 0/1; median prior lines of therapy 3 (range 1−6). Pts had MET IHC H-score range of 73−270 and 5−75% cells with 3+ staining (data available for 6/11 pts). Treatment-emergent AEs reported in 11 pts (100%; 55% grade ≥3); most commonly, neutropenia (55%), anemia (46%), nausea (46%), and leukopenia (46%). Confirmed partial response observed in 8 pts (ORR = 73%, 95% CI: 39, 94) per investigator review and RECIST v1.1; 6 pts had ongoing response. Median progression-free survival was 10.8 months (95% CI: 1.2, not reached [NR]), duration of response and overall survival NR; longest ongoing response was >9 months.

Conclusions: ABBV-400 monotherapy showed promising tolerability and efficacy in pts with various *MET* amp advanced solid tumors. Based on these results, *MET* amp cohort will be expanded to 60 more pts.

Clinical trial identification: NCT05029882.

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692P First-in-human study of ELU001, a targeted nanoparticle drug conjugate, in subjects with folate receptor α (FRα) overexpressing solid tumors

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Background: ELU001 is small nanoparticle drug conjugate (∼6 nm), designed to penetrate deep into solid tumors and be eliminated rapidly by the kidneys to reduce toxicity versus antibody drug conjugates. ELU001 has ∼13 folic acid targeting moieties and ∼21 cathepsin-B cleavable exatecans, a topoisomerase-1 inhibitor, covalently bound to short polyethylene glycol chains surrounding a silica core. ELU001 binds cancer cells expressing FRα releasing exatecan intracellularly. ELU001 demonstrated efficacy in preclinical models with low to high levels of FRα.

Methods: Phase 1 / 2 multicenter, open label clinical trial. Part 1, Dose Escalation, enrolled patients with cancers likely to overexpress FRα. Escalating doses of ELU001, administered once a week (QW) (0.58-1.94 mg/m^2 for 3 weeks, 1 week rest), every other week (Q2W) (1.5-2.25 mg/m^2), or every three weeks (Q3W) (2.75-3.5 mg/m^2). Primary objective of Part 1: identify the starting dose and regimen for Part 2, Tumor Group Expansion.

Results: As of May 8, 2023, 40 patients (18 ovarian, 7 endometrial, 10 colorectal, 3 non-small cell lung and 2 cholangiocarcinoma) enrolled in Part 1 (15 QW, 14 Q2W, 11 Q3W), median prior lines of therapy 5 (2-13). To date 23 were evaluable for first tumor assessment at ∼8 weeks after first dose (1 Partial Response,18 Stable Disease and 4 Progressive Disease). 7 patients continued treatment for >6 cycles (4 for >8, 3 for >11). Treatment-Emergent Adverse Events: Grade 3 and 4 (≥ 10%): QW/Q2W/Q3W: neutropenia (46.7%/28.6%/50%), anemia (46.7%/28.6%/30%), leukopenia (40.0%/14.3%/10.0%), and thrombocytopenia (20%/7%/40%). Grade 1 and 2, (All regimens ≥ 20%): anemia (38.5%), fatigue (23.1%), neutropenia (30.8%), diarrhea (20.5%) and vomiting (23.1%). No evidence of ocular, liver, renal or cardiac toxicities, interstitial lung disease or peripheral neuropathy. Preliminary half-life ∼22 hours. The Q2W regimen had a better hematological safety profile with no related discontinuations.

Conclusions: Safety and efficacy of ELU001 demonstrated expected, manageable safety profile based on the payload, exatecan, with promising activity in heavily pretreated patients across several cancer indications with low, moderate or high FRα expression.

Clinical trial identification: NCT05001282.

Legal entity responsible for the study: Elucida Oncology.

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693P Preclinical activity of HLX43, a PD-L1-targeting ADC, in multiple PD-1/PD-L1 refractory/resistant models

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Background: PD-1/PD-L1 monoclonal antibodies have revolutionised the landscape of cancer treatment. Nonetheless, some PD-L1+ patients do not respond to or become resistant to such therapy. The elevated expression of PD-L1 in tumours makes it an attractive target for ADC development, which could potentially alter the treatment for PD-1/PD-L1 inhibitor refractory/resistant (R/R) cancers.

Methods: HLX43 is a novel PD-L1-targeting ADC consisting of an engineered anti-PD-L1 humanised IgG1 antibody linked to a camptothecin-based toxin, with a drug to antibody ratio of 8. Our innovative linker-payload is activated preferentially in the tumour microenvironment, enabling its tumour-specific release of the toxin without needing internalisation of the ADC. Toxin release in PD-L1+ cancer cells is efficient and tumour-specific, minimizing damage to normal cells and reducing systemic toxicity from non-specific toxin release in periphery. HLX43 was examined in antigen binding, internalisation, and plasma stability assays; efficacy studies were performed in multiple CDX and PDX models.

Results: HLX43 has been shown to have similar affinity and internalisation rates as the parental antibody. It was stable in the plasma of rats and cynomolgus monkeys. In *in vivo* efficacy studies, HLX43 induced tumour regression in multiple PD-L+ CDX and PDX models, and was well tolerated across all dosing groups. Weekly administration of HLX43 8 mg/kg for three times significantly reduced tumours in the MDA-MB-231 model without causing weight loss. HLX43 exhibited superior anticancer efficacy compared to anti-PD-L1-GGFG-Dxd at equal doses in all models tested, including those with low PD-L1 levels, high heterogeneity, and non-responsiveness to PD-1/PD-L1 inhibitors. Preliminary toxicity assessments demonstrated good tolerability of HLX43 in rats and cynomolgus monkeys, with the maximum tolerated dose being 60 mg/kg in rats and 10 mg/kg in non-human primates. GLP toxicology studies will explore a higher dose at 20 mg/kg.

Conclusions: HLX43 showed promising efficacy and tolerability in preclinical assessments. It may offer a novel treatment for PD-1/PD-L1 inhibitor R/R cancers like NSCLC, HNSCC, ESCC, MEL, and OVC.

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694P Full efficacy analysis of phase I/II trial investigating bexmarilimab, a novel macrophage-guided immunotherapy in refractory solid tumors

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Background: Clever-1 is an immunosuppressive scavenger receptor expressed on tumor associated macrophages. Bexmarilimab (FP-1305) is a novel humanized anti-CLEVER-1 IgG4-antibody capable of switching tumor macrophage phenotype leading to T-cell mediated anti-tumor responses.

Methods: MATINS (Macrophage Antibody To INhibit immune Suppression) trial is a first-in-human phase I/II study (NCT03733990) to assess safety and preliminary efficacy of Bexmarilimab (Bex) in patients with refractory advanced solid tumours. Part I has been completed with initial adequate safety profile, preliminary signs of efficacy, and initial recommended dose of 1mg/kg Q3W for part II. In Part II, 10 patients with distinct solid tumour types and variable doses and dosing frequency of Bex were studied to investigate safety, tolerability and efficacy.

Results: At the data cut-off of Apr 17th 2023, 214 patients have been enrolled to the study. In the alternative dosing cohorts, 66 patients were exposed to Bex with 1-3mg/kg Q1W, 1-3mg/kg Q2W, or 3-30mg/kg Q3W dosing. Bex was well tolerated with fatigue (15.9%) and pyrexia (5.6%) being the most frequent treatment related adverse event (TRAE) and 7.9% of the patients experiencing grade 3-4 TRAE. Disease control rate (DCR) was 13.0% (n=28) overall. Highest disease control rates (DCR) were observed in hepatocellular cancer (36%), ER+ breast cancer (33%), cutaneous melanoma (22%), and cholangiocarcinoma (21%). DCR was associated with Bex-induced immune activation in blood and tumor. Median progression-free survival was 2.0 and overall survival 5.6 months. 18-month survival rates (landmark analysis) were 32.9% in patients achieving DCR while this was 5.5% in non-DCR patients. The PFS ratio (defined by the PFS on bex/duration of previous treatment line) was >1.3 in 46.4% of the DCR patients while this was 9.6% in non-DCR patients ($p<0.0001$). In the alternative dosing regimens, no dose-dependency was observed to adverse events or DCR rates.

Conclusions: Bexmarilimab demonstrates promising anti-tumour activity as a monotherapy in several refractory solid tumours. A dose of 1mg/kg Q3W is considered feasible for further monotherapy studies in solid tumors.

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695P A phase I/Ib study evaluating the safety and tolerability of NIZ985 alone and in combination with spartalizumab (anti −PD-1) in patients (pts) with solid tumors or lymphoma

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Background: NIZ985, an investigational recombinant heterodimer of interleukin (IL)-15 and IL-15 receptor alpha, binds the IL-2/IL-15 receptor on immune cells. NIZ985 activates immune cells in pts with advanced cancer and may help overcome resistance to checkpoint inhibitors (CPIs).

Methods: This is a phase I/Ib, open-label, multicenter, dose-escalation (ESC)/-expansion (EXP) study (NCT04261439) of NIZ985 alone and with spartalizumab (SPA) in pts with advanced solid tumors or lymphoma. Eligible pts had previously responded and progressed on a CPI. ESC comprised two arms: (1) single-agent (SA), subcutaneous NIZ985 at 2−16 μg/kg weekly, 3 weeks on/1 week off and (2) in combination with SPA 400 mg (N+S) intravenously on Day 1 of each 28-day cycle. Study objectives were to evaluate safety, tolerability, preliminary antitumor activity and PK.

Results: Fifty-six pts have been treated in the ESC SA NIZ985 (n=27) and N+S (n=29) arms. Pts received a median 3 (1−7) and 4 (1−9) prior therapies, with a median 1 prior CPI-containing regimen (ranges 1−3 and 1−4), respectively. At data cut-off, 21 (77.8%) and 24 (82.8%) pts had discontinued treatment in each arm respectively, mainly due to progressive disease (66.7% and 48.3%). Three DLTs during the first cycle included grade (gr) 3 fatigue, gr 2 bullous dermatitis and gr 2 injection site reaction. Gr ≥3 treatment-related AEs (TRAEs) were reported in 4 (14.8%) pts in the SA arm (pyrexia, fatigue, increased ALT, cutaneous vasculitis, and linear IgA disease) and in 4 (13.8%) pts in the N+S arm (increased ALT, hyperprogression, soft tissue infection, and increased transaminases). Of the 42 pts evaluated, 2 had a PR and 16 had SD. PK were dose proportional up to 12 μg/kg NIZ985, and overlapping exposures were observed with 16 μg/kg NIZ985. Biomarker data showed strong peripheral immune activation; increased Ki67 expression in CD8+ and NK cells and increases in systemic pro-inflammatory cytokines were noted.

Conclusions: NIZ985 +/- SPA was generally well tolerated with evidence of immune activation. The RDE was declared as 12 μg/kg NIZ985 SA and in combination. Additional pts with NSCLC have enrolled in EXP with tislelizumab.

Clinical trial identification: EudraCT 2109-0040690-42.

Legal entity responsible for the study: Novartis.

Funding: Novartis.

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696P SIM1811-03 (SIM0235), an anti-tumor necrosis factor receptor-2 (TNFR2) monoclonal antibody, in patients with advanced solid tumor and/or cutaneous T cell lymphomas (CTCL): Preliminary results from an on-going first-in-human phase I trial in China

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Background: TNFR2 drives immune escape and tumor proliferation, and is highly expressed on tumor cells, immunosuppressive cells in the tumor microenvironment. SIM1811-03 is a humanized IgG1 monoclonal antibody that targets TNFR2,which demonstrated antitumor active in non-clinical models as single agent. SIM1811-03 is being evaluated in the First-in-Human study in patients with advanced solid tumors.

Methods: The study enrolled patients with advanced tumors who were not eligible for standard of care treatment. Patients received one dose of SIM1811-03 in cycle 0 and subsequently once every 2 weeks in dose from 0.5mg/mg to 25mg/mg. Based on emerging data a once every 3 weeks schedule in 40mg/kg dose was tested. The primary objectives were to determine the maximum-tolerated dose or recommended dose and to evaluate preliminary anti-tumor activity using either RECIST v1.1 for solid tumors. Secondary objectives were to assess safety and tolerability and to characterize pharmacokinetics and pharmacodynamics profiles.

Results: As of April 18, 2023, 22 patients received SIM1811-03 at doses of 0.5 mg/kg (n=3), 1.5 mg/kg (n=4), 5 mg/kg (n=4), 15 mg/kg (n=4), 25 mg/kg (n=4) Q2W and 40 mg/kg Q3W (n=3). No dose-limiting toxicity was observed and the MTD was not been reached. Majority of adverse events were Grade 1 or 2.There were two subjects with Grade 3/4 treatment-related adverse event. Two patients experienced treatment-related serious adverse event. SIM1811-03 showed a non-linear PK profile at the lower dose levels and a linear PK profile at the higher dose levels (15 to 40 mg/kg) with a half-life of about 12 days. TNFR2 receptor occupancy increased with SIM1811-03 concentration, and reached sustained saturation in peripheral blood CD14+ and CD16+ cells with the concentrations higher than about 10 ug/mL.

Conclusions: SIM1811-03 was well tolerated without DLTs reported across all dose levels and MTD was not reached. The preliminary PK and PD results support every 3-week dosing at 40mg/kg as the recommended dose for expansion. The clinical development of SIM1811-03 in combination with immunotherapy is planned.

Clinical trial identification: NCT05781386.

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697P Open-label, phase I, dose escalation/expansion trial of the anti-SIRPα monoclonal antibody BI 770371 in patients with advanced solid tumours, alone or in combination with the anti-PD-1 monoclonal antibody ezabenlimab

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Background: BI 770371, a pan-specific anti-signal regulatory protein alpha (SIRPα) monoclonal antibody (mAb), reactivates innate and adaptive anti-tumour immune responses. This phase I, non-randomised, open-label, multicentre trial (NCT05327946) aimed to determine the maximum-tolerated dose (MTD) and recommended dose for expansion of BI 770371 ± ezabenlimab.

Methods: BI 770371 was administered alone or in combination with ezabenlimab IV once every 3 weeks in patients with advanced solid tumours. Treatment continued until progressive disease, unacceptable toxicity or other withdrawal criteria. Dose escalation was guided by a Bayesian Logistic Regression Model with overdose control. Primary endpoint was dose-limiting toxicities (DLTs) in the MTD evaluation period. Secondary endpoints were adverse events (AEs) and DLTs in the on-treatment period.

Results: As of 31 March 2023, 18 patients (monotherapy, n=15; combination therapy, n=3) have been treated in Canada, Japan and the US. In the patients who received monotherapy, the most common tumour types were colorectal, ovarian and prostate cancer (n=2 patients with each). 53% of patients were male, 53% had ECOG PS 0 and all had received >2 prior lines of treatment. AEs were reported in 12 patients (80%) and grade 3 AEs were reported in one patient (peripheral oedema, atrial fibrillation). Treatment-related AEs were observed in 10 patients (67%; all grade 1/2); the most common were pruritus (n=5) and peripheral oedema (n=2). Serious AEs were reported in four patients (27%; atrial fibrillation, decreased appetite, encephalitis, hypoxia, disease progression). Only one patient had an AE leading to treatment discontinuation (encephalitis). In 14 evaluable patients, 11 (73%) achieved a best response of stable disease. In the MTD evaluable set (n=15 monotherapy, n=3 combination therapy), no DLTs were reported during the MTD evaluation period. The MTD has not been reached; dose escalation is ongoing.

Conclusions: BI 770371 showed manageable toxicity alone and in combination with ezabenlimab. The trial is ongoing.

Clinical trial identification: NCT05327946.

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698P Interim results from a phase I/II study of HPN328, a tri-specific, half-life (T1/2) extended DLL3-targeting T cell engager in patients (pts) with small cell lung cancer (SCLC) and other neuroendocrine neoplasms (NEN)

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Background: HPN328 is a delta-like canonical Notch ligand 3 (DLL3)-targeting T-cell engager (TCE). HPN328 has 3 binding domains including anti-DLL3 for target engagement, anti-albumin for half-life extension, and anti-CD3 for T cell engagement and activation.

Methods: Pts with relapsed/refractory, metastatic SCLC and other NEN associated with DLL3 expression are eligible. Primary objectives are safety, determination of the maximum tolerated dose (MTD), and pharmacokinetics (PK). Secondary objectives are immunogenicity and efficacy. HPN328 is administered IV once weekly with a priming dose preceding the target dose in higher dose cohorts. Adverse events (AEs) are graded (G) by CTCAE 5.0, and ASTCT for cytokine release syndrome (CRS).

Results: As of 18Apr23, 44 pts received HPN328 doses of 0.015-24 mg across 11 cohorts (SCLC [n=29;66%]; NE prostate cancer [NEPC, n=6;14%]; other NEN [n=9;20%]). Median number of prior regimens was 2 (1-5); 59% previously received a PD-1/PD-L1 blocker. Treatment is ongoing in 20 pts. Treatment-related AEs in >10% of pts included CRS (46%), fatigue (23%), dysgeusia (21%), nausea (18%), pyrexia and vomiting (16% each), and anemia (11%). The 27 CRS events were G1 (n=14); G2 (n=11); G3 (n=2). G3 CRS was a dose-limiting toxicity (DLT) in 2 pts at a priming dose of 2 mg; dose escalation continues with a reduced priming dose to 1 mg. Three pts (2 SCLC, 1 NEN) have had confirmed partial response and an additional pt with SCLC had an initial report of complete response following the data cut-off date. Three pts remained on therapy for >1 year. HPN328 exhibited linear PK with dose-proportional increases in exposure and a median $T_{1/2}$ of 71 hrs. Transient increases in cytokines up to 24 hrs post-dose and T-cell activation were observed.

Conclusions: HPN328 is well tolerated and clinically active. MTD determination and dose escalation are ongoing. Future planned cohorts include every other week dosing and HPN328 + atezolizumab. Updated safety and efficacy results including pts recently enrolled in backfill cohorts will be presented.

Clinical trial identification: NCT04471727.

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699P Immunogenicity and reactogenicity of BNT162b2 COVID-19 mRNA vaccine in long-survivor (LS) patients with metastatic lung cancer (mLC) after primary immunization (PV) and booster (BD): COVALENCE study

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Background: As COVID-19 will likely became an epidemic disease, vaccination planning will be crucial for LS-mLC receiving anti-cancer therapy (ACT) in order to prolong effective immunity

Methods: According to the timing of BD and Sars-Cov2 infection (Cov-I) during oncological history, LC pts were allocated in three cohorts: A) Cov-I before PV or third BD; B) uninfected who completed PV during ACT; C) uninfected LC who had completed PV before cancer diagnosis and will receive BD after stating of ACT. As control cohorts, we included other cancer patients (mOC pts) who had completed PV and were candidate to BD during myelosuppressive (cohort D) or not-myelosuppressive (cohort E) ACT. The primary endpoints were seroprevalence of IgG Anti-spike-RBD (anti-S IgG) at two pre-defined time-points (T1: +30-90 days after BD; T2: + 6 months +/- 4 weeks after BD). As exploratory endpoint, we compared median pre-vaccination value of four cytokines (IL-6, IL-2R, TNF-α, IL-10) with post-BD values in immunotherapy-treated pts (IT-pts)

Results: Between October 2021 and February 2022, 113 LS-mLC patients were assigned in cohort A (20 pts), in cohort B (61 pts) or in cohort C (32 pts); 55 LS-mOC patients were allocated in cohort D (25 pts) and in cohort E (30 pts). Throughout the Omicron variant spread, 40 pts (24%) experienced Cov-I before T2 evaluation. Anti-S IgG qualitative seropositivity rate was 100% at T1 and 98.8% at T2. After 6-months FU, hybrid immunization (Cov-I before or after BD), was associated with higher median anti-S IgG trier compared to vaccine alone-induced immunity ($p = <0.0001$). In uninfected pts, median anti-S IgG titre was significantly lower in IT-treated patients compared to non-IT treated patients ($p = 0.02$); no difference was found when comparing myelosuppressive or not ACT. Among 68 IT-pts, 5 pts (7.3%) showed significant increase ($\geq$ 1.5 fold) of at least two cytokines in post-BD samples, without reporting ir-AE

Conclusions: Administration BDs of COVID-19 mRNA vaccine in LS-mLC pts resulted effective and safe. In IT-pts without recent Cov-I, additional BDs should be considered to prolong serological immunity

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700P First-in-human dose-escalating study of ABSK043, a novel and oral small-molecule inhibitor of PD-L1, in patients with advanced solid tumors

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Background: Immunotherapies targeting the PD-1/PD-L1 pathway with therapeutic antibodies have shown remarkable anti-tumor effects. Comparing to antibodies, small molecules render lower immunogenic risk and convenience in administration. ABSK043 is an oral small molecule PD-L1 inhibitor that potently blocks PD-1 and PD-L1 interaction. Here, we report the preliminary results from the first-in-human (FIH) study of ABSK043.

Methods: The FIH study evaluated the safety, tolerability, PK, PD, and preliminary efficacy of ABSK043. Dose escalation adopted the BOIN design, and ABSK043 was given orally QD or BID in patients with advanced solid tumors. PD assessments included PD-L1 inhibition and T-cell function.

Results: As of February 2023, 19 pts were enrolled in 5 doses from 200mg QD to 800mg BID in Australia. No DLT was observed and MTD was not reached. The most common (≥10%) TRAEs were rash (10.5%) and decreased appetite (10.5%). No peripheral neuropathy was reported. A grade 3 treatment-related thyroiditis with hyperthyroidism was reported in one patient (400mg BID) who recovered after steroid therapy. No grade 4 or 5 AEs occurred. Among 7 response evaluable pts in BID dosing, two were genomic instability, one endometrial carcinoma with MSI-H/dMMR (600mg BID) and one breast cancer with Lynch syndrome (400mg BID), both achieved partial response and were IO-naïve. ABSK043 depleted over 90% of surface PD-L1 on ex vivo stimulated whole blood in a dose dependent manner. BID dosing enhanced PD-L1 inhibition. Furthermore, ABSK043 decreased soluble PD-L1 levels in serum. Increases in IL-2 with ex vivo stimulation, CXCL9, and IFN-γ levels were observed post-treatment, indicating the activation of T cells.

Conclusions: ABSK043 was well tolerated up to 800 mg BID with no DLT reported. On-target PD effects were consistent with PD-L1 inhibition and data reported by anti-PD-(L)1 mAbs. Preliminary anti-tumor activity was observed, and further studies are warranted to explore the efficacy in a larger number of patients.

Clinical trial identification: NCT04964375.

Legal entity responsible for the study: Abbisko Therapeutics Australia Pty. Ltd.

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701P NCI10221: Phase II multicenter biomarker driven combination trial of copanlisib and nivolumab in patients with molecularly-selected advanced solid tumors (BaCoN)

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Background: Preclinical data showed antitumor efficacy with PI3K and PD-1 combined blockade. We hypothesized that efficacy will be enriched in tumors with *PIK3CA* hotspot and *PTEN* mutations vs those without. This provided rationale for this 3-arm trial of copanlisib (pan-PI3K inhibitor) and nivolumab (PD-1 inhibitor) in patients (pts) with: (1) activating *PIK3CA* hotspot mutations, (2) inactivating *PTEN* mutations or *(3)* wildtype (WT) for *PIK3CA/PTEN* mutations (NCT04317105).

Methods: Copanlisib was started as monotherapy in cycle 1 at 60 mg IV D1, 8, 15, before nivolumab was added from cycle 2 at 480 mg IV every 28 days. Fresh tumor biopsies and ctDNA were mandated in all pts at baseline, copanlisib monotherapy, on combo and at progression. Prior PD-1/L1 or PI3K inhibitors (PD-1/L1i or PI3Ki) were allowed. Objectives were safety, antitumor activity and analyses of sequential tumors (WES; RNA-Seq; RPPA) and ctDNA.

Results: 50 pts (M:F 17:33; ECOG PS 0:1 18:32; mean age 58 years (27-79) with ovarian (n=12), breast (n=10), HNSCC (n=4), bile duct (n=3), NSCLC (n=3), prostate (n=3), colon (n=3), gallbladder (n=2), leiomyosarcoma (n=2), salivary gland (2), bladder, cervical, endometrial, liposarcoma, sarcoma, skin (n=1) cancers enrolled. Pts with *PIK3CA* hotspot (n=16), *PTEN* (n=18), and WT (n=16) tumors enrolled. 31/50 pts had ≥3 lines of prior therapy; 23 (46%)/50 pts had prior PD-1/L1i and 3 (6%)/50 prior mTOR inhibitors. Common toxicities: G1/2 nausea (35%), rash (24%), diarrhea (24%), mucositis (20%), anemia (20%), fatigue (18%), hyperglycemia (18%); ≥ G3 transient hypertension (24%). RECISTv1.1 CR/PR in *PIK3CA* and *PTEN* cohorts were achieved in 4 (27%)/15 (1 cPR; 3 uCR/PR) pts and 3 (20%)/15 (3 cPR) pts, vs 0/15 (0%) pts in WT cohort. Responses were deep (up to -100%) and durable (up to 15+ months). Clinical benefit rate (SD>4 months/CR/PR) was 29% across cohorts; 40% in *PIK3CA* hotspot cohort, 33% in *PTEN* cohort and 13% in WT cohort.

Conclusions: The combination of copanlisib and nivolumab is well tolerated with antitumor activity in pts with *PIK3CA* hotspot and *PTEN* mutations including PD-1/L1i-exposed pts. Translational analyses are ongoing.

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702P Characterization of germline HLA genotypes in patients (pts) with solid tumors treated with immunotherapy

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Background: Human leukocyte antigens (HLAs) are expressed in a variety of cells, including cancer cells and immune cells. Recent studies have shown that germline HLA gene zygosity, supertype and individual HLA genotypes may be associated with immunotherapy (IO) outcomes. We aimed to evaluate whether germline HLA-A gene haplotype and zygosity is associated with response to IO.

Methods: Pts enrolled in phase 1 clinical trials in the Vall dHebron Institute of Oncology Early Drug Development Unit with available HLA-A testing were reviewed. Median progression free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: From 2021 to 2023 a total of 247 eligible pts were reviewed. Median age was 59y, 63% female, main types of tumor with positive HLA biomarker were colorectal/anal cancer 19% (47pts), gynecological tumors 14%(34pts); and breast cancer 14% (34pts). Alleles present at >5% samples: 02:01:01 25%, 01:01:01 11%, 03:01:01 11%, 24:02:01 9%, 29:02:01 8%. Twenty-five (10.20%) pts presented HLA-A homozygosis. Homozygosis occurred in the most common haplotypes: 02:01:01 (14pts), 01:01:01 (2pts), 03:01:01 (4pts%), 24:02:01 (2pts%) and 29:02:01 (2pts). Eighty-five (34.5%) pts received IO; main types of tumors that received IO were genitourinary tumors 67% (10pts), gynecological tumors 45% (16pts) and colorectal/anal tumors 27% (13pts). Pts treated with anti-PD1 were 17 (20%), anti-PDL1 17 (20%) and other combinations 20 (24%). Twelve patients (17%) had PR, and thirty eight (45%) SD. Overal PFS and OS was 6.1 months and 29.6 months respectively. Presence of 03:01:01 was associated with a higher likelihood of response. Six pts with HLA homozygosis received inmunotherapy, all of them achieved SD as best response (NS).

Conclusions: Prevalence of HLA 02:01:01 in our population is significantly lower than reported in other populations. Presence of Homozygoses was not significantly associated with lack of response to inmunotherapy.

Legal entity responsible for the study: The authors.

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703P Prognostic scores for immunotherapy-based phase one trials (P1T): To GRIm or not to GRIm?

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Background: Prognostic scores are useful to better select patients (pts) who may benefit from P1T. The Royal Marsden Hospital (RMH) score (Lactate deshydrogenase (LDH), albumin, number of metastatic sites) was the first validated prognostic score in the area of chemotherapy and targeted agents (TA) P1T. More recently, GRIm-Score (LDH, albumin, neutrophil-to-lymphocyte ratio) was shown as a better prognostic score for patients treated with immune-checkpoint therapies. We aimed to compare RMH and GRIm scores in the area of new immunotherapy (IT) agents P1T, monotherapy or in combination.

Methods: We performed a retrospective analysis of adult pts enrolled into P1T evaluating at least one IT at the Centre Léon Bérard, between 2012 and 2022. Univariate and multivariate analyses were conducted to assess the prognostic value of RMH and GRIm scores at screening for overall survival (OS) and progression-free survival (PFS).

Results: We identified 411 pts from 36 P1T, of whom 119 (29.0%) received IT monotherapy, 240 (58.4%) bi-IT, 49 (11.9%) IT monotherapy associated with TA and 3 (0.7%) IT triplet. The median age was 62 years [20 - 83] and the median number of previous lines was 2 [0 - 11]. The most common tumor types were colorectal (n=69), pancreatic (n=52), breast, (n=45), lung cancers (n=45), melanoma (n=31) and urothelial carcinomas (n=27). The median OS was 8.8 months [95%CI 7.7 − 10.0] and the median PFS, based on iRECIST criteria, was 2.2 months [95%CI 2.0 − 2.7]. At screening, 77.1% of patients (n=317) had a favorable RMH score (<2) and 81.5% (n=326) had a favorable GRIm-score (<2), with a discordance of 14.8% between both scores. In multivariate analyses, a favorable GRIm-score was associated with better OS (HR 0.47 [95% CI 0.34-0.65, $p < 0.001$), together with Performans Status (PS) 0 vs 1 (HR 0.76 [95% CI 0.59-0.99], $p = 0.039$) whereas RMH was not (HR 0.75, 95%CI [0.53-1.05], $p = 0.091$). Similarly, GRIm-score and PS were associated with better PFS, with respective HR 0.65 [95%CI 0.50 − 0.85], $p = 0.002$ and 0.66 [95% CI 0.53-0.82], $p < 0.001$, contrary to RMH.

Conclusions: While our results confirm RMH as suboptimal to determine the prognosis of patients included in P1T trials evaluating IT, GRIm-score and PS at screening both appear as highly reliable prognostic factors.

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704P Regional differences in drug-induced lung disease (DILD) caused by anticancer drugs between the US, EU and Japan: A large-scale data-based analysis using the FDA Adverse Event Reporting System (FAERS)

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Background: DILD is a significant adverse event with a high fatality rate, and risk factors related to DILD have not been determined. Previous reports indicated regional differences in DILD. However, no large-scale data-based analyses investigating regional differences in DILD have been reported.

Methods: Adverse events report from the FAERS between January 2010 and December 2020 were collected. Regional differences in DILD incidence were examined based on data from the United States (US), Europe (EU), and Japan (JP). Multivariable logistic regression analysis, including the type of agent (tyrosine kinase inhibitors: TKIs, immune checkpoint inhibitors: ICIs, antibody-drug conjugate: ADCs, and cytotoxic agents) as confounding factors, was performed to calculate the reporting odds ratios (RORs).

Results: We identified reports of DILD from the US, EU and JP (74548, 31009, and 23004). Results of univariate analysis showed significantly higher RORs of anticancer drugs for reports from JP and EU compared to those from the US (JP, ROR 4.432 [95% CI, 4.366-4.499], $p<0.001$; EU, ROR 1.291 [95%CI, 1.274-1.308], $p<0.001$). Results of multivariable analysis for each single agent regimen of anticancer drugs showed that, for all regimens, reports from JP had significantly higher RORs compared to those from the US (TKIs, ROR 3.274 [95%CI, 3.105-3.451], $p<0.001$; ICIs, ROR 2.170 [95%CI, 2.025-2.325], $p<0.001$; ADCs, ROR 2.335 [95%CI, 1.666-3.272], $p<0.001$; cytotoxic agents, ROR 3.989 [95%CI, 3.776-4.215], $p<0.001$). Reports from the EU showed higher RORs for TKIs and cytotoxic agents than the US, but no significant difference between ICIs and ADCs (TKIs, ROR 1.679 [95%CI, 1.594-1.769], $p=0.0034$; ICIs, ROR 1.041 [95%CI, 0.965-1.123], $p=0.2960$; ADCs, ROR 1.046 [95%CI, 0.763-1.434], $p=0.7804$; cytotoxic agents, ROR 1.418 [95%CI, 1.354-1.485], $p<0.001$).

Conclusions: Reports from JP had significantly higher RORs than those from the US for all anticancer drug regimens. Further, reports from the EU had higher RORs than the US for TKIs and cytotoxic agents, but no significant difference among ICIs and ADCs. Japanese patients may have a higher risk for DILD than US and EU patients.

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705P TIMES: A ctDNA tumor fraction based and externally validated nomogram to predict survival in cancer patients referred for early phase trials

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Background: Typical entry criteria in early phase studies include expected life expectancy greater than 3 months. However, this evaluation is quite subjective and more objective and reproducible tools are needed to improve patient selection for phase I trials. The quantification of ctDNA shed by measuring tumor fraction (TF) has been associated with prognosis in patients with solid tumors. Our objective was to develop and validate a nomogram integrating TF to predict overall survival in cancer patients referred for early phase studies.

Methods: All consecutive adult patients with an advanced solid tumor included between December 2020 and December 2021 in two precision medicine studies (BIP, NCT02534649, sponsor: Institut Bergonié, Bordeaux, France) and STING (NCT04932525, sponsor: Institut Gustave Roussy, Villejuif, France). All patients underwent comprehensive genomic profiling with the 324-gene FoundationOne®. TF was analyzed as a binary variable, indicating whether a specimen had TF $\geq$10% or TF $<$10%. Other variables included previously validated prognostic scores such as the Royal Marsden (RMHs: albumin, LDH, number of metastatic sites) and the GRIm (LDH, neutrophil/lymphocyte ratio, albumin) scores as well as their individual components.

Results: TF $>$ 10, the GRIM score and the RMH score were independent prognostic factors in the training dataset (BIP study n= 965 patients). We generated a nomogram based on TF, number of metastatic sites, albumine level and neutrophil/lymphocyte ratio. To determine the clinical usefulness of our nomogram, we compared it with the RMH and GRIM scores. For our nomogram, the area under the receiver operating characteristic curve (AUC) was 0.79 as compared with 0.65 and 0.68 for the RMH and GRIM scores respectively. In the validation dataset (STING study, n= 947), the AUC was 0.76 as compared with 0.60 and 0.64 for for the RMH and GRIM scores respectively. The nomogram was well-calibrated in both the training and validation datasets.

Conclusions: This is the first prospective analysis confirming that TF is a strong prognostic factor in patients with advanced solid tumors. The TIMES nomogram represent an helpful tool in the process of patient selection for phase I trial entry.

Clinical trial identification: NCT02534649; NCT04932525.

Legal entity responsible for the study: Institut Bergonié.

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Disclosure: All authors have declared no conflicts of interest.

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706P The IMPRESS-Norway trial: Improving public cancer care by implementing precision cancer medicine in Norway - Safety analysis of the first 126 patients included in the trial

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Background: IMPRESS-Norway is a national, prospective, investigator-initiated, open-label, non-randomized combined basket and umbrella precision medicine trial. Patients with advanced malignancies with no further treatment options are included and treated in multiple treatment cohorts, defined by tumor type, molecular alteration and study drug.

Methods: The trial started recruitment in April 2021, and by February 2023, 126 patients were included in treatment cohorts. Patients were treated with: trametinib (n=28); pertuzumab+trastuzumab (n=25); atezolizumab (n=19); vemurafenib+cobimetinib (n=16); trametinib+dabrafenib (n=12); alpelisib (n=11); pemigatinib (n=6); atezolizumab+ bevacizumab (n=4); vismodegib (n=3); alectinib (n=1) and imatinib (n=1). Per protocol, adverse events (AEs) grade $\geq$ 3 and serious adverse events (SAEs) are collected, allowing us to perform a preliminary safety analysis of currently treated patients.

Results: In total, 172 AEs and 131 SAEs were reported by February 2023. 32% of all AEs, were considered as not related or unlikely related to treatment, 35% were classified as possibly related and 27% as related to treatment. Conversely, 60% of the SAEs we considered as not related or unlikely related to treatment, 28% as possibly related and 10% as related to treatment. Ten AEs and two SAEs were still not evaluated at the time of data collection. Six deaths were registered during the treatment period, one considered to be treatment related, and four suspected unexpected serious adverse reactions (SUSARs) were reported. Nine patients discontinued treatment permanently due to AE**.** Detailed analysis and updated results will be presented.

Conclusions: We report preliminary safety analysis of eleven drugs or drug combinations used in the IMPRESS-Norway trial. All drugs are used outside of their current indications. These first results show safety profiles consistent with toxicities reported in earlier trials.

Clinical trial identification: EudraCT 2020-004414-35; NCT04817956.

Legal entity responsible for the study: Oslo University Hospital.

Funding: The regional health authorities of Norway, Norwegian Cancer Society, The Norwegian Radium Hospital Legats and Nordforsk is offering financial support. Roche, Novartis, Eli Lilly, AstraZeneca, Incyte and Merck are providing the study drugs and financial support.

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Novartis satellite meeting, Nordic Lung Cancer meeting, 2022: Novartis; Financial Interests, Institutional, Other, Debate, precision medicine, Oslo 2022 : Merck; Financial Interests, Institutional, Other, Participation, round table, Cholangiocarcinoma; Nordic meeting 2021: Incyte; Financial Interests, Institutional, Coordinating PI, Funding of 500 FMliquid test to patients in the IMPRESS-Norway trial: Roche Norway; Financial Interests, Institutional, Coordinating PI, Funding of TSO500 liquid tests for 500 patients in the IMPRESS-Norway trial: Illumina; Non-Financial Interests, Leadership Role, InPreD is an establishment in the public health care, securing disciplinary work when implementing precision diagnostics for cancer: National Infrastructure for Precision Diagnostics (InPreD); Non-Financial Interests, Leadership Role, A network structure established as part of the public health care system, to share knowledge, build competence and work with harmonisation and standardisation to implement precision medicine: National Competence Network for Precision Medicine; Non-Financial Interests, Leadership Role, Head of working group for molecular pathology and for the Norwegian association for molecular pathology: The Norwegian Association of Pathology. K. Tasken: Financial Interests, Personal, Advisory Board, Company established based on innovation in my lab. Holds stock and Scientific advisor: Serca Pharmaceuticals; Financial Interests, Personal, Stocks/Shares, Stock and Stock options, and royalty agreement through Oslo UniversityHospital / University of Oslo Tech Transfer Office Inven2 AS: Serca Pharmaceuticals; Financial Interests, Personal, Stocks/Shares: Ledidi; Financial Interests, Personal, Royalties, Stock and Stock options, and royalty agreement through Oslo UniversityHospital/University of Oslo Tech Transfer Office Inven2 AS: Serca Pharmaceuticals; Financial Interests, Institutional, Steering Committee Member, IMPRESS-Norway trial Trial Management & Steering Committee: Roche; Financial Interests, Institutional, Steering Committee Member, IMPRESS Norway trial Trial Management & Steering Committee: Novartis, Lilly, Incyte, Merck KGaA, AstraZeneca, Illumina. A. Helland: Financial Interests, Institutional, Advisory Board, Advisory boards: Jansen, Takeda, AstraZeneca, AbbVie, Roche, BMS, Pfizer, MSD, Bayer, Lilly,; Financial Interests, Institutional, Invited Speaker, talks at meetings: AstraZeneca, Roche, AbbVie, Pfizer; Financial Interests, Institutional, Coordinating PI, BMS provides drug to patients in an investigator initiated clinical trial: BMS; Financial Interests, Institutional, Coordinating PI, Ultimovacs provides drug and funds for investigator initiated clinical trial: Ultimovacs; Financial Interests, Institutional, Coordinating PI, AstraZeneca provides drug and funds for investigator initiated clinical trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, Roche provides drug and funds for investigator initiated clinical trial: Roche; Financial Interests, Institutional, Coordinating PI, Novartis provides drug and funds for clinical trial: Novartis; Financial Interests, Institutional, Coordinating PI, Eli Lilly provides drug and funds for clinical study: Eli Lilly; Financial Interests, Institutional, Coordinating PI, Incyte provides drug and funds for clinical study: Incyte; Financial Interests, Institutional, Coordinating PI, Illumina provides assays for patients in a clinical trial: Illumina; Non-Financial Interests, Other, Board member in the patient organisation until 2022. Provides advice and gives talks: The lung cancer patients organisation. All other authors have declared no conflicts of interest.

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707P Personalised dosing of oral targeted therapies in oncology: The era of therapeutic drug monitoring

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Background: Although oral targeted therapies used in oncology demonstrate high interpatient variability in pharmacokinetics (PK), resulting in overdosing (>15%) and underdosing (30%) of patients (pts), a standard fixed dose for all pts is still used. This could lead to unnecessary toxicity and decreased efficacy, considering the established exposure—response and —toxicity relationships for many of these drugs. Personalised dosing through therapeutic drug monitoring (TDM) — individual dose adjustments based on measured PK—levels — could improve treatment outcomes. Results of 600 pts were published last year (Groenland et al, Ann Oncol. 1071-82, 2022 Oct). We hereby provide results of additional enrolment up to a 1000 pts, longer follow—up and newly reviewed cohorts.

Methods: This ongoing prospective study focusses on the feasibility, efficacy and tolerability of TDM of multiple oral targeted therapies in oncology. PK—levels are measured at 4—8—12 weeks after start of treatment and every 12 weeks thereafter. Recommendations are given based on established efficacy targets. Recommended interventions include dose adjustments, intake with food, split of intake moments, emphasize compliance and adjustment of interacting medication. An intervention is considered successful if there is a PK—level above target after intervention and if there is no dose limiting toxicity observed within one month.

Results: As of May 1st 2023, this study includes 1006 pts from 14 hospitals using one of 24 different oral targeted therapies. The largest cohorts are abiraterone (n = 189), imatinib (n = 165), sunitinib (n = 112) and pazopanib (n = 106). Among 916 evaluable pts, 41.3% (n = 378) had all PK—levels above target, while 58.7% (n = 538) had ≥1 PK—level below target. A PK-guided intervention was possible in 55.4% (n = 298), and was successful in 69.1% of cases. Of all pts with a PK-level below target, intervention was successful in 38.3%. As a result, there was a 22.5% gain in pts with PK-levels above target, reaching a total of 63.8% (n = 584).

Conclusions: The results of this study support the feasibility of TDM of oral targeted therapies in oncology. Before implementation, efficacy of TDM still requires further evaluation. For the largest cohorts this evaluation will be performed.

Clinical trial identification: Netherlands Trial Register NTR6866, Release date: 6 December 2017.

Legal entity responsible for the study: Netherlands Cancer Institute-Antoni van Leeuwenhoek.

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708P Final clinical outcomes of nationwide precision oncology pilot study; KOrean Precision Medicine Networking Group Study of MOlecular profiling guided therapy based on genomic alterations in advanced Solid tumors (KOSMOS) KCSG AL-20-05

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Background: Next generation sequencing (NGS) has become widely available but molecular profiling guided therapy (MGT) has not been established in the real world

due to a lack of available therapies and expertise to interpret and match treatment in Korea.

Methods: Patients with advanced solid tumors without remaining standard treatment were enrolled. Virtual, central molecular tumor boards (cMTB) reviewed patients' NGS reports and recommended clinical trials or investigational medicinal products (IMPs) as previously described (https://doi.org/10.1016/j.esmoop.2022.100653). Primary variable was to assess the proportion of patients with actionable genomic alterations and patients receiving MGT as MTB recommendations. Other variables were duration of treatment (DoT), overall response rate (ORR), disease control rate (DCR) and safety.

Results: From Feb 2021 to Feb 2022, 198 patients were enrolled. Median time from case submission to MTB discussion was 7 days (range, 2-20) and concordance rate between pre-MTB physicians' choice and MTB recommendations were 60.1% (119/198). A total of 107 (54.0%) received IMPs based on MTB decision (32, TE; 21, AZ; 14, TP; 13, BE; 8, AP; 6, CA; 5, DT; 4, AL; 3, EL; 1, BV). ORR and DCR were 13.3% (1 CR, 9 PR, 45 SD, and 20 PD), and 73.3%. DoT was 3.6 months (95% CI, 2.8-5.0) and 4 months DoT rate (4MDoTR) was 45.5%. DoT>12 months were observed in 10 (9.3%). TE showed a durable DoT, regardless of ERBB2 amplification and mutation (5.8 and 4.0 months), previous exposure of anti-HER2 targeted agents (4.0(No) vs. 5.4 months (Yes)), and high (6>) vs. low (6<) copy number variation (4.0 and 8.0 months).

Table: 708P

IMPs	ORR	DCR	4MDoTR	DoT(months)
Alectinib (AL)	33.3%	33.3%	50.0%	3.4
Alpelisib (AP)	50.0%	50.0%	42.9%	1.4
Atezolizumab (AZ)	21.4%	57.1%	30.0%	1.9
Bevacizumab (BV)	0.0%	100.0%	100.0%	8.3
Bevacizumab + erlotinib (BE)	9.1%	54.5%	33.3%	3.4
Capecitabine (CA)	0.0%	100.0%	0.0%	1.6
Dabrafenib + trametinib (DT)	50.0%	100.0%	60.0%	6.9
Erlotinib (EL)	0.0%	100.0%	66.7%	6.5
Trastuzumab and pertuzumab (TP)	0.0%	100.0%	57.1%	4.6
Trastuzumab emtansine (TE)	8.3%	75.0%	56.7%	4.2
All	13.3%	73.3%	45.5%	3.6

Conclusions: KOSMOS suggested the feasibility of nationwide cMTB guided MGT and also showed modest ORR, and a promising DCR in heavily pre-treated patients. KOSMOS-II (NCT05525858) is currently underway to confirm this in larger number of patients.

Legal entity responsible for the study: Korean Society of Medical Oncology, Korean Cancer Study Group.

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709P Challenges and opportunities to the implementation of adaptive design in phase III oncology trials: Results from a cross-sectional analysis

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Background: Adaptive design (AD) trials have been developed as an innovative alternative to conventional design (CD) trials with the aim of accelerating innovative medicinal products (InMP) clinical development. Despite AD concept adoption by major competent authorities the use and implementation of AD remains substantially lower than CD. There is an emerging need to better understand the operational characteristics contributing to the challenges and opportunities for wider implementation of AD into oncology InMP development.

Methods: Oncology InMPs approved by the FDA in 2018 were selected for cross-sectional analysis. The ClinicalTrial.gov (CT.gov) platform was used to identify phase III trials conducted with those InMPs between 2010-2021. Analysis was then accomplished by PubMed search for full manuscripts associated with these trials, as additional source to describe trial design and methodology.

Results: Of the 63 indentified phase III trials, 47 (75%) were CD and 16 (25%) were AD. Among the AD, 81% were conducted in solid tumours and 19% in haematological malignancies. AD was associated with several distinct operational characteristics vs CD: i) with comparable number of patients enrolled, median number of sites/trial was higher in AD (203 sites) vs CD (106 sites) leading to substantial differences in median number of patients per individual site observed in CD (35.9 patients) and AD (3.8 patients); ii) AD was clearly associated with higher median number of secondary endpoints (18 endpoints) vs CD (12 endpoints) and substantially shorter median duration of trial (43 months) vs CD (60 months; p=.0129), with potential cost savings of up to 30%; iii) limited details on the AD methodology and decision-making process at the time of interim analysis.

Conclusions: The implementation of AD in oncology InMP development remains low as compared to CD. A degree of AD operational complexity vs CD could have been balanced by assumed stricter patient monitoring and compliance to the study protocol and collection of a larger set of scientific data. With a comparable number of enrolled patients, AD could substantially shorten overall study duration, which in turn leads to trial's cost savings of up to 30%.

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710P A retrospective study on the safety and adequacy of fresh biopsies for next generation sequencing in early-phase clinical trials

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Background: Early-phase clinical trials are a unique opportunity for patients with cancer to benefit from innovative treatments. These trials usually demand newly-collected tumor tissue for research purpose, requiring patients to undergo new biopsies. Some trials require a prescreening by next-generation sequencing (NGS), but the analysis can be challenged by both the quality and the quantity of the samples. Biopsies may have procedural complications with negative impact on patients.

Methods: We retrospectively reviewed the records of patients referred to the Early Drug Development (EDD) Unit of European Institute of Oncology, who performed fresh biopsies for research purpose. We aimed at assessing safety of the biopsies and the adequacy of the tumor tissue for NGS testing.

Results: A total of 731 patients were referred to the EDD Unit from January 2014 to December 2022. Median age was 56 years (range 20 — 83) and 79% of patients were female. The most common tumor type was breast cancer (40%), followed by lung adenocarcinoma (6.2%), cholangiocarcinoma (5.8%), and carcinoma of unknown primary (5.8%). Three hundred fifty-five patients (48.6%) underwent a new biopsy at trial entry. Liver (148, 41.7%), lymph nodes (64, 18%), skin (47, 13.2%) and breast (7.3%) were the most frequent sites for biopsy. The median time from trial's informed consent to biopsy was 3 days (range 0 — 83). The tumor tissue was commonly adequate for histological diagnosis (98%); NGS testing was successful in 122 (88.4%) of the 138 cases in which the trial required NGS testing. Nine out of the 16 unsuccessful NGS were performed on liver tissue. Eleven patients (3.1%) had procedural complications from the biopsy (5 pain, 3 minor bleeding, 2 pneumothoraxes, 1 bradycardia), but none required hospitalization nor led to sequelae. The only treatments administered were painkillers.

Conclusions: Approximately half of the patients referred to our EDD Unit performed a fresh biopsy. The procedure was generally safe, with only a minority of patients (3%) having non-serious complications. About 10% of NGS failed due to poor sample quality or quantity, highlighting the importance to implement specific information and Standard Operating Procedure for samples intended for NGS.

Legal entity responsible for the study: Edoardo Crimini.

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711TiP A phase I/II, first-in-human, open-label, dose-escalation study of TAK-186, an EGFR × CD3ε COBRA T cell engager, in adult patients with unresectable, locally advanced, or metastatic solid tumors

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Background: TAK-186 is a COnditional Bispecific Redirected Activation (COBRA) T-cell engager designed to bind to epidermal growth factor receptor (EGFR). Protease-mediated activation of the prodrug, primarily in the tumor microenviroment, generates an active dimer of EGFR-bound TAK-186 which engages CD3 T cells via the CD3ε binding domain. As the tumor microenvironment has increased protease activity vs healthy tissues, TAK-186 could potentially have an improved safety profile and therapeutic efficacy in solid tumors compared with other T-cell engagers that do not depend on conditional activation.

Trial design: This is a first-in-human, open-label, phase 1/2 study of TAK-186 (NCT04844073), with a planned enrollment of ∼123 patients (pts) with unresectable, locally advanced/metastatic *EGFR*-expressing solid tumors, including but not limited to non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and head and neck squamous cell cancer (HNSCC). Eligibility criteria include age ≥18 yr, ECOG PS ≤1, and measurable disease per RECIST v1.1. Pts who received an immune checkpoint inhibitor (ICI) prior to enrollment must have ICI immune-related toxicity resolved to Grade ≤1 or baseline (prior to ICI). Key exclusion criteria include history of autoimmune disease, major surgery ≤8 wks or radiation therapy <2 wks before first dose of TAK-186, history of clinically significant cardiac or gastrointestinal disorders. The study will be conducted in two phases: a dose-escalation phase (sequential cohorts of escalating doses) followed by a cohort-expansion phase (advanced/metastatic *EGFR*-expressing NSCLC, CRC, HNSCC). Pts will be followed for survival after treatment discontinuation. The primary objective is characterization of safety, tolerability, and dose-limiting toxicities. Secondary objectives include characterization of pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary anti-tumor activity. Tumor evaluation will be done using RECIST 1.1 and modified RECIST 1.1. Safety data will be summarized by CTCAE v5.0. Cytokine release syndrome will be reported by ASTCT consensus grading. Recruitment is ongoing.

Clinical trial identification: NCT04844073.

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712TiP A phase I/II multicenter, open-label, dose-escalation, safety, pharmacodynamic, and pharmacokinetic study of Q901 administered via intravenous infusion in adult patients with selected advanced solid tumors with a cohort expansion at the recommended phase II dose

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Background: CDK7, part of the CAK complex regulates cell cycle progression, making it a potential therapeutic target for malignancies with aberrant cell cycle regulation. Cell cycle arrest in cancer cells affects DNA damage repair and genomic instability, potentially triggering apoptosis and anti-tumor immune response. Q901, is a potent covalent CDK7 inhibitor, with demonstrated *in vivo* activity against resistant models, and has potential as a treatment for various cancers where standard care has failed.

Trial design: This phase 1/2 multicenter, open-label study (NCT05394103) evaluates the safety, pharmacodynamics, and pharmacokinetics of Q901 in adult patients with solid tumors in the USA and Korea. In phase 1 dose escalation, Q901 is administered intravenously once weekly for four weeks, then once every two weeks in patients with advanced or metastatic ovarian, CRPC, HR^+ $HER2^-$ breast, endometrial, colorectal, small-cell lung, or pancreatic cancers. The study will establish the MTD, DLT, and RP2D of Q901 monotherapy, using a modified Toxicity Probability Interval (mTPI) design targeting a DLT rate of ∼30%. Up to 6 dose levels/50 patients will be evaluated in phase 1. Upon determining the RP2D, the study advances to phase 2. Cohort 1 will recruit HR^+ $HER2^-$ breast cancer patients receiving Q901 combined with fulvestrant, who have received at prior endocrine and CDK4/6 targeted treatment, along with up to two additional prior lines of systemic anticancer therapy. Cohort 2 consists of extensive-stage SCLC patients treated with Q901 monotherapy after failing first-line standard of care. Each cohort will enroll up to 20 patients to assess safety and activity in selected cancer types.

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713TiP **A phase I study of PRT3789, a potent and selective degrader of SMARCA2 in patients with advanced or metastatic solid tumors and a SMARCA4 mutation**

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Background: Genes encoding subunits of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex are often mutated in cancer, occurring in 20% of all human cancers (Shain *PLOS One* 2013 ; Fernando *Nat Commun* 2020). The SWI/SNF complex contains 1 of 2 mutually exclusive ATP catalytic enzymatic subunits, SMARCA2 (BRM) or SMARCA4 (BRG1). Cells with SMARCA4 loss rely on its paralog, SMARCA2, making it an attractive therapeutic target (Helming *Cancer Cell* 2014 ; Hoffman *PNAS* 2014 ; Oike *Cancer Res* 2013). Multiple tumor types have *SMARCA4* mutations, including thoracic sarcomas, lymphomas, and cancers of the lung, ovaries, and skin (Shain 2013 ; Fernando 2020). PRT3789 induces proteosome-dependent degradation of SMARCA2. Preclinical data indicate that PRT3789 is a potent and selective degrader of SMARCA2, which induces robust synthetic lethality in SMARCA4-deficient cancers.

Trial design: This phase 1 (NCT05639751), open label, multicenter, dose-finding study evaluates the safety, tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of PRT3789. Adults with advanced or metastatic solid tumors with a SMARCA4 mutation, who have progressed on, or are intolerant to, standard therapy are eligible to enroll. Other key eligibility criteria include measurable disease by RECIST v1.1 or nonmeasurable (but evaluable) disease, ECOG PS 0—1, and resolved acute effects of prior therapy. Successive cohorts will receive escalating doses of intravenous PRT3789 once weekly for 3 weeks (1 cycle). PRT3789 treatment will continue until disease progression or unacceptable toxicity, whichever occurs first. A Bayesian optimal interval method will inform dose escalation, de-escalation, or maintenance based on the number of patients with dose-limiting toxicities (DLTs), until the maximum tolerated dose and recommended phase 2 dose (RP2D) are determined. The primary endpoints are safety, tolerability, DLTs, and RP2D. Secondary endpoints include objective response rate, progression-free survival, duration of response, disease control rate, and PK and PD profiles of PRT3789. The study began enrolling patients in January 2023.

Clinical trial identification: NCT05639751.

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Calvo: Financial Interests, Personal, Advisory Board: Adcendo, Amunix, Anaveon, AstraZeneca, BMS, Janssen, MonTa, MSD, Nanobiotix, Nouscom, Novartis, Servier, TargImmune, T-knife, Chugai, Elevation Oncology, Ellipses Pharmacy, SyneosHealth, Genmab, Diaccurate; Financial Interests, Personal, Invited Speaker: OncoDNA, PharmaMar, Roche/Genentech; Financial Interests, Personal, Full or part-time Employment, Director, Clinical Research: HM Hospitales Group; Financial Interests, Personal, Full or part-time Employment, Medical Oncologist. Clinical Investigator. Director, Clinical Research: START Madrid - CIOCC (Centro Integral Oncológico Clara Campal); Financial Interests, Personal, Member of Board of Directors, External Independent member of Board of Directors: PharmaMar; Financial Interests, Personal, Ownership Interest: START, Oncoart Associated; Financial Interests, Personal, Steering Committee Member, Member of Data Monitoring Committee: BeiGene, Sanofi, Merus; Financial Interests, Personal, Steering Committee Member: Novartis; Non-Financial Interests, Other, Non-for-profit Foundation. President and co-founder: INTHEOS (Investigational Therapeutics in Oncological Sciences) non-for-profit Foundation; Non-Financial Interests, Advisory Role: PsiOxus; Non-Financial Interests, Other, Chair of the Independent Data Monitoring Committee: EORTC IDMC; Non-Financial Interests, Member of Board of Directors, Non-for-profit Foundation, trustee member: Non-for-profit Foundation PharmaMar; Non-Financial Interests, Advisory Role, Non-for-profit foundation: CRIS Cancer Foundation, non-for-profit ; Non-Financial Interests, Member: ASCO, ESMO, SEOM, EORTC. V. Moreno Garcia: Financial Interests, Personal, Advisory Board: BMS, Janssen, Roche, Basilea, Bayer, AstraZeneca; Financial Interests, Personal, Full or part-time Employment: START; Financial Interests, Institutional, Local PI, AbbVie, AceaBio, Adaptimmune, ADC Therapeutics, Aduro, Agenus, Amcure, Amgen, Astellas, AstraZeneca Bayer Beigene BioInvent International AB, BMS, Boehringer Ingelheim, Boston, Celgene, Daiichi Sankyo, Debiopharm, Eisai, e-Terapeutics, Exelisis, Forma Therapeutics, Genmab, GSK, Harpoon, Hutchison, Immutep, Incyte, Inovio, Iovance, Janssen, Kyowa Kirin, Lilly, Loxo, MedSir, Menarini, Merck, Merus, Millennium, MSD, Nanobiotix, Nektar, Novartis, Odonate Therapeutics, Pfizer, Pharma Mar, PharmaMar, Principia, PsiOxus, Puma, Regeneron, Rigontec, Roche, Sanofi, Sierra Oncology, Synthon, Taiho, Takeda, Tesaro, Transgene, Turning Point Therapeutics, Upshersmith: Multiple. A.A. Adjei: Financial Interests, Institutional, Coordinating PI, funding for clinical trial: Vyriad; Non-Financial Interests, Advisory Role, uncompensated Advisory Board member: Merck AG, Cagent Pharmaceuticals; Non-Financial Interests, Advisory Role, uncompensated Advisory Board Member: Zai Labs; Non-Financial Interests, Advisory Role, uncompensated Chair of Advisors: Swiss Rockets; Non-Financial Interests, Advisory Role, uncompensated advisor: Johnson and Johnson; Other, Editor-in-Chief of Journal of Thoracic Oncology and JTO CRR: International Association for the Study of Lung Cancer. P. Lorusso: Financial Interests, Personal, Advisory Board: AbbVie, Genmab, Genentech, CytomX, Takeda, Cybrexa, Agenus, IQVIA, TRIGR, Pfizer, ImmunoMet, Black Diamond, GSK, QED Therapeutics, AstraZeneca, EMD Serono, Shattuck, Astellas, Salarius, Silverback, MacroGenics, Kyowa Kirin, Kineta, Zentalis, Molecular Templates, ABL Bio, STCube, Bayer, Seagen, imCheck, Relay Therapeutics, Stemline, Compass BADX, Mekanist, Mersana, BAKX Therapeutics, Scenic Biotech, Qualigen, Roivant Sciences, NeuroTrials; Financial Interests, Personal, Other, Data Safety Monitoring Board: Agios, Five Prime, Halozyme; Financial Interests, Personal, Other, imCORE Alliance: Roche-Genentech; Financial Interests, Personal, Other, Consultant: Sotio, SK Life; Financial Interests, Personal, Other, Data Safety Monitoring Committee: Tyme; Financial Interests, Personal, Advisory Board, Advisory Board & Consultant: I-Mab; Financial Interests, Personal, Stocks/Shares: BAXK; Financial Interests, Institutional, Local PI: AbbVie, ADC Therapeutics, ALX Oncology, Astellas Pharma, Astex Pharmaceuticals, AstraZeneca, Bayer, Black Diamond, Boehringer Ingelheim, Calico Life Sciences, Corvus Pharmaceuticals, CytomX Therapeutics, Eisai Pharmaceuticals, Eli Lilly, EMD Sernono, Five Prime, FLX Bio, F-Star Delta Limited, Genentech, Genmab, Incyte, Linnaeus Therapeutics, MedImmune, Merck Sharp & Dohme, Moderna Therapeutics, NextCure, Pfizer, Ribon Therapeutics, Sotio, Stemline Therapeutics, Takeda, Tesaro, Jounce; Non-Financial Interests, Other, AACI Clinical Research Innovation Steering Committee - Member: Association of American Cancer Institutes; Non-Financial Interests, Other, AACR Methods in Clinical Cancer Research Workshop-Co-Director: American Association for Cancer Research; Non-Financial Interests, Other, AACR Annual Report Committee-Member: American Association for Cancer Research; Non-Financial Interests, Other, Continuing Medical Education Committee-Member: American Association for Cancer Research; Non-Financial Interests, Other, Molecular Cancer Therapeutics Editorial Board-Member: American Association for Cancer Research; Non-Financial Interests, Other, ASCO Conquer Cancer Young Investigator Award Grand Selection Committee - Member: American Society of Clinical Oncology; Non-Financial Interests, Other, New Drugs in Oncology Seminar Planning Committee - Member: American Society of Clinical Oncology; Non-Financial Interests, Other, New Agents Committee: Translational Research Panel-Chair: Cancer Research Unite Kingdom; Non-Financial Interests, Other, Scientific Advisory Board-Member: Targeted Anti-Cancer Therapies; Non-Financial Interests, Other, Chair-Phase 0 Task Force: American Association of Cancer Research; Non-Financial Interests, Member: American Association for Cancer Research, ASCO; Other, Investigational Drug Steering Committee-Committee Member: National Cancer Institute; Other, Phase I Special Emphasis Panel-Grant Reviewer/Discussion Leader: National Cancer Institute; Other, NeXT Special Emphasis Panel-Grant Reviewer: National Cancer Institute/National Institute of Health; Other, Board of Scientific Counselors, Clinical Sciences & Epidemiology: National Cancer Institute; Other, Young Investigator Meeting, Cancer Therapy Evaluation Program - Professor: National Cancer Institute; Other, Academic Advisory Board SPORE GI Malignancies - Case Western Reserve University: Case Western Reserve University; Other, External Advisory Board - Member: University of Arizona; Other, External Scientific Advisory Board-Member: University of New Mexico; Other, Scientific External Advisory Board-Member: University of California at San Diego. S. Punekar: Financial Interests, Institutional, Local PI, Clinical Trial PI: Revolution Medicine, Simcere Pharmaceuticals, Astellas Pharmaceuticals, Constellation, A2Bio, Vitrac; Non-Financial Interests, Principal Investigator, Clinical Trial PI: Revolution Medicine, A2Bio, Simcere, Constellation, Vitrac, Astellas Pharmaceuticals. T.A. Leal: Financial Interests, Personal, Advisory Role: Janssen, Mirati, Merck, AstraZeneca, Daiichi-Sankyo, Takeda, EMD Serono, Eisai, Novocure, Amgen, Roche, Regeron, Jazz; Financial Interests, Institutional, Research Funding: Pfizer, Advaxis. T.A. Yap: Financial Interests, Personal, Other, Consultant: Almac, Aduro, AstraZeneca, Atrin, Axiom, Bayer, Bristol Myers Squibb, Clovis, Cybrexa, EMD Serono, Guidepoint, Ignyta, I-Mab, Jansen, Merck, Pfizer, Repare, Roche, Schrodinger, Varian, Zai Labs, AbbVie, Acrivon, Adagene, Amphista, Artios, Athena, Avoro, Baptist Health Systems, Calithera, Beigene, Boxer, C4 Therapeutics, Cancer Research UK, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Institut Gustave Roussy, Diffusion, Idience, ImmuneSensor, Intellisphere, Kyn, MEI Pharma, Mereo, Natera, Nexys, Novocure, Pegascy, PER, Piper-Sandler, Prolynx, resTORbio, Theragnostics, Xinthera, OHSU, OncoSec, Ono Pharma, Versant, Vibliome, ZielBio, Radiopharm Theranostics, Sanofi, CUHK Committee, Pliant Therapeutics, Ellipses.Life, LRG1, Panangium, Seagen, Synthis, Tessellate Bio, TD2 Theragonostics, Tome Biosciences, Zentalis; Financial Interests, Personal, Other, University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios): MD Anderson Cancer Center, Institute for Applied Cancer Sciences; Financial Interests, Personal, Stocks/Shares: Seagan; Financial Interests, Institutional, Other, Grant/Research support: Bayer, Cyteir, EMD Serono, GlaxoSmithKline, Karyopharm, Pfizer, Repare, Sanofi, Artios, AstraZeneca, Beigene, BioNTech, Blueprint, BMS, Clovis, Constellation, Eli Lilly, Forbius, F-Star, Haihe, ImmuneSensor, Ionis, Ipsen, Jounce, Ribon Therapeutics, Genentech, Novartis, KSQ, Kyowa, Merck, Mirati, Regeneron, Tesaro, Rubius, Scholar Rock, Seattle Genetics, Vivace, Acrivon, Zenith; Financial Interests, Institutional, Research Grant: Ideaya, Boundless Bio; Financial Interests, Institutional, Other, Grant/Research Support: Acrivon. A. Italiano: Financial Interests, Personal, Other, Honoraria: AstraZeneca, Bayer, BMS, Lilly, Merck, MSD, Novartis, Parthenon, PharmaMar, Roche; Financial Interests, Personal, Advisory Role: AstraZeneca, Bayer, BMS, Lilly, Merck, MSD, Novartis, Parthenon, PharmaMar, Roche; Financial Interests, Personal, Research Funding: AstraZeneca, Bayer, BMS, Lilly, Merck, MSD, Novartis, Parthenon, PharmaMar, Roche. W. Novotny: Financial Interests, Personal, Full or part-time Employment: Prelude Therapeutics; Financial Interests, Personal, Leadership Role: Prelude Therapeutics; Financial Interests, Personal, Stocks or ownership: Prelude Therapeutics; Financial Interests, Personal, Other, Travel,

Accommodations, Expenses: Prelude Therapeutics. C. Tankersley: Financial Interests, Personal, Full or part-time Employment: Prelude Therapeutics; Financial Interests, Personal, Stocks or ownership: Prelude Therapeutics; Financial Interests, Personal, Other, Travel, accommodation or paid expenses: Prelude Therapeutics. S. Rowe: Financial Interests, Personal, Full or part-time Employment: Prelude Therapeutics. W. Sun: Financial Interests, Personal, Financially compensated role: Prelude Therapeutics. A.I. Spira: Financial Interests, Personal, Other, Consulting or Advisory Role: Incyte, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Array Biopharma, Blueprint Medicines; Financial Interests, Personal, Other, Consulting or Advisory Role / Honoraria: Amgen, Novartis, Takeda, AstraZeneca/MedImmune, Merck, Bristol Myers Squibb; Financial Interests, Personal, Other, Honoraria: CytomX Therapeutics, Janssen Oncology, Bayer; Financial Interests, Institutional, Officer, CEO: NEXT Oncology Virginia; Financial Interests, Personal, Stocks/Shares: Eli Lilly; Financial Interests, Institutional, Local PI: LAM Therapeutics, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Newlink Genetics, Incyte, AbbVie, Ignyta, Trovagene, Takeda, Macrogenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen Oncology, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Kezar, Revolution Med. B. Besse: Financial Interests, Institutional, Funding: 4D Pharma, AbbVie, Amgen, Aptitude Health, AstraZeneca, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Celgene, Cergentis, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, GSK, Janssen, Onxeo, OSE Immunotherapeutics, Pfizer, Roche-Genentech, Sanofi, Takeda, Tolero Pharmaceuticals; Financial Interests, Institutional, Research Grant: Chugai pharmaceutical, EISAI, Genzyme Corporation, Inivata, Ipsen, Turning Point Therapeutics. All other authors have declared no conflicts of interest.

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714TiP A phase Ia/Ib, first-in-human, dose-escalation study evaluating the safety, tolerability, and efficacy of IOS-1002, a LILRB1, LILRB2, and KIR3DL1 targeting HLA-derived fusion protein administered alone or in combination with a PD-1 antibody in patients with advanced solid tumors

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Background: IOS-1002 is a recombinant homodimer of the human leukocyte antigen B57 free heavy chain linked to a human IgG4 Fc backbone associated with human β2 microglobulin. The binding of IOS-1002 to LILRB1, LILRB2, and KIR3DL1 receptors blocks the interaction with tumor-expressed ligands such as HLA-G. Through this mechanism, IOS-1002 enhances the immune response of diverse sets of both innate and adaptive immune cells and leads to tumor cell killing. The anti-tumor effect is enhanced by combining IOS-1002 with a PD-1 check point blockade inhibitor in preclinical models The present study evaluates the safety, tolerability, pharmacokinetics, efficacy, immunogenicity, and pharmacodynamics of IOS-1002 as monotherapy and as combination therapy with a PD-1 monoclonal antibody in subjects with advanced solid tumors.

Trial design: The phase 1a/1b trial is being conducted at five sites in Australia and has started enrollment as of March 2023. The trial is separated in 2 parts: Dose Escalation (A): Subjects are enrolled into 10, 30, 100, 300, 800, and 1200 mg dose levels sequentially and treated with IOS-1002 Q2W IV. Guided by the dose-limiting toxicities (DLTs) observed, an accelerated dose titration design is used for the first 3 dose levels followed by a 3+3 dose escalation. The DLT period is defined as 4 weeks following cycle 1 day 1 infusion. Once monotherapy reaches the 800 mg dose level, the combination therapy with a 3 + 3 dose escalation starts at a dose of 300 mg Q2W for IOS-1002 in combination with a PD-1 mAb at approved dose and schedule. The IOS-1002 RP2D or MAD as identified for monotherapy and PD-1 combination will then be used in the dose expansion part. Dose Expansion (B): Following the toxicity and activity profile observed in part A, a tumor-specific cohort expansion study in up to 6 potential disease entities with 20 patients per cohort will be initiated, 3 as IOS-1002 monotherapy and 3 as IOS-1002 + PD-1 combination. Depending on the disease entity and line of treatment, the PD-1 cohort will include PD-1 naïve, pre-exposed and refractory patients, respectively.

Clinical trial identification: Clinical Trials Registry Number: NCT05763004.

Legal entity responsible for the study: ImmunOs Therapeutics AG.

Funding: ImmunOs Therapeutics AG.

Disclosure: C. Berger, M. Gualandi, A. Rafiei, C. Renner: Financial Interests, Personal, Full or part-time Employment: ImmunOs Therapeutics. All other authors have declared no conflicts of interest.

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715TiP ARTS-021-1001: Phase I/II study of ARTS-021, a potent, oral administrated, selective CDK2 inhibitor, in advanced or metastatic solid tumors

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Background: ARTS-021 is an investigational, reversible, orally administrated CDK2 selective inhibitor that inhibits CDK2 at nanomolar potency and with over 600-fold selectivity against CDK1. Results from pre-clinical research support ARTS-021 as a monotherapy in CCNE1-amplified cancers and in combination with CDK4/6 inhibitors in ER+ breast cancer.

Trial design: This is a first in human, open label, multicenter phase1/2 dose escalation and dose expansion study to evaluate the safety, tolerability, PK, PD, and anti-tumor activity of ARTS-021 1) as a single agent in advanced or metastatic CCNE-1 amplifed solid tumors; 2) in combination with Carboplatin to treat refractory/resistant CCNE-1 amplified ovarian cancer that has failed standard therapies; 3) in combination with endocrine therapy (fulvestrant/letrozole) and CDK4/6 inhibitor(palbociclib/ribociclib/abemaciclib) to treat HR+ HER2- breast cancer patients have failed standard therapies. The phase 1 (dose-escalation) portion will have an accelerated dose escalation followed by a BOIN design. After R2PD is identified, the combination arms will be initiated at one dose level below the monotherapy R2PD. Phase 1 primary endpoints are assessment of safety, tolerability, and pharmacokinetics (PK). The secondary endpoint is preliminary efficacy. Once the RP2D is defined for both monotherapy and in combination, the trial will be advanced into three phase 2 expansion cohorts: monotherapy cohort (basket cohort), combination with Carboplatin (ovarian cohort), and combination with endocrine therapy (fulvestrant/letrozole) + CDK4/6 inhibitor (palbociclib/ribociclib/abemaciclib) (HR+ HER- breast cancer cohort). In addition, a food effect cohort will be included in the monotherapy basket cohort. The phase 2 primary end point is to estimate the anti-tumor efficacy in CCNE1 amplified cancer patients or CDK4/6 inhibitor resistant breast cancer patients. Objective tumor response rate will be measured per RECIST v1.1. The secondary endpoint of phase 2 study will be safety/tolerability. Archival tumor and paired fresh tumor biopsy will be collected throughout the study for exploratory pharmacodynamics (PD) and biomarker evaluation.

Legal entity responsible for the study: Allorion Therapeutics, Inc.

Funding: Allorion Therapeutics, Inc.

Disclosure: All authors have declared no conflicts of interest.

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716TiP DETERMINE: A pioneering UK precision medicine trial for rare cancers

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Background: Precision medicine (PM) is transforming outcomes in cancer. Increasingly, through the nationwide uptake of genomic profiling, actionable alterations are identified in patients that could benefit from targeted therapies licensed in other indications. Rare cancers are under-represented in PM trials yet account for 22% of cancers overall and have limited treatment options. There is also a lack of translational research to understand differential outcomes in treatment response. Opportunity exists to fine-tune biomarker selection to repurpose existing therapies in rare cancer indications and identify novel therapeutic targets.

Trial design: DETERMINE (www.cruk.org/determine) is an innovative, multi-pharmaceutical open-label phase II 'umbrella-basket' platform trial developed with patient and public involvement. The study will evaluate the efficacy of licensed targeted medicines in unlicensed indications in rare adult, paediatric and teenage young adult cancers with actionable genomic alterations. All patients will undergo a mandatory baseline biopsy to facilitate a comprehensive translational research programme, evaluating the genomic, transcriptomic, and immune microenvironment of rare tumours. Main eligibility criteria include children and adults (age agnostic), diagnosed with an advanced cancer (tumour agnostic), actionable genomic alteration (identified through standard of care profiling), and good performance status. The co-primary outcome measures are objective response and durable clinical benefit (absence of disease progression for at least 24 weeks). Eligible patients will be matched to treatment arms by a national molecular tumour board. A Bayesian adaptive design accounting for tumour histology, age and translational context will enable signals of efficacy to be identified in small numbers of patients, enabling application of learned observations for refinement of patient selection. Promising cohorts will be submitted to the CDF, who together with the NHS Clinical Policy team, will decide if a period of data collection is necessary to consider the drug as a routine treatment on the NHS. The study (opened Nov 2022) will enrol up to 650 patients over a 5 year period across the Experimental Cancer Medicine Centre network.

Clinical trial identification: NCT05722886.

Legal entity responsible for the study: Cancer Research UK Centre for Drug Development.

Funding: Roche Products Ltd. (UK) are providing seven drugs as part of the clinical study and have financially supported the initial set up of the study. Novartis Pharmaceuticals UK Limited are providing funds to support a treatment arm for the study.

Disclosure: G. Middleton: Financial Interests, Personal, Other, Honoraria: Bristol Myers Squibb, Servier, Pfizer, AstraZeneca ; Financial Interests, Personal, Advisory Role: Pfizer, Servier; Financial Interests, Personal, Speaker's Bureau: Roche, Bristol Myers Squibb, Servier, AstraZeneca; Financial Interests, Personal, Other, Travel, Accomodation, Expenses: Pfizer; Financial Interests, Personal, Research Funding: AstraZeneca. L. Marshall: Financial Interests, Personal, Advisory Board: Bayer, Illumina, BMS, Tesaro, Eli Lilly, Novartis; Financial Interests, Personal, Invited Speaker, Co-organiser with Bayer of 2 Paediatric Preceptorship (online webinar workshops) in paediatric precision medicine. Co-chair and speaker: Bayer; Financial Interests, Personal, Other, eDMC member for 2 clinical trials: Eisai; Financial Interests, Personal, Other, eDMC member for a clinical trial: Merck; Financial Interests, Institutional, Coordinating PI, National CI for Paediatric Pembrolizumab Phase I/II Trial: Merck; Financial Interests, Institutional, Coordinating PI, National CI for Paediatric Ponatinib Phase I trial: Incyte; Financial Interests, Institutional, Coordinating PI, National CI for Novartis Paediatric Dabrafenib/Trametinib Rollover Trial: Novartis; Financial Interests, Institutional, Coordinating PI, National CI for Roche Paediatric Idasanutlin Trial: Roche; Financial Interests, Institutional, Local PI, Local PI for Paediatric Phase I Olaparib trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, National CI for CRISP (Crizotinib) phase IB trial: Pfizer; Financial Interests, Institutional, Coordinating PI, National CI of Paediatric SCOOP phase I trial (Niraparib + Dostarlimab): GSK; Financial Interests, Institutional, Coordinating PI, National CI of Bayer Phase IB Regorafenib trial: Bayer; Financial Interests, Institutional, Local PI, Local PI of BI phase I Afatinib Trial: Boehringer-Ingelheim; Financial Interests, Institutional, Coordinating PI, National CI of Paediatric Pomalidomide phase I trial: Celgene; Financial Interests, Institutional, Coordinating PI, National CI of Paediatric Phase I Alectinib trial: Roche; Financial Interests, Institutional, Coordinating PI, National CI of Paediatric Phase I/II Ribociclib trial: Novartis; Financial Interests, Institutional, Local PI, Local PI for Pfizer Palbociclib phase II trial: Pfizer; Financial Interests, Institutional, Coordinating PI, National CI of Roche Entrectinib Phase I trial: Roche; Financial Interests, Institutional, Coordinating PI, National CI of Roche phase I Cobimetinib Trial: Roche; Financial Interests, Institutional, Local PI, Local PI for Paediatric Durvalumab/Tremelimumab phase I Trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, National CI for Roche phase I Atezolizumab trial: Roche; Non-Financial Interests, Other, Member of Scientific Advisory Board (non-remunerated): Children with Cancer UK; Other, Paediatric Lead on the CRUK-sponsored DETERMINE Platform Trial and Local PI-institutional funding received: Cancer Research UK (CRUK). 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Hargrave: Financial Interests, Personal, Invited Speaker, Masterclass on managing NF1 associated tumours: Alexion; Financial Interests, Institutional, Expert Testimony, Preliminary meeting with NICE: Novartis; Financial Interests, Personal, Advisory Board, Advice on MTX-110: MidaTech; Financial Interests, Institutional, Advisory Board, Alectinib, Cobimetinib paediatric indications: Roche; Financial Interests, Institutional, Invited Speaker, Research Grant for a Clinical Trial Selumetinib: AstraZeneca; Non-Financial Interests, Principal Investigator, Dabrafenib and Trametinib clinical trials: Novartis; Non-Financial Interests, Principal Investigator, Tovorafenib clinical trial: Day One Therapeutics; Non-Financial Interests, Principal Investigator, Immuno-oncology trial: AstraZeneca, BMS; Non-Financial Interests, Principal Investigator, Alectinib trial: Roche; Non-Financial Interests, Principal Investigator, Avapritinib trial: Blueprint therapeutics. S. Danson: Financial Interests, Institutional, Full or part-time Employment, National Specialty Lead for Early Phase Cancer: NIHR; Financial Interests, Institutional, Other, Consultancy: Oxcia, Orion; Financial Interests, Institutional, Invited Speaker, Dante lead: NIHR; Financial Interests, Institutional, Invited Speaker, Fortitude pi: Amgen; Financial Interests, Institutional, Research Grant, Ecmc lead: Cancer research uk; Non-Financial Interests, Leadership Role, Lion steering group chair: NIHR; Non-Financial Interests, Leadership Role, Concorde steering group member: Cancer research UK. P. Roxburgh: Financial Interests, Personal, Invited Speaker: GSK, MSD; Financial Interests, Personal, Other, consultancy: Starpharma; Financial Interests, Institutional, Invited Speaker: Starpharma, Eisai, AstraZeneca, Bayer, Atrios, Immunocore, Immutep, Sierra, Mersana, Iovance, Nucana, PsiOxus, Replimune; Financial Interests, Institutional, Research Grant: Atrios; Non-Financial Interests, Institutional, Product Samples: Tesaro/GSK; Non-Financial Interests, Leadership Role, Clinical lead for cancer genomics: Scottish Strategic Network for Genomic Medicine. A.D. 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Krebs: Financial Interests, Personal, Advisory Board: Bayer, Roche, Janssen, Guardant Health; Financial Interests, Personal, Invited Speaker: Roche, Janssen; Financial Interests, Institutional, Expert Testimony: AstraZeneca; Financial Interests, Institutional, Advisory Board: Seattle Genetics; Financial Interests, Institutional, Invited Speaker: AstraZeneca, Blueprint, Astex, Bayer, BerGenBio, Carrick, Immutep, Janssen, Novartis, Nurix, Nuvalent, Pyramid Biosciences, Roche, Seattle Genetics, Turning Point Therapeutics; Financial Interests, Institutional, Research Grant: Roche, Novartis; Other, Travel expenses for congress: Immutep, Janssen. All other authors have declared no conflicts of interest.

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717TiP An open-label, multicentre, dose-escalation, first-in-human phase I study to evaluate safety, tolerability and antineoplastic activity of OATD-02 (dual arginase 1 and arginase 2 inhibitor) in patients with selected advanced and/or metastatic solid tumors

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Background: Despite recent therapeutic progress, patients with advanced/metastatic solid tumors have limited options after standard of care therapies and high unmet medical needs. The arginine metabolism pathway is hyperreactive in several cancers and overexpression of arginases, arginase 1 (ARG1) and arginase 2 (ARG2), is considered as a poor prognostic factor and major contributor to the immunosuppressive tumor microenvironment. OATD-02 is the only small molecule with dual activity against intracellular ARG1 and ARG2. Data from non-clinical studies showed dose-dependent tumor growth inhibition with an associated increase in arginine levels in monotherapy setting. Prediction of human pharmacokinetics (PK) of OATD-02 resulted in a moderate oral bioavailability of 35% and the half-life of approx. 33 h.

Trial design: This phase I, open-label First-In-Human clinical study aims to determine if OATD-02 administration as a monotherapy is safe and results in immune activation effects through increased arginine levels and/or intrinsic anti-tumor activity. OATD-02 will be administered in patients with advanced and/or metastatic colorectal cancer, ovarian cancer, pancreatic ductal adenocarcinoma, or renal cell carcinoma. Up to 40 patients will be enrolled to receive OATD-02 orally q.d. until disease progression. The study will follow Bayesian Optimal Interval (BOIN) dose escalation/de-escalation design with overdose control based on dose-limiting toxicities (DLTs) during the evaluation period (first cycle). Six pre-defined dose levels are planned to be explored ranging from 2.5 mg to 30 mg. Primary endpoints include nature, frequency and severity of adverse events (AEs), and occurrence of DLTs. Secondary endpoints: PK and arginine assessments, anti-tumor activity parameters. Exploratory endpoints for safety and biologic effects include pharmacodynamic biomarkers (e.g. arginase, ornithine, microRNA), orotic acid and metabolites characterisation. As of May 2023, two patients have been enrolled. The study is ongoing. Clinical trial information: NCT05759923.

Clinical trial identification: EudraCT 2022-000697-25. Study Protocol No: OATD-02-C-01. Protocol version and date: Final version 2.0, 13 December 2022. NCT05759923.

Legal entity responsible for the study: Molecure SA.

Funding: Molecure SA.

Disclosure: M.A. Dudek, Z. Zasłona, R. Błaszczyk, M.M. Grzybowski, T. Rejczak, A. Cabaj, P. Dera, K. Lisiecki, P. Iwanowski, T. Charitos, S. Fung: Financial Interests, Personal, Full or part-time Employment: Molecure SA.

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718TiP DEKA-1 a dose-finding phase I trial: Observing safety and biomarkers using DK210 (EGFR) for inoperable locally advanced and/or metastatic EGFR+ tumors with progressive disease failing systemic therapy

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Background: Both interleukin-2 (IL-2) and interleukin-10 (IL-10) have been extensively studied for their stimulatory function on T cells and their potential to obtain sustainable tumor control in RCC, melanoma, lung, and pancreatic cancer as monotherapy, as well as combination with PD-1 blockers, radiation, and chemotherapy. While approved, IL-2 retains significant toxicity, preventing its widespread use. The significant efforts undertaken to uncouple IL-2 toxicity from its anti-tumor function have been unsuccessful and early phase clinical safety observed with PEGylated IL-10 was not met in a blinded phase 3 trial. Deka Biosciences has engineered a novel molecule coupling wild-type IL-2 to a high affinity variant of Epstein Barr Viral (EBV) IL-10 via a scaffold (scFv) that binds to epidermal growth factor receptors (EGFR). This patented molecule, termed $DK2^{10}$ (EGFR), is retained at high levels within the tumor microenvironment for days after dosing. In addition to overlapping and non-redundant anti-tumor function, IL-10 reduces IL-2 mediated cytokine release syndrome risks and inhibits IL-2 mediated T regulatory cell proliferation.

Trial design: $DK2^{10}$ (EGFR) is being evaluated in an open-label, dose-escalation (phase 1) study with 5 (0.025-0.3 mg/kg) monotherapy dose levels, and (expansion cohorts) in combination with PD-1 blockers, or radiation or chemotherapy in patients with advanced solid tumors overexpressing EGFR. Key eligibility criteria include: 1) confirmed progressive disease on at least one line of systemic treatment, 2) EGFR overexpression or amplification documented in histology reports, 3) at least a 4 week or 5 half-lives window since last treatment, and 4) excluding subjects with long QT syndrome, multiple myeloma, multiple sclerosis, myasthenia gravis or uncontrolled infectious, psychiatric, neurologic, or cancer disease. Plasma and tissue samples will be investigated for pharmacodynamic and predictive biomarkers and genetic signatures associated with IFN-gamma secretion, aiming to select subjects for treatment in phase 2.

Clinical trial identification: NCT05704985.

Legal entity responsible for the study: Deka Biosciences Inc.

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Disclosure: E. Moser, D. Kientop, J. Mumm: Financial Interests, Personal, Full or part-time Employment: Deka Biosciences. A. Marabelle: Financial Interests, Personal, Advisory Board: Deka Biosciences. All other authors have declared no conflicts of interest.

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719TiP A phase I/Ib study of the Werner (WRN) helicase inhibitor HRO761 as single agent and in combination with irinotecan or tislelizumab in patients with microsatellite instability-high (MSIhi) or mismatch repair deficient (dMMR) advanced solid tumors

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Background: HRO761 is a first-in-class selective WRN inhibitor that binds allosterically to the helicase domain of the WRN protein locking it in an inactive conformation. HRO761 has shown anti-tumor activity in MSIhi preclinical models.

Trial design: This is a phase I/Ib (NCT05838768), global, multicenter (approximately 27 sites to open across 14 countries) dose finding study that consists of a dose escalation part to allow the determination of a dose range for optimization (DRO) or a recommended dose (RD) for HRO761 single agent (s.a.), and an optional randomized dose optimization part (Arm A). HRO761 will be administered orally daily in a 28-day cycle. The dose escalation part will enroll MSIhi/dMMR advanced/metastatic (a/m) CRC and solid tumors (approximately 40 patients), and the randomized dose optimization part will enroll patients with a/m MSIhi /dMMR CRC (20 patients per dose) and solid tumors (up to 10 pts per dose). Based on an integrated analysis of the safety, tolerability, pharmacokinetic, pharmacodynamic, and preliminary anti-tumor activity data of HRO761, RD will be determined and subsequently tested in optional expansion arms of a/m MSIhi/dMMR CRC (20-40 patients), and solid tumor (20-40 patients). HRO761 at the RD will be investigated in a dose escalation in combination with either tislelizumab (Arm B) or irinotecan (Arm C) to determine the RD of the combinations. After the determination of the RDs, the combination treatments will be tested in expansion cohorts of a/m MSIhi or dMMR CRC and other solid tumors. AEs will be assessed according to CTCAE v5. Tumor response will be determined according to RECIST 1.1 criteria. Key eligibility criteria include: 1) Patients with advanced unresectable or metastatic MSIhi or dMMR solid tumors who have progressed after or are intolerant to prior standard therapy; 2) patients should have received at least one prior line of chemotherapy or targeted therapy, and prior immune checkpoint inhibitor therapy (Arm A and C). Checkpoint inhibitor therapy is permitted but not required and prior adjuvant therapy is allowed in Arm B.

Clinical trial identification: NCT05838768, First posted 3 May 2023.

Legal entity responsible for the study: Novartis Pharmaceuticals.

Funding: Novartis Pharmaceuticals.

Disclosure: M. Moschetta, H. Möbitz, I. Jaco, M. Cortes Cros, S. Ferretti, D. Jankovic, M. Thérier, G. Clementi, Y. Li, R. De Kanter, C. Quadt: Financial Interests, Personal, Stocks/Shares: Novartis; Financial Interests, Personal, Full or part-time Employment: Novartis. T. Doi: Financial Interests, Institutional, Research Grant: Taiho, MSD, AbbVie, Eisai, Pfizer, BMS, Janssen Pharma, Daiichi Sankyo, Chugai Pharma, Boehringer Ingelheim, PRA Health Sciences, Amgen, GSK, SHIONOGI, RIN Institute, ONO Pharma; Financial Interests, Personal, Advisory Role: Noile-Immune Biotech, Oncolys BioPharma, Boehringer Ingelheim, A2 Healthcare, Nano Carrier, PRA Health Sciences, KAKEN Pharma, Chugai Pharma, Sumitomo Pharma, Shionogi, Otsuka Pharma, Takeda, Kyowa Kirin, Rakuten Medical, Gilead; Financial Interests, Personal, Invited Speaker: Daiichi Sankyo. Y. Kuboki: Financial Interests, Institutional, Research Grant: Taiho, Astellas, Eli Lilly, Takeda, Daiichi Sankyo, AstraZeneca, Boehringer Ingelheim, Chugai, Genmab, Incyte, AbbVie, Amgen, Merk ; Financial Interests, Personal, Advisory Role: Incyte, Takeda, Boehringer Ingelheim, Amgen; Financial Interests, Personal, Speaker, Consultant, Advisor: Taiho, Eli Lilly, Takeda. R. Sundar: Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD, GSK, DKSH, Astellas; Financial Interests, Personal, Invited Speaker: MSD, Eli Lilly, BMS, Roche, Taiho, AstraZeneca, DKSH, Ipsen; Financial Interests, Personal, Stocks/Shares: Teladoc; Financial Interests, Institutional, Advisory Board: Paxman Coolers; Financial Interests, Personal and Institutional, Local PI: Taiho, MSD, BMS, Novartis; Non-Financial Interests, Advisory Role: Paxman Coolers; Non-Financial Interests, Principal Investigator: MSD, Natera.

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720TiP Phase I, open-label, first-in-human (FIH) study of JZP815 in advanced or metastatic solid tumors harboring mitogen-activated protein kinase (MAPK) alterations

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Background: MAPK activation by RAS and RAF mutations often drives human cancer. Targeting MAPK represents a promising route for drug development. JZP815 is a potent, selective pan-RAF kinase inhibitor that binds RAF proteins which inhibits MAPK signaling and tumor cell growth. Preclinically, JZP815 inhibited solid tumor growth in xenograft models harboring *RAS/BRAF* mutations, repressed a MAPK signaling marker, and generated synergy with other MAPK inhibitors.[1] JZP815 also inhibited BRAF-CRAF dimer activity, representing a known resistance mechanism to $BRAF^{V600E}$-specific inhibitors. The profile of JZP815 supports its progress into this FIH study.

Trial design: This phase I, open-label, multicenter study (NCT05557045) investigates the safety, dosing, and JZP815 antitumor activity in patients $\geq$18 years old with advanced or metastatic solid tumors harboring a documented, clinically significant alteration in MAPK. The study comprises a dose exploration phase (Part A) to characterize safety and tolerability, determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and pharmacokinetic (PK) profile; Part B is an expansion phase to further assess RP2D and examine antitumor activities across patient subsets based on mutation and/or tumor type, including $NRAS^{Q61}$-mutated melanoma. The starting dose is 20 mg twice daily (oral capsules). In Part A, MTD will be based on dose-limiting toxicities (DLTs) using a Bayesian optimal interval design. Patients ($n \leq 6$) may then be enrolled in pre-expansion cohorts at doses at or below MTD to obtain further safety, PK, and pharmacodynamics data before identifying RP2D. Patients will be treated until disease progression, death, unacceptable toxicity, or withdrawal. Primary endpoints include incidence and nature of DLTs (Part A), objective response rate per RECIST 1.1 (Part B), duration of response (Part B), and adverse events, changes in laboratory values or vital signs, and dose interruptions and reductions (Parts A and B). The study is enrolling with planned enrollment up to 332 patients. 1 Hauptschein R, et al. *Cancer Res*. 2022;82:2677. https://doi.org/10.1158/1538-7445.AM2022-2677

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722TiP CLAUDIO-01: A multicentric phase I/II trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care (SoC) in patients with gastric, gastroesophageal junction(GEJ), and pancreatic adenocarcinoma

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Background: SOT102 is an antibody-drug conjugate targeting CLDN18.2, based on a highly specific monoclonal antibody conjugated to PNU-159682, an anthracycline derivative, using site-specific conjugation technology. Preclinical data support the development of SOT102 in the clinical setting.

Trial design: CLAUDIO-01 is a multicenter, multimodular phase I/II trial in gastric/GEJ and pancreatic cancer patients in both advanced and first line. The trial consists of the following modules: • Part A: First-in-human, CLDN18.2 agnostic, single-agent dose escalation trial of SOT102 in advanced or metastatic gastric/GEJ or pancreatic cancer patients • Part B gastric, GEJ cohort/pancreatic cohort: CLDN18.2 agnostic dose escalation trial of SOT102 in combination with SoC for first-line treatment of patients with advanced or metastatic gastric/GEJ cancer (SoC: mFOLFOX with nivolumab) or pancreatic cancer (SoC: nab-paclitaxel/gemcitabine), which will start once monotherapy SOT102 dose level 3 in Part A is deemed safe The following expansion cohorts are planned upon identification of the recommended phase 2 dose (RP2D): • Part C gastric, GEJ/pancreatic cohort: Single-agent SOT102 in CLDN18.2 positive gastric/GEJ cancer patients after two or more prior systemic therapies and in pancreatic cancer after one or more prior systemic therapies. • Part D gastric, GEJ/pancreatic cohort: SOT102 in combination with SoC for first-line treatment in CLDN18.2 positive gastric/GEJ and pancreatic cancer patients Dose escalation follows an accelerated modified Fibonacci scheme with cohort sizes of 3+3 and includes safety observation periods. Monotherapy dose escalation is ongoing at the third dose level without dose-limiting toxicity. Enrollment to dose level 4 of Part A and to dose level 1 in both cohorts of Part B are planned to begin in June 2023. Primary objectives and endpoints: -To determine the MTD and RP2D of SOT102 as monotherapy and in combination with first-line SoC treatment (Parts A and B) - To assess the efficacy of SOT102 in monotherapy and in combination with first-line SoC treatment by ORR (Parts C and D).

Clinical trial identification: NCT05525286, 31 August 2022.

Legal entity responsible for the study: SOTIO Biotech AG.

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A. hollebecque: Financial Interests, Personal, Invited Speaker: Servier, Incyte, Eisai; Financial Interests, Personal, Advisory Board: Basilea, Tahio, Relay Theraeutics, QED Therapeutics, Debiopharm, MSD, Boehringer Ingelheim; Financial Interests, Institutional, Funding: Incyte; Financial Interests, Institutional, Research Grant: AstraZeneca; Non-Financial Interests, Principal Investigator, M19-345: AbbVie; Non-Financial Interests, Principal Investigator, CO42216; WP42627; CO40939: Roche; Non-Financial Interests, Principal Investigator, MCLA-158: Merus; Non-Financial Interests, Principal Investigator, SGNB6A: Seatle Genetics; Non-Financial Interests, Principal Investigator, TAS-120-202: Tahio; Non-Financial Interests, Principal Investigator, Krystal-10: Mirati; Non-Financial Interests, Principal Investigator, ADP-0033: Adaptimmune; Non-Financial Interests, Principal Investigator, ACT16902: Sanofi; Non-Financial Interests, Principal Investigator, C4201002: Pfizer; Non-Financial Interests, Principal Investigator, RLY-4008: Relay Therapeutics; Non-Financial Interests, Principal Investigator, CC-90011: Celgene/BMS; Non-Financial Interests, Principal Investigator, Loxo-IDH: Loxo/Lilly; Non-Financial Interests, Principal Investigator: AstraZeneca; Non-Financial Interests, Principal Investigator, SN-201 study: SOTIO; Non-Financial Interests, Principal Investigator, Tropics-03: Gilead; Non-Financial Interests, Principal Investigator, BI1403: Boehringer Ingelheim. 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Van Cutsem: Financial Interests, Personal, Advisory Board: AbbVie, ALX, Amgen, Array, Astellas, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Takeda, Terumo, Taiho, Zymeworks; Financial Interests, Institutional, Research Grant: Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier. R.S. Conde: Financial Interests, Institutional, Other, Travel, Accomodations, Expenses: AstraZeneca. A. Hanauske: Financial Interests, Institutional, Stocks/Shares: Eli Lilly; Financial Interests, Institutional, Other, Honoraria: Ameos, Helios, SOTIO, Imaging Endpoints, Emergence Therapeutics, Yamaha, Apogenics, Ptc Therapeutics, Lilly Deutchland. J. Tabernero: Financial Interests, Personal, Advisory Board, scientific consultancy role: Orion Biotechnology, Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. 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ENDOCRINE TUMOURS

723O Cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system: A multi-cohort basket phase II trial (CABATEN/GETNE-T1914)

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Background: Angiogenesis plays a key role in development and progression of endocrine neoplasms and synergism has been observed when combined with immune-checkpoint inhibitors in other tumors. We aimed to demonstrate the activity and safety of cabozantinib (cabo) plus atezolizumab (atezo) in different endocrine neoplasms refractory to standard therapies.

Methods: This is a prospective, multi-center, open-label, phase II study including patients (pts) with advanced and refractory endocrine tumors in 6 independent cohorts (C): (1) well-differentiated neuroendocrine tumors of the lung (LungNET), (2) anaplastic thyroid cancer (ATC), (3) adrenocortical carcinoma (ACC), (4) pheochromocytoma/ paraganglioma (PPGL), (5) well-differentiated gastroenteropancreatic NET (GEPNET), (6) grade 3 extrapulmonary neuroendocrine neoplasms (G3 EP-NEN). All pts received atezo 1200 mg IV Q3W plus cabo 40 mg/day PO until progression or unacceptable toxicity. The primary endpoint was Overall Response Rate (ORR) by RECIST 1.1. With a Simon II stage design, 1 response of 9 pts/C were needed at 1st stage to continue accrual in 2nd stage. C1 and C6 did not pass 1st stage, and C2 and C4 were closed due to slow accrual.

Results: 93 pts were enrolled. Cabo and atezo were administered for a median of 5.8 m (95% CI: 3.4-7.5) and 6.3 m (95% CI: 3.5-7.7), respectively. Most frequent grade $\geq$3 toxicities were fatigue (7.5%), neutropenia (6.5%) and liver enzyme increase (6.5%). 2 pts died due to drug-related ischemic stroke and pancreatitis. Due to AE's, cabo and atezo treatment was interrupted in 67.7% and 35.5% of pts, and discontinued in 16.1% and 14% of pts, respectively. Cabo was reduced to 20 mg/day in 41.9% of pts. Survival was similar regardless of cabo reduction.

Table: 723O

	LungNET	ATC	ACC	PPGL	GEPNET	G3 EP-NEN
N	9	14	24	13	24	9
ORR (%)	0	21.4	8.3	7.7	16.7	0
median PFS (m [95% CI])	8.4 [7.7-NR]	4.1 [2.7-NR]	2.9 [2.8-5.7]	8.6 [5.7-NR]	13 [11.2-NR]	2.7 [2.6-NR]

Conclusions: Cabo plus atezo showed limited activity in progressive / refractory endocrine malignancies, surpassing the futility threshold in ATC. Atezo does not improve the outcomes of cabo as a single agent in NEN.

Clinical trial identification: EudraCT 2019-002279-32; NCT04400474.

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724O EO2401 (E) peptide immunotherapy + nivolumab (N) in adrenocortical carcinoma (ACC) and metastatic pheochromocytoma/paraganglioma (MPP): EOADR1-19/ SPENCER

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Background: E expands memory T cells recognizing proteins from gut bacteria, which cross-react with tumor associated antigens. E contains 3 CD8 HLA-A2 epitopes with mimicry to IL13Rα2, BIRC5, and FOXM1, and the CD4 epitope UCP2.

Methods: Patients (pt) received E (300 µg/peptide, q2w x4 then q4w) with N (240 mg q2w x3 then 480 mg q4w) in cohorts: C1 (safety lead-in); ACC in C2a and C2b with 2nd/3rd and 1st -line systemic therapy metastatic disease, respectively; MPP in C3a after prior and in C3b as 1st -line systemic therapy. Based on C2a results, a randomized extension, RND-C2a, was initiated (65 pt, 4:1:1, E/N vs E vs N).

Results: Recruitment to C1, C2a and C2b is completed, MPP cohorts and RND-C2a are recruiting (Table). EN was well tolerated in C1 (3 pt) and thereafter, with E associated events limited to local skin events (50% of pt Gr 1/2, 4% Gr 3) and N-tox in expected range. Two main groups for C2a efficacy, one with no benefit (10 pt PD/death <week 8), one with better outcome (10 pt SD > week 8). No impact of TMB, MSI-status, PD-L1 expression, cytokines, chemokines, or hormones on efficacy. Post-hoc analyses identified predictors of lack of efficacy (no mitotane, ECOG > 1, ACC 1st diagnosis $\leq$9 months(mo), lesion size >125 mm, >3 organs involved, lymphopenia >grade 1); C2-post hoc group was created applying these factors.

EN induced specific T cell expansion in 91% of tested pt (67% of all treated pt); durations up to 19 mo. Strength of immune response correlated with progression-free survival.

Table: 724O

Cohort	Ongoing trt	DC = SD/PR/CR	Duration DC*˜	OR = PR/CR	Duration OR^	Progression-free survival*	Survival*	Alive	Follow-up survival*
ACC 2nd/3rd line									
C2a n=26	12%	38%	9.1 (2.3-24.3)	12%	9.6 (3.7-17.0)	1.9 (0.4-24.3)	11.9 (1.0-24.3)	31%	22.5
C2a-post hoc n=14	21%	64%	11.3 (3.7-24.3)	21%	9.6 (3.7-17.0)	3.9 (1.7-24.3)	22.9 (1.7-24.3)	50%	23.2
RND-C2a n=12	58%	"	"	"	"	"	"	83%	2.3
ACC 1st line									
C2b n=7	0	29%	3.5 (3,2-3.7)	0	-	1.9 (1.2-3.7)	20.3 (1.2-25.0)	57%	22.6
MPP after prior systemic									
C3a n=11	18%	64%	5.2 (2.6-15.0)	0	-	4.7 (0.03-15.0)	11.4 (0.03-23.6)	36%	17.0
MPP1st line systemic									
C3b n=4	50%	100%	19.6 (3.9-19.6)	25%	12.9	19.6 (3.9-19.6)	NR (15.3-20.2)	100%	19.5

DC disease control; SD stable disease; PR partial response; CR complete response; OR objective response; NR not reached; *median (range) in months; ˜local therapies allowed for symptoms; "too early, futility assessment at n∼19.

Conclusions: EO2401/N was well tolerated generating durable immune responses correlating with efficacy. Based on the greater efficacy in C2-post hoc group a randomized extension is currently recruiting.

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725MO Phase I trial of the DLL3/CD3 IgG-like T cell engager BI 764532 in patients (pts) with DLL3-positive (+) tumours: Focus on neuroendocrine carcinomas

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Background: DLL3 is highly expressed on small-cell lung cancer (SCLC) tumours and neuroendocrine carcinomas (NECs). BI 764532 is a DLL3/CD3 IgG-like T cell engager with potent preclinical activity. NCT04429087 is an ongoing phase I dose-escalation trial of BI 764532 in adults with locally advanced/metastatic DLL3+ (confirmed centrally) SCLC, extrapulmonary (ep) NEC or large cell neuroendocrine lung carcinoma. Here we focus on pts with epNEC.

Methods: BI 764532 was given intravenously in 4 regimens: Regimen A (RA; fixed dose q3w); RB1 (fixed dose qw); RB2 (step-in doses, then fixed dose); RB3 (step-in, followed by target dose). Treatment (Tx) continued until progressive disease, unacceptable toxicity, other withdrawal criteria or maximum Tx duration (36 months). Main objective: maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532. Other objectives: safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy based on investigator review (RECIST v1.1).

Results: As of 26 July 2023, 129 pts received ≥1 dose (≥ 0.03 µg/kg) of BI 764532 (RA: n=24; RB1: n=10; RB2: n=79; RB3: n=16). Male: 59%; median age: 60 (range 32−81); ECOG PS 0/1: 28/71%; prior PD1/PD-L1 Tx: 49%; ≥2 prior lines of Tx: 70%. Dose limiting toxicities: 1 pt on RA (Grade [G]3 confusion) and 6 pts on RB2 (G5 immune effector cell-associated neurotoxicity syndrome [ICANS]; G4 cytokine release syndrome [CRS]; G3 CRS; G3 ICANS; G3 nervous system disorder and G2 infusion-related reaction). MTD has not been reached; dose escalation is ongoing. 53 pts with epNEC have been treated (ongoing in 14). TRAEs (any/G≥3): 92/17%. The most common TRAEs (any/G≥3) were: CRS (72/4%); pyrexia (26/0%); dysgeusia (19/0%) and fatigue (17/0%); there were no Tx discontinuations due to TRAEs.
In the efficacy population, there were 46 pts with epNEC (gastrointestinal: n=23; genitourinary: n=16; unknown origin: n=7). ORR/DCR was 22/41%. In pts who received clinically active doses of BI 764532 (n=36), ORR/DCR was 28/47%.

Conclusions: BI 764532 showed clinically manageable tolerability; MTD has not been reached. Promising efficacy was observed in pts with epNEC. The study is ongoing.

Clinical trial identification: NCT04429087.

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726P Circulating cell-free DNA-based biomarkers as a new tool for prognosis and surveillance of adrenocortical carcinoma

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Background: Adrenocortical carcinoma (ACC) is a rare aggressive endocrine cancer with heterogeneous behaviour. Disease surveillance relies on frequent imaging, which comes with significant radiation exposure. We investigated the role of circulating cell-free DNA (ccfDNA)-related biomarkers (BM) for prognostication and monitoring of ACC.

Methods: We studied 33 patients with primary ACC and 23 healthy subjects (HS) as controls. ccfDNA was extracted by commercial kits from pre-surgical and serial EDTA plasma samples and quantified by fluorimeter (BM1). All ccfDNA samples passed the quality check showing a desired fragment length of 150-200 bp. Primary tumour DNA was isolated from paraffin-embedded tissue for 25/33 patients. Next-generation sequencing was performed using a customised panel of 30 ACC-specific genes (Cell3^{TM} Target Nonacus). Leucocyte DNA was sequenced to discriminate germline from somatic variants (BM2). BM1 and BM2 were merged into a combined ccfDNA-BM score to be correlated with clinical outcome.

Results: ccfDNA concentrations were higher in ACC than HS (median 0.40 *vs* 0.05 ng/µl, $P<0.001$) and correlated with tumour stage and ki67 index (R=0.48 and 0.55, respectively). 94% of ACC were positive for BM1 (cut off 0.146 ng/µl, median HS+2SD) and 45.5% for BM2 (at least one somatic mutation in ccfDNA, variant allele frequency 1.0-30.5%). Mutational status at ccfDNA matched with tumour DNA in 60% of cases (additional variants in 16% and missed variants in 12%). ccfDNA-BM score (0-1=negative, 2-3=positive) was strongly associated with progression-free and overall survival ($P=0.0004$, HR=8.68, 95%CI=2.88-26.5, and $P=0.003$, HR=3.35, 95% CI=1.34-8.37, respectively). Among 13 patients followed up for at least 3 months (range 1-6), 10 tumour-free at last imaging and 1/3 with early relapse had negative ccfDNA-BM score (100% *vs* 33%). In two recurrent cases, somatic mutations in ACC-specific genes remained detectable during monitoring.

Conclusions: ccfDNA-related BMs are frequently detected in patients with ACC, representing a promising non-invasive tool to predict early disease recurrence and complement imaging for monitoring. Our findings will be validated in a larger cohort of ACCs with long-term follow up.

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727P Clinical outcome of anlotinib (A) and tislelizumab (T) in metastatic adrenocortical carcinoma(mACC): A one-arm single-center experience

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Background: Adrenocortical carcinoma is a rare malignant disease with few treatment options. The combination of etoposide, doxorubicin and cisplatin with or without mitotane known as EDP/M, is recommended as first -line regimen based on FIRMACT study. It shows limited efficacy and intolerable toxicities. There is no standard second-line treatment, but antiangiogenesis therapy and PD-1 checkpoint inhibitors are widely applied in clinical practice. Here, we report the efficacy and safety of A, a multi-targeted tyrosine kinase inhibitor that inhibits VEGFR, FGFR, PDGFR, and c-Kit, combined with T, an immune checkpoint inhibitor, in the treatment of mACC.

Methods: Data was collected from electronic medical system at our center between 2019 and 2022. Patients who were diagnosed as mACC and treated with A+T regardless of prior therapy were included. Patients accepted A 12 mg once daily PO from day 1 to 14 and T 200mg IV on day 1 every 3 weeks. Baseline characteristics were recorded. Objective response rate(ORR) and disease control rate(DCR) were evaluated according to RECIST v1.1 and treatment related adverse events(TRAE) according to CTCAE v5.0. Progression free survival(PFS) and overall survival(OS) were analyzed using Kaplan Meier method.

Results: Overall, 37 patients were included. Median age was 50 years(19-76). 51.4%(19/37) were male. Median number of metastatic sites was 3. Median follow-up was 41 months. ORR was 35.1%(1 CR and 12 PR) and DCR was 78.4%(29/37). Median PFS was 8.2 months(95%CI 1.4-24.7) and median OS had not reached. Any grade TRAE rate was 89.2%(33/37) and grade 3/4 TRAE rate was 29.7%(11/37). No treatment related death was observed. Most common grade 3/4 TRAE included proteinuria(10.8%, 4/37), fatigue(8.1%, 3/37), adrenal crisis(5.4%, 2/37) and hepatic enzyme increase(5.4%, 2/37).

Conclusions: The combination of A and T showed promising clinical benefits with moderate toxicities in mACC patients. A+T might become a potential treatment option which need to be further confirmed in the randomized controlled clinical trial.

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728P Brain metastases in advanced thyroid carcinoma: Clinical and molecular characteristics and outcomes

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Background: Brain metastases (BrM) from thyroid cancer are considered rare. Staging brain MRI is not routinely recommended by guidelines. Prognostication, management, and outcomes remain understudied in this population.

Methods: This is a single-center retrospective study of advanced (unresectable or metastatic) thyroid cancer treated at the Princess Margaret Cancer Centre from 2000

to 2020 who developed BrM. All patients (pts) had tumour next generation sequencing (NGS) by targeted gene panel. Clinical, molecular characteristics and treatment modalities were reviewed. Overall Survival (OS) was estimated from the date of BrM diagnosis using the Kaplan-Meier method.

Results: Of 166 consecutive pts with advanced thyroid cancer who had NGS, 36 pts had documented BrM (21,7%). Median age was 52,8yo. Most BrM pts (80,6%) were of follicular cell origin (papillary TCs beig the most frequent) and the remaining (19,4%) was of C-cell origin (Medullary TC) Most pts (72%) were asymptomatic and diagnosed with BrM incidentally from staging head/neck CT scan (16/26) or brain MRI/CT (9/26). 42% of pts were on systemic treatment before BrM diagnosis. The most frequent molecular alterations were: BRAFV600E (n=16), NRAS (n=8), TERT promoter (n=8), and RET (n=7). Median OS (mOS) from BrM to death was 20,1 months (m) (95% CI 1,87-39,1). Treatment for BrM included surgery (14%) and radiation (89%). Histological subtypes were not significantly associated with OS. Pts harboring *BRAF* or *NRAS* mutations had mOS of 38.4 m, while *RET* and other alterations had mOS of 18.5 m and 1.2m, respectively (p=0.01). Pts with 1-3 BrM had better OS than those with $\geq$ 4 BrM (p = 0,025); Pts who underwent BrM resection had a trend to improved OS compared to radiation alone (61.2 vs 18.1 m, p=0.38).

Conclusions: This study is the one of the largest analyses of BrM from advanced thyroid cancer with detailed clinical and genomic characterization including all histology subtypes. We found a higher incidence of BrM than previously reported. Most were diagnosed with BrM incidentally. Number of BrM (1-3), BrM treatment modality and Molecular subtype may be prognostic. Staging brain MRI may facilitate earlier BrM detection. Further studies are needed to confirm the impact of earlier BrM diagnosis on pts outcomes.

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729P Prognostic significance of nodal micrometastases in patients with non-functioning pancreatic neuroendocrine tumors (NF-PanNETs): A survival analysis from a prospective observational study

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Background: Nodal metastases (N+) are one of the most powerful predictors of disease recurrence after surgery for non-functioning pancreatic neuroendocrine tumors (NF-PanNETs). However, the prognostic role of nodal metastases $<$ 5 mm, defined as micrometastases, has been poorly investigated so far. The aim of this study was to compare clinico-pathological features and survival outcomes between patients with NF-PanNETs without nodal involvement (N0), with nodal micrometastases (microN+) and with nodal macrometastases (macroN+).

Methods: Consecutive patients who underwent a formal pancreatic resection for NF-PanNETs at San Raffaele Hospital (Milan, Italy) between 2018 and 2021 and were enrolled in the DETECTYON trial were considered (NCT03918759). Nodal metastases were further classified as microN+ when their maximum diameter was $<$ 5 mm, or as macroN+ when their maximum diameter was $\geq$ 5 mm.

Results: Overall, 100 patients were included. Of these, 58 had N0 PanNETs, 15 had microN+ and 27 had macroN+. Patients with macroN+ had significantly larger tumors [median 35 mm (IQR 28-47)] as compared to patients with microN+ [25 mm (IQR 24-35), p=0.040] and N0 neoplasms (26 mm (IQR 18-34), p=0.003]. The rate of G2-G3 neoplasms was comparable between patients with N0 and microN+ PanNETs (45% versus 27%, p=0.203), whereas it was significantly higher among subjects with macroN+ tumors (n=21/27 - 78%). Median Ki67 was 2% in patients with N0 and microN+ neoplasms (p=0.429), whereas it increased to 6% in patients with macroN+ (p=0.006). After a median follow-up of 37 months, 16 patients (16%) experienced disease relapse. Patients with N0 PanNETs had a 4-year DFS rate of 97% as compared with 88% and 43% in patients with microN+ (p=0.152) and macroN+ (p<0.001), respectively. At multivariable analysis, distant metastases (HR 5.826, p=0.026) and macroN+ (HR 6.281, p=0.034) were identified as independent determinants of disease relapse.

Conclusions: NF-PanNETs with microN+ seem to be associated with a risk of recurrence similar to N0 neoplasms. MicroN+ may be regarded as a clinicopathological entity separate from macroN+, with a possible impact on postoperative surveillance protocols.

Clinical trial identification: These are the long-term outcomes of a prospective observational study: NCT03918759.

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730P The outcome of combine radioligand and CAPTEM therapy in patients with advanced, unresectable, progressive GEP-NET

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Background: Prospective, single-arm, open-label, case series study evaluating efficacy and safety of combined radioligand therapy (RLT) and CAPTEM in advanced, unresectable progressive GEP-NET (NCT04194125). Primary endpoint: progression-free survival (PFS) secondary: ORR, DCR, clinical response, OS, safety.

Methods: Twenty-one patients in group of 23 screened subjects between February 2019 to May 2023 included into analysis. All patients with histopathological confirmation of GEP-NETs. Therapy consists of combine RLT (^{177}Lu DOTATOC) and CAPTEM. Disease status and treatment efficiency were evaluated by clinical assessment including PS, ORR, also biochemical response and safety profile of combine therapy.

Results: Clinical follow-up at least 48 months. Mean age 58.6 +12.6. Pancreatic (panNET) n=14, midgut n=7; NETG1=9, G2=10, G3=2. Cumulative activity ^{177}Lu (GBq) of whole therapy; median=25.1GBq (20.4-27.0), per therapy median=6.5 GBq (5.8-6.8). Median PFS for all (IQR) 31.5 months (16.0-n.r.), panNET PFS=28.0 m (14.0-n.r.), midgut PFS=31.5 m (24.5-n.r). After 6 weeks of follow-up 9 (42%) had partial response (PR) and 11 (52%) had stable disease (SD), after 3 m 9 had PR, 8 had SD, single had disease progression (DP). After 6 m 9 PR, 9 SD and 2 DP, after 12 m single 1 complete response, 10 PR, 5 SD and 2 DP. DCR after 6 weeks all patients, after 3 months 17 subjects (90%), 6 months 18 patients (85%) and after 12 months 16 subjects (89%). Clinical evaluation including 12 subjects with PS=1 improved to PS=0 in 6 subjects in 2 with PS=2 improve to PS=1, no change in 7 subjects. The most common AEs was a transient lymphopenia G2 (44%) and G3 (8%); others AEs and their significant intensity (at least G3) were observed sporadically, no G4, during and after therapy. Persistent lymphopenia noted in 16% of cases.

Conclusions: Combine therapy composed with RLT and CAPTEM is very effective therapy in advanced, GEP-NET in terms of improvement of PFS in those who had documented DP. Clinical response, DCR of combine therapy seen in most of subjects during follow-up. Significant benefit in terms of ORR reported in panNET but not in midgut. In panNET who had PR four of them had primary tumor removal, single with CR for 4 years.

Clinical trial identification: NCT04194125.

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731P REWENEC: REal-World Evidence in NEC provides a reliable external control arm to avoid randomization for second-line clinical trials - A post hoc proof of concept analysis with the randomized phase II BEVANEC study

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Background: Neuroendocrine carcinomas (NECs) are rare aggressive cancers. After first-line platinum—etoposide, there is no standard second-line treatment. The phase II randomized clinical trial BEVANEC evaluated a randomized treatment arm (RTA) FOLFIRI + bevacizumab (Fb) and a randomized control arm (RCA) FOLFIRI (F) with a long period of enrolment (5 years) and demonstrated no benefit of Fb. We hypothesized that a single-arm trial of Fb compared to an external control arm (ECA) of F could have led to the same results.

Methods: We compared the patient's characteristics and outcome in the RCA of BEVANEC versus a full or hybrid ECA generated with real world data of NEC patients from 2 retrospective French cohorts (CEPD and RBNEC) who received second-line F. We emulated a synthetic trial, REWENEC, incorporating an ECA of F and compared the results to that of BEVANEC. We assessed the potential impact of unmeasured

Table: 731P

		RCA	RTA		ECA
n		66	59		66
	Baseline characteristics				
		RCA vs RTA (rando)		**RTA vs ECA (IPW-PS)**	
sex	Male	63.6	67.8	61.6	65.2
	Female	36.4	32.2	38.4	34.8
Age		63.0	65.1	60.5	61.5
Ki67 index (%)	≤55	20.3	9.3	21.2	18.3
	>55	79.7	90.7	78.8	81.7
Cell size	SCNEC	52.7	53.1	47.6	48.3
	LCNEC	47.3	46.9	52.4	51.7
Metastatic sites	non liver	21.2	15.3	18.9	20.7
	liver	78.8	84.7	81.1	79.3
Primary tumour	colorectal	27.3	30.5	31.9	34.1
	other	72.7	69.5	68.1	65.9
	OS (%) [95%CI]				
		RCA	**RTA**		**ECA**
6m		60.5 [49.7;73.5]	56.6 [45.1;71.0]		54.7 [46.5;64.3]
12m		32.4 [22.6;46.5]	29.6 [19.5;44.9]		32.0 [24.6;41.6]
18m		15.9 [8.70;29.0]	20.0 [11.3;35.4]		19.9 [13.8;28.7]
median		6.6 [4.9;11.5]	8.9 [5.9;11.4]		6.9 [5.88;8.00]

confounders. An inverse probability weighting propensity score (IPW-PS) approach was used to balance measured confounders (MC) in the ECA.

Results: The ECA included 66 patients comparable to ETA and RCA. Measured confounders were more balanced between the RTA of BEVANEC and the ECA after IPW-PS than between the RTA and the RCA after randomization (Table). OS were similar in both ECA and RCA (Table). When substituting the RCA by the ECA and comparing it to the RTA, the synthetic REWENEC trial led to similar outcomes and conclusions as in the BEVANEC trial with no difference in median overall survival between Fb and F (Table). This suggest that randomization may not have been required in this setting.

Conclusions: Externally controlled trials might be an appropriate compromise between RCT and single-arm trials in NECs. Maintaining a platform of existing good quality data from prospective and retrospective studies would help to design these types of trials and accelerate clinical research in NECs.

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ANNALS OF ONCOLOGY driving innovation in oncology

GERM CELL (TESTICULAR) CANCER AND PENILE CANCER

732P Efficacy and safety of high-dose chemotherapy as second or subsequent salvage therapy in relapsed or refractory germ cell cancer patients: A multicentric analysis

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Background: Recurrent metastatic germ cell cancer (GCC) is treated with salvage chemotherapy (CTX), either with high-dose (HD) CTX such as carboplatin and etoposide (HD-CE) or conventional-dose cisplatin-based chemotherapy (CD CTX). For relapse after first salvage CD CTX, HD-CTX is still a curative option, but data on efficacy and safety of HD-CTX in this setting is limited. This retrospective study aimed to explore the efficacy and safety of HD-CTX used as either first or subsequent salvage treatment.

Methods: Data on patients (pts.) characteristics, treatment outcome and safety were retrospectively collected from international expert centres to compare between Group A (HD-CTX as first salvage therapy) and Group B (HD-CTX at recurrence after or progression during salvage CD CTX). Analysis was conducted using *R* with Wilcoxon, χ^2 and log-rank test to compare characteristics and survival.

Results: A total of 275 GCC pts. from 18 centers were included in this analysis, 159 pts. (57.8%) in group A and 116 patients (42.2%) in group B. Treatment was conducted with HD-CE in 238 pts. (86%), with a median follow-up time from first salvage CTX of 27 months (SD 51.9) in group A and 35 months (SD 58.7) in group B. Patient characteristics including primary histology, IGCCCG risk, IPFSG score and locations of metastases were equally distributed in both groups. The median OS from first salvage treatment initiation was not reached (group A) versus 68.8 months (group B) (p=0.073), and from HD-CTX treatment not reached (group A) versus 31.2 months (group B) (p=0.002). The 2- and 5-year OS rates after HD-CTX were 76%/65% for group A and 56%/42% for group B, respectively. The objective response rate following HD-CTX was 79% (group A) versus 60% (group B) (p=0.013). Regarding toxicity, adverse events (other than hematologic) were reported in 59% in group A and 73% in group B (p=0.028). Treatment associated deaths were described in 8 patients (2.9%) with no difference between group A versus group B (p=0.221).

Conclusions: Salvage HD-CTX has curative potential in relapsed and refractory GCC patients leading to 65 % long-term survival when used as first salvage therapy and approximately 41% when used in the subsequent salvage setting.

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733P Testicular cancer: Trends in incidence and demographics from 23,214 cases in California from 2000-2020

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Background: The incidence of testicular cancer (TC) has been rising over the past five decades for reasons currently unknown. As marijuana use is believed to increase the risk of TC, we sought to assess recent trends in incidence rates in California to see if further changes might be due to recent policy initiatives such as marijuana legalization.

Methods: Men diagnosed with TC between 2000 and 2020 were identified through the California Cancer Registry database (n = 23,214). Cancer occurrence by age and race/ethnicity were examined. Incidence rates by year of diagnosis and race/ethnicity were calculated, and age-adjusted to the 2000 US Standard Population.

Results: The incidence of TC among all racial/ethnic groups has been rising in California between 2000 and 2020. In particular, incidence has been rising at faster pace among Hispanic men and Asian/Pacific Islander men during this period. Among Hispanic men, the incidence rate was 4.2/100,000 in 2000 and rose to 6.7/100,000 in 2020. Similarly, the incidence rate for Asian/Pacific Islander men was 2.0/100,000 in 2000, decreased to 1.2/100,000 in 2002 and rose to 2.5/100,000 in 2020. This increasing trend for incidence rates is mainly observed among men below age 40.

Table: 733P Incidence rates for male malignant testicular cancer in California, 2000-2020

Year	All groups	Non-Hispanic white	Non-Hispanic black	Hispanic	Asian/Pacific Islander
2000	5.3	7.3	1.7	4.2	2
2001	5.2	7.4	2.1	3.7	1.6
2002	5	7.1	1.5	3.8	1.2
2003	5.3	7.7		4	1.4
2004	5.3	7.5	1.4	4.2	1.5
2005	5.5	7.8	1.3	4.3	2
2006	5.5	7.3	1.6	4.8	1.8
2007	5.5	7.5	1.9	4.6	2.1
2008	5.7	7.9	2.2	4.9	1.5
2009	5.6	7.3	1.9	5.1	2.2
2010	5.8	7.8	1.9	5.1	2.1
2011	5.5	7.3	1.3	5.3	2
2012	5.7	7.3	1.8	5.5	2.1
2013	6	8.3	1.8	5.3	2.4
2014	6.2	8	1.5	5.9	2.5
2015	6	7.2	1.3	6.3	2.2
2016	6.3	8.3	2	5.7	2.3
2017	6.4	7.7	1.7	6.6	2.6
2018	6.4	8	1.9	6.4	2.6
2019	6.3	7.3	1.6	6.8	2.4
2020	6.4	7.6	2	6.7	2.5

Rates are per 100,000 and age-adjusted to 2000 US Std Population (19 age groups — Census P25-1130) standard.

Conclusions: This is one of the largest epidemiological studies on TC. The incidence of TC has been rising in California since 2000, particularly among Hispanic and Asian/Pacific Islander men. The rise in TC rates started prior to the year of marijuana legalization (2015), thus suggesting other factors may be leading to rising incidence rates.

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734P Primary retroperitoneal germ-cell tumours (pR-GCT): Evaluation of treatment outcomes of an international collaboration (PRIMERE study-IGG05)

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Background: pR-GCT corresponds to the clinical case of retroperitoneal ascertained GCT without radiological evidence of primary testicular tumor and accounts for up to 40 % of extragonadal GCTs. An occult primary testicular tumor is often missed at diagnosis. Treatment modalities and outcomes have not been specifically addressed, preventing robust recommendations. We performed an international call to assess prognosis of treatment outcomes of these patients.

Methods: Clinical, pathological and treatment data pts with pR-GCT between 04/1988 and 01/2022 were retrospectively collected across 4 referral centers. Kaplan Meier methods, univariable and multivariable Cox regression models (MCRMs) were used.

Results: Ninety-nine patients (median age 37 yrs - IQR: 29-45) were collected. Ninety-three (94%) had histological diagnosis by biopsy or primary retroperitoneal lymph-node dissection (RPLND): 60 (62.5%) had non-seminomatous pR-GCTs (pR-NSGCTs) and 33 (34.4%) had seminomatous pR-GCTs (pR-SGCTs). IGCCCG prognostic allocation was possible in 91 pts: 34 (35.8%) were good, 23 (24.2%) intermediate and 34 (35.8%) poor risk, respectively. All pts underwent cisplatin-based chemotherapy, usually BEP regimen (94.9%). After chemotherapy, 25 (25.3%) pts underwent orchiectomy: viable tumor was present in 8 (32%), burn-out lesions in 6 (24%) and no lesion in 11 (44%) cases. After a median follow-up of 45 mos (IQR:15-90), the 5-years OS was 58%, being 85% in case of pR-SGCT and 46% in case of pR-NSGCT. According to IGCCCG classification 5-years OS was 83.3% for good, 57% for intermediate and 42% for poor risk patients, respectively. No difference in term of OS (60% vs 56%, p-value 0.81) was observed between patient who had or not radical orchiectomy. At MCRMs only IGCCCG poor risk category (HR 3.2, CI: 1.18-8.84, p-value 0.02) was independent predictors of a worse OS.

Conclusions: Eventually, a significant proportion of pts with a pR-GCT had a misclassified primary testicular tumor. 5 yrs-OS according to IGCCCG classification is worse than expected. The role of a surgical exploration of the suspected primary tumor remains controversial and the existence of a real category of p-GCT cannot be excluded.

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735P Causes of death in a complete cohort of testicular cancer patients diagnosed in Norway 1980-2009, with detailed treatment information

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Background: Testicular germ cell tumors (TGCT) have an excellent prognosis. This study aimed to provide population-based clinical data on cause-specific deaths with detailed treatment information, as such data are scarce.

Methods: From the Cancer Registry of Norway we identified 6167 men with testicular cancer diagnosed 1980-2009, of whom 714 died before 2011. Excluding non-TGCT, clinical or post-mortem diagnoses, 588 were included. Information on Royal Marsden clinical stage (CS), comorbidity, treatment, follow-up and cause of death was obtained from patient journals.

Results: Of 588 deceased patients, 311, 191 and 86 were diagnosed in the 1980s, 90s and 00s, respectively. Most had seminoma (55%), and 48% were concurrent smokers. Median time to death (MTD) of TGCT, treatment complications or other causes was 1.5, 0.4 and 12.1 years, respectively. Of 315 deceased patients with initial CS1, 4% died of relapsed TGCT or treatment complications, while 35% died of non-TGCT cancer. Of 273 deceased patients with initial metastatic TGCT, 149 (55%) died of TCGT or treatment complications. Most had nonseminoma (77%). The primary treatment in these 149 patients was a combination of chemotherapy and surgery in 41%, chemotherapy alone in 33%, radiotherapy alone in 3%, trimodal treatment in 11%, radiotherapy and chemotherapy in 7%, while 4% received no treatment. Of the 149 patients, 95 (64 %) had CS4: pulmonary metastases, non-pulmonary visceral metastases or both were reported in 84, 42 and 34 patients, respectively. According to IGCCCG, 61%, 27% and 4% belonged to the poor, intermediate and good prognosis groups, respectively. Most (58%) died in primary treatment before entering follow-up. Of all 273 patients, 14 % died of non-TGCT cancer.

Conclusions: In this complete three-decade cohort, cause-specific death of TGCT was exceedingly rare in CS1 or good prognosis metastatic disease. TGCT death was rare if patients went into follow-up after primary treatment. Cause-specific mortality was most pronounced in patients receiving chemotherapy following post-chemotherapy surgery, in patients with nonseminoma or with visceral metastases.

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736P Residual masses after salvage chemotherapy in men with metastatic seminoma: The Semi-ResMass multicenter retrospective study

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Background: Only limited data exist on the management of residual masses in men who have received two lines of chemotherapy for advanced seminoma. Therefore, the role of FDG PET/CT scans, surgery and other additional treatments remains controversial in these men.

Methods: Data from men with pure seminoma and residual masses after salvage chemotherapy were retrospectively collected from 13 high-volume centers. We analyzed the clinical management of residual masses (imaging, surgery, pathological data, and additional treatment modalities) and long-term outcomes. Residual mass was defined as a lesion of $\geq$1 cm after two lines of platinum-based chemotherapy.

Results: Data from 92 patients (pts) with non-progressing residual masses after second-line chemotherapy have been collected and have been included in this analysis. A post-chemotherapy FDG PET/CT was performed in 54 (59%) pts. Viable seminoma was found in 3/12 pts who had a biopsy (bio+). Surgery was performed in 47 (51%) pts, irrespectively of FDG uptake (no=8, yes=16). Complete necrosis was found in 42 (89%), viable seminoma in 3 (6%), teratoma in 1, and leiomyoma in 1 pt, respectively. No viable tumor cells were found in 8 men with a negative PET (PET-) who underwent surgery (2bio+). 16/28 pts with a positive PET (PET+) underwent surgery: 12 complete necrosis, 2 viable seminoma, 1 teratoma, and 1 leiomyoma. Among those with a PET+, 5/28 pts (18%) experienced either viable seminoma in residual subsequent relapse. A second relapse occurred in 13/92 (14%). Only 4/47 (8%) pts who had residual masses resected post 1st salvage chemotherapy subsequently relapsed (3 had viable seminoma in the residuals). At a median follow-up of 4.35 years, 88 (92%) pts were alive. 4/92 patients died of cancer progression.

Conclusions: Most men with seminoma residual masses after 1st salvage chemotherapy may achieve a cure. Pending validation with more pts in this rare situation, FDG PET/CT may help guide the selection of post-chemotherapy resection candidates. PET/CT appears of high negative predictive value when negative (100% [95%CI 63-100]), while PET+ scans have a remarkable risk of being false positive (positive predictive value 16% [95%CI 3-40]).

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737P Vascular fingerprint tool to identify testicular cancer patients at high-risk for early cardiovascular events after cisplatin-based chemotherapy

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Background: Testicular cancer (TC) patients treated with chemotherapy (CT) have an increased risk of early cardiovascular events. This study aims to validate a vascular fingerprint tool developed to identify TC patients at high-risk for such events (Lubberts, Eur J Cancer 63:180, 2016).

Methods: A multicenter prospective study (NCT02573584) was performed in metastatic TC patients (IGCCCG good or intermediate risk; retroperitoneal mass <5 cm). The vascular fingerprint was assessed before start of CT and consists of 5 risk factors: smoking, overweight (BMI>25 kg/m^2), hypertension (blood pressure >140/90 mmHg), dyslipidemia (fasting cholesterol >5.1 mmol/L or LDL >2.5 mmol/L) and diabetes mellitus (fasting glucose $\geq$ 7.0 mmol/L). Presence of $\geq$ 3 risk factors was defined as high-risk vascular fingerprint. A log-rank test was performed using a cardiovascular event within 1 year after start of CT as primary endpoint.

Results: 196 TC patients were included; 15 patients (7.7%) developed a cardiovascular event: [4 (2.0%) arterial events and 11 (5.6%) venous thrombotic events]. TC patients with a high-risk vascular fingerprint (n=62) had a higher risk of developing a cardiovascular event (HR: 3.27; 95% CI: 1.16 − 9.18; Log-rank: p=0.017). All patients with an arterial event had a high-risk vascular fingerprint compared to 5/11 patients with a venous event. Patients who developed a cardiovascular event were older (Table).

Table: 737P Risk factors before start of CT in TC patients with or without cardiovascular events

	Cardiovascular event (n = 15)	No cardiovascular event (n = 181)	
	Median (range) / n (%)	Median (range) / n (%)	*P**
Age at start of CT, years	40 (22-50)	31 (17-48)	**0.013**
Smoking	5 (33.3)	63 (34.8)	0.908
Overweight	13 (86.7)	107 (59.4)	**0.037**
Hypertension	7 (46.7)	47 (26.6)	0.132
Dyslipidemia	13 (86.7)	113 (70.2)	0.238
Diabetes mellitus	1 (6.7)	6 (3.5)	0.445
Total score vascular fingerprint	3 (0-4)	2 (0-4)	**0.035**
High-risk vascular fingerprint	9 (60.0)	53 (30.5)	**0.041**

*X^2-, Fisher's exact- or Mann-Whitney U test

Conclusions: The vascular fingerprint tool is effective in identifying TC patients at high-risk for early cardiovascular events and can be used to select TC patients for preventative strategies.

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738P Penile squamous cell carcinoma with high and very high tumor mutational burden (TMB): A genomic landscape and "real-world" clinical outcome study

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Background: TMB is an established biomarker of efficacy with immune-checkpoint inhibitors (ICI) in a pan-cancer indication. TMB, however, has not been specifically considered for penile squamous cell carcinoma (PSCC).

Methods: We analyzed 397 PSCC cases to identify genomic alterations (GA) in >300 cancer-associated genes, genomic signatures, and TMB using a hybrid capture-based comprehensive genomic profiling (CGP) assay. TMB was categorized as low (<10 mutations [mut]/Mb), high (10-19), and very high (≥20). Tumor cell programmed cell-death ligand-1 (PD-L1) expression was determined by immunohistochemistry (IHC, Dako 22C3) and defined as tumor proportion score (TPS) ≥1%. Germline status of GA was predicted using a validated somatic-germline computational method. Separately, real-world clinical outcomes (RWCOS) data of patients with metastatic penile cancer receiving first-line ICI were obtained from the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine clinico-genomic database (FH-FMI CGDB), which originated from approximately 280 US cancer clinics (∼800 sites of care).

Results: There were 339 (85.4%) TMB-low, 40 (10.1%) TMB-high and 18 (4.5%) TMB-very high PSCC. TMB ≥10 vs TMB-low PSCC revealed an enrichment of GA of PIK3CA (48.3% vs 18.3%; p<0.001) and KMT2D (29.3% vs 7.7%; p<0.001), and less frequent GA of CDKN2A (25.9% vs 45.7%, p=0.050). Most of these GA did not co-occur. PD-L1 expression was not impacted by TMB status. HPV identification was more frequent as TMB increased: 28.3% for the TMB-low, 50% for the TMB-high and 58.8% for the TMB-very high groups. In total, 95/1,377 (6.9%) GA were predicted to be of germline nature. In the FH-FMI CGDB cohort, 10 patients receiving ICI, 4 (40%) had a real-world overall survival (rwOS) >12 months with sustained benefit in 3/3 patients with TMB ≥10 mut/Mb.

Conclusions: Evaluation of advanced/metastatic PSCC by CGP based on TMB level revealed significant differences in biomarkers for the near 15% of cases that have high and very high TMB ≥10 mut/Mb. These PSCC cases represented a distinct tumor subgroup deserving further clinical investigation.

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739P Penile squamous cell carcinoma tissue associated macrophages captured by multiplex immunfluorence are associated with clinical outcomes

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Background: Penile squamous cell carcinoma (PSCC) is rare and the immune enviroment of PSCC remains poorly characterized. In this study, we characterize the immune microenvironment using multiplex immunofluorescence (mIF) and image analysis approaches in 57 patients with PSCC.

Methods: Representative tissue microarrays blocks of 57 patients with primary PSCC treated at H. Lee Moffitt Cancer Center (Tampa, FL) were stained for 10 immune markers: CD20, CD3, CD4, CD8, CD45RO, CD68, CD206, CD163, NKp46, FOXP3. Two experienced pathologists using an image analysis system divided each tissue core into tumor and stroma compartments and assessed the densities of cell phenotypes.For analyses focusing on overall survival (OS) we used Cox regression and Log-rank test for Kaplan-Meier plots. The maximally selected rank statistics test was used to identify cut-points of continuous variables with maximal discriminatory value for clinical outcomes.

Results: 57 PSCC patients were included with median age 60 [IQR, 53-73]). 25 (44%) were pathologic stages 1-2, 25 (44%) were stage 3, and 7 (12%) were stage 4. 34 (60%) were HPV-negative. We did not observe significant differences in cell densities as defined by mIF in HPV(+) compared to HPV(−) PSCC. In univariable analysis, higher density of CD8+ cells in the tumor and stroma were associated with inferior median OS (36.6 months [95% CI, 19.0-84.1] vs 161.7 months [95% CI, 16.2-161.7]). Similarly, greater infiltration by tumor-associated (M2) macrophages in the tumor and stroma (CD68+CD163+CD206+) were associated with inferior median OS (13.3 months [95% CI, 1.0-not estimable) vs 80.1 months [95% CI, 27.1-161.2]. In Cox regression controlling for pathologic stage and M2 density as a continuous variable, the latter remained significantly associated with OS.

Conclusions: Multiplex image analysis of primary PSCC found no difference in the immune contexture of HPV(+) and HPV(-) patients. High levels of tumor-associated macrophages M2 was associated with inferior survival outcomes. Further characterization of T-cell subsets to gauge the exhausted status of T-cells is underway to explain the paradoxical effect noted, similar to that in kidney cancer immune environment.

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GYNAECOLOGICAL CANCERS

740MO Dostarlimab + chemotherapy for the treatment of primary advanced or recurrent endometrial cancer (pA/rEC): Analysis of progression free survival (PFS) and overall survival (OS) outcomes by molecular classification in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial

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Background: In the phase 3 RUBY trial (NCT03981796) dostarlimab (D) + carboplatin-paclitaxel (CP) significantly improved PFS vs CP alone in the mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H; HR, 0.28) and overall population (HR, 0.64) with a favorable OS trend (HR, 0.64). Four molecular EC subgroups were identified for prognostic and potential predictive value. Validated surrogate methods more readily available include POLε mutation (mut), dMMR, TP53 abnormal, and no specific molecular profile (NSMP). Here, we present exploratory efficacy outcomes by molecular classification.

Methods: Patients (pts) with pA/rEC were randomised 1:1 to receive dostarlimab, or placebo (PBO), plus CP, followed by dostarlimab or PBO monotherapy for up to 3 years. POLε and TP53 status were determined by DNAseq; MMR/MSI status was determined by testing used for study enrollment (immunohistochemistry, polymerase chain reaction, or next generation sequencing). Order of classification was POLεmut → dMMR/MSI-H → TP53mut → NSMP. PFS and OS were assessed for each subgroup.

Results: Of 494 pts enrolled and randomised, mutational data were available for 400 pts (81.0%), classified as: 5 (1.3%) POLεmut, 91 (22.8%) dMMR/MSI-H, 88 (22.0%) TP53mut, and 216 (54.0%) NSMP. PFS and OS results favored the D+CP arm in the dMMR/MSI-H, TP53mut, and NSMP subgroups, with the largest benefit observed in the dMMR and TP53mut groups. No pts with POLεmut progressed in either arm as of data cut (Table). Safety was reported previously.

Conclusions: Dostarlimab+CP is associated with improved PFS and OS in the dMMR/MSI-H, NSMP, and TP53 subgroups and adds prognostic value in pA/rEC. Patients with POLεmut had the best prognosis, as expected. Further research may help to validate these exploratory findings.

Table: 740MO

	D+CP	PBO+CP
Overall, n	245	249
PFS by INV, HR (95% CI)	0.64 (0.507—0.800)	
OS, HR (95% CI)	0.64 (0.464—0.870)	
Patients with both MMR/MSI status and mutational data, n	191	209
POLεmut, n	2	3
PFS by INV, HR (95% CI)	NA[a]	
OS, HR (95% CI)	NA[a]	
dMMR/MSI-H, n	39	52
PFS by INV, HR (95% CI)	0.31 (0.17—0.56)	
OS, HR (95% CI)	0.4 (0.17—0.95)	
TP53mut, n	47	41
PFS by INV, HR (95% CI)	0.55 (0.3—0.99)	
OS, HR (95% CI)	0.41 (0.2—0.82)	
NSMP, n	103	113
PFS by INV, HR (95% CI)	0.77 (0.55—1.07)	
OS, HR (95% CI)	0.87 (0.56—1.36)	

[a]No PFS or OS events were observed for patients classified as POLεmut in either arm
INV, investigator assessment; NA, not applicable

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741MO Luveltamab tazevibulin (STRO-002), an anti-folate receptor alpha (FolRα) antibody drug conjugate (ADC), demonstrates clinical activity in recurrent/progressive epithelial endometrial cancer (EEC): STRO-002-GM1 phase I dose expansion

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Background: Luveltamab tazevibulin (luvelta) is a novel FolRα-targeting ADC with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR 4) that induces cytotoxic and immunogenic cell death. Using site-specific conjugation technology and proprietary cell-free protein synthesis platform, luvelta is designed to target a broad range of FolRα expressing cancers, including EEC.

Methods: Following completion of the STRO-002-GM1 phase 1 study, a dose expansion cohort was enrolled consisting of metastatic EEC with progression after ≥ 1 platinum or immunotherapy-based regimen ($\leq$ 3 total lines) with $\geq$ 1% FolRα expression (any intensity using Ventana FolR1 IHC assay). Luvelta dose was 5.2 mg/kg q3w. In patients (pts) with prior pelvic irradiation, a dose of 4.3 mg/kg q3w was administered. The primary endpoint is objective response rate (RECIST v1.1) with secondary endpoints of safety and PK.

Results: 17 pts were enrolled (8 pts at 5.2 mg/kg and 9 pts at 4.3 mg/kg). Prior therapy: median lines=2; prior platinum=17 pts; and prior PD-1=4 pts. Median exposure was 12 weeks (range 3-38). Initial efficacy data is presented in the table.

Table: 741MO Best response (RECIST v1.1)

	Response evaluable patients (n=16)	Response evaluable patients with FolRα ≥ 25% (n=8)
Response (PR+PRu)	6 (37.5%)	4 (50%)
PR	4 (25%)	2 (25%)
PRu (unconfirmed PR)	2 (12.5%)	2 (25%)
SD	5 (31.3%)	3 (37.5%)
PD	5 (31.3%)	1 (12.5%)
Disease control rate (PR+PRu+SD)	11 (68.8%)	7 (87.5%)

The safety profile was consistent with prior reported data in ovarian cancer pts treated with luvelta. The most common Grade 3 or higher (G3+) adverse events (AEs) were neutropenia (53%), anemia (24%), and arthralgia(18%). There were no G3 eye disorder AEs, 1 G3+ pulmonary AE (G3 COVID pneumonia) and no G5 AEs. A single pt had an AE leading to discontinuation (G3 arthralgia).

Conclusions: Advanced EEC remains an area of high unmet need with a poor prognosis and limited treatment options. Preliminary data indicate that luvelta has a predictable and manageable safety profile with encouraging clinical activity in pts with recurrent/progressive FolRα expressing EEC. Luvelta warrants further development as a targeted agent for EEC.

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742MO Neoadjuvant immune checkpoint blockade in mismatch repair deficient endometrial cancer

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Background: Recent studies suggest neoadjuvant immune checkpoint blockade (ICB) may be more efficacious than adjuvant treatment in mismatch repair deficient (MMRd) cancers. However, this has not been explored for endometrial cancer (EC). Here, we report results from a phase I feasibility study of neoadjuvant pembrolizumab in 10 MMRd EC patients.

Methods: MMRd EC patients of any stage or grade at intent-to-treat with primary surgery (at least a hysterectomy) were eligible for participation, and 10/10 patients have been recruited. Patients were treated with 2 three-weekly cycles of pembrolizumab monotherapy (200mg iv) prior to standard-of-care resection and adjuvant treatment if indicated. Radiologic and pathologic response rates, treatment-related adverse events (trAEs) and immune correlates of treatment were assessed.

Results: Patients had stage I-II (n=4) or stage III (n=6) disease at diagnosis, remained on-protocol and underwent definitive surgery. In patients with measurable disease on MRI (n=8), a partial radiologic response was observed in 3/8 patients. A pathological response (<90% viable cancer cells) was observed in 5/10 patients, with 2 major pathologic responses (<10% viable cancer cells). To date, no recurrences have been observed, with a median and longest disease-free survival of 17 and 26 months, respectively. Subclonal MMRp was observed in 2 patients after neoadjuvant treatment. 9/10 patients experienced grade 1/2 trAEs. A treatment-induced immunological response was detected in 9/10 patients with increased lymphoid infiltrates, clonal T cell expansion and diverse T cell phenotypes in post-treatment samples. In tumour-draining (sentinel) lymph nodes, significant clonal overlap with treatment-induced intratumoural T cell expansion was demonstrated.

Conclusions: Neoadjuvant ICB is safe and feasible in MMRd EC. Two cycles of pembrolizumab induced pathologic, radiologic and immunologic responses. Investigation of extended neoadjuvant treatment is warranted and currently being evaluated.

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743MO Efficacy and safety of QL1706 plus paclitaxel and cisplatin/carboplatin +/- bevacizumab (Bev) as 1L treatment in recurrent or metastatic cervical cancer (r/mCC): A single-arm, multicenter phase II study

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Background: Pembrolizumab plus chemotherapy +/- Bev has been approved as the 1L treatment for r/mCC patients (pts) with PD-L1 CPS $\geq$1. QL1706, a bifunctional Mabpair product of anti-PD-1 and anti-CTLA-4 antibodies, has shown good safety and promising efficacy in previously treated r/mCC pts in a phase Ib study. Here we report the latest efficacy and safety results from a Ph 2 study of QL1706 plus paclitaxel and cisplatin/carboplatin +/- Bev as 1L treatment of r/mCC.

Methods: In this open-label, single arm, non-randomized, phase II study, eligible pts were pathologically confirmed r/mCC and had no prior systemic treatment. Pts were treated with QL1706 (5 mg/kg, IV, D1) plus paclitaxel (175 mg/m^2 or 135 mg/m^2, D1) and cisplatin (50 mg/m^2, D1/D2)/carboplatin (AUC = 5, D1) (cohort 1) or with Bev (15 mg/kg, D1/D2) (cohort 2) once every 3 weeks for 6 cycles. Thereafter, treatment maintained with QL1706 +/- Bev, until disease progression, intolerable toxicity, or other discontinuation events. The primary and secondary endpoints were safety and efficacy, respectively.

Results: A total of 60 pts were enrolled. As of data cutoff (Apr 24, 2023), the median follow-up time was 14.0 months. Overall 58 pts had $\geq$1 post baseline tumor assessment and analyzed for efficacy. The ORR was 81% (95% CI, 68.6—90.1) (8 CRs and 39 PRs). The DCR was 98.3% (95% CI, 90.8—100.0). The mPFS was 14.3 months (95% CI, 9.2-NE). The mPFS was numerically longer in cohort 2 vs cohort 1 (16.4 vs 12.5 months). The mOS was not reached. TRAEs occurred in 60 (100%) pts. The most common TRAEs ($\geq$30% in total population) were WBC count decreased (73.3%), neutrophil count decreased (58.3%), anemia (43.3%), platelet count decreased (38.3%), and alopecia (33.3%), Grade $\geq$3 TRAEs occurred in 43 (71.7%) pts. Treatment-related SAEs occurred in 20 (33.3%) pts. TRAEs leading to treatment discontinuation occurred in 16 (26.7%) pts. irAEs occurred in 36 (60%) pts (Grade $\geq$3, 13.3%).

Conclusions: QL1706 plus platinum-based chemotherapy +/- Bev was well tolerated and showed promising antitumor activity as 1L treatment of r/mCC. Ph 3 study of QL1706 plus platinum-based chemotherapy +/- Bev as 1L treatment of r/mCC is ongoing.

Clinical trial identification: NCT05179317.

Legal entity responsible for the study: Qilu Pharmaceutical Co., Ltd.

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744MO AdvanTIG-202: Phase II randomized, multicenter, open-label study of tislelizumab (TIS) with or without ociperlimab (OCI) in patients (pts) with previously treated recurrent/metastatic (R/M) cervical cancer (CC)

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Background: Pts with R/M CC have poor prognoses with high unmet clinical needs and few treatment (tx) options. Dual targeting of solid tumors with anti-T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) and anti-PD-1 mAbs enhances antitumor activity in preclinical studies and clinical studies of other tumors. AdvanTIG-202 (NCT04693234) is investigating the efficacy and safety of TIS (anti-PD-1 mAb) $\pm$ OCI (humanized Fc-intact IgG1 anti-TIGIT mAb) in pts with R/M CC. Primary analysis results are reported here.

Methods: Eligible pts with R/M CC had received $\geq$1 line of chemotherapy and were not amenable to curative tx. In Stage 1, 80 pts were randomized (1:1) to receive 200 mg TIS IV Q3W + 900 mg OCI IV Q3W (Cohort [C]1) or TIS monotherapy (C2) until disease progression, unacceptable toxicity, or withdrawal of consent. In Stage 2, C1 enrolled 98 additional pts. Primary endpoint: ORR per RECIST v1.1 by IRC for C1. Secondary endpoints: DoR, PFS, OS, and safety.

Results: As of June 16, 2022, 138 pts were enrolled and treated in C1 (median age 53.0 y); median study follow-up: 7.4 mo. In the safety analysis set (SS), the ORR was 22.5%, with 13 complete responses (CR; Table); 76.8% had a durable response of $\geq$6 mo. ORR was 26.2% in pts with PD-L1+ tumors (PD-L1 score $\geq$5%), with 10 CRs. Both analysis sets showed significant improvement in ORR vs historical control ORR of 15% in pts treated with anti-PD-1 therapy ($P<0.05$). Around 67% of pts experienced $\geq$1 tx-related adverse event (TRAE). Only 13% of pts experienced $\geq$grade 3 TRAEs; the most frequently reported were anemia (2%) and rash (1%). With limited enrollment in C2 (n=40), the ORR was 32.5%.

Table: 744MO

Cohort 1	Safety analysis set[a] (n=138)	PD-L1 + (n=84)
ORR, % (95% CI)	22.5 (15.8, 30.3)	26.2 (17.2, 36.9)
	n (%)	
Complete response	13 (9.4)	10 (11.9)
Partial response	18 (13.0)	12 (14.3)
Stable disease	56 (40.6)	34 (40.5)
Progressive disease	39 (28.3)	20 (23.8)
Not determined	12 (8.7)	8 (9.5)
mDoR, mo	NE	NE
95% CI	(5.6, NE)	(5.6, NE)
mPFS, mo	3.5	4.2
95% CI	(2.6, 4.9)	(2.7, 6.9)
mOS, mo	9.0	10.4
95% CI	(8.1, 10.4)	(8.1, NE)

Data cutoff: June 16, 2022.
Efficacy assessed by IRC.
[a]Pts who received $\geq$1 dose of any study drug. DoR, duration of response; IRC, independent review committee; m, median; mo, months; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

.

Conclusions: OCI + TIS showed promising antitumor activity and durable responses, regardless of PD-L1 expression, and was well tolerated in pts with previously treated R/M CC.

Clinical trial identification: NCT04693234.

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745MO Raludotatug deruxtecan (R-DXd; DS-6000) monotherapy in patients with previously treated ovarian cancer (OVC): Subgroup analysis of a first-in-human phase I study

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Background: R-DXd is an antibody—drug conjugate comprised of a humanised IgG1 antibody against cadherin 6 (CDH6), a stable linker selectively cleaved within tumour cells, and a membrane permeable topoisomerase I inhibitor. Overexpression of CDH6, a cell adhesion protein, occurs in the majority of OVC cases and is associated with poor prognosis. In an ongoing phase 1 trial (NCT04707248), R-DXd demonstrated an acceptable safety profile and an early efficacy signal.

Methods: All patients received prior taxane and platinum therapies and were unselected for CDH6 tumour expression. Part A (dose escalation) assessed the tolerability of R-DXd at 1.6 to 9.6 mg/kg, and 8.0 mg/kg was determined to be the maximum tolerated dose. Doses of 4.8 to 8.0 mg/kg were expanded in Part B. A subgroup analysis of patients with OVC who received R-DXd at 4.8 to 8.0 mg/kg is reported here.

Results: As of 03 March 2023, 42 patients with OVC had received R-DXd at 4.8 ($n = 7$), 6.4 ($n = 20$), and 8.0 ($n = 15$) mg/kg: 40 (95%) had platinum-resistant disease, 29 (69%) had received prior bevacizumab, and 26 (62%) had received prior PARP inhibitors. The median prior lines of therapy was 4.0 (range 1 − 13). Twenty-one patients (50%) were still receiving study treatment. The median treatment duration was 18.1 wks (range, 3.0—93.9). Any-grade treatment-emergent adverse events (TEAEs) were experienced by 37 patients (88%), and grade ≥ 3 TEAEs were observed in 21 (50%). The most common all-grade TEAEs were nausea (55%), fatigue (40%), vomiting (38%), and diarrhoea (33%). AEs led to R-DXd discontinuation in 14% of patients. The confirmed overall response rate (RECIST v1.1) in patients with measurable disease was 38% (13 of 34): 67% (95% CI, 22.3 − 95.7; 4/6, including 1 CR) at 4.8 mg/kg, 33% (95% CI, 11.8 − 61.6; 5/15) at 6.4 mg/kg, and 31% (95% CI, 9.1 − 6.4; 4/13) at 8.0 mg/kg. Two patients with unconfirmed partial responses were still on treatment. Eleven of 21 GCIG-evaluable patients (52%) had a CA-125 response.

Conclusions: In heavily pretreated OVC patients without CDH6 preselection, R-DXd demonstrated acceptable safety and encouraging preliminary efficacy, which supports further clinical development in OVC.

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746MO Randomized phase II trial of durvalumab in combination with olaparib and cediranib (DOC) compared to olaparib and cediranib (OC) or durvalumab and cediranib (DC) or standard of care chemotherapy (SOC) in platinum-resistant ovarian cancer with prior bevacizumab (NRG-GY023)

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Background: In platinum-resistant ovarian cancer, non-platinum chemotherapy is the standard of care after progression on combination bevacizumab and chemotherapy. We assessed the activity of DOC, DC or OC compared to SOC in bevacizumab pre-exposed population.

Methods: NRG-GY023 is an open-label, randomized, phase II trial conducted in the United States with a targeted sample size of 164 patients (pts). Eligibility included high-grade serous/endometrioid, or clear cell platinum-resistant ovarian cancer with 2-5 prior systemic therapies. Prior use of bevacizumab is required. Treatments were randomly assigned 1:2:2:2 to SOC (weekly paclitaxel, topotecan or liposomal doxorubicin), DOC, DC or OC. The primary end point was progression-free survival (PFS). Secondary end points included overall survival and overall response rate. Interim futility analysis was planned when 28 PFS events (60% information) were available in any pair of one experimental arm with the SOC; arms with a hazard ratio (HR) estimate (ref: SOC) $>$ 0.87 would be discontinued.

Results: By the data cutoff (10/31/2022), 120 pts were enrolled with a median age 65 yo [IQR: 58-69] and 10% were with germline or somatic BRCA mutation. All received prior bevacizumab in either the upfront or recurrent setting. Other prior therapies included PARP inhibitor (49%) and immunotherapy (11%). 103 pts were treated (15 SOC, 30 DOC, 28 DC, and 30 OC, respectively). At the data cutoff, median follow-up time was 4.3 months (IQR: 2.0-7.9). Median PFS was 4.2 (95% CI, 1.9-5.0), 2.6 (95% CI, 2-4.2), 2.3 (95% CI, 2-4.6), and 2.3 (95% CI, 2.1-3.9) months with SOC, DOC, DC and OC, respectively. The HR estimates (ref: SOC) were 1.01 (95% CI, 0.44-2.31), 1.21 (95% CI, 0.52-2.84), and 1.34 (95%CI, 0.58-3.08) for DOC, DC and OC, respectively. Hematologic adverse events were more common with SOC. Safety signals were consistent with past experience.

Conclusions: None of the experimental arms improved PFS compared with SOC. SOC was active in this heavily pretreated population.

Clinical trial identification: NCT04739800.

Legal entity responsible for the study: NRG Oncology.

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747MO First results from the ENGOT-GYN2/GOG-3051/BOUQUET phase II biomarker-directed platform study: Cobimetinib (cobi) or atezolizumab (atezo) + bevacizumab (bev) for persistent/recurrent rare epithelial ovarian cancer (eOC)

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Background: BOUQUET (NCT04931342) is an ongoing platform study evaluating multiple treatments in biomarker-selected patients (pts) with rare eOC that tends to respond less well to standard therapies. We report interim results from the cobi (MEK1 inhibitor) and atezo (anti-PD-L1) + bev (anti-VEGF) arms.

Methods: Eligible pts had measurable persistent/recurrent platinum-resistant (not primary-refractory) non-high-grade serous/non-high-grade endometrioid eOC by central pathological assessment and had received 1–4 prior lines of non-hormonal systemic therapy. Tumour samples were tested centrally using the FoundationOne CDx NGS assay. Pts with *BRAF/KRAS/NRAS* or *NF1* alterations were treated with oral cobi 60 mg/d, d1–21 q28d. Pts ineligible for any open biomarker-selected arm received IV atezo 1200 mg + bev 15 mg/kg both on d1 q21d. The primary efficacy endpoint is investigator-assessed confirmed objective response rate (cORR) per RECIST v1.1.

Results: As of the clinical cut-off date, 20 pts have received cobi (8 low-grade serous ovarian cancer [LGSOC], 5 mucinous carcinoma [MUC], 5 clear-cell carcinoma [CCC], 1 carcinosarcoma [CS], 1 mesonephric-like adenocarcinoma [MLA]) and 21 atezo + bev (15 LGSOC, 3 CCC, 2 MUC, 1 CS). Pts were heavily pretreated ($\geq$3 prior lines: 65% of cobi pts, 48% of atezo + bev pts). cORRs were 16% with cobi and 14% with atezo + bev (Table). For cobi-treated LGSOC + MLA, cORR was 33% (3/9) and disease control rate (complete/partial response [CR/PR] or stable disease $\geq$16 wks) was 89% (8/9). At data cut-off, treatment was ongoing in 9 pts in the cobi arm and 15 in the atezo + bev arm; all CR/PR in both arms were ongoing.

Table: 747MO

Parameter	Cobi (n=20)[a]	Atezo + bev (n=21)
Clinical cut-off date	8 Sep 2022	13 Oct 2022
Median follow-up, mo (range)	6.9 (0–10)	7.4 (2–10)
cORR, n/N (%) [95% CI]	3/19 (16) [3–40]	3/21 (14) [3–36]
CR, n (%)	1 (5)	0
PR, n (%)	2 (11)	3 (14)
Disease control rate, n (%) [95% CI]	8 (42) [20–67]	15 (71) [48–89]
6-month progression-free survival rate, % (95% CI)	41 (18–63)	75 (56–94)
Median treatment duration, mo (range)	3.6 (0–10)	Atezo/bev: 6.3/6.9 (1–10)
Adverse events, n (%)		
Grade 3/4	7 (35)	9 (43)
Grade 5	1 (5)[b]	0
Leading to any treatment discontinuation	0	2 (10)

[a]n=19 for efficacy (no measurable disease at baseline in 1 pt).
[b]Cardiac arrest, not considered treatment related.

Conclusions: The 33% cORR with cobi in heavily pretreated LGSOC/MLA is promising; additional pts will be enrolled. Tolerability was consistent with prior experience. BOUQUET continues to evaluate biomarker-driven therapies for rare eOC.

Clinical trial identification: NCT04931342.

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748P Outcomes for patients (pts) with advanced endometrial cancer (aEC) who completed pembrolizumab (pembro) and continued lenvatinib (LEN) in the phase III Study 309/KEYNOTE-775

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Background: The primary analysis of Study 309/Keynote-775 demonstrated clinically and statistically significant progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) improvements in pts with aEC randomized to LEN + pembro vs chemotherapy (all-comers and pts with mismatch repair-proficient [pMMR] tumors). Pts received pembro for up to 2 yrs and continued LEN until progression or toxicity. This exploratory analysis reports outcomes in pts who completed 2 yrs of pembro and continued LEN at the final prespecified OS analysis (cutoff: 1 Mar 22).

Methods: Pts with aEC and 1 prior platinum-based chemotherapy (up to 2 if 1 given in [neo]adjuvant setting) were randomized to LEN 20 mg PO QD + pembro 200 mg IV Q3W (up to 35 cycles) or chemotherapy (doxorubicin 60 mg/m^2 IV Q3W or paclitaxel 80 mg/m^2 IV QW [3 wks on; 1 wk off]), and stratified by MMR status (pMMR pts were further stratified by ECOG PS, geographic region, and pelvic irradiation history). We report PFS, OS, ORR, duration of response (DOR), and safety in all-comer and pMMR pts who completed 35 cycles (≈2 yrs) of pembro and continued LEN.

Results: Of 411 pts randomized to LEN + pembro (pMMR n=346), 41 (pMMR n=30) completed 35 pembro cycles, continued LEN, and are included in the analysis. Median PFS (95% CI) was 34.1 mos (20.1-not evaluable [NE]) in pMMR pts and 34.1 mos (27.7-NE) in all-comers. Median OS (95% CI) was not reached (NR [NE]) in pMMR pts and all-comers. ORR (95% CI) was 63.3% (43.9-80.1) in pMMR pts and 63.4% (46.9-77.9) in all-comers; 7 pMMR pts and 8 all-comers had a complete response. Median DOR was NR (range, 3.5-39.5+) in pMMR pts and all-comers. Grade ≥3 treatment-related adverse events occurred in 80.5% of all-comers (Table).

Table: 748P

	pMMR pembro completers (n=30)	All-comer pembro completers (n=41)
Median PFS[a,b] (95% CI), mos	34.1 (20.1-NE)	34.1 (27.7-NE)
Median OS[b] (95% CI), mos	NR (NE-NE)	NR (NE-NE)
OS rate at 36 mos[b] (95% CI), %	84.3 (63.2-93.8)	89.0 (73.1-95.7)
ORR[a] (95% CI), %	63.3 (43.9-80.1)	63.4 (46.9-77.9)
CR[a] (95% CI), %	23.3 (9.9-42.3)	19.5 (8.8-34.9)
Median DOR[a,b] (range), mos	NR (3.5-39.5+)	NR (3.5-39.5+)
Probability of pts with extended DOR[a], %[b]		
≥24 mos	78.3	83.8
≥36 mos	69.6	70.9
Drug-related AEs[c], n (%)		
Any grade		41 (100)
Grade ≥3		33 (80.5)

[a]Blinded Independent Central Review, RECIST v1.1
[b]Product-limit (Kaplan-Meier) method for censored date.
[c]Reported in all-comers only.
AE, adverse event; CR, complete response.

Conclusions: Ongoing clinical benefit in pembro completers who continued LEN supports LEN + pembro as standard of care in pts with aEC who received prior platinum therapy.

Clinical trial identification: NCT03517449.

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749P Patient-reported outcomes (PROs) in patients (pts) with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (pA/rEC) in the ENGOT-EN6-NSGO/GOG3031/RUBY trial

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Background: In the RUBY (NCT03981796) trial, dostarlimab (D)+carboplatin/paclitaxel (CP) demonstrated significant PFS improvement compared to placebo (PBO)+CP in pts with pA/rEC. PROs are reported here for the dMMR/MSI-H population.

Methods: Pts with pA/rEC were randomized 1:1 to D+CP or PBO+CP Q3W (6 cycles) followed by D or PBO monotherapy Q6W $\leq$3 years or disease progression. EORTC QLQ-C30 and EORTC QLQ-EN24 were secondary endpoints. PROs were administered at baseline (BL), day 1 of each cycle (C), end of treatment (EOT), and all follow-ups. Change (chg) from BL to EOT was calculated for assessed scales. Mixed models for repeated measures were used to generate least-squares means (LSM), adjusting for within-pt correlations across time points within a pt and controlling for BL values. Improvement is indicated by higher scores for QoL and functional scales and lower scores for symptom scales.

Results: Of 494 pts enrolled, 118 were dMMR/MSI-H. Mean BL scores and mean chg from BL to EOT for global QoL, functional scales, and select symptom are shown in the

Table: 749P

	D+CP		PBO+CP	
	BL Mean (SD)	BL to EOT Mean chg (SD)	BL Mean (SD)	BL to EOT Mean chg (SD)
EORTC QLQ-C30				
Global QoL	66.7 (25.9)	3.0 (19.4)	67.3 (23.9)	-11.1 (29.1)
Physical F	74.9 (21.8)	-5.0 (17.1)	69.1 (23.3)	-6.1 (26.9)
Role F	66.6 (32.2)	0.9 (29.7)	72.9 (32.2)	-7.8 (36.6)
Emotional F	75.9 (18.1)	9.2 (17.5)	75.9 (20.1)	-6.7 (30.4)
Cognitive F	86.3 (20.7)	-1.5 (17.8)	88.0 (19.3)	-9.3 (31.5)
Social F	74.5 (30.3)	6.1 (34.7)	80.2 (27.2)	-12.0 (33.8)
Pain[a]	32.3 (27.3)	-3.0 (29.7)	32.3 (32.1)	8.2 (32.8)
Fatigue[a]	33.9 (25.2)	-5.1 (26.9)	35.1 (27.7)	7.2 (36.0)
EORTC QLQ-EN24				
Back and pelvis pain[a]	35.3 (31.0)	-10.8 (24.0)	36.5 (32.7)	-3.1 (38.3)

[a]Lower scores indicate reduced symptom severity F, function

table. Mean chg from BL to EOT showed improvement in global QoL, emotional and social function, pain, and back/pelvis pain for D+CP. Only back/pelvis pain showed improvement for PBO+CP. Significant differences (LSM [standard error]) between arms were reported for chg from BL to EOT for QoL (14.7 [5.45]; P=0.008), role (12.7 [5.92]; P=0.032), emotional (14.3 [4.92]; P=0.004) and social function (13.5 [5.43]; P=0.014), and fatigue (-13.3 [5.84]; P=0.025).

Conclusions: Pts receiving D+CP demonstrated improvements in several QoL domains relative to BL at EOT, with significant improvements over PBO+CP, in global QoL, role, emotional, and social function, and fatigue. Dostarlimab+CP significantly improved PFS while maintaining QoL, further supporting its use as a standard of care in pts with dMMR/MSI-H pA/rEC.

Clinical trial identification: NCT01847274.

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750P PFS2 and adjustment of overall survival (OS) for subsequent anticancer therapy in patients (pts) with primary advanced or recurrent endometrial cancer (pA/rEC) treated with dostarlimab plus chemotherapy or chemotherapy alone in the ENGOT-EN3-NSGO/GOG-3031/RUBY trial

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Background: The RUBY trial (NCT03981796) evaluated the efficacy and safety of dostarlimab (D)+carboplatin-paclitaxel (CP) vs CP alone in pA/rEC. D+CP significantly improved progression-free survival (PFS) in the mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H; HR, 0.28) and overall population (HR, 0.64) with a favorable OS trend (HR, 0.64). Here, PFS2 and OS adjusted for subsequent anticancer therapy are reported.

Methods: Pts were randomised 1:1 to receive D+CP or placebo (PBO)+CP Q3W for 6 cycles, followed by D or PBO monotherapy Q6W for up to 3 years. PFS2 was a secondary endpoint for the dMMR/MSI-H and overall populations. Post hoc treatment switching-adjustment (for subsequent use of dostarlimab, pembrolizumab, durvalumab, nivolumab, or pembrolizumab with lenvatinib) was implemented using 2 methods: inverse probability of censoring weighting (IPCW) and rank-preserving structural failure time (RPSFT).

Results: Of 494 pts randomised (D+CP, n=245; PBO+CP, n=249), 118 were dMMR/MSI-H (D+CP, n=53; PBO+CP, n=65). Overall, 15.5% of pts in the D+CP arm and 34.5% of pts in the PBO+CP arm received subsequent immunotherapy. PFS2 benefit was observed with D+CP for all populations (Table). When adjusted for subsequent therapy, the HRs for OS for D+CP vs PBO+CP for both IPCW and RPSFT were similar to the unadjusted HR for OS in all populations, with increased survival with D+CP (Table). Safety was reported previously.

Conclusions: Consistent with results of the primary efficacy analysis, dostarlimab+CP demonstrates PFS2 and OS benefits vs PBO+CP in pts with pA/rEC despite the use of subsequent therapies. These results provide additional support for the use of dostarlimab+CP as standard of care in pts with pA/rEC..

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Table: 750P

	dMMR/MSI-H		MMRp/MSS		Overall	
Variable, HR (95% CI)	**D+CP N = 53**	**PBO+CP N = 65**	**D+CP N = 192**	**PBO+CP N = 184**	**D+CP N = 245**	**PBO+CP N = 249**
PFS[a]	0.28 (0.16–0.50) $P<0.0001$		0.76 (0.59–0.98)		0.64 (0.51–0.80) $P<0.0001$	
PFS2	0.37 (0.19–0.73)		0.71 (0.54–0.95)		0.65 (0.50–0.84)	
Subsequent immunotherapy, n (%)	8 (15.1)	25 (38.5)	30 (15.6)	61 (33.2)	38 (15.5)	86 (34.5)
OS	0.30 (0.13–0.70)		0.73 (0.52–1.02)		0.64 (0.46–0.87) $P=0.0021$	
IPCW, n	52	65	188	181	240	246
IPCW-adj OS	0.35 (0.12–1.00)		0.67 (0.44–1.03)		0.62 (0.42–0.90)	
RPSFT, n	53	65	192	184	245	249
RPSFT-adj OS	0.24 (0.09–0.67)		0.69 (0.47–1.03)		0.59 (0.41–0.85)	
Acceleration factor[b]	3.465		1.408		1.613	

[a]Investigator assessment per RECIST v1.1 [b]D+CP increases survival by AF

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751P Patients with endometrial cancer: Expectations and understanding of genetic counseling and hereditary carcinomas - First results of an international NOGGO/GCIG/ENGOT survey (EXPRESSION XI/IMPROVE)

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Background: With the introduction of molecular classification of endometrial cancer (EC), the importance of Lynch syndrome and hereditary EC has been emphasized. For a successful conduct of EC-therapy, the patient's expectations, preferences, and needs should be considered. The aim of this survey was to evaluate the status quo and the patients' understanding of their own condition, including genetic counseling.

Methods: We developed an international online and paper survey with 80 questions for endometrial cancer patients. It included questions on demographics, medical history, tumor classification, therapy, preferences and expectations concerning treatment modalities.

Results: To date, 656 endometrial cancer patients (mean age: 65.0 [20.0; 92.0] years) completed the survey from a total of seven countries, mainly from Germany (56.1%) and Switzerland (40.5%). The majority of patients (77.4 %) were in follow-up and not receiving current cancer therapy, while 16.1 % were still receiving treatment, of which 6.4 % were due to cancer recurrence. Overall, 14.3% of the patients suffered from a recurrent disease. One third of patients (35.1%) reported that their tumor had been tested for molecular classification, and more than half (56.9%) did not know if this had occurred. Genetic counseling was only given to 21.7% of patients, 63.1% did not receive any form of it. From the patients understanding, 19.6% believe that a family history or genetic alteration could be responsible for tumorigenesis – 30.6% do not know. On the contrary, 68.1% of the patients answered that there were cases of cancer in their blood relatives – 19.1% had one or more cases of colorectal cancer in the family history, 13.9% endometrial, 10.9% gastric and 3.9% ovarian cancer. 16.4% of all patients had a second malignancy in their medical history. In general, 32.4 % of patients would like doctors to spend more time on explanations.

Conclusions: This survey underlines the great need for better access to molecular profiling and genetic counseling in women with endometrial cancer. Programs should be developed to empower patients and to educate medical staff.

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752P Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic squamous cell cervix carcinoma: Subgroup analysis of the PEVOsq basket trial

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Background: Adding pembrolizumab (P) to standard first-line chemotherapy +/- bevacizumab in cervical cancer significantly improved survival. However, more than half of patients (pts) will present a relapse before 12 months. Virtually all cases of cervical cancer are attributable to HPV infection. Preclinical evidence suggests that histone deacetylase inhibitor vorinostat (V), might be active in both HPV 16 and HPV 18 related infections and might improve immunotherapy efficacy giving the rationale for combining P + V in cervical cancer.

Methods: PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of P+V in pts with recurrent and/or metastatic squamous carcinomas. Pts had to be PD1/PD-L1 antagonist-naïve with no restriction in terms of prior lines of treatments. P dose was 200 mg Q3W IV, and V 400 mg QD PO. Sample size was determined using an A'Hern design. Primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

Results: Among 112 included pts, 25 were included in the cervix cohort. Median age was 52 years [range(r): 31-75]. The median number of prior lines of therapies was 1 [r: 0-3]. Among 23 pts evaluable for activity criteria, ORR was 39.1% [95%CI: 19.7-61.5]. Median PFS was 4.2 months [95%CI: 2.3-8.2] and OS was 10.3 months [95%CI: 5.7-NR]. DOR was 15.2 months [95%CI 1.4-NR]. Grade 3/4 Treatment related AE were frequent (44%). Seventeen pts (68%) had at least one treatment interruption and/or dose reduction due to toxicity for V including hematotoxicity, gastrointestinal disorders, asthenia, and creatinine increase. Six pts (24%) had at least one administration delayed due to toxicity for P. Median dose intensity for V was 271.4 mg/j [r: 108.7 — 400]. Dose intensity for V was 271.1mg/d [r: 108.7-400.0] and 260.5mg/d [r: 199.4-400.0] in pts with ORR and others (SD/PD), respectively. Results according to PDL1, MSI, TMB and HPV will be presented at the meeting.

Conclusions: Combining P and V in cervical cancer was effective even though dose adaptations for V were frequent.

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753P IN10018 in combination with pegylated liposomal doxorubicin (PLD) in platinum-resistant ovarian cancer (PROC): A single-arm, phase Ib clinical trial

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Background: IN10018 is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK). Our previous work showed promising objective response rate (ORR) and progression-free survival (PFS) of IN10018 in combination with PLD in PROC patients (Wu et al, ASCO2022). Here we present the fully enrolled study data, especially the overall survival (OS).

Methods: In this single-arm, open-label, phase Ib trial, PROC pts (high-grade serous only) received IN10018 in combination with PLD treatment until intolerable toxicity or disease progression. The primary endpoint was ORR, the second endpoints including disease control rate (DCR), duration of response (DOR), PFS, OS, and safety.

Results: As of April 28, 2023, a total of 61 PROC pts (median age 55 years) were enrolled with median follow-up duration of 14.0 months (range: 0.9 - 32.8 months). 90.2% (55/61) pts had 1-3 prior lines of therapy, 34.4% (21/61) had prior bevacizumab treatment and 27.9% (17/61) had prior PARPi treatment. The safety profile of the combination is comparable to these single agents alone without additive toxicities. No IN10018 related death was observed, and 9.8% (6/61) pts reported IN10018 related SAEs which were also PLD related. The most frequently reported IN10018 related AEs assessed by investigators were proteinuria, decreased appetite, fatigue and AEs of gastrointestinal origin such as nausea, diarrhea, vomiting. Majority of these IN10018 related AEs were grade 1 and 2. No IN10018 related grade 4 or 5 AEs were reported. Efficacy (as assessed by investigator) was evaluable in 54 pts. 25 responders (including 1 confirmed CR, 21 confirmed PRs and 3 unconfirmed PRs) and 20 SDs were reported. The ORR was 46.3% (95% CI: 32.6%, 60.4%), the DCR was 83.3% (95% CI: 70.7%, 92.1%). The mDOR was 6.9 months (95% CI: 4.2 — 9.1 months). The mPFS was 7.3 months (95% CI: 5.2 — 9.0 months). The mOS was 20.9 months (26/61 OS events, 95% CI: 14.4 — NA) in all treated population and maturing.

Conclusions: The combination of IN10018 with PLD showed manageable safety profile and prolonged survival in PROC pts. A placebo-controlled, randomized, double-blind phase II trial is ongoing to confirm the observed efficacy and safety.

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754P Ubamatamab (MUC16xCD3 bispecific antibody) with cemiplimab (anti-PD-1 antibody) in recurrent ovarian cancer: Phase I dose-escalation study

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Background: Ubamatamab (REGN4018) is a mucin16 (MUC16) x CD3 bispecific antibody. Cemiplimab, an anti-PD-1 antibody, enhanced its activity in preclinical studies. In phase 1 (NCT03564340), ubamatamab monotherapy resulted in an acceptable safety profile and durable responses. We now present ubamatamab combined with cemiplimab dose escalation results.

Methods: Patients (pts) with recurrent platinum-experienced ovarian cancer (OC) received weekly intravenous (IV) ubamatamab at a dose range of 1—450 mg after initial step-up dosing. Cemiplimab 350 mg IV every 3 weeks was added beginning Day 29—36. Dose escalation initially followed a modified 3+3 design, then Bayesian optimal interval design. Primary endpoints were safety and PK. Secondary endpoints included confirmed objective response rate (ORR), Kaplan-Meier estimated duration of response (DoR) and progression-free survival (PFS) (RECIST 1.1), and CA125 response (GCIG).

Results: 35 pts were enrolled, 29 (82.9%) received ≥1 dose of cemiplimab. Median number of prior therapies was 5 (range 1—10). Median duration of ubamatamab and cemiplimab exposure was 11 (range 2—75) and 12 (3—69) weeks, respectively. The most common treatment-emergent adverse events (TEAE) were pain (82.9%) and cytokine release syndrome (68.6%, all Grade [G] 1/2). The most common G≥3 TEAE were anaemia (25.7%), pain (20.0%) and neutropaenia (11.4%, 1 dose-limiting toxicity [DLT], 60 mg). Ubamatamab 1—250 mg weekly with cemiplimab was tolerable. In the highest dose cohort (450 mg), haemophagocytic lymphohistiocytosis (G4, DLT) was observed. Objective responses were observed at ubamatamab doses 10—250 mg (n=25). In 22 of these pts receiving ≥1 dose of cemiplimab, ORR was 18.2% (95% CI: 5.2—40.3), median DoR 8.3 months (4.2—not estimable), CA125 response rate 22.7% (7.8—45.4) and 6-month PFS 47.6% (25.7—66.7). Two pts with target lesion growth (+17%, +31%) before adding cemiplimab to ubamatamab had subsequent partial responses. Ubamatamab PK was not impacted by cemiplimab.

Conclusions: In pts with heavily pretreated OC, an acceptable safety profile and durable responses were observed with ubamatamab + cemiplimab. A randomised phase 2 expansion of ubamatamab +/- cemiplimab is ongoing.

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755P Retifanlimab in patients with recurrent microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) endometrial cancer: Final results from the POD1UM-101 study (Cohort H)

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Background: Retifanlimab (Zynyz™) is a programmed death receptor-1 (PD-1)—blocking antibody recently approved in the United States for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma. POD1UM-101 (NCT03059823) is an ongoing first-in-human dose finding and cohort expansion study in patients with advanced solid tumours. We have previously reported significant clinical activity with safety for retifanlimab representative of the class in the MSI-H or dMMR endometrial cancer expansion cohort (Berton D, SITC 2021). We present final study results.

Methods: Eligible patients had histologically proven, unresectable recurrent/metastatic MSI-H or dMMR endometrial cancer, Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$1, disease progression during or following 1 to $\leq$5 prior systemic treatments, measurable disease (per RECIST v1.1), and were naïve to prior immune checkpoint inhibitors. MSI-H and dMMR status were centrally confirmed. Patients received retifanlimab 500 mg every 4 weeks for up to 2 years. The primary study endpoint was safety. Confirmed best overall response and duration of response were evaluated by independent central reviewer (ICR).

Results: A total of 76 patients with centrally confirmed MSI-H (65 [85.5%]) or dMMR (11 [14.5%]) disease were enrolled, with the last patient initiating treatment on 29 December 2020. Median age was 67 (range 49—88) years, 70 (92%) had endometrioid histology, 67 (88%) had metastatic disease, and 61 (80%) had visceral metastases. Most patients had received prior radiotherapy (54 [71%]) or surgery (68 [90%]). All patients except for one, had received prior chemotherapy for advanced disease with 33 (43.4%) patients receiving $\geq$2 prior systemic therapies. The overall response rate by ICR was 43% (95% CI: 32—55). Final results for this cohort including safety and secondary efficacy endpoints will be presented.

Conclusions: Retifanlimab has shown notable clinical activity in previously treated MSI-H or dMMR endometrial cancer, which is consistent with other checkpoint immunotherapies.

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756P First-in-human phase I study of a novel claudin 6 (CLDN6) targeted antibody drug conjugate (ADC) TORL-1-23

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Background: CLDN6 is expressed at high levels in multiple cancers with little to no expression in normal tissues and has been implicated in the initiation, progression, and metastasis of some cancers. CLDN6 is an ideal target for development of new therapeutics. TORL-1-23 is first-in-class ADC targeting the tumor-specific antigen CLDN6.

Methods: This ongoing first in human study (TORL123-001, NCT05103683) characterizes the safety, tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of TORL-1-23 in participants with advanced solid tumors. Pharmacokinetics (PK), immunogenicity and clinical efficacy are also assessed. TORL-1-23 is administered IV every 3 weeks. In Dose Escalation, cohorts up to 6 participants are evaluated at each dose level according to an accelerated titration design. In Dose Expansion, patients with CLDN6-expressing cancers will be evaluated to confirm the RP2D in ovarian cancer, NSCLC, and other CLDN6+ cancers using an IHC companion diagnostic. Doses above the historic MTD for MMAE containing ADCs are being evaluated given the favorable safety/tolerability at doses $<$2.4 mg/kg.

Results: 30 patients with ovarian (n=22), testicular (n=5), and endometrial (n=3) cancers were enrolled across 9 dose levels ranging from 0.2 to 3 mg/kg IV every 3 weeks (as of 01MAY2023). 93% of pts had received $\geq$ 3 prior lines of treatment in the metastatic setting. The most common treatment-related adverse events were Gr1/2 fatigue (n=6), anemia (n=5), and peripheral neuropathy (n=4). No DLTs were observed at doses $\leq$2.4 mg/kg. Sustained PK exposure of TORL-1-23 over the dosing interval and low levels of circulating MMAE are noted. Partial responses (PR) were observed in 7/22 (32%) efficacy evaluable participants with CLDN6+ disease (6 ovarian, 1 testicular) across dose levels. 3/3 (100%) participants with CLDN6+ ovarian cancer responded at the 2.4 mg/kg dose level. Data from 3 mg/kg are pending.

Conclusions: In participants with heavily-pretreated CLDN6-expressing ovarian cancer, the novel TORL-1-23 ADC has a favorable safety/tolerability profile and encouraging antitumor activity in a phase 1 dose finding study. Further evaluation in ovarian cancer and other CLDN6+ cancers is warranted.

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757P The efficacy and safety of recombinant human adenovirus type 5 (H101) intra-tumor therapy in patients with recurrent or metastatic cervical cancer: A prospective, open-label, single-arm study

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Background: H101 has promising efficacy and favorable safety in patients with persistent /recurrence/metastasis (P/R/M) gynecological cancer, but the evidence regarding the effect of H101 on cervical cancer remains rare. Thus, the purpose of this study is to evaluate the efficacy and safety of H101 intra-tumor injection in P/R/M cervical cancer.

Methods: This is a prospective, open-label, single-arm study, with an expected sample size of 60. P/R/M cervical cancer patients who had received at least one line of systemic therapy or could not tolerate chemotherapy were eligible. Patients were given H101 intro-tumor injection ($0.5\text{-}1.5\times10^{12}$) viral particles from day 1 to day 5 combined with or without radiotherapy in sequential, 3 weeks for a cycle (1-4 cycles totally). The primary endpoint is local control (LC) and the secondary endpoints include objective response rate (ORR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs). This trial was registered at www.clinicaltrials.gov with identifier number NCT 05051696.

Results: Between September 2021 to April 2023, 53 patients were enrolled, in which 49 patients (92.45%) completed at least 1 tumor assessment with a median follow-up time of 8 months (95%CI: 7-11months). The LC rate at 3 months was 73.5% (95%CI: 60.7%-86.3%), and the median PFS and OS were currently not reached. The ORR was 69.4% (95%CI: 56%-82.8%), and the disease control rate (DCR) was 81.6% (95%CI: 70.4%-92.9%) by RECIST1.1. The most frequently reported AEs were fever (62.8%), fatigue (32.65%), vomiting (20.41%), bleeding (16.3%), pain (16.3%) and bird-flue like symptoms (16.3%). All frequently occurring AEs were grade 1 or 2. High grade AE was only observed in 3 patients with rectovaginal fistula grade 3. Neither unexpected safety signals nor treatment related death occurred.

Conclusions: We present here for the first time that H101 is a strong candidate for virotherapy in P/R/M cervical cancer. These results demonstrate that H101 combined with or without radiotherapy could improve clinical outcomes significantly in patients with P/R/M cervical cancers with acceptable toxicity.

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758P Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic vulvar and vaginal squamous cell carcinoma: Subgroup analysis of the PEVOsq basket trial

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Background: Vulvar and vaginal squamous cell carcinoma (VVSCC) are rare, representing 4% of gynecologic cancers. At recurrent/metastatic stage systemic treatments are limited without gold-standard, chemotherapy response rate is poor. Immunotherapy has been approved for some metastatic SCC. Translational analyzes suggest that SCC share common molecular features as epigenetic. Modulating the epigenome might improve the efficacy of immunotherapy. Combining pembrolizumab (P) to an epidrug vorinostat (V) has been proposed in the PEVO basket trial. We described here the VVSCC cohort.

Methods: PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of P combined to V in patients with recurrent/metastatic SCC of the cervix, head and neck, anus, vulva/vagina, penis, and lung. Patients had to be PD1/PD-L1 antagonist-naïve. There was no selection based on PD-L1 expression, HPV status, or number of prior lines of treatments. P dose was 200 mg Q3W IV, and V 400 mg QD PO. Sample size was determined using an A'Hern design with the following hypotheses (alpha=5%, power=90%, p0=5%, p1=30%). The primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS).

Results: Among 112 included patients, 17 had a VVSCC metastatic/recurrent cancer. Median age was 63 years old [range: 40-85], 14 (82.4%) had a metastatic disease and 3 (17.6%) a locally advanced relapse. Lung 50.0%) and lymph nodes (78.6%) were the major metastatic sites. Inclusion in PEVOsq was the first-line treatment for most of patients, with a median number of prior treatment lines of 0 [range: 0-1]. Three patients out of 16 evaluable patients (18.8%) had an OR: 1 (6.3%) CR and 2 (12.5%) PR. Median PFS was 1.3 months [95%CI: 1.1-4.3]. Median OS was 17.5 months [95% CI: 2.3-NR]. Four patients (23.5%) had a G3/4 treatment related AE. Results according to PDL1, MSI, TMB and HPV will be presented at the meeting.

Conclusions: P combined with V is safe and produce encouraging efficacy in VVSCC patients.

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759P Nimotuzumab combined with concurrent chemo-radiotherapy in patients with locally advanced cervical squamous cell carcinoma: A randomized, controlled, open-label, multicenter study

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Background: Concurrent chemo-radiotherapy (CCRT) with platinum-based regimen is the standard treatment for locally advanced cervical cancer (LACC), however, 30% of patients developed recurrence and metastasis. Epidermal growth factor receptor (EGFR) is highly expressed in most cervical squamous cell carcinomas with poor survival prognosis. Nimotuzumab combined with CCRT had good antitumor activity and safety in LACC. In order to evaluate the efficacy and safety of nimotuzumab combined with CCRT in locally advanced cervical squamous cell carcinoma patients, we conducted a randomized, controlled, open-label, multicenter study (NCT04678791).

Methods: All patients with locally advanced cervical squamous cell carcinoma were randomized (1:1) to receive nimotuzumab (400mg, iv, weekly, for 6 weeks) combined with CCRT (cisplatin: 40 mg/m^2, weekly, for 6 weeks; IMRT/VMAT: 45-50.4 Gy/25-28f; high-dose rate brachytherapy: 30-40 Gy, in 8 weeks) or CCRT alone. The primary endpoint was 3-year progression free survival (PFS) per RECIST v1.1. The secondary endpoints were 3-year overall survival (OS), objective response rate (ORR), complete response (CR) rate per RECIST v1.1, and safety per CTCAE v5.0.

Results: Totally 291 patients were enrolled. 147 patients in the Nimo group (nimotuzumab combined with CCRT) and 144 in the CCRT group (CCRT alone). The median follow-up time was 1.8 months, and follow-up is ongoing. The baseline characteristics were balanced between the two groups. The median PFS of the Nimo group was longer than that of CCRT group (9.5 vs. 7.0 months, P=0.129), the 3-year PFS and 3-

year OS were not reached. A total of 28 (19.05%) patients achieved partial response (PR) and 99 (67.35%) achieved CR in the Nimo group, 17 (11.81%) and 93 (64.58%) in the CCRT group, respectively. The ORR was 86.39% vs. 76.39% (P=0.028). The incidence of grade 3 or higher adverse reactions had no significant difference between the two groups (P > 0.05).

Conclusions: Nimotuzumab combined with concurrent chemo-radiotherapy showed longer survival trend and significantly improved the ORR in patients of locally advanced cervical squamous cell carcinoma with a good tolerance.

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760P Efficacy and safety of nimotuzumab plus radiotherapy for elderly patients with locally advanced cervical squamous cell carcinoma

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Background: Although concurrent chemoradiotherapy is the standard treatment for locally advanced cervical cancer, elderly patients are often intolerable to chemotherapy. It's urgent to explore a suitable regimen for these population. Cervical squamous cell carcinoma (CSCC) is characterized by the high expression of epidermal growth factor receptor (EGFR). Nimotuzumab is a recombinant humanized anti-EGFR monoclonal antibody with good safety. This study aimed to investigate the efficacy and safety of nimotuzumab plus radiotherapy in the treatment of elderly patients with locally advanced cervical squamous cell carcinoma (LACSCC).

Methods: It's a prospective, multicenter, and single-arm trial. Key inclusion criteria included aged $\geq$ 65 years, histologically diagnosed CSCC with clinical stage IB3-IVA, ECOG 0-2, and refusing chemotherapy. Patients received nimotuzumab with 200mg/w for 6 weeks, underwent radiotherapy, including intensity-modulated radiotherapy (IMRT), volumetric intensity modulated arc therapy (VMAT) (45-50.4Gy, 1.8-2.0Gy/f, 25-28f), and brachytherapy (HR-CTV D90, 80-85Gy). Brachytherapy combined with external beam radiotherapy was completed within 8 weeks. The current endpoints include objective response rate (ORR), complete response rate (CRR), disease control rate (DCR), and safety.

Results: This trial enrolled 122 elderly LACSCC patients from Nov 2021 to Jan 2023. The median age was 72.5 years old (range from 65 to 92) with clinical stage IB3-IVA. The addition of nimotuzumab to radiotherapy exhibited a significant improvement in short-term efficacy with ORR of 87.70% (107/122), CRR of 42.62% (52/122), and DCR of 92.62% (113/122). The partial response was 45.08% (55/122), progressive disease was 2.50% (3/122), and stable disease was 4.92% (6/122). So far, no drug-related adverse events have occurred.

Conclusions: Nimotuzumab plus radiotherapy provided significant improvements in ORR, CRR, and DCR in elderly patients with LACSCC. No drug-related adverse events were observed. Our results demonstrate that nimotuzumab combined with radiotherapy may provide a choice for this population with better efficacy and tolerance.

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761P A phase II trial of avelumab in combination with pegylated liposomal doxorubicin in recurrent/metastatic endometrial cancer (GEICO 70-E): analysis according to molecular classification

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Background: The Cancer Genome Atlas (TCGA) classified endometrial cancer (EC) into molecular subgroups with different prognosis and predictive value of response to immunotherapy or chemotherapy. Testing for surrogate biomarkers (BM) of TCGA groups may be clinically cost-effective. According to these BM groups, we evaluated differences in efficacy of avelumab (A) and pegylated liposomal doxorubicin (PLD) in recurrent EC pts.

Methods: Open-label, single-arm, multicenter, phase II study in recurrent/metastatic EC. Pts were treated with intravenous A 10 mg/kg (q2W) and PLD 40 mg/m^2 (q4W). Primary endpoint was 6 months (m) progression free survival (PFS). Archival tumor tissue was collected for molecular classification according to BM of the TGCA groups. POLE mutations, mismatch repair markers (MMR) and p53 abnormalities were analysed to classify EC tumors. EC groups were as follows: POLE (POLE mutant); P53-ABN (POLE wt, p53 abnormal): MSI (microsatellite instability) (POLE wt, p53 wt, abnormal MMR); MSS (microsatellite stable) (POLE wt, p53 wt, normal MMR). Differences in PFS and overall survival (OS) were evaluated among BM groups.

Results: BM analysis was performed in 41 pts: 26 (63.4%) were p53-ABN, 7 (17.1%) MSI, 7 (17.1%) non-specific molecular profile (NSMP), and 1 (2.4%) POLE. MSI/MSS classification showed 33 (80.5%) MSS tumors, 7 (17.1%) MSI, and 1 (2.4%) POLE. 6-m PFS was 45% [95% CI 31.9%-63.4%] with a median PFS of 5.68m [95% CI 3.58-7.98]. NSMP group showed the best PFS results: 6-m PFS, 66.7% and median, 9.2m (95% CI 1.7 — NR). 6-m PFS of MSI and P53-ABN groups was 28.6% and 42.3%, respectively. 6-m PFS was numerically better in MSS (46.9%) than in MSI (28.6%). Median OS time was 11.6m [95%CI; 7.4-NR] and 12-m OS was 47.5% [34.3%-65.8%]. Median OS in the NSMP, p53-ABN and MSI groups was 26.0m, 12.6m and 5.3m, respectively. OS was better in p53-ABN group than in MSI (HR: 3.44 [1.36; 8.69], p=0.01). OS was also better in MSS group than in MSI (HR: 3.78 [1.52; 9.43], p<0.01).

Conclusions: A and PLD has activity in pre-treated recurrent EC. Pts with MSS and p53-ABN had better outcomes than those with MSI. Interestingly pre-treated NSMP pts show a median OS >2 y.

Clinical trial identification: EudraCT number: 2018-000843-14.

Legal entity responsible for the study: Grupo Español de Investigación en Cáncer de Ovario (GEICO).

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762P Pamiparib combined with surufatinib as a neoadjuvant therapy for advanced ovarian cancer patients in the entire population: Preliminary results of a prospective, exploratory, single-arm phase II clinical study

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Background: Optimal tumor reduction surgery is crucial for for advanced ovarian cancer (OC) prognosis. Neoadjuvant chemotherapy can increase surgery chances for OC, but the benefit to patients (pts) is limited. PARP inhibitors combined with anti-angiogenic drugs have significant benefits in the first-line maintenance and recurrence treatment of OC. This study aims to evaluate the efficacy and safety of Pamiparib combined with Surufatinib neoadjuvant therapy (NAT) for advanced unresectable OC in the entire population.

Methods: This is a single-center, single-arm, phase II study following Simon's two-stage design. 20 pts with newly diagnosed unresectable (Fagotti score $\geq$ 8 or upper abdominal CT score $\geq$ 3) FIGO III-IV OC were recruited. Enrolled pts will receive NAT with Pamiparib (40 mg bid q3w for 3 cycles) combined with Surufatinib (250mg bid q3w for 2 cycles), followed by interval debulking surgery (IDS) and4 cycles of platinum-containing chemotherapy. The primary endpoint is complete resection rate (R0), and secondary endpoints include objective response rate (ORR), pathologic complete response(pCR) rate, progression-free survival, overall survival, and safety.

Results: As of Aug 30, 2023, of the 20 enrolled pts, 16 had completed genetic testing, and 14 were homologous recombination deficiency (HRD) positive, with 9 cases of BRCA1/2 mutations. By Aug 30, 2023, 17 pts completed NAT and IDS with an ORR of 100%. 15 pts achieved R0 surgery (88.24%), and 2 pts achieved R1. All 20 pts were evaluable by GCIG CA125 criteria, and CA125 response was all observed (100%). Grade 3 or 4 treatment-related adverse events that occurred are neutropenia, thrombocytopenia, anemia, and hepatic dysfunction.

Conclusions: Pamiparib combined with Surufatinib as a new neoadjuvant "chemotherapy-free" regimen showed extremely high R0 and ORR rates with manageable toxicity profiles. Currently, the experiment is still ongoing and further analysis and reporting of more data will be conducted.

Clinical trial identification: NCT05652283, Release date: 6 December 2022.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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763P Penpulimab + anlotinib plus chemo-less therapy in first-line treatment for persistent, recurrent, or metastatic cervical cancer: A single-arm, phase II study (ALTN-AK105-II-06)

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Background: Anlotinib is a novel multi-target tyrosine kinase inhibitor, inhibiting tumour angiogenesis and proliferative signalling. Penpulimab is a novel human immunoglobulin G1 (IgG1) anti-programmed cell death-1 (PD-1) antibody. ALTN-AK105-II-06 (ChiCTR2200062897) aimed to assess the effiacy and safety of penpulimab + anlotinib plus chemo-less therapy as fist-line therapy for persistent, recurrent, or metastatic cervical cancer.

Methods: Eligible adults with persistent, recurrent, or metastatic cervical cancer not previously treated with systemic chemotherapy and not amenable curative treatment, with CPS more than 1% PD-L1 expression, and ECOG 0-1 were considered eligible for enrolment. Patients received 2 cycles of chemotherapy (paclitaxel 175 mg/m2 + cisplatin 50 mg/m2 or carboplatin AUC 5) + penpulimab 200mg Q3W + anlotinib 10mg, following with penpulimab and anlotinib for maintenance therapy. Patients were treated on continuous 3 weeks of penpulimab for up to 2 years, until disease progression, or unacceptable toxicities. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS), 6-month PFS, safety and quality of life.

Results: From Sep 2022 to May 2023, 15 patients were recruited with a median age of 47 years (range: 44-66), FIGO histopathological stage IIB (26.7%), III (46.7%) and IV (26.7%) were enrolled. 46.7% patients had ECOG PS 1. At data cutoff date (May 08, 2023), 14 patients had at least one post treatment anti-tumor assessment. 1 (7.1%) patient achieved CR, 11 (78.6 %) patients achieved PR, 1 (7.1%) SD and 1 (7.1%) patient NE. The ORR was 85.7%. Median PFS and OS were not reached. Grade $\geq$3 TRAEs incidence was 42.86% (hypertension: 21.43%, neutropenia: 21.43% leukopenia: 14.29%, and hypertriglyceridemia: 7.14%).

Conclusions: This chemo-less therapy of only 2 cycles of chemotherapy + penpulimab + anlotinib in first-line treatment, maintaining with penpulimab and anlotinib showed promising efficacy with a favourable toxicity profile for patients with persistent, recurrent, or metastatic cervical cancer.

Clinical trial identification: ChiCTR2200062897 (China Clinical Trial Registry).

Legal entity responsible for the study: Q. Xu.

Funding: ChiaTai Tianqing Pharmaceutical Group Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

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764P Tislelizumab (Anti-PD-1) combined with definitive chemoradiotherapy in recurrent and/or metastatic cervical cancer (PILOT-2020-511): A single-arm, phase II trial

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Background: Tislelizumab is an investigational, humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death-1 (PD-1) emerging as promising investigational agents for the treatment of advanced cervical cancer. This phase II trial evaluated the combination of Tislelizumab plus definitive chemoradiotherapy in patients with recurrent and/or metastatic cervical cancer who relapsed after prior platinum-based therapy.

Methods: PILOT-2020-511 was a single-arm, phase 2 trial done at Fudan University Shanghai Cancer Center (Shanghai, China). Patients aged 18-70 years with recurrent and/or metastatic cervical cancer, with an ECOG performance status of 0-2, and adequate organ and bone marrow function were eligible for inclusion. Patients received concurrent radiotherapy (58-60 Gy in 28 fractions), chemotherapy (4-6 cycles of intravenous paclitaxel [135 mg/m2] and carboplatin [AUC=5]), and tislelizumab (200 mg intravenously every 3 weeks for up to 1 year, or until disease progression or unacceptable toxicity). The primary endpoint was the complete response rate at 3 months after radiotherapy by investigator assessment. Secondary endpoints were overall survival, progression-free survival, duration of response, quality of life (not reported here), and safety. The trial is registered with Chictr.org.cn, ChiCTR2000034748 and follow-up is ongoing.

Results: Between September 1, 2020, and December 25, 2022, 41 patients were enrolled. The median age was 58 years (IQR 52-67), 30 (73.2%) of 42 patients had lymphatic metastasis, and 11 (26.8%) patients were organic metastasis. 40 (97.6%) of 41 patients completed the planned chemoradiotherapy and 32 (78%) of 41 had a complete response. The 1-year overall survival was 66.8% and 1-year progression-free survival was 61.8%. The most common grade 3 or worse adverse event was lymphopenia. The most common immune-related adverse event was thyroid dysfunction.

Conclusions: Combining Tislelizumab with definitive chemoradiotherapy provided encouraging activity and acceptable toxicity in patients with recurrent and/or metastatic cervical cancer, and this regimen warrants further investigation.

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Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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765P SABRINA study: A phase II study of senaparib monotherapy for patients (pts) with BRCA1/2 mutated recurrent platinum-sensitive ovarian cancer (PSOC)

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Background: Senaparib (IMP4297) is a novel, high potency PARP inhibitor and showed promising antitumor activity for advanced ovarian cancer in phase I studies. This open label, multicenter, single arm, phase II study aimed to evaluate the efficacy and safety of senaparib in pts with BRCA mutated recurrent PSOC.

Methods: Pts with germline and/or somatic BRCA mutated recurrent PSOC who had previously received $\geq$ 2 lines of platinum-based chemotherapy were enrolled. Senaparib 100 mg was administered orally once daily. The primary endpoint was independent review committee (IRC)-assessed objective response rate (ORR) and secondary endpoints included investigator (INV)-assessed ORR, progressive free survival (PFS), duration of response (DOR), overall survival (OS) and safety.

Results: As of 30 Jan 2023, 93 pts were enrolled. Treatment was still ongoing in 26 pts. Median age was 55 y (range 31—77), and 59%/41% pts were partially/fully platinum sensitive, with a median 2 prior systemic therapies (range 2-7). After a median follow up of 15.7 months, efficacy was assessed in 91 pts who received treatment of senaparib and $\geq$ 1 tumor evaluated and met the criteria for the response evaluable set. The INV-assessed confirmed ORR was 59.3% (95% CI, 48.4-69.2) and disease control rate (DCR) was 93.4% (95% CI, 86.2-97.5). Median DOR was 10.3 mo (95% CI, 8.2-12.0). Median PFS was 11.1 mo (95% CI, 8.3-13.8). Median OS was 31.6 mo (95% CI, 25.2-not reached) with 90% and 69% of 1 year and 2 years survival rate. IRC had not finished the assessment. 4% of pts discontinued treatment. The most common ($\geq$ 20%) TEAEs were anemia (71%), decreased white blood cell count (55%), decreased platelet count (54%), decreased neutrophil count (50%), and nausea (28%). Grade $\geq$3 TEAEs in $\geq$5% of pts were anemia (42%), decreased neutrophil count (17%), decreased white blood cell count (16%), and decreased platelet count (16%). 2 pts reported fatal TEAEs, both of which were judged not related to treatment.

Conclusions: Senaparib demonstrated clinically meaningful antitumor activity and manageable safety profile in BRCA1/2 mutated recurrent PSOC. The OS was immature but seemed to be improved.

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Disclosure: All authors have declared no conflicts of interest.

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766P A comparative study of sequential and interdigitated brachytherapy with chemoradiation in patients of locally advanced carcinoma cervix

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Background: Prolongation of overall treatment time (OTT) in carcinoma cervix is well known to adversely affect local control and survival. The OTT would be unduly prolonged if brachytherapy (BT) was started only after completion of external beam radiation (EBRT) as multiple insertions are required for high-dose-rate BT. This study was carried out to compare treatment outcomes of shortening the OTT by interdigitated BT as opposed to conventional sequential BT in terms of late toxicities, disease free survival (DFS) and overall survival (OS).

Methods: The study included 70 patients of cancer cervix who met the inclusion criteria. Patients were randomized into study and control arms. All the patients received EBRT (45Gy/20 fractions over 4 weeks) with concurrent Cisplatin and 3 fractions of BT (7 Gy/fraction). Patients in the control arm received weekly BT after one week following EBRT to complete the entire treatment in 7 weeks. In the study arm, BT was interdigitated with EBRT after 15 fractions. Subsequent BT fractions were given on days 27 and 34 to complete the treatment in 5 weeks. The two groups were compared in terms of late toxicities, DFS and OS at a follow up of two years.

Results: A total of 63 patients completed the planned treatment. The OTT and mean biologically equivalent dose (BED_{10Gy}) after reduction for accelerated repopulation was significantly better in the study arm (p=0.001). At two years of follow up, 80% of patients in the study arm and 72.72% in the control arm had no local or distant failure. Also, death occurred in 13.33% patients and 18.18% patients in the study and control arm, respectively. No statistically significant difference was reached in terms of OS and DFS despite a trend towards better DFS in the interdigitated BT arm. The incidence of late lower gastro-intestinal toxicities was found to be higher in the study arm but this difference was not significant.

Conclusions: Interdigitated BT with chemoradiation appears to be an acceptable option for shortening OTT with similar survival outcomes and acceptable toxicities in comparison to sequential brachytherapy. Owing to a shorter OTT, this approach is radiobiologically superior with a more efficient utilization of machines at centers with heavy patient load.

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Disclosure: All authors have declared no conflicts of interest.

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767P Phase I/II study of toripalimab with cisplatin-based concurrent IMRT for local advanced cervical cancer

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Background: Cisplatin-based concurrent chemoradiation therapy (CCRT) has been increasingly used for local advanced cervical cancer (LACC). However, recurrence is common after cisplatin-based CCRT. Several treatment strategies have been explored to further improve the outcome. We aimed to evaluate the safety and efficacy of anti-PD-1 (Toripalimab, a humanized immunoglobulin G monoclonal antibody against programmed death 1) combined with cisplatin-based concurrent IMRT for locally advanced cervical cancer.

Methods: This is an open-label, nonrandomized, prospective phase I/II study in a single arm. Patients with untreated LACC (2018 FIGO stage IB3, IIA —IVA) were enrolled. All patients were treated with CCRT for 56 days including cisplatin (40 mg/m2, Q1W) combined with image-guidance volume modulated Arc therapy (IG-VMAT) to pelvis (50.4Gy in 28 fractions, pelvic and paraortic nodes with simultaneous nodal boost to 59.4 Gy, 28 fractions), and followed by HDR intracavitary (30-36 Gy in 5-6 fractions) brachytherapy. Toripalimab was administered intravenously at 240 mg every 2 week for 4 cycles. The primary endpoint was incidence and severity of acute adverse events up to 3 months of completing treatment. The secondary endpoints were ORR and PFS.

Results: From Sep 2020 to Sep 2022, a total of 30 patients were enrolled. Median age was 58 years [range: 23—71]. The median follow-up duration was 8.5 months [range: 3.2—27.3]. 29 patients (29/30, 96.7%) completed the treatment, 1 patient (1/30, 3.3%) terminated the treatment because of hemophagic syndrome, who with a history of liver fluke disease. ORR was 100.0% (30/30) at 3 months after treatment. Treatment-related grade 3 or 4 adverse events occurred in 80% (24/30) of patients, primarily leukopenia (63.3%), lymphopenia (36.7%), anemia (26.7%), neutropenia (16.7%). The grade 1-2 potentially immune-related adverse events were chromatosis 5 (16.7%), rash 2 (6.7%), pruritus 2 (6.7%), hypothyroidism 2 (6.7%), adrenal insufficiency 2 (6.7%), No treatment-related deaths occurred.

Conclusions: Toripalimab combined with cisplatin-based concurrent IMRT was tolerable and showed promising antitumor activity in patients with LACC, while immunotherapy-related toxicities should be carefully managed.

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Legal entity responsible for the study: The authors.

Funding: Shanghai Junshi Biomedicine Technology Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

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768P Preliminary results of an open-label, multicentric, phase Ib/II study to assess the safety and efficacy of AsiDNA, a DNA repair inhibitor, in addition to PARP inhibitor in patients with relapsed platinum sensitive ovarian cancer already treated with PARPi for at least 6 months (RevoCAN)

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Background: The duration of progression-free survival (PFS) in patients with platinum-sensitive recurrent ovarian cancer after response to platinum-based therapy is significantly longer with poly (ADP-ribose) polymerase inhibitors (PARPi). Unfortunately, after initial disease control, resistance to PARPi always occurs at some point. AsiDNA™ is a first-in-class DNA damage repair (DDR) inhibitor designed to prevent the repair of DNA damage in tumor cells. It is an oligonucleotide that mimics DNA double strand breaks, producing a false signal noise which acts as a decoy to disrupt the DDR at the "real" sites of DNA damage. The objective was to reverse acquired resistance to PARPi.

Methods: Patients (pts) who received a PARPi (niraparib, olaparib or rucaparib) in maintenance after platinum-based therapy for at least 6 months and who had an isolated increase of CA125 according to Rustin criteria without RECIST progression were includable. Part A: to assess the feasibility of the association of AsiDNA™ 600 mg in a IV weekly perfusion (higher active dose) + PARPi (last dose taken by the patient before entering the study) Part B: to assess the preliminary efficacy on CA-125 (decrease of 50%). Evaluation was to be done at 10, 15, 20 and 25 pts.

Results: 6 patients were included in the dose de-escalation part. No DLT was observed (no related gr 3-4 AE). No more gr 3-4 AE was observed during the treatment of the 10 patients. Among the 10 patients evaluable for efficacy, none had a CA125 response. However, according to RECIST criteria, there were 6 pts with a stable disease, 1 with complete response and 3 with progressive disease. Study was stopped after 12 pts (the company stopped the fabrication of AsiDNA™ for new pts).

Conclusions: AsiDNA in addition to PARPi in pts with biological progression under PARPi is safe, and stabilization (> 6 months) has been observed in 3 pts.

Clinical trial identification: EudraCT 2020-000825-18.

Legal entity responsible for the study: Gustave Roussy Cancer campus.

Funding: ONXEO.

Disclosure: P. Pautier: Financial Interests, Personal, Advisory Board, 2015, 2022: PharmaMar; Financial Interests, Institutional, Advisory Board, 2020 : Roche, Clovis; Financial Interests, Institutional, Advisory Board, 2021 : AstraZeneca; Financial Interests, Personal, Advisory Board, 2019-2020: AstraZeneca; Financial Interests, Institutional, Advisory Board: GSK; Financial Interests, Personal, Advisory Board, 2018-2019: Roche; Financial Interests, Institutional, Advisory Board, 2022: MSD; Financial Interests, Personal and Institutional, Research Grant: PharmaMar; Financial Interests, Research Grant: ONXEO. F. Bazan: Financial Interests, Personal, Advisory Board: Daiichi Sankyo, Novartis, Eisai, Menarini; Financial Interests, Personal, Invited Speaker: AstraZeneca. A. Leary: Financial Interests, Personal, Advisory Board: Zentalis; Financial Interests, Personal, Invited Speaker, Educational: GSK, Medscape; Financial Interests, Personal, Writing Engagement, Educational: Onko+; Financial Interests, Institutional, Other, Steering committee: MSD; Financial Interests, Institutional, Advisory Board: GSK, AZ, Clovis, Ability Pharma, MSD, Merck Serono, Apmonia, Blueprint; Financial Interests, Institutional, Invited Speaker, Educational: Kephren publishing; Financial Interests, Institutional, Other, Consultancy: Orion; Financial Interests, Institutional, Invited Speaker: AZ, Clovis; Financial Interests, Personal, Other, Consultancy: GLG; Financial Interests, Institutional, Research Grant, PI translational research: ARCAGY-GINECO, Sanofi, AZ; Financial Interests, Institutional, Funding, CI clinical trial: AZ; Financial Interests, Institutional, Research Grant, Int CI clinical trial: OSE Immuno; Financial Interests, Institutional, Funding, PI clinical trial: Agenus, BMS, Iovance, GSK; Financial Interests, Institutional, Funding, PI 5 clinical trials: Roche; Financial Interests, Institutional, Funding, PI 2 clinical trials: AZ; Financial Interests, Institutional, Funding, PI 3 clinical trials and steering committee: MSD; Non-Financial Interests, Institutional, Other, Academic research project: Owkin, LXRepair; Non-Financial Interests, Personal, Proprietary Information, IDMC member: Clovis; Non-Financial Interests, Personal, Proprietary Information, IDMC chair: Pfizer; Non-Financial Interests, Member: GCIG. All other authors have declared no conflicts of interest.

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769P Pharmacokinetic boosting of olaparib: An open-label, prospective, cross-over study

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Background: Pharmacokinetic (PK) boosting is the intentional use of a drug-drug interaction to enhance systemic drug exposure. PK boosting of olaparib, a CYP3A-substrate, has the potential to reduce PK variability and financial expenses. The aim of this study was to investigate equivalence of a boosted, reduced dose of olaparib compared to the non-boosted standard dose.

Methods: This randomized, cross-over, multicenter trial compared the PK of olaparib 300 mg twice daily (BID) followed by olaparib 100 mg BID boosted with the non-therapeutic CYP3A-inhibitor cobicistat 150 mg BID for 7 days, or *vice versa,* in patients treated with olaparib. Equivalence was defined as a geometric mean ratio (GMR) of area-under-the-curve over one dosing interval ($AUC_{0\text{-}12h}$) and 90% Confidence Interval (CI) within the no-effect boundaries of 0.57-1.25.

Results: Of 15 included patients, 12 were eligible for PK analysis. The $AUC_{0\text{-}12h}$ increased with the boosted reduced dose with a GMR of 1.45 (90% CI 1.27-1.65). The maximum plasma concentration was comparable (GMR 0.97; 90%CI 0.84-1.12), and the trough plasma concentration increased (GMR 4.14; 90%CI 3.25-5.27). PK parameters of both therapies are shown in the table. No grade ≥3 adverse events were reported during the study.

Table: 769P Pharmacokinetic parameters of the standard monotherapy and boosted therapy of olaparib. Data are represented as geometric mean (CV%) [Confidence interval]

	Monotherapy [95%CI]	Boosted therapy [95%CI]	Geometric mean ratio [90%CI]
$AUC_{0\text{-}12h}$ (mg*h/L)	29.4 (46%) [22.2 — 38.9]	42.7 (41%) [33.2 — 55.1]	1.45 [1.27 — 1.65]
C_{max} (mg/L)	6.37 (37%) [5.07 — 8.00]	6.19 (28%) [5.19 — 7.39]	0.97 [0.84 — 1.12]
T_{max} (h)	1.25 (66%) [0.85 - 1.83]	1.67 (42%) [1.30 — 2.16]	1.34 [1.03 — 1.75]
C_{trough} (mg/L)	0.39 (107%) [0.21 — 0.73]	1.56 (77%) [0.99 — 2.46)	4.14 [3.25 — 5.27]

Conclusions: Boosting a 100 mg olaparib dose with the strong CYP3A-inhibitor cobicistat increases olaparib exposure with 45%, compared to the standard dose of 300 mg. Boosting of olaparib is therefore a promising strategy to reduce the olaparib dose. These results encourage a prospective study of boosted olaparib with toxicity-guided dose reductions. If adequate tolerability is established, boosting can lead to a substantial reduction in olaparib therapy costs. Drs. N.A.D. Guchelaar and M.I. Mohmaed Ali have equally contributed to the study.

Clinical trial identification: NCT05078671.

Legal entity responsible for the study: The authors.

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770P Tolerability and efficacy of trabectedin plus pegylated liposomal doxorubicin (PLD) in elderly patients with ovarian cancer (OC): GEICO 105-O study

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Background: Scarce data have been published for elderly patients (pts) (≥70 years) with OC, who are often underrepresented in clinical trials. Trabectedin (T) plus PLD is approved for relapsed platinum-sensitive OC, and there is a need to gain insights into the safety and efficacy of this scheme in the elderly.

Methods: GEICO conducted a retrospective study with 15 Spanish hospitals, including pts ≥70 years at the start of T+PLD, with relapsed platinum-sensitive high-grade OC (platinum-free interval [PFI] ≥6 months). Pts received at least one cycle of T+PLD according to Summary of Product Characteristics between January 2015 and December 2019. Toxicity, efficacy, dosing, and patient characteristics data were extracted from medical charts.

Results: Forty-three pts with a median of 74 years (70-86) were recruited. The most common FIGO stage at diagnosis was IIIC (51.2%). At baseline, the median PFI was 9 months (81.4% 6-12, 18.6% >12), ECOG 0/1/2 (32.6%, 39.5%, 9.3%), 81.4% of pts had measurable disease, and 76.7% had relevant comorbidities (21.4% hypertension). The median of previous lines was 2 (1-5). The initial dose of T was 1.1 mg/m2 in 81.4% of pts and 79.1% received PLD 30 mg/m2 (reduced initial doses were given due to pts fragility). The median number of T+PLD cycles was 5 (1-21) (46.5% received ≥6 cycles) and 51.2% of pts had delayed infusions. Treatment ended due to personal decision (7.0%), medical decision (23.3%), progression (39.5%), toxicity (23.3%), and other (7.0%). There were no toxic deaths. The main G3-4 adverse reactions were neutropenia (18.6%), asthenia (11.6%), thrombocytopenia (7.0%), mucositis (4.7%), transaminitis (4.7%), and anemia (2.3%). The mPFS was 7.7 months (95% CI 4.4-9.4) with a favorable disease control rate of 72.1% (CR 9.3%, PR 32.6%, SD 30.2% RECIST 1.1). Median OS was 19.5 months (95% CI 12.8-27.2). Seven pts had s/gBRCA1/2 (16.2%) and 13 (30.2%) BRCA unknown. For BRCAmut, T+PLD response was CR 28.6%, PR 42.9%, SD 14.3%, PD 14.3%.

Conclusions: T+PLD is well tolerated by OC pts with 70 years or older. The adverse reactions are comparable to those published for younger pts and efficacy remains beneficial. Albeit in a small sample, a high overall response rate was observed for BRCAmut pts.

Legal entity responsible for the study: Grupo Español de Investigación en Cáncer de Ovario (GEICO).

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771P Genomic characterization of advanced endometrial carcinosarcoma: Identification of potentially actionable targets

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Background: Endometrial carcinosarcoma is an aggressive variant of high-grade endometrial carcinoma, whose genomic landscape is poorly studied due to the low disease prevalence and the lack of known druggable molecular drivers. In this study, we explored the genomic profiles of this tumor to assess new targeted therapy and immunotherapy options for this uncommon and challenging disease.

Methods: We retrospectively analyzed 2,177 cases of endometrial carcinosarcoma from the Foundation Medicine database containing results from comprehensive genomic profiling (CGP) performed by next generation sequencing, to detect genomic alterations (GA), microsatellite instability (MSI), tumor mutational burden (TMB), and genomic loss of heterozygosity (gLOH,) as a surrogate for homologous recombination deficiency (HRD). PD-L1 was evaluated using DAKO 22C3.

Results: The median age in the cohort was 67y (interquartile range: 61-72y). *TP53* was the most common GA, found in 83.7% of cases. Additionally, samples harbored GAs in *PIK3CA* (34.2%), *PTEN* (23.5%), *KRAS* (16.0%), *ARID1A* (14.8%) *ERBB2* (8.5%), *BRCA2* (2.7%) and *BRCA1* (2.0%). Immune checkpoint biomarkers were also prevalent; 171/2177 (7.9%) of assessable samples were TMB-high (≥10 mutations/megabase), 141/2170 (6.5%) were MSI-high, 795/1382 (30.7%) had PD-L1 positivity (TPS≥1%). HRD (gLOH≥16%) was observed in 351/1727 (20.3%) cases. A co-occurrence analysis revealed unique molecular subsets. *TP53* was mutually exclusive with GAs in *PTEN* and *ARID1A* (OR = 0.2, p<1E-4). *PTEN* and *ARID1A* were highly co-occurrent (OR = 9.2, p<1E-4) and strongly overlapped the MSI-High subset (OR>40, p<1E-4). *ERBB2* GAs, while co-occurrent with *TP53* (OR = 2.2, p = 0.01), showed mutually exclusivity with *PTEN* (OR 0.4, p<1E-4) and TMB-high status (OR 0.3, p = 0.02).

Conclusions: To our knowledge, this is the largest reported series of endometrial carcinosarcoma, which could open new avenues for personalized approaches based on the identified targets including *PIK3CA*, HRD/gLOH, MSI, TMB, *ERBB2* and *ARID1A*.

Legal entity responsible for the study: Ugo De Giorgi.

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773P Real-world results of homologous recombination deficiency testing: Comparison between two methods on 2,655 ovarian cancer patients in Spain

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Background: Homologous Recombination Deficiency (HRD) is assessed by detection of mutations in *BRCA1/2* genes (*BRCAm*) and/or genomic instability score (GIS+). In ovarian cancer, HRD has become an important biomarker to stratify patients for appropriate clinical management and treatment. Myriad myChoice CDX Plus is currently the gold standard for assessing HRD on tumor samples. There is an increasing interest in transitioning into inhouse HRD assays that fulfill analytical concordance and, also, demonstrate clinical validation. Sophia DDM Dx HRD solution is one of the alternatives, which has reached an overall percent agreement of 93% with Myriad, demonstrating also clinical validation in PAOLA-1 trial. In this study, we present the real-world results of HRD testing in Spain.

Methods: Phase 1 (Apr2021-Jun22), consisted in the analysis of 1322 cases from 90 centers, using Myriad myChoice. Phase 2 (Jul2022-Dec22) included 1333 cases from 135 centers, analyzed with Sophia HRD solution in 4 academic centers, after an internal validation.

Results: Phase 1 reported 47% BRCAwt/GIS-, 24% BRCAwt/GIS$^+$, 14% BRCAm (BRCAm/GIS- y BRCAm/GIS+), and 15% inconclusive cases using myChoice. In phase 2, Sophia HRD identified 47% BRCAwt GIS-, 25% BRCAwt/GIS+, 15% BRCAm, and 13% inconclusive cases. The distribution of HRP (range 42.4-50%) and HRD (range 35.7-40.7%) cases was similar among the reference centers. In addition to GIS and *BRCA1/2*, Sophia reported *CCNE1* amplification (5.3%), as well as mutations in *BRIP1* (2.4%), *RAD51C* (1.1%), *RAD51D* (1.2%) and *PALB2* (1.9%). As expected, *CCNE1* amplification was more frequent in HRP (86.5%) than HRD (13.5%).

Conclusions: The results obtained from a cohort of 2655 ovarian cancer samples by two different methods, Myriad myChoice and Sophia HRD, confirm the analytical concordance between HRD assays. Percentages of BRCAwt/GIS-, BRCAwt/GIS+, BRCAm, and invalid cases were almost identical. In conclusion, Sophia DDM^{TM} Dx HRD solution shows a high interlaboratory agreement, providing clinically relevant molecular information, and improving the interaction between referral and reference centers.

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774P CCNE1 amplification defines a good prognostic subgroup among BRCAwt/HRDneg advanced high-grade ovarian cancer (HGOC)

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Background: Around 50% of HGOC is characterized as negative for homologous recombination deficiency (HRDneg) based on lack of *BRCA* mutation and low genomic instability score (GIS). ∼15% of HGOC patients harbor *CCNE1* amplification (*CCNE1amp*) which has been presumed to be associated with chemoresistance, HRDneg and poor prognosis. We aimed to determine the genomic profiles and outcome of *CCNE1*amp HGOC in comparison to non-*CCNE1amp* HRDneg HGOC.

Methods: We conducted a retrospective analysis of patients (pts) with advanced HGOC (excluding clear-cell and mucinous histology) with available genomic data from Institut Gustave Roussy, France and National University Cancer Institute, Singapore. *CCNE1amp BRCA1/2 and RAD51C/D* mutations were detected by next-generation sequencing on tumor samples. GIS was evaluated by Myriad MyChoice or Foundation Medicine LOH. Progression free survival (PFS) (date of diagnosis to first progression) and pathological response to neoadjuvant chemotherapy by chemotherapy response score (CRS) were collected.

Results: We identified 55 *CCNE1amp* and 104 HRDneg non-*CCNE1*amp tumors. Pts with *CCNE1amp* tumor were significantly older (64 versus 61.5 years, $p<0.01$). Overall, 81% were high-grade serous, 8% carcinosarcomas, and 62% benefited from complete cytoreductive surgery. As expected, no *BRCA1/2* or *RAD51C/D* mutations were detected in the *CCNE1amp* cohort. 19% of *CCNE1amp* tumors were classified HRD positive and 81% HRDneg. Among *CCNE1amp*, 31% of patients experienced a good pathological response (CRS3) versus 18% in the HRDneg cohort ($p=0.26$). Median PFS was 21.1 months in the *CCNE1amp* cohort versus 14.2 months in the HRDneg cohort ($p=0.008$) and median overall survival was 55.3 months versus 42.9 months ($p=0.044$). In multivariate analysis including completeness of surgery, *CCNE1amp* was statistically associated with better PFS, HR=1.6 (95%CI 1.06-2.5).

Conclusions: We report clinical and molecular features associated with *CCNE1* amplification in advanced HGOC. As expected *CCNE1* amplifications are mutually exclusive from *BRCA* mutations, however 20% were HRD according to GIS. We observed unexpected high rates of CRS3, and significantly improved outcomes compared to non-*CCNE1amp* HRDneg tumors.

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775P A gene expression signature to predict benefit from intraperitoneal (IP) carboplatin chemotherapy in ovarian carcinoma (OC): Translational research study from the intraperitoneal therapy for ovarian cancer with carboplatin (iPocc) phase II/III trial

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Background: The phase 3 iPocc trial reported improved progression-free survival (PFS) in OC patients receiving IP over intravenous (IV) carboplatin with IV dose-dense paclitaxel. We sought to identify biomarkers that can predict sensitivity to IP therapy.

Methods: 117 pre-treatment frozen samples were subjected to mRNA profiling (Affymetrix HTA 2.0) and ACT Genomics ACTOnco®+ next generation sequencing. Cox regression analyses were performed to identify genes significantly correlated with PFS following IP treatment ($p < 0.05$). Homologous recombination repair deficiency (HRD) is defined by loss-of-heterozygosity (LOH) score ≥ 0.48.

Results: Patients receiving IP (n=61) or IV (n=56) had similar clinico-pathological distributions. We identified a 72-gene signature that was significantly correlated with PFS in IP but not in IV patients. Tumors harboring a signature with reduced VEGFA/VEGFR2 and PI3K signaling had low IP resistant score (IPRS) and were associated with improved outcomes for IP therapy. There was no difference in IPRS between BRCA1/2 wildtype and mutant tumors ($p = 0.55$). HRD tumors had a significantly higher IPRS than non-HRD tumors ($p = 0.03$). A high IPRS was significantly correlated with poorer PFS after IP therapy (median: ~18 months vs not reached/NR, $p < 0.0001$), with no correlation seen after IV therapy (median: 25 vs 24 months, $p = 0.9$). Low IPRS IP patients had improved PFS compared with low IPRS IV patients (median: NR vs 25 months, $p = 0.0261$). Paradoxically, when IPRS is high, IP patients have worse PFS than IV patients (median: ~18 vs 24 months, $p = 0.004$). Low IPRS was also able to predict improved outcomes in appendiceal cancer patients receiving hyperthermic IP therapy with the DNA cross-linking agent mitomycin-c (median PFS: 4.4 vs 1.5 years, $p = 0.01$).

Conclusions: The IPRS shows promise in identifying a subset of OC patients likely to benefit from IP platinum treatment. Validation in a larger cohort is warranted.

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776P Multi-omics analysis of chemo-refractory high-grade serous carcinoma patients: Insights from the DECIDER study

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Background: Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is a treatment strategy recommended for patients with high-grade serous carcinoma (HGSC), who are ineligible for primary debulking surgery (PDS). The presence of the inherently resistant cancer phenotype in the primary tumor is a key factor determining disease progression in such cases.

Methods: We collected the data from 159 NACT-treated patients enrolled in the prospective, longitudinal, multi-region DECIDER study which aims to develop effective means to overcome drug resistance in HGSC. 60 patients with platinum-free interval (PFI) above 6 months and partial/complete response as primary therapy outcome according to the RECIST1.1 criteria were considered as responsive, and 31 patients with PFI below 45 days and progressive/stable disease — as refractory. We integrated multiple types of patient data focusing on the pre-NACT samples, explored potential links between genomic features and patient survival, and specifically employed bulk-RNA sequencing data for hypothesis-generating.

Results: In terms of many different clinical or genomic features, samples derived from chemo-refractory patients resembled chemo-responsive. Homologous recombination (HR)-related mutation signatures and loss of the core HR genes were less frequent in the chemo-refractory patients than in the NACT-patients with at least partial response to the primary therapy. Using PRISM to retrieve the epithelial ovarian carcinoma (EOC)-specific expression profiles and PROGENy to infer pathways activity scores, we found a significantly lower activity (p value = 0.022) of JAK-STAT pathway in the refractory, as compared to the reference group. Further analysis using GSEA supported this conclusion, revealing lower expression levels of transcriptional target genes affected by the Interferon alpha/beta and gamma pathways. Kassandra deconvolution algorithm detected a significantly lower infiltration (p value = 0.026) of CD4 T-cells in the refractory group.

Conclusions: Altogether, these results highlight the importance of the immune component in HGSC primary tumors in the context of intrinsic resistance to NACT.

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777P Targeting cadherin-6 in epithelial ovarian cancer: Clinical significance of its expression and efficacy of raludotatug deruxtecan (R-DXd) in patient-derived cell models

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Background: Cadherin-6 (CDH6) is a transmembrane glycoprotein, whose aberrant expression has been reported in several human carcinomas. Raludotatug deruxtecan (R-DXd) is an antibody-drug conjugate (ADC) targeting CDH6 with a topoisomerase I inhibitor (DXd) as a payload which is being developed for several malignancies, including epithelial ovarian cancer (EOC). Our aim was to understand the clinical

significance of CDH6 expression in EOC and investigate the efficacy and specificity of R-DXd in EOC using patient-derived cell (PDC) models.

Methods: We performed immunohistochemical staining (IHC) for CDH6 in 232 EOC surgical samples and 23 ascites cell blocks. CDH6 IHC was scored for intensity and percent tumor cell staining. A score greater than or equal to 1+ intensity in $\geq$10% of tumor cells was defined as positive. The in vitro cytotoxicity and specificity of DS-6000a were evaluated in PDC models of EOC in 3-dimensinal (3D) cell culture using a luminescence-based 3D cell viability assay.

Results: A total of 117 (64.6%) of 181 patients tested positive for CDH6 expression in archival specimens from primary surgery. CDH6 expression was more frequently observed in high-grade serous carcinomas (89.0%, $p < 0.0001$). CDH6-positive patients showed shorter overall survival than CDH6-negative patients ($p = 0.0006$). 38 of the 51 (74.5%) tumors and 15 of the 23 (65.2%) ascites cells specimens from patients with recurrent disease tested positive for CDH6, respectively. Recurrent tumors had higher CDH6 scores than tumors at primary surgery, using 24 paired samples ($p = 0.0039$). R-DXd, DXd (free payload), control ADC and anti-CDH6 naked antibody were tested for their cytotoxicity in two CDH6-positive and two CDH6-negative PDC models. R-DXd showed significant cell growth inhibitory effect against both CDH6-positive but not in either CDH6-negative PDC models. DXd demonstrated cytotoxicity in all PDC models, regardless of CDH6 expression, whereas control ADC and anti-CDH6 naked antibody showed no growth inhibitory effects.

Conclusions: CDH6 is an attractive target for EOC and R-DXd is a promising agent for the treatment of CDH6-expressing EOC.

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778P Combined targeting poly (ADP-ribose) polymerase and receptor tyrosine kinase inhibits ovarian clear cell carcinoma progression via disrupted ribosomal biogenesis

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Background: Advanced ovarian clear cell carcinoma (OCCC) has extremely poor prognosis. AT-rich interactive domain 1A *(ARID1A)* mutation-related chromatin remodeling errors are key molecular features of OCCC. Dysregulated of receptor tyrosine kinases-related signaling pathways are common in OCCC.

Methods: We employed combination of poly (ADP-ribose) polymerase (PARP) inhibitors (nirapaib) and lenvatinib targeting key kinases in OCCC to reinforce single-inhibitor initiated pathway rewiring in cell lines, OCCC xenografts, patient-derived xenograft (PDX) model, and ex vivo tumor studies. The potential mechanisms were explored by RNA sequencing before and after combination treatment and related pathways of differentially expressed genes analyzed.

Results: The combination of niraparib and lenvatinib exhibited significant synergistic effects against platinum-resistant OCCC cell lines, in OCCC xenografts, and ex vivo tumor studies. Moreover, the combination of the niraparib and lenvatinib enhanced induction of apoptosis and prolonged survival in PDX model ($p = 0.0032$). RNA sequencing analyses revealed significant enrichment in structural constituent of ribosome ($p = 0.00078$). Four ribosomal protein expressions (RPS2, RPS5, RPL3 and RPL9) were validated by real-time quantitative PCR. Nucleophosmin (NPM1) expression, which has been implicated in ribosome biogenesis, was found inhibited by niraparib and lenvatinib. Using Kaplan-Meier plotter database (https://kmplot.com/analysis/) of 1435 ovarian cancer patients, increased NPM1 mRNA expression portended a poor overall survival ($p = 0.0025$). Our findings taken together imply that combination of niraparib and lenvatinib reduces OCCC progression via attenuation Src phosphorylation, NPM1 expression, and ribosomal biogenesis in OCCC.

Conclusions: Our study supports exploring combination of niraparib and lenvatinib in the treatment of platinum-resistant OCCC.

Legal entity responsible for the study: The authors.

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779P Assessment of the RAD51 test to determine homologous recombination deficiency (HRD) in patients (pts) with newly diagnosed advanced high-grade epithelial ovarian cancer carcinoma (HGOC)

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Background: HRD is used to identify HGOC patients most likely to benefit from PARPi. Unlike commercially available genomic scar HRD tests (CT), functional testing by RAD51, have potential to provide a real-time readout of actual HR status and may be more reliable to detect HRD.

Methods: This single-institution study assesses the immunofluorescence-based RAD51 foci test and correlates it to CT and treatment outcomes in newly diagnosed advanced HGOC pts between 2020-2023. Tumors with <10% RAD51+ tumor cells in S/G2-phase were classified as HRD positive (HRD+). HRD status agreement rate between CT and RAD51 was calculated. Median progression-free survival (mPFS) was estimated in each subgroup.

Results: Overall, 53 pts had CT and RAD51 tests performed on archival tumour samples. Both tests were contributive for 38 pts. As 1st line therapy, all pts received platinum chemotherapy. As maintenance, 47% received PARPi and 18% Bevacizumab alone. % of HRD+ according CT and RAD51 was 55.3% (21/38) and 42.1% (16/38), respectively. Concordance rate between both tests was 50% (95%CI 34.8-65.2), with 12 and 7 pts identified as HRD+ only by CT and RAD51.

Table: 779P

HRD test	HRD RAD51	HRP RAD51
HRD CT	9	12
HRP CT	7	10

Based on CT, mPFS of HRD+ and HRP pts was 19.4m and 16.1m, respectively (HR 0.69; 95%CI, 0.26-1.85). Based on RAD51, mPFS for HRD and HRP pts was 19.4m and 14.3m (HR 0.70; 95%CI, 0.25-1.93), respectively. Among pts with consistent HRD test results, mPFS was 19.4 m and 11 m for HRD and HRP pts, respectively. Among disparate results, mPFS was 17.4m and 16.1m for pts defined as HRD only by CT and RAD51, respectively.

Conclusions: Our preliminary data showed both tests identified HRD and HRP subpopulations with similar outcomes despite low correlation between them. Among pts with HRP by CT, RAD51 identified a subset of HRD+ with better mPFS. Combination of genomic and functional HRD tests could improve molecular diagnostic accuracy of HGOC.

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780P Role of BRCA1 promotor methylation in homologous recombination deficiency (HRD) in high-grade ovarian cancer

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Background: In high-grade ovarian cancer (OC) TCGA found *BRCA1*meth inferior to *BRCA*mut regarding prognosis probably due to lower sensitivity to platinum (Pt^{++})-based chemotherapy.

Methods: In 143 high-grade OCs tested for *BRCA* mutations, additionally *BRCA* DNA methylation was determined using MethyLight PCR and genome-wide LOH and Aneuploidy Normalized Telemetric imbalance (ANTI) by means of SNP-Array analysis (GSA-24 v 3.0/Illumina) as surrogates of genome-wide DNA-scarring. For LOH and ANTI a "clinical-threshold" was calculated by Pt^{++}-response, determined at the first recurrence. Both were integrated in a common HRD-Score (cut-off: $\geq$1.912 for HRD positivity).

Results: In the present cohort, *BRCA1* DNA methylation (me*BRCA1*) was detected in 15 (10%) and mostly *BRCA*wt OCs (n=14, 17%). Only one *BRCA1*mut OC had concomitant me*BRCA1. BRCA2* DNA methylation was not observed. In terms of genomic scars, me*BRCA*wt and *BRCA*mut OCs had similar HRD scores, which were higher than those in unmethylated *BRCA*wt OCs ($p<0.003$). In *BRCA*wt OCs, *BRCA1* methylation levels *(PMR-values)* were higher in HRD pos. than in HRD negative OCs ($p<0.001$). Progression free survival (PFS) of patients with me*BRCA1* OCs was non-inferior to that of *BRCA*mut OC patients. Worst PFS and OS was found in the subgroup of unmethylated *BRCA*wt OCs compared to patients with *BRCA*mut and me*BRCA1* OCs in univariate (p=0.003; p=0.022) and multivariate survival analysis (p=0.006, p=0.018). All but one of the cancers classified as Pt^{++}-refractory or -resistant at first relapse (92%) were unmethylated *BRCA*wt OCs. None of the me*BRCA1* cancers were rated Pt^{++}-refractory or -resistant, and only one *BRCA*mut OCs was associated with a Pt^{++}-resistant first relapse. 98.6% of the recurrences originating from OCs with genetically or epigenetically altered *BRCA* genes were Pt^{++}-sensitive, of which 77% were considered highly sensitive.

Conclusions: High-grade OCs without genetic or epigenetic *BRCA* alterations exhibit worst PFS. Based on genome-wide scarring, *BRCA1* promotor methylation seems to exert an equivalent detrimental effect on the DNA repair by homologous recombination as pathogenic BRCA mutations.

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781P Chemotherapy sensitivity score based on ex vivo 3D tumour testing to predict clinical response for ovarian cancer patients

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Background: Precision medicine for cancer patients has brought effective novel therapy options over the past decades. However, treatment for high-risk ovarian cancer is still based on platinum containing chemotherapy. Around 30% of primary disease patients do not respond, and 40% of complete responders relapse within a year. Strong predictive markers are lacking. This study reports a predictive chemotherapy sensitivity score to support patient-centred and better informed treatment decisions.

Methods: 89 ovarian cancer patients eligible for chemotherapy were included in the trial between 2019 and 2022 in the Netherlands (IRB P18.032). Tumour clusters were isolated from ascites and solid tumour, seeded into a 384-well plate, and exposed to carboplatin, paclitaxel, three second-line chemotherapies, PARPi, and six immunotherapies. Next, ex vivo drug sensitivity was quantified using high-throughput 3D imaging and extraction of morphological features. The chemotherapy sensitivity score was generated by correlation of the assay results with the patients' response to carboplatin-paclitaxel. In parallel, patients' relative sensitivity to other chemo-, targeted- and immunotherapies was assessed.

Results: The platform enabled accurate prediction of carboplatin-paclitaxel with a classification accuracy of 80%. Differential ex vivo patient response profiles were observed across second-line therapies, and 11% of the samples demonstrated a strong response to at least one of the immune compounds, indicating that our test method could provide alternative treatment options. For doxorubicin, the ex vivo results match clinical response (n=3), providing further evidence for the predictivity of the assay. Importantly, the assay has a success rate of 89%.

Conclusions: The prediction of clinical response to first-line therapy and identification of patient-specific sensitivity to ten second-line therapies in parallel, allows the support of informed treatment decisions for multiple treatment classes. Its two-week timeline makes the assay applicable in a clinical environment. A prospective trial for patients with suboptimal response and recurrent disease is ongoing.

Clinical trial identification: CME LUMC-P18.032.

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782P Correlation between chemotherapy response score (CRS) and germline BRCA1/2 (gBRCA) status in women diagnosed with FIGO stage IIIC/IV high-grade serous ovarian cancer (HGSOC)

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Background: CRS after neoadjuvant chemotherapy (NACT) and g*BRCA* status predict survival outcomes of women diagnosed with advanced HGSOC. We investigated the correlation between CRS and g*BRCA* to understand the potential of CRS as an inexpensive biomarker for PARPi therapy.

Methods: Analysis of the OC g*BRCA* testing database from a tertiary referral centre. Eligible criteria included women with FIGO stage IIIC/IV HGSOC who received NACT and had g*BRCA* tested between 01/09/2017 and 31/12/2022. Univariable and Multivariable (MV) Cox Proportional-Hazards Models were applied to assess the association between PFS, OS and clinical factors. Two-Proportions Z Test was applied to assess the proportions of CRS1+2 or CRS3 between g*BRCA*.

Results: 536 women were eligible. Mean age 66 years (range 36—89). 139 had FIGO stage IVB HGSOC. 71% received 3-weekly carboplatin with paclitaxel. Median PFS was 14.4 months (95%CI 13.6—15.4) and OS 38.0 months (95%CI 34.8—42.6) in the overall population. Performance status (0—1 vs. 2—4), cytoreductive surgery (Yes vs. No) and g*BRCA* status (mutant[MT] vs. wild type[WT]) were predictive (PFS) and prognostic (OS) in the overall population (all $P<0.05$). 363 women underwent delayed primary surgery (DPS) and had a CRS. Of these, 90% received 3—4 cycles of NACT and 96% had optimal ($\leq$1 cm) cytoreduction. In the NACT-DPS group, MV analysis showed that residual disease ($\leq$1 vs. >1 cm), CRS (3 vs. 1+2) and g*BRCA* status (MT vs. WT) were predictive (PFS) (all $P\leq0.02$). Proportion testing showed women with g*BRCA2* were more likely to have CRS3 vs. CRS1+2 than those with g*BRCA1* (P=0.008). Women with g*BRCA1* (P=0.075) and g*BRCA2* (P=0.078) were not more likely to have CRS3 vs. CRS1+2 then those with WT.

Conclusions: We found a correlation between CRS3 and g*BRCA2*, but not g*BRCA1*, in women with FIGO stage IIIC/IV HGSOC treated with NACT-DPS. CRS should be evaluated in a prospective study as a predictor of PARPi efficacy.

Table: 782P

CRS	g*BRCA1*	g*BRCA2*	WT	PFS, months (95%CI)
1	7	1	60	12.1 (11.5—15.7)
2	19	9	146	15.4 (14.4—16.7)
1+2	26 (84%)	10 (45%)	206 (66%)	14.9 (14.0—16.0)
3	5 (16%)	12 (55%)	104 (34%)	22.8 (20.7—27.9)

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783P The role of JARID1B in ovarian cancer

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Background: JARID1B (jumonji A/T rich interactive domain) is a lysine specific demethylase which is able to remove tri- and di-methyl marks from H3K4 (histone 3 — H3, lysine 4 — K4). It is overexpressed in many tumors. In ovarian cancer (OC) high *JARID1B* mRNA-expression is associated with poor outcome and chemoresistance. The aim of this study was to explore the role of *JARID1B* mRNA-expression in OC.

Methods: *JARID1B* mRNA-expression was investigated in 238 epithelial OCs and put in relation to clinicopathological characteristics, *BRCA1/2*-mutational status, homologous recombination deficiency (HRD) status and *BRCA1/2* mRNA-expression levels. Additionally, nineteen non-neoplastic fallopian tubal and sixteen non-neoplastic ovarian samples were used as a control group.

Results: *JARID1B* mRNA-expression in OCs was significantly higher compared to non-neoplastic tubal and ovarian tissue ($P<0.001$ and $P=0.003$, respectively). High *JARID1B* mRNA-expression was associated with worse PFS and OS in univariate analysis, which could be confirmed in multivariate Cox-regression analysis (PFS: HR=1.577, P=0.035 and OS: HR=1.710, P=0.009). A strong correlation between *JARID1B* and *BRCA1/2* mRNA-expression was found ($r^2=0.233$, P=0.001 and $r^2$0.196, P=0.011; respectively). *JARID1B* expression was significantly lower in *BRCA1*-mutated OCs compared to BRCA1 wild-type cancers (P=0.021). Regarding *BRCA2* mutational status, no significant differences in *JARID1B* expression between wildtype and mutated cancers were revealed. In tumors with HRD levels of *JARID1B* were significantly lower compared to HR proficient tumors (P=0.006).

Conclusions: High *JARID1B* mRNA-expression is associated with worse PFS and OS. As *JARID1B* is known to inhibit the expression of the anti-angiogenic and anti-metastatic epithelial chemokine CCL14 it is conceivable that the low *JARID1B* expression observed in *BRCA1*-mutated cancers may contribute to the better prognosis generally seen in these cancers. This could also be underlined by the significant lower levels of *JARID1B* expression in cancers with high HRD scores. In order to further investigate the role of JARID1B in OC analyses on its interplay with CCL14 are ongoing.

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784P HPV integration promotes HPV carcinogenesis via remodeling chromatin interactions between universal stripe factors and super-enhancer in HPV-related carcinoma

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Background: The incidence of HPV integration is increased during the disease progression from precancerous lesions to carcinoma, and HPV integration is reputed as a key effect to escape eliminations from the host cells. Although HPV integration is identified in HPV-related carcinoma, the mechanisms underlying HPV carcinogenesis remain unclear.

Methods: Here, 6768 HPV integration sites from cervical carcinoma (CESC) and 470 from head & neck carcinoma (HNSC), high-through chromosome conformation capture (Hi-C), ChIP-seq, ChIP-PCR and RNA-seq were analyzed to identify the HPV integration characteristics in HPV-host interactions. Manual HPV-integration cells, an HPV integration mouse model (K14-HPV, FVB/N), and CRISPR-Cas9 knock-out cells were performed to demonstrate the chromatin remolding between universal stripe factors (USFs) and super-enhancers.

Results: In CESC and HNSC, USF motifs were enriched in HPV integration sites and integrated HPV-host interaction regions. In addition, HPV integration sites and integrated HPV-host interaction regions marked increased chromatin accessibility (ATAC-seq) and super-enhancer elements (H3K27ac, H3K4me1, and H3K4me3), with USF motifs enrichment in these regions. By dividing the tumor samples according to HPV status, USF genes were found to be upregulated in CESC and HNSC, which could be validated by tumor samples, manual HPV-integration cells, and the K14-HPV integration mouse model. Furthermore, three-dimensional chromatin analyses reveal the chromatin interactions between USF genes and super enhancers in tumor cells. The expression patterns of USF genes and chromatin interactions between USF genes and the super-enhancer were reversed via super-enhancer CRISPR-Cas9 knock-out, thus reversing malignant phenotypes of tumor cells in vitro and in vivo.

Conclusions: Overall, we identify that HPV integration remodels chromatin interactions between USFs and super enhancers to promote malignant phenotypes in HPV-related carcinoma, which provides insight into the three-dimensional mechanism in HPV-related carcinogenesis.

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785P The predictive role of circulating exosomal PD-L1 in cervical cancer immunotherapy

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Background: The purpose of this study is to investigate the effect of radiotherapy on programmed death ligand 1 (PD-L1) expression and explore the predictive role of exosomal PD-L1 (ExoPD-L1) in immunotherapy for cervical cancer.

Methods: The consecutive tumor sample of 40 primarily diagnosed CC patients who accepted radical radiotherapy (RT) were collected before and during RT. Blood samples of 37 advanced CC patients who accepted ICIs combination therapy were collected from each participant before and during treatment. Exosomes were identified by Western blot (CD9/TSG101/Calnexin), transmission electron microscope and nanoparticle tracking analysis. ExoPD-L1 detection was conducted by ELISA. The knockout of PD-L1 was conducted via CRISPR/Cas9 assay and the overexpress of PD-L1 was conducted by lentiviral transfection. Lymphocyte were detected by multicolor flow cytometry.

Results: The consecutive detection of PD-L1 showed a dynamic change during RT. Compared with the level before RT, PD-L1 expression elevated in most patients (87.5%) after RT. And the responders (n=18) had elevated ExoPD-L1 level at the first two circles in the ICIs combination therapy ($P<0.001$). The median follow-up time was 14.13m. The mPFS in increased vs. decreased group: NR vs.11.02m ($P=0.025$). Continuous blood sampling of mice models also found that effective therapeutic intervention could increase ExoPD-L1 in the early stage. The combination of exosome inhibitor GW4869 and anti-PD-1 further inhibited tumor growth. Mice were injected with external ExoPD-L1^{OE}and ExoPD-L1^{KO}. The results showed that ExoPD-L1^{OE} suppressed body immunity and promoted tumor growth. The results of flow cytometry showed that ExoPD-L1^{OE} inhibited CD8$^+$T cells from releasing interferon-γand granzyme B. And ExoPD-L1^{OE} also suppressed the CD8$^+$T cells proliferation in spleen. The coculture of CD8$^+$T cells and exosomes in vitro also confirmed the above conclusion.

Conclusions: Compared with unstable tumoral PD-L1, ExoPD-L1 can better predict the efficacy of immunotherapy in CC, which was with easy accessibility and continuation. Exosome PD-L1 played an immunosuppressive role by inhibiting the proliferation and functional factor release of CD8$^+$T cell.

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786P Antitumor activity of farletuzumab ecteribulin in a panel of endometrial cancer patient-derived xenografts with four different molecular subtypes

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Background: Endometrial cancer (EC) is the most common gynecological malignancy, and treatments based on its molecular subtypes have recently been proposed. Patient-derived xenografts (PDX) are models that preserve the heterogeneity and histology of tumors, and may mimic the effects of drugs in patients. Here, we report a preclinical study of farletuzumab ecteribulin (MORAb-202, FZEC), a novel antibody-drug conjugate (ADC) targeting folate receptor alpha (FRα), using a panel of EC-PDX models with different molecular subtypes.

Methods: We developed a panel of 36 EC-PDX models with four molecular subtypes. We investigated FRα expression based on the H-scores. The antitumor activity of FZEC was evaluated in 24 EC-PDX models, including three POLE-mutated, two MSI-H hypermutated, 11 copy number (CN)-high, and eight CN-low tumors, with various levels of FRα expression in the four treatment groups (control saline, FZEC 5 mg/kg, 12.5 mg/kg, and eribulin 3.2 mg/kg, n=6 in each group). Each drug was administered intravenously, and tumor size was measured twice a week for a 21-day observation period. The intratumoral distribution of eribulin was periodically visualized using an anti-eribulin antibody with the Opal multi-fluorescent staining system.

Results: The median H-scores of FRα expression in the 36 PDX and original tumors were 9.5 (0−184) and 74 (11-184), respectively, indicating a trend toward decreased FRA expression on the PDX. There was no relationship between FRA expression and molecular subtypes. The efficacy of FZEC was evaluated using 24 EC-PDX models. Antitumour activity was observed across all four molecular subtypes. Tumor shrinkage was associated with FRα expression in FZEC 5 mg/kg group, whereas an overall FRA-independent tumor shrinkage was observed in FZEC 12.5 mg/kg and eribulin 3.2 mg/kg groups. Intratumoral imaging analysis using tumors on day 21st showed an association between the antitumor effect and intratumoral accumulation of eribulin.

Conclusions: These results suggest that FZEC may be a promising treatment for FRα-expressing EC of all four molecular subtypes.

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787P A NGS panel for molecular classification of endometrial carcinoma

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Background: The conventional classification tools for endometrial carcinoma (EC) is tiresome, including DNA sequencing, IHC or PCR-CE. Large NGS panels are used to simplify test but costly. Here, we propose a concise NGS panel for economically classifying EC.

Methods: Retrospectively enrolled EC cases of hysterectomy with bilateral salpingo-oophorectomy from Fudan University Shanghai Cancer Center from 2020 to 2022 were assessed. A 46-gene NGS Panel was used to identify POLE exonuclease domain mutations, microsatellite instability-high (MSI-H), TP53 mutations, and other clinically valuable targets.

Results: Tumor tissue samples of 331 EC patients were evaluated. The median age of patients was 55 years (range, 49-62), and 284 (85.8%) cases were endometrioid endometrial carcinoma. Patients in stage IA and IB EC were 204 (61.6%) and 52 (15.7%), respectively. The median follow-up time was 18.5 months (n=303). According to WHO classification criteria, patients were stratified into POLE mut (n=47; 14.2%), MMRd (n=79; 23.9%), NSMP (n=148; 44.7%) and p53 abn (n=57; 17.2%), whose prognosis was consistent with previous studies, POLE mut with most favorable prognosis and p53 abn with the worst. NGS reached 91.8% (n=269) concordance with IHC when detecting MMRd. The 24 inconsistent samples were validated by PCR, of which 17 (70.8%) were consistent between PCR and NGS. The concordance of NGS and IHC in detecting p53 was 65.0% (n=201), but patients detected by NGS alone had significantly worse prognosis than those detected by IHC alone, implying higher accuracy of the panel. Given NGS panel performance, particularly in detecting MMRd and p53 abn, our panel provided a reliable EC classification approach. In addition, the most frequent genetic alterations detected in at least 20% of patients were PTEN (83.4%), PIK3CA (59.2%), ARID1A (58.6%), TP53 (29.3%), CTNNB1 (27.8%), and KRAS (23.6%), which might guide the following treatment.

Conclusions: Our study demonstrates that the concise NGS panel is an effective "one-stop" strategy to precisely classify EC with high clinical availability. Further follow-up data are needed to testify to the effect of the classification on the prognosis of different adjuvant therapies or rare pathological subtypes.

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788P Molecular profiling of p53 mutant endometrial cancer reveals distinct subgroups with opportunities for personalized therapeutic approaches

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Background: Endometrial cancer (EC) can be classified into four molecular subgroups: *POLE* mutant, MSI/dMMR, non-specific profiles and *P53* mutant (P53mut). P53mut EC comprise ∼20% of cases and have the worst prognosis. There is an urgent medical need to better understand P53mut EC in order to propose effective new therapeutic strategies.

Methods: We conducted a retrospective analysis of P53abn EC patients from PORTEC3 (NCT00411138) with available DNA for a large-scale panel sequencing (Discovery Cohort). Results were confirmed on an independent cohort of EC patients (Gustave Roussy, France and National University Cancer Institute, Singapore) identified by their molecular profile using FoundationOneCDX or FoundationOne Liquid CDX panel (Validation Cohort). Molecular findings were correlated with clinicopathologic features from medical record review.

Results: 39 P53abn cases were included in the discovery cohort. Molecular profiling was able to distinguish 4 mutually exclusive subgroups: *CCNE1* amplified (15%), *ERBB2* amplified (21%), *PTEN* alteration (21%) and a non-specific group. In the Validation Cohort, 71 P53mut EC patients were included. 40 patients were molecularly characterized on tumor tissue and 31 on circulating tumor DNA. Median age was 66 years, 38% presented with primary metastatic diseases, 40% were serous, 30% endometrioid and 20% carcinosarcoma. We detected the same four molecular subgroups defined by *CCNE1amp (13%)*, *ERBB2amp* (16%), and *PTEN* mutation or loss (34%). These subgroups were also almost exclusive to one another. Only two patients (3%) harbored co-alterations. In terms of outcomes, we did not observe any overall survival difference between these subgroups.

Conclusions: Among *P53mut* EC, we detected 3 nearly mutually-exclusive molecular subgroups: *CCNE1* amplified, *ERBB2* amplified and *PTEN* loss, accounting together for 60% of cases. Whether these subgroups might benefit from personalized therapeutic strategies is currently being explored.

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Leary: Financial Interests, Personal, Advisory Board: Zentalis; Financial Interests, Personal, Invited Speaker, Educational: GSK, Medscape; Financial Interests, Personal, Writing Engagement, Educational: Onko+; Financial Interests, Institutional, Other, Steering committee: MSD; Financial Interests, Institutional, Advisory Board: GSK, AZ, Clovis, Ability Pharma, MSD, Merck Serono, Apmonia, Blueprint; Financial Interests, Institutional, Invited Speaker, Educational: Kephren publishing; Financial Interests, Institutional, Other, Consultancy: Orion; Financial Interests, Institutional, Invited Speaker: AZ, Clovis; Financial Interests, Personal, Other, Consultancy: GLG; Financial Interests, Institutional, Research Grant, PI translational research: ARCAGY-GINECO, Sanofi, AZ; Financial Interests, Institutional, Funding, CI clinical trial: AZ; Financial Interests, Institutional, Research Grant, Int CI clinical trial: OSE immuno; Financial Interests, Institutional, Funding, PI clinical trial: Agenus, BMS, Iovance, GSK; Financial Interests, Institutional, Funding, PI 5 clinical trials: Roche; Financial Interests, Institutional, Funding, PI 2 clinical trials: AZ; Financial Interests, Institutional, Funding, PI 3 clinical trials and steering committee: MSD; Non-Financial Interests, Institutional, Other, Academic research project: Owkin, LXRepair; Non-Financial Interests, Personal, Proprietary Information, IDMC member: Clovis; Non-Financial Interests, Personal, Proprietary Information, IDMC chair: Pfizer; Non-Financial Interests, Member: GCIG. 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789P Real-world (RW) duration of treatment in first-line maintenance (1Lm) niraparib monotherapy in epithelial ovarian cancer (EOC): CHAR1ZMA study

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Background: RW data on 1Lm niraparib use in patients (pts) with EOC are sparse. The CHAR1ZMA study described treatment (tx) discontinuation for pts with EOC prescribed 1Lm niraparib monotherapy using a US RW database.

Methods: Eligibility criteria were previously described [1]. Pts were selected from the nationwide electronic health record-derived de-identified Flatiron Health database. Time to tx discontinuation (TTD; index [start of 1Lm niraparib] to 1Lm niraparib end date) was estimated via Kaplan-Meier methods. Results were stratified by early discontinuers (pts discontinued ≤90 days) and persisters (pts discontinued >90 days post-initiation/censored), and by breast cancer gene (*BRCA*)/homologous recombination deficiency (HRD) status.

Results: Among 414 EOC pts, 83% had stage III/IV disease, 26% were HR-deficient (HRd), and median age at index was 67 yrs. Median follow-up was 12.4 mo. Median TTD was 7.5 mo (95% confidence interval [CI] 5.9, 9.0) overall and increased by 4.9 mo to 12.4 mo (95% CI 10.3, 17.3) for persisters (n=296). Drug toxicity was cited as a reason for tx discontinuation in 67% of early discontinuers (n=118) and 22% of persisters (n=133) (Table). Disease progression was cited as a reason for tx discontinuation in 32% of early discontinuers and 74% of persisters. Dose modifications varied by discontinuation status (no dose modification was reported in 28% of persisters and 59% of early discontinuers). In the HRd subgroup, median TTD was 13.1 mo (95% CI 9.2, 22.2) overall (n=106), and increased by 9.1 mo to 22.2 mo (95% CI 13.5, not reached) for persisters (n=83).

Conclusions: This RW study demonstrates pts with EOC on 1Lm niraparib for >90 days have a much longer TTD than all pts. Effective clinical management of drug toxicity among 1Lm niraparib pts in the first 90 days of tx may help pts stay on tx and experience full therapeutic benefit.

Table: 789P

n (%)	Overall (n=414)	Early discontinuers (n=118)	Persisters (n=296)
BRCA*/HRD status			
HR-deficient	106 (25.6)	23 (19.5)	83 (28.0)
HR-proficient	71 (17.1)	15 (12.7)	56 (18.9)
BRCA wild-type	346 (83.6)	98 (83.1)	248 (83.8)
BRCA mutant	48 (11.6)	9 (7.6)	39 (13.2)
Discontinued	251 (60.6)	118 (100.0)	133 (44.9)
Reasons for tx discontinuation†			
Toxicity	108 (43.0)	79 (66.9)	29 (21.8)
Disease progression	137 (54.6)	38 (32.2)	99 (74.4)
Other‡	25 (10.0)	17 (14.4)	8 (6.0)
Unknown	3 (1.2)	0 (0.0)	3 (2.3)

**BRCA*/HRD not mutually exclusive groups.
†Of pts who discontinued, pts may report ≥1 reason for discontinuation.
‡Other includes, but is not limited to, disease-related symptoms not specific to tx.

[1] Coleman RL, et al. Presented at ESMO Gyn 2023 (43P).

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790P Uniform prospective molecular analysis of endometrial carcinoma: Feasibility, outcomes, and effect on management

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Background: Endometrial carcinoma (EC) guidelines (NCCN, ESGO) suggest molecular analysis (MA) for incorporation into risk criteria. Prognostic value of TCGA-based classification has been validated, but adoption into adjuvant treatment decisions is still under evaluation. Examples of real-world upfront MA analysis in EC are scarce. We aim to evaluate our routine implementation of Next Generation Sequencing (NGS) of EC patients.

Methods: In November 2020, we implemented routine immunohistochemistry (IHC) (p53, MMR) & NGS for TCGA-based prognostication of all EC primary resections at a single institution. NGS was a 69 gene panel including *POLE*, *TP53*, *PTEN*, *CTNNB1*, *KRAS*, *ERBB2*, & *PIK3CA*. A questionnaire directed to treating oncologists evaluating impact of MA on adjuvant management decisions and counselling was utilized.

Results: 189 patients amongst 7 treating gynecologic oncologists were evaluated over the initial 13 months. Primary stage of disease was; I: 139 (73.5%), II: 11(5.8%), III: 27 (14.3%), IV: 12 (6.4%). Prognostic classifiers were: POLE: 10 (5.3%); MMRd 52 (27.5%); NSMP: 86 (45.5%); and p53: 41 (21.7%), including multiple-classifiers: 10 (5.3%) MMRd-p53 and 4 (2.1%) POLE-p53. The classifiers with the most impact for providers were MMRd: 27 (14.3%) and p53: 22 (11.6%). Prognostic classification impacted patient counselling in 72 (38.1%) of patients (POLE 66.7%; MMRd 59.5%; p53 52.5%; NSMP 12.6%; $p<0.001$), with NSMP having the least impact. MA impacted treatment recommendations in 19 (10%) of patients. MA altered treatment recommendations compared to recommendations by histological properties in 8 (4.2%) patients. MA significantly impacted treatment recommendations with increasing stage (I: 5.8%, II: 9.1%, III: 22.2%, IV: 33.3%, $p=0.002$). MA significantly altered treatment recommendations deviating from histological recommendations with increasing stage (I: 1.4%, II: n/a, III: 14.8%, IV: 16.7%, $p=0.002$).

Conclusions: Comprehensive uniform molecular analysis of endometrial carcinoma via combined IHC and NGS upon primary resection is feasible and contributes to patient counseling and treatment recommendations.

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791P Development and validation of nomograms to predict survival in patients with high-grade serous ovarian cancer

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Background: The current American Joint Committee on Cancer TNM and FIGO systems are without sufficient details encompassing the variety of ovarian cancer. To develop and validate nomograms for overall survival (OS) and cancer-specific survival (CSS) in patients with high-grade serous ovarian cancer (HGSOC).

Methods: The collection of data from California, Connecticut, Detroit, Georgia, Hawaii Iowa was formed as the development cohort. A cohort of data from Kentucky, Louisiana, New Jersey, New Mexico, Seattle, and Utah formed the external validation cohorts. We developed the nomograms using the Cox prediction model. We applied five-method comparisons to screen the best model for both nomograms, and the nomogram models underwent successful independent external validations to support their reliability. We assessed nomogram model performance by examining overall accuracy (Brier score), calibration (calibration plots and Hosmer—Lemeshow calibration test), and discrimination (Harrell C index).

Results: The development cohorts included 2465 patients which were split into two parts (7:3) for the development (n=1726) and internal validation (n=739) for the model, and the 5-year overall survival was 18·6% (458/2465). The OS nomogram showed that Scope Reg LN Sur (0-100), AJCC_N (0-89.37), Systemic Sur Seq (0-74.25), the year of diagnosis (0-69.15), and Surg Prim Site(0-51.52) shared the larger contribution to prognosis. Followed by AJCC_ M (0—48.42) and age (0—45.31). The C index of 5-year OS and CSS nomograms was 0.715 (95% CI 0.688—0.741) and 0.719 (0.693—0.745) in the development cohort, 0.695 (0.646—0.744) and 0.702 (0.653—0.750) in the internal validation cohorts. The external validation cohorts included 961 patients, were 0.684 (0.644—0.724) and 0.687 (0.648—0.727). The nomograms performed well according to overall accuracy, discrimination, and calibration when they were applied to the validation cohorts.

Conclusions: Our nomograms are credible methods that can be used to predict OS and CSS in patients with HGSOC. They should be offered to clinicians to assess patient prognosis, make prognosis-based decisions and be conducive to stratifying patients in clinical trials or population-based analyses, and inform patients clinically.

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792P Prognostic role of the modeled CA-125 KELIM in early FIGO stage I and II ovarian cancers (OC): A GCIG individual-patient data meta-analysis

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Background: The curative role of surgery in early stage I & II OC is well established. Nevertheless, a significant number of them relapse. The modeled CA-125 KELIM score estimated during 1st-line chemotherapy is a prognostic factor, thought to be a pragmatic indicator of the tumor intrinsic chemosensitivity. We assessed the prognostic value of KELIM in patients with optimally debulked FIGO stage I & II diseases regarding PFS and OS in the GCIG meta-analysis dataset (MAOV), where different adjuvant chemotherapy regimens were assessed.

Methods: Individual patient KELIM values were previously estimated in 5,884 patients included in MAOV (Corbaux, 2021). Patients with optimally resected FIGO I & II diseases were selected. The prognostic value of KELIM was assessed using univariate & multivariate analyses, according to histological subtype, and disease stage I or II.

Results: 628 and 515 patients had optimally resected stages I & II OC, respectively, including clear cell (CCC) (46.7%); serous (23.7%); endometrioid (12.4%); and mucinous carcinomas (3.9%). 52% had CA-125 $\geq$ 35 UI/L after surgery. The respective median standardized KELIM values were 1.32, 1.18, 1.16, and 1.08 ($P < 0.0001$). In univariate & multivariate analyses, a favorable KELIM score $\geq$1.0 (vs unfavorable KELIM score $<$1.0) was associated with longer PFS and OS (5-year PFS, 68.3% vs 55.9%, $P<0.0001$, HR 0.61 [0.48-0.77]; 5-year OS, 80.7% vs 72.8 %, $P<0.0001$, HR 0.50 [0.36-0.68]), as was the histological subtype. CCC was associated with worse OS, HR 1.84 [1.17 — 2.90], and endometroid with better OS, HR 0.33 [0.17 — 0.66]). When assessed within histological subtypes, KELIM was a significant prognostic factor in CCC (PFS, HR 0.41 [0.30-0.56]; OS, HR 0.33 [0.23-0.47]) and in serous carcinomas (PFS, HR 0.54 [0.39-0.75]; OS, HR 0.59 [0.37-0.94]), but not in endometrioid and mucinous carcinomas.

Conclusions: KELIM during adjuvant chemotherapy plays an important prognostic role in optimally resected stage I-II ovarian cancers, especially in CCC and serous carcinomas, suggesting the potential role of chemosensitivity beyond surgery. KELIM may help identify pts at higher risk of relapse/death, requiring closer follow-up.

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793P Strong relationships between the CA-125 KELIM score and the tumor biological effects after neo-adjuvant chemotherapy in advanced ovarian cancer patients: CHIVA trial (GINECO)

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Background: The modeled CA-125 longitudinal kinetic parameter KELIM^{TM} during 1st-line chemotherapy is as a pragmatic indicator of the tumor primary chemosensivitiy. However, the links between KELIM^{TM} and the beneath chemotherapy-induced tumor biological effects had to be explored. We studied the links between KELIM^{TM} values and pathological response, and changes in TILs, in ovarian cancer patients treated with neo-adjuvant chemotherapy (NACT) +/- interval debulking surgery (IDS).

Methods: In the randomized phase II trial CHIVA (NCT01583322), 188 patients were treated with NACT carboplatin-paclitaxel +/- nintedanib, +/- IDS. Patient KELIMs were previously calculated. The pathological response was assessed with the Chemotherapy Response Score on the omentum (CRS 1-3), and with an enriched pathological response pR score based on the available tumor tissue block when omentum was lacking (pRS 1-3), obtained after NACT. Changes in stromal TILs (sTILs, % of the stromal surface on lymphocytes) and intra-epithelial TILs (ieTILs, qualitative appreciation, 0-2) in baseline tissue and after NACT were analyzed.

Results: A strong association was found between patient KELIM^{TM} value and the omentum CRS after NACT (n=67; median KELIM^{TM}, 0.71 for CRS-1; 1.26 for CRS-2; 1.66 for CRS-3; P<0.01). Consistent, a correlation was observed between KELIM and tumor pRS (n=103; median KELIM^{TM}, 0.73 for pRS-1; 1.25 for pRS-2; 1.61 for pRS-3; P <0.01). At baseline before NACT, no relationships between KELIM^{TM} and TILs were found. After NACT, a significant association was observed between higher patient KELIM^{TM} values and higher intra-epithelial TILs infiltrate after NACT (n=99; median KELIM, 0.88 for ieTILs score 0-1; vs 1.26 for ieTILs score 2; P = 0.03).

Conclusions: High consistency was found between patients KELIM^{TM} and the pathological response after neo-adjuvant chemotherapy, assessed with the omentum CRS score, or the larger tumor pRS score. Omentum may not necessarily needed to assess the pathological response. Intra-epithelial TILs change after NACT was strongly associated with KELIM^{TM}-assessed chemosensitivity, thereby opening hypotheses about mechanisms of platinum-sensitivity.

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794P Efficacy of gemcitabine (gem) based therapy in ovarian clear cell carcinoma (OCCC)

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Background: OCCC, compared to other histologies, are less responsive to platinum based chemotherapy and suffer a worse prognosis. *ARID1A* mutations (mt) are the most common mt in OCCC. *ARID1A* loss has been described to increase replication stress in various tumor models. Anti-metabolites like gem are effective in *ARID1A*-mt in-vitro.

Methods: We performed a retrospective analysis of the molecular features and treatment outcomes of advanced or relapsed OCCC pts treated at our institution between January 2000 to May 2022. Treatment response was assessed per RECIST1.1. Next-generation sequencing (NGS) was performed where sufficient archival tissue was available (n=60). We hypothesize that gem is more effective than non-gem therapies, especially in *ARID1A*-mt.

Results: Of 90 advanced or relapsed OCCC patients (pts), median age was 53 years, with median 1 prior line of treatment received. 67 (74.4%) received 2 or more lines, of whom 35 (52.2%) included gem based therapy, mostly in 2nd line (19/35). 12 pts received platinum-gem with bevacizumab (bev), 18 pts received platinum-gem, 5 received gem monotherapy. 30/60 (50%) were *ARID1A*-mt. Across all treatment lines, the disease control rate (DCR) to gem was 61.1%. In 2nd line, DCR was significantly better for gem over non gem (Odds Ratio (OR) OR 6.5, p=0.004), seemingly more for *ARID1A*-mt (OR of mt VS wild-type (wt) 28 VS 4.2). Early use of gem (2nd against later lines) and incorporation of bev significantly improved DCR on multivariate analysis (Early use OR 4.1, p: 0.04; Bev OR 7.2, p: 0.02). There was a trend to improved median

progression-free survival (mPFS) of 2L gem against non-gem based therapy (7.2 versus 3.2 months(m); Hazard Ratio (HR): 3.48, p = 0.06). This was significant in ARID1A mts (gem VS non-gem: 295 VS 70 days; HR: 4.3, p=0.04) but not in ARID1A-wt (p=0.14). Overall survival was not statistically significant in this study.

Conclusions: This is the largest study of OCCC pts receiving gem based therapy. We show that gemcitabine improved DCR for all OCCC patients, and mPFS in *ARID1A*-mt especially when used earlier. To maximise gem efficacy, earlier treatment combined with bevacizumab should be considered in OCCC.

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795P Tolerability and effectiveness of niraparib in long-term responders with platinum-sensitive recurrent ovarian cancer (GEICO-88R study)

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Background: The GEICO-88R study assessed the real-world use of niraparib as maintenance treatment in patients (pts) with platinum-sensitive recurrent high-grade ovarian cancer (OC) within the Spanish expanded access program. A preplanned sub-analysis of long-term responders (LTR) is presented.

Methods: In this retrospective study across 57 Spanish sites pts received niraparib at a fixed starting dose (FSD) of 300 mg/day or individualized starting dose (ISD) according to weight and platelet count. A specific assessment of LTR to niraparib maintenance treatment (exposure ≥1 year) was performed, describing patient characteristics, niraparib dosing, tolerability, and effectiveness.

Results: This sub-analysis included 107 pts (33.8% of 316 from general study), with median age 64 years (43-88) and a median of 2 previous lines (53.3% 1-2, 46.7% ≥3). Main initial FIGO stages were III (58.8%) and IV (18.6%). Forty-five (42%) pts received prior bevacizumab and 81.3% were gBRCAwt. 99 pts had surgery at primary diagnosis (72.7% primary and 27.3% interval debulking), R0 in 69.9%. 31 (29%) pts had surgery at relapse, R0 in 64.5%. At baseline, ECOG was 0 (56.1%) or 1 (43.9%). Relevant comorbidities were reported in 46.7% of pts. Niraparib was initiated at FSD in 24 pts and at ISD in 83 (80.7% at 200 mg/day; 19.3% at 300 mg/day). Overall median dose was 200 mg. Median treatment duration was 26.2 months (12-60.7). 68.2% of pts required at least one dose interruption or reduction. 39 (36.4%) pts remained on treatment upon analysis (91.1% discontinued due to progression, 2.9% toxicity, and 4.4% physician/patient decision). The most frequent all-grade adverse events were thrombocytopenia (42.1%), anemia (36.4%), and asthenia (29.9%), with no significant differences between FSD vs ISD pts. Of 85 pts with pre-niraparib measurable disease, PR+CR was 63.5%. With median follow-up of 29.95 months, median PFS, PFS2 an OS were 27.2 (95% CI 23.6- 29.6), 42.3 (95% CI 34.2-NA) and not reached (85.4% of pts alive).

Conclusions: A durable response was achieved in a substantial proportion of pts, even despite the high risk of this population (majority BRCAwt, pre-treated, significant comorbidities) with a good tolerability profile in a real-world setting.

Clinical trial identification: NCT04546373.

Legal entity responsible for the study: Grupo Español de Investigación en Cáncer de Ovario (GEICO).

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796P Initial management and long-term outcome of advanced low-grade serous ovarian cancer (LGSOC) exploring role of surgery and maintenance therapy in the French multicentre ESME database

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Background: LGSOC is a rare disease. Few data of large size have been published.

Methods: We conducted a multicenter retrospective analysis of LGSC patients selected from the French Epidemiological Strategy and Medical Economics Ovarian Cancer database between 2000 and 2019. This database includes all ovarian cancer pts treated in 18 French Comprehensive Cancer Centers. The main objective was to describe the management of these patients. Secondary objectives were to analyse progression-free survival (PFS) and overall survival (OS) and prognostic factors in the stage III/IV population.

Results: Out of the 13032 pts, 230 (1.8%) with a confirmed diagnosis of stage III (n=171)/IV (n=59) LGSOC were identified. Median age at diagnosis was 55.5y (19.8-88.2). 128 (55.6%) pts had primary debulking surgery (PDS) and 35 (15.2%) neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS). 49 (21.3%) pts did not have debulking surgery and 18 (7.9%) patients had surgery after 6 courses of NACT. 223 pts (97.0%) received platinum-based chemotherapy (PBC) including bevacizumab (Bev) for 79 pts (34.3%). Endocrine therapy maintenance was given in 27 pts. After a median follow up of 73.6m [69.9-80.0], median OS was 93.4m (95%CI [71.2-176.9]) in the whole population. Median OS according to timing of surgery was 146.0m (95%CI [110.4-NR]) with PDS vs. 75.5m (95%CI [48.7-Not Reached]) with NACT-IDS vs. 61.8m (95%CI [42.4-NR]) with 6 courses of NACT and closing surgery. Patients not candidate for surgery received PBC (n=49) +/-Bev (14/49) +/- maintenance endocrine therapy (13/49). With a median follow-up of 64.6m (38.6-93.6), median PFS and OS were 15.9m (95%CI [13.4-20.6]) and 38.0 m (95%CI [33.0-65.0]) respectively. OS multivariable analyses are shown in the table.

Table: 796P

	HR	95%CI	p value
Initial FIGO stage			
III			
IV	2.40	1.48,3.91	**<0.001**
Timing of surgery			
Primary debulking surgery			
Interval debulking surgery or closing surgery	1.93	1.13, 3.34	**0.018**
No surgery	2.65	1.50;4.68	**<0.001**
Age (continuous variable)	1.01	1.00, 1.03	**0.038**
Bevacizumab first line			
No			
Yes	0.82	0.51, 1.30	0.393

Conclusions: In this large size population of advanced LGSOC, FIGO IV stage, absence of PDS and age are associated with poorer OS.

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797P Impact of consolidation cycles in predicting recurrence in patients treated with EMA-CO for high-risk gestational trophoblastic neoplasia

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Background: EMA-CO is the most used combined chemotherapy regimen for treating high-risk gestational trophoblastic neoplasia (GTN) patients. It is administered weekly until normalization of hCG levels, followed by two consolidation cycles. Premature discontinuation of EMA-CO chemotherapy due to dose-limiting toxicities may occur before achieving the target hCG threshold. Despite its widespread use, the effectiveness of consolidation cycles in preventing recurrence in GTN patients remains unclear. In this study, we aimed to evaluate the impact of EMA-CO consolidation cycles on recurrence.

Methods: We conducted a non-interventional, retrospective study in patients selected from the French Center for Trophoblastic Diseases in Lyon and identified 276 patients with a GTN diagnosis and treated with EMA-CO regimen between November 1999 and November 2020 from our database. Exclusion criteria for this study included resistance to EMA-CO chemotherapy (n=31). We assessed the impact of two cycles of EMA-CO consolidation on the 2-year recurrence-free survival (RFS).

Results: A total of 245 patients met the eligibility criteria for this study, of whom 88.6% (217/245) received consolidation cycles of EMA-CO. Choriocarcinomas were diagnosed in 42% (102/245) of the patients, while invasive mole was observed in 58% (143/245) of cases. The median FIGO score was 8 (range 1 − 19). After a median follow-up of 23 months, the 2-year RFS was 93% (95%CI 0.90 to 0.96) in the consolidation group and 90% (95% CI 0.79 to 1.0) in the group of patients who didn't receive consolidation cycles (HR 0.79; 95% CI 0.23 to 2.72, p=0.71). Grade $\geq$ 2 adverse events occurred in 43% of patients, with neutropenia being the most frequent (31%).

Conclusions: In this study, the 2-year RFS was not significantly different between the groups. These findings suggest that consolidation cycles may not influence recurrence in patients with gestational trophoblastic neoplasia. Considering the non-negligible toxicity of EMA-CO, our results raise the question of optimizing therapy through de-escalation and/or shortening of chemotherapy after hCG normalization.

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798P Survival analysis of non-metastatic gestational choriocarcinoma (NMGCC) patients treated with chemotherapy

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Background: To date, there is no consensus on the FIGO recommendations for NMGCC in which chemotherapy (CTX) should be initiated after diagnosis in these patients. Therefore, we conducted the first study involving a large sample of patients with NMGCC to evaluate the effect of chemotherapy on overall survival (OS) and cancer-specific survival (CSS) in patients with NMGCC.

Methods: Data were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2019. Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology; not the first tumor or other malignancies in the body; not arising from the placenta; unknown data; or metastatic status. Chi-square tests were used to compare clinicopathological features, while survival rates and prognostic factors were identified using the Kaplan-Meier estimator, log-rank tests, and Cox proportional hazard regression.

Results: The study population comprised 526 patients. Among them 128 patients with "Surgery," 127 patients with "CTX" and 261 patients with "Surgery + CTX". Most patients (55.3%) were aged 30 years or older, with a median age of 32 years. The largest racial group was white (63.5%; n=334). A total of 54.4% of the patients had a tumor size greater than 4 cm, with a median tumor size of 4.2 cm. Most cases were localized (71.5%, n=376). "Surgery + CTX" had the most favorable survival outcome with a 5-year OS of 96.6%, followed by "Surgery" (95.9%) and then "CTX" (93%). No significant differences were found in OS or CSS between the groups ($P<0.33$ and $P<0.57$, respectively). Older age was a poor prognostic factor for the OS and CSS. Multivariable analysis confirmed that there was no statistically significant difference between the effect of all therapeutic groups on OS and CSS, "Surgery + CTX" (HR=0.7, 95%CI:0.28-1.8 and HR=0.65, 95%CI:0.2-2, respectively).

Conclusions: The results of this study showed that CTX did not affect OS or CSS in patients with NMGCC. Multicenter prospective studies are needed to validate and build upon these findings; however, our results provide a starting point for a better understanding of these rare cancers.

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799P Clinicopathological characteristics and oncological outcomes of three subtypes of neuroendocrine carcinoma of the cervix: A multicenter retrospective study of 288 patients

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Background: Neuroendocrine carcinoma of the cervix (NECC) is a rare type of cervical cancer, and is divided into small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC) and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN). Present studies on NECC mainly focus on SCNEC, and the clinical features of LCNEC, especially MiNEN, are not well understood.

Methods: The multicenter, retrospective study enrolled 288 patients. The primary outcomes were progression-free survival (PFS) and overall survival (OS). The Kaplan-Meier method and Cox proportional hazard analysis were performed.

Results: With a median follow up of 25 months, the 5-year PFS of NECC, SCNEC, LCNEC and MiNEN was 40.2%, 40.4%, 30.3%, and 41.6%; and the 5-year OS was

45.4%, 44.0%, 32.3%, and 50.3%. In the whole cohort, it showed that LVSI (HR=1.996, 95%CI:1.275～3.126, p=0.003) and >2/3 stromal invasion (HR=2.009, 95% CI:1.222～3.303, p=0.006) were independent risk factors of PFS; age>45 (HR=1.956, 95%CI: 1.170～3.272, p=0.011), LVSI (HR=1.722, 95%CI: 1.016～2.918, p=0.043) and >2/3 stromal invasion (HR=1.778, 95%CI: 1.024～3.087, p=0.041) were independent risk factors for OS. In patients undertaking surgery, it revealed that LVSI (HR=1.996, 95%CI:1.275～3.126, p=0.003) and NACT (HR=1.691, 95%CI: 1.040～2.748, p=0.034) were independent risk factors, and that adjuvant chemoradiotherapy was an independent protective factor of PFS (HR=0.201, 95%CI: 0.103～0.428, p<0.001); age>42 (HR=2.377, 95%CI: 1.417～3.986, p=0.001) and LVSI (HR=2.450, 95%CI: 1.388～4.324, p=0.002) were independent risk factors of OS, and that adjuvant chemoradiotherapy was an independent protective factor of OS (HR=0.175, 95%CI: 0.079～0.388, p<0.001).

Conclusions: This multicenter retrospective study first focused on three pathological subtypes of NECC. SCNEC has a worse biological behavior than the other two types. Patients with MiNEN did not show better prognosis than the other two. LVSI and >2/3 stromal invasion and adjuvant chemoradiotherapy are prognostic factors for PFS; age, LVSI, and >2/3 stromal invasion and adjuvant chemoradiotherapy are prognostic factors for OS in patients with NECC.

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800P Response to chemotherapy following PARP inhibition in UK ovarian cancer (OC) patients

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Background: *BRCA* mutated recurrent platinum sensitive OC patients (pts) who received a maintenance poly-adenosine ribose phosphatase inhibitor (PARPi) show a lower-than-expected response to subsequent chemotherapy in retrospective trial analysis. What are real world outcomes for UK pts, including *BRCA* wild-type (WT)?.

Methods: Retrospective data analysis of OC pts who received subsequent chemotherapy following a PARPi (minimum 14 days) between 01/01/18-31/12/21 across 10 UK sites. Responses were evaluated by imaging/CA125 or clinical status, with DCR (defined as CR/PR or SD at first post-chemotherapy assessment, excluding pts with progression). Statistical tests used: Kaplan-Meier (OS and PFS) and Fisher's Exact Test (DCR and ORR).

Results: 311 OC patients: stage III (n = 180, 58%) and IV (n = 106, 34%). 21% were *BRCA* mutant (MT) (n = 64). PARPis included olaparib (n = 47, 15%), niraparib (n = 220, 71%) and rucaparib (n = 44, 14%), with median duration of use of 189 days (range 14-1351). First post-PARPi chemotherapy was platinum-based (PBC) in 72% (n = 223); 2nd line in 37% (n = 116), 3rd line 47% (n = 147), later line in 15% (n = 48). 234 pts had evaluable responses: ORR to first post-PARPi treatment was 28% for PBC, 27% for non-platinum chemotherapy (NPC) (non-significant, ns); DCR was 44% to PBC, 33% to NPC (ns), median PFS was 5.8 months (m) for PBC, 5.4 m for NPC (ns). Across the 311 pts, median OS was 17.4 m for PBC and 13.6m for NPC (HR 0.56, p = 0.001). Preliminary analysis shows no significant difference in duration of PARPi use, ORR, DCR, according to *BRCA* status. PFS/OS data will be presented with respect to number of lines and *BRCA* status. Limitations include retrospective non-trial based follow up..

Conclusions: UK OC patients show similar PFS, OS, ORR and DCR to subsequent treatment following maintenance PARPi irrespective of *BRCA* status.

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802P Real-world data of olaparib maintenance therapy in patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer: Final results of the C-PATROL study

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Background: Maintenance treatment with olaparib has demonstrated significant improvements in median progression-free survival (PFS) compared with placebo in patients with platinum-sensitive relapsed ovarian cancer (PSROC) who are in response to platinum-based chemotherapy (PBC). Olaparib was the first-in-class poly (ADP-ribose) polymerase inhibitor (PARPi) approved as monotherapy in the EU in 12/2014 (hard capsules, HC, 400 mg twice daily) in *BRCA*-mutated (*BRCA*m) PSROC. In addition, film-coated tablets (FT, 300 mg, twice daily) were approved in 05/2018 in PSROC regardless of BRCA status. After entering routine clinical practice, real-world data on olaparib were limited and this non-interventional study (NIS) was initiated. Here, final survival results are reported.

Methods: The prospective NIS C-PATROL (NCT02503436) was performed at 68 sites (50 hospitals, 18 office-based) in Germany. Routine clinical data were collected of *BRCA*m PSROC patients treated with olaparib according to label.

Results: Between 28 Oct 2015 and 30 Sep 2019, 282 patients were enrolled. Of these, 269 patients were included in the analysis (median age: 60 yrs; ECOG ≤1: 93%; ≥2 relapses: 32%; ≥3 prior PBC: 34%). 46 patients started with FT and 223 patients with HC; 70 patients switched from HC to FT. Median follow-up was 23.5 months (range 0.00 − 80.5) and median olaparib treatment duration was 13.6 months (0.1−80.9). 10% of patients received olaparib for ≥5 years. Median PFS was 14.3 months (95% CI 12.2−18.0). Median overall survival was 35.4 months (95% CI 29.2−47.1). 132

Table: 800P Response to first post PARPi treatment in 227 pts with known *BRCA* status

Endpoint	First post PARPi treatment					
	Platinum based			Non-platinum based		
	BRCA MT	*BRCA* WT		*BRCA* MT	*BRCA* WT	
ORR (%)	28	28	*OR = 0.99, p = 1*	17	28	*OR = 0.53, p = 1*
DCR (%)	38	47	*OR = 0.70, p = 0.3*	17	33	*OR = 0.41, p = 0.6*
PFS (m)	5.3	6.1	*HR = 0.84, p = 0.3*	9.4	5.4	*HR = 1.0, p = 1*
OS (m)	18.0	17.2	*HR = 0.93, p = 0.7*	15.6	13.1	*HR = 0.71, p = 0.4*

patients received at least one subsequent medication. Adverse events (AEs) were consistent with known tolerability profile of olaparib. 31 patients (11.3%, safety set: total n=274) discontinued olaparib treatment and 60 patients (21.9%) received reduced olaparib dose due to AEs.

Conclusions: This real-word study supports efficacy and tolerability of olaparib maintenance therapy after PBC in patients with *BRCA*m PSROC. Long-term exposure to olaparib was observed with no new safety signals.

Clinical trial identification: NCT02503436.

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803P Pre-treatment systemic inflammatory markers predict survival in endometrial cancer cases: A Japanese gynaecologic oncology group 2043 exploratory data analysis

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Background: Japanese Gynecologic Oncology Group (JGOG) 2043 was a trial to assess the efficacy of three different chemotherapeutic regimens as adjuvant therapy in endometrial cancer (EC) patients with post-operative recurrent risk. Inflammation predisposes patients to tumorigenesis by damaging DNA, stimulating angiogenesis, and potentiating pro-proliferative and anti-apoptotic processes. This study investigated whether pre-treatment systemic inflammatory markers (PTSIMs) are associated with survival outcomes in EC.

Methods: Women with EC were recruited to the JGOG 2043 study, excluding patients who did not receive chemotherapy and those lost to follow-up. PTSIMs, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin, albumin, lymphocyte, and platelet (HALP) score were analysed in terms of clinicopathological factors, progression-free survival (PFS), and overall survival (OS). Optimal cut-off values for NLR, PLR, and HALP score were determined using the web application Cutoff Finder for PFS and OS. Survival estimates were calculated using the Kaplan—Meier method. Differences in survival between groups were assessed using a log-rank test.

Results: In total, 712 patients were enrolled in the JGOG 2043 study, with a median age of 59 years (interquartile range (IQR), 52—64) and body mass index (BMI) of 22.4 kg/m^2 (IQR 19—25). The optimal cut-off values for PFS were 1.478 for NLR, 0.01695 for PLR, and 35.52 for HALP score. Similarly, the optimal cut-off values for OS were 1.88 for NLR, 0.02623 for PLR, and 19.87 for HALP score. Regarding the optimal cut-off values for PFS, NLR was associated with BMI; PLR with age, BMI, and surgical stage; and HALP score with BMI, surgical stage, and lymph node metastasis. For the optimal cut-offs for OS, NLR was associated with BMI, PLR, and BMI; and HALP score was associated with age and BMI. In PFS, HALP score was the prognostic factor (NLR: p=0.068; PLR: p=0.086; HALP score: p=0.025). In OS, PLR and HALP score were prognostic factors (NLR: p=0.1; PLR: p=0.028; HALP score: p=0.028).

Conclusions: PTSIMs are associated with survival outcomes in EC. In particular, HALP score was a prognostic factor for both PFS and OS.

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805P Tumor-informed ctDNA detection as a predictive marker for postoperative residual disease in epithelial ovarian cancer: A feasibility study

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Background: Complete tumor resection is the most relevant prognostic factor for overall survival in high grade serous ovarian cancer (HGSOC) patients. The current standard for classification of postoperative residual disease (RD) is surgeon's subjective evaluation at the end of surgery. Thus, a reliable objective predictive marker is currently missing.

Methods: In this prospective single-center feasibility study, patients with HGSOC, who underwent surgery between July 2021 to December 2022, were included. Tumor tissue was assessed intraoperatively and blood samples were performed preoperatively, at day 2 and 10 postoperatively and subsequently at cycle 1, 3 and 6 of chemotherapy. Low-coverage whole genome sequencing (WGS) was used to identify structural variants (SV), single nucleotide variants (SNVs) and indels in tumor tissue in order to develop personalized digital PCR (dPCR) fingerprint assays.

Results: So far, 33 patients are included in the present analysis, with a median follow up time of 7 (IQR 2-10) months. In all tumor samples, dPCR assays were successfully developed and validated, with a median of 5 biomarkers (SVs and SNVs) per patient. For each patient, an individual SV profile could be established, which remained largely constant throughout multiple tumor localizations of each patient. 32/33 (97%) patients had circulating tumor DNA (ctDNA) detected at baseline at levels ranging from 0.0005 - 31% VAF. Three (10%) patients have been lost to follow without postoperative ctDNA samples. ctDNA was persistently detected in all patients with macroscopic tumor residuals. A significant decrease in ctDNA was observed in all patients with stage I-IIIB disease who had macroscopic complete resection (8 patients). In 8/22 (36%) patients with complete resection, ctDNA decreased below the detection limit. Clinical follow up is ongoing, and analysis of longitudinal samples will be presented at the congress.

Conclusions: In this feasibility study, tumor-informed ctDNA was preoperatively detectable in 97% participants. In patients with multiple tumor biopsies, the fingerprint could be used for monitoring of each location. A decrease in ctDNA detection correlated with complete tumor resection.

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806P Pilot ambulatory malignant bowel obstruction (MBO) electronic monitoring program in patients with gynecologic cancers

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Background: MBO is a severe complication of advanced cancer. An interprofessional ambulatory outpatient MBO program with nurse-led proactive call management was established to support patients (pts) with gynecologic cancers at Princess Margaret Cancer Centre, showing reduction of hospitalization needs and improved outcomes.

Methods: "My Bowels on Track" is a pilot ambulatory electronic monitoring program for pts with gynecologic cancers with or at risk of MBO. Educational materials, secure messaging systems and $\leq$13 questions (Q) are offered weekly/biweekly. Based on Q answers, an alerting system flags pts with symptoms (yellow and red alerts indicate moderate and high concern, respectively) and no response to Q. Pts are contacted by nurses following clinical or compliance alerts. The primary objective is to assess the adherence ($\geq$70% Q completion considered adherent) on the first two months on the program. A secondary objective is to assess the sensitivity of the alerts to trigger recommendations. Adherence was calculated as a rate. Alert sensitivity was assessed with a generalized estimation equation.

Results: 40 pts enrolled between 08/21 and 09/22. Median age was 64.5 years (range 29-79). Primary diagnosis was ovarian (75%), uterine (17.5%) or cervical (7.5%) cancer, and 92.5% of pts were on systemic therapy. Clinical/radiological active MBO was present in 30% and 12.5% of pts prior to and at enrollment, respectively. Median duration of the program was 55 days (range 8-121). The two-month adherence was 65% (95% CI 50-80%), and the overall adherence was 60% (95% CI 43-75%). 65 symptom related alerts (75% yellow; 25% red) were reported in 60% (24/40) of pts. There were 59 recommendations triggered by alerts (29% dietary, 22% laxatives, 20% clinic assessment, 16% other medication, 8% emergency department referral, 5% other). The sensitivity of the alerts to trigger actions was 72% (95% CI 58-82%).

Conclusions: This pilot electronic MBO monitoring program with real-time patient reported outcome assessment was feasible, with 65% adherence at two months. Based on questionnaire answers an alerting system flagged symptoms of concern in 60% of participants, with a high sensitivity to provide actions or recommendations as a response to alerts.

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807P Predicting surgical outcomes in patients with advanced ovarian cancer through MRI based preoperative evaluation

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Background: Ovarian cancer (OC) is the most lethal gynecologic tumor and is characterized by a widespread metastasis in abdominal cavity. Accurate preoperative evaluation is important for the specification of surgical procedures and prediction of surgical outcomes.Currently, a variety of imaging techniques can be used for preoperative evaluation of ovarian cancer such as the Computed Tomography (CT) Suidan score. However, the Magnetic resonance imaging (MRI) based preoperative evaluation was not fully explored. Here, our study explores the feasibility of MRI as a preoperative assessment in OC patients.

Methods: This is a prospective, non-randomized, single-center trial of 134 epithelial ovarian cancer (EOC) patients treated with surgical cytoreduction between 2018 and 2022. All patients underwent preoperative MRI scan. The imaging score consists of lesion size scores in 33 areas of the abdominal cavity.

Results: Complete cytoreduction (CC) was achieved in 81 (60.4%) of 134 patients. CC patients with a median MRI score of 10(4 - 44) and the median MRI score of patients who were incompletely cytoreduced (IC) was 15(5 - 48). By comparing imaging scores with those seen in surgery, we found that MRI evaluation is in good agreement with intraoperative observation. However, for areas such as the small bowel mesentery, the MRI score is lower than the intraoperative score, while for lymph node metastases the MRI score is higher than the intraoperative score. Through multi-factor analysis, we have screened clinical and imaging criteria related to IC including CA125 level, prognostic nutritional index (PNI), diaphragmatic surface of spleen lesion, gallbladder fossa lesion and small bowel mesentery lesion. Based on these criteria, we have constructed preoperative imaging scores and the 'predictive score' was assigned to each criterion based on its multivariate OR.

Conclusions: Our research explores the feasibility of incorporating tumor load into MRI based preoperative assessment for OC patients. Also, we identified 5 criteria associated with IC, and developed a predictive model which may be helpful in treatment planning.

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808P Cell-free human papillomavirus (HPV) DNA is a sensitive biomarker for monitoring treatment response and for detecting relapse in locally advanced cervical cancer

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Background: Human papillomavirus (HPV) is the cause of the majority of cervical cancer cases and has been suggested to be released as cell-free DNA (ctHPV DNA) into the circulation. We here analyse if ctHPV DNA could be detected in plasma from patients with locally advanced cervical cancer (LACC) and if ctHPV DNA could be used as a prognostic biomarker and/or to detect relapses earlier than by traditional methods.

Methods: 74 patients with LACC were included, 66/74 had biopsies positive for one of 13 high-risk HPV-types using a bead-based assay. Droplet digital PCR (ddPCR) assays were developed for the HPV-types found. 418 longitudinal plasma samples from these 66 patients were then analysed using ddPCR assays for the corresponding HPV-type found in the biopsies. Results were correlated to tumor- and clinical characteristics.

Results: 92.4% of pre-treatment plasmas were positive for ctHPV DNA. ctHPV DNA levels were correlated to tumor stage. Persistent ctHPV DNA in end-of-treatment or early follow-up (1-4 months after finished treatment) plasma were correlated with worse progression-free survival (log rank test, $p < 0.001$) compared to if ctHPV DNA was not found. The positive predictive value (PPV) of ctHPV-status at early follow-up for predicting disease progression was 87.5% and the negative predictive value (NPV) was 89.3%. ctHPV DNA was found in plasma before relapse was diagnosed on radiology (median 315 days, mean 280 days) in all patients (n=10) who experienced relapsed after complete clinical response to treatment.

Conclusions: ctHPV DNA in follow-up plasma is a promising prognostic biomarker in patients with locally advanced cervical cancer, useful for analysis of response to therapy and for early detection of relapses. Drs. E. Tham and K. Hellman have equally contributed to the study.

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809P Mental and socioeconomic burden in endometrial and cervical cancer patients: A Swedish population-based study of survivorship

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Background: Gynecological cancer may have severe implications in women, as these diagnoses are likely to have negative consequences on mental health and socioeconomic status. We used the Swedish national population and healthcare registries to assess the association between diagnosis of endometrial or cervical cancer and risk for mental disorders, as well as for socioeconomic consequences.

Methods: We performed a population-based nested case-control study based on more than 5 million women in Sweden, identifying 6,060 cases of cervical cancer and 17,932 cases of endometrial cancer diagnosed during 2006-2018. Each cancer case was matched with five healthy controls randomly selected from the population born in the same year. Data on comprehensive set of mental disorders, loss of employment, early retirement or need for sickness benefit, family receipt of financial assistance, decrease of individual income and family income before versus after cancer diagnosis were retrieved from population registries. Conditional logistic regression and stratified Cox regression models with confounder adjustment were conducted to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results: Mental disorders were prevalent to a moderate degree before diagnosis among cervical cancer patients, but less prevalent in endometrial cancer patients. After cancer diagnosis, incident (i.e. new) mental disorders started emerging within the first 2-5 years and then persisted. The risk was higher following cervical cancer (OR=3.7, 95% CI=3.5-4.1) as compared to endometrial cancer (OR=2.1, 95% CI=2.0-2.2). Before cancer diagnosis, economic status was comparable between cancer patients and control women. Financial assistance and income decrease rose early after diagnosis, with 1.2-2.1 times increased risk among cancer patients. Unemployment, early retirement and need for sickness benefit doubled from two years after cancer diagnosis and onwards. Impact was more pronounced among cervical cancer patients.

Conclusions: Women with cervical cancer and endometrial cancer are affected mentally and financially after the cancer diagnosis. The impact is more pronounced among cervical cancer patients.

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810P The influence of preoperative conization (pc) to patient's (pts) outcome and tumor biology of cervical cancer (CC)

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Background: Recent studies suggested that tumor size reduction by means of pc prior to radical surgery might improve survival outcomes (SO) in CC pts. Whether pc has a beneficial effect in CC pts undergoing radical surgery in the form of total mesometrial resection (TMMR) is unclear. Because of the prevention of intraoperative tumor spillage by performing a closed colpotomy is essential to all TMMR, we hypothesized that pc would not affect SO in TMMR pts.

Methods: We performed a retrospective analysis of data which was collected in the Leipzig Mesometrial Resection trial. All pts had been treated for primary CC staged IB1 – IVA (2018-FIGO) by open abdominal hysterectomy performed as total or extended mesometrial resection (TMMR/EMMR). Recurrence-free (RFS) and overall survival (OAS) were analyzed. Cox proportional hazards regression models (Cox-R) were built to define the effect of pc. RFS and OAS within the conization group were analyzed to determine whether there is a difference between R0 (tumor removed completely) and R1 (tumor removed incompletely) conization.

Results: 542 pts were included, of which 202 had received pc. After 1:1 propensity score matching including 163 pts with conization and 163 controls, pc was associated with significantly increased RFS (95.6% vs. 82.3%, HR 3.2, $p<0.001$) and OAS (99.2% vs. 85.6%, HR 6.4, $p<0.001$). In multivariable Cox-R pc was the only independent factor affecting RFS (HR 0.3, $p<0.01$). Analysis of the martingale residuals in a Cox regression null-model only including tumor-size revealed a continuous increase of recurrence risk with each increment in maximum tumor diameter for pts without pc, reaching a recurrence risk of 45% at a tumor size of 70 mm. In contrast, the recurrence risk for pts who had undergone pc plateaued at 12% at a tumor size of 37 mm. The sub analysis between R0 and R1 conization pts showed no difference in RFS and OAS.

Conclusions: In this study, pc was independently associated with improved survival in CC pts treated with TMMR/EMMR. Since intraoperative tumor spillage was avoided by closed colpotomy, factors other than the prevention of local tumor cell dissemination might play a role in improving survival. There is a need of further research to understand the concrete effect of pc to tumor biology.

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Disclosure: All authors have declared no conflicts of interest.

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811P Epidemiological landscape of cervical cancer in Latin America: EVITA LATAM (LACOG 0820)

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Background: Cervical cancer disproportionately affects patients (pts) in developing countries and is one of the leading causes of death in Latin America (LatAm). Understanding the epidemiological landscape of cervical cancer is warranted to plan prevention and treatment strategies for the continent.

Methods: The **EVITA LATAM (LACOG 0820)** study is a multicenter retrospective and prospective cohort of pts with cervical cancer FIGO Stage IB2 to IVA diagnosed after January 2018. Its primary objective is to describe the histologic subtypes and stages of cervical cancer in Latin America. We hereby describe demographic, clinical, and pathologic characteristics, and explore factors associated with diagnosis in earlier stages.

Results: From Nov/2021 to Jan/2023, 516 pts were included in 12 centers across Brazil, Argentina, Peru, and the Dominican Republic. Median age was 45.0 (range: 21.8 – 90.5) years, 213 (41.3%) were white and 244 (47.3%) were of mixed race. Current or former smoking was reported by 133 (25.7%) pts; 265 (51.3%) pts did not complete secondary education, and 441 (85.5%) were treated in public institutions. Four (0.8%) pts had received HPV vaccination and 73 (14.1%) never used contraception. PAP smear had never been performed by 62 (12.0%) patients and 126 (24.4%) received PAP smear regularly. Regarding histology, 420 (81.4%) pts presented with squamous cell carcinoma, and 66 (12.8%) with adenocarcinoma. Stages are described in the table. ECOG PS was 2 or worse in presentation for 58 (11.2%). Performing PAP smears regularly was associated with diagnosis at earlier stages (OR 1.69, 95%CI 1.15 - 2.49, P-value 0.0072).

Table: 811P FIGO stages and screening program adherence

	Overall	Regular PAP smear	Not regular PAP smear
	N = 508	N = 122	N = 386
Stage (N, %)[a]			
I	32 (6.3%)	12 (9.8%)	20 (5.2%)
II	170 (33.5%)	48 (39.3%)	122 (31.6%)
III	247 (48.6%)	52 (42.6%)	195 (50.5%)
IV	59 (11.6%)	10 (8.20%)	49 (12.7%)

Ordinal regression, OR 1.69, 95%CI 1.15 - 2.49, P-value 0.0072.
[a]Eight patients did not have stage information so they were excluded from this table.

Conclusions: This large study in LatAm findings showed that low rates of HPV vaccination and PAP smear coverage remain alarming, and less than half of pts received PAP smear regularly. More efficient HPV vaccination strategies synchronized with well-conducted Pap smear-based screening should be prioritized in LatAm countries.

Clinical trial identification: NCT04947605.

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812P Mental and socioeconomic burden in co-parents and children of patients with endometrial and cervical cancer: A Swedish population-based study

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Background: Gynecological cancer in women may have negative mental and societal consequences impacting not only patients, but also their family members. The impact may differ between families afflicted by cervical and endometrial cancer, as the two cancers develop at different ages (median age at diagnosis 49 vs. 60 years, respectively), and is not well understood. We assessed the health and education status of family members to a woman with cervical or endometrial cancer, to elucidate potential mental and socioeconomic consequences in these.

Methods: We performed a population-based nested case-control study in Sweden, identifying 11,602 cases of cervical cancer and 34,007 cases of endometrial cancer diagnosed during 1991-2016. Each cancer case was matched with five healthy controls randomly selected from the population with same birth year. Their children and respective co-parents were identified through the Swedish multi-generation register and mental health and educational outcomes traced through the Swedish Patient Register and Statistics Sweden. A comprehensive set of mental disorders of co-parents and children and attained highest level of education of the children after mother's diagnosis, were assessed.

Results: Co-parents and children of cervical cancer patients had 30-40% increased risk of mental disorders after women's cancer diagnosis compared to relatives of healthy controls. The increase among children emerged right after cancer diagnosis (OR=1.32, 95%CI=1.05-1.65), whereas among the co-parents emerged from 2 years after (OR=1.42, 95%CI=1.02-1.98). For endometrial cancer, the association was present but weaker. Children aged 0-18 at mothers' cervical cancer diagnosis were less likely to reach a higher level of education as compared to children to women without cervical cancer (OR 0.87, 95%CI 0.83-0.91). The corresponding educational impact on children of women with endometrial cancer was inconclusive.

Conclusions: Children and co-parents of women with cervical or endometrial cancer are affected adversely mentally after the cancer diagnosis, and children to mothers with cervical cancer display a generational impact in terms of lower education attainment.

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814P Clinical significance of isolated pulmonary recurrence in patients with endometrioid endometrial cancer who achieved complete remission after primary treatment

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Background: This study was to evaluate the clinical significance of pulmonary recurrence for patients who achieved complete remission after primary treatment of endometrioid endometrial cancer.

Methods: This multicenter retrospective study included patients who had undergone primary treatment for endometrial cancer at six different hospitals between 2009 and 2019. Inclusion criteria were patients with endometrioid histology and no evidence of residual disease after primary treatment including standard surgical procedure. Patients who developed pulmonary metastasis during follow-up were identified. Time to second objective disease progression (PFS2) was defined as time from the start of second-line therapy to second recurrence, and second-line overall survival (OS2) was defined as time from the start of second-line therapy to death.

Results: Of the 1074 patients who met the inclusion criteria, 90 experienced recurrences. Pulmonary recurrence was the most frequent site of first recurrence, accounting for 34.4% (31/90) of all recurrences. Isolated pulmonary recurrence accounted for 64.5% (20/31) of all pulmonary recurrences, whereas 35.5% (11/31) of patients had concurrent recurrences at other sites. The median PFS2 and OS2 of patients with isolated pulmonary recurrence were significantly longer than those with concurrent recurrences at other sites (PFS2, 17.0 vs. 9.0 months, log-rank $P = 0.004$; OS2, not reached vs. 28.0 months, log-rank $P = 0.001$). During the median follow-up period of 88.0 months, 73.7% of patients with isolated pulmonary recurrence had recurrence or progression after second-line treatment, but only 15.8% of the patients died. On the other hand, during the median follow-up period of 33.0 months, 88.9% of patients with concurrent recurrence at other sites had recurrence or progression after second-line treatment and 66.7% died. Multivariable analysis identified isolated pulmonary recurrence as an independent factor for longer OS2 (HR, 0.18; 95% CI, 0.03-0.59; $P = 0.009$).

Conclusions: Our study showed that isolated pulmonary recurrence is associated with prolonged OS2 in patients with recurrent endometrioid endometrial cancer.

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815P Clinical outcome of metastatic endometrial carcinoma patients treated with chemotherapy: ENDOVIE, a GINECO national observational cohort study

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Background: Incidence of metastatic endometrial carcinoma (EC) is increasing worldwide. Recent therapeutic innovations reinforce the need to better understand patients (pts) characteristics, treatment patterns and clinical outcome in the real-world setting.

Methods: Patients beginning 1st or 2nd line chemotherapy (chemo) during the year 2019 were included in this multicenter, retrospective cohort study and were followed until December 31, 2021 or death. Up to 9 pts were included in each of the 30 centers across France. Two hundred pts, 127 in 1st line (cohort 1) and 73 in 2nd line (cohort 2), were enrolled. Median age was 71 years (min: 39 max: 93) and 31 % were > 75 years old. Significant comorbidities included overweight (BMI > 25 kg/m^2) in 49 % of pts, medically treated hypertension, diabetes mellitus and deep venous thrombosis in 28.5%, 14.5% and 11%, respectively. ECOG performance status was 2 or 3 in 12% of pts. Endometrioïd carcinoma was the most common histological subtype (62%), followed by serous carcinoma (22%) and carcinosarcoma (5%). One third of pts had a FIGO IVB disease. MMR status was available only in 34% of pts and 21% of them was deficient.

Results: In 1st line, most pts received carboplatin and paclitaxel association (79%) or other platinum-based combinations (17%). Median PFS and OS were 8.5 months (mos) (CI 95%: 6.3-10.5) and 13.2 mos (CI95%: 10.9-16.6), respectively. The presence of liver metastases was the main prognostic factor for PFS and OS. In 2nd line, data from pts in cohorts 1 (49% received 2nd line chemo during the follow-up period) and 2 were pooled (n=135). Anthracycline and weekly paclitaxel as a single agent were used in 52% and 10%, respectively while platinum-based protocol was used in 23% of patients. Median PFS and OS were 4.0 mos (CI95%: 3.5-5.3) and 9.6 mos (CI95%: 8.3-11.8), respectively. A 3rd line of chemo was administered to 78 pts (39%): 31% received gemcitabine and 17% a platinum-based combination. Median PFS was 2.6 mos (CI95%: 2.1-4.1).

Conclusions: In this real-life cohort, metastatic EC affected older and frail women and was associated with poor overall survival despite chemo. There is an urgent need of new therapeutics.

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Disclosure: J. Alexandre: Financial Interests, Personal, Advisory Board: Eisai, MSD, GSK, Janssen, Pfizer; Financial Interests, Personal, Invited Speaker: Eisai, MSD, AstraZeneca, GSK, Novartis; Financial Interests, Institutional, Research Grant: Janssen, GSK, MSD; Financial Interests, Institutional, Local PI: MSD, Eisai, Agenus, GSK, Immunogen, Incyte. E. Kalbacher: Financial Interests, Personal and Institutional, Advisory Role: AstraZeneca, Eisai, GSK, Leopharma, Roche, Sanofi, Seagen, Tesaro, Viatris. B. Asselain: Financial Interests, Personal, Advisory Board: BMS, Pierre Fabre; Financial Interests, Personal, Advisory Role: AstraZeneca, Daiichi Sankyo, Gilead; Financial Interests, Personal, Training: Servier, Roche. S. Emambux: Financial Interests, Personal, Advisory Role: BMS, Eisai, Janssen; Financial Interests, Personal, Other, Travel: Pfizer, Chugai. G. Babin: Financial Interests, Personal, Advisory Role: MSD, GSK. C. Lescure: Non-Financial Interests, Personal, Other, attend congress (ESMO 2022): Viatris; Non-Financial Interests, Personal, Other, attend congress (St Paul de Vence 2022 & 2023): Lilly. P. Heudel: Financial Interests, Personal, Advisory Board: AstraZeneca, Pfizer, Novartis, Seagen, Lilly, MSD, Gilead; Financial Interests, Personal, Ownership Interest: GeodAIsics. N. Delanoy: Financial Interests, Personal, Advisory Role: GSK, Clovis Oncology, Eisai. P. Combe: Financial Interests, Personal and Institutional, Advisory Board, + Investigator: AstraZeneca, BMS, MSD, Novartis; Financial Interests, Personal, Advisory Board: Eisai, Sanofi, Daiichi Sankyo, Clovis Oncology, GSK, Amgen. F. Selle: Financial Interests, Personal and Institutional, Advisory Role, + Clinical Trial: AstraZeneca, GSK, MSD; Financial Interests, Personal, Advisory Role: Novartis, Clovis Oncology; Financial Interests, Institutional, Other, Clinical Trial: Roche, Immunogen, Incyte, Agenus. A. Hakme, L. Cagnan: Financial Interests, Personal, Full or part-time Employment: MSD. S. De Percin: Financial Interests, Personal, Invited Speaker: Eisai; Financial Interests, Personal, Advisory Board: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

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816P Laparoscopic versus open-surgery in FIGO stage II endometrioid endometrium cancers: Is there a prognostic effect?

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Background: Based on two randomized trials (LACE and LAP2) minimal invasive surgery has turned into surgical standard in early stage endometrial cancer (EC) including "high-risk" patients. These recommendations are predominately based on "low-risk" cancers, which were mainly represented in both trial collectives. We herein provide a retrospective study focusing on potential differences in clinical outcome in early stage endometrioid ECs treated by laparoscopy or open surgery.

Methods: 420 early stage ECs were retrospectively dichotomized according to the surgical approach and correlated to recurrence rate and clinical outcome. In addition, subgroup analyses were performed according relevant clinical risk parameters, namely FIGO stage, grading and LVSI.

Results: The analyzed collective consisted of 73.8% stage IA, 19.5% stage IB, and 6.7% stage II cases. 23% of patients exhibit G3 tumors and LVSI was detected in 12.4%. Minimal invasive surgery was performed in 54.5% of study patients. During a median follow-up of 5.0 years, recurrence or death were observed in 8.3% and 6.7%, respectively. Recurrences were located in the vaginal cuff (60.0%), in locoregional lymph nodes (31.4%), and in 8.6% in both sides. No distant metastases were observed. Under consideration of the mentioned clinicopathologic parameters, surgical approach in FIGO stage I did not influence recurrence rate and survival. However, in stage II disease, a laparoscopic approach was clearly associated with a higher recurrence rate (85.7% vs. 14.3%; $p = 0.013$). All recurrences were located in the vaginal cuff, and in one case, additional relapse was found in loco-regional lymph nodes. Moreover, laparoscopy in stage II disease was associated with impaired progression-free and overall survival (HR 8.86 (1.01 – 20.85) and HR 6.36 (1.10 – 28.61)).

Conclusions: We herein demonstrate that a laparoscopic approach in stage II endometrial cancer is associated with higher recurrence rates and impaired clinical outcome. These data could be interpreted in line with results of the LACC trial in cervical cancer. Although, grounded on a retrospective analysis, these hypothesis-generating results warrants a confirmatory trial, which is ongoing.

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817P A systematic review of recruitment of ethnic minorities to RCTs of systemic anti-cancer therapies in gynaecological cancers

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Background: Emerging evidence suggests pharmacogenomic differences between ethnic groups contributes to disparate treatment effects in cancer patients treated with systemic anti-cancer therapies (SACT). It is important to understand the representation of ethnic minority groups in research, and how this relates to patient outcomes. This systematic review compared participation of ethnic minority groups in contemporary gynae-oncology RCTs of SACT, and described the global distribution of research sites.

Methods: Medline, Embase and ClinicalTrials.gov databases were systematically searched. Phase II & III RCTs of SACT for ovarian, cervical, endometrial, vaginal and vulvar cancers of any stage, published 01/11/2012-01/11/2022 and reporting ethnicity were included. SACT licensed at time of search were eligible. Studies of non-systemic agents, vaccines, radiotherapy or surgery alone were excluded. Outcomes were recruitment by ethnicity and location of research sites. Recruitment by ethnicity was extracted, participation calculated for each group and compared by indication, trial phase and publication period, as well as to incidence in real-world populations. PRISMA guidance was used to report results.

Results: 26 RCTs met inclusion criteria. 17,041 patients participated; 79.8% (13,595) were "Caucasian", 9,1% (1552) "Asian", 3.7% (630) "Black/African American", and 6.1% (1,031) "Other/Unknown". The remaining 1.3% (233) comprised other groups. "Caucasian" patients were over-represented in RCTs for each disease indication, and recruited at a higher rate to phase II than phase III RCTs. "Black/African American" patients recruited at a lower rate to phase III than phase II RCTs.Of 26 studies, 20 were conducted in multiple countries, 5 only in the US, and 1 only in Italy. Of 5478 sites, 4,390 (80.1%) were located in North America or Europe, 187 (3.4%) in East Asia, and 901 (16.5%) in other regions. Notably, no sites were located in Africa or South Asia.

Conclusions: Ethnic minorities are under-represented in contemporary gynae-oncology RCTs. Efforts must be made to include ethnic minority patients to ensure findings are generalisable to real-world populations.

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818TiP REFRaME-O1/ENGOT-OV79/GOG-3086: A phase II/III open-label study evaluating the efficacy and safety of luveltamab tazevibulin versus investigator's choice of chemotherapy in women with relapsed platinum-resistant epithelial ovarian cancer expressing folate receptor alpha (FolRα)

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Background: Folate receptor alpha (FolRα) is a validated target in the treatment of platinum resistant ovarian cancer (PROC) with high FolRα expression. There continues to be a high unmet need to treat PROC with low to moderate expression levels of FolRα. Luveltamab tazevibulin (luvelta) is a novel FolRα targeting ADC, with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR4) that induces cytotoxic and immunogenic cell death. Luvelta is generated using cell free antibody production and site-specific conjugation technology and is designed to target a broad range of FolRα expressing cancers. Luvelta demonstrated preliminary efficacy data (ORR of 37.5%; mDOR of 5.5 months; mPFS of 6.1 months) in 32 patients with advanced relapsed EOC who had FolRα expression of >25% of any intensity in a

phase 1 study STRO-002-GM1 (NCT03748186). Sub-analysis demonstrated a higher ORR at 5.2 mg/kg (43.8% versus 31.3%, n=32) compared to 4.3 mg/kg. The safety profile was shown to be manageable, with the most common grade 3 and higher adverse events consisting of neutropenia, arthralgia, and anemia. This data forms the basis for a pivotal study of luvelta in patients with PROC whose tumors express a broad level of FolRα expression.

Trial design: REFRaME-O1 is a multicenter, international, open-label, 2-part seamless phase 2/3 study of luvelta in subjects with relapsed PROC expressing FolRα. Part 1 consists of a dose-optimization stage and will randomize ∼50 subjects 1:1 to the treatment of luvelta at 4.3 mg/kg Q3W or luvelta 5.2 mg/kg Q3W + prophylactic pegfilgrastim for 2 cycles followed by 4.3 mg/kg Q3W. Part 2 will commence with the selected optimized dose and will include a control arm consisting of investigator's choice chemotherapy, with a 2:1 randomization schedule. Key inclusion criteria are progressive PROC, up to 3 prior regimens, TPS of ≥25% for FolRα expression, and measurable disease. Key exclusion criteria are primary platinum refractory disease and prior treatment with a FolRα ADC or ADC containing a tubulin inhibitor.

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819TiP FONTANA: A phase I/IIa study of AZD5335 as monotherapy and in combination with anti-cancer agents in patients with solid tumours

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Background: Folate receptor α (FRα), a cell-surface protein encoded by the folate receptor 1 gene, is upregulated in epithelial ovarian cancers and lung adenocarcinomas. AZD5335 is an antibody-drug conjugate comprising an antibody portion that binds with high affinity to FRα conjugated to a topoisomerase 1 inhibitor (TOP1i) payload. Upon binding, AZD5335 releases TOP1i within the cell. The TOP1i payload then traps TOP1 on the replicating DNA and induces DNA double-strand breaks, ultimately resulting in cell death. AZD5335 is active in preclinical models of high-grade ovarian cancer (Gymnopoulos et al. Presented at AACR 2023; abstract LB025).

Trial design: FONTANA (NCT05797168) is a modular, first-in-human, open-label, multicentre study of AZD5335 in patients with advanced solid tumours. The study will evaluate AZD5335 as monotherapy in patients with ovarian cancer or lung adenocarcinoma (Module 1), or AZD5335 in combination with AZD5305, a selective poly(-ADP-ribose) polymerase 1 inhibitor, in patients with ovarian cancer (Module 2). Each module consists of a dose-escalation and dose-optimisation cohort. Key features of this study include the use of randomised dose-optimisation cohorts and a Bayesian-logistic regression model-based dose escalation in Module 2. Eligible patients are aged ≥18 years, ECOG performance status 0−1, must have received prior therapy, and have adequate organ and marrow function. Asymptomatic and stable brain metastases are allowed. The primary objectives are to assess the safety and tolerability, and to establish the dose limiting toxicity. Secondary objectives include assessment of objective response rate, duration of response, disease control rate, and progression-free survival by RECIST v1.1, and overall survival; characterising the pharmacokinetics of AZD5335 when given as monotherapy or in combination; and assessing immunogenicity. The study will be open to recruitment by 25 May 2023.

Clinical trial identification: NCT05797168.

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820TiP A randomized phase II study of secondary cytoreductive surgery (CRS) in patients with relapsed ovarian cancer who have progressed on PARP inhibitor maintenance (KGOG 3067/SOCCER-P trial)

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Background: Although recent two phase 3 randomized controlled trials showed survival benefit of secondary cytoreductive surgery (CRS) in first relapsed ovarian cancer, the patients who received PARP inhibitor (PARPi) as first-line maintenance were not included in these trials. In addition, the treatment consensus for recurrence after PARPi has not been established because subsequent platinum-based chemotherapy is not sensitive in relapsed patients after PARPi maintenance. Therefore, there is a significant need for optimal strategy including secondary CRS in patients

whose cancer progresses while using a PARPi. The aim of SOCCER-P is to find out whether secondary CRS is beneficial in patients who have progressed on PARPi maintenance.

Trial design: It is a multicenter, randomized phase II trial of secondary CRS in patients with relapsed ovarian cancer who have progressed on PARPi. This trial included patients with the first recurrence of platinum-sensitive ovarian cancer who had a progression-free interval of at least 6 months after the end of the last platinum-containing therapy and progressed on PARPi maintenance. Patients who are considered likely to be completely resected according to the international model (AGO or iMODEL) or based on a consensus between the surgeon and designated radiologist are eligible for this study. 124 subjects are randomly assigned to undergo secondary CRS and subsequent chemotherapy (carboplatin [AUC 5, day 1] plus pegylated liposomal doxorubicin [30 mg/m2, day 1] every 4 weeks) plus or minus bevacizumab (six cycles of bevacizumab [10 mg/kg, days 1 and 15] followed by maintenance bevacizumab [15 mg/kg every 3 weeks]), or to receive chemotherapy plus or minus bevacizumab alone. The primary endpoints were progression-free survival (PFS). And we also assess overall survival and PFS2 defined as the time from randomization to tumor progression on a next-line tretment or death. A one-sided log-rank test with an overall sample size of 124 subjects (62 in the control group and 62 in the treatment group) achieves 80.1% power at a 0.100 significance level to detect a hazard ratio of 0.6500 when the hazard rate of control group is 1.05.

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821TiP Phase I study of ceralasertib (cerala) in combination with AZD5305 in patients (pts) with advanced/metastatic ovarian cancer (OC) previously treated with PARP inhibitors (PARPis)

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Background: Combined inhibition of ATR and PARP has been shown to overcome resistance to PARPis in PARPi-resistant cell lines and pt-derived xenograft (PDX) models. Cerala, a selective and potent ATR inhibitor, in combination with olaparib, has demonstrated activity in pts with homologous recombination deficiency-positive, PARPi-resistant OC (CAPRI; NCT03462342). However, in combination with olaparib, the dose and duration of cerala treatment is limited by haematological toxicity. Compared to approved PARPis which target both PARP1 and PARP2, AZD5305 is a highly selective and potent PARP1i which may improve upon the current safety profile of the olaparib and cerala combination. AZD5305 monotherapy was well tolerated in an ongoing phase 1 study of pts with *BRCA1/2-*, *PALB2-* or *RAD51C/D*-mutant advanced breast, prostate, pancreatic or OC (PETRA; NCT04644068); AZD5305 in combination with cerala demonstrated durable tumour regression in *BRCA1/2*-mutant, PARPi-resistant, breast and OC PDX models. Thus, combining cerala and AZD5305 may provide a better therapeutic index compared with olaparib and cerala.

Trial design: D5330C00004 (NCT02264678) is a modular, phase 1, open-label trial assessing cerala in combination with anti-cancer agents in pts with advanced solid malignancies. Module 5 investigates cerala in combination with AZD5305 in pts with recurrent platinum-sensitive, high-grade, epithelial ovarian, fallopian tube or primary peritoneal cancer (including serous or endometrioid histology), in dose escalation (Part A) and expansion (Part B) cohorts. Key inclusion criteria are age $\geq$18 years and prior PARPi treatment. Pts in Part B must have a known or suspected *BRCA*, *RAD51C/D* or *PALB2* mutation. Primary objectives are safety and tolerability of cerala in combination with AZD5305 including the number of adverse events (AEs) and serious AEs, in order to select a recommended phase 2 dose (Part A). Secondary objectives include assessment of antitumour activity, pharmacokinetics and pharmacodynamic biomarkers. Recruitment started in April 2023 and sites across North America, Europe and Asia Pacific will enrol up to 150 pts in total.

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822O Activation of γ9δ2 T cells by ICT01 as a novel immunotherapeutic approach for relapsed/refractory hematologic cancers (EVICTION trial)

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Background: ICT01, an anti-BTN3A targeted mAb that selectively activates γ9δ2 T cells, is being studied in the ongoing phase 1/2a EVICTION Trial in advanced solid and hematologic cancers (NCT04243499). ICT01-activated γ9δ2 T cells are known to kill acute myeloid leukemia blasts and lymphoma cell lines both *in vitro* and *in vivo*, making γ9δ2 T cells of interest as a novel immunotherapeutic strategy against hematologic cancers. Here we present data from the EVICTION phase 1 in relapsed/refractory hematological cancers.

Methods: Patients with hematologic cancers who failed available standard of care received IV ICT01 alone (200 µg to 75 mg) every 21 days. Antitumor assessment by imaging or bone marrow analysis was done every 8 weeks after using the Response Evaluation Criteria in Lymphoma (RECIL) and IWG Criteria for AML. Safety reviews were conducted prior to dose escalation. Disease Control Rate (DCR) was the primary efficacy endpoint and defined as the sum of complete response (CR), CR with incomplete recovery (CRi), partial response (PR) and stable disease (SD). Blood samples were collected for pharmacokinetic and pharmacodynamic analyses.

Results: Dose escalation was completed with 26 patients (1 Diffuse Large B-cell Lymphoma, 1 Follicular Lymphoma, 24 AML), with no dose-limiting toxicities and a good safety profile similar to that in solid tumors. First-dose infusion-related reaction, nausea, fever and vomiting (Grade 1/2) were the most common treatment-related AEs. Only 2 Grade 3 events of neutropenia were reported and resolved with continued treatment. Target occupancy on circulating T cells $\geq$ 30% was observed 30 min post doses $\geq$ 700 µg, with activation and migration of >95% γ9δ2 T cells from the blood within 24hrs of dosing. Ten of 26 patients were evaluable at week 8 with an observed DCR of 30%. One DLBCL patient still receiving ICT01 at 7 mg has had a PR from Wk 40 to Wk 94/C32. In the 20 mg dose group, two AML patients achieved stable disease at week 8 with one still on study at Wk 53/C19.

Conclusions: The good safety profile and encouraging clinical activity data in these last-line patients support further testing of ICT01 in a first-line AML phase 2a expansion cohort in combination with VEN/AZA in EVICTION that will start mid-2023.

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823O Preliminary pharmacokinetics (PK) and pharmacodynamic (PD) analysis of the CD123 NK cell engager (NKCE) SAR443579 in patients (pts) with relapsed or refractory acute myeloid leukemia (R/R AML), B cell acute lymphoblastic leukemia (B-ALL) or high risk-myelodysplasia (HR-MDS)

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Background: SAR'579, a trifunctional anti-CD123 NKp46×CD16 NKCE, enabling a cytolytic synapse between natural killer (NK) cells and CD123+ tumor cells leading to NK cell activation and tumor cell killing. We report preliminary PK/PD of SAR'579 from a phase 1/2 trial in pts with R/R AML, B-ALL or HR-MDS (EudraCT 2021-004287-98 Apr 26, 2023/NCT05086315).

Methods: SAR'579 was administered IV twice weekly or once weekly (QW) per dose level (DL) in first 2 weeks of cycle 1 and QW for rest of induction cycles. Peripheral blood (to measure plasma concentrations and immunogenicity assessment) and bone marrow samples were collected for PK/PD analysis during each induction cycle. Analysis of cytokines, as potential safety and PD markers, including IL-6, TNFα and IFNγ, was performed using Meso Scale Discovery®.

Results: From Dec 14, 2021, to Oct 17, 2022, 19 pts were treated across 5 DLs (3 in DL1 and 4 each in DL2 to DL5) between 10-3000 µg/kg/dose. No dose limiting toxicities were observed. At 1000 µg/kg QW, 3/8 pts achieved complete remission (CR) (2 CR/1 incomplete hematologic recovery). Early immunogenicity was 26% with no impact on safety/efficacy. Post first administration of SAR'579, circulating maximum (max) concentration increased with dose increase with a supra-dose proportionality between DL1 and DL5. PK linearity was achieved at 3000 µg/kg QW (DL5) at the end of cycle 1.

Table: 823O Median (max) peak cytokine concentrations (pg/mL) observed during DL1-5

	DL1	DL2	DL3	DL4	DL5
IL-6	63.6 (1355.4)	118.3 (264.3)	62.7 (450.1)	29.7 (126.7)	52.3 (445.3)
TNFα	12.6 (14.7)	19.2 (88.0)	9.7 (12.1)	7.2 (11.9)	17.9 (27.4)
IFNγ	21.4 (50.7)	88.7 (233.4)	81.8 (152.8)	123.8 (420.4)	58.1 (256.6)

Cytokine release syndrome levels of IL-6 (>500/1000 pg/mL) were measured in a single DL1 pt.

Conclusions: SAR'579 was well tolerated till 3000 µg/kg QW with clinical benefit in pts with R/R AML. Observed peak cytokine levels did not show significant dose-related increase and no association between elevated peak cytokine levels and clinical

responses. The results are consistent with the improved safety profile compared to CD123-targeted T-cell engagers.

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824O Treatment and survival in patients with localized primary ocular adnexal MALT lymphoma: A large bicentric cohort study

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Background: Despite the generally favorable prognosis of POAML, There is limited understanding of the extent to which primary ocular adnexal mucosa-associated lymphoid tissue lymphoma (POAML) impacts a patient's risk of death and how different treatment managements affect prognosis and toxicities in this specific MALT site.

Methods: This study analyzed major long-term outcomes of patients with POAML lymphoma and the prognostic significance of baseline clinical features. We reviewed the clinical features, treatments, disease course and long-term outcome of 262 patients with Ann-Arbor stage IE POAML diagnosed between 2000 to 2012. Outcomes were analyzed using crude overall survival (OS) and relative survival (RS) by standardized mortality ratio (SMR). A cross-sectional study was conducted using OSDI questionnaires to evaluate the long-term ocular adverse effects.

Results: The median age was 55 years. With a median follow-up of 66 month, the 5-year OS, lymphoma-specific mortality and competing non-lymphoma mortality were 96.8%, 0.4% and 2.3%, respectively, and the estimated 10-year corresponding rates were 90.0%, 0.4% and 4.2%; the overall SMR was 1.02 (95% confidence interval [CI]: 0.60-1.61, P = 0.963). The OS and RS rates were similar across the treatment groups; however, RT associated with significantly decreased risks of failure (11.0%, n = 82, p = 0.006), compared to observation (33.3%, n = 81), surgery (28.6%, n = 70), and CT/IT groups (24.1%, n = 29). The cross-sectional study indicated that RT wasn't obviously increased the intermediate-severe grades of dry eye diseases for a relative long-time after treatment.

Conclusions: Overall, a diagnosis of stage IE POAML lymphoma had similar long-term survival to the general population. RT associated with lower failure rates and minor ocular adverse effects.

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825O Genomic traits of therapeutic response to anti-PD-1 therapy in peripheral T cell lymphoma

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Background: The use of immune checkpoint inhibitors has revolutionized the treatment of solid tumors and hematologic malignancies, clinical evidence has demonstrated anti-PD-1 therapy to be effective tools in PTCL. However, factors that may influence primary sensitivity or resistance to anti-PD-1 therapy in PTCL, such as TMB and genomic alterations, have not yet been clarified.

Methods: We enrolled 89 peripheral T cell lymphoma (PTCL) patients in phase II clinical trial of geptanolimab and performed targeted next-generation sequencing for 440 cancer-associated genes. Clinical data were collected and correlated with genetic mutations. In vitro, studies were conducted to evaluate the effect of *JAK3* mutations on PD-L1 expression.

Results: PD-L1 expression was significantly elevated in complete response (CR)/partial response (PR) patients compared to progressive disease (PD) patients, while tumor mutation burden (TMB) didn't exhibit significant prognostic value which may be confounded by the variation across PTCL subtypes. The most frequent mutations occurred in *TP53*, *KMT2C*, *KMT2D*, *JA3*, *LRP1B,* and *SETD2*. Shorter time to death was related to mutations in *SETD2* (HR=5.73, P=0.0135) or *KME2D* (HR=3.17, P=0.0533). Shorter PFS was correlated with *JAK3* mutations (HR=5.97, P=0.0144). The subset PTCL patients (86.4%) with enrichment of non-APOBEC-related mutation signature had higher TMB level (P=0.076) and superior PFS (P=0.031) to non-APOBEC-enriched samples. In vitro experiments revealed *JAK3* A573V, M511I, and E958K mutations led to lower PD-L1 expression through downregulated of the expression of PI3K and MAPK.

Conclusions: In this study we comprehensively depicted the pre-treatment mutation profiles of PTCL and identified genetic alterations with prognostic value for anti-PD-1 therapy. Notably, we found *JAK3* mutations which are vital and prevalent in PTCL reduced PD-L1 levels in vivo and in vitro, which are of great clinical and biological sense.

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826O A single-arm, multicenter clinical study of radiotherapy combined with toripalimab in stage I/II extranodal NK/T cell lymphoma

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Background: The current standard of care for extranodal NK/T cell lymphoma (ENKTL) is L-asparaginase or pegaspargase-based multiagent chemotherapy combined with radiotherapy. However, overall survival was significantly lower in those patients with inadequate response to L-asparaginase-based multiagent chemotherapy.

Methods: In this prospective, single-arm, multicenter, phase II clinical study, patients with stage I/II ENKTL who did not achieve CR after 2-3 cycles of multiagent chemotherapy containing L-asparaginase or pegaspargase were enrolled. Patients received toripalimab (240 mg, d1, Q3w) plus radiotherapy (95% PTV 56 Gy/28f, d1-d5/w), sequentially with or without 2 to 4 cycles chemotherapy. Then patients received toripalimab for 1 year or until disease progression or intolerable toxicity. The primary endpoint was CR rate.

Results: From February 2019 to present, 22 patients were enrolled who have received the response assessment at least once after radiotherapy. All were originated from the upper aerodigestive tract with a median age of 45 years (range 26-64). 14 were male. 17 (77.3%) and 5 (22.7%) patients were Lugano stage I and II, respectively; 81% were primary tumor invasion (PTI). 8/22 patients (36.4%) had PR, 8/22 had (36.4%) SD, 6/22 (27.2) had PD after previous 2-3 cycles chemotherapy. All patients completed the radiotherapy. The ORR was 90.9%, including 17 CR (77.3%), 3 PR (13.6%), 2 PD (9.1%). 8 patients who responded to previous chemotherapy continued 2 cycles of chemotherapy after completion of radiotherapy. Others received toripalimab alone (median dose: 11; range 3-17). Up to date, the median follow-up time was 23 months (range 3-78), the 2-year PFS rate was 81.6%, and all patients survived. The main adverse events during and after radiotherapy were oral mucositis and hypothyroidism. No grade 3 or higher toxicity occurred.

Conclusions: Toripalimab combined with radiotherapy is safe and have promising efficacy for stage I/II ENKTL who have poor response after previous standard chemotherapy.

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827P Mutational spectra of the Korean patients with germline predisposition in hematologic malignancies: Five years of experience at a tertiary university hospital

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Background: An expanding number of genes predisposing to hematologic malignancies are being discovered by next-generation sequencing (NGS) technology. The 5th edition of the World Health Organization and International Consensus Classification revised their classification of hematologic neoplasms with germline predisposition acknowledging this development. We aimed to identify the mutational spectrum of germline predisposition in hematologic malignancies from Korean patients.

Methods: The study included 444 patients tested for hematologic malignancy panel testing at Pusan National University Yangsan Hospital from January 2019 to December 2022. The assay consisted of 200 genes related to hematologic malignancies and was performed with NGS on genomic DNA extracted from bone marrow specimens or peripheral blood. We identified potential germline variants by retrospective analysis of NGS results. Variant allele frequency $>$ 0.3 of pathogenic or likely pathogenic variants in a known germline predisposition gene was considered potential germline variants. We could not confirm each variant's germline status due to the absence of cultured skin fibroblast specimens.

Results: Thirty-seven (8.33%) patients harbored 38 potential germline variants. *DDX41* (21.62%, 8 patients), *RUNX1* (10.81%, 4 patients), *GATA2* (10.81%, 4 patients), and *PAX5* (10.81%, 4 patients) were the most common genes. One patient had 2 variants in the *SBDS* gene, a compound heterozygote. Frameshift (18 variants, 47.37%) and missense (10 variants, 26.32%) were the main proportion of the 38 potential germline variants.

Conclusions: We found that *DDX41*, *RUNX1*, *GATA2*, and *PAX5* are the most common genes in potential germline variants in hematologic malignancies in Korea. This study provides insight into the pathophysiology of germline predisposition in hematologic malignancies.

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828P Clinical features and outcomes of neurologic paraneoplastic syndromes in Hodgkin lymphoma

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Background: Neurologic paraneoplastic syndromes (NPS) due to Hodgkin lymphoma (HL) affect both the central nervous system (CNS) and peripheral nervous system (PNS) with wide-ranging manifestations, such as limbic encephalitis, cerebellar degeneration, and neuropathies. We summarize the clinical findings and outcomes of 23 patients with HL associated with NPS.

Methods: Medical charts of adult patients at Mayo Clinic were retrospectively analyzed based on common endpoints and clinical features. Clinical diagnosis of NPS was made utilizing established criteria by Graus et al (*Neurol Neuroimmunol Neuroinflamm*, 2021). Survival analysis was performed using Kaplan-Meier estimates.

Results: We analyzed 23 patients with HL with NPS seen at Mayo Clinic from 1995 to 2022. Baseline disease included 17 patients with classical HL and 6 patients with nodular lymphocyte-predominant HL. Median follow-up was 97.1 months (95% CI 66.3-150.3). Baseline demographics included mean age 40 years with 61% males and 87% Caucasian patients. CNS PS was seen in 17 patients. Death had occurred in 5 patients at the time of review, including 4 without PS resolution, although no patients died from PS. NPS was the presenting sign of HL relapse in 39% patients. Following HL treatment, PS relapse was observed in 2 of 5 patients with prior complete PS resolution, temporally linked to HL relapse. Median overall survival (mOS) in patients with no PS improvement was 38.4 months, whereas mOS could not be reached in patients with complete/partial PS resolution (p=0.043). All 6 patients without PS improvement had CNS syndromes, whereas 3 of 5 patients with complete PS resolution had PNS disease. Paraneoplastic antibodies (anti-Tr most common) were detected in 7 of 21 tested patients without mortality or relapse associations. All 5 patients who experienced complete resolution of PS exhibited HL remission.

Conclusions: In our series of 23 patients with HL and NPS, survival was significant higher in patients with complete PS resolution. Despite HL treatment, NPS may be irreversible due to cytoxic neuronal loss; thus, timely recognition of PS is essential in providing effective therapy, requiring oncologic treatment as shown in our series of patients who only achieved complete resolution of NPS with HL remission.

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829P Age and sex related genomic profiles of follicular lymphoma

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Background: Follicular lymphoma (FL) is the second most common B-cell non-Hodgkin lymphoma that is defined by unique somatic mutation and gene expression profile. Differences in the genomic profile of FL by age and by sex have not been well characterized.

Methods: We analyzed data from 155 patients with FL who underwent next generation sequencing and RNA expression analysis using the Genomic Testing Cooperative Hematology Plus platform. The DNA and RNA panels assessed 179 genes and 1408 genes, respectively. Our analysis was based on sex (male n=75, female n=80) and age ($<$50 years, n=20; 50-74 years, n=109; $>$75 years, n=26). Data and statistics were analyzed with Bioconductor R package Maftools and Broad Institute Gene Set Enrichment Analysis.

Results: At least one somatic mutation in epigenetic genes: *KMT2D* (n=106), *CREBBP* (n=98), *EZH2* (n=41) and *EP300* (n=27) were present in 95% of all patients (n=155). Mutations in *B2M* were significantly enriched in females (10% vs 1.3%, p=0.035), while mutations in *MEF2B* were significantly enriched in males (24% vs 10%, p=0.030). Mutations in *EP300* were enriched in the young cohort ($<$50; 35% vs 14%, p=0.047). Mutations in genes: *BCR* (Breakpoint Chain Region; 23% vs 3.9%, p=0.0033), *CREBBP* (81% vs 60%, p=0.047), *STAT6* (23% vs 8.5%, p=0.042) and *TET2* (19% vs 6.2%, p=0.045) were enriched in the elderly cohort ($>$75). All *BCR* mutations (missense and truncations), occurred within the N-terminus kinase domain of the gene. These mutations have not been well characterized in FL and are predicted to be deleterious; involving a coiled-coil domain essential for oligomerization and gene function. These mutations may compromise its function as a regulator of RAC1 and RHOA proteins. Correlation with limited available clinical data also suggests that these mutations are seen with aggressive FL or FL undergoing transformation. RNA expression did not show any significant differences based on age or sex.

Conclusions: Our study suggests that there are age and gender specific genomic alterations in FL. We plan to follow up with validation studies in a larger cohort.

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830P Isolation of cell-free DNA of patients with mucosa-associated lymphoid tissue (MALT) lymphoma

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Background: To evaluate treatment efficacy for gastric extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma), histologic assessment via multiple gastric biopsies every 3 months constitutes the current gold standard. Currently, non-invasive diagnostic measures including PET-MRI to monitor therapy response in MALT lymphoma patients remain experimental for the time-being. While liquid biopsies isolating cell-free DNA (cfDNA) are used in other tumor entities for diagnostic and treatment monitoring measures, no data for gastric MALT-lymphoma have been published so far. Thus, we performed a pilot series to assess cfDNA in therapy-naïve gastric MALT-lymphoma patients.

Methods: For the isolation of cfDNA, blood from patients with MALT lymphoma was collected using PAXgene Blood ccfDNA tubes (Qiagen). cfDNA was isolated using the QIAamp Circulating Nucleic Acid Kit (Qiagen). DNA concentration was measured using fluorescence quantification (Qubit, Thermo Fisher). Quantitative data were compared to 68-Ga-Pentixafor-PET/MRI performed within 4 weeks assessing active lymphoma volumes. Clinical parameters were obtained by chart review.

Results: A total of 15 patients (4 males, 11 females) with MALT lymphoma at a median age of 64 years (range: 44-79) were included in this study. cfDNA could be isolated in all patients with a median concentration of 5.4ng/ml plasma (range: 3.6-12.4ng/ml). Compared to a healthy control cohort (n=5), cfDNA levels were significantly increased in MALT lymphoma patients (3.8ng/ml vs. 5.9ng/ml, $p=0.025$). In 12/15 patients, a follow-up blood draw could be obtained after a median 3.3 months (range 0.9-7.0 months). cfDNA levels remained stable during that time period with a mean concentration of 5.7ng/ml at baseline and 6.3ng/ml at follow-up ($p>0.05$). Correlation between metabolically active tumor volume and cfDNA concentration will be reported as soon as radiologic reclassification is completed.

Conclusions: cfDNA may be used as a non-invasive biomarker for disease monitoring in patients with MALT lymphoma.

Legal entity responsible for the study: the authors.

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831P Decitabine sensitized TP53-mutated diffuse large B cell lymphoma to R-CHOP treatment via activation of endogenous retrovirus

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Background: *TP53* mutations (*TP53*^{mut}) occur in 10-20% of diffuse large B-cell lymphoma (DLBCL) and is an unfavorable biomarker of DLBCL progression, conferring resistance to immunochemotherapy, high-dose chemotherapy, autologous stem cell transplantation, and anti-CD19 chimeric antigen receptor T-cell therapy. How to target *TP53*^{mut} remains a great challenge in treating DLBCL.

Methods: Survival of 667 newly diagnosed DLBCL patients were assessed, including 576 patients with R-CHOP and 91 patients with decitabine plus R-CHOP (DR-CHOP, NCT02951728 and NCT04025593). RNA sequencing data from *TP53*^{mut} and *TP53*^{wt} DLBCL tumors were analyzed. To further elucidate the underlying mechanisms of decitabine sensitizing *TP53*^{mut} DLBCL to R-CHOP treatment, *TP53*^{mut} DLBCL cell lines (*TP53*^{mut} p.R248Q, p.R273C and p.R175H) and patient-derived xenograft models (PDX, p.R248Q, p.R273C and p.R175H) were established and treated with decitabine, or doxorubicin ± decitabine.

Results: *TP53*^{mut} independently predicted inferior prognosis in R-CHOP-treated DLBCL, which could be counteracted by DR-CHOP treatment. In *TP53*^{mut} patients, multiple viral regulation pathways were repressed, accompanied by inhibition of immune modulation. *TP53*^{mut} DLBCL possessed increased methyltransferase *SUV39H1* expression and H3K9 trimethylation (H3K9me3), contributing to repression of endogenous retroviruses (ERVs) and immunosuppressive tumor microenvironment. In *TP53*^{mut} DLBCL cell lines, decitabine downregulated *SUV39H1*, inhibited H3K9me3 occupancy on ERVs, triggered ERV expression, thereby unleashed interferons program, and CD4^{+}T/CD8^{+}T cell activation. In *TP53*^{mut} PDX models and *TP53*^{mut} patients, improved anti-tumor effect was observed upon combined treatment of decitabine and doxorubicin via SUV39H1-H3K9me3-ERVs axis.

Conclusions: The present study demonstrated decitabine induced a viral mimicry pathway with peripheral blood CD4^{+}T/CD8^{+}T cell activation in *TP53*^{mut} DLBCL and sensitized *TP53*^{mut} DLBCL to R-CHOP treatment. Our findings highlighted an ERV regulatory circuitry in *TP53*^{mut} DLBCL and assigned essential roles of ERVs for epigenetic reprogramming tumor microenvironment in *TP53*^{mut}-driven cancers.

Clinical trial identification: NCT02951728, NCT04025593.

Legal entity responsible for the study: The authors.

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832P Characterisation of EXS73565: A potent and selective MALT1 inhibitor with low drug-drug interaction risk and potential in lymphoma

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Background: MALT1 plays a key role in antigen receptor signalling and preclinical data indicate that MALT1 protease inhibition may have benefit in tumours with dysregulated NF-κB signalling, including activated B-cell-diffuse large B-cell lymphoma (ABC-DLBCL). MALT1 inhibitors are in clinical development as monotherapies and in combination with other agnets for the treatment of oncology and haematology indications, including lymphoma.

Methods: EXS73565 ('565) was designed using generative design, machine learning and molecular dynamics approaches. The compound was characterised in MALT1 protease assays and DLBCL functional studies. *In vivo* efficacy of '565 was assessed in mouse xenograft models, alone and in combination with the BTK inhibitor ibrutinib. Profiling of '565 was undertaken in a range of selectivity and preclinical studies.

Results: '565 is a potent and selective allosteric inhibitor of the MALT1 protease and inhibits the production of IL-10 and proliferation of DLBCL cells. In ABC-DLBCL xenograft studies, '565 demonstrated significant tumour growth inhibition. Tumour target engagement was demonstrated through measurement of the MALT1 protease target, RelB, and effects on NF-κB target genes. In an ABC-DLBCL xenograft model with low sensitivity to single-agent MALT1 and BTK inhibition *in vivo*, combining '565 and ibrutinib provided significant synergistic efficacy. Evaluation of '565 showed limited activity against CYP450 enzymes, hepatic and renal transporters. Notably, '565 avoids inhibition of UGT1A1 (an enzyme involved in metabolising bilirubin and certain small molecule drugs) in comparison to some clinical stage MALT1 inhibitors which carry a high UGT1A1 inhibition risk.

Conclusions: We describe the characterisation of EXS73565, an allosteric inhibitor of MALT1 which is currently in IND/CTA-enabling studies. Importantly, we show that '565 exhibits a low drug-drug interaction and hyperbilirubinemia risk, offering the prospect of fully exploring the potential of MALT1 inhibition as a monotherapy and/or in combination with other targeted agents.

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833P New targets for adult T cell leukemia/lymphoma (ATLL): A map for ATLL immunotherapy

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Background: In this study, we summarize the chemokines that are involved in malignant HTLV-1 associated disease, adult T cell leukemia/lymphoma (ATLL) progression. The interaction of virus and host were evaluated in chemokine level.

Methods: The expression of CCR6, CXCR-3, the HTLV-1 proviral load (PVL), HTLV-1-Tax, and HBZ were assessed in 12 asymptomatic HTLV-1carriers (ACs), 12 healthy controls (HCs) and 12 ATLL patients. We applied quantitative real-time PCR (qRT-PCR) and TaqMan method.

Results: As per results, the level of CXCR3 gene expression in ATLL patients compared to HTLV-1 virus carriers and healthy people showed a significant difference (P=0.00 and P=0.008). Also, the mean expression of CCR6 genes in ATLL patients compared to HTLV-1 virus carriers had a significant difference of P=0.04, but in the ATLL group there was no significant difference compare to the healthy group.

Conclusions: Our study results illustrate that the expression of chemokine receptors is directly related to the course and stages of the disease as well as the prognosis of the disease. In carriers, compared to healthy individuals, we still have a higher level of expression of chemokine. In addition with the progression of the conflict and the progression to malignancy and involvement of T lymphocytes (the producer of these chemokines) as shown in our study, we can conclude that with decreased levels of these chemokine receptors can lead to malignancy with a poor prognosis. Our findings confirms previous studies that Tax protein may not be expressed in ATLL patients. Additionally an oncoprotein may involve in inducing malignancy, but in the absence of Tax, HTLV-1-HBZ protein implicated in the maintenance of mechanism of the virus to escape from the host cell immune system. We also found an increase in virus load as HTLV-1 carriers move toward. So these chemokines could be suggested as influential targets for the prognosis and proper therapy of ATLL.

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834P Phase II clinical study of VR-CAP regimen for first-line treatment of marginal zone lymphoma

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Background: Marginal zone lymphoma (MZL) is a relatively common group of inert B-cell non-Hodgkin's lymphoma (B-NHL) originating from peripheral memory lymphocytes. Some patients cannot achieve complete remission or relapse quickly after standard first-line treatment. Studies have shown that the NF-KB signal pathway in MZL is in an abnormally activated state, while bortezomib is a proteasome inhibitor targeting the NF-KB pathway. This multicenter phase II clinical study evaluated the efficacy and safety of VR-CAP regimen in the first-line treatment of MZL, and explored the best beneficiaries of VR-CAP regimen (rituximab, cyclophosphamide, epirubicin, bortezomib and prednisone).

Methods: The patient received 6 cycles of VR-CAP first-line treatment. Each cycle lasts for 3 weeks, and rituximab (375 mg/m2) is given intravenously on the 0th day, cyclophosphamide (750 mg/m2) and epirubicin (70 mg/m2) are given intravenously on the 1st day, bortezomib (1.3 mg/m2) is given subcutaneously on the 1st and 4th days, and prednisone (100 mg) is given orally on the 1st to 5th days. The primary end point was 2-year progression-free survival (PFS), and the secondary end point was objective response rate (ORR), including complete response (CR) and partial response (PR); Total survival (OS) and security.

Results: At present, 23 patients were enrolled, the median age was 55 years (25-74 years). By February 2023, 15 patients had completed all six courses of treatment; 6 patients completed 4 courses of treatment; Two patients stopped treatment by themselves, and 22 patients could evaluate the curative effect. Sixteen patients (72.7%) and five patients (22.7%) achieved CR/CRu and PR respectively. PFS and OS were 82.2% and 82.0% respectively in two years. Among the 13 patients who have completed all the treatment, the common therapeutic adverse events are anemia (73.9%), gastrointestinal reaction (52.2%), thrombocytopenia (30.4%), pulmonary infection (21.7%), neurotoxicity (8.7%), rituximab-related rash (8.7%).

Conclusions: VR-CAP first-line treatment of lymphoma in the marginal region has a good effect, the objective response rate (ORR) is 95.5%, and the patient is well tolerated. All adverse events are mainly 1-2 grades.

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835P A safe and effective immunochemotherapy with oral sobuzoxane and etoposide for untreated diffuse large B cell lymphoma patients aged 80 and over

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Background: Very old patients usually have various comorbidities, poor performance status and poor frailty. Therefore, as patients get aged, they generally tend to be intolerable to intensive chemotherapy. In Japan, sobuzoxane, which is an oral anti-cancer drug that inhibits DNA topoisomerase II, was approved in 1994 and has been used for patients with lymphoma. Thus far, we have treated lymphoma patients with an attenuated chemotherapy, oral sobuzoxane and etoposide plus rituximab (R-PVP).

Methods: We retrospectively analysed 30 patients aged 80 and over who were newly diagnosed with diffuse large B-cell lymphoma (DLBCL) and initially treated with R-PVP therapy from 2008 to 2022.

Results: The median age of the patients was 84 years (range, 80-93). The median number of Charlson Comorbidity Index (CCI) was 4 (range, 2-11). Median four doses of both sobuzoxane 400 mg and etoposide 25 mg were orally administered every other day per cycle, and rituximab 375 mg/m^2 intravenously once. Patients received a median of six cycles of R-PVP at a four-week interval. With a median follow-up of 26.4 months (range, 5.4-72.9), median progression 'free survival (PFS) and overall survival (OS) time was 13.9 and 32.0 months, with a 5-year PFS and OS rate of 24% (95% CI, 8-46%) and 28% (95% CI, 10-49%), respectively. The most frequent grade 3 or 4 adverse event was neutropaenia (53%). No deaths were documented due to the toxicities of the treatment. A multivariate logistic regression analysis revealed that serum LDH value of >=1.5x upper limit of normal was the only unfavourable variable for both PFS and OS in R-PVP therapy (PFS: hazard ratio (HR), 5.60; 95% CI, 1.64-19.11; $p = 0.006$; OS: HR, 4.83; 95% CI, 1.22-19.17; $p = 0.025$). In a cohort of 20 patients who underwent R-PVP and 25 R-miniCHOP over the past decade, using the Kaplan-Meier method, there were no statistical differences between the groups regarding PFS and OS (median PFS: R-PVP 9.3 months vs. R-miniCHOP 26.4 months, $p = 0.307$; median OS: R-PVP not reached (NR) vs. R-miniCHOP NR, $p = 0.375$).

Conclusions: Our findings may suggest that R-PVP therapy is one of safe and effective treatments for a subgroup of patients, *i.e.* those who have high CCI or low tumour burden, among untreated DLBCL patients aged over 80.

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836P EX103, a re-designed CD20xCD3 bispecific antibody, showed a favorable safety and potent single-agent antitumor activity in heavily pretreated relapsed/refractory patients with B cell non-Hodgkin lymphoma

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Background: In recent years, T cell engaging bispecific antibody emerged as a promising therapy in relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL). However, severe cytokine release syndrome (CRS) remains to be a significant challenge in TCB treatment. To overcome this issue, we re-designed a new CD20xCD3 bispecific antibody (EX103) with a much lower affinity to CD3. The new molecule induced significantly lower IL-6 release in preclinical tox study. Preliminary EX103

phase I dose escalation data demonstrates a favorable safety and a promising single-agent antitumor activity, in heavily pretreated R/R B-NHL patients.

Methods: The dose-escalation part (8 cohorts ranging from 1.2 to 36 mg) of this phase I, multicenter, single-arm, open-label clinical trial has enrolled at 4 study sites in China. Objectives include safety, dose finding (RP2D), and antitumor activity. Eligible patients received intravenous(iv) step-up doses of EX103 (with 1 priming dose and 2 intermediate doses followed by 1 target dose) in a 28-day dose limiting toxicity (DLT) period, and then a target dose every 2 weeks for up to 24 cycles or until disease progression or unacceptable toxicity. As of July 2023, 5 cohorts were completed.13 patients were evaluable. The median number of prior lines of treatment was 5 (2−8).

Results: Maximum tolerated dose was not reached. The most common adverse events were CRS and pyrexia, all were grade (Gr) 1-2, no Gr 3 or higher. Most CRS occurred in 1st or 2nd cycle, and resolved within 48 hours. No neurologic AE occurred. In DLBCL patients received EX103 ≥6mg (n=4), the overall response rate (ORR) was 75.0%, including 3 Complete Response (CR) (1 each in 6 or 12 or 18 mg) . In FL/MZL patients ≥6mg (n=4), ORR was 100.0%, 3 FL (1 each in 6 or 12 or 18 mg) and 1 MZL (12 mg) achieving Partial response (PR). 1 MCL patient (3mg) achieved CR. 1 CLL patient (3mg) achieved SD.For 2 patients who failed prior CAR-T therapy, one achieved PR (12mg) and another achieved SD (18mg). The preliminary Disease Control Rate (DCR) is 84.6% (11/13).

Conclusions: The preliminary data show favorable safety and remarkable antitumor activity, even at low doses, in heavily pretreated patients with R/R B-NHL, including those who failed prior CAR-T therapy.

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Disclosure: W. Zhang: Financial Interests, Personal and Institutional, Leadership Role: Guangzhou Excelmab Inc. D. Yang: Financial Interests, Personal and Institutional, Full or part-time Employment: Guangzhou Excelmab Inc. J. Lu, J. Li, Y. Cheng, Y. Li: Non-Financial Interests, Personal and Institutional, Full or part-time Employment: Guangzhou Excelmab Inc. All other authors have declared no conflicts of interest.

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837P Phase II study of anbal-cel, novel anti-CD19 CAR-T therapy with dual silencing of PD-1 and TIGIT: Drug characteristics, immunologic and genetic biomarkers associated with treatment outcome and toxicities

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Background: Anbalcabtagene autoleucel is a novel anti-CD-19 CAR-T therapy that has shown promising clinical results, with a complete response (CR) rate of 73.7% in relapsed or refractory LBCL patients at interim analysis. This biomarker analysis aims to understand the mechanism associated with the treatment outcome.

Methods: Patients with relapsed or refractory LBCL were enrolled to receive Anbal-cel at a dose of $2x10^6$ cells/kg. Tumor biopsies were performed at baseline to assess the expression levels of CD19, PD-L1, and CD112/CD155. Peripheral blood mononuclear cell (PBMC) samples for immune phenotyping and serum sampled for ctDNA analysis were collected at day 0, 14, 28, and 3-month intervals thereafter until progression.

Results: PD-1 and TIGIT were highly expressed on baseline PBMC. PD-1 was expressed more on $CD8^+$ CAR^+ T-cells whereas TIGIT on $CD4^+$ CAR^+ T-cells. PD-1, LAG-3 and TIM-3 expressions were significantly increased from D14 at non-CR group. TIGIT expression was significantly increased at D28 at non-CR group. The non-CR group demonstrated the significantly increased level of IL-4^+/ IL-5^+ Th2 type CAR^+ T-cells whereas $GATA^+$ Th2/Tc2 type CAR^+ T-cells were significantly lower in non-CR group. Additionally, $CD57^+CD27^-CAR^+$ T-cells, a marker of terminal differentiation/ functional senescence, were significantly increased in the non-CR group from D14. CD226+ CAR+ T-cells were also significantly lower in the non-CR group. $CD45RA^+$ CAR+ $T_{EFF/EMRA}$ cells post-infusion were significantly lower in the non-CR group and $CD38^+HLA\text{-}DR^+$ CAR^+ T-cells, a marker of susceptibility of cell death, were significantly higher in the non-CR group. The activation of CAR+ T-cells measured by ICOS, 4-1BB, CD226 and CD94 was not different between the two groups. The most frequently detected mutations were related to cell cycling, epigenetic regulation, immune escape, apoptosis etc. Changes in ctDNA concentration were reversely correlated with treatment outcome.

Conclusions: Anbal-cel's unique immunologic and genetic changes demonstrated potential to correlate with treatment outcomes and warrant to confirm with more data.

Clinical trial identification: CRC01-01 (NCT04836507).

Legal entity responsible for the study: Curocell Inc.

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838P Matching-adjusted indirect comparison (MAIC) of axicabtagene ciloleucel (axi-cel) and epcoritamab (epcor) in relapsed/refractory (R/R) large B cell lymphoma (LBCL) after at least two prior systemic therapies (3L+)

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Background: Axi-cel, a chimeric antigen receptor T-cell (CAR T) therapy evaluated in ZUMA-1, and epcor, a bispecific antibody evaluated in EPCORE NHL-1, are treatments for R/R LBCL. In the absence of a head-to-head trial, we conducted an unanchored MAIC to estimate relative treatment effects of axi-cel versus epcor in 3L+ R/R LBCL.

Methods: ZUMA-1 patient-level data were matched (using a logistic propensity score model) to baseline characteristics representing pre-specified clinically relevant prognostic factors in EPCORE NHL-1 (N=157): International Prognostic Index score, ECOG performance status, disease stage, response to last therapy, number of prior lines, primary refractoriness, LBCL subtype, and prior autologous stem cell transplant. Outcomes were objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and grade ≥3 cytokine release syndrome (G3+ CRS). Neurotoxicity was not analysed as definitions differed. Relative effects were hazard/odds ratios (HR/OR). Base case analyses included ZUMA-1 pivotal Cohorts 1+2 (C12; N=101). Scenario analyses of OS and CRS added ZUMA-1 safety Cohorts 4+6 (C1246; N=182).

Results: The effective sample size (ESS) for axi-cel was 30 in the base-case (Table). Axi-cel improved PFS (median 12.5 months) versus epcor (median 4.4 months). ORR, DOR and OS results were comparable with point estimates favoring axi-cel. A higher rate of G3+ CRS was associated with axi-cel but the difference was reduced in the scenario analysis.

Table: 838P MAIC results

Outcome	Weighted axi-cel versus epcoritamab (95% confidence interval)	
	Base case (C12) ESS=30	Scenario (C1246) ESS=43
ORR OR	1.55 (0.65−3.69)	N/A
PFS HR	0.51 (0.31−0.85)	N/A
DOR HR	0.84 (0.46−1.52)	N/A
OS HR	0.77 (0.45−1.30)	0.67 (0.41−1.10)
G3+ CRS OR	5.31 (1.21−23.32)	4.43 (1.10−17.92)

Conclusions: Our MAIC suggests axi-cel may be more efficacious in terms of PFS versus epcor but with a higher risk of CRS G3+. Of note, median follow-up was short in EPCORE NHL-1 (10.7 months) compared to ZUMA-1 (60 months [C12] and 24 months [C46]) and differences in prior CAR T exposure could not be adjusted for (39% in EPCORE NHL-1 vs 0% in ZUMA-1).

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839P Matching-adjusted indirect comparison (MAIC) of axicabtagene ciloleucel (axi-cel) and glofitamab (glofit) in relapsed/refractory (R/R) large B cell lymphoma (LBCL) after at least two prior systemic therapies (3L+)

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Background: Axi-cel is a chimeric antigen receptor T-cell (CAR T) therapy evaluated in ZUMA-1 while glofit is a bispecific antibody evaluated in NP30179. Without direct evidence, we estimated relative treatment effects of axi-cel versus glofit in 3L+ R/R LBCL using an unanchored MAIC.

Methods: A logistic propensity score model was used to weigh ZUMA-1 patient-level data to match the baseline characteristics of NP30179 (N=155) on pre-specified clinically relevant prognostic factors: ECOG performance status, disease stage, response to last therapy, prior lines of therapy, lactate dehydrogenase, primary refractoriness, LBCL subtype, and prior autologous stem cell transplant. Outcomes were objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and grade ≥3 (G3+) cytokine release syndrome (CRS) and neurological events (NE). Relative effects were hazard/odds ratios (HR/OR). Base case analyses included ZUMA-1 pivotal Cohorts 1+2 (C12; N=101) while scenario analyses of OS, CRS, and NE included ZUMA-1 safety Cohorts 4+6 (C1246; N=182).

Results: Axi-cel improved ORR and PFS versus glofit (Table; effective sample size [ESS] = 32). Median PFS for axi-cel versus glofit were 15 and 11.4 months, respectively. DOR and OS were comparable with point estimates favoring axi-cel. In the scenario analysis, OS was also improved with axi-cel (ESS = 63). Axi-cel was associated with higher rates of G3+ CRS and NEs but the former was comparable in the scenario analysis.

Table: 839P MAIC results

Outcome	Weighted axi-cel versus glofitamab (95% confidence interval)	
	Base case (C12) ESS=32	Scenario (C1246) ESS=63
ORR OR	2.32 (1.01−5.33)	N/A
PFS HR	0.62 (0.40−0.96)	N/A
DOR HR	0.72 (0.35−1.48)	N/A
OS HR	0.70 (0.42−1.18)	0.63 (0.42−0.95)
G3+ CRS OR	4.93 (1.42−17.08)	2.83 (0.89−8.97)
G3+ NE OR	22.59 (7.25−70.36)	15.54 (5.53−43.63)

Conclusions: Findings suggests axi-cel may be more efficacious in terms of ORR and PFS compared to glofit but with a higher risk of certain adverse events. Of note, median follow-up was shorter in NP30179 (12.6 months) than ZUMA-1 (60 months [C12] and 24 months [C46]) and differences in prior CAR T use could not be accounted for (34% in NP30179 versus 0% in ZUMA-1).

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Disclosure: F.L. Locke: Financial Interests, Institutional, Advisory Role, Honoraria from Gilead and Pfizer; scientific advisory role and consultant to AbbVie, ADC, Curio Science, Epizyme, Gilead, Janssen, Kite, a Gilead Company, Pfizer, Nektar, Novartis, Syncopation, and TGR therapeutics: Kite Pharma. J.M. Chen, K. Chan, I. Zhang, S. Keeping: Financial Interests, Institutional, Full or part-time Employment, PRECISIONheor received consulting fees from Kite, a Gilead Company: PRECISIONheor. M.D. Ray, C. Fu, A.R. Patel: Financial Interests, Personal and Institutional, Full or part-time Employment, Is a stockholder and current employee of Kite, a Gilead Company: Kite Pharma. O.O. Oluwole: Financial Interests, Institutional, Advisory Role, Scientific advisory role and consultant to Kite Pharma, Allogene, CERo Therapeutics, Novartis, BlueBird Bio, Bristol Myers Squibb, National Cancer Institute, Leukemia and Lymphoma Society: Kite Pharma.

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840P Genomic landscape, immune characteristics and prognostic mutation signature of extranodal NK/T cell lymphoma, nasal type in China

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Background: This study aimed to obtain a deeper understanding of the molecular mechanisms underlying extranodal NK/T-cell lymphoma, nasal type (ENKTCL) by conducting Next-Generation Sequencing (NGS) of patients with ENKTCL.

Methods: This study included patients with ENKTCL who had complete tissue NGS results from two prior prospective studies. Group 1 comprised early-stage patients, while advanced-stage or relapsed patients were classified into Group 2. R language was used to visualize the mutation data.

Results: 40 out of 98 patients with ENKTCL from two prospective clinical trials were included. Group 1 comprised 67.5% (n=27) of the patients, while group 2 accounted for 32.5% (n=13). Mutations in KLRC2 (29.6%), CIITA (25.9%), KLRC1 (25.9%), ITK (18.5%) were exclusively observed in group 1, with KLRC2 mutations occurring significantly more frequently in group 1 than group 2 (P = 0.037). KMT2D and TP53 exhibited the highest mutation rates and displayed different amino acid alterations in the two groups. The top KEGG pathway enriched by mutated genes was non-small cell lung cancer in group 1, and hepatitis B pathway in group 2. Patients with JAK3 wild-type exhibited remarkably improved PFS and OS rates than those with JAK3 mutations (P = 0.003, P = 0.033). Improved OS was also observed in patients with BCOR wild-type, although no significantly difference was found in PFS (P = 0.049, P = 0.172). Patients with PD-L1-positive expression had a significantly longer OS compared to those with PD-L1-negative expression ($P = 0.037$). Patients with PD-L1 expression < 50% were more likely to have BCOR mutations (41.7% vs. 0%, P = 0.012) and JAK3 gene mutations (33.3% vs. 0%, P = 0.033) than those with PD-L1 expression ≥ 50%.

Conclusions: The present study has, for the first time, explored disparities in mutation rates, mutation sites, and associated pathways among patients with early-stage versus advanced-stage/relapsed ENKTCL. JAK3 mutations, BCOR mutations, and PD-L1-negative expression were associated with poor prognosis of ENKTCL. Patients with PD-L1 expression < 50% were more likely to have BCOR mutations and JAK3 mutations than those with PD-L1 expression ≥50%.

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841P Ki67-revised risk index to risk-stratify patients with extra-nodal natural killer/T cell lymphoma

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Background: Although several clinical parameters-based prediction indexes of extra-nodal natural killer/T-cell lymphoma (ENKTL) are proposed, these indexes include none of pathological index and had insufficient accuracy. A superior clinically feasible prediction index for ENKTL in the modern chemotherapy era is warranted.

Methods: 600 ENKTL patients receiving non-anthracycline based therapy from Sun Yat-sen University Cancer Center were subdivided into training and internal validation datasets. An external validation dataset included 191 patients from West China Hospital was enrolled. Ki67 proliferative index and 14 pretreatment clinical parameters were tested against overall survival (OS) and progression-free survival (PFS). A prediction model was constructed and validated.

Results: Factors independently associated with inferior OS were as follows: Ki67 ≥ 70%; age > 60 years; ECOG PS ≥ 2; B symptoms; stage-III/-IV disease and detectable EBV-DNA copy number. Each of these six factors contributed one point to a prediction model that stratified patients into four risk groups: 0-1 point, low-risk; 2 points, intermediate-risk;3 points, intermediate high-risk; 4-6 points, high-risk. In the training dataset, the 5-year OS rates were 91%, 75%, 65% and 26% for the low-, intermediate-, intermediate high- and high-risk group, respectively ($P < 0.001$). The 5-year PFS rates were 79%, 62%, 48% and 15%, respectively ($P < 0001$). The time-dependent area under the receiver-operator characteristic (AUROC) curve and Harrell's C-statistic of Ki67-revised Risk Index (KRI) for OS and PFS prediction demonstrated a better performance than that of the international prognostic index (IPI), Korean prognostic index (KPI), prognostic index of natural killer lymphoma (PINK) and nomogram-revised

risk index (NRI). Concordant results were successfully validated in both internal and external validation datasets.

Conclusions: KRI is a new promising prediction index to risk-stratify patients with ENKTL receiving non-anthracycline based therapy.

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842P Multicenter real-world study of newly diagnosed advanced-stage extranodal natural killer/T cell lymphoma (ENKTL): Proposal for intensive therapy

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Background: Advanced-stage ENKTL is characterized by its low prevalence, poor prognosis, and inconclusive optimal therapy. This study investigated the treatment of newly diagnosed advanced-stage ENKTLs.

Methods: Newly diagnosed stage III/IV ENKTL patients from two large Chinese cancer centers in the last 10-15 years were retrospectively analyzed.

Results: With a median follow-up of 75.03 (range, 0.33-292.13) months, the median overall survival (OS) for the 195 newly diagnosed stage III/IV ENKTL patients was 19.43 (range, 0.33-292.13) months, and estimated 1-, 2-, 3-, and 5-year OS were 59.5%, 46.3%, 41.8%, and 35.1%, respectively. First-line multi-modality therapy prolonged OS compared to single-modality therapy ($P<0.001$). Chemotherapy (CT)+radiotherapy (RT) compared to CT alone ($P=0.007$), and hematopoietic stem cell transplantation (HSCT) compared to non-HSCT ($P<0.001$) both significantly improved OS. For patients $\leq$60 years yet ineligible for HSCT, other therapies with complete remission led to comparable OS ($P=0.141$) with no significant differences in baseline features. Patients treated with chidamide maintenance therapy (MT) achieved a median progression-free survival (PFS) of 55.83 (range, 53.27-92.33) months and a median OS of 60.65 (range, 53.70-95.70) months. Non-anthracycline (ANT)- compared to ANT-, asparaginase (ASP)- compared to non-ASP-, and gemcitabine (GEM)- compared to non-GEM-based CT regimens, led to prolonged PFS ($P=0.031$; $P=0.005$; $P=0.009$) and OS ($P=0.010$; $P=0.086$; $P=0.003$), respectively. GEM+ASP combinations slightly improved PFS and OS compared to regimens containing GEM or ASP alone ($P>0.05$). GEM+ASP combinations led to significantly superior PFS ($P=0.058$ [log-rank], $P=0.036$[Breslow]) and OS ($P=0.008$) compared to ANT+ASP regimens. First-line intensive therapy, including CT, RT, HSCT, and chidamide MT, was therefore proposed and could improve long-term survival for advanced-stage ENKTLs.

Conclusions: We propose the first-line intensive therapy for newly diagnosed advanced-stage ENKTLs, including CT, RT, HSCT, and chidamide MT. GEM+ASP combinations appear to yield the optimal efficacy and survival. RT, consolidative HSCT, or chidamide MT are recommended.

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844P Progression -free survival prediction of multiple myeloma patients in five European countries using machine learning models

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Background: The objective of this study is to apply machine learning (ML) models to multiple myeloma(MM) patient-level data to evaluate if ML models can identify high-risk features linked to faster disease progression.

Methods: Data for 15,931 MM patients in France, Spain, UK, Germany, and Italy were extracted from Oncology Dynamics (OD), a large cross-sectional survey that collects drug-treated patient-level data through a panel of cancer specialists. The analyses include 6 years (2017-2022) of records. Progression-free survival (PFS) was measured as the time from start of therapy to date of progression. The underlying data included treatment regime, line of therapy (LOT), ECOG status, stem cell transplant (SCT) eligibility, Durie-Salmon stage, cytogenetic risk, and age and gender. Machine Learning-based survival models (Gradient Boosted Survival Trees, Random Survival Forest) were applied to predict outcomes. Additionally, Shapley values were calculated to assess the model's decision making and identify key risk drivers.

Results: Data was split into Training (80%) and Test Data (20%). The output of the model was the ML derived risk score: higher risk score was associated with shorter PFS. Model performance was good (Harrell's C-Index = 0.741). Data shows that higher LOTs and not being eligible for SCT are associated with increased risk of disease progression. Inversely, being in the 1st LOT, ECOG asymptomatic and certain drug regimens (e.g., Lenalidomide or Dexamethasone/Lenalidomide) are associated with longer PFS.

Conclusions: This is a first successful step in leveraging OD data for the development of a prognostic score for MM patients using machine learning algorithms. ML models applied to secondary market research can support optimal disease management and planning of clinical trials. Also, given the heterogeneity of treatment plans across Europe, further investigation into country-specific differences in PFS may be studied.

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845P A machine learning based clinical platform for cancer subtyping and data integration in hematological malignancies

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Background: Next Generation sequencing (NGS) has greatly advanced precision oncology. The growing amount and complexity of NGS data, along with other clinical data such as drug responses and measurable residual disease (MRD), present a big challenge for data integration and interpretation. Machine learning, especially deep neural networks, offer a promising approach for efficiently analyzing intricate relationships within large datasets, with the potential of improving clinical outcomes.

Methods: We performed targeted RNA sequencing in routine diagnostics and sequenced 1849 cases with hematological neoplasms, primarily pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL). We used featureCounts in megSAP pipeline and Uniform Manifold Approximation and Projection (UMAP) to analyze the gene expression data, and Bokeh to create the web interface for data integration and visualization. Scikit-learn and PyTorch were used to develop shallow machine learning models and deep learning neural networks (NN), respectively.

Results: Our platform integrates various genetic and clinical data based on UMAP analysis of gene expression patterns. It improves the point-of-care decision making and facilitates the discovery of new patterns such as subpopulations with different genetic and clinical features. The platform is supported by machine learning algorithms for cancer subtyping. Six basic machine learning algorithms were coupled with feature selection methods and the best F1 score achieves 98%. We also built a biologically informed deep NN that can accurately predict BCP-ALL subtypes (F1=97%) with a good interpretability, which helps to identify crucial genetic aberrations associated with disease subtypes.

Conclusions: Our machine learning based platform can not only provide support for clinical decision-making but also bring novel translational insights for hematological malignancies.

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846P Artificial intelligence-driven identification of onco-hematology patients who may develop severe COVID-19

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Background: The widespread implementation of COVID-19 vaccines achieved a great success in the general population. However, an unmet medical need exists for onco-hematological and other immunocompromised patients for whom vaccines may not provide optimal protection. Identifying these patients to consider additional layers of protection, including passive immunization with monoclonal antibodies, has been a challenge. Herein, we propose an artificial Intelligence (AI) driven methodology to aid the identification of patients at risk of severe COVID-19 via a minimal number of variables.

Methods: A multi-centric training (340 patients) and an external testing (103 patients) retrospective cohort with homogeneous population characteristics were built. Inclusion referred to hematological or lung cancer patients with COVID-19 infection and absence — except vaccination — of any COVID-19 preventive treatments. The E-CRF included 70+ clinical and demographic variables. Patients were classified into two different COVID-19 severity populations, mild and moderate/severe, based on oxygen support. We sought to identify (i) the minimal set of independent variables (signatures) characterizing these populations, and (ii) the best AI solution acting on these signatures to predict the severity of infection via an end-to-end integration of statistical importance and AI methods.

Results: Using the training cohort we identified 7 variables (age and cancer stage ranked as most important) enabling the prediction of moderate/severe cases with a balanced accuracy of 72% (AUC 0,76) on the internal cohort. The model performed equally well on the external testing cohort yielding a similar balanced accuracy of 73% (AUC 0,77). Most importantly the model reached a 85% performance on the severe cases.

Conclusions: The conducted analysis leads to promising insights towards identifying onco-hematological patients who are most vulnerable to develop severe COVID-19. This may help to offer additional prevention strategies to protect them from COVID-19 and can potentially be further extended to other immunocompromised populations.

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847P Fatal infections among leukemia patients

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Background: Infection is an important cause of death in patients with leukemia, while no studies have reported its incidence. We conducted a population-based analysis of fatal infections in patients with leukemia to analyze trends and address the current lack of evidence.

Methods: Data were collected from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program registries. SMR was estimated as the ratio of the number of leukemia patients with fatal infections to the number of fatal infections in the general population with similar age, sex, race and calendar year distribution.

Results: Of 137820 leukemia patients, 2863 had a fatal infection. The fatal infection rate per 100,000 person-years was 389.32 and the SMR was 3.38 (95% CI 3.67-3.99, $p < 0.05$). Patients with acute monocytic leukemia had the highest SMR (SMR=89.01;95% CI 50.87-144.54). SMR for fatal infections decreases gradually with age, with the highest being in patients aged 0-19 years SMR=222.47; 95% CI 183.18-267.69). Notably, the risk of fatal infections continues to rise in patients with leukemia compared to the general population, with the highest risk in patients diagnosed in 2011-2018 (SMR= 9.87; 95% CI 8.58-11.30).

Conclusions: The risk of fatal infections has increased in recent years with the introduction of novel drugs. Prevention and treatment of fatal infections remains an important aspect of improving the overall survival. Close monitoring of patients with acute monocytic leukemia, as well as younger patients, should be considered for the timely administration of antibiotics and modification of chemotherapy regimens.

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848P Mortality after rasburicase vs allopurinol anti-hyperuricemia monotherapy in patients with liquid tumors

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Background: This observational real-world study used propensity score matching (PSM) to compare tumor lysis syndrome (TLS) associated mortality in patients (pts) with hematological malignancies who received either rasburicase or allopurinol monotherapy. Goldman/Cairo previously published that rasburicase significantly, more rapidly reduces uric acid exposure (AUC) compared to allopurinol in pts with/at risk of TLS.

Methods: In 2021, 266 oncologists provided anonymized data for 715 liquid tumor pts treated in past year for hyperuricemia (HU) risk and TLS potential. Out of 715, 282 rasburicase and allopurinol pts without spontaneous TLS or TLS before HU treatment (Tx) were matched using 11 pre-HU Tx covariates: acute renal failure, age, anti-cancer Tx, creatinine, gender, LDH, perceived risk, renal disease, tumor type, uric acid, and white blood cells. Matched pts met 1:1, nearest neighbor, caliper matching requirements (width=0.2) of standard deviation of logit of the PSM (d score) on covariates, regardless of whether pts later developed TLS post-HU Tx. Assessments include mean uric acid (UA) levels, anti-cancer Tx, and, as feasible, timing of death relative to HU Tx.

Results: The PSM was almost 0.6 before and near 0 after matching; no covariate had a large imbalance ($|d| > 0.25$) before and after. Of 141 pts in each pt group, TLS-associated mortality was significantly less likely among rasburicase pts (2.1% [$n = 3$] vs. 7.1% [$n = 10$], $P = 0.047$) (71% reduction). Of 63 pt subset who developed TLS after HU Tx, TLS-associated fatalities were even less likely among rasburicase vs. allopurinol pts (8.3% [$n = 3$] vs. 37% [$n = 10$], $P = 0.005$). Comparing 13 who died vs. 269 who lived, no significant difference in mean UA was found (13.5 mg/dL vs. 11.4, respectively). Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone regimen (R-CHOP) was the predominant Tx among those who did not die (15%, $n = 41$). Only 1/13 pts died of R-CHOP. Seven pts died within 2 weeks of allopurinol ($n = 6$) or rasburicase ($n = 1$) monotherapy (timing not established for other 6).

Conclusions: PSM corrects before and after overall covariate and individual baseline covariate imbalances and rasburicase compared with allopurinol significantly reducing TLS-associated mortality.

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849P Long non-coding RNA signatures and their role in the progression of childhood T cell acute lymphoblastic leukemia

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Background: Many disease processes are thought to be impacted by altered long non-coding RNAs (lncRNAs) expression. lncRNAs are typically expressed differently throughout healthy and cancerous hematopoiesis. In the domains of haematology and oncology, they represent a class of biomarkers that is receiving increasing attention. According to recent studies, the expression levels of particular lncRNAs are correlated with the prognosis of paediatric patients with acute lymphoblastic leukaemia. To determine the potential roles of lncRNAs involved in pathogenesis of T-ALL, we analyzed the expression profile of lncRNAs in pediatric T-ALL.

Methods: Twenty five pediatric T-All patients were enrolled and subjected to whole transcriptome analysis in comparison with healthy controls. The results from NGS were validated ex vivo, using real time PCR in the same cases and in a different cohort of 25 T-ALL cases and healthy controls. The results were also comapred with public databases in silico. Potential functions of subtype-specific lncRNAs were determined by using coexpression-based analysis on distally (trans-pattern) located protein-coding genes.

Results: A total of 672 differentially expressed lncRNAs were identified. Moreover, the top 10 upregulated lncRNAs were selected and further assessed by RT-qPCR in vitro in the same samples and a different cohort. We found that lncRNAs LINC01221, LINC00977, RP11-472G21.2 and CTD-2291D10.4 were highly over expressed (>10 fold) in the patients while PCAT18, CRNDE, and RP11-620J15.3 showed mild overexpression (2 to 5 fold increase). The expression of these lncRNAs were also increased in Peer and CCRF-CEM cell lines. Finally, expression correlation analyses using weighted gene co-relation analysis of T-ALL selected lncRNAs and mRNAs suggested that lncRNAs LINC01221, LINC00977, CTD-2291D10.4 may play a possible role in lymphocyte activation and cell.

Conclusions: These results showed that several lncRNAs are aberrantly expressed in T-ALL patients and play potential roles in T-ALL development, and can be useful for diagnostic and/or prognostic purposes in pediatric T-ALL. This study provides the keystone to future clinical studies determining the theragnostic value of the characterized long non-coding transcriptome panorama in a clinical setting for childhood patient management.

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850P A zebrafish model of MYC-driven acute myeloid leukemia reveals that neutrophil resistance to oncogenic transformation depends on their ability to promote PP2A-mediated MYC proteasomal degradation

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Background: Acute Myeloid Leukemia (AML) is the most common acute leukemia in adults. The origin can be found in chromosomal translocations as well as in accumulated mutations in genes involved in hematopoietic proliferation and differentiation. Despite being considered a heterogeneous malignancy, AML possesses many genetic aberrations, including the overexpression of MYC and the downregulation of PP2A, both essential regulators of cell proliferation, apoptosis, and differentiation, and they, directly and indirectly, regulate each other's activity. We have generated a zebrafish model of MYC-driven AML to rapidly test the effects of different drugs in tumor development.

Methods: After the generation of a transgenic zebrafish line expressing the human MYC under the control of the neutrophils-specific promoter lysozyme (*lyz:hMYC*), we checked the expansion of neutrophils in whole larvae and the colonization of the adult hematopoietic organ. We investigated the effects of chemical manipulation of PP2A activity on neutrophil expansion and on MYC phosphorylation and degradation. Single-cell RNA sequencing analysis has been performed to shed light into the mechanisms of PP2A/proteasomal-mediated degradation of oncogenic MYC in AML.

Results: *In vivo* imaging of whole larvae revealed a robust expansion of neutrophils in zebrafish larvae which expressed MYC from 3 to 8 days post-fertilization (dpf). Surprisingly, the neutrophil number gradually returned to normal levels from 10 dpf onwards, coinciding with degradation of MYC. Pharmacological inhibition of the proteasome resulted in the stabilization of MYC protein and further expansion of transformed neutrophils. Similarly, inhibition of PP2A phenocopied the effects of proteasome inhibition. Otherwise, pharmacological activation of PP2A prevented neutrophil expansion and increased phosphorylation of S62 and T58 of MYC, suggesting a critical role PP2A in MYC proteasomal degradation.

Conclusions: Our results show that PP2A critically regulates MYC degradation in neutrophils preventing their oncogenic transformation. In addition, the zebrafish model of AML is a unique tool for chemical screening.

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851P Characterization of a zebrafish model of MYC-driven acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) is a clonal malignancy of the stem cell precursors of the myeloid lineage associate with uncontrolled proliferation and impaired differentiation of hematopoietic stem cells. Among the different genes found amplified in AML, the oncogene MYC is one of the prognostic factors with an impact of AML. Albeit MYC is a well know factor associated with the uncontrolled proliferation of AML, the mechanism that led to the oncogenesis established by MYC are not well known. Zebrafish has recently emerged as a valid model organism to study cancer development because of its genetic accessibility.

Methods: After the generation of a transgenic zebrafish line expressing the human MYC under the control of the neutrophils-specific promoter lysozyme (*lyz:hMYC),* we proceeded with FACS analysis of adult whole kidney marrow (WKM) of *lyz:hMYC* fish. Immunohistochemical analysis (IHC) of whole zebrafish was made to check the infiltration of cells and possible metastasis. May-Grunwald stain was made to check the kidney marrow population. Gene expression profile of WKM was performed to check the expression of genes associated with *myc* and its patthway. We conducted a Metagenomic analysis on possible variations in the intestinal microbiota associated with the disease causing its progression.

Results: FACS analysis of lyz:hMYC zebrafish revealed the expansion of myeloid cells with a significant reduction of erythroid cells, associated with anemia. The IHC analysis of whole lyz:hMYC zebrafish showed infiltration of myeloid cells into different organs confirming that those cells can proliferate unconditionally and metastasise. May-Grunwald analysis showed a higher number of blast cells unable to differentiate towards mature granulocytes in lyz:hMYC zebrafish than in their wild type siblings. The gene expression profile of WKM demonstrated the overexpression of exogenous MYC and of endogenous myc, suggesting a positive auto-regulation of MYC. Metagenomic analysis revealed that the gut microbes of AML fish were significantly altered with the possibility to be associated the progression of AML.

Conclusions: The model developed here is an excellent tool to further understand the mechanisms involved in MYC-induced AML and the relevance of gut microbiota on this disease.

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852P c-MAF-driven metabolic reprogramming mediates H3K27 hyperacetylation to regulate super enhancer-associated genes

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Background: Overexpression of transcription factor c-MAF is found in about 50% of multiple myeloma cases, and associated with the prognostically unfavorable t(14;16) translocation subtype. Genetic alterations can modify the epigenome through metabolite availability that act as substrates in histone modifications, but how this translates into specificities in gene regulation is unclear.

Methods: We integrated a multi-omics approach using metabolome profiling to characterize the metabolic phenotype and RNA-sequencing to identify key metabolic genes as a means to uncover novel associations involved in the distinct reprogramming of t(14;16) metabolism.

Results: Here, we report a novel involvement of c-MAF in metabolically-driven histone acetylation, including the superenhancer mark H3K27ac, through altering acetyl-CoA metabolism. To sustain high levels of acetylation, c-MAF acquired the metabolic flexibility to utilize glutamine in addition to glucose, feeding into the tricarboxylic acid (TCA) cycle as acetyl-CoA sources. Loss-of-function studies indicated that c-MAF is important for citrate-derived acetyl-CoA and H3K27ac levels through metabolic enzymes citrate synthase (CS) and ATP-citrate lyase (ACLY). Furthermore, blocking citrate export from mitochondrial via CRISPR/Cas9 targeting of SLC25A1 reproduced the reductions in H3K27ac. Silencing of c-MAF also displayed defective mitochondrial oxidative phosphorylation attributed to reduced metabolic flux through TCA cycle and downregulation of electron transport chain complex I/II expression, without affecting mitochondrial DNA content. To identify c-MAF-regulated superenhancer genes, we overlapped our previously published H3K27ac ChIP-seq dataset on t(14;16) MM cell lines with c-MAF RNA-seq data. We found signal enrichment of H3K27ac at ZC3H3 locus responsible for its transcriptional upregulation, and knockdown of ZC3H3 inhibited cell growth specifically in the t(14;16) subtype.

Conclusions: Altogether, we demonstrated a non-canonical c-MAF role in epigenetics that is connected to its altered metabolic state, and suggest metabolic disruptions as a new therapeutic direction in t(14;16) myeloma.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

HEAD AND NECK CANCER, EXCL. THYROID

853O OMITting frontline chemotherapy in head and neck cancer (HNSCC) patients with 1-3 oligometastases using stereotactic ablative radiotherapy (SABR), the GORTEC 2014-04 "OMET" randomized phase II trial

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Background: Most trials in metastatic HNSCC compare systemic therapies; HNSCC were underrepresented in the few multihistology SABR trials; none has assessed SABR-alone vs chemo-SABR in often frail/heavily-pretreated HNSCC patients. The GORTEC 2014-04 phase IIR study assesses impact on survival without definitive quality of life (1yOS-QoL) deterioration of omitting frontline chemotherapy in oligo-metastatic HNSCC patients (pts) by using SABR alone.

Methods: SABR-alone (experimental arm) or chemo (SOC Extreme)-SABR to 1-3 metastases (mets) was evaluated using survival, PFS, definitive QoL deterioration (global, 10 points), toxicities (highest-grade/patient), QoL dimensions. Salvage treatments were left to physician's appreciation (repeat SABR allowed).

Results: 69 pts treated at 11 centers in 2016-22, male 81.2%, mean age 62.7, had lung-only mets in 57 (82.6%), isolated mets in 40 (58.0%). Median baseline global QoL score was 66.7 (Q1-Q3 50.0-83.3). Of 57 pts eligible for 1yOS-QoL (QoL & follow-up missing in 10 & 2 pts/69), it was equivalent in both arms, with better Kaplan-Meier estimates of physical functioning & cough score deterioration-free survival with SABR-alone. In ITT analysis (69 pts), 1-year & median survival were 63.4 (95%CI 47.6-84.5), 47.2 with SABR-alone vs 61.7 (CI 46.2-82.4) & 42.3 months (m) with chemo-SABR. Median follow-up was 55.3m (CI 42.5-72.1) & 45.4m (CI 36.7-69.1) in the SABR-alone & chemo-SABR arms. One-year PFS rate were 38.2% with SABR-alone & 53.3% with chemo-SABR (1st CT done earlier in SABR-alone arm, p NS). Following relapse (N=58, 48 pts), 16 (10 in chemo-SABR, 6 SABR-alone arms) new out-of-field lesions and 1 in-field (in SABR-arm) mets were retreated with SABR-alone (17/58, 29.3%). Rates of all grade toxicities were 43/69 (62.3%): 10/34 (29.4%) with SABR-alone & 33/35 (94.3%) with chemo-SABR. Rates of severe G3-4 toxicities were 24/69 (34.8%): 2/34 (5.9%) with SABR-alone & 21/35 (60.0%) with chemo-SABR.

Conclusions: Omission of frontline chemotherapy in oligometastatic HNSCC pts led to lower severe toxicity rates, similar rates of survival & 1yOS without QoL deterioration. Medicoeconomic results will be provided.

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854O INTERLINK-1: Phase III study of cetuximab (CTX) ± monalizumab (M) in participants (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) with disease progression on/after platinum chemotherapy (CT) and previously treated with an immune checkpoint inhibitor (ICI)

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Background: First-line (1L) treatment for R/M HNSCC includes ICI +/- CT or CT + CTX. Treatment after 1L failure is not clearly defined. Preliminary data suggest M (anti-NKG2A) + CTX may have clinically useful antitumour activity in R/M HNSCC.

Methods: In INTERLINK-1 (NCT04590963), pts with incurable R/M HNSCC (oral cavity/oropharynx/hypopharynx/larynx) were randomised 2:1 to M (750 mg IV Q2W) or placebo (P) + CTX (400 mg/m^2 IV then 250 mg/m^2 IV Q1W). Primary endpoint was overall survival (OS) in pts with human papillomavirus unrelated (uHPV) cancer (any non-oropharyngeal cancer [OPC] and HPV negative OPC). Secondary endpoints included OS in the full analysis set (FAS; includes uHPV and HPV positive OPC); progression-free survival (PFS) and objective response rate (ORR) in the uHPV set and FAS; and safety in all pts who received study treatment (safety analysis set [SAS]). Futility was assessed at interim analysis 1 (IA1) with 25% information fraction.

Results: At data cut-off (IA1 11 May 2022), 175 and 89 pts in the FAS (N=264) and 145 and 71 pts in the uHPV set (N=216) were randomised (on/before 11 March 2022) to M + CTX and P + CTX, respectively. OS hazard ratio (HR) for M + CTX vs P + CTX in the uHPV set was 1.00 (95% confidence interval [CI], 0.66−1.54; p=0.989) and in the FAS was 1.03 (95% CI, 0.70−1.53; p=0.891; Table). PFS HR was 1.11 (95% CI, 0.79−1.57) in the uHPV set and 1.11 (95% CI, 0.82−1.51) in the FAS. ORR was numerically higher with P + CTX vs M + CTX; duration of response (DoR) was similar between arms. M + CTX was tolerable.

Table: 854O

	uHPV		FAS		SAS	
	M + CTX; N=145	P + CTX; N=71	M + CTX; N=175	P + CTX; N=89	M + CTX; N=246	P + CTX; N=122
m duration of follow-up, mo; IQR	7.16; 5.16–12.16	8.38; 4.99–11.96	7.16; 4.93–12.16	8.38; 4.80–10.87		
OS						
Events, n; %	67; 46.2	34; 47.9	82; 46.9	40; 44.9		
m, mo; 95% CI	8.8; 6.9–10.4	8.6; 6.0–14.5	8.8; 6.9–10.8	8.9; 6.0–15.1		
PFS						
Events, n; %	106; 73.1	52; 73.2	132; 75.4	68; 76.4		
m, mo; 95% CI	3.6; 3.1–3.7	3.8; 2.4–4.9	3.5; 2.3–3.7	3.7; 2.2–4.2		
ORR, %	15.2	23.9	13.1	19.1		
OR; 95% CI; p	0.56; 0.27–1.15; p=0.115		0.60; 0.30–1.23; p=0.162			
Complete response, %	1.4	1.4	1.1	1.1		
mDoR, mo; IQR	5.7; 5.5–8.1	5.6; 4.4–NR	5.7; 5.3–8.1	5.6; 4.4–NR		
Grade 3/4 AEs, %					38.6	30.3
AEs leading to treatment discontinuation, %					5.7	1.6

AE, adverse event; IQR, interquartile range; m, median; mo, months; NR, not reached; OR, odds ratio.

Conclusions: In this incurable pt population previously treated with CT and ICI, M + CTX did not improve OS compared with P + CTX. The safety profile was acceptable. ORR with P + CTX was higher than previous reports.

Clinical trial identification: NCT04590963.

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857O MACH-EGFR: Individual patient data (IPD) meta-analysis of anti-EGFR monoclonal antibodies (Ab) in patients (pts) with locally advanced (LA) squamous cell carcinomas of head and neck (SCCHN)

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Background: The epidermal growth factor receptor (EGFR) pathway is involved in HNSCC progression. Multiple trials have studied anti-EGFR Ab combined to locoregional treatment (LRT) in LA HNSCC with conflicting results. We report the results of the IPD meta-analysis.

Methods: Randomized trials in pts with LA HNSCC comparing curative LRT +/- chemotherapy (CT) vs same treatment + anti-EGFR Ab (comparison 1) or LRT + CT vs LRT + anti-EGFR Ab (comparison 2) and that completed enrolment before 2019 were eligible. IPD were collected and combined using fixed-effect models. Overall survival (OS) was the main endpoint. Data on locoregional/distant progressions and toxicity were also collected.

Results: The table presents trials/pts' characteristics. In comparison 1, the addition of anti-EGFR Ab did not significantly increase OS with a pooled HR of 0.92 (95%CI 0.82;1.03), p=0.13. Differences were seen according to type of Ab: HR (95%CI) was 0.85 (0.73;1.00) for cetuximab, 0.82 (0.66;1.01) for nimotuzumab, 1.59 (0.89;2.85) for panitumumab, 1.21 (0.92;1.58) for zalutumumab. Younger pts (<50 years) benefited more from addition of anti-EGFR Ab. Interaction with p16 in oropharyngeal cancer (OPC) will be presented at the meeting. In comparison 2, anti-EGFR Ab was significantly associated with decreased OS compared to CT, with a pooled HR of 1.21 (95%CI 1.05;1.39), p=0.007, corresponding to an absolute OS decrease of 4.5% at 3 years. Administration of induction CT (ICT) could influence HR: 1.04 (0.84;1.29) in case of ICT vs 1.36 (1.13;1.63) in absence of ICT (p=0.07). Benefit of CT over anti-EGFR Ab on OS was higher in females and in OPC than in other sites.

Table: 857O

Trials	Comparison 1	Comparison 2
	Nb trials (Nb pts)	
	9 (3097)	10 (3036)
Anti-EGFR Ab		
cetuximab	5 (1686)	8 (2565)
nimotuzumab	2 (642)	0
panitumumab	1 (150)	2 (471)
zalutumumab	1 (619)	0
Patients/tumors	**Nb pts (%)**	
Male	2617 (85%)	2602 (86%)
< 60 years	1854 (60%)	1700 (56%)
≥ 60 years	1243 (40%)	1336 (44%)
ECOG PS		
0	1861 (60%)	2181 (72%)
1	1185 (38%)	847 (28%)
2	33 (1%)	4 (<1%)
Location		
Larynx	691 (22%)	219 (7%)
Hypopharynx	437 (14%)	295 (10%)
Oral cavity	89 (3%)	185 (6%)
Oropharynx	1875 (61%)	2329 (77%)
p16 positive/negative/UK	631/413/831	1784/100/445
Stage (AJCC 7)		
I-II	67 (2%)	15 (<1%)
III	552 (18%)	383 (13%)
IV	2476 (80%)	2634 (87%)
Median follow-up (years)	4.0	3.9
Number of deaths (% of pts)	1209 (39%)	798 (26%)

Conclusions: There was no survival benefit with the addition of Ab to LRT for either comparison. Importantly, replacing CT with anti-EGFR Ab, as systemic treatment added to LRT, results in inferior survival.

Clinical trial identification: *PROSPERO: CRD42017056939.*

Legal entity responsible for the study: MACH-EGFR collaborative group.

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858O Minimal residual disease (MRD) diagnosed by a plasma tumor-agnostic circulating tumor DNA (ctDNA) assay after curative therapy in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN) predicts disease relapse and survival

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Background: 40-50 % of patients (pts) with LA SCCHN recur despite multimodal treatment. ctDNA has the potential to detect MRD and predict clinical outcome. SCCHN is a heterogenous disease with genomic alterations that occur mostly in tumor suppressor genes, making ctDNA detection challenging. We developed a plasma tumor-agnostic ctDNA assay to detect MRD in HPV-positive and negative SCCHN, without the need of tumor sequencing.

Methods: A 26-gene NGS panel was constructed that included the most frequently mutated genes in SCCHN and two HPV type 16 genes. ctDNA was sequenced with the addition of unique molecular identifiers to reach a mean read depth above 2000x. MRD was detected through an in-house personalized informatic workflow, informed by the somatic mutations identified in the pre-treatment plasma samples. The presence of MRD was defined as detection of ctDNA in one plasma sample collected within 6-12 weeks after the end of the curative treatment. Primary endpoint was the PFS rate at 2 years with a least 32 pts to be included with the hypothesis that 2y-PFS rate was >80% in MRD-negative pts and <30% in MRD-positive pts (α= 0.05, β= 0.9).

Results: The DNA from 176 plasma samples were sequenced, from 53 LA SCCHN pts who underwent curative-intent treatment. ctDNA was detected in 41/53 (77%) patients in the pre-treatment samples. The most frequent variants were found in *TP53* (67%) and *NOTCH1* (38%). Out of these 41 patients, 17 (41%) had MRD diagnosed by the presence of ctDNA after treatment. The 2-year PFS rate was 27% and 87% in MRD-positive and MRD-negative patients, respectively (p < 0.001). Median survival was 36 months in MRD-positive and was not reached in MRD-negative pts (p=0.007). Cox regression analyses showed that MRD positivity was an independent predictor of relapse (OR=23; 95% CI [4.5-120.9]; p<0.001) and survival (HR=4; 95% CI [1.1-15.6]; p=0.037).

Conclusions: Our ctDNA assay detects MRD in LA SCCHN and predicts disease relapse and survival, without the need of tumor sequencing, making this approach easily applicable in daily practice.

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Legal entity responsible for the study: Cliniques Universitaires Saint-Luc, Brussels, Belgium.

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855MO Adjuvant immunotherapy after salvage surgery in head and neck cancer squamous cell carcinoma (HNSCC): Phase II trial evaluating the efficacy and the toxicity of Nivolumab (ADJORL1)

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Background: Treatment of locoregional failures or second primary in HNSCC in previously irradiated areas is a challenge. Reirradiation is currently the only treatment which can improve disease-free survival (DFS) after salvage surgery (SS) even if it has no impact on the overall survival (OS) because of high toxicity, showing the need to investigate other adjuvant therapies (AT) such as immunotherapy. The objectives of this study were to evaluate the 2-year DFS and OS of patients (pts) treated with nivolumab (N) after SS, the toxicity of N in this population and to determine biomarkers of response.

Methods: This multicentric non-randomized phase II add trial pts with recurrence or second primary of HNSCC in previously irradiated area, operated by SS with curative intent, more than 6 months after initial radiotherapy and of bad prognosis justifying an AT. Within 8 weeks of SS, 240 mg of adjuvant N was administrated every 2 weeks during the first 3 months, and then N 480 mg every 4 weeks was administrated for the next 3 months. The design was performed using a binomial test with a 2-year DFS $<$ 40% as ineffective (α=10%, power=80%).

Results: Between February 2018 and March 2021, 57 patients were included and treated. Median age was 61 years, 80% male. Median number of cycles of N was 9 (from 3 to 10). The reasons for off treatment were: 60% treatment completion, 21% tumor progression, 12% toxicity, 7% Others. 2-year DFS was 46.6%, 90%CI[36.1-57.5%] for the main endpoint and 2-year OS was 67.3%, 95%CI[54.2-78.2%]. Median follow-up was 48.2 months (from 5.3 to 59.6). 17 adverse events (AEs) grade $\geq$3 were related to N (mainly pancreatic hepatobiliary disorders, colitis, myositis andmyocarditis) and occurred in 11 pts (19%). No drug-related death occurred. Biomarkers data (CPS, Immunoscore) will be presented.

Conclusions: N as AT after SS is well tolerated. The 2-year DFS and OS compared favorably with those from historical data of reirradiation trials. In JANORL2 trial (Radiother Oncol 2018), 2-year DFS and OS were respectively 33.4%, 95%CI [22.1-47.0%] and 54.0%, 95%CI [40.6-66.8%]. These encouraging results warrant further investigations.

Clinical trial identification: NCT03406247.

Legal entity responsible for the study: Gustave Roussy Promotion.

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Disclosure: A. Daste: Financial Interests, Personal, Advisory Board: Merck, BMS, MSD. J. Fayette: Financial Interests, Personal, Advisory Board: AstraZeneca, BMS, MSD, Innate Pharma, Merck Serono, Roche, Seagens, Iteos, Elevar, Hookipa; Non-Financial Interests, Principal Investigator: AstraZeneca. F. Rolland: Financial Interests, Personal, Advisory Board: Pfizer, Eisai, MSD, Merck Serono; Financial Interests, Institutional, Coordinating PI: Exelixis; Financial Interests, Institutional, Local PI: BMS, Ipsen. A.C. Johnson: Financial Interests, Institutional, Invited Speaker: Gilead; Financial Interests, Institutional, Local PI, Skyscraper 09 trial: Roche; Financial Interests, Institutional, Local PI, Buran trial: Adlai Nortye; Other, Conference & travel expenses: Lilly, Gilead, AstraZeneca. C. Even: Financial Interests, Personal, Advisory Board: BMS, MSD, Innate Pharma, Merck Serono; Financial Interests, Institutional, Advisory Board: F Star Therapeutics, Novartis, Elevar; Financial Interests, Institutional, Local PI: BMS, AstraZeneca, ISA pharmaceutics, MSD, Debiopharma, Ayala, Gilead; Financial Interests, Institutional, Coordinating PI: BMS, Novartis, Sanofi. All other authors have declared no conflicts of interest.

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856MO A randomized phase II study of concurrent vs. sequential pembrolizumab with chemoradiation (CRT) in locally advanced head and neck cancer (LA HNSCC): 4-year results and tumor-immune microenvironment analysis

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Background: We previously reported numerically better efficacy with CRT with sequential (S) vs. concurrent (C) pembrolizumab (P). We now report updated results at 4-years and tumor-immune correlates.

Methods: Patients (n=80) with HPV (-) LA HNSCC and intermediate risk HPV + oropharyngeal ($>$ 10 pack years or T4 or N3) were randomized 1:1 to C (n=41) with P starting 1 week prior to CRT (cisplatin 40 mg/m^2 weekly + RT 70 Gy in 35 fractions) vs. S (n=39) with P starting 2 weeks after CRT. P was 200mg q 3 weeks X 8 doses. Biopsies pre and on treatment (tx; during week 2 of CRT) were available in the first 33 (18C and 15S) patients (pts). Immune landscape was investigated using OPAL 7-color multispectral Vectra imaging, with cell segmentation and phenotyping in QuPath (cite). Cell densities (log % of total) for PD-L1$^+$, CD8T (CD3$^+$CD8$^+$), and Treg (CD3$^+$CD8$^-$FOXP3$^+$) cells were computed within tumor (PanCK$^+$) or stroma (PanCK$^-$) compartment. Pre/on tx differences by patient were compared using two-sided paired t-test at FDR corrected $\alpha = 0.05$. Survival endpoints were summarized with the Kaplan-Meier method and compared between the two treatment arms with a Univariate Cox model.

Results: With a median follow up of 43 months, outcomes at 4-years in C vs. S are: Locoregional control (LRC) [64% vs. 96%, HR 0.12 95% CI (0.02, 0.94), p $=$ 0.043], PFS [49% vs. 67%, HR 0.57 95% CI (0.26, 1.28), p=0.173], OS [71% vs. 83%, HR 0.51 95% CI (0.19, 1.37), p=0.181]. Analysis of paired pre/on-tx patient samples showed a significant increase in tumor PD-L1$^+$ (p $=$ 0.002) and stroma PD-L1$^+$ cell densities in C (p $=$ 0.048), with no change in tumor PD-L1$^+$ cell density in S, after tx relative to baseline. No change was detected in CD8T infiltrates, Tregs, or CD8T to Treg ratio upon tx in C. Decreased stromal CD8T (p $=$ 0.04) and Treg (p $=$ 0.03) infiltrates were observed in S.

Conclusions: Longer follow-up shows continued better outcomes in S, and a significant improvement in LRC. Our study uniquely compared pre and on tx paired patient samples by arm, with a significant decrease in stromal CD8 T cells and Tregs in S and increase in PD-L1$^+$ cells in C, at two weeks into CRT. Further correlative analysis is ongoing.

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Legal entity responsible for the study: UPMC Hillman Cancer Center.

Funding: Merck.

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859MO Sacituzumab govitecan (SG) in patients (pts) with relapsed/refractory (R/R) advanced head and neck squamous cell carcinoma (HNSCC): Results from the phase II TROPiCS-03 basket trial

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Background: Although programmed death (ligand) 1 (PD-[L]1) inhibitors have improved outcomes in pts with advanced HNSCC, most pts experience disease progression and need subsequent treatment. SG is a Trop-2-directed antibody-drug conjugate. TROPiCS-03 (NCT03964727) is an open-label, multicohort, phase 2 study evaluating SG in pts with metastatic or locally advanced solid tumors. Here, we report initial data from the HNSCC cohort.

Methods: Adult pts with R/R metastatic or locally advanced HNSCC that progressed after prior platinum-based chemo and anti-PD-(L)1 therapy (in combination or sequentially in either order) received SG 10 mg/kg on Days 1 and 8 of a 21-day cycle. The primary endpoint was objective response rate (ORR) by investigator assessment (INV) per RECIST v1.1. Key secondary endpoints included clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), overall survival, and safety. Pts who received $\geq$1 dose of SG were included in the safety and efficacy analyses.

Results: As of 18 April 2023, 43 pts received $\geq$1 dose of SG. Median age was 62 years (range, 46-75) and 79% of pts had an ECOG performance status of 1. Median number of prior therapies was 3 (range, 2-9). With median follow-up of 7.5 months (range, 0.6-19.7), ORR was 16%, CBR was 26%, and median DOR was 4.2 months (Table). Median PFS was 4.1 months (Table). Treatment was ongoing for 5 (12%) pts. Any-grade treatment-related adverse events (TRAEs) occurred in 100% (grade $\geq$3, 44%) of pts. No TRAEs leading to discontinuation of study treatment were reported to date. Three (7%) deaths due to AEs were reported, and only 1 (2%) was considered related to study treatment.

Table: 859MO

Efficacy	Advanced HNSCC SG n = 43
ORR (95% CI),[a] %	16 (7-31)
BOR,[a] n (%)	
CR	0
PR	7 (16)
SD	21 (49)
PD	9 (21)
CBR (95% CI),[a,b] %	26 (14-41)
Median DOR (95% CI),[a] mo	4.2 (2.6-NR)
Median PFS (95% CI),[a] mo	4.1 (2.6-5.1)

[a]By INV. [b]Pts with CR + PR + SD for $\geq$ 6 mo. BOR, best overall response; CI, confidence interval; CR, complete response; mo, months; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions: SG demonstrated single agent activity and manageable safety, with no TRAEs leading to discontinuation to date, in heavily pretreated pts with advanced HNSCC.

Clinical trial identification: NCT03964727.

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860MO MRG003: A novel EGFR-targeted antibody-drug conjugant (ADC) for recurrent/metastatic nasopharyngeal carcinoma

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Background: There is an unmet need for more effective treatments in recurrent/metastatic nasopharyngeal carcinoma (r/m NPC) after chemo- and immune-therapy. MRG003 is a novel ADC composed of a humanized anti-EGFR mAb conjugated to MMAE via a vc-linker. Here we report the primary dose finding study results of MRG003 in r/m NPC.

Methods: This is a phase IIa study to evaluate the safety and efficacy of MRG003 in patients (pts) with pathologically documented r/m NPC, who had failed prior platinum and/or PD-(L)1 therapy. The study investigated two dose levels of MRG003 (2.0 or 2.3mg/kg, Q3W) to identify an optimal dose. The primary endpoint is objective response rate (ORR) per RECIST 1.1. Secondary endpoints include disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) and safety.

Results: A total of 61 pts received at least 1 dose of MRG003, 30 pts at 2.0 mg/kg (DL1) and 31 pts at 2.3 mg/kg (DL2). Most pts (52/61) received $\geq$2 lines of prior treatment and 53 (86.9%) pts had prior platinum and PD-1/L1 therapy. By the cut-off date (March 15, 2023), 28 pts were evaluable in the DL1 cohort, the ORR and DCR were 39.3% and 71.4%, respectively. The ORR and DCR of 29 evaluable pts in the DL2 cohort were 55.2% and 86.2%, respectively. Median DoR (mDoR) was 6.8 months (95%CI: 5.7, 16.3) in DL1 and 6.8 months (95%CI: 2.9, 9.8) in DL2. The median PFS (mPFS) in DL1 cohort was 7.3 months (95%CI: 2.9, 9.7), while it was immature in DL2 cohorts. Most commonly reported treatment-related AEs (TRAEs) assessed by investigators were rash (49.2%), pruritus (41.0%), anemia (34.4%), and alopecia (31.1%); majority of TRAEs were grade 1 or 2 per CTCAE 5.0. The incidence of treatment related severe adverse event (SAE) was 11.5% (7/61). Dose reduction rate due to TRAEs were 13.1% (8/61) and 3 pts discontinued treatment (4.9%). No treatment related deaths were observed.

Conclusions: MRG003 demonstrated promising antitumor activity in the late line r/m NPC patients, and with an acceptable tolerance and manageable safety profile. Based on numerically higher ORR and potentially better efficacy than 2.0 mg/kg group and well tolerated safety profile, 2.3mg/kg is the recommended dose for further pivotal study.

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861P Combined patient specific tumor and HPV sequencing enables high sensitivity detection of ctDNA in HPV-associated oropharyngeal carcinoma patients

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Background: HPV-associated oropharyngeal carcinoma (OPC) patients shed viral DNA which has been employed to monitor treatment response. The sensitivity of this approach, however, appears to be limited in OPC patients with low-burden disease. We hypothesized that circulating tumor DNA (ctDNA) detection through personalized tumor-specific alterations in combination with HPV ctDNA offers a more sensitive yet specific approach in early-stage HPV OPC patients.

Methods: Cell-free DNA (cfDNA) from HPV+ OPC patients enrolled in a phase II chemoradiation (CRT) de-escalation trial (NCT03323563) was collected. All patients underwent resection of the primary tumor before CRT and a baseline plasma was drawn at this time. DNA from the tumor and matched normal underwent whole-exome sequencing to identify somatic variants and for HPV typing. A dual MRD-HPV assay was developed based on the Invitae's Personalized Cancer Monitoring™ (PCM) assay including personalized tumor-specific and custom HPV-specific primers targeting high-risk HPV types. The MRD-HPV assay was applied to plasma cfDNA samples.

Results: 158 patients with T0-2/N1-N2c HPV-OPC were enrolled. The MRD-HPV assay was successfully designed for 111 patients targeting a median of 50 mutations per patient (range: 26-50). 64.0% (71/111) of patients had HPV16-related tumors and available baseline plasma, and all subsequent analyses were conducted on this group. While ctDNA detection by HPV testing resulted in sensitivity of 85.9% (61/71), ctDNA detection by MRD increased sensitivity to 90.1% (64/71). Furthermore, ctDNA detection by either HPV and/or MRD increased sensitivity to 95.8% (68/71). The 10 patients with negative HPV ctDNA tests harbored tumors with lower tumor volume and lower levels of genome instability than HPV ctDNA positive patients. Two of the three patients with negative baseline MRD-HPV had detectable ctDNA within 1 month from the start of treatment.

Conclusions: The combination of PCM MRD and HPV ctDNA assays provide a highly sensitive approach for detection of low disease burden in early HPV-associated OPC patients.

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862P Clinical utility of circulating tumor HPV16 DNA detection in plasma from oropharyngeal squamous cell carcinoma patients

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Background: Human papillomavirus-driven (HPV) oropharyngeal cancers (OPC) are treated with aggressive multimodality regimens, despite their usually favourable prognosis. Yet, ~25% of cases will develop recurrent or distant metastasis. Clinical monitoring of tumour progression and treatment response is often insufficient to detect asymptomatic lesions, delaying salvage treatment and reducing chances of cure. Therefore, we are exploring the clinical utility of measuring circulating tumour HPV DNA (ctHPVDNA) in HPV-driven OPC patients to guide outcome stratification and improve disease monitoring.

Methods: ctHPV16DNA levels were measured in plasma samples from OPC patients and controls from South America and Europe using droplet digital PCR (ddPCR). HPV16E6 serology results and well-annotated lifestyle and clinical information were available, and findings were tested for associations between ctHPV16DNA status/levels and patient clinical information. All samples were part of the HEADSpAcE study,

coordinated by the International Agency for Research on Cancer (IARC). Funding: INCa_16295 and EUH2020_825771.

Results: Baseline plasma samples from HPV-seropositive (n=75) and seronegative (n=26) OPC cases, and 57 HPV-seronegative controls (n=57) were tested, and we reached 100% specificity and an overall sensitivity of 92.0% (69/75) in detecting ctHPV16DNA in HPV16-seropositive cases. 10/11 patients with small volume disease (cT1/T2 N0) were positive for ctHPVctDNA, and increasing levels were observed according to N (p=0.01) and clinical stage (p=0.0029). Moreover, baseline detection of ctHPV16DNA was associated with a reduced risk of death (HR= 0.38; p=0.034) and disease relapse (HR= 0.2; p=0.028).

Conclusions: We showed a high accuracy of plasma ctHPVDNA detection by ddPCR in a case series of OPC from Europe and South America. ctHPV16DNA levels/status in baseline plasma were associated with disease volume, and a reduced risk of relapse and death, suggesting its use in patient outcome stratification. Next, we will test ctHPVDNA in post-treatment plasma samples as a potential tool for improving patient management through a more efficient monitoring of minimal residual disease during patient surveillance.

Legal entity responsible for the study: Ana Carolina de Carvalho, International Agency for Research on Cancer.

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863P Microbiota and cytokines profile in patients (pts) affected by recurrent metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with immune checkpoint inhibitors (ICIs) +/- chemotherapy (CT) and prebiotic inulin in the PRINCESS study

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Background: ICIs +/- CT have positive but marginal clinical effects in R/M HNSCC. Gut microbiota (GM) modulation might improve activity of ICIs. Inulin, a mixture of polymers of fructosyl units, may modify GM.

Methods: PRINCESS study explores longitudinal changes of GM and circulating cytokines in R/M HNSCC pts treated with ICIs +/- CT plus inulin. Pts receive oral inulin (10 g daily) and ICIs (nivolumab 240 q14 or pembrolizumab 200 q21 +/- CT). Stools and blood samples are collected at scheduled time points (TPs): baseline (T0) and at each radiological assessment (T1-4) until progression. Species-level genome bins (SGB) estimation of taxonomic composition of each stool sample was carried out. Differences in GM of same patients among TPs were explored. 18 cytokines (IL-2, IL-12, CXCL-10, CCL-2, TNF-α, IFN-γ, IL-4, IL-5, IL-10, IL-13, CCL-22, CCL4, IL-6, IL-8, TGF-β, VEGF, IL-21, and IL-15) were measured in plasma at each TPs.

Results: Between November 2021 and April 2023 16 pts have been evaluated. 9 pts had progression-free survival (PFS) $>$ 6 months. No difference in microbial complexity of pts among TPs was found. Samples were not separated according to TPs (p=0.21) while they were segregated by patient. We identified few microbial species (SGBs) differentially abundant between T0 and T1: *S. salivarius* SGB8007, *Roseburia* SGB4938, *Dorea* SGB4571 being increased in T0, while *A. shahii* SGB2295, *I. butyriciproducens* SGB15126, *B. wadsworthia* SGB15452, *D. welbionis* SGB15078, *F. plautii* SGB15132, *B. caccae* SGB1877, *B. uniformis* SGB1836 were significantly increased in T1. *B. uniformis* SGB1836 increased in T2 with respect to T0. At T1 progressed (P) pts showed increase of IL-5 and IL-10 (p=0.03) while IL-12 increased in non-P pts (p=0.01). P pts had higher values of IL-6, IL-8, CCL2, and VEGF ($p<0.05$) at T1.

Conclusions: With the limits of a small population, we found preliminary longitudinal differences in pts GM composition and cytokines Th2 vs Th1 pattern during ICIs +/- CT plus inulin. No safety signals were recorded. Due to our preliminary results, pts accrual will be enlarged to generate more solid data.

Clinical trial identification: *NCT0582175 (April 20, 2023)*.

Legal entity responsible for the study: Danilo Galizia.

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864P Serial cell-free tumor DNA in prognosing survival in patients with head and neck squamous cell carcinoma treated with upfront surgery

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Background: Cell-free tumor DNA (ctDNA) is an emerging biomarker in head and neck squamous cell carcinoma (HNSCC) that noninvasively provides molecular information and may allow for more accurate disease staging, risk stratification and early relapse detection through minimal residual disease assessment. We investigated the prognostic value of serial ctDNA in patients with HNSCC treated with upfront surgery.

Methods: Forty-one HNSCC patients treated with curative-intent surgery from the SCANDARE cohort (NCT03017573) were evaluated for longitudinal ctDNA-based NGS. Personalized dedicated NGS panels (OncoFOLLOW) were designed to detect up to 60 somatic variants. Twenty-one/41 patients (51%) received adjuvant (chemo)radiotherapy, and 31/41 patients (76%) experienced recurrence. Serial plasma samples were collected from 41 patients at surgery, 36 patients within a median time of 3.3 weeks after surgery (range, 1-19 weeks), 20 patients at six months, and 22 patients at recurrence. Results of serial ctDNA analyses were correlated with progression-free survival (PFS) and overall survival (OS).

Results: ctDNA was detected at surgery (n = 21/41; 51%), within 1-19 weeks after surgery (n = 15/36; 42%), at six months (n = 6/20; 30%), and at recurrence (n = 15/22; 68%). Recurrence occurred in 15 cases (including four patients [27%] who did not receive adjuvant therapy) with detected ctDNA within 1-19 weeks after surgery. Detection of ctDNA within 1-19 weeks after surgery was associated with shorter PFS (HR = 3.5; 95% CI, 1.5-7.8; $P = 0.003$) and OS (HR = 3.0; 95% CI, 1.0-9.3; $P = 0.05$) in univariate but not in multivariate analysis. Detection of ctDNA at six months correlated with poorer PFS (but not OS) in univariate (HR = 8.9; 95% CI, 2.2-37.0; $P = 0.003$) and multivariate (HR = 30.7; 95% CI, 2.6-370.8; $P = 0.007$) analyses. In addition, we found that ctDNA positivity at surgery correlated with poorer OS (but not PFS) in univariate but not in multivariate analysis (HR = 3.4; 95% CI, 1.1-11.3; $P = 0.04$).

Conclusions: Serial ctDNA analyses at surgery and in the postoperative setting had a strong prognostic value. Early detection of ctDNA after surgery might be of interest to stratify HNSCC patients for adjuvant therapy when treated with upfront surgery.

Clinical trial identification: NCT03017573 SCANDARE.

Legal entity responsible for the study: C. Le Tourneau.

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865P Molecular analysis of surgical margins in early oral carcinomas (OSCC)

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Background: The prognosis of early OSCC is strongly correlated with local disease control. However, patients with T1-T2 OSCC and clear margins have a 5-year local relapse rate of around 15%. The evaluation of the quality of surgical resection is therefore essential.

Methods: A prospective multicenter trial based on patients with T1-T2 OSCC treated surgically with clear margins, showed the interest of a molecular analysis (microsatellite instability (MSI)) of surgical margins to evaluate the minimal residual disease (MRD) while adapting the postoperative strategy (NCT00232960). Recently, innovative techniques for detecting circulating tumor DNA have been developed. Our main objective was, then, to evaluate the feasibility of detecting MRD by identifying specific molecular abnormalities with Whole Exom Sequencing (WES) and Shallow Whole Genome Sequencing (ShWGS) in the primary tumor and looking for it on the margins.

Results: 310 patients were included initially with 216 tumor/margins samples available for molecular analysis. Tumor was informative for MSI analysis in 63% of cases (n=133). Positive molecular margins were observed in 23 cases, leading to a postoperative treatment. Median follow-up was 58 months [30;83]. In informative tumor,

molecularly driven treatment seemed to lower the 5-year local recurrence rate from 14.1% to 6.4% (p=0.15). Among the initial cohort, 108 primary tumors were secondary screened by WES with an informative rate of 78.6%. With a 10X depth for molecular analysis, we observed 13 patients with at least one positive margin. Then, analyzing retrospectively the oncologic outcomes, we observed a significant benefit for local control at 5 years for patients with WES negative margins (91.7% versus 64.1%, p=0.02). We, then, performed a ShWGS analysis on a sub-group of 39 patients. Patients with positive margins both in WES and ShWGS had a higher risk of local relapse at 5 years (p<10-3).

Conclusions: Molecular analysis of surgical margins for early OSCC lead to a better assessment of microscopic residual disease while postoperative decision making according to WES and ShWGS could improve local control.

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866P Prognostic performance of a genome-wide methylome enrichment platform in head and neck cancer

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Background: The utilization of plasma-based tests to quantify circulating tumor DNA (ctDNA) is emerging as a promising new approach to cancer management. ctDNA quantification can be used to assess prognosis and to detect minimal residual disease following initial treatment. Here we demonstrate the feasibility of using a tumor-uninformed genome-wide methylome enrichment platform for ctDNA quantification and prognostic prediction in head and neck cancer.

Methods: Biobanked pre-treatment samples from individuals with newly diagnosed stage I-IV head and neck cancer (University Health Network) were analyzed with a bisulfite-free, non-degradative genome-wide DNA methylation enrichment platform using 5-10 ng of cell-free DNA isolated from plasma. ctDNA was quantified from average normalized counts across informative regions. Events were defined as recurrence or progression. A ctDNA quantity threshold was set such that 95% of samples without an event fell below the threshold (i.e. 95% specificity). Time to recurrence or progression event was compared for samples with ctDNA quantities above the threshold to those below the threshold.

Results: Among 93 samples included (7 stage I, 17 stage II, 23 stage III, 46 stage IV), the median follow-up time was 50.6 months, with 25 events. The likelihood of recurrence or progression was significantly higher in samples with ctDNA above the threshold [hazard ratio (HR) 3.18 (95% CI 1.09, 9.28), log-rank P=0.026]. In multivariate analysis accounting for cancer stage and clinical characteristics (sex, age, smoking history, BMI), ctDNA quantification above the threshold showed a similar association [HR 3.51 (95% CI 1.1, 11.19), P=0.034].

Conclusions: This analysis demonstrates the feasibility of using a blood-based, tumor-uninformed genome-wide methylome enrichment platform for ctDNA quantification and prognostic prediction in head and neck cancer, using treatment-naïve plasma samples. Future studies in post-treatment and longitudinal samples will be required to evaluate the utility of this genome-wide methylome enrichment platform for cancer management applications.

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867P Predicting HPV-association using regular H&E slides can identify subgroups of patients with favorable prognosis at a highly detailed level

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Background: Oropharyngeal squamous cell cancer (OPSCC) related to Human Papilloma Virus (HPV) is a subgroup of head and neck cancer that can be identified by p16 immunohistology and HPV-DNA testing. Although the prognosis is generally favorable, there has been a lack of success in implementing therapy de-escalation, owing to the heterogeneity of the disease. This underscores the need for precise biomarkers to facilitate patient stratification.

Methods: Our retrospective, multi-institutional study enrolled 906 patients and utilized deep learning to develop an algorithm that accurately predict HPV-association and strongly correlates with prognosis, based on regular H&E slides.

Results: When comparing our algorithm with HPV status, it showed good overall performance (AUROC = 0.83; 95% CI=0.77-0.9). In a subset of the validation cohort (n=639) the implementation of a fixed threshold for filtering resulted in increased AUROC to 0.88, with n=258 cases meeting threshold criteria. The algorithm was compared to the gold standard of HPV-testing in terms of its prognostic relevance and produced better results than the HPV test, indicated by its higher likelihood-ratio test value (LR, 49.23, p<0.001), higher concordance index (0.71), and higher 5-year overall survival rate (OS, 96%, 95% CI=90-100%). In contrast, the HPV test had lower LR (39.72, p<0.001), lower concordance index (0.65), and lower OS (80%, 95% CI=71-90%). The multivariate analysis using three prognostic groups demonstrated good discrimination. The algorithm had a high hazard ratio (HR) of 0.15 (95% CI=0.05-0.44) for the high-risk group, a medium HR of 0.58 (95% CI=0.34-0.98) for the intermediate-risk group, and a significant p-value of 0.043 for the entire group of 211 patients. In comparison, HPV testing had an HR of 0.29 (95% CI=0.15-0.54) and a highly significant p-value of <0.001 for the same group of 211 patients.

Conclusions: Our algorithm can identify patients with OPSCC who have a favorable prognosis using standard hematoxylin and eosin (H&E) histologic slides. In multiple scenarios, our stratification method performs better than the gold standard (p16/HPV-DNA) and could potentially be used to select patients for therapy de-escalation strategies.

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868P A DNA methylation classifier to predict recurrence from clear surgical margins

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Background: Many patients with oral (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) experience disease recurrence after surgery with curative intent despite R0 resection and adjuvant treatment. Several methods, including frozen section analysis, are available to evaluate surgical margins. However, precancerous epigenetic disturbances may predate morphological changes. This study aimed to address the unmet need for intraoperative recurrence prediction based on molecular features in clear resection margins.

Methods: Infinium EPIC BeadChip 850k methylation analysis of 71 OPSCC primary tumors (TU), 16 contralateral healthy mucosa (HM), and 70 resection margins (RM: OPSCC & OSCC) was conducted. Oncogenic features were selected based on TU vs. HM differential methylation analysis (Kruskal Wallis Tests: $\eta^2 > 0.14$ and FDR < 0.05). Baseline classifiers were trained, and the best-performing classifier was optimized by hyperparameter tuning and feature selection, allowing the integration of 46 TCGA R0 margin (normal adjacent tissue) data. Features selected were checked for common single nucleotide polymorphisms (SNP), and correlation analysis between loci methylation and gene expression (RNAseq) was conducted. Four margin samples analyzed with Epic BeadChip were also sequenced with Oxford Nanopore Technology (ONT) Mk1C.

Results: Forty-nine thousand features were selected to train six baseline classifiers, and XGBoost was chosen. XGBoost training with 10-fold cross-validation, hyperparameter tuning, and seven features (hypomethylated in TU compared to HM) selection led to the construction of a classifier model that predicts recurrence with a mean area under the ROC curve (AUC) of 0.80 (95% CI = 0.73 - 0.87). None of the seven loci used in constructing the model harbored a common SNP (MAF < 0.01). A significant correlation between the methylation level of five of the CpG loci and RNA expression was discovered ($p < 0.05$). ONT methylation output exhibited a strong positive correlation with Epic BeadChip for all the intersected loci ($r = 0.83$, $p < 0.001$), but most importantly, the seven selected features ($r = 0.90$, $p < 0.001$).

Conclusions: Disease recurrence can be predicted from morphologically clear surgical margins using a methylation classifier.

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869P Utilizing H&E images and digital pathology to predict response to buparlisib in SCCHN

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Background: This study aimed to evaluate a novel methodology to identify subjects that could derive benefit from Buparlisib treatment in metastatic SCCHN patients. The analysis was focused on image analysis of H&E images to select features associated with improved clinical benefit from paclitaxel+buparlisib.

Methods: BERIL-1 (NCT01852292) was a multicenter, randomized, double-blind, placebo-controlled phase II study evaluating treatment with either buparlisib + paclitaxel or placebo + paclitaxel in adult patients with metastatic SCCHN. H&E stained whole slide images (WSI) were used to develop a model to identify features of the tumor and the tumor immune microenvironment through digital pathology. We then evaluated spatial biomarkers from 145 subjects associated with improvement in efficacy endpoints of Progression Free Survival (PFS) and Overall Survival (OS) between the treatment and control arms.

Results: A deep learning model was developed that can accurately identify and classify tumor, necrotic and stromal areas as well as fibroblast, endothelial and immune cells (plasma, lymphocyte, granulocyte), from H&E images. The accuracy of this model was developed against the ground truth of human pathology analysis of the same images. This analysis demonstrated that a >10% infiltration of TILs ($p=0.00058$, $HR=0.195$) as well the heterogeneity of cells in the TME ($p=0.015$, $HR=0.53$) are both associated with a survival advantage in patients receiving the combination treatment when compared to placebo. Proximity of granulocytes to tumor cells ($p=0.00006$, $HR=0.32$) is also associated with improved survival in patients treated with buparlisib + paclitaxel.

Conclusions: This analysis highlights a novel approach, utilizing the common and cost-effective biomarker of H&E to identify metastatic SCCHN subjects that could derive therapeutic benefit from Buparlisib + paclitaxel. This approach also highlights interesting and novel biological observations that underscore the mechanisms of this therapeutic combination that could lead to studies evaluating novel therapeutic combinations. The results of this analysis can be expanded to the ongoing phase III BURAN study to further optimize and validate this method of identifying subjects for therapeutic intervention.

Clinical trial identification: BERIL-1 (NCT01852292).

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Disclosure: D. Soulieres, J. Lorch: Non-Financial Interests, Advisory Board: Adlai Nortye USA Inc.. J. Lucas, N. He, K. Dreyer, T. Tang: S. Lu: Financial Interests, Institutional, Financially compensated role: Adlai Nortye USA Inc.. O. Matcovitch-Natan, A. Bart, A. Laniado, S. Rosen Zvi, Z. Rachmiel, J. Kaplan Kerner, H. Yehezkeli: Financial Interests, Institutional, Financially compensated role: Nucleai. A. Gutwillig: Financial Interests, Financially compensated role: Nucleai. L.F.L. Licitra: Non-Financial Interests, Institutional, Advisory Board: Adlai Nortye USA Inc.. All other authors have declared no conflicts of interest.

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870P Dynamic cfHPV DNA changes during induction chemotherapy as an early indicator of treatment responsiveness for locally advanced head and neck cancer patients

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Background: Imaging response to induction chemotherapy (IC) has been used as a chemoradiation (CRT) de-intensification strategy in HPV-related head and neck cancer (HPV-HNC). However, radiographic response can be difficult to interpret and may lag biological response. We evaluate serial cell free HPV DNA (cfHPV DNA) levels during IC and CRT to determine a quantitative measure of early biologic response.

Methods: Patients with locally advanced, HPV-HNC receiving IC with 1-2 cycles of weekly platinum/taxane and definitive CRT were eligible. Peripheral blood was collected biweekly during IC, weekly during CRT, and at 3-4mo follow up visit. cfHPV DNA levels were measured with the Safe-SEQ HPV test from Sysmex Inostics, which is an NGS-based, CLIA-certified assay designed to sensitively detect and quantify HPV16 and HPV18 DNA in plasma.

Results: 163 samples across 15 patients completing curative-intent treatment were processed. The primary tumors were oropharyngeal (OPX, n=11), sinonasal/nasopharyngeal (NPX, n=3), and laryngeal (n=1). Median follow up was 13.2 mo. We defined a subset of patients who had ≥95% reduction in baseline cfHPV DNA levels by day 22 of IC as "rapid responders". This included 4 OPX and 1 NPX patients. All rapid responders had either T4 or N3 disease and three had >15 pack-year smoking history. Mean tumor volume change measured from pre-IC to post-IC CT imaging (median of 43 elapsed days) was a 71% reduction for rapid responders (range: 55% to 89% reduction) and a 32% reduction for non-rapid responders (range: 31% increase to 62% reduction). All rapid responders were alive and locoregionally controlled at 1 year follow up. In contrast, 50% of the non-rapid responders experienced in-field locoregional failure by this time-point, with two dying with disease. Each of the rapid responders completely cleared cfHPV DNA by the end of week 4 of CRT, but one rapid responder rebounded to a low detectable level (1.5 copies/mL) at 3.4mo post-treatment, followed by clinical detection of distant recurrence 10 months later.

Conclusions: cfHPV DNA kinetics after a short course of IC can provide an early, quantitative indication of favorable biology even for clinically high-risk, locally advanced HPV-HNC.

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871P Detection of circulating tumor DNA in operable loco-regionally advanced HPV-negative head and neck squamous cell carcinoma

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Background: Despite multimodal treatment, half of the patients with operable loco-regionally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC) will relapse. We aimed to evaluate the detection rate of circulating tumor DNA (ctDNA) before and after surgery and its correlation with baseline characteristics.

Methods: This prospective study (NCT03896412) included forty patients with HPV-negative HNSCC, treated by curative intent for a locally advanced (T3/T4 or node positive (N+)) by surgery followed by radio or radiochemotherapy. We looked for genes alteration on tumor tissue and ctDNA. Blood sampling was performed right before and the day after surgery. We used a custom panel targeting all exons of genes *AJUBA*, *TP53*, *CASP8*, *PIK3CA*, *NOTCH1*, *HRAS*, *CDKN2A*, *FAT1*, *NFE2L2*, *NSD1* and *EPHA2*. Analyses were performed with two bioinformatics pipelines; CLC software by Qiagen and a homemade pipeline. A pathogenic variant was considered if present in both pipelines. The sequencing depth was 2000X for tumors and 9000X for ctDNA.

Results: Among the 40 patients, 18 (45%) had a T4 stage disease, 25 (62.5%) a N+ disease. All patients underwent surgery. Regarding tumors, 36/40 (90%) had enough DNA amount and quality for NGS analysis. At least one pathogenic variant was identified in 30/36 tumors (83.3%): *TP53* was mutated in most of cases (93.3%), *PIK3CA* mutated in 8.3%, *FAT1* mutated in 5.6% and *CASP8* mutated in 2.8% of patients. No pathogen variant were found for *AJUBA*, *NOTCH1*, *HRAS*, *CDKN2A*, *NFE2L2*, *NSD1* and *EPHA2*. Analysis of ctDNA before surgery revealed at least one pathogenic variant in 8 patients. In all cases, the variant in ctDNA was detected in the matched tumor. For 3 patients, multiple variants were detected in ctDNA. Allelic frequency in ctDNA varied from 0.33% to 29.95%. Cell free DNA (cfDNA) rate was significantly increased after surgery (11.24 ng/mL vs 14.70 ng/mL, $p<0.0001$). Analysis of ctDNA the day after surgery did not identify any pathogenic variant.

Conclusions: In this cohort of locally advanced HPV-negative HNSCC, our NGS custom panel identified pathogenic variants in 83.3% of the tumors, but only in 20 % of preoperative ctDNA samples. Despite cfDNA increase after surgery, no pathogenic variant was identified in blood samples.

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872P Prognostic value of pathological intratumor heterogeneity in patients with head and neck squamous cell carcinoma treated with upfront surgery

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Background: Intratumor heterogeneity (ITH) is a major cause of treatment failure in cancer. Data on ITH are scarce in head and neck squamous cell carcinoma (HNSCC). We evaluated pathological ITH (pITH) and assessed its prognostic value, along with classical prognostic parameters.

Methods: HNSCC patients treated with curative-intent primary surgery from SCANDARE (NCT03017573) were included. A pITH score (I, II, III-low and III-high) was assessed on biopsies, according to the relative contribution of poorly- and well-differentiated tumor contingents. Univariate and multivariate prognostic Cox models of recurrence-free survival (RFS) were made on pITH score and clinical (age, sex, smoking history, alcohol consumption, AJCC T- and N-stage, HPV status), pathological (differentiation, tumor-infiltrating lymphocytes [TILs], and PD-L1 combined positive score (CPS) features. We tested associations between pITH score and these parameters.

Results: A total of 88 patients were included. Most frequently tumor locations were oral cavity (51%). Most patients had low T-stage (T1-2, 59%) and HPV-negative tumor (74%). Ten patients (11%) had a I/II ITH score, 49 (56%) a III-low and 29 (33%) a III-high. Median follow-up was 17 months and median RFS was 18 months (95% CI, 14-40). In univariate analysis, the pITH score did not correlate with RFS ($P = 0.6$). T-stage, N-stage and TILs enrichment were associated with RFS (T3-4 vs T1-2, HR = 2.7, 95% CI, 1.4-5.3; N1-2 vs N0, HR = 1.9, 95% CI, 1.0-3.7; TILs $\geq$10% vs TILs $<$10%, HR = 0.3, 95% CI, 0.1-0.8). We found that low T-stage (T1-2) and high TILs enrichment (TILs $\geq$10%) were associated with a reduced risk of relapse in multivariate analysis (HR = 0.4, 95% CI, 0.2-0.9 and HR = 0.2, 95% CI, 0.04-0.5, respectively). In comparison with non-smokers, smokers had a higher proportion of tumors with I-II ITH score (19% vs 3%) and a lower proportion of tumors with III-low ITH score (48% vs 65%, adjusted $P = 0.05$).

Conclusions: We reported an association between pITH score and smoking history. pITH score was not found to be prognostic whereas TILs enrichment $\geq$10% was associated with a favorable prognosis in patients with HNSCC treated with upfront surgery. This finding is to be confirmed in an independent population.

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873P Identification of PIK3CA mutation as a novel predictor of efficacious immunotherapy in head and neck cancer

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Background: PIK3CA mutations led to the activation of PI3K-AKT-mTOR signaling pathway. This pathway controls cell proliferation, growth, differentiation, migration, and apoptosis. In clinical practice, only a minority of patients with HNSC derive benefit from immunotherapy and the need for the discovery of novel biomarkers to optimize treatment strategies is becoming increasingly more relevant. Whether mutations of PIK3CA are associated with clinical efficacy of immunotherapy (ICIs) in HNSC have not been reported.

Methods: We used cBioportal to collected clinical and mutation data of the MSKCC cohort including 139 patients receiving ICIs. Gene expression data and WES mutation data of 502 samples in the TCGA were obtained for further analysis of the potential biological mechanisms between PIK3CA-MT and PIK3CA-WT tumors. TMB was calculated as the total number of somatic non-synonymous mutations per megabase in both MSKCC and TCGA cohorts. CIBERSORT algorithm was applied to infer 22 human immune cell type proportions in TCGA HNSC.

Results: The TMB level of PIK3CA-Mut patients was higher than PIK3CA-WT patients in both MSKCC (Median [IQR]: 7.02[4.92-10.53] vs. 4.91[2.63-7.90], P=0.006) and TCGA (Median [IQR]: 3.03[1.98-4.42] vs. 2.62[1.66-3.92], P=0.045) cohort. In MSKCC cohort, compared to PIK3CA-WT patients, the PIK3CA-Mut patients achieved prolonged OS (median OS: 25.0 vs. 9.0 months, HR (95%CI): 0.51(0.27-0.94), P=0.029).

Moreover, a multivariable analysis across the MSKCC cohort using Cox proportional-hazards regression demonstrated that PIK3CA-Mut was associated with better OS (HR= 0.49; 95%CI, 0.26-0.91; P=0.025), after adjusting for age, gender, metastasis and treatment. Then we used CIBERSORT to explore infiltration of immune cells and two types of immune cells (CD8+ T-cells, CD4+ naïve T-cells) were higher expression in PIK3CA-Mut tumors ($P<0.05$). These results indicated PIK3CA-Mut tumors had an activated antitumor immune microenvironment.

Conclusions: PIK3CA-Mut is associated with higher TMB in ICI-treated HNSC patients. Survival analysis shows PIK3CA-Mut have a good link with longer OS after immunotherapy. These findings indicate that PIK3CA mutation may serve as a potential predictive biomarker for ICIs in HNSC.

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874P Artificial intelligence (AI)-powered spatial tumor-infiltrating lymphocyte (TIL) analysis in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) patients treated with immune checkpoint inhibitor (ICI) treatment

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Background: ICI has demonstrated survival benefit and became a part of standard therapy for the systemic treatment of R/M HNSCC. However, the identification of practical and reliable biomarkers to predict therapeutic response remains an unmet need. AI-powered spatial TIL analysis has demonstrated significant predictive value of immunotherapies in multiple cancer types including squamous cell carcinoma. The objective of this study is to investigate the influence of AI-powered TIL analysis in predicting the response to ICIs in R/M HNSCC.

Methods: H&E-stained whole-slide images (WSIs) of pre-treatment tumor samples and clinical data were collected from r/m HNSCC patients treated with ICI at Severance Hospital in Korea. Lunit SCOPE IO, an AI-powered WSI analyzer, was applied to assess the density of intratumoral TIL (iTIL), stromal TIL (sTIL), and TIL in tumor microenvironment (tTIL). For clinical outcome analysis, the median densities of TILs were applied as cut-off (high vs low).

Results: Of 108 pre-treatment samples included, primary tumor sites were oral cavity (42.6%), oropharynx (27.8%), hypopharynx (15.7%), and other (13.9%). Overall, the median tTIL density was 392/mm^2 (interquartile range [IQR] 150-1095), and the median values of oropharynx and of non-oropharynx were 446/mm^2 (IQR 221-1836) and 326/mm^2 (IQR 109-1006), respectively (p=0.163). Objective response rate of ICI per RECIST v1.1 was higher in high-tTIL compared to low-tTIL (21.6% vs 5.7%; p=0.0220). Median progression-free survival (mPFS) of ICIs was favorable in high-tTIL than low-tTIL (3.2 vs 1.6 months; hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.39-0.90, p=0.0151). Interestingly, mPFS was more significantly different by iTIL density (HR 0.64, 95% CI 0.42-0.97, p=0.0367) compared to sTIL density (HR 0.70, 0.46-1.07, p=0.0999). Overall survival was not significantly different by TIL densities.

Conclusions: AI-powered assessment of TIL density in tumor microenvironment, especially intratumoral TIL density, is associated with favorable treatment outcomes to ICI in R/M HNSCC.

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875P Proteomic and phosphoproteomic profiling of HNSCC and the role of CDKs as potential drug targets

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Background: There is an unmet need for novel targets and predictive biomarkers for head and neck squamous cell carcinoma (HNSCC) in the recurrent metastatic setting. Molecular subtypes assessed by transcriptomic data have been defined and correlations between basal subtype and response to EGFR blockage have been shown. To improve tumor subtyping, and define potential drug targets and predictive biomarkers, we performed proteomic and phosphoproteomic profiling of an extended set of HNSCC patient derived tumor models (PDX) that have been characterized for their response to multiple drug compounds and further evaluated treatment combinations.

Methods: 64 HNSCC PDX tumors were analyzed by established Tandem Mass Tag (TMT)-based mass spectrometry workflow. Bioinformatic analysis was performed by integrating proteomics and phosphoproteomic with clinical annotation, drug response data, gene expression and mutation profiles of these tumors. More than 8,500 human proteins and 15,000 phosphosites were quantified across the 64 PDXs.

Results: NMF clustering on proteome and phosphoproteome levels resulted in three distinct clusters overlapping partly with RNA-based classification termed classical, mesenchymal, and basal subtypes. Differential expression analysis validated clinical biomarkers for human papillomavirus (HPV) status and highlighted additional proteins so far not connected to HNSCC. Interestingly, CDK4 expression was associated with HPV positive tumors, whereas the homolog kinase CDK6 was found to be upregulated in HPV-negative tumors belonging to the basal-like proteomic subtype. Dependency Map (DEPMAP) analysis validated that CDK6 has strong codependency with EGFR in cell lines derived from HNSCC. All evaluated models were treated with cetuximab and 25 PDX models with CDK4/6 inhibitor palbociclib as single agent treatment. Combined treatment of cetuximab and palbociclib was evaluated in EGFR resistant, CDK6 high expressing tumor models.

Conclusions: Integrative proteogenomic tumor analysis is a powerful tool for cancer classification, may predict the efficacy of targeted therapies more accurately and displays new subtype-specific druggable protein targets.

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876P Gene expression analysis in oral potentially malignant disorders (OPMD) with dysplasia identifies patients at high risk of malignant transformation

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Background: Despite surgical resection, Oral Potentially Malignant Disorders show a rate of malignant transformation varying from 3% to 17.5%. Clinical and histological factors outside dysplasia and previous oral cavity carcinoma failed to identify OPMDs at higher risk of malignant transformation (MF). We previously identified six clusters of transcriptomic data able to stratify Head and Neck Squamous Cell Carcinoma (HNSCC) that also applied to OPMD. The primary objective of the current study was to validate the stratification by the transcriptional signature in an independent series of dysplastic OPMD.

Methods: We collected a retrospective series (3/1996 to 11/2019) of completely excised OPMDs with any grade of dysplasia at the University of Brescia. Clinical/

histological data were retrieved. Library preparation for gene expression profiling was conducted QuantSeq 3'mrna-seq (Lexogen) and pooled libraries were sequenced by NextSeq500 (Illumina). Finally, previously identified molecular clusters based on main biological characteristics and de-regulated signaling pathways were associated with the risk of MF.

Results: We identified 106 consecutive patients with OPMDs. Of these, 66 had available material for gene expression analysis. A slight majority were male (53.4%), with a median age of 65 years (33-95); 17% had a previous diagnosis of HNSCC. With a median follow-up of 53 months (IQR 91), 23% experienced a MF with a median time to transformation of 30 months (3—195). After stratification based on our previously reported clusters, OPMDs were classified as mesenchymal, hypoxia, defense response, classical, and immunoreactive clusters constituted 8%, 15%, 27%, 9%, and 41% of our cohort, respectively. Hypoxia cluster showed a higher risk of malignant transformation ($p<0.0001$).

Conclusions: OPMDs gene expression clustering allows stratifying patients according to different risk of MF. Among them, hypoxia cluster had the highest probability of cancerization. A more in-depth analysis of this cluster is required, both to better characterize the mechanisms of MF and to develop customized prevention strategies.

Legal entity responsible for the study: Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, 25123 Brescia, Italy.

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877P ROS1 mutations as potential negative predictor for response of immunotherapy in patient with head and neck cancer

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Background: The c-ros oncogene 1 (ROS1) gene has aroused great research interest for its role as an oncogenic driver of malignancies, as well as its untapped potential for novel therapeutic target. Despite the success of targeted therapy in ROS1-rearranged across multiple cancers, there were few studies on variations other than rearrangement concerning ROS1, and what role the ROS1 mutation would act in ICI treatment of Head and Neck cancer (HNSC) has not yet been studied. We sought to elucidate the predictive effect of ROS1 mutation, instead of rearrangement, for the efficacy of immunotherapy in HNSC

Methods: 139 HNSC patients with NGS and immunotherapy data obtained from MSKCC cohort were used to explore the association between ROS1 mutation and efficacy of ICIs. TMB was defined as the total number of somatic non-synonymous mutations. The sequencing, mRNA and survival data of 502 patients with HNSC from TCGA was used to explore the underlying mechanism

Results: In the MSKCC cohort, we observed 7 (5.04%) patients harbored ROS1 somatic mutation. As indicated by Kaplan-Meier analysis, the patients with ROS1-Mut had significantly worse OS in the MSKCC cohort (P=0.011, HR=3.22, 95%CI=1.26-8.19). This link was still existing when controlling for age, sex, stage, tumor site type, TMB and therapy type in the multivariate Cox regression analysis (P=0.006, HR=4.08, 95%CI=1.48-11.2). Patients with ROS1-Mut had higher TMB compared to patients with wild-type ROS1 in both MSKCC (P=0.043) and TCGA cohort ($P<0.001$). While as shown above, ROS1-Mut was an independent indicator of poorer outcomes beyond TMB status, suggesting the negative prognosis of ROS1-Mut receiving ICIs treatment may attribute to other factors. In TCGA, no association was observed between ROS1-Mut and survival (P=0.26). These results suggested that ROS1-Mut was a potential negative predictor for immunotherapy, instead of a prognosis factor for HNSC. Immune cell analysis showed that Regulatory Tregs T-cells were significantly less abundant in the ROS1-Mut group (P=0.037), indicating an deactivated antitumor immune microenvironment.

Conclusions: We identified that ROS1 mutation predicted the resistance to ICIs in HNSCs. The clinical delivery of ICIs should be cautious in those patients.

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878P INHBA is overexpressed in HPV-negative oropharyngeal squamous cell carcinoma and contributes to an aggressive phenotype

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Background: There has been considerable progress in comprehending the molecular mechanisms involved in oropharyngeal squamous cell carcinoma (OPSCC). However, the fundamental factors contributing to the aggressiveness of HPV-negative OPSCC compared to the more indolent HPV-positive OPSCC remain unclear. Additionally, the therapeutic options available for this particular cancer subtype are limited. This study aimed to identify potential therapeutic targets for HPV-negative OPSCC by investigating the distinct molecular pathways differentiating HPV-negative from HPV-positive OPSCC.

Methods: Bulk mRNA sequencing of 23 HPV-negative and 39 HPV-positive OPSCC tumors ($n = 62$) was performed. Gene set enrichment analysis identified the top enriched biological processes in HPV-negative compared to HPV-positive OPSCC. The most upregulated gene in HPV-negative tumors, inhibin subunit beta A (INHBA) was knocked down in an HPV-negative OPSCC cell line to confirm its impact on proliferation, migration, clonogenic survival and cell death. Correlation analyses were conducted to assess the impact of INHBA on the immunologic tumor microenvironment.

Results: Epithelial-to-mesenchymal transition (EMT) was the most enriched process in HPV-negative OPSCC, with INHBA as the most upregulated gene. Knockdown of INHBA led to a downregulation of EMT transcription factors and reduced migration, proliferation, clonal expansion, and cell death resistance of OPSCC cells. We discovered that INHBA was associated with an immunologic pro-tumor microenvironment, as it negatively correlated with anti-tumor CD8+ T and B cells and positively correlated with pro-tumor M1 macrophages. Three miRNAs were identified as potential regulators of INHBA expression.

Conclusions: In conclusion, the upregulation of INHBA promotes cancer aggressiveness. INHBA may be targeted therapeutically (e.g. using metformin) in INHBA-enriched tumors in HPV-negative OPSCC patients to improve their outcome. Our findings may explain the counter intuitive observations that HNSCC patients receiving metformin for diabetes mellitus display a longer overall survival.

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879P Targeted next-generation sequencing reveals CDKN2A alterations as a prognostic biomarker in recurrent or metastatic head and neck squamous cell carcinoma mostly treated with immune checkpoint inhibitors

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Background: To screen potential biomarkers in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with a subgroup analysis based on the patients treated with immunotherapy and examine the prognostic significance of CDKN2A mutations.

Methods: This single-center retrospective study analyzed the Foundation Medicine (FM) next-generation sequencing (NGS) data from patients with recurrent or metastatic HNSCC who underwent NGS between January 1, 2019, to December 31, 2021. The patients were grouped according to CDKN2A loss-of-function (LOF) vs. wild-type (WT). A subgroup analysis was performed on the patients treated with immunotherapy.

Results: Seventy-seven patients (62 with immunotherapy) were included. The median follow-up was 22.6 months. The median OS was 16.5 months in the CDKN2A LOF group and 30.0 months in the CDKN2A WT group (P=0.014). The female sex (HR=4.526, 95%CI: 1.934-10.180, P=0.0003) and CDKN2A LOF (HR=2.311, 95%CI: 1.156-4.748, P=0.019) were independently associated with mortality in patients with recurrent or metastatic HNCSS. In patients with immunotherapy, the median OS was 19.8 months, or 11.7 months in the CDKN2A LOF group and 22.5 months in the CDKN2A WT group (P=0.017). The female sex (HR=4.022, 95%CI: 1.417-10.710, P=0.006), CDKN2A LOF (HR=4.389, 95%CI: 1.782-11.460, P=0.002), and CPS <1 (HR=17.20, 95%CI: 4.134-79.550, $P<0.0001$) were independently associated with

mortality in patients with recurrent or metastatic HNCSS treated with immunotherapy.

Conclusions: LOF alterations in the CDKN2A gene are independently associated with poor survival in patients with HNSCC, including those treated with immunotherapy.

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880P ctHPV16-DNA in Liquid Biopsy: A promising biomarker to monitor disease status in patients with HPV-positive oropharyngeal squamous cell carcinoma

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Background: Globally the incidences of oropharyngeal squamous cell carcinoma (OPSCC), especially those associated with high-risk human papillomavirus are rising. Although patients with HPV-positive OPSCC present with better survival, up to 25% develop recurrent disease. Biomarkers to monitor therapy response, minimal residual disease and tumor burden during follow-up are urgently needed. The detection of cell-free (cf)HPV-DNA in blood plasma offers the opportunity for minimally invasive disease monitoring and early recurrence detection.

Methods: We examined 34 patients with HPV-related OPSCC and 21 controls (healthy donors and HPV-negative OPSCC patients) to investigate cfHPV16-DNA status prior to and during therapy as well as throughout follow-up. qPCR and ddPCR were applied to quantify the concentration of cfHPV16-DNA in plasma, using the viral gene E6 as a target.

Results: No cfHPV16-DNA or $<$10 copies per ml plasma were detected in healthy donors or HPV-negative OPSCC patients. Plasma samples from patients with HPV-positive OPSCC collected prior to treatment. At the cut-off of 10 copies/ml plasma, ddPCR showed 79% sensitivity, 80% specificity, 70% NPV, and 90% PPV, whereas qPCR showed 73% sensitivity, 80% specificity, 60% NPV, 90% PPV. Patients without clinical evidence of recurrence had significantly lower cfHPV16-DNA concentrations after therapy, whereas increase of copy number was correlated to recurrent disease.

Conclusions: Our results demonstrate that ddPCR is a more sensitive method compared to qPCR for detection of cfHPV16-DNA in plasma of patients with HPV16-positive OPSCC. cfHPV16-DNA correlated with tumor burden and therefore presents a promising diagnostic tool. Nevertheless, prospective studies with expanded patient cohorts are necessary to investigate the kinetics of cfHPV16-DNA in relation to therapy response and the development of recurrent and metastatic disease.

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881P SOTO study: Prospective study to correlate the treatment sensitivity of patient-derived organoids (PDOs) with treatment outcomes in head and neck cancer patients

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Background: Apart from HPV status, there is no accurate way of predicting patients' response to treatment in head and neck squamous cell carcinoma (HNSCC). Moreover, there is no easy way to test radiosensitivity and chemosensitivity of these tumours. Large living biobanks of PDOs have been developed from several tumours and they were shown to preserve the characteristics of the original tumour. This study aims to generate PDOs from HNSCC samples and to collect preliminary data on the ability of PDOs to predict patients' treatment response.

Methods: This is a prospective observational study to generate PDOs from HNSCC patients' samples (NCT05400239). The study aims to recruit 3 groups: cohort 1 surgically resectable disease, cohort 2 primary radical radiotherapy +/- concurrent chemotherapy, cohort 3 recurrent or metastatic disease. Samples collected include tumour and relevant normal tissues samples at baseline (+/-recurrence) for generation of PDOs and genetic analysis, blood, and saliva samples (baseline and different time points during treatment) for PBMC isolation/analysis and ctDNA analysis. The successfully generated PDOs are subjected to increasing radiotherapy dose (2Gy,4Gy,8Gy), cisplatin (0.1μM-100μM) and cetuximab (1-1000μg/ml). The recapitulation of PDOs to that of the human samples will be investigated using immunohistochemistry and genetic analysis.

Results: This is an ongoing study and to date, 15 patients with HNSCC have been consented and appropriate samples were collected (Cohort 1: n=9, Cohort 2: n=3, Cohort 3: n=3). 9 patients were treated with surgery, 10 patients received radiotherapy (7 post-op; 3 radical). Following protocol optimisation, 6 samples were successfully generated into PDOs. Response to radiotherapy and chemotherapy varied across the different organoid lines.

Conclusions: We provide the preliminary results from utilising HNSCC PDOs as an ex-vivo pre-clinical model to predict patient's response to treatment in a personalised cancer treatment approach. Moreover, further translation research will be conducted to investigate the role of ctDNA and peripheral immune system as potential prognostic and predictive biomarkers.

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882P Claudin-1 (CLDN1) expression in head and neck squamous cell carcinoma (HNSCC) patients

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Background: Recent evidence has shown that the tight junction protein Claudin-1 (CLDN1) is overexpressed in different solid tumors. CLDN1 can be targeted through specific agents to revert its effects. The present work aims to explore CLDN1 expression in a cohort of HNSCC patients (pts).

Methods: A single center cohort of 100 loco-regionally advanced HNSCC pts included in the BD2Decide project was analyzed [PMID 33107152]. All pts received treatments with curative intent. Primary tumor specimens were profiled for gene expression by Affymetrix ClariomD chips and processed using the Transcriptome Analysis Console Software (ThermoFisher). Normalized and log2 CLDN1 were retrieved from the data matrix and used to analyze: i) data distribution based on anatomical subsites, HPV status, and molecular subtypes assessed by Kruskal-Wallis test; ii) prognostic value

having overall survival (OS) as endpoint estimated with Kaplan-Meier method and compared with the log-rank test. Hazard ratios (HR) were estimated with Cox proportional hazard model.

Results: The clinical characteristics of the pts cohort are reported in the following table.

Table: 882P

Characteristics		N (%)
Sex	M F	76 (76) 24 (24)
Median age		60 years (range 21-80)
Primary HNSCC site	Oral cavity HPV+ OPC HPV- OPC Hypopharynx Larynx	20 (20) 20 (20) 20 (20) 20 (20) 20 (20)
Stage	HPV+ I II III HPV- HNSCCs III IVa/b	- 6 (30) 6 (30) 8(40) - 25 (31) 55 (69)
CLDN1	High (>4.4) Low (<4.4)	15 (15) 85 (85)
Median follow-up		64.44 months [m] (95% CI: 54.24-66.91)
Median DFS	Overall HPV+ HPV- CLDN1-high CLDN1-low	42.79 m (95% CI: 22.5-72.2) 53.91 m (95% CI: 13.09-53.91) 35.53 m (95% CI: 15.43-72.2) 22.9 m (95% CI: 7.96-35.79) 65.1 m (95% CI: 22.5-72.2)
Median OS	Overall HPV+ HPV- CLDN1-high CLDN1-low	94.24 m (95% CI: 59.08-94.24) Not reached 72.2 m (95% CI: 43.88-94.24) 26.2 m (95% CI: 14.31-94.24) Not reached

CLDN1 expression significantly differed (p=0.0158) among HNSCC primary sites (in decreasing order of expression): hypopharynx, HPV+ oropharynx (OPC), larynx, HPV- OPC, oral cavity. Survival was significantly shorter in pts with high vs low CLDN1 (Table): OS HR=3 (95% CI 1.43-6.28, p=0.0023), DFS HR=2.14 (95% CI 1.11-4.11, p=0.02).

Conclusions: CLDN1 expression is heterogeneous in HNSCC pts, and has a prognostic significance. These results may guide pts selection for future clinical studies with anti CLDN1-antobody, which is currently under development.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

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884P Prognostic value and immune characteristics of LGALS1 in head and neck squamous cell carcinoma

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Background: Head and neck squamous cell carcinoma (HNSC) is the sixth most common form of cancer in the world and the 5-year survival rate is approximately 60%. Searching for effective biomarkers to predict prognosis is urgently needed. LGALS1 belongs to a family of carbohydrate binding proteins which regulates a wide variety of tumor suppressors and tumor promoters. The present study aimed to analyze the prognostic value of LGALS1 and its association with the tumor immune microenvironment.

Methods: Gene expression profiles were retrieved from the Cancer Genomic Atlas (TCGA)-HNSC cohort (n = 563). We used GEPIA2 to study the expression of LGALS1 in HNSC compared to the normal tissue. We assessed the effect of LGALS1 expression on the overall survival (OS) in HNSC using the Kaplan Meier plotter. We used the TIMER 2.0 for immune inhibitory cell infiltrates analysis. We used the cBioPortal tool for tumor mutational burden (TMB). Enrichment analysis of function and signaling pathways of differentially co-expressed genes were performed by gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomics (KEGG) analysis using LinkedOmics.

Results: LGALS1 is differentially expressed and upregulated in HNSC compered to normal tissues ($P < 0.001$). Higher LGALS1 expression correlated with worse OS in HNSC patients (HR: 1.51, 95% CI: 1.15 - 1.98, $P = 0.003$). LGALS1 expression was positively correlated with the infiltration of macrophage ($r = 0.229$, $P < 0.001$), myeloid dendritic cells ($r = 0.286$, $P < 0.001$) and CD8+ cells ($r = 0.129$, $P = 0.004$), but negatively with B cells ($r = -0.13$, $P = 0.004$). TMB count was inversely associated with LGALS1 expression ($r = -0.13$, $P = 0.004$). GO analysis for LGALS1 co-expressed genes indicated a molecular function role in extracellular matrix structural constituent and biological process in extracellular structure organization with a cellular component in extracellular matrix.

Conclusions: Our results imply that high expression of LGALS1 is an indicator of poor prognosis in HNSC. This might be due to the infiltration of macrophage, myeloid dendritic cells, lower B cells and even though there were also higher CD8+ cells. However, further research is needed for a better understanding of the LGALS1 value in HNSC.

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885P Clinical significance of folate receptor-positive circulating tumor cells detected by ligand-targeted polymerase chain reaction in nasopharyngeal carcinoma

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Background: This study aimed to investigate the feasibility of using ligand-targeted polymerase chain reaction (LT-PCR) to detect folate receptor-positive circulating tumor cells (FR+CTCs) and their potential role as an auxiliary marker for diagnosis and treatment monitoring in nasopharyngeal carcinoma (NPC).

Methods: This was a single-center, prospective, non-interventional clinical study at Fujian Cancer Hospital. The study included newly diagnosed nasopharyngeal carcinoma patients with at least one measurable lesion and a benign control group. Patients underwent comprehensive treatment based on radical radiotherapy, and the level of FR+CTC was dynamically detected after treatment. FR+CTC was quantitated using ligand-targeted PCR and verified using immunofluorescence. The ROC curve was used to determine specificity and sensitivity thresholds, and the AUC was calculated. Comparisons between groups were performed using statistical tests, and $p < 0.05$ was considered statistically significant.

Results: A total of 254 subjects were included in the study, including 145 newly diagnosed NPC patients and 109 healthy volunteers. The study found that the level of FR+CTC was significantly higher in NPC patients than in healthy individuals, and the levels were also higher in stage III and IV patients. The FR+CTC detection method had a higher AUC, and the cut-off value between the NPC and control groups was 9.380 FU/3ml, with a sensitivity of 99.1% and a specificity of 79.2%. The study also found that FR+CTC levels were associated with gender, age, TNM stage, and MPTD, but not with the level of EB-DNA. After radiotherapy, most patients showed a significant decrease in FR+CTC levels, indicating the potential of FR+CTC as a dynamic biomarker for monitoring treatment response in NPC.

Conclusions: This study demonstrates that LT-PCR technology can accurately detect FR+CTCs in NPC patients. FR+CTC has the potential to be used not only as an auxiliary biomarker for early detection and diagnosis of nasopharyngeal carcinoma, but also as a potential marker for dynamic assessment and monitoring of disease progression, recurrence, and metastasis.

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886P Prospective evaluation of dynamic changes of cell-free HPV-DNA (cfHPV-DNA) in locoregional HPV associated (HPV+) oropharyngeal cancer (OPC) treated with neoadjuvant chemotherapy and response-stratified treatment

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Background: Response-adaptive de-escalation is promising to optimize survival while reducing toxicity. cfHPV-DNA in plasma represents a promising biomarker to grade treatment response and monitor for recurrence. We studied the feasibility of dynamic cfHPV-DNA assessment during response-stratified treatment in HPV+ OPC.

Methods: Patients (pts) with locoregional HPV+ OPC were assigned risk category: High risk (HR) [T4, N3, or ≥20 pack-year smoking history (PYH)]; Low risk (LR) [all other pts]. All pts received three cycles of neoadjuvant carboplatin/paclitaxel. Arm A: Single-modality [transoral robotic surgery or radiation alone to 50Gy] for LR with ≥50% response. Arm B: Intermediate de-escalation (chemoradiation (CRT) to 50Gy/cisplatin) for HR with ≥50% response or LR with <50% response. Arm C: Regular dose (CRT to 70Gy/cisplatin) for all others. cfHPV-DNA was assessed during neoadjuvant, CRT, and post-treatment.

Results: Forty-six eligible patients started induction between 2020 and 2022. Median age 62 (range 38-74), 13% female, 22% ≥20PYH smoking, 70% tonsil, 30% base of tongue, 52% HR, and 48% LR. Response rate to induction≥30% shrinkage was 91%, and≥50% shrinkage was 73%. Arm A (n=16), Arm B (n=21), Arm C (n=8). One patient died during induction. At a median follow-up of 15 months, progression free survival (PFS) at 1-year was 93%. By response-stratified treatment, 1-year PFS was 100% among de-escalated (Arm A and B) and 75% among Arm C (p=0.05). cfHPV-DNA was detectable (+) at baseline in 98% of pts. Clearance rate of cfHPV-DNA after 2 cycles was 72% and associated with a 1-year PFS of 100% vs 79% 1-year PFS with (+) cfHPV-DNA (p=0.1). Of 41 patients with at least 1 cfHPV-DNA assessment≥3 months after treatment, n=5 had (+)cfHPV-DNA. All four recurrences were detected by (+) cfHPV-DNA (sensitivity=100%), and positive predictive value was 80% (4/5). Following surgical salvage (n=2), (+)cfHPV-DNA predicted post-operative recurrence.

Conclusions: These findings demonstrate that plasma cfHPV-DNA clearance after two cycles of chemotherapy has prognostic utility. Post-treatment (+)cfHPV-DNA predicts recurrence. Longer follow-up is planned.

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887P Antitumor activity of the radioenhancer NBTXR3 on injected lesions to estimate overall survival: Exploratory analyses from a phase I in cisplatin-ineligible locally advanced HNSCC patients

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Background: Assessment of treatment effect on surrogate and OS outcomes is a challenge for novel therapies. NBTXR3 is a first-in-class radioenhancer, composed of hafnium oxide nanoparticles, injected once intratumorally (IT) and activated by radiotherapy (RT) amplifying RT anti-tumoral response. Preliminary signs of NBTXR3 anti-tumor activity were evaluated in the dose expansion part of a phase I in cisplatin-ineligible patients (pts) with LA-HNSCC. Due to the unique features of NBTXR3, exploratory analyses aimed at defining if anti-tumor activity is a valuable metric for estimating OS.

Methods: Analyses were performed in 56 pts treated (April 2019-January 2022) with IT NBTXR3 in primary tumor followed by RT for primary tumor and involved lymph node. 44 pts were evaluable for objective tumor response. Correlation between response-related endpoints of IT lesion and LPFS with OS were compared with those using overall response and PFS. Restricted mean survival time (RMST) analyses were performed to assess if the RMST of response duration of the IT lesion and LPFS could estimate the probability of "success" for OS over clinically meaningful time points.

Results: In the evaluable population, best IT lesion and overall response rates were 81.8% and 79.5%, respectively: CR of 63.6% for IT lesion and 52.3 % for overall lesions. Median duration of response of IT lesion and overall lesions were 19 and 12 months, respectively. OS was 23 Months. Correlation between IT lesion response, LPFS, and OS tends to be higher than between overall response, PFS, and OS. RMST of LPFS and IT lesion response duration are closer to RMST of OS than PFS and overall response duration for all timepoints.

Conclusions: NBTXR3 radioenhancement may drive the objective response duration effect as noted in the difference between injected and non-injected lesions treated with the same dose of RT. Correlation and RMST analyses suggest that NBTXR3 effects on injected lesions might better estimate OS. These results support our ongoing phase III NANORAY-312 study design which allows injection of involved lymph nodes, and might be translated in higher OS than in our phase I.

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888P Phase I study of olaparib combined with loco-regional radiotherapy in patients with head and neck squamous cell carcinoma

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Background: PARP-inhibitors have potent radiosensitising properties in pre-clinical models; their use as radiation response modifiers in the clinic, however, are less well characterised. To identify the maximum tolerated dose (MTD) of the PARP inhibitor olaparib in combination with radiotherapy in patients with head and neck squamous cell carcinoma (HNSCC), a single institutional phase I dose escalation trial was conducted.

Methods: Twelve patients with HNSCC (laryngeal cancer (cT2N0M0 or cT1-2N1-2bM0), HPV-negative oropharyngeal cancer or HPV-positive oropharyngeal cancer associated with a history of smoking $\geq$ 10 pack-years (cT1-2N1-2bM0 or cT3N0-2bM0) or locally-advanced disease from both tumour sites), scheduled for radiotherapy, were entered in the study; nine were eligible for analysis. The starting dose of olaparib was 25 mg BID, combined with radiotherapy to a total dose of 70 Gy in 35 fractions of 2 Gy. The MTD was defined as the highest dose level at which not more than 20% of patients experience dose-limiting toxicities (DLT) or as the highest reached dose in the absence of DLT.

Results: Olaparib administration started 1 week prior to radiotherapy. In dose level I, this was followed by accelerated radiotherapy (70 Gy in 6 weeks) in combination with olaparib (25 mg BID). Because of DLT in 3 of 4 patients (acute tracheotomy in 2 patients at 5 and 7 months after treatment and osteoradionecrosis in 1 patient at 7 months after treatment), the olaparib dose was de-escalated to 25 mg QD, and combined with conventional radiotherapy (70 Gy in 7 weeks; dose level II). No DLT was observed in 5 patients in dose level II. After a median follow-up of 60 months, the 4-year local-regional control and overall survival rates were 77.8% and 88.9%, respectively.

Conclusions: Olaparib 25 mg QD combined with conventionally fractionated radiotherapy was well tolerated and identified as the MTD. This combination might be further explored in future olaparib dose escalation studies in patients with locally advanced HNSCC unfit for concurrent chemo- or bio-radiotherapy.

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889P CT-based radiomics models to predict progression in locally advanced head and neck cancer treated with definitive chemoradiation

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Background: Definitive chemoradiation (ChRT) is the treatment of choice in both unresectable and larynx-preservation locally advanced head and neck cancer (LAHNSCC). Validated biomarkers are needed to optimize the prediction of cancer outcomes. Imaging biomarkers can improve patient risk stratification and help personalize therapy.

Methods: Clinical data and baseline CT scans from retrospective LAHNSCC patients treated with definitive ChRT were collected. The dataset was split into training (80%) and test (20%). A 5-fold cross-validation was performed in the training set. From the primary tumor, 108 radiomic features were extracted. Survival analysis models and classification models were developed to assess actuarial progression-free survival (PFS) and 5-year progression (Yes/No), respectively. For the former, performance was evaluated using IPCW, C-Index (CI) and AUC, and for the latter, AUC, sensitivity (S), specificity (Sp), and accuracy (Acc) were used. Feature importance was measured by the SHAP method. Independent analyses using radiomics features +/- clinical variables were performed. Patient risk stratification in two groups using survival analysis models was assessed through Kaplan—Meier curves.

Results: Final dataset included 171 LAHNSCC patients; 55%, 21% and 24% were stage IVA, IVB and III respectively. Disease progression at 5 years was observed in 53% of patients. To predict PFS, a random survival forest model including 4 radiomic features and TNM provided the best results, with AUC of 0.64 and CI of 0.66. The model allowed patient stratification into low and high risk of progression (log-rank $p < 0.005$, HR 1.23 95%CI:0.60-2.54). A XGBoost model with 12 radiomic features and 4 clinical variables (primary tumor site [oral cavity the most important], TNM, age and smoking) to predict 5-year progression provided the best performance. This model yielded an AUC of 0.74, a S of 0.53, a Sp of 0.81 and an Acc of 0.66.

Conclusions: A model trained with clinical and radiomic data to predict 5-year progression outperformed that trained only with clinical variables. This model yielded more robust results than the PFS model, whose metrics resulted insufficient to draw solid conclusions. Further validation is required.

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890P Real-world survival outcomes and survival risk factors in elderly patients with locally advanced squamous cell carcinoma of the head and neck

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Background: Treatment options for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) include definitive non-surgical treatment with radiotherapy (RT) ± chemotherapy (CT) or primary resection followed by adjuvant RT ± CT. We aim to understand survival outcomes and survival risk factors in elderly patients with LA SCCHN who receive treatment.

Methods: The SEER-Medicare database (patients ≥65 years) was used. Patients with ≥1 year of baseline information and a diagnosis of stage III, IVa, or IVb SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx between January 2014 and December 2017 were included. Patients were followed until death, subsequent cancer, health plan enrollment change, or December 2019. We examined overall survival (OS) and used Cox proportional hazards models to estimate the association of baseline characteristics with survival.

Results: 2,303 patients were identified, with a mean age of 73.4 years. Of these patients, 64.6% received definitive non-surgical treatment, 32.7% received primary resection, and 2.7% received CT alone. In patients who received definitive non-surgical treatment, median OS was 15.3 mo for oral cavity cancer, 34.1 mo for hypopharyngeal cancer, and 34.6 mo for laryngeal cancer. In patients who were treated with primary resection, median OS was 30.6 mo for oral cavity cancer and 30.0 mo for laryngeal cancer. There were too few patients with hypopharyngeal cancer who received primary resection to report. Median OS in patients with oropharyngeal cancer was not reached in either treatment group. Age ≥70 (age ≥70 vs. <70, hazard ratio [HR], 1.2; $P<.05$); advanced disease stage (stage IVa vs stage III, HR, 1.4; $P<.05$; stage IVb vs stage III, HR, 2.8; $P<.05$) and higher National Cancer Institute (NCI) comorbidity scores (per unit; HR, 1.1; $P<.05$) were associated with worse survival.

Conclusions: Survival outcomes in elderly patients with LA SCCHN, and especially in patients ≥70 years, with advanced disease stage, and with higher NCI comorbidity scores, are poor. Innovative, effective treatments are needed for the elderly LA SCCHN patient population.

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891P Changing landscape of head and neck squamous cell carcinoma (HNSCC) treatment and survival in Thailand: A 13-year multicenter retrospective study of 6,319 patients

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Background: HNSCC is a heterogeneous group with diverse incidence and survivals worldwide. Factors such as ethnicity, lifestyle, and healthcare systems contribute to these differences. This study aimed to describe the landscape of HNSCC patient characteristics, treatments, and survival outcomes in Thailand over 13 years.

Methods: We retrospectively analyzed data from a multicenter database of patients with HNSCC treated between 2008 and 2020 in Thailand.

Results: A total of 6,319 patients from 4 large cancer centers were analyzed. Most patients had nasopharynx (NP 33%), oral cavity (OC 23%), oropharynx (OR 17%), larynx (LA 15%), or hypopharynx (HP 8%) as primary sites. The incidence of HPV-related oropharyngeal squamous cell carcinoma had been rising from 13% in 2008 to 42% in 2019-2020. Most patients presented with locally advanced (LA) stage (stage IVa/b 50%, and III 26%), and the proportion of LA stages increased annually. Chemoradiotherapy (CRT) (43%) and surgery (31%) with or without adjuvant (chemo) radiotherapy were the most common definitive treatments. Cisplatin (79%) was most used with CRT, followed by carboplatin (20%) and cetuximab (1%). Local, regional, and distant recurrences were observed in 46%, 19%, and 35% of all patients, respectively. Overall survival (OS) improved annually across all subsites. The use of intensity-modulated radiotherapy (IMRT) increased from 25% in 2008 to 90% in 2019-2020. Patients treated with IMRT had significantly longer OS compared to non-IMRT (HR 0.52, 95% CI 0.46-0.58; p<0.001).

Table: 891P

	3-yr OS	5-yr OS	10-yr OS
Year of diagnosis 2008 2009-10 2011-12 2013-14 2015-16 2017-18 2019-20	43% 62% 74% 71% 70% 73% 78%		
Primary site NP OP OC LA HP	69% 51% 58% 71% 47%	60% 45% 54% 64% 42%	48% 38% 44% 53% 35%
Radiotherapy technique 2D 3D IMRT	58% 63% 79%	49% 54% 71%	34% 44% 59%

Conclusions: This is the largest study of HNSCC patients in Thailand, highlighting the increasing survival outcomes despite the presentation of locally advanced stages. The growing utilization of IMRT might contribute to the improvement of survival outcomes for HNSCC patients in Thailand.

Legal entity responsible for the study: The authors.

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892P Real-world data validation of university of San Diego nomogram for the prediction of benefit of intensive treatment for locoregionally advanced head and neck cancer

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Background: Definitive concurrent chemoradiation (ChRT) +/- induction chemotherapy (ICT) is the only potentially curative strategy for unresectable locally advanced head and neck cancer (LAHNSCC) patients. However, it is an intensive treatment with high rate of acute and late toxicity. The nomogram developed in the University of San Diego (3 RTOG trials) and validated in the Veterans Affairs (VINCI dataset) allows risk stratification and identification of patients who benefit from intensive therapy (IT) (omega w score ≥ 0.80.) in overall survival (OS) through an online tool to calculate the w score. http://comogram.org//. Aim: to validate this nomogram in a Spanish population.

Methods: Clinical and treatment data from retrospective 290 LAHNSCC patients treated with definitive ChRT +/- ICT between 2010-2020 were collected. Performance of the nomogram for OS was assessed using: the area under the curve (AUC) and c-index (CI), Akaike information criterion (AIC), and the Nagelkerke test (of 0 to 1, the closer to 1 the better). Kaplan-Meier (log-rank test) and univariate Cox analysis to evaluate the interaction between IT (yes/no) and the w score (<0.8 or ≥0.8) were performed.

Results: 170 patients obtained a w score ≥0.8. The application of the nomogram in our series obtained a moderate yield (AUC:0.68; CI:0.67; AIC:332, Nagelkerke:0.84). It was shown that an w score >= 0.8 is a statistically significant independent risk factor for OS (HR 2.058, p-value < 0.001). In the population with w score <0.8 patients

treated with IT had not reached the median OS, while those without IT had an estimated median OS of 52.4 months. In contrast, in the population with w score ≥0.8, the median OS was 33.3 months (95% CI 2.7-66.3) in patients without IT, compared to 36.4 months (95% CI 22.8-49.3) in those patients treated with IT (p-value=0.005).

Conclusions: Our results support the utility of this nomogram in daily clinical practice in the Spanish population. It allowed an adequate stratification into 2 risk groups (high and low) based on the w score (<0.8 or ≥0.8) which was an independent prognostic factor, though we did not observe a differential effect of IT in these risk groups (benefit from IT in both).

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893P Tumor node stage shift following leukocyte interleukin injection neoadjuvant extends overall survival in treatment-naïve locally advanced oral cavity/soft palate squamous cell carcinoma

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Background: A 3-week pre-surgery peri-tumoral/peri-lymphatic administration of a pro-inflammatory cytokine complex biologic (LI) with CIZ (single low dose cyclophosphamide IV, 300 mg/m^2), indomethacin (po 25mg tid) and yinc multivitamins (po 15-45mg yinc) + Standard of Care (SOC) to treatment-naïve oral/soft palate (OSP) locally advanced SCC, resulted in CRs/PRs prior to surgery (RECIST 1.0) (pathology confirmed) significantly extend overall survival (OS) in NCCN-defined Lower risk for recurrence (LR) intent to treat (ITT) population vs SOC alone. Joint TN (jTN) stage determined at screening, prior to planned surgery, confirmed at surgery.

Methods: Subjects (923 ITT; 380 [LR], 467 higher-risk) AJCC Stage III/IVa OSP SCC, treatment naïve were randomized 3:1:3 to treatment (Tx) arms LI (+/- CIZ) + SOC or Control (SOC only). LI treated (Tx) received ½ dose 200IU peritumorally + ½ dose daily peri-lymphatically x5/wk for 3 weeks before surgery. Each Tx had comparable (55-56 months median) follow up.

Results: TN data were available at screening and surgery for 815/923 ITT subjects; and 43 pre-surgery responders (R), a general trend of worsening in jTN stage entry to surgery with 6-7% more improved jTN for both LI-Tx vs SOC.

Table: 893P

Treatment	jTN Surgery Outcome Relative to Screening				
	Worse (W)	Same	Improved (I)	2-sided p-value (I vs W)	2-sided p-value vs SOC
LI+CIZ+SOC	118 (34.0%)	134 (38.6%)	95 (27.4%)	0.1315	0.2781
LI+SOC	40 (34.8%)	43 (37.4%)	32 (27.8%)	0.4096	0.4792
Combined LI	158 (34.1%)	177 (38.3%)	127 (27.5%)	0.0754	0.2552
SOC	121 (34.2%)	158 (44.8%)	74 (21.0%)	0.00094	-

No significant differences at screening for subsequent R vs non-R; significant improvement in jTN stage from screening to surgery for LI R (88% improved); jTN differences (p<0.0001) between LR vs HR allowing differentiation of LR from HR at entry. LI-Tx subjects with jTN (I) had >50% 5-year overall survival (OS), while 5-yr OS was <50% for SOC. LI+CIZ+SOC 5-yrs OS >60% (I vs W) p <0.0001; 5-yr OS 30% (W), 50% (Same); LR LI+CIZ+SOC R 5-yr OS >75%, p <0.0001.

Conclusions: jTN differentiated LR vs HR at entry enabling us to search for LR subjects as ideal for neoadjuvant LI-Tx to extend OS. LI neoadjuvant jTN improvement is highly associated with OS joining pre-surgery response to LI as another surrogate marker for OS.

Clinical trial identification: (IT-MATTERS; NCT01265849).

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894P Is pathological complete response (PCR) a surrogate endpoint of overall survival in patients with technically unresectable oral cavity cancers? A real-world data study of 900 plus patients

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Background: Technically unresectable oral cavity squamous cell cancers (OCSCC) are non-amenable to upfront surgery. Neo-adjuvant chemotherapy (NACT) can down-stage the tumor and facilitate surgical resection. Pathological complete response (PCR) post NACT is a surrogate endpoint of overall survival in rectal and breast cancers. However, it's importance in patients with borderline resectable OCC is unknown.

Methods: This was an institutional review board approved retrospective analysis of a prospectively collected dataset of borderline resectable OCSCC patients who received NACT. Adult patients with an Eastern Co-operative Gncology Group (ECOG) performance status (PS) 0-2 who were deemed as technically unresectable in a multi-disciplinary clinic (MDC) were included. These patients received 2-3 cycles of NACT (3-weekly) and underwent a response assessment. Depending on response and general condition, they were re-assessed in MDC and further therapy was decided. Patients with good general condition who became resectable underwent surgery followed by appropriate adjuvant therapy. Overall survival (OS) was calculated from date of diagnosis to date of death. Kaplan-Meier method was used for estimation of OS. Impact of pathological response on OS was assessed using the log-rank method.

Results: 929 patients underwent surgery followed by adjuvant CTRT in 26.7% patients or adjuvant RT in 1.3% patients. 76 (8.2%) patients attained pathological complete response. 871 (93.8%) achieved negative margins. Three hundred forty (39.3%) patients had pT4 disease. Lympho-vascular invasion was seen in 53 (5.7%) while peri-neural invasion was seen in 186 (20.0%) patients, and 338 (36.4%) had extra-nodal extension. The median OS of entire cohort was 17 months (95% CI: 14.7 — 19.3 months). The median OS of patients who attained PCR was 55 months (95% CI: 22.9 — 87.1 months) vs 16 months (95% CI: 13.9—18.1 months) for those who did not attain PCR (p=0.004). The corresponding 10-year OS were 21.1% (SE-3.2%) and 40.5% (SE-7.4%).

Conclusions: Pathological complete response is a surrogate marker of long-term overall survival in patients of technically unresectable oral cavity cancers.

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895P Neoadjuvant PD-1 inhibitor combined with Nab-paclitaxel and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NCT05522985): A randomized, controlled, open label, phase II clinical trial

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Background: Many previous clinical trials have confirmed that induction chemotherapy can improve the functional retention rate of head and neck squamous cell carcinoma (HNSCC) and improve the quality of life. However, pts have no long-term survival benefits from it. Immunotherapy has brought hope for long-term survival to pts with recurrent and metastatic HNSCC. The exploration of neoadjuvant immunotherapy in HNSCC is gradually being carried out.

Methods: This was a randomized, controlled, open label, phase II study. 122 pts were panned to enrolled. Key inclusion criteria: histologically or cytologically confirmed stage III or IV resectable HNSCC; without prior systemic anticancer therapy. Eligible pts were randomized 1:1 to A or B arm. A arm received 3 cycle of nab-paclitaxel (260 mg/m^2 , d1, q3w) and cisplatin (75mg/m^2, q3w); B arm received 3 cycle of toripalimab (240mg, D1, q3w), the rest of treatments were the same as A arm. Then surgery and pathological remission evaluation were performed. The primary endpoint was pathologic complete response (pCR) rate. Secondary endpoints were major pathological response (MPR), objective response rate (ORR), 2-year progression-free survival (PFS) rate, 2-year overall survival (OS) rate, and safety.

Results: Up to Dec. 2022, 99 pts were enrolled (A 47, B 52). Median age was 59 years (range: 34—76) and 83.8% were male. After neoadjuvant treatment, 68 pts underwent surgery (A 30,B 38). More pts achieved pCR (55.3% vs. 36.7%) and MPR (81.58% vs. 53.55%, p=0.01) in the B arm. Higher clinical downstage rate (36.54% vs. 25.53%) and pathologic tumor response-2 (pTR-2) rate (47.37% vs. 16.67% ,p=0.008) was observed in the B arms. Grade ≥3 treatment-related adverse events (TRAEs) were 14.29% in A arm, 27.91% in B arm. No new safety signals were observed and no TRAEs leading to death.

Conclusions: Compared with chemotherapy, neoadjuvant immunochemotherapy can significantly improve the MPR and pTR-2 rate of HNSCC. Moreover, adverse events are controllable. This study is ongoing. And we look forward to demonstrating that neoadjuvant immunochemotherapy is expected to improve the long-term survival of HNSCC.

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Disclosure: All authors have declared no conflicts of interest.

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896P Efficacy and safety of pembrolizumab with preoperative neoadjuvant chemotherapy in patients with resectable locally advanced head and neck squamous cell carcinomas

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Background: This study aimed to explore the efficacy and safety of pembrolizumab combined with chemotherapy as neoadjuvant therapy in patients with resectable locally advanced head and neck squamous cell carcinomas (LA-HNSCCs).

Methods: In this prospective, single-arm, single-centre clinical trial, patients meeting the inclusion criteria were treated neoadjuvant therapy of preoperatively with 200 mg pembrolizumab combined with 75 mg/m^2 cisplatin and 175 mg/m^2 paclitaxel. This was followed by surgery and postoperative adjuvant therapy. The primary endpoint was the postoperative pathological complete response (PCR) rate. All statistical analyses were performed using SPSS 26.

Results: A total of 22 patients were enrolled, and the baseline characteristics were shown in Fig. 1. The postoperative PCR rate, was 36.4% (8/22), and there was no delay to surgery due to adverse drug reactions. The rate of laryngeal function preservation was 90.9% (20/22). Delayed wound healing was the main surgical complication, with an incidence of 22.7% (5/22). The median follow-up time was 9.5 months, and only 1 patient (4.55%) suffered a regional recurrence.

Table: 896P

Variables	Number of patients	%
Male/Female	21/1	
Age (mean ± SD, years)	58.1±10.49 (22～69)	–
Primary site		
Oropharynx	6	27.3
hypopharynx	15	68.2
Oral Cavity	1	4.5
Hypopharynx invasion (N=15)		
Fixed vocal cord	9	60
Extend to esophagus	2	13.3
Tobacco		
YES	16	72.7
NO	6	27.3
Alcohol		
YES	15	68.2
NO	7	31.8
P16 states		
Positive	4	18.2
Negative	18	81.8
T stage		
T1-T2	8	36.4
T3	7	31.8
T4	7	31.8
N stage		
N0-N1	3	13.6
N2	19	86.4
Stage		
II	3	13.6
III	3	13.6
IV	16	72.7
PD-L1 combined positive score		
< 5	7	31.8
5-10	2	9.1
≥10	13	59.1

Conclusions: Preoperative treatment with pembrolizumab and chemotherapy in resectable LA-HNSCC has a high PCR rate with no significant impact on surgical safety. This treatment was found to increase the rate of laryngeal function preservation. However, the effects of neoadjuvant immunotherapy on long-term prognosis in LA-HNSCCs require further study.

Clinical trial identification: Trial registration: Chinese Clinical Trial Registry, ChiCTR2200055719, Registered 16 January 2022.

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897P Nanosomal docetaxel lipid suspension (NDLS) or docetaxel based neoadjuvant therapy in Head and neck squamous cell carcinoma: Post hoc analysis of a prospective, randomized study

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Background: TPF (Docetaxel, Platinum & 5-Fluorouracil) or TP regimen as neoadjuvant chemotherapy (NACT) in head and neck cancer are associated with a high rate of adverse events. Many of these adverse events are contributed by docetaxel. We wanted to analyze whether a change in formulation from conventional docetaxel to nanosomal docetaxel lipid suspension (NDLS, Doceaqualip) leads to decreased adverse events.

Methods: This was an exploratory analysis from the data of a prospective, single-center, phase 3 randomized study. The patients received either the TPF or TP regimen as a part of randomized study. The choice of docetaxel was at physician discretion. The adverse events rate during NACT were captured as per NCI- Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Out of 495 patients, data for adverse events and formulations was captured in 479 patients. Among these, we had 4 groups- Group-1 : NDLS in all cycles (192 (40.1%)), Group 2: docetaxel in all cycles (172(35.9%)), Group 3 : 1st cycle NDLS and rest docetaxel (64 (13.4%)) and Group 4: 1st cycle docetaxel and rest NDLS (51 (10.6%)). For this analysis we have restricted the comparison between group 1 & 2. A univariate analysis with Fisher's test was performed to study whether the different formulations had any impact on adverse event rate. The response rate and overall survival (OS) were compared between the 2 formulations.

Results: The use of NDLS led to a significant decrease in the incidence of mucositis and neutropenia (Table). The efficacy was statistically similar between group 1 and 2 with respect to response rates (24.7% versus 29.6%, P=0.301), and median OS (10.1 [8.526-11.674] versus 11.37 [10.320-12.414], P=0.07). Any Grade

Table: 897P

Parameter, n (%)	Group 1 (n=192) NDLS	Group 2 (n=172) Docetaxel	P-value
Mucositis	**84 (43.8)**	**113 (65.7)**	**0.000**
Weight loss	27 (14.1)	31 (18)	0.373
Nausea	65 (33.9)	59 (34.3)	0.132
Vomiting	50 (26)	52 (30.2)	0.830
Diarrhea	100 (52.1)	109 (63.4)	0.174
Neutropenia	**79 (41.1)**	**97 (56.4)**	**0.012**
Anemia	154 (80.2)	143 (83.1)	0.189
Thrombocytopenia	50 (26)	66 (38.4)	0.092
Rise in creatinine	17 (8.9)	6 (3.5)	0.088
Hyponatremia	161 (83.9)	147 (85.5)	0.290
Hypokalemia	**75 (39.1)**	**103 (59.9)**	**0.001**
Hypomagnesemia	**103 (53.6)**	**110 (64.0)**	**0.022**
SGOT rise	48 (25.0)	37 (21.5)	0.620
SGPT rise	72 (37.5)	48 (27.9)	0.080

Conclusions: Use of NDLS formulation instead of conventional docetaxel leads to a decrease in adverse events like mucositis and neutropenia when used as neoadjuvant therapy in oral squamous cell carcinoma with similar efficacy.

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898P Meta-analysis of two placebo-controlled trials of avasopasem manganese (AVA) in patients with locally advanced, head & neck cancer (LAHNC)

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Background: Oral mucositis (OM) is severe in up to 70% of patients receiving standard chemoradiation (7 weeks of RT and concurrent cisplatin). Cisplatin contributes to the acute toxicity (acute kidney injury, tinnitus, myelosuppression) during treatment but also causes irreversible chronic kidney disease (CKD) in up to 30% of patients in the years following treatment. Two randomized, placebo-controlled, blinded studies, ROMAN (NCT03689712) and GT-201 (NCT02508389), evaluated avasopasem 90mg (AVA) for the reduction of severe OM (SOM, WHO grade 3-4) and both met their primary endpoints.

Methods: The ROMAN phase 3 (ITT N=407) and GT-201 phase 2b trials (ITT placebo and 90 mg N=144) results were aggregated using conventional methods for fixed-effects meta-analysis. In ROMAN, prospectively defined follow-up of serum creatinine (sCr) and estimated glomerular filtration rates (eGFR) were assessed every 3 months for 1 year following 7 weeks of CRT.

Results: The meta-analysis of ROMAN and GT-201 (N=551 [313 AVA/238 PBO]) showed a 19% relative reduction in SOM incidence (52% vs 64%; *P*=0.0053), 58% relative reduction in SOM duration (median, 8 vs 19 days; *P*=0.0002), 32% reduction in Grade 4 incidence (22% vs 32%; *P*=0.0102), and 28% delay in median days to SOM onset (median 50 vs 39 days; *P*=0.0005). Adverse event frequencies were mostly comparable between treatment groups with a trend towards reduction of certain IMRT- and cisplatin-related toxicities including tinnitus which was reported less with AVA in both studies. At 1-year follow-up, AVA was associated with significant improvements in preservation of eGFR (*P*=0.0008) and sCr (*P*=0.006) levels vs PBO. Grade 3+ CKD results through 12 months show 10% AVA vs 20% PBO (relative risk 0.55, *P*=0.0043).

Conclusions: AVA produced statistically significant, clinically meaningful improvement of SOM vs PBO that was consistent across multiple measures of SOM, with an adverse event profile consistent with expectations for IMRT/cisplatin. At 1-year follow-up, AVA appears to reduce cisplatin-related CKD in the study population.

Clinical trial identification: GTI-4419-301, 13 July 2020 (NCT03689712).

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899P Impact of COVID-19 pandemic on treatment and survival in head and neck squamous cell carcinoma (HNSCC) patients (IMPACCT Study)

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Background: Standard of care (SOC) treatment (ttm) of HNSCC patients (pts) was compromised and had to be adapted during the COVID-19 pandemic due to collapse of the healthcare system. The IMPACCT study evaluated the impact of COVID19 on ttm and outcome in pts diagnosed during the first-wave (Guillen, P. ASCO 2021, P6061). The 3-year follow-up results are presented.

Methods: Retrospective cohort analysis of newly diagnosed HNSCC pts from January to June 2020 treated with curative intent (CT20) at Institut Català d'Oncologia (ICO). A cohort treated during the same period at ICO from 2018 and 2019 was used as a control group (CG). Pts were followed until 3 years after diagnosis. Clinical characteristics were obtained from in-house prospective database. Ttm deviations from SOC per COVID-19 contingency protocol (CCP) in CT20 were collected. Recurrence-free survival (RFS) and overall survival (OS) rates from 6 to 36 months (m) were compared among cohorts by Log-rank test.

Results: A total of 306 pts were included: CT20=99; CG=207. Despite balanced disease characteristics, a lower proportion of pts underwent surgery as primary ttm in CT20 vs CG (47 vs 60%, p=0.04). In conservative treated pts, persistence disease rate was higher in CT20 vs CG (25 vs 10% p=0.03). CT20 had significantly lower RFS and OS rates only at 6 and 12m, when compared to CG (see table). Within CT20 pts, 39% had ttm modifications from SOC: 27% due to CCP (surgery to conservative ttm 13%, reduction of high-dose cisplatin to 2 cycles 10%, altered radiotherapy 2%, no induction/adjuvant ttm 2%) and 12% due to COVID-19 (delay of ttm start 9%, upstaging 3%). 3-year RFS nor OS did not differ in pts with ttm modifications vs unmodified ones (57 vs 43% p=0.2; 67 vs 55% p=0.1, respectively).

Table: 899P

	6m	12m	18m	24m	36m
RFS (%)					
CG	88 (83.5-92,7)	76.0 (70.2-82.3)	68.2 (62.0-75.1)	63.0 (56.5-70.2)	57.3 (50.7-64.7)
CT20	79.8 (71.9-88.6)	65.2 (56.0-75.9)	61.8 (52.5-72.8)	58.4 (49.0-69.6)	48.6 (39.1-60.4)
	p=0.082	p=0.055	p=0.19	p=0.29	p=0.13
OS (%)					
CG	95.8 (93.0-98.7)	85,3 (80.5-90.5)	78.5 (72.9-84.6)	74.9 (69.0-81.3)	69.6 (63.4-76.5)
CT20	88.9 (82.6-95.6)	83.3 (76.0-91.4)	72.2 (63.5-82.1)	67.7 (58.7-78.1)	61.6 (52.3-72.7)
	p= 0.025	p=0.58	p=0.23	p=0.20	p=0.16

Conclusions: The COVID-19 pandemic led to ttm modifications from SOC and had an early detrimental impact on RFS and OS when compared to prior years. Ttm modifications did not seem to explain survival differences. Further analyses are ongoing.

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Plana Serrahima: Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Invited Speaker: MSD; Financial Interests, Institutional, Other: Nanobiotix. M. Oliva: Financial Interests, Personal, Invited Speaker: BMS, Merck, MSD; Financial Interests, Personal, Other, Teaching activities: Merck, MSD; Financial Interests, Personal, Advisory Board: Merck, MSD; Financial Interests, Personal, Writing Engagement: MSD; Financial Interests, Personal, Other, IDMC: Transgene; Non-Financial Interests, Institutional, Local PI: AbbVie, ALX Oncology, Ayala Therapeutics, Bayer, Boehringer Ingelheim, Debiopharm, Gilead, ISA Therapeutics BV, Merck, MSD, Roche, Seagen; Non-Financial Interests, Institutional, Funding: GSK; Non-Financial Interests, Personal and Institutional, Funding: Roche. All other authors have declared no conflicts of interest.

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900P COVID-19 in patients with head and neck cancers (HERODOTUS): An international, registry-based, cohort study

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Background: We aimed to study the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections on patients with head and neck malignancies and evaluate the efficacy of vaccination.

Methods: The Head and Neck cancERs international cOviD-19collabOraTion (HERODOTUS) registry is a multicentre observational study comprised of a retrospective component and a prospective cohort component. Eligibility criteria were the presence of any head and neck cancer (including salivary gland, thyroid, nasal and paranasal cancer) and a COVID-19 diagnosis. Clinical data were extracted from medical records of consecutive patients from November 1, 2019 until September 30, 2022. Associations between demographic or clinical characteristics and outcomes were measured by odds ratios (ORs) with 95% CIs using univariable and multivariable logistic regression; sex, age, smoking status, and HPV status (for oropharynx cancer) were the covariates included in the multivariable analysis. End points include mortality, hospitalization, symptomatic COVID-19 infection, asymptomatic COVID-19 infection, and delay in cancer therapy.

Results: 395 COVID-19+ head and neck cancers were identified, out of which, there were 76 deaths. Univariable analyses revealed that age >63 years (OR 3.4, CI 1.9-5.9)); being a current or former smoker (OR: 2, CI: 1.1-2.8), having comorbidities (OR: 2.4, CI: 1.2-5), having a history of COPD (OR: 3.6, CI: 1.7-8), having squamous cell carcinoma (HNSCC) (OR: 4.3, CI: 1.8-10.2), or receiving treatment with chemotherapy and cetuximab (OR: 3.8, CI: 1.4-10.5) were associated with increased risk of death, whereas vaccination was protective (OR: 0.20,CI: 0.11 — 0.34). On multivariable analysis, age>63 yo (OR: 2.3, CI: 1.0-5.2), COPD (OR: 4.9, CI: 1.8-13.8), and chemotherapy with cetuximab (OR: 6.1, CI: 1.9-20) were associated with increased risk of death. Non-vaccinated HNSCC pts had an OR for death of 27.7 (CI: 6.2-122).

Conclusions: This is the largest, to our knowledge, cohort of patients with Head and Neck Cancer and COVID-19. The data show the negative impact of age, COPD and the chemotherapy plus cetuximab regimens on survival while vaccination was protective.

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901P Gut microbiome metagenomics and toxicity outcomes from chemoradiation therapy in head and neck squamous cell carcinoma

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Background: Chemoradiation (CRT) in patients (pts) with locally advanced head and neck squamous cell cancer (HNSCC) is associated with significant toxicities, including oral mucositis (OM). The gut microbiome (GM) is an emerging biomarker of treatment outcomes and adverse events. This study aimed to investigate the role of GM composition to predict CRT toxicities in HNSCC pts, including development of severe OM.

Methods: We prospectively collected fecal samples of 52 pts with HNSCC undergoing CRT. Using shotgun metagenomic sequencing and MetaPhlAn4 pipeline, LefSe differences in GM composition at baseline were assessed according to CTCAE v4.0 toxicity grading including OM and enteral feeding tube requirement. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method.

Results: Most tumors (n=40) were p16-positive, including oropharyngeal (n=35) and unknown primaries (n=4). TNM staging was III-IV in 54% (n=28). After a median follow-up of 27 mo, the 12-mo OS and PFS were 96% and 84%, respectively. In terms of toxicity, OM was seen in all pts, and 22 pts (42%) developed grade ≥3 OM. Thirteen pts (25%) required enteral feeding. Grade ≥3 OM was associated with a significant decrease in OS (p=0.02) even when accounting for staging and p16 status in multivariate analysis (MVA; p<0.05), as well as a numerically shorter PFS (p=0.09). No baseline characteristic correlated with increased risk of severe OM in MVA. However, GM beta-diversity differed between grade 1-2 and grade 3 OM (PERMANOVA p=0.04) but there was no difference in alpha-diversity. Pts with severe OM had distinct GM enriched with *Mediterraneibacter* (*Ruminococcus gnavus)* and members of the Clostridiaceae family, including *Hungatella hathewayi*. In pts with mild OM, *Eubacterium rectale*, *Alistipes putredinis* and members of the Ruminococcaceae family were overrepresented. We observed similar microbiome differences in pts requiring enteral feeding.

Conclusions: Severe OM was associated with decreased OS and PFS in pts with HNSCC undergoing CRT. Pts who developed severe OM or required enteral feeding had a distinct GM enriched with deleterious bacteria that have been associated with resistance to immune checkpoint inhibitors.

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902P Cisplatin-induced ototoxicity in head and neck cancer: The patterns and prediction

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Background: Cisplatin (CDDP) is the most frequently used chemotherapeutic agent for head and neck cancer (HNC). The objectives of this study were to estimate the incidence rate of CDDP-induced ototoxicity (CIO) and the threshold dose causing ototoxicity, and reveal the related factors in HNC.

Methods: Three hundred and thirty-two patients of HNC received chemotherapy containing CDDP at Kyoto University Hospital from June 2009 to December 2022. The distortion product otoacoustic emission (DPOAE), tympanometry (TPG), and pure-tone audiometry (PTA) were measured after each administration of CDDP. Patients with bilateral conductive hearing loss, and/or the ear side with otitis media were excluded. The factors associated with CIO synergistically were investigated by evaluating the baseline characteristics.

Results: A total of 304 of the 332 patients were included in the analysis. The mean age before CDDP administration was 60.5 years (range, 24-79). Primary sites were nasopharynx (6.6%), oropharynx (21.1%), hypopharynx (20.7%), larynx (7.2%), oral cavity (28.3%), paranasal sinuses (8.9%), and other sites (7.2%). The mean cumulative CDDP doses were 200.0 mg/m2 (range, 48- 800, median 190.0). Dose-dependent hearing threshold shift was observed mainly in the high-frequency speech range. The incidence rate of ototoxicity detected by DPOAE and PTA were 46.4% and 37.8%, respectively. The median cisplatin doses causing deterioration of DPOAE were lower than PTA (210.0 mg/m^2 v.s.258.0 mg/m^2, $p < 0.05$). Above 300 mg/m^2 of cumulative CDDP dose, CIO was detected in 56.5% by PTA. Related factors for CIO were the cumulative doses of CDDP, concurrent use of radiotherapy, and high-frequency hearing impairment before treatment ($p < 0.05$, respectively).

Conclusions: Implicit hearing loss caused by CDDP was observed at dose of 211 mg/m^2, although subjective hearing loss appeared at dose of 258 mg/m^2. Cumulative doses of CDDP, concurrent use of radiotherapy, and high-frequency hearing impairment before treatment were identified as risk factors for CIO. Monitoring of hearing level is suggested for early detection of CIO especially in patients with high-frequency hearing impairment before treatment.

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903P AL101 therapy in patients with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC): Final ACCURACY trial results and meta-analysis of clinical outcomes

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Background: Approved therapies for R/M ACC are lacking. Notch mutations (Notch^{mut}) are found in ∼20% of ACC and are linked to aggressive disease and poor prognosis. AL101 is a gamma-secretase inhibitor that blocks Notch signaling, which is being prospectively studied in this biomarker driven high-risk population.

Methods: ACCURACY is a phase 2, multicenter, open-label study of AL101 (4 or 6 mg IV QW) in patients (pts) with R/M ACC and Notch1-4^{mut} with evidence of disease progression. The primary endpoint was investigator-assessed objective response rate (ORR) by RECIST v1.1 (or modified MDACC bone criteria). A benchmark for the ACCURACY results was developed from a meta-analysis of outcomes among R/M ACC pts (regardless of Notch status) treated in other clinical trials.

Results: ACCURACY enrolled 87 pts with median age 50 and 59 years in the 4 mg and 6 mg arms, respectively. Prior systemic therapy was used in 60% of 4 mg and 51% of 6 mg pts. As of the data cutoff of 27 Oct 2022, among 77 evaluable pts, ORRs of 14.6% for 4 mg and 8.3% for 6 mg compared favorably with ORRs from the meta-analysis (Table). The most common treatment-related adverse events (TRAE) for pooled doses were diarrhea (70%), fatigue (51%), nausea (47%), hypophosphatemia (38%), vomiting (28%), and cough (25%). Grade 3 and 4 TRAE occurred in 35 (40%) and 2 (2%) pts, respectively. TRAE led to discontinuation of AL101 in 6 (7%) pts (3 on 4 mg and 3 on 6 mg) and 2 (2%) deaths (pneumonia and acute respiratory syndrome).

Table: 903P Tumor response rates in ACCURACY trial and meta-analysis of other clinical trials. *Inverse variance method, no transformation, 0.5 continuity correction. ORR: CR + PR; DCR: CR + PR + SD

	Objective Response Rate (ORR) % (95% CI)	Disease Control Rate (DCR) % (95% CI)
ACCURACY Trial (unconfirmed-local)	**Proportion**	**Proportion**
AL101 4 mg (n=41)	14.6 (5.6, 29.2)	70.7 (54.5, 83.9)
AL10 6 mg (n=36)	8.3 (1.8, 22.5)	66.7 (49.0, 81.4)
Meta-analysis	**Pooled Proportion***	**Pooled Proportion***
All studies	3.3 (2.2, 4.4) (58 studies)	75.4 (69.7, 81.0) (50 studies)
Studies reporting RECIST v1.1 + progressive disease (PD) in 2015-2022	3.4 (1.5, 5.2) (22 studies)	79.8 (71.0, 88.6) (18 studies)

Conclusions: AL101 showed acceptable safety and tolerability in ACC pts with Notch^{mut} and a response rate comparable to pooled estimates for available therapies in pts regardless of Notch status.

Clinical trial identification: NCT03691207, EudraCT 2019-000309-64.

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904P Retrospective analysis of adjuvant systemic anti-hormonal therapy for resected androgen receptor-positive (AR+) salivary duct carcinoma (SDC)

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Background: Salivary duct carcinoma (SDC) is one of the salivary gland cancers. Standard treatment consists of tumor resection followed by post-operative radiotherapy. Approximately 70% of patients experience recurrent/metastatic (R/M) disease. The added value of adjuvant androgen deprivation therapy (ADT) or combined androgen blockade (CAB) has already been studied in a small cohort (n=22), showing increased 3-year disease-free survival (DFS) as compared to a historical cohort. Here, we retrospectively investigated whether adjuvant systemic anti-hormonal therapy is beneficial for DFS and overall survival (OS) in a larger poor-risk SDC cohort.

Methods: The adjuvant-treated cohort described by Van Boxtel et al. (2019) was extended with 40 resected stage IV A/B SDC patients that have been treated with adjuvant ADT/CAB at Radboudumc between 2014 and January 2023. Treatment consisted of bicalutamide, goserelin, or a combination of both. The historical cohort was not modified nor expanded (n=114). The endpoints included DFS and OS.

Results: Sixty-one patients were treated with adjuvant ADT/CAB, with a median duration of therapy of 12 months. Differences in DFS/OS between adjuvant ADT and CAB have not been found. Median follow-up for the adjuvant patients was 24 months (range: 0 – 114 months) and 30 months for the control cohort (range: 0 – 216 months). Adjuvant-treated patients had longer mDFS and mOS as compared to the historical cohort (mDFS: 33 months [95% CI 6.5 – 59.5] *vs.* 20 months [95% CI 15.3 – 24.7; HR 0.676, 95% CI 0.433 – 1.057; $p=0.086$]; mOS: 73 months [95% CI 43.8 – 102.2] *vs.* 45 months [95% CI 32.8 – 57.2; HR 0.595, 95% CI 0.343 – 1.033; $p=0.060$]). The adjuvant-treated patients generally exhibited better DFS and OS at 3 years than the control group (adjuvant: 46% and 68%, respectively, control: 33% and 54%, respectively).

Conclusions: Poor-risk AR+ SDC patients treated with adjuvant systemic anti-hormonal therapy showed prolonged, however not significant, DFS and OS as compared to non-adjuvant treated historical controls.

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905P Hot topics in salivary gland carcinomas treatment: An EORTC young investigator and early career investigator survey

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Background: Recently, ASCO and ESMO guidelines on Salivary Gland Carcinomas (SGCs) have been released. Several crucial points lack strong recommendations, due to low or intermediate quality of evidence. We conducted a survey in the EORTC Head and Neck Cancer Group (HNCG) members, on behalf of the EORTC Young and Early Career Investigator to better address such "grey zones" of the guidelines.

Methods: The survey included 29 questions, covering diagnostic and therapeutic issues of SGC patients and was shared among 539 members of the EORTC HNCG. Responses were collected from December 2022 to March 2023. The primary aim was to evaluate decision criteria guiding physician's on areas of low evidence of SGCs guidelines.

Results: Among 102 responders, aged 40-55 years (55%), 45%, 28%, 22%, and 5% were medical oncologists, radiation oncologists, ENT surgeons, and other specialists, respectively. Respondents were distributed across Europe (mainly Italy 19%, Belgium 10%, and Spain 8%). Chemoradiotherapy (CRT) in the definitive and adjuvant (adj) settings in case of pathological high risk features was recommended by 35% and 30% of them, respectively. In case of R0 resection of highly aggressive SGC, at pT1-2 stage, 37% proposed close follow up, while 38% proposed adj lymph node (LN) field RT; for pT3-4 stage, 48% proposed adj LN field RT in all cases, and 44% proposed adj LN field RT only based on risk factors. After salvage surgery for locoregional relapse, the most important factors guiding decision to give adj RT were previous radiotherapy, margin status, and presence of extranodal extension. Fifty% of respondents would propose adjuvant antiHER2 or anti androgen receptor (AR) treatment within clinical trial (if positive receptor status). In case of combined positivity to HER2 and AR, responses were heterogeneous regarding the choice for first-line treatment.

Conclusions: Due to a lack of high-level evidence, international guidelines do not provide strong recommendations in several fields of SGCs diagnosis and treatment, contributing to inconsistent approaches in clinical practice. Further prospective trials are required to better address these topics.

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906P Multi-parameter flow cytometry analysis of circulating immune cell populations in recurrent/metastatic adenoid cystic carcinoma

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Background: Adenoid cystic carcinoma (ACC) is characterized by high recurrence rates despite surgery and radiotherapy, and anti-PD-1/PD-L1 therapy has limited clinical efficacy in the recurrent/metastatic setting. This study sought to characterise circulating immune cell sub-sets and identify candidate targets for novel immunotherapies in ACC.

Methods: Blood samples from 22 anti-PD1/PDL1 naive ACC patients, 26 anti-PD1/PDL1 naive head and neck squamous cell carcinoma (SCC) patients and 13 healthy volunteers underwent multi-parameter flow cytometry for comprehensive classification of the immune cell populations, using commercially available validated panels. Results were analysed using FlowJo.

Results: This study identified significant expansion of CD14hi/CD16+ monocytes compared with healthy volunteers in a sub-population of ACC patients (mean 28%, range 10% to 58%, versus 9% range 1% to 20% $p<0.05$). This monocyte sub-set was also seen in the comparator group of SCC patients (mean 36%, range 12%-78%.) Expression levels of PDL1 on CD14+ monocytes was greater in ACC monocytes compared to samples from our SCC patient cohort (mean 60% v 32%; $p=0.09$). Furthermore, 55% of ACC patients had elevated COX-2 expression (greater than 30%), by intracellular fluorescence activated cell sorting in CD14+ monocytes compared with 22% in our SCC group. With regards to T cells, peripheral blood from ACC patients had a decreased CD4+/CD8+ ratio compared to SCC (2.85 vs 5.5.) Furthermore, a significantly higher proportion of CD8+ cells were naïve as defined by CCR7+/CD45RA+ (Mean 38% vs 16% $p<0.01$). No differences were observed in the proportions of NK T cells, though we did identify a highly significant reduction of TIGIT on them in ACC compared with SCC patients (16% versus 40% of total CD3+ $p=<0.001$).

Conclusions: This study provides insights into distinct immune cell subsets in ACC patients. Our findings suggest that novel immunotherapies, including targeting of COX-2, may be have a rationale in ACC. Additionally, TIGIT is associated with exhaustion and so the reduced expression of TIGIT on NK-T cells in ACC may help guide future trial selection.

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907P Radiosensitivity signature in adenoid cystic carcinoma (ACC) of salivary glands origin is associated with ACC type II

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Background: Adenoid cystic carcinoma (ACC) is characterized by multiple relapses and a poor prognosis. It is commonly considered a radioresistant tumor, indeed particle radiotherapy is especially indicated in ACC. Recently, ACC was stratified in two clusters with a different prognosis, ACC type I and II, according to distinct molecular features i.e. NOTCH activating mutation and TP63 upregulation, respectively. We aimed to disclose molecular profiles predictive of radiosensitivity or radioresistance features.

Methods: The study cohort comprised 54 patients with ACC of salivary gland origin, treated with surgery plus photon beam radiotherapy (R) or R alone. A survey in the literature yielded a list of 15 signatures including pan-cancer or different tumor-specific models (e.g. head and neck; breast cancer; glioblastoma; prostate cancer) with a total of 141 genes. The expression levels of these genes were retrieved and signatures scores were imputed following the methods described in the original papers. Log2-trasformed transcripts per million mapped reads values were retrieved from Ferrarotto et al. [PMC7854509]. Clinical and follow-up data were updated at 31st December 2022; overall survival (OS) as endpoint was estimated with the Kaplan-Meier method.

Results: Only the signatures developed on breast cancer gene-expression datasets among those investigated were able to stratify ACC patients; in particular, we focused on an immune-radiosensitivity signature [PMC8984882] able to reach HR=7.59, 95% CI 3.19-18.09, p=1e-07. The predicted radiosensitivity of this signature was significantly associated with ACC type II and lack of NOTCH mutations.

Conclusions: Molecular profile of ACC type II is significantly associated with an intrinsic radiosensitivity. The association of ACC radiosensitivity to breast cancer signatures warrants further research on the biology behind ACC and its molecular similarities.

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908P Efficacy of NOTCH inhibitors (Ni) relative to prior systemic therapy or observation in patients (pts) with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC)

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Background: ACC is a heterogeneous malignancy with no standard treatment for R/M disease. Around 20% of ACC carry *NOTCH1* (N1) activating mutations associated with poor prognosis. We hypothesized that Ni is an active therapy for ACC pts with N1 mutation or pathway activation.

Methods: Retrospective study of 29 R/M ACC pts with N1 mutation or pathway activation (assessed by cleaved N1 IHC) treated with Ni at MD Anderson (MDA). Ni included AL101, a gamma-secretase inhibitor, or OMP-52M51, an antibody targeting N1. Efficacy endpoints were objective response rate (ORR), clinical benefit rate (CBR), and progression-free survival (PFS) per RECIST or MDA bone criteria (for pts with bone disease only). These endpoints were assessed at two timepoints: during Ni therapy and immediately prior to Ni (pre-Ni) during systemic therapy or observation for the same pts.

Results: Out of the 29 ACC pts, 18 (62%) were males with median age 45 y (26-72 y). Of 24 genotyped ACC, 23 (96%) had N1 mutation. 15 (75%) of 20 pts with reported ACC histology had a solid component. 18 (62%) pts received AL101 and 11 (38%) received OMP-52M51. Ni was given in 2nd line or beyond in 18 (62%) pts, with the most common prior regimen being platinum-based chemotherapy (55%). The ORR to Ni was 17% (5/29), CBR was 72% (21/29) and median PFS was 4.2 mos (95%CI 2.9-8.6 mos). Tumor progression on Ni occurred on non-target lesions in 10/29 (34%) pts. 23 of 29 (79%) pts were eligible for PFS analysis immediately prior to Ni; 13 (57%) had received systemic therapy and 10 (43%) were under close observation. The median PFS on Ni vs. pre-Ni was 4.2 vs. 3 mos, respectively (HR 0.42 [95%CI 0.22-0.81], p=0.0076). Considering only the 13 pts who were on systemic therapy pre-Ni, ORR pre-Ni was 0% (0/13) and CBR was 8% (1/13). Median PFS on Ni vs. prior systemic therapy was 3.7 vs. 2.1 mos, respectively (HR 0.34 [95%CI 0.13-0.93], p= 0.029).

Conclusions: Ni has activity in ACC pts with N1 mutation or pathway activation. The efficacy of Ni compares favorably with efficacy of systemic therapies administered prior to Ni. The limited PFS and high rate of tumor progression on non-target lesions suggests Ni combination therapy may be necessary to address ACC heterogeneity.

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909P TROP2 expression in salivary gland adenoid cystic carcinoma (ACC): A new potential therapeutic target for the non-solid subtype

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Background: ACC is a neoplasm of salivary gland (SsG) characterized by biphasic ductal and myoepithelial components and solid, cribriform, and/or tubular architectural patterns (AP). Based on clinical and transcriptional features, two distinct subtypes are described: ACC-I (aggressive and mostly comprised of solid AP) and ACC-II (indolent and mainly represented by tubular and cribriform AP). Our ACC transcriptomic analysis revealed that TROP2 is upregulated, especially in the ACC-II subtype. TROP2 is a transmembrane glycoprotein involved in oncogenic pathways. Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) targeting TROP2 that showed promising results in metastatic breast cancer. Despite the clinical and biological heterogeneity of ACC, there is no difference in therapeutic strategies and no standard treatment for recurrent/metastatic (R/M) disease. Hence, we aimed to investigate TROP2 as a potential target for ACC.

Methods: Immunohistochemistry for TROP2 (EPR20043, 1:4000) was performed in a tissue microarray and manually scored as negative ($<$ 1% of any intensity), weak ($\leq$ 70% of weak or $\leq$ 30% of moderate expression), moderate ($>$ 70% of weak or $>$30% of moderate or $\leq$ 30% of strong expression), and high ($>$70% of moderate or $>$30% of strong expression). The AP was grouped as non-solid (NS, tubular and/or cribriform), predominant solid (S), or S+NS subtypes. A TROP2 expressing ACC cell line from a PDX organoid was treated with SG for 72hrs, and viability was assessed through luminescent cell viability assay.

Results: Out of 165 ACCs, 64% were from minor and 24% from major SsG and 13% from other secretory glands. TROP2 expression was high in 59%, moderate in 30%, weak in 8%, and negative in 3%. NS ACC AP was significantly correlated ($p<0.001$) with high (73%) expression of TROP2 compared to S+NS (12% high) and S (17% high). SG impaired the viability of the ACC TROP2-positive cell line.

Conclusions: TROP2 is widely expressed in ACC, mainly in non-solid AP, and an antiproliferative effect was observed in an ACC cell line treated with TROP2-ADC SG. Therefore, we provide a biological rationale for using TROP2 as a potential target for R/M ACC.

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910P Machine learning-based survival prediction model for postoperative parotid mucoepidermoid carcinoma

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Background: Parotid mucoepidermoid carcinoma (P-MEC) is a major histopathological subtype of salivary gland cancer, characterized by heterogeneity and complexity. Traditional clinical models and treatment plans are limited in providing personalized treatment recommendations and clinical management. This study aims to develop a machine learning-based prognostic model to improve survival rate prediction accuracy for P-MEC patients.

Methods: We used SEER database data (2004-2015) for 882 postoperative P-MEC patients. Single-factor Cox regression and four machine learning algorithms (Random Forest, LASSO, XGBoost, Best Subset Regression) were employed for variable selection and importance evaluation. The optimal variable selection model was determined using stepwise backward regression, AIC, and AUC. Bootstrap resampling was applied for internal validation.The model's prediction accuracy was assessed through C-index, ROC curve, and calibration curve. The clinical utility of the model was evaluated via DCA.

Results: The 3-, 5-, and 10-year OS rates for postoperative P-MEC patients were 0.887, 0.841, and 0.753. XGBoost, BSR, and LASSO demonstrated good predictive performance in variable selection and identified 7 independent prognostic factors: age, pathological grade, T stage, N stage, radiation therapy, chemotherapy, and marital status. A nomogram was developed based on the identified predictive variables. Internal validation with 1000 bootstrap resamples yielded consistent results for C-index (3-year, 0.841, 95%CI=0.839-0.844; 5-year, 0.842, 95%CI=0.840-0.845) and AUC (3-year, 0.858, 95%CI=0.856-0.860; 5-year, 0.872, 95%CI=0.870-0.875). The calibration plot indicated good prediction fit.

Conclusions: This study identified age, pathological grade, T stage, N stage, radiation therapy, chemotherapy, and marital status as independent prognostic factors in postoperative P-MEC patients. Machine learning algorithms outperformed traditional analysis methods in variable selection, predictive performance, and variable importance visualization. The developed machine learning-based nomogram offers high accuracy, robust calibration, and clinical application value for postoperative P-MEC patients.

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911P Post-radiotherapy (RT) Epstein-Barr virus (EBV) DNA dynamics identifies optimal timepoint for stratification of high-risk nasopharyngeal carcinoma (NPC)

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Background: Detectable plasma EBV DNA post-RT portends for a poor prognosis in NPC patients. Adjuvant chemotherapy (AC) trials however failed to yield a survival benefit in these high-risk patients. Studies have shown that post-RT EBV DNA levels and kinetics could further stratify NPC patients into risk-groups with disparate survival. There is thus a need to correctly identify patients who benefit from AC. Here, we investigated whether an early (0-2 w) or delayed (8-12 w) measure of plasma EBV DNA better predicts for disease relapse.

Methods: We curated a prospective single institution NPC registry for patients with a plasma EBV DNA result at 0-2 w post-RT and a minimum follow-up of 2 years. A subset of patients had a duplicate test done at 8-12 w post-RT. Plasma EBV DNA was quantified using the international harmonised BamH1 PCR-based assay. Primary clinical endpoint was disease-free survival (DFS).

Results: 297 patients with an EBV DNA result at 0-2 w post-RT were analysed. Median follow up was 51 (IQR: 47-55) mo. 71% (210/297) had TNM-stage III-IVA NPC; and 41% (122/297) reported pre-RT EBV DNA of $\geq$4000 copies/mL. At 0-2 w post-RT, 82% (243/297) had 0 EBV DNA copy/mL, while 16% (14/297) and 2% (7/297) had 1-264 copies/mL and $\geq$265 copies/mL, respectively. Using different EBV DNA level cut-offs of 0, 1-499, and $\geq$500 copies/mL, we validated the RPA model by Hui et al. with the high-risk group ($\geq$500 copies/mL) yielding the worst HR of 4.9 (95%CI: 1.9-12.5) relative to the low-risk group. Next, we observed substantial EBV DNA changes in 109 patients with a repeat EBV DNA at 8-12 w. Specifically, 65% (22/34) with a detectable EBV DNA at 0-2 w had 0 copy/mL subsequently. We found that a detectable EBV DNA at 8-12 w was a stronger predictor of relapse than a positive result at 0-2 w; AUCROC for DFS was 0.806 (95%CI: 0.727-0.886) for stage+EBV $DNA_{8\text{-}12w}$ versus 0.679 (95% CI: 0.576-0.783) for stage+EBV $DNA_{0\text{-}2w}$.

Conclusions: Our findings revealed that post-RT EBV DNA levels are dynamic, and an EBV DNA test at 8-12 w more accurately identifies high-risk patients than a test at 0-2 w post-RT. This has potential implications on AC trials that adopt an early EBV DNA result for treatment stratification.

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912P Toripalimab in combination with anlotinib in previously treated recurrent or metastatic nasopharyngeal carcinoma: The interim analysis of the single-arm, phase II TORAL study

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Background: The immune checkpoint inhibitors (ICIs) have been recommended as the second-line or beyond treatment for recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC), however, the overall response rate (ORR) was only approximately 20%. Anlotinib, an anti-angiogenetic multi-targeted TKI, showed an ORR of 17.6% as third-line or beyond treatment for R/M NPC in our previous study (ESMO 2020, #2502). Here, we reported the interim results of the phase II TORAL study (NCT04996758).

Methods: Patients aged 18-70 years with R/M NPC who failed the first-line platinum-based chemotherapy were treated with toripalimab (240mg, iv drip, d1) plus anlotinib (12mg QD, P.O., d1-14) every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was ORR. The secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and adverse events (AEs).

Results: Between October 2021 and January 2023, a total of 30 patients were enrolled. Sixteen patients had received previous ICI treatment. Baseline characteristics were listed in Table. The median cycle was 8 (2-25), and 14 patients received 10 or more cycles. The ORR and DCR were 36.7% (11/30) and 90.0% (27/30), respectively. For patients with or without previous ICI treatment, the ORR were 25.0% and 50.0%, respectively. With a median follow-up of 10.3 months, the median PFS was 9.5 months. Most patients (96.7%) patients had AEs at any grade. The most common (≥20%) grade 3/4 AEs were mucositis (26.7%,) and hand-foot syndrome (23.3%). Dose reductions of anlotinib occurred in 14 patients due to AEs (hand-foot syndrome, n=7; mucositis, n=5; proteinuria, n=1; joint effusion, n=1).

Table: 912P Baseline features

Characteristics	Patients (N=30)
Age (years)	
Median	46.5
Range	31.0-67.0
Gender	
Female	6 (20.0%)
Male	24 (80.0%)
ECOG PS	
0	10 (33.3%)
1	20 (66.7%)
Previous curative radiotherapy	
Yes	15 (50.0%)
No	15 (50.0%)
Previous ICI treatment	
Yes	16 (53.3%)
No	14 (46.7%)
Prior chemotherapy regimen(s)	
1	19 (63.3%)
2	9 (30.0%)
3	2 (6.7%)
EBV DNA level (copies/mL)	
≥4000	12 (40.0%)
< 4000	18 (60.0%)

Conclusions: The combination of toripalimab and anlotinib showed encouraging efficacy and acceptable safety for R/M NPC. The efficacy and toxicity data with larger sample size will be further evaluated at the completion of this trial.

Clinical trial identification: NCT04996758.

Legal entity responsible for the study: Qingqing Cai.

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913P Oral chemotherapy versus observation alone in nasopharyngeal carcinoma patients with persistently detected circulating cell-free Epstein-Barr virus DNA during follow-up

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Background: Despite the high risk of tumor recurrence, patients with nasopharyngeal carcinoma (NPC) with persistently (at least twice) detected circulating cell-free Epstein-Barr virus (EBV) DNA levels during follow-up are routinely recommended to keep observation. For these patients, whether administering more aggressive treatment could improve survival outcomes remains unknown.

Methods: We retrospectively included 431 patients with nonmetastatic NPC with persistently detected EBV DNA during follow-up, who do not have clinical or imaging evidence of recurrence. Among these patients, 79 were administered oral chemotherapy, and the remaining 352 underwent observation alone. Baseline characteristics were balanced with propensity score matching (PSM) analysis. The primary endpoint was modified disease-free survival (mDFS), defined as time from detectable EBV DNA result to tumor recurrence or death. The secondary endpoints were disease-free survival (DFS) and overall survival (OS).

Results: One-to-three PSM resulted in 251 eligible patients (oral chemotherapy group, 73; observation group, 178). In the matched cohort, the oral chemotherapy group had higher median mDFS (12.9 months [95% confidence interval [CI] 9.6-16.3] vs. 6.8 months [5.8-7.8], p=0.009) and DFS (24.1 months [95% CI 18.5-29.7] vs. 16.7 months [14.4-19.1], p=0.035) than the observation group. The median OS was numerically higher in the oral chemotherapy group than in the observation group (57.9 months [95% CI 42.5-73.3] vs. 50.8 months [39.7-61.9], p=0.71). After adjusting for other confounders in the multivariate analysis, oral chemotherapy remained a significantly favorable factor for both mDFS (hazard ratio [HR] 0.67, 95% CI 0.50-0.89; p=0.006) and DFS (HR 0.68, 95% CI 0.51-0.91; p=0.01), but not a significant factor for OS (HR 0.89, 95% CI 0.62-1.27; p=0.52).

Conclusions: In patients with NPC having persistently detected EBV DNA levels but without clinical or imaging evidence of recurrence during follow-up, oral chemotherapy significantly prolongs mDFS and DFS. The use of oral chemotherapy, rather than observation alone, could be a more aggressive treatment option for these patients.

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915P Survival outcomes and toxicity profiles among patients with nonmetastatic nasopharyngeal carcinoma treated with Intensity modulated radiotherapy (IMRT) versus IMRT + Carbon-ion beam radiotherapy (CIRT): A propensity score-matched analysis

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Background: To compare survival outcomes and toxic effects among patients with newly diagnosed nonmetastatic nasopharyngeal carcinoma (NPC) when treated with Intensity modulated radiotherapy (IMRT) versus IMRT + carbon-ion radiotherapy (CIRT).

Methods: We performed a retrospective propensity score matching analysis (1:1) of patients treated with IMRT and IMRT + CIRT. Survival was estimated using the Kaplan—Meier method. Multivariate Cox proportional hazards regression analysis was used to identify the independent predictors of survival. We examined the association between risk factors and adverse events (AEs) using Chi-squared tests. AEs analyses were performed using a Cox model and logistic regression.

Results: 109 patients who received IMRT + CIRT were included and the median follow-up time was 20.6 months (range: 4.6-82 months). There were no statistically significant differences in locoregional failure—free survival, distant metastasis—free survival, disease-free survival, or overall survival between the two groups, but potentially better in IMRT + CIRT group ($P > 0.05$, respectively). Nodal boost was the only significant factor associated with LRFS and DFS on multivariable analysis. 37 patients (34.0%) developed grade 3 acute OMs and no grade 4 acute OMs were observed in IMRT + CIRT group. All patients in IMRT + CIRT group developed grade 1 dermatitis. IMRT +CIRT treatment was associated with a significant trend of lower grades of OM and dermatitis ($P < 0.05$, respectively). Any severe (ie, grade 3) chronic AEs, such as xerostomia, skin fibrosis, temporal lobe necrosis, osteoradionecrosis, or radiation-induced optic neuropathy, was not observed.

Conclusions: IMRT + CIRT for primary nonmetastatic NPC was associated with significantly reduced oral mucositis and dermatitis compared with full course of IMRT, with excellent survival outcomes. Patients with persistent disease after primary

treatment and treated with nodal boost had a worse outcome. More accurate assessments of IMRT + CIRT to primary nonmetastatic NPC patients will be imperative.

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916P Reducing radiation-induced temporal lobe injury by changing tumor prescription dose in nasopharyngeal carcinoma

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Background: Radiation-induced temporal lobe injury (TLI) is one of the most common radiation-induced toxicities in nasopharyngeal carcinoma (NPC) treated by intensity-modulated radiotherapy (IMRT), especially in patients with cavernous sinus invasion whose planning target volume of nasopharynx (PTVnx) and temporal lobe (TL) is often overlapped. We named the overlap area as the sub-volume of PTVnx and TL (PTVsv-TL) and gave it independent prescription dose, and investigated its efficacy and feasibility in this study.

Methods: From 2015 to 2020, T4 stage NPC patients with cavernous sinus invasion treated by independent prescription dose of PTVsv-TL (60-64Gy) were enrolled in study group, while T4 stage patients with cavernous sinus invasion treated by prescription dose recommended as international guidelines were enrolled in control group. The primary endpoint is the 3-year cumulative incidence of TLI, and secondary endpoints included dose parameters of TL, local recurrence rate and pattern, regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS) and overall survival (OS). SPSS 25.0 was used for statistical analysis.

Results: Totally, 137 and 357 patients were enrolled in the study group and control group, respectively. The median follow-up time was 33.0 months (inter-quartile range, 22.0-44.0 months). 17.6% patients (87/494) were diagnosed as TLI by MRI. The 3-year cumulative incidence of TLI in the study and control group were 15.3% and 28.5% (P=0.006). The dose parameters of TLs in two groups were as follows: D_2, $D_{0.5cc}$, D_{1cc} and D_{2cc} were 62.0 vs 70.5Gy, 66.1 vs 73.2Gy, 64.1 vs 72.1Gy, and 61.8 vs 70.0Gy (all P<0.001). The 3-year cumulative local recurrence rate were 6.2% and 10.4% in the study and control groups (P=0.170), with 2 cases of marginal failure in each group and none out-field failure. The 3-year PFS and OS rates were 87.8% vs 90.4% (P=0.275), 86.3% vs 88.2% (P=0.649), and 97.2% vs 97.3% (P=0.581).

Conclusions: Giving independent prescription dose to PTVsv-TL could significantly reduce the irradiated dose of TLs and decrease the incidence of TLI, meanwhile achieved satisfactory local control and long-term survival. Further prospective study is warranted.

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917P Radiation-induced nasopharyngeal necrosis in locally-recurrent nasopharyngeal carcinoma patients after re-radiotherapy

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Background: Re-radiotherapy (re-RT) is the main treatment for locally recurrent nasopharyngeal carcinoma (lrNPC) patients, and commonly leads to radiation-induced nasopharyngeal (NP) necrosis. The aim of this study was to evaluate the cause and impact of radiation-induced NP necrosis in lrNPC patients who received re-RT.

Methods: Totally 252 lrNPC patients who received re-RT between January 2013 and December 2020 were retrospectively collected. The inclusion criteria were as follows: (1) no NP necrosis before re-RT; (2) complete medical records; (3) conventional fractionated radiotherapy. All patients received intensity-modulated radiotherapy ± chemotherapy. Radiation-induced NP necrosis was diagnosed by magnetic resonance imaging and/or electronic nasopharyngoscopy. Dosimetric factors of the planning target volume of primary tumor (PTVp) were extracted from the dose-volume histogram (DVH), which was rescaled to an equivalent dose of 2 Gy per fraction. Logistic regression was used to identify the independent prognostic factors for generating the nomogram.

Results: With a median follow-up of 44.63 months (inter-quartile range [IQR], 27.70 − 69.20 months), 47.6% of patients (120/252) occurred radiation-induced NP necrosis. The 3-year overall survival was 83.0% *vs* 39.7% (P < 0.001) in lrNPC patients with or without radiation-induced NP necrosis. Except for the fractionated dose, other dosimetric factors of PTVp were not significantly different between two groups, including D_{98} (dose to 98% of PTVp), D_{50}, D_2 and homogeneity index. Furthermore, multivariate analysis showed that age (HR [95%CI]: 1.04 [1.01 − 1.07], P = 0.004), tumor volume (HR [95%CI]: 1.03 [1.02 − 1.05], P < 0.001), and fractionated dose > 2.22 Gy (HR [95%CI]: 2.29 [1.28 − 4.09], P = 0.005) were independent factors in predicting radiation-induced NP necrosis, which yielded a C-index of 0.742 (95% CI, 0.681 - 0.803) for NP necrosis in the nomogram.

Conclusions: The incidence of radiation-induced NP necrosis was high in lrNPC patients who received re-RT. Patients with older age, larger tumor volume or receiving fractionated dose over 2.22 Gy were greater risk of NP necrosis. There is a need to explore novel treatment strategies to improve patient survival.

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918P SPP1-related M2 macrophage signatures predict prognosis and immunotherapy response in patients with nasopharyngeal carcinoma

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Background: The M2 macrophages in the tumor immune microenvironment (TIME) have been identified as independent prognostic factors in nasopharyngeal carcinoma (NPC). However, the clinical significance of SPP1-related M2 macrophages remains largely unexplored.

Methods: To reconstruct a pseudotime trajectory of macrophage polarization in NPC and analyze the gene expression patterns along the trajectory, we applied publicly available single-cell sequencing data (GSE150825). GeneSwitches was used to sequence the critical regulatory genes during M2 macrophage activation and identify their order. To construct the M2 macrophage-activation genes signature (MAGens), we analyzed the transcriptome data of the Fujian NPC dataset (N=188) and the published dataset (GSE102349, N=88) using 101 combinations of machine learning algorithms that included univariate and correlation analyses.

Results: We utilized single-cell transcriptomics and GeneSwitches analyses to identify SPP1 as the top switching gene in M2 macrophage activation and determine the order of the switch. Analysis of the bulk transcriptome revealed that high expression of SPP1 is associated with poor prognosis and increased infiltration of M2 macrophages, which was validated using immunohistochemistry. We then established a 13-gene MAGens that accurately predicts progression-free survival in patients with nasopharyngeal carcinoma (NPC) (5-year AUC: 0.95) and serves as an independent prognostic factor based on uni- and multivariate analyses. We found that the low MAGens group had a higher level of immune infiltrating cells and immune modulators, indicating an

inflamed but relatively immunosuppressive microenvironment that could potentially benefit from immunotherapy. Lastly, we verified the predictive value of MAGens in the Fujian NPC dataset, where MAGens score exhibited a significant positive correlation with known immunotherapy indicators CD8, PD-1, and PD-L1.

Conclusions: As a new predictive biomarker, MAGens offer significantly improved precision in selecting the NPC population that could benefit from immunotherapy. We recommend the immediate validation and application of these unique MAGens.

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919P A prognostic model of nasopharyngeal carcinoma based on 18F-FDG PET-CT radiomic parameters and clinical characteristics of patients

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Background: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET-CT) is a non-invasive imaging modality. This study aimed to investigate the effects of radiometric parameters and clinical characteristics of 18F-FDG PET-CT on the prognosis of patients with nasopharyngeal carcinoma (NPC).

Methods: A total of 801 patients with metastatic NPC were enrolled between 2016 and 2020, and all participants underwent 18F-FDG PET/CT before treatment. We assessed the following 18F-FDG PET parameters: standardized uptake value (SUV), SUV-avg (average), SUV-peak (maximum), and total lesion glycolysis (TLG) of the primary tumor and regional lymph nodes. We used multivariate Cox proportional hazards models and multiple machine learning techniques to identify independent predictors of survival based on radiomic parameters and patient clinical characteristics. After selecting the features, we established prognosis models using a COX stepwise regression model. Finally, we performed internal validation, and a nomogram was created for NPC comprehensive diagnosis.

Results: In this study, we developed a stable and robust model incorporating five independent prognostic features based on COX regression. The area under the curve (AUC) of the model was 0.75 (95% CI = 0.52—0.97) at 1 year, 0.80 (95% CI = 0.71—0.89) at 3 years, and 0.86 (95% CI = 0.78—0.94) at 5 years. The AUC at 3 years and 5 years were calculated as 0.7276 and 0.7242, respectively. The model was validated using receiver operating characteristic (ROC), consistency index, and multivariate analysis, which showed high accuracy and consistent performance. Moreover, patients in the low-risk score group exhibited significantly better outcomes than those in the high-risk score group ($P < 0.001$).

Conclusions: Our findings suggest that age, SUV-Tmax, SUV-Tavg, SUV-Tpeak, and TLG-T are valuable parameters for predicting long-term survival in patients with NPC. The nomogram based on metabolic parameters combined with other variables showed good prognostic accuracy in predicting NPC prognosis.

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920P Envafolimab plus chemoradiotherapy for locally advanced nasopharyngeal carcinoma (NPC), a prospective, single-armed phase II trial

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Background: Gemcitabine plus cisplatin (GP) prior to concurrent chemoradiotherapy (CCRT) has favorable survival outcomes with acceptable toxicity in patients with locoregionally advanced nasopharyngeal carcinoma (LANPC). Immune checkpoint blockade therapy plus GP has been shown to improve the survival in recurrent or metastatic NPC. We aim to evaluate the efficacy and safety of envafolimab (PD-L1) with curative chemoradiotherapy in previously untreated LANPC.

Methods: In this single-arm, phase 2 study, eligible patients were of age 18-65, diagnosed with staged TxN2-3M0 or T4N1M0(AJCC 8th) non-keratinizing LANPC. Enrolled patients received 3 cycles of intravenous gemcitabine (1000 mg/m^2, d1/8, Q3W)+cisplatin (80 mg/m^2, d1, Q3W), in combination with subcutaneous envafolimab injections (300mg, d1, Q3W) for induction chemotherapy, followed by CCRT, during which, every patient would receive 2 cycles of DDP (100 mg/m^2, d1, Q3W)+envafolimab (300mg, d1, Q3W). Then patients would receive envafolimab (300mg, d1, Q3W) for maintenance treatment for a year, until disease progression or intolerance of treatment. The primary endpoint was 3-year progress-free survival, the secondary endpoints included objective response rate (ORR), the disease control rate (DCR), locoregional failure-free survival, distant metastasis-free survival, and toxicity. All enrolled patients have finished induction chemotherapy treatment, the study is ongoing.

Results: From June 14th 2022 to December 13th, 2022, a total of 36 patients (median age 44y, 63.9% male) were enrolled at Sun Yat-sen University Cancer Center. As of May 4th, 2023, the median follow-up is 7.38 months. The ORR and DCR rate were 94.4%(95%CI: 81.3%, 99.3%) and 97.2%(95%CI: 85.5%, 99.9%).Compared to standard regimen, in combination with envafolimab did not increase the incidence of hematological toxicity events., and no irAEs for grade 3/4 were observed.. Long-term efficacy is awaited.

Conclusions: Envafolimab plus chemoradiotherapy was effective and safety in the treatment of LANPC. Further follow-up is needed to confirm the long-term efficacy.

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921P HB-200 arenavirus-based immunotherapy plus pembrolizumab as a first-line treatment of patients with recurrent/metastatic HPV16 positive head and neck cancer

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Background: Treatment options are limited for patients with recurrent/metastatic (R/M) human papillomavirus (HPV) 16+ head and neck squamous cell carcinoma (HNSCC). HB-200 is comprised of an alternating sequence of two replicating attenuated arenavirus vectors derived from LCMV (HB-201) and Pichinde virus (HB-202), respectively. HB-200 vectors express the same non-oncogenic HPV16 E7E6 fusion protein and induce E6 and E7-specific CD8 T cell responses. Previously, we reported the recommended phase 2 dose (RP2D) and antitumor activity of HB-200 monotherapy. Here, we report preliminary phase 2 results of HB-200 therapy in combination with pembrolizumab as first-line (1L) treatment of patients with HPV16+ programmed death ligand 1 (PD-L1)+ R/M HNSCC.

Methods: A run-in with HB-201 1-vector plus pembrolizumab was conducted prior to initiation of HB-200 plus pembrolizumab. HB-200 was administered intravenously (every 3 weeks [Q3W] then Q6W) in combination with pembrolizumab (200 mg Q3W or 400 mg Q6W, as indicated). Two dose levels of HB-200 were explored. Safety, immunogenicity and preliminary antitumor activity were assessed.

Results: As of March 31, 2023, 20 patients with checkpoint inhibitor-naïve, HPV16+ PD-L1+ R/M HNSCC (19 oropharynx) were treated with HB-200 plus pembrolizumab in the 1L setting. Characteristics of this cohort included: median age 66 years (range 50-76), 19 (95%) male, 17 (84%) White, 7 (35%) with $\geq$ 10 pack/year smoking history, and 10 (50%) tumors with PD-L1 combined positive score $\geq$ 20. Treatment-related adverse events (AEs) included: Grade $\geq$3 AEs in 2 (10%) patients and serious AEs in 1 (5%). No treatment-related discontinuations or deaths were reported. Among 14 evaluable patients (those with $\geq$ 2 tumor response assessments) receiving HB-200 plus pembrolizumab, the overall response rate was 43% (1 complete, 5 partial, all confirmed) and the disease control rate was 71%.

Conclusions: Preliminary data with HB-200 arenavirus-based immunotherapy plus pembrolizumab demonstrate a favorable safety profile and preliminary efficacy when given as a 1L treatment of patients with R/M HPV16+ PD-L1+ HNSCC. Clinical trial# NCT04180215.

Clinical trial identification: H-200-001 August 01, 2019.

Legal entity responsible for the study: Hookipa Biotech GmbH.

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922P Dose expansion results of the bifunctional EGFR/TGFβ inhibitor BCA101 with pembrolizumab in patients with recurrent, metastatic head and neck squamous cell carcinoma

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Background: Pembrolizumab (P) is approved for recurrent, metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). BCA101 is a first-in-class bifunctional EGFR/TGFβ inhibitor with a manageable safety profile and preliminary efficacy in advanced solid tumors (ESMO 2022 731MO). Here we report the preliminary results from the fully enrolled expansion cohort combining BCA101+P as first line therapy in R/M HNSCC.

Methods: This ongoing single-arm, multicenter dose expansion cohort enrolled patients (pts) with R/M HNSCC, PD-L1 CPS$\geq$1 with no prior systemic therapy for R/M disease, ECOG 0-1, and measurable disease (RECIST v1.1). Pts received BCA101 (1500 mg IV on days 1, 8, 15) with P (200 mg IV on day 1) every 21-days. Primary endpoint: safety; secondary endpoints: overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival. Exploratory: molecular and immunologic predictors of response.

Results: Thirty-one of 33 pts were evaluable and each had at least two restaging scans. Pts were more often men (n=23, 70%); median age: 65 (range: 31-80). Eighteen (55%) had baseline PD-L1 CPS scores of 1-19, 15 (45%) were $\geq$20. Oropharynx (19, 58%) [12/19 (63%) HPV/p16+] and oral cavity (10, 30%) were the most common subsites. Twenty-five pts (76%) had distant disease. The ORR was 48% (1 CR, 14 PRs) with 65% (13/20) of HPV(-) pts achieving a response, including 5/10 (50%) responders with CPS 1-19. Median PFS has not been reached among HPV(-) pts with 13/20 responses ongoing (five $>$6 months). Grade 3+ treatment-related adverse events (TRAEs) were observed in 9/33 pts (27%). There were no treatment-related deaths. Acneiform rash was the most common TRAE of any grade (24/33, 73%). Response data for the full cohort (n=39) will be available at the time of the meeting.

Conclusions: BCA101+P exhibits encouraging anti-tumor activity particularly among HPV(-) pts, and the combination is well tolerated among this R/M HNSCC population. Further investigation is warranted.

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Legal entity responsible for the study: Bicara Therapeutics.

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923P Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic head & neck squamous cell carcinoma – subgroup analysis of the PEVOsq basket trial

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Background: Targeting the PD1/PD-L1 axis in head and neck squamous cell carcinoma (HNSCC) patients improves survival. However, only a minority of patients (pts) respond to treatment. Preclinical data suggests that vorinostat (V), an HDAC inhibitor, might improve immunotherapy efficacy by modulating the epigenome.

Methods: PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of pembrolizumab (P) in combination with V in pts with recurrent and/or metastatic squamous carcinomas. Pts had to be PD1/PD-L1 antagonist-naïve with no restriction in terms of prior lines of treatments. P dose was 200 mg Q3W IV, and V 400 mg QD PO. A'Hern design with the following hypotheses (alpha=5%, power=90%, p0=10%, p1=35%). Primary endpoint was objective response rate (ORR) according to RECIST 1.1. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

Results: Among 112 included pts, 27 and 26 HNSCC pts were evaluable for safety and efficacy. Median age was 59 years old [range: 18-77]. Median number of prior lines of therapies was 0 [range: 0-1]. Five pts (19.2%, [95%CI: 6.6-39.4]) had an objective response. Median DOR was 3.2 months [95%CI: 1.3-NR]. Median PFS and OS were 4.1 [95%CI: 1.5-4.4] and 9.2 months [95%CI: 6.8-14.4], respectively. Ten pts (37.0%) developed G3/4 treatment related adverse events. P and V were stopped for toxicity in 3.8% and 30.8% of pts, respectively. 40.7% of pts had a dose-reduced of V for toxicity including hematotoxicity, gastrointestinal toxicity, asthenia, and creatinine increase. Results according to PDL1, MSI, TMB and HPV will be presented at the meeting.

Conclusions: P combined with V produced encouraging antitumor activity in HNSCC pts independant of PD-L1 expression, although the V dose had to be reduced in a substantial proportion of pts.

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Legal entity responsible for the study: UNICANCER.

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924P Polyfunctional HPV16-Specific T cell responses in subjects receiving PDS0101 and pembrolizumab combination treatment for recurrent/metastatic HPV16-positive head and neck squamous cell carcinoma (HNSCC)

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Background: Generation of multifunctional, anti-tumor T cell responses and immune memory are critical to effective long term control of tumor growth and clinical outcomes. The investigational T cell activating HPV-targeted immunotherapy PDS0101 is being studied in combination with pembrolizumab (NCT04260126) in patients with HPV16-positive head and neck cancer. Biomarkers of response are undetermined.

Methods: The Isoplexis IsoCode single-cell proteomic assay was utilized to assess the functional state of tumor-specific CD4 and CD8 T cells. Cryopreserved PBMCs were thawed and rested overnight in the presence of IL-2, with magnetic bead column enrichment and surface staining for CD8/CD4 subsets following *in vitro* stimulation for 16 hrs with an overlapping HPV16 E6/E7 peptide pool. Single-cell production of 32 immune analytes was measured and polyfunctionality was assessed at 3 timepoints: pre-treatment, and 12 and 36 weeks following 4 and 5 cycles of combination therapy, respectively.

Results: Eighteen subjects with confirmed HPV16-positive tumors and CPS $\geq$1 (72% with CPS $\geq$20), median age 63 yrs (range 46-83), 94% male, 94% immune checkpoint inhibitor (ICI)-naïve, had specimens for this analysis and had received a minimum of 4 cycles of combination therapy. Confirmed objective response (OR; 1 CR and 5PR) was seen in 6 subjects (33%); 10 subjects (56%) had SD and 2 subjects had PD (11%). Polyfunctional T cells expressing 2-5+ proteins were observed in subjects with CPS 1-19 and CPS $\geq$ 20 and in both CD4 and CD8 subsets. Across timepoints and subjects, the proteins secreted with the highest frequency were Granzyme B, IL-8, IL-9, MIP-1α, MIP-1β and TNFα. There was no difference in polyfunctionality scores in subjects with confirmed OR versus those with stable or progressive disease.

Conclusions: The PDS0101/pembrolizumab combination generates polyfunctional CD4 and CD8 T cells that secrete multiple cytokines and chemokines associated with a predominant effector, stimulatory functional profile. Further investigation of T cell polyfunctionality and correlation with clinical outcomes is warranted.

Clinical trial identification: NCT04260126.

Legal entity responsible for the study: PDS Biotechnology.

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925P Treatment discontinuation of immune checkpoint blockade in patients with head and neck squamous cell carcinoma experiencing complete or nearly complete remission

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Background: PD-1 antibodies have become standard of care in the treatment of recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) in first or second-line palliative treatment. After 4 years of follow up, 17% of the initial Keynote-48 study population is alive. In clinical routine, it remains an unresolved question how to deal with the situation of complete remission concerning treatment continuation.

Methods: In a retrospective case analysis we collected patients with HNSCC who experienced complete or very good partial remission under PD-1 inhibition. A very

good partial remission was defined as a residual tumor substrate without contrast enhancement on CT and no change in residual tumor mass within the last 6 months.

Results: 53 patients derived from 6 centers in Germany were identified. PD-L1 CPS was 0 in 2 pts, 1-20 in 13 pts. >20 in 13 pts and missing in 25. Nivolumab was given in 28 pts. (52%), pembrolizumab in 18 pts (34%), pembrolizumab/chemotherapy in 3 and other immunotherapies in 4 pts. At the first staging after therapy initiation, 28 pts (52%) had a partial remission (PR) and 6 (11%) a complete remission (CR). The median time to very good partial or CR was 7 months. Of the 53 patients, 17 remain on treatment to date of data collection. 36 patients discontinued treatment, 11 because of toxicity. Of the 36 patients, 9 experienced disease progression of whom 7 patients were treated again with PD-1 inhibitor. First course of ICI had a median duration of 25 months. The majority of patients (75%) remained in remission after treatment discontinuation with a median follow up of 7 months. Of the 7 patients who were re-challenged 4 had a PR, 1 SD, 1 PD and 1 missing.

Conclusions: To our knowledge, this is the first case collection of patients with complete or very good partial remission of head and neck SCC patients receiving PD-1 inhibitors for whom treatment discontinuation may be considered. After treatment discontinuation, the majority of patients remain in remission and 71% of patients experience disease control when re-exposed to PD-1 inhibitors. Extension of this case collection and long-term follow-up is needed to guide patient counseling in regard to the question of safe treatment discontinuation.

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926P UK national real-world outcome data of first-line pembrolizumab treatment in head and neck squamous cell cancer (HNSCC)

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Background: Immunotherapy has significantly improved survival in patients with several solid tumours including head and neck squamous cell carcinoma (HNSCC). Pembrolizumab received approval in the UK in 2020 as first-line treatment for recurrent or metastatic (R/M) HNSCC based on KEYNOTE-048 trial data which demonstrated an extended overall survival (OS) when compared to the EXTREME chemotherapy regime in patients with R/M HNSCC tumours with a combined positive score (CPS)≥1 (Burtness, 2019). Here we, provide real-world data on the clinical outcomes of the use of pembrolizumab as first-line systemic treatment for HNSCC in the United Kingdom (UK).

Methods: Retrospective data analysis of patients with HNSCC treated with pembrolizumab as first-line treatment across 18 centres in UK from 20/03/20 to 31/05/2021.

Results: 211 patients were included; the median age was 66.0 (range=39-88.1), 73.0% of patients were male and >65% of patients had a smoking history or alcohol history. In addition to patients with R/M HNSCC, 47 patients had locally advanced disease deemed not suitable for curative treatment at diagnosis; a group of patients not included in KEYNOTE-048. Analysis showed an overall response rate (ORR) of 24.7%, median progression free survival (PFS) of 4.8 months (95% confidence interval [CI]: 3.6-6.1) and median OS of 10.8 months (95% CI 9.0-12.5). 53 patients proceeded to second line treatment and the median PFS2 was 10.2 months (95% CI: 8.8-11.5), similar to PFS2 of 10.3 months for those with CPS≥1 in KEYNOTE-048. The treatment was well-tolerated and only 18 patients (8.5%) stopped pembrolizumab due to an immune-related toxicity (IRT). Moreover, patients with a documented IRT had a statistically significant longer median PFS (11.3 vs 3.3 months; log-rank p-value=<0.001) and median OS (18.8 vs 8.9 months; log-rank p-value <0.001) compared to the groups of patients with no documented IRT.

Conclusions: In this real-world retrospective cohort, we have shown a similar ORR, longer PFS, similar PFS2 and a shorter OS compared to the results of KEYNOTE-48. Those with locally advanced disease deemed not suitable for curative treatment at diagnosis had similar ORR, PFS and OS compared to patients with recurrent or metastatic disease.

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927P Patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) treated with nivolumab (NIVO) in the first-line (1L) or later-line (2L+) settings in Germany: Updated results from the real-world HANNA study

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Background: Real-world data for pts with R/M SCCHN receiving NIVO, particularly in the 1L setting, are limited. Here, we present updated results from the HANNA study (NCT03114163) that collected real-world data from pts with R/M SCCHN initiating NIVO treatment (tx) in the 1L or 2L+ settings in Germany.

Methods: This multicenter, prospective, non-interventional study included adults with R/M SCCHN progressing on or after platinum (Pt)-based therapy and treated with NIVO according to the approved label, including the 1L population (pts with Pt-sensitive or Pt-refractory disease who progressed > 6 or ≤ 6 months (mo) of Pt-based therapy, respectively). The primary objective was overall survival (OS); secondary objectives included duration of tx (DOT), time to next therapy (TTNT), and safety.

Results: This updated analysis (database lock: Jan 16, 2023) included data from May 2017—Jan 2023. Median follow-up was 44.4 mo. Baseline characteristics of the overall population (N = 478) and 1L subset (n = 223) were similar. Median (95% CI) OS was 10.5 (9.0—11.9) mo (overall) and 11.7 (9.5—13.7) mo (1L); median OS was similar in pts with Pt-refractory (11.9 mo [95% CI, 7.9—15.4]) and Pt-sensitive (11.2 mo [8.8—14.9]) disease in the 1L subset. OS by other subgroups is presented (Table). In the 1L subset, 36 (16.1%) pts received subsequent therapy, mainly cetuximab (n = 21; 58.3%). Median DOT was similar in the overall population (5.3 [95% CI, 4.0—5.8] mo) and 1L subset (5.4 [4.0—5.9] mo); median (range) TTNT was 21.0 (2.0—563.0) and 28.0 (3.0—563.0) days, respectively. Overall, any-grade and grade 3/4 tx-related or immune-related adverse events occurred in 156 (32.6%) and 57 (11.9%) pts, respectively.

Table: 927P OS outcomes

	Overall population		1L subset	
	n	Median (95% CI) OS, mo	n	Median (95% CI) OS, mo
OS in all patients	478	10.5 (9.0–11.9)	223	11.7 (9.5–13.7)
OS by ECOG performance status* 0 1 ≥ 2	68	19.2 (12.8–35.0)	32	19.2 (11.7–37.1)
	215	11.0 (9.5–14.7)	101	12.6 (9.7–17.6)
	146	5.3 (4.1–8.8)	70	4.8 (3.0–8.8)
OS by primary tumor location* Oropharynx Oral cavity	181	8.4 (5.6–11.9)	87	12.8 (9.2–17.6)
Hypopharynx Larynx Nasopharynx/paranasal sinus	106	8.0 (5.1–12.2)	50	9.1 (5.2–12.1)
	91	8.9 (4.6–11.1)	39	9.7 (3.6–17.2)
	70	9.5 (6.6–13.5)	31	12.6 (6.6–NR)
	20	10.9 (4.1–29.8)	11	15.3 (4.1–NR)

*Missing data and data with n ≤ 5 were not included. NR, not reached

Conclusions: Updated results from the real-world HANNA study continue to support NIVO as a safe and effective tx in the 1L or 2L+ settings for pts with R/M SCCHN in Germany.

Clinical trial identification: NCT03114163.

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928P Prognostic value of body composition and nutritional assessment in recurrent/metastatic squamous cell carcinoma of head and neck (R/M SCCHN) treated with immunotherapy (IO)

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Background: Low skeletal muscle index (SMI) and malnutrition (MN) have been associated with poor outcomes in R/M SCCHN patients (pts) treated with IO. The "Immuno-Nutri" study (NCT04721184) evaluates the impact of SMI and MN on outcomes in R/M SCCHN pts treated with IO.

Methods: Single-institutional, prospective observational study recruiting IO-naïve R/M SCCHN pts treated with IO alone or in combination. Planned accrual = 120 pts. A CT scan at L3 vertebra level is performed to assess SMI. MN was evaluated by Patient-Generated Subjective Global Assessment (PG-GSA). Clinical, nutritional and body composition data were collected. Overall response rate (ORR) was evaluated with RECISTv.1.1. Median overall survival (mOS) and progression-free-survival (mPFS) were estimated by Kaplan-Meier; multivariant analysis (MVA) and logistic regression were performed to identify predictors of PFS/OS and ORR, respectively.

Results: 61 pts were recruited between 01/2021-04/2023 and 49 had response evaluation at data cut-off (see table). With a median follow up of 9 months (m), mPFS was 2.5m (CI95% 2.1-4.4) and mOS 11.7m (CI95% 8-NR); SMI and MN had no effect on PFS nor OS, only locoregional+metastatic recurrence negatively impacted on OS (HR 3.5 CI95% 1.1-19 p=0.04). In pts treated with IO alone, type of recurrence impacted in both PFS (HR 3.8 CI95% 1.2-13 p=0.03) and OS (HR 4.5 CI95% 1.1-19 p=0.04); a trend for MN in PFS was noted [HR 3 CI95% 0.9-10 p=0.06]. ORR trended to be enhanced in high SMI pts (HR 0.9 CI95% 0.8-1 p=0.06).

Table: 928P Cohort characteristics

Variable	N (%)
Primary tumour	
Oral cavity Oropharynx - HPV+ Hypopharynx Larynx	19 (31) 12 (20) – 5 (8) 11 (18)
Other	8 (13) 11 (18)
Type of recurrence	
Locoregional Metastatic Locoregional + metastatic	30 (49) 11 (18) 20 (33)
Treatment	
AntiPD-(L)1 monotherapy.	36 (69) 14 (23) 11 (18)
AntiPD-(L)1 + CT AntiPD-(L)1 + other IO	
SMI (cm2 / m2)*	44 (7)
MN by PG-SGA*	42 (68.9)
Response	
ORR Stable disease Progression	14 (29) 11 (22) 24 (49)

*Continuous variables: mean (standard deviation)

Conclusions: Preliminary results showed a high SMI could predict IO response but did not impact on PFS/OS. Accrual continues and further analysis are on-going.

Clinical trial identification: NCT04721184.

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929P Pembrolizumab plus nab-paclitaxel and platinum as first-line treatment in patients with with recurrent/ metastatic head and neck squamous-cell carcinoma (R/M SCC) of the nasal cavity and paranasal sinuses

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Background: Pembrolizumab plus platinum and fluorouracil is the standard first-line treatment in patients with recurrent/ metastatic head and neck squamous-cell carcinoma (R/M HNSCC). However, there is no relevant data on nasal cavity and paranasal sinuses in KN-048. As the first prospective study of immunotherapy combined with chemotherapy in the treatment of SCC of nasal cavity and paranasal sinuses, it aims to verify its efficacy.

Methods: Patients with untreated R/M SCC of nasal cavity and paranasal sinuses and with ≥1 measurable lesion according to RECIST 1.1 were included. Patients received pembro 200mg, nab-paclitaxel 260mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC5 on day 1 every 21 days for up to six cycles followed by pembro maintenance therapy until progression or unacceptable toxicity or 35 cycles, whichever occurred first. The primary endpoint were ORR and PFS. Secondary endpoints were safety, DCR and OS.

Results: From August 26 2021 until March 3 2023, 16 patients were enrolled. The baseline characteristics are shown in the table. 1 patient with SD after 4 cycles of treatment was not treated for COVID-19. The ORR was 50% and 1 (5%) patient was CR (also this patient's CPS<1). The DCR was 100%. Median follow-up was 10.7 months, the median PFS and the median OS were not reached, and median Time of Treatment (TOT) was 7.7 months (2.1-20.3). Currently, only 1 patient who had achieved objective response has shown disease progression, and mTOT was 8.55 months (4.6-20.3). Grade 3 and 4 TRAEs reached 70%, and mainly come from chemotherapy-related neutropenia. 1 patient with grade 3 thrombocytopenia. Thyroid dysfunction is the most common irAEs. There was no TRAEs leading to treatment discontinuation.

Table: 929P

Patient Characteristic		N=16 n(%)
Age, median (range), years		61 (22-69)
Gender (male / female)		12/4
Primary tumor	nasal cavity	5 (31.3)
	maxillary sinus	11 (68.7)
Stage	IVA	9 (56.3)
	IVB	2 (12.5)
	IVC	5 (31.2)
PD-L1 combined positive score	< 1	2 (12.5)
	1-19	4 (25.0)
	≥20	8 (50.0)
	unknow	2 (12.5)
Disease condition	distant metastatic disease	2 (12.5)
	local disease	10 (62.5)
	distant and local disease	4 (25.0)

Conclusions: Pembrolizumab plus nab-paclitaxel and platinum shows encouraging antitumor activity accompanied with a manageable side effect profile in untreated R/M SCC of the nasal cavity and paranasal sinuses patients.

Clinical trial identification: This study is registered at Chinese Clinical Trial Registry, number ChiCTR2200057343, and the release date is March 9, 2022.

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930P Platinum and taxane (PT) plus immunotherapy versus immunotherapy alone in patients with recurrent/metastatic (R/M) head and neck cancer (HNSCC)

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Background: Immune-checkpoint inhibitors (ICI) are currently the standard of care as a first line treatment for pts with R/M HNSCC. There is limited data on the impact of adding PT to ICI in this population.

Methods: We retrospectively analyzed pts with R/M HNSCC who received first line ICI alone or along with PT, between July 1st 2016 and November 1st 2022. We collected data on original tumor site, P-16 status, combined positive score (CPS), absolute lymphocyte count (lymph) prior to starting ICI, time elapsed between finishing radiation to the original tumor site and starting ICI (RT-ICI), response to therapy, progression free survival (PFS), and overall survival (OS). PFS was defined as the time from ICI initiation and disease progression or death. OS was defined as the time from ICI initiation and death. Descriptive statistics were used to explore study variables.

Results: Of the 207 pts analyzed, 81% were male, median age 61 years (IQR: 56, 68). Tumor site: Oropharynx 85 (41%), oral cavity 54 (26%), others 68 (33%). 138 pts (67%) received ICI alone, 69 (33%) PT+ICI triweekly. 64 pts (31%) had RT-ICI of less than 6 months (mo). 144 pts (70%) had CPS available. CPS values: 0 (43 [30%]), 1-20 (50 [35%]), 21-100 (51 [35%]). Median follow-up: PFS: 4.4 mo (IQR: 2.3, 9.8), OS: 8.5 mo (IQR: 3.7, 17.7). Overall response rate (ORR): PT+ICI (33%), ICI (16%), p=0.002. Median survival time: PFS: 4.5 mo (95% CI: 4, 6.2), OS: 11 mo (95% CI: 8.8, 14.3). Median OS: PT+ICI: 15.4 mo (95% CI: 11.3, –), ICI: 9.1 mo (95% CI: 7.1, 13), p=0.062. On multivariable analysis for OS: PT+ICI had reduced hazard compared to ICI (HR: 0.79, 95% CI: 0.53, 1.17, p=0.2); P-16 positive had reduced hazard compared to p-16 negative (HR: 0.46, 95% CI: 0.31, 0.68, p <0.001); high lymph compared to low lymph (HR: 0.48, CI: 0.32, 0.73, p <0.001); CPS of 1-20 and 21-100 had reduced hazard compared to CPS of 0 (HR: 0.72, 95% CI: 0.44, 1.2; HR: 0.48, 95% CI: 0.29, 0.82; respectively, p=0.024); RT-ICI of more than 6 mo had reduced hazard compared to 0-6 mo (HR: 0.68, 95% CI: 0.47, 0.99; p=0.11).

Conclusions: In pts with R/M HNSCC, the addition of PT to ICI was associated with better ORR. Negative P-16, low lymph, CPS of 0, and relapse within 6 mo of finishing RT, were all associated with worse survival outcomes.

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931P Early recurrence, time-to-recurrence, and recurrence patterns: Assessing their impact on survival outcomes in recurrent/metastatic head and neck squamous cell carcinoma (R/M-HNSCC) patients

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Background: Patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M-HNSCC) ineligible for curative local therapy typically receive first-line (1L) systemic treatment with platinum-based chemotherapy and pembrolizumab or cetuximab. However, early recurrent patients (<6 months from the last curative local treatment) have been excluded from most 1L systemic treatment studies. Therefore, treatment outcomes for early recurrent patients, the impact of different time-to-recurrence intervals (TTRI), and the influence of recurrence patterns on survival remain unclear.

Methods: We analyzed non-curable R/M-HNSCC patients at our institution between 1/2008 and 6/2020. The study aimed to evaluate outcomes of early recurrent patients

receiving 1L systemic treatment and assess TTRIs and recurrent patterns' impact on survival.

Results: 234 of 1,281 eligible patients were included. Platinum-based doublet chemotherapy was the predominant 1L treatment. Significant differences in PFS and OS were observed among TTRI groups. In early recurrent patients, those receiving platinum-based doublet and monotherapy showed significantly longer OS compared to best supportive care (BSC). Locoregional recurrence was the most common pattern (47%), followed by distant metastasis (22%) and both (20%). Different R/M-HNSCC patterns were significantly associated with OS (p=0.019), but not PFS (p=0.790). In multivariate analysis, TTRI of ≥12 months correlated with PFS (HR 0.51; p=0.004) and OS (HR 0.58; p=0.009), while recurrence pattern did not.

Table: 931P

TTRI	<6 month (47%)	6-12 month (22%)	>12 month (20%)	De novo M1 (11%)	p-value
All PFS (months)	2.9	2.8	5.0	3.8	0.028
All OS (months)	4.1	5.1	8.8	5.3	0.006
OS of patients with 1L treatment Platinum-doublet Monotherapy BSC	5.8 4.1 2.5	8.4 12.7 2.3			<0.001

Conclusions: In our study, R/M-HNSCC patient survival was significantly influenced by TTRI, while recurrence pattern was not. Despite poor prognosis, early recurrent patients benefited from systemic treatments. TTRI should be a stratification factor in future clinical trials, as varying prognoses were observed.

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932P Survival in patients with relapsed/metastatic head and neck squamous cell carcinoma (HNSCC) treated with pembrolizumab or cetuximab-based therapy: A real-worlddata study with the TriNetX platform

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Background: Pembrolizumab alone or with platinum-based chemotherapy is a standard first-line systemic treatment for recurent/metastatic (R/M) HNSCC in Europe, based on results of KEYNOTE-048 phase III trial. Real-world data (RWD) are scarce since aprpoval by EMA in 2019. We present real-world data (RWD) of overall survival (OS) of three cohorts of R/M HNSCC patients: cohort 1 (pembrolizumab plus chemotherapy, P+CT), cohort 2 (pembrolizumab alone, P), and cohort 3 (cetuximab plus chemotherapy, C+CT). Data were extracted from TriNetX, the global federated health research network that includes several hospitals in Europe and America.

Methods: The TriNetX network was used to search and analyze clinical anonymized information. The analysis process included two main steps: 1) Defining the cohorts through query criteria: R/M HNSCC, no prior systemic therapy, survival information available, P or P+CT or C+CT. 2) Setting up and running the analysis. Research was done in in a time window of 3 years. Index event was defined as the diagnosis of metastasis. Kaplan-Meier analysis was used to estimate survivals and comparison between cohort 1 vs 3 and cohort 2 vs 3.

Results: Number of patients matching the search criteria were: cohort 1 (P+CT) N=2965, cohort 2 P) N=2138, cohort 3 (C+CT) N=3947. Median age was 61.8, 65.6, and 62.7 yr for cohort 1, 2, and 3, respectively. Male percentage was 74.8%, 72.8%, and 78.3%, respectively. Primary tumor in oropharynx was present in 37.4%, 16.2% and 54.2%, respectively. Unspecified or ill-defined primary tumor location was present in 32.5%, 23.4%, and 43.1%, respectively. Information about PD-L1 status was not available. Median OS for cohort 1 and 2 were not reached; it was 951 days for cohort 3. Log-rank comparison was significantly different for cohort 1 vs 3 ($p<0.001$), and for 2 vs 3 ($p<0.001$), demonstrating superiority for either of the anti-PD1 cohorts.

Conclusions: OS with pembrolizumab-based therapy is superior compared to cetuximab plus CT in these RWD cohorts of first-line treatment for R/M HNSCC. An unexpected high median overall survival was found in all cohorts. The TriNetX system has limitations that must be detected and improved.

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933P Real-world patterns of immunotherapy utilization and outcomes in recurrent/metastatic head and neck cancer (R/M HNC) patients across European countries: A multicenter retrospective federated analysis

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Background: Limited real-world data exists on treatment patterns and outcomes in R/M HNC pts receiving anti-PD-1 immunotherapy (IT). This study provides insights into contemporary IT use and sequencing. Preliminary results from five centers in four European countries (Italy, Poland, Portugal, Slovenia) are presented.

Methods: A retrospective federated analysis of R/M HNC pts who received IT between March 2017 and May 2022 was conducted. Data were analyzed at each center using a common R script. Overall survival (OS) and real-world progression-free survival (rwPFS) were calculated from IT start. Lines of systemic therapy (line) included concomitant chemotherapy (ChT) used with radiotherapy (CRT).

Results: A total of 224 pts with a median age of 58—67 yrs across countries were included. 43.8% of pts had metastatic disease as opposed to locoregional only at IT start, 64.7% had platinum refractory disease, and 19.2% were tested for PD-L1 expression. 9.8% of pts began their treatment with IT, whereas most pts. received anti-PD-1 after previous CRT or as a 2nd line (pembrolizumab 10.0%, pembrolizumab+ChT 4.4%, nivolumab 85.6%). In the first line, the most common systemic treatments beside platinum-based CRT (39.3%) were platinum-containing combination ChT without cetuximab (37.5%) and ChT+cetuximab (12.0%). The maximum number of lines in any patient was 10 and nivolumab was the most used agent overall (25.6%) followed by non-platinum monochemotherapy (21.4.%). Median overall survival from anti-PD-1 initiation across countries was 5.9—13.6 months (ms), and the median rwPFS ranged from 2.8—4.8 ms. The overall occurrence of irAEs ranged from 18.3—81.3% across countries, with the most common irAEs being gastrointestinal (25.8%) and endocrinal disorders (17.9%). There were 57.3% grade 2, 6.6% grade 3 and no grade 4 or 5 irAEs.

Conclusions: This real-world study across four European countries shows variable IT utilization and outcomes, irAEs occurrence, and treatment patterns in R/M HNC. Further research is needed to optimize IT use, considering pts characteristics and treatment-related factors.

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934P Antitumor activity and safety profile of camrelizumab plus docetaxel, cisplatin, and capecitabine for induction therapy in advanced stage hypopharyngeal carcinoma

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Background: Locally advanced hypopharyngeal carcinoma (LAHC), an aggressive type of head and neck cancer (HNC), generally exhibits poor prognosis. Currently, The programmed death 1 inhibitors, implicated in antitumor activity, emerge as meaningful option in patients with recurrent or metastatic HNC, but the role of camrelizumab remains uncertain. Aim to determine effects and safety of induction therapy of camrelizumab plus TPF (docetaxel, cisplatin, and capecitabine) in LAHC.

Methods: In this single-arm, phase 2, prospective, and single-center trial, patients with T3-4aN0-3M0 LAHC received induction therapy for three cycles: camrelizumab 200 mg on day 1, docetaxel 75 mg/m^2 on day 1, cisplatin 25 mg/m^2 on day 1-3, capecitabine 800 mg/m^2 bid on day 1-14, every three weeks. Patients were assigned to radiotherapy and immunotherapy if they had a complete response or partial response (PR) or assigned to surgery and adjuvant (chemo)radiotherapy if they had stable disease (SD) or progressive disease that was defined by using a tumor volume evaluation system. Camrelizumab was maintained postradiotherapy and immunotherapy for a total of 18 doses. This trial was registered with ClinicalTrials.gov, No. NCT04156698 and is ongoing.

Results: Fifty-one patients were enrolled from May 21, 2020, to April 15, 2023, and the mean duration of follow-up was 16.5 $\pm$ 8.7 months. After induction therapy, 42 (82.4%) patients showed PR, and 9 (17.6%) showed SD. Treatment-related adverse events were recorded, leading to treatment suspension in 9 (17.6%) patients but no death. The most common adverse event was alopecia (100%), followed by RCCEP (90.2%), nausea/vomiting (84.3%), and fatigue (58.8%) in the induction therapy period. Twenty-six (51.0%) patients experienced grade 3 or 4 induction therapy-related adverse events. The two-year overall survival, progression-free survival, and laryngeal function preservation rates were 85.5%,72.8%, and 65.4%, respectively.

Conclusions: Camrelizumab plus TPF was well tolerated and demonstrated effective antitumor activity in LAHC, indicating future therapy options of camrelizumab as antitumor MAb for advanced HNC.

Clinical trial identification: NCT04156698.

Legal entity responsible for the study: The authors.

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935P A phase II study of monalizumab and durvalumab in patients with recurrent/metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN): Results of the I2 cohort of the EORTC-HNCG-1559 trial (UPSTREAM)

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Background: Monalizumab (mona), a IgG4 Ab targeting the NKG2A receptor, has limited activity as monotherapy in RM SCCHN. Targeting the NKG2A-HLA-E pathway with PD(L)1 blockade improved tumor control in mice. Preliminary data of mona and durvalumab (durva), have shown encouraging activity in pretreated MSS colorectal cancer.

Methods: The UPSTREAM trial is an umbrella trial of targeted therapies and immunotherapy for RM SCCHN (post platinum, ECOG 0-1). The immunotherapy 2 (I2) cohort was a phase II, randomized, open label substudy evaluating the efficacy of the combination of durva (iv, 1500mg Q4W) and mona (iv, 750mg Q2W or Q4W) (D+M) vs physician's choice (control, ctrl) (2:1 ratio). Pts non-eligible for the biomarker-driven cohorts and pretreated with PD(L)1, were included in the I2 cohort. The primary endpoint was objective response rate (RECISTv1.1) during the first 16 weeks (2-stage Simon design applied to the D+M arm, H1 15%, H0 3%, 1-sided α 10%, power 90%). Secondary endpoints included response duration, toxicity, PFS, and OS.

Results: 66 RM SCCHN pts were included in the I2 cohort (D+M: n=45, ctrl: n=21). 61 pts were evaluable (D+M: n=43, ctrl: n=18): median age 62 yrs; oral cavity 20%, oropharynx 39%, hypopharynx 20%, larynx 21%; 87% with 2 or 3 previous lines. In D+M 1 partial response (PR) was recorded and stable disease (SD) was observed in 11 pts (26%). 1 PR was reported in the ctrl arm and SD in 8 (44%). The median PFS was 2.0 mo (95% CI: 1.8-2.4) and 3.1 mo (95% CI: 1.9-3.9) in the D+M arm and ctrl arm, respectively. The median OS was 4.4 mo (95% CI: 3.3-9.2) and 8.0 mo (95% CI: 3.1-14.9) in the D+M and ctrl arm, respectively. In the D+M arm, 4 pts (9%) reported grade >/= 3 treatment-related adverse events.

Conclusions: The substudy of mona and durva did not meet its primary objective. No benefit was seen in PFS and OS. These are preliminary results, definitive results will be presented at the congress. ClinicalTrials.gov: NCT03088059.

Clinical trial identification: NCT03088059.

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936P Triple oral metronomic chemotherapy (OMCT) versus physician choice chemotherapy after failure of platinum-based therapy in advanced head and neck squamous cell cancer (HNSCC): A phase III randomized open-label study

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Background: Advanced HNSCC patients with platinum-refractory disease have limited treatment options and poor outcomes, especially in resource-constrained settings. Triple metronomic therapy, a low-dose continuous chemotherapeutic strategy, has shown promise in phase 2 trials but requires further validation. We aimed to evaluate triple OMCT's efficacy in improving overall survival (OS) compared to physician-choice chemotherapy (PCC).

Methods: In this phase 3 open-label study, 214 advanced HNSCC patients previously treated with platinum-based chemotherapy (October 2021-August 2022) were randomized 1:1 to receive triple OMCT (Arm A) with Methotrexate 9 mg/m^2 PO weekly, Celecoxib 200 mg twice daily and erlotinib 150 mg daily, or PCC (Arm B), stratified by age and performance status. Primary endpoint was OS, with secondary endpoints including progression-free survival (PFS), Quality of Life (QoL) assessments, and safety. OS and PFS were analyzed using Kaplan-Meier and log-rank tests, with hazard ratios estimated by Cox proportional hazard models. QoL was assessed using EORTC QLQ-C30.

Results:

Table: 936P Baseline characteristics of the patients

Characteristics	Arm A (Triple OMCT) n (%)	Arm B (Physician Choice) n (%)	p-value (Chi-square)
Age (in years) <60 60 or more	86 (80.4) 21 (19.6)	85 (79.4) 22 (20.6)	0.865
Sex Female Male	6 (5.6) 101 (94.4)	4 (3.7) 103 (96.3)	0.517
Baseline Hemoglobin level (gm/dL) ≤ 12 > 12	68 (63.6) 39 (36.4)	78 (72.9) 29 (27.1)	0.142
Comorbidities Yes No	7 (6.5) 100 (93.5)	16 (15.0) 91 (85.0)	0.077
ECOG Performace Status 1 2	68 (63.6) 39 (36.4)	62 (57.9) 45 (42.1)	0.401
Site of Tumor Oral Cavity Others	70 (65.4) 37 (34.6)	71 (66.4) 36 (33.6)	0.885

Most patients had ECOG PS 1 (60.7%) and tumor site in the oral cavity (65.9%). With a median follow-up of 11 months, the median OS was 9 months in Arm A and 5 months in Arm B (HR, 0.63; 95% CI, 0.47−0.83; p=0.00011). Median PFS was 4 months in Arm A and 2 months in Arm B (HR, 0.67; 95% CI, 0.52−0.87; p<0.0001). Multivariate analysis identified age, hemoglobin level, and comorbidity as significant OS prognostic factors. No significant QoL score differences were observed. Triple OMCT showed fewer grade 3 or higher adverse events than PCC (28.0% vs 39.3%, p=0.03).

Conclusions: Triple OMCT is an effective, safe treatment for advanced HNSCC patients previously treated with platinum-based chemotherapy, offering improved OS and tolerable side effects compared to physician-choice chemotherapy.

Clinical trial identification: Clinical Trial Registry-India CTRI/2021/09/036296.

Legal entity responsible for the study: The authors.

Funding: Indian Cooperative Oncology Network (ICON) Trust.

Disclosure: All authors have declared no conflicts of interest.

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937P Survival outcomes in phase I trial combining VCN-01 and durvalumab (MEDI4736) in subjects with recurrent/metastatic head and neck squamous cell carcinoma refractory to previous immunotherapy treatment

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Background: VCN-01 is an oncolytic adenovirus expressing hyaluronidase that increases immune check-point inhibitor uptake in preclinical models suggesting it could reduce resistance to anti-PD(L)-1 therapies. Initial results from phase 1 trial NCT03799744 showed that sequential administration of VCN-01 and Durvalumab is feasible with an acceptable safety profile. Here we present the clinical outcomes data.

Methods: VCN-01 at 3,3E12 and 1E13 viral particles [vp] were administered with a fixed dose of Durvalumab (1500 mg) in a 3+3 design in R/M HNSCC pts previously treated with anti-PD(L)-1 agents. Concomitant (single dose VCN-01 + Durvalumab on day 1, CS), and sequential (single dose of VCN-01 on day -14 + Durvalumab on day 1; SS) schedules were tested. Durvalumab continued q4 weeks until progression in both schedules. Fresh tumor biopsies were taken at baseline, post-VCN-01 and post-Durvalumab.

Results: 20 patients were enrolled (median prior lines: 4, range: 1-7), from which 6 in the CS (all 3.3E12 vp) and 12 in the SS (6 at 3,3E12vp and 6 at 1E13 vp) were evaluable for response. Objective response rate (ORR), median PFS and OS (95% CI) in the CS at 3,3E12vp were 0% 1,7 months (1.6-NE) and 10.4 months (8.9-NE), respectively. For SS patients at 3.3E12 vp, ORR, median PFS and OS were 16%, 3.7 months (2.2-NE) and 15.5 months (15.1-NE) respectively. Values for SS patients at 1E13 vp were 0%, 2.1 months (1.4-NE) and 15+ months. 11 patients (61.1%) were alive >12 months (2 in CS; 5 in SS at 3.3E12 vp, 4 in SS at 1E13 vp). Unexpectedly most of them appeared to benefit from subsequent treatment. The 3 patients with the longest survival showed immune-mediated DLT. Increase of PDL1-CPS (16/21; p=0.013) and CD8 T-cells (12/21; p=0.007) from baseline were found in tumor biopsies both post-VCN-01 and post-Durvalumab. A correlation between OS and CPS at D8 was observed (p=0.005). Viral genome analysis and other biologic markers confirmed sustained VCN-01 replication.

Conclusions: Encouraging survival was observed in patients progressing to anti-PD(L)-1 agents after systemic VCN-01 with Durvalumab. VCN-01-induced upregulation of PD-L1, which correlated with enhanced patient survival.

Clinical trial identification: NCT03799744.

Legal entity responsible for the study: Institut Català d'Oncologia.

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Institutional, Product Samples: ROCHE. A. Hernando Calvo: Other, Other, Travel support: Merck Serono, Kyowa Kirin. C. Erasun Lecuona: Financial Interests, Personal, Full or part-time Employment: BMS. A. Mato-Berciano: Financial Interests, Personal, Full or part-time Employment: Theriva Biologics. M.V. Maliandi: Financial Interests, Personal, Full or part-time Employment: Theriva Biologics. C. Le: Financial Interests, Full or part-time Employment: Theriva Biologics. P.G. Nuciforo: Financial Interests, Personal, Advisory Board: BAYER, MSD ONCOLOGY; Financial Interests, Personal, Invited Speaker: NOVARTIS; Financial Interests, Personal, Other, Consultant: TARGOS Molecular Pathology. R. Alemany: Financial Interests, Personal, Stocks/Shares: Theriva Biologics; Financial Interests, Institutional, Research Funding, T: Theriva Biologics SL; Financial Interests, Institutional, Speaker, Consultant, Advisor: Theriva Biologics SL. G. Capella: Financial Interests, Personal, Other, Consultancy: THERIVA BIOLOGICS; Financial Interests, Personal, Stocks/Shares: THERIVA BIOLOGICS; Non-Financial Interests, Member of Board of Directors, Chairperson 2022-2024: International Society for the Study of Hereditary Gastrointestinal Cancer; Non-Financial Interests, Member of Board of Directors: FUREGA Fundació Per la Recerca en Gastroenterologia; Non-Financial Interests, Member: ASCO, EACR-ASEICA, EHTG European Hereditary Tumor Group. C. Blasco: Financial Interests, Personal, Full or part-time Employment: Theriva Biologics SL. M. Cascallo Piqueras: Financial Interests, Personal, Full or part-time Employment: Theriva Biologics SL; Financial Interests, Personal, Stocks/Shares: Theriva Biologics. R. Mesia Nin: Financial Interests, Personal, Advisory Board: Merck, MSD, Bayer, Seattle Genetics, Nanobiotix, Boehringer, Segean; Financial Interests, Personal, Invited Speaker: Merck, MSD, BMS; Non-Financial Interests, Principal Investigator, Clinical Trial PI: BMS; Non-Financial Interests, Principal Investigator, Observational trial PI: Merck. All other authors have declared no conflicts of interest.

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938P Nivolumab (nivo) in recurrent and/or metastatic squamous cell carcinoma of head and neck (R/M SCCHN): real-world effectiveness, quality of life (QoL) of patients and their caregivers in France (ProNiHN study)

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Background: ProNiHN is a prospective, observational, and multicenter study of patients (pts) with R/M SCCHN treated with nivo after progressing on or after platinum-based therapy. We report here the effectiveness and QoL for pts and their caregivers (cg).

Methods: Based on a minimum follow-up of 17-months (mo), progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier method. QoL changes of pts were measured with 3 questionnaires (FACT-H&N & EQ-5D-3L&VAS) between inclusion (incl) and week-6, mo-3, 6, 12 and 18. QoL and needs of cg were estimated with CarGOQoL and SCNS-P&C-F questionnaires at incl and at 6 mo.

Results: Among 487 patients, median PFS and OS were 3.3 mo and 9.3 mo, respectively. OS rates were 64% at 6 mo, 40% at 12 mo and 28% at 18 mo. The number of pts completing FACT-H&N was 354 at incl and decreased to 39 at 18 mo. QoL of overall population tended to be stable or improved over time (Table). Same trend was observed for EQ-5D-3L&VAS. For pts (n=121) who completed FACT-H&N both at incl and 6 mo, overall total score significantly decreased (mean: -4.7; p=0.003), in particular for pts who stopped nivo within the 6 mo (-8.8; p<0.001) whereas it remained stable (0.0; p=0.986) for pts still on nivo. No significant difference was observed for pts (n=64) between incl and 12 mo (-2.4; p=0.291). 292 pts mentioned a cg, mostly spouse (71.4%). Among them, 48 cg completed CarGOQoL at incl and 6 mo. Psychological well-being improved over time (43.8 vs. 52.0; p=0.027) while relationship with healthcare decreased (62.0 vs. 53.1; p=0.045). FACT-H&N and CarGOQoL results were correlated at incl (0.226, p=0.003) and at 6 mo (0.362; p=0.006).

Conclusions: Nivo showed similar effectiveness and QoL in the real-world as in pivotal trial. QoL of pts tended to be stabilized over time, especially for patients still treated with nivolumab at 6 mo. QoL of cg and pts seems to be correlated.

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Legal entity responsible for the study: Bristol Myers Squibb.

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939P Efficacy and safety of a novel anti-EGFR ADC MRG003 in recurrent or metastatic squamous cell carcinoma of the head and neck patients

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Background: Patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) who failed platinum and/or immune check-point inhibitor have a poor prognosis with OS ~ 6 moths. Epidermal growth factor receptor (EGFR) is aberrantly over-expressed in R/M SCCHN pts with high frequency. MRG003 is a novel ADC composed of a humanized anti-EGFR mAb conjugated to MMAE via a vc-linker. This study was designed to evaluate the efficacy and safety of MRG003 in R/M SCCHN.

Methods: Histologically or cytologically confirmed R/M SCCHN (including oral cavity, oropharynx, hypopharynx, and larynx) pts were divided into two groups of MRG003 (2.0 or 2.3 mg/kg, Q3W). Eligible pts were aged 18-75 years old and had progressed at least one line of standard therapy. The primary endpoint was the objective response rate (ORR). The secondary endpoints included disease control rate (DCR), median progression-free survival (mPFS), median overall survival (mOS), and safety.

Results: Sixty-seven pts in total were enrolled with 35 pts received 2.0 mg/kg of MRG003, and 32 pts received 2.3 mg/kg. The median age was 54 (26-75) years, and 91% of pts' ECOG performance status was 1. The immunohistochemistry detection of EGFR expression was performed in 65 pts, and 62 pts (95.4%) were EGFR-positive. The median line of prior therapy was 2 (1-5). Most pts had received prior platinum (95.6%), PD-1/L1 inhibitor (76.1%), cetuximab (47.8%). At the data cutoff, the ORR was 30.6% in all EGFR-positive pts. In the 2.3 mg/kg dose group, the ORR and DCR was 43% and 86% in 2/3-line pts who had failed prior platinum and PD-1/L1 inhibitor, and the mPFS and mOS were 4.2 months and 11.3 months, respectively. The common treatment-related adverse events (TRAEs) included constipation (25.8%), pruritus (24.2%), and anemia (22.6%). Common grade 3 or above TRAEs included white blood cell count decreased (6.5%), anemia (4.8%).

Conclusions: MRG003 was well tolerated with a manageable safety profile, and showed promising efficacy in 2/3-line R/M SCCHN pts who failed prior platinum and PD-1/L1inhibitor. A phase III study is currently ongoing to further explore the efficacy of MRG003 in compared with cetuximab/methotrexate in this setting.

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Table: 938P

Overall patients		Inclusion (n=354)	6 weeks (n=258)	3 mo (n=205)	6 mo (n=145)	12 mo (n=77)	18 mo (n=39)
FACT-H&N [0-148] ***mean (±SD)***		88.1 (± 22.5)	91 (± 20.6)	91.4 (± 21.3)	93 (± 22.5)	97.3 (± 20.7)	94.1 (± 21.6)
Change in FACT-H&N	Improved/stable (>-6)	N/A	64.0%	60.7%	52.9%	60.9%	58.8%
from baseline (MID =6)	Deteriorated (≤-6)	N/A	36.0%	39.3%	47.1%	39.1%	41.2%

940P Salvage chemotherapy after progression on nivolumab in patients with squamous cell carcinoma of the head and neck included in the phase II TOPNIVO trial

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Background: Immune checkpoint inhibitors (ICIs) changed the treatment landscape of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) and approved in first-line setting as monotherapy or in combination with chemotherapy as well as in platinum refractory disease. Recent retrospective data showed that salvage chemotherapy (SCT) after progressing on ICIs was associated with an overall response rate (ORR) of 30%. We report herein data of patients with R/M SCCHN included in the TOPNIVO phase II trial who progressed on nivolumab (N) and received SCT.

Methods: TOPNIVO is a multicenter phase II safety trial of nivolumab in patients (pts) with platinum refractory R/M SCCHN, ECOG 0-2. Pts received N 3mg/kg every 2 weeks intravenously. Overall, 343 pts received N.

Results: 143 pts (84% male, 17% $\geq$70 years) received SCT after a median of 7 injections of N [range 1-47]. Best response under N was complete response for 2%, partial response for 14%, stable disease for 27%, progression for 56%. The ORR of SCT of the 143 pts was 22% (95% confidence interval (CI) 16;30) and the disease control rate was 38%. The median overall survival (OS) since SCT start was 7.9 months (mo) (95% CI 5.4;9.7) and the 12-mo OS rate was 34%. The median OS was 9.1 mo in 96 pts treated with cetuximab (C) or taxanes (T) based SCT vs 3.9 mo in 31 pts treated with methotrexate or other regimens (p=0.0007). The median OS was 18.3 mo in 17 pts treated with C and T based SCT vs 7.5 mo in 58 pts treated T based SCT without C (p=0.09). 40 pts received C-based SCT with an ORR of 25%, and 79 pts received T-based SCT with an ORR of 30%. In C-based SCT, the ORR was 29% (7/24) in those who already received C prior to N vs 19% (3/16) in those who did not receive, and the median OS was 17.7 mo vs 9.4 mo (p=0.17). In T-based SCT, the ORR was 27% (4/15) in patients who already received T prior to N versus 31% (20/64) in those who did not already receive T and the median OS was 5.7 mo vs 8.8 mo (p=0.37).

Conclusions: SCT was associated with an ORR of 22% in pts with SCCHN who progressed on nivolumab confirming previous results. Re-challenge with cetuximab was associated with ORR of 29%, and re-challenge with taxanes was associated with ORR of 27%.

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941P Risk factors for progressive disease after immune checkpoint inhibitors (ICIs) in advanced head and neck squamous cell carcinoma (HNSCC): Who might not be candidate for ICI?

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Background: Immune checkpoint inhibitors (ICI) do not always show favorable outcomes in patients with advanced head and neck squamous cell carcinoma (HNSCC)). Once progressive disease (PD) occurs, the patient becomes deteriorated and ineligible for subsequent cytotoxic chemotherapy. Therefore, avoiding PD prior to ICI treatment is crucial. The purpose of this study is to identify the clinical features in patients who developed PD after ICI therapy.

Methods: We conducted a retrospective analysis of 125 patients with recurrent and/or metastatic (R/M) HNSCC treated with ICI between January 2013 and December 2018 at 11 medical centers in the Republic of Korea. We evaluated best response by RECIST1.1, progression-free survival and overall survival (OS). The associations between these outcomes and various clinical factors were analyzed.

Results: The median age was 57 years. 41.6% of the patients received ICIs as a third or later line of palliative chemotherapy. The complete response rate was 3.2%, partial response rate was 12.0%, stable disease rate was 25.6%, and the rate of PD was 54.4%. Hyper PD, defined as tumor growth kinetics ratio $>$2, was observed in 14.4%. The median PFS and OS were 2.3 months and 6.6 months, respectively. In univariate analysis, a neutrophil-to-lymphocyte ratio (NLR) $>$4, a sum of the target lesions $>$40 mm, and prior chemotherapy lines $\geq$2 were significant predictors of PD (P=0.014, 0.031, and 0.042, respectively). Multivariate logistic analysis showed high NLR, large tumor size, prior line of chemotherapy, type of ICI were independent predictors for PD. Furthermore, NLR $>$4 (HR 2.80, p$<$0.001), a poor performance status (ECOG$\geq$2) (HR 4.76, p$<$0.001), and a sum of the target lesions $>$40mm (HR 1.70, p=0.048) were independently associated with poor OS. Patients who experienced PD had significantly shorter median OS (7.4 vs. 18.4 months, p$<$0.0071).

Conclusions: Our study identified clinical features that were associated with PD to ICIs in patients with R/M HNSCC. NLR, tumor size, and number of prior chemotherapy lines can serve as clinical predictors for the likelihood of PD for ICI. Clinicians can utilize these findings to personalize treatment plans and enhance patient outcomes.

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942P Response to salvage chemotherapy with paclitaxel +/- cetuximab after progression on immune checkpoint inhibitors in platinum-refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) patients (CeTax study)

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Background: Immune checkpoint inhibitors (ICI) and platinum-based chemotherapy are the standard treatments of R/M SCCHN patients (pts). After progression on these therapies, there is a lack of data and no standard of care exists.

Methods: This is a multicentric retrospective study (3 French and 3 Swiss centers). We analyzed the efficacy and safety of paclitaxel alone (P) or in combination with the epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab (PC) beyond ICI progression in platinum-refractory and taxane naïve R/M SCCHN pts treated from January 2016 to August 2022. Primary endpoint was objective response rate (ORR) according to RECIST 1.1 criteria.

Results: We included 152 pts treated with P (69 pts, 45%) or PC (83 pts, 55%): 73% were males, 81% smokers. Median age was 67 (24-86). The ORR was 45% in the total population (TP), 22.4% in P group and 63.5% in PC group ($p<0.001$). The disease control rate (DCR) was 68.5% in the TP, 56.7% in P group and 78.1% in PC group ($p=0.007$). The median overall survival was 8.0 months (m) [95% CI: 7.0-9.4] in the TP, 6.9 m [95% CI: 5.5-8.2] in the P group and 9.4 m [95% CI: 8.0-11.8] in the PC group ($p=0.02$). The median progression free survival was 4.0 m [95% CI: 3.3-4.7] in the TP, 2.8 m [95% CI: 2.5-3.7] in the P group and 4.9 m [95% CI: 4.3-5.7] in the PC group ($p<0.001$). The rate of G3/G4 adverse event (AE) was 18.8% in P group and 21.7% in PC group. One patient died of septic shock in PC group. The most common G3/G4 AE were neuropathy (8.6%) in P group and acneiform rash (10%) in PC group.

Table: 942P Response Rate according to type of treatment CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; NE: Not evaluable

	Total population N=152	Paclitaxel N=69	Paclitaxel-Cetuximab N=83
CR	4 (2.7%)	1 (1.5%)	3 (3.7%)
PR	63 (42.3%)	14 (20.9%)	49 (59.8 %)
SD	35 (23.5%)	23 (34.3%)	12 (14.6%)
PD	47 (31.5%)	29 (43.3%)	18 (22%)
NE	3	2	1

Conclusions: Taxane-based chemotherapy is highly active and well-tolerated after ICI failure in platinum-refractory R/M SCCHN pts. Our results suggest a potential additional benefit of cetuximab combined with paclitaxel in this population and deserves further investigation in prospective randomized clinical trials.

Legal entity responsible for the study: CHUV - Centre Hospitalier Universitaire Vaudois.

Funding: Has not received any funding.

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943TiP PEMDA-HN, an open-label, phase II, randomized controlled study of danvatirsen plus pembrolizumab compared to pembrolizumab alone in recurrent or metastatic head and neck squamous cell carcinoma (RM HNSCC)

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Background: Signal transducer and activator of transcription 3 (STAT3) plays a critical role in survival of tumor cells, as well as promotion of an immune-suppressive tumor microenvironment. Danvatirsen (DAN) is a 16-nucleotide, generation 2.5 antisense oligonucleotide designed to down-regulate the expression of human STAT3 messenger RNA. Over 500 patients with hematologic malignancies or solid tumors have been exposed to DAN monotherapy or in combination. A tolerable safety profile has been demonstrated and toxicities are manageable. The SCORES Study (ESMO 2018) in RM HNSCC patients naïve to programmed cell death (ligand)1 (PD-(L)1) therapy demonstrated that DAN in combination with the PD-L1 inhibitory antibody durvalumab approximately doubled the objective response rate (ORR) seen with durvalumab alone in previous studies. Several patients had complete responses (CR). The response was enhanced in patients with a PD-L1 tumor proportion score $\geq$20. The current study aims at evaluating the combination of DAN with pembrolizumab, an anti-PD-1 agent approved as first line monotherapy for RM HNSCC.

Trial design: PEMDA-HN is a multicenter, open-label, randomized phase 2 study. Approximatively 81 RM HNSCC patients with a PD-L1 combined positive score (CPS) $\geq$20 will be randomized in a 2:1 ratio to receive either DAN (3 mg/kg intravenously [IV] weekly) and pembrolizumab (200 mg IV every 3 weeks) or pembrolizumab alone (200 mg IV every 3 weeks) as a first line therapy for recurrent or metastatic disease. After the screening period, eligible patients will receive study treatment until disease progression or discontinuation. The primary endpoint of the study is to determine the ORR by response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) as assessed by the investigator. Key secondary objectives are safety, additional antitumor activity evaluation (CR rate, duration of response, disease control rate, progression free survival, and overall survival) and pharmacokinetics. Exploratory endpoints include but are not limited to target engagement and biomarker evaluation. The study is being conducted at US study centers.

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Legal entity responsible for the study: Flamingo Therapeutics NV.

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944TiP Randomized phase II study of immune stimulation with pembrolizumab and radiotherapy of recurrent and/or metastatic head and neck squamous cell carcinoma : The IMPORTANCE trial

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Background: PD-1-inhibitors were found effective in large clinical trials in first- and second-line therapy of recurrent and/or metastatic head and neck squamous cell carcinoma (rmHNSCC). Despite relative low objective response rates (ORR), overall survival (OS) improved significantly. It is generally assumed, that an improvement of the ORR will directly result in a further improvement of OS. Radiotherapy (RT) not only kills tumor cells, but also changes the tumor cell phenotype and the tumor microenvironment, which might result in induction of anti-tumor immune responses. In preclinical experiments the combination of RT and PD-1/PD-L1 pathway blockade improved local tumor control, and also induced systemic tumor immunity. Consequently, metastases distant from the irradiated tumor responded after RT and the survival rate of the animals improved. Thus, local RT, acting as in situ vaccination, is probably able to improve the ORR to pembrolizumab (P) in rmHNSCC.

Trial design: IMPORTANCE (NCT03386357) is an open-label, randomized, prospective, multicenter phase II clinical trial of P with or without local RT in patients (pts) with rmHNSCC after progression to platinum-based therapy or as first line treatment if CPS$\geq$1. All pts will receive P 200 mg administered every third week until confirmed disease progression according to iRECIST criteria, unacceptable toxicity, pts' wish to stop therapy or a maximal treatment time of 12 months. Pts in treatment arm A will receive RT of one, two or three tumor lesions with a total tumor volume of at least 2 ml (if possible, $\geq$5 ml) intended to induce immunogenic tumor cell death. RT will be performed conventionally with single doses of 3 Gy to a total dose of 36 Gy. Pts in arm B will only receive P. The objectives are to show that addition of local RT of 1-3 lesions to P improves the ORR, duration of response, progression free survival and OS. Further objective is the assessment of distinct immune changes, safety and tolerability of the combination of P and RT. Recruitment started in July 2018 and is ongoing. Until March 2023, 100 pts were randomized. The planned sample size is 130 patients, the recruitment is estimated to be completed by January 2024.

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Legal entity responsible for the study: Dean of the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg.

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HEPATOCELLULAR CARCINOMA (HCC)

945MO AdvanTIG-206: Phase II randomized open-label study of ociperlimab (OCI) + tislelizumab (TIS) + BAT1706 (bevacizumab biosimilar) versus TIS + BAT1706 in patients (pts) with advanced hepatocellular carcinoma (HCC)

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Background: Pts with advanced HCC have poor prognosis, with 5-year survival of 18%. Coinhibition of programmed death ligand-1 (PD-L1) and VEGF provides survival benefit in 1st line (1L) HCC. In preclinical studies of HCC and clinical studies of other tumors, coinhibition of T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and PD-1 enhances antitumor activity of anti-PD-1. AdvanTIG-206 (NCT04948697) is investigating the efficacy/safety of adding OCI (anti-TIGIT) to TIS (anti-PD-1) + BAT1706 backbone as 1L therapy in advanced HCC pts.

Methods: Eligible adults had histologically confirmed HCC that is BCLC Stage B or C, not amenable to or progressed after loco-regional therapy, and with no prior systemic therapy. Pts were randomized 2:1 to OCI 900 mg + TIS 200 mg + BAT1706 15 mg/kg (O+T+B) or T+B every 3 weeks until loss of clinical benefit at investigator (INV) discretion. Primary endpoint was INV-assessed objective response rate (ORR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: As of 27 Feb 2023, 94 pts (median age 58.5 years) were randomized to O+T+B (n=62) and T+B (n=32). INV-assessed ORR was 35.5% with O+T+B vs. 37.5% with T+B (Table). For O+T+B and T+B, respectively, Grade ≥3 treatment-related adverse events (TRAEs) were 50.0% and 25.8%, most common (≥5% incidence) TRAEs were hypertension (14.5% and 6.5%) and proteinuria (both 6.5%); TRAEs that led to any treatment discontinuation were 16.1% and 6.5%. Three (4.8%) treatment-related deaths occurred with O+T+B vs. none with T+B.

Conclusions: In pts with advanced HCC, TIS + BAT1706 demonstrated promising ORR, while adding OCI to the doublet was not associated with improved anticancer activity. No new safety signals were identified in either arm. The OS data are premature and need further follow-up.

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946P Sintilimab plus lenvatinib as conversion therapy in patients with unresectable hepatocellular carcinoma: A prospective, non-randomized, open-label, phase II, expansion cohort study

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Background: Hepatocellular carcinoma (HCC) patients (pts) with major vascular invasion (MVI) or extrahepatic metastases were generally recommended systemic treatment by guidelines, and pts have missed the opportunity for curative resection. Conversion therapy that can convert unresectable HCC into resectable HCC may improve patient survival. Here we report the Sintilimab plus Lenvatini as a conversion therapy for unresectable HCC.

Methods: Briefly, the main inclusion criteria of the study was: Aged 18 to 75 years unresectable HCC pts diagnosed pathologically and/or radiologically, with at least one measurable lesion (mRECIST). The criteria for Successful Conversion: 1. Child-Pugh score < 7. 2. ECOG PS score ≤1. 3. Downstaging to BCLC-A or PR according to mRECIST, and extrahepatic lesions can be resected at the same time. 4. Intact vascular structure of the reserved liver and sufficient FLR.

Results: A total of 137 pts were enrolled in the study by April 10, 2023 and accepted the Sintilimab plus Lenvatinib as conversion therapy,100 pts were finally included for evaluation, in which 58 pts with PVTT (39 pts were classified as VP4), 4 with IVCTT and 7 with both. 26 pts had extrahepatic metastases, and 92 pts were HBV-positive. According to mRECIST, the ORR was 54% and DCR was 77%. Successful conversion rate based on radiology was 51%, and 47% pts received hepatectomy. With a median follow-up of 17 months (range, 1-43), the median OS was 25 months (95% CI, 15.9—34.1) among all pts, the median OS of the pts was not reached [95% CI not reached] in the surgical group and 15 months (95% CI, 10.3—19.7) in the non-surgical group. The median RFS was 25 months (95% CI, 13.6—36.4) in the surgical group and the median PFS was 7 months (95% CI, 3.5—10.5) in the non-surgical group. All pts were evaluable for toxicity, and 83 (83%) pts had at least one treatment-related AE (TRAE). TRAEs occurring in ≥10% of pts were rash (27%), hypertension (18%), hand foot syndrome (17%), and diarrhoea (16%). 28 pts had grade 3 TRAEs.

Conclusions: The combination therapy of Sintilimab plus Lenvatinib can be reviewed as a reasonable and promising conversion therapy option for unresectable HCC with safety and effectiveness.

Table: 945MO Efficacy

Best overall response[a], n (%)	O+T+B (n=62)	T+B (n=32)	
Complete response	0	0	
Partial response	22 (35.5)	12 (37.5)	
Stable disease	26 (41.9)	11 (34.4)	
Progressive disease	10 (16.1)	7 (21.9)	
Not evaluable	4 (6.5)	2 (6.3)	
ORR[a], % (95% CI)	35.5 (23.7, 48.7)	37.5 (21.1, 56.3)	*2-sided P*=0.8350
DOR[b](months), median (95% CI)	12.6 (7.0, NE)	10.6 (4.2, NE)	
PFS (months), median (95% CI)	8.3 (5.5, 10.0)	6.9 (4.1, NE)	Hazard ratio = 1.08 (0.59, 1.96) *1-sided P*=0.4056

Median follow-up was 9.2 months P-value is for descriptive purpose only. NE, not estimable [a]INV-confirmed per RECIST v1.1 [b]Only includes pts with confirmed complete/partial response

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947P The efficacy and safety of cadonilimab combined with lenvatinib for first-line treatment of advanced hepatocellular carcinoma: A phase Ib/II clinical trial

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Background: Immunotherapy, targeted therapy and their combination has been developed as first-line treatment for advanced HCC.The combination therapy has improved the antitumor effects compared with targeted therapy,but tended to have higher incidence of adverse reactions.This study aims to assess the efficacy and safety of Cadonilimab, a humanized, tetravalent, bispecific antibody targeting PD-1 and CTLA-4,with lenvatinib(len) in first-line treatment of HCC.

Methods: This multicenter, open-label, phase Ib/II study included patients with histologically or clinically confirmed unresectable HCC to receive either 6mg/kg Cadonilimab every 2 weeks plus len(cohort A) or 15mg/kg Cadonilimab every 3 weeks plus len(cohort B). The primary endpoint was objective response rate (ORR) by RECIST v1.1, the secondary endpoint includes safety, progression-free disease (PFS), overall survival (OS), disease control rate (DCR), duration of response (DoR) and time to response (TTR).

Results: A total of 59 patients were enrolled (cohort A, n=31; cohort B, n=28).As the date of data cutoff July 28,2023, the median follow-up duration was 27.4 months.ORR was 35.5% (95% CI, 23.6-49.1) in cohort A and 35.7% (95% CI, 18.6-55.9) in cohort B. The median PFS was 8.6 months (95%CI, 5.2-17.9) and 9.8 months (6.9-15.2), respectively.The median OS was 27.1 months (95%CI , 15.7,NE) for cohort A,while it was not reached for cohort B. Grade $\geq$ 3 TRAEs occured in 66.1% of patients, and serious AEs were reported in 39.0% of cases.All AEs were expected and manageable.All the deaths were related to disease progression and not related to Cadonilimab.

Table: 947P Summary of Efficacy analysis and tumor response by investigator review per RECIST v1.1

	Cohort A n=31	Cohort B n=28
Objective response rate,n(%)	11 (35.5)	10 (35.7)
Disease control rate,n(%)	28 (90.3)	26 (92.9)
mTTP,m	2.8	1.4
Min-Max	1.3-8.3	1.3-6.9
mDOR,m	13.6	13.7
95% CI	4.14, NE	3.52, NE
mPFS,m	8.61	9.82
95% CI	5.19,15.15	6.87,15.18
mOS,m	27.1	NR
95% CI	15.7,NE	19.3,NE

Conclusions: This novel combination therapy of PD-1/CTLA4 bispecific monoclonal antibody and lenvatinib showed promising efficacy and manageable toxicity that could provide an option of treatment in first-line setting of aHCC.

Clinical trial identification: NCT04444167.

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948P Phase (Ph) I/II study of sitravatinib (Sitra) alone or with tislelizumab (TIS) in advanced hepatocellular carcinoma (HCC) and gastric/gastroesophageal junction cancer (GC/GEJC)

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Background: Sitra, a spectrum-selective tyrosine kinase inhibitor, may enhance the efficacy of programmed cell death protein 1 (PD-1) inhibition. TIS, an anti-PD-1 antibody, has demonstrated efficacy in multiple advanced solid tumors. SAFFRON-104 is a multi-cohort Ph 1/2 study investigating sitra +/- TIS in patients (pts) with advanced HCC or GC/GEJC (NCT03941873).

Methods: Eligible pts had histologically/cytologically confirmed unresectable locally advanced or metastatic HCC or GC/GEJC. Pts enrolled in Ph 1 (dose escalation) received free base sitra (80 or 120 mg orally once daily) alone or combined with TIS (200 mg IV once every 3 weeks); Ph 1 determined the recommended Ph 2 dose (RP2D). Ph 2 evaluated sitra alone in pts with HCC who were naïve or refractory/resistant (R/R) to anti-PD-(L)1 therapy and sitra + TIS in pts with anti-PD-1/programmed death-ligand 1 (PD-L1)-naïve HCC, anti-PD-(L)1 R/R HCC, and anti-PD-(L)1-naïve GC/GEJC. Primary endpoints were safety/tolerability (Ph 1) and objective response rate (ORR) by RECIST v1.1 (Ph 2). Secondary endpoints included disease control rate (DCR), duration of response (DoR), and progression-free survival (PFS).

Results: As of Jan 4, 2023, 111 pts were enrolled, of whom 102 were efficacy-evaluable (median study follow-up 9.1 months [range 0.7-34.0]). The RP2D of sitra determined in Ph 1 was 120 mg orally once daily. In pts receiving sitra +/- TIS, respectively, any-grade treatment-related adverse events (TRAEs) were reported in 74 (89.2%) and 24 (100%); $\geq$grade 3 TRAEs in 37 (44.6%) and 13 (54.2%); and serious TRAEs in 19 (22.9%) and 6 (25.0%). TRAEs leading to treatment discontinuation were reported in 10 (12.0%) pts and 1 (4.2%) pt receiving sitra +/- TIS, respectively. Pooled efficacy data from Ph 1 and 2 by indication are shown in the Table.

Conclusions: Sitra +/- TIS was generally well tolerated and showed preliminary antitumor activity in pts with advanced HCC and GC/GEJC.

Table: 948P

	HCC			GC/GEJC[a]
Treatment	**Sitra**	**Sitra + TIS**		**Sitra + TIS**
Prior anti-PD-(L)1 treatment	Naïve or R/R (n=20)	Naïve (n=26)	R/R (n=21)	Naïve (n=31)
ORR, n (%)	5 (25.0)	3 (11.5)	2 (9.5)	5 (16.1)
DCR, n (%)	18 (90.0)	22 (84.6)	17 (81.0)	22 (71.0)
Median DoR, mo (95% CI)	7.7 (2.8, NE)	5.7 (4.1, NE)	NR (5.4, NE)	5.5 (2.7, NE)
Median PFS, mo (95% CI)	6.8 (4.0, 7.4)	6.8 (2.8, 8.3)	4.2 (2.7, 6.8)	3.6 (2.8, 4.7)

Efficacy analysis set. [a]Four patients with GC/GEJC enrolled in Ph 1 were not included in the efficacy or safety analysis by indication because they were either anti-PD-(L)1 R/R or received sitra monotherapy. CI, confidence interval; mo, months; NE, not estimable; NR, not reached.

Clinical trial identification: NCT03941873 (first posted July 05, 2018).

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949P Regorafenib combined with immunotherapy versus regorafenib as second-line therapy in patients with advanced hepatocellular carcinoma: A multicenter real-world study

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Background: Based on the favorable efficacy and acceptable safety demonstrated by the RESORCE and REFINE studies, multikinase inhibitors, represented by regorafenib (rego), remain the standard and widely-used second-line strategy for advanced hepatocellular carcinoma (HCC). The advent of numerous immune checkpoint inhibitors (ICI) has significantly altered the treatment paradigm for patients (pts) with advanced HCC in recent years. However, there is sitll a lack of large-scale multicenter real-world evidence concerning the concurrent use of rego with ICI. In this study, we aimed to evaluate whether combining rego with ICI provides greater clinical benefit than rego monotherapy.

Methods: This retrospective real-world study was conducted in 5 centers in China between November 2018 to October 2022. A total of 208 pts with advanced HCC receiving either rego plus ICI or rego monotherapy as second-line treatment were included. We compared Overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs).

Results: Overall, 143 pts received rego plus ICI and 65 pts received rego. The median follow-up period was 13.8 (95% CI: 13.1-14.5) months. The rego plus ICI group demonstrated significantly higher ORR (23.8% vs. 9.2%, P=0.014) and DCR (74.8% vs. 53.8%, P=0.003) compared to the rego monotherapy group based on mRECIST criteria. Median PFS (7.5 vs. 3.4 months, P<0.001) and OS (25.6 vs. 16.4 months, P=0.010) were also significantly longer in the rego plus ICI group. The rate of Grade 3-4 AEs was slightly higher in the rego plus ICI group than the rego group (23.8% vs. 20.0%, P=0.546), and no treatment-related deaths occurred in either group.

Conclusions: Regorafenib combined with ICI is a promising second-line treatment option for advanced HCC, demonstrating encouraging efficacy with an acceptable safety profile compared to regorafenib monotherapy.

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Disclosure: All authors have declared no conflicts of interest.

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950P Phase II clinical study of sorafenib combined with tislelizumab in the treatment of first-line unresectable hepatocellular carcinoma and the predictive effect and correlation of CTC

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Background: In this study, we aimed to evaluate the safety and efficacy of combining PD-1 antibody Tislelizumab with Sorafenib for the treatment of advanced hepatocellular carcinoma(HCC). Additionally, we sought to investigate the relationship between the circulating tumor cells (CTCs) count/ programmed death-ligand 1 (PD-L1) expression of CTCs and the prognosis of patients with advanced hepatocellular carcinoma.

Methods: The study Enrolled patients (pts) with unresectable HCC patients (pts) to receive tislelizumab combined with sorafenib. Tislelizumab, 200mg/q3w intravenous infusion, sorafenib 400 mg/bid oral dose; Evaluate every 3 cycles (9 weeks) to evaluate the safety and effectiveness of the drug regimen CTCs count and PD-L1 expression of CTCs were performed in all patients before enrollment. Primary endpoint was ORR by RECISTv1.1 per investigators. The secondary endpoints aimed to assess the relationship between the count of CTCs or the expression of PD-L1 and the prognosis of HCC.

Results: As of November 2022, 32 patients were enrolled in the study received combination treatment. For 32 pts, ORR was 17% (95% CI 33.0%-75.2%) and DCR was 65% (95% CI 71.2%-91.9%) by RECIST v1.1. When evaluated by mRECIST, ORR and DCR improved to 24.2% (95% CI 55.8%-93.8%) and 75% (95% CI 74.2%-92.9%), respectively. Treatment-emergent adverse events (TEAEs) occurred in 75% of pts, 35% of which was ≥grade 3. Of which 31 patients (96.8%) were positive for CTC, ranging from 1 to 45, with a median of 7 (3, 11), 25 (78.1%) PD-L1+CTC was detected in 32 patients. The median follow-up time was 6 months (range, 2-14 months). Correlation analysis found that The 1-year progression-free survival rates of patients in the PD-L1+CTC group and those in the non-detected PD-L1+CTC group were 54.1% vs 28.6% respectively (P=0.036).

Conclusions: Tislelizumab combination with Sorafenib showed promising antitumor activity with relatively high ORR and a tolerable safety profile in 1st line HCC treatment. Baseline CTC PD-L1+ can be used as a predictive indicator for screening HCC patients for PD-1/PD-L1 blockade therapy, and dynamic measurement of CTC changes can monitor the therapeutic effect of patients.

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Legal entity responsible for the study: Che Xu.

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Table: 949P

Tumour response

	RECIST 1.1			mRECIST		
	Regorafenib+ICI (n=143)	Regorafenib (n=65)	*P* value	Regorafenib+ICI (n=143)	Regorafenib (n=65)	*P* value
Best overall response						
Complete response	2 (1.4)	0 (0)	1	2 (1.4)	0 (0)	1
Partial response	22 (15.4)	6 (9.2)	0.228	32 (22.4)	6 (9.2)	**0.023***
Stable disease	83 (58.0)	30 (46.2)	0.111	73 (51.0)	29 (44.6)	0.390
Progressive disease	36 (25.2)	27 (41.5)	**0.017***	36 (25.2)	28 (43.1)	**0.010***
Not evaluable	0 (0)	2 (3.1)	0.097	0 (0)	2 (3.1)	0.097
Objective response	24 (16.8)	6 (9.2)	0.151	34 (23.8)	6 (9.2)	**0.014***
Disease control	107 (74.8)	36 (55.4)	**0.005***	107 (74.8)	35 (53.8)	**0.003***

Notes: data was presented as number (percentage).

951P HAIC combined with anlotinib and TQB2450 as adjuvant therapy for patients with hepatocellular carcinoma (HCC) at high risk of recurrence after hepatectomy: A single-centre, non-randomised, open clinical study

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Background: Preventing post-operative recurrence and metastasis has become a critical factor in determining the success of hepatectomy for HCC patients (pts). However, the optimal treatment strategy for adjuvant therapy is still under debate. The aim of this study was to evaluate the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) combined with anlotinib and TQB2450 (PD-L1 monoclonal antibody) as adjuvant therapy for pts with HCC at high risk of recurrence after hepatectomy.

Methods: Pts diagnosed as HCC with one or more of the high risk factors after hepatectomy were eligible. Eligible pts received FOLFOX-HAIC (1 cycle) within 1 months after hepatectomy, and on the 2nd day after HAIC, anlotinib (10mg, 4 cycles or 8 cycles) and TQB2450 (1200mg, 4 cycles) were given. The primary endpoint was disease free survival (DFS). Secondary endpoints included overall survival (OS), time to recurrence (TTR) and safety.

Results: At April 18 2023, 72 pts were enrolled and 68 were available to be analyzed. Among them, 34 pts have completed treatment, 26 pts were still on treatment, 8 pts discontinued treatmentearly due to adverse events (AE). 70.6% with liver cirrhosis, 67.7% with MVI, 33.8% with preoperative intrahepatic lesions≥8cm, 7.4% with-≥3tumor lesions, 2.9% with tumor thrombus, and 2.9% with preoperative rupture of the tumor or invasion of adjacent organs. At median follow-up of 6.0 (range 0.9-15.1) months, 1 pts relapsed (DFS was 10.87 months).1-year DFS rate was 85.7%, and the longest DFS was over 16.92 months in all pts. The median DFS and OS were not available. Safety profile indicated that 67 pts (98.5%) experienced treatment-related adverse events (TRAEs), and common grade 3 TRAEs included hypertension (8.8%), neutropenia (7.4%) and thrombocytopenia (5.9%).

Conclusions: HAIC combined with anlotinib and TQB2450 as adjuvant therapy for pts with HCC at high risk of recurrence after primary hepatectomy exhibits promising prognosis and tolerable safety profile, and further follow-up is needed for this study to obtain mature data.

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Disclosure: All authors have declared no conflicts of interest.

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952P Efficacy and safety of a PRospective, Observational trial of Lenvatinib cOmbined with transarterial chemoembolization (TACE) as initial treatment for advaNced staGe hepatocellular carcinoma (PROLONG): A multicenter, single-armed, real-world study

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Background: Transarterial chemoembolization (TACE) in combination with lenvatinib has been reported in several exploratory clinical studies in Chinese patients with hepatocellular carcinoma (HCC). Studies have showed good tumor response and survival benefit for combination therapy based on TACE plus lenvatinib in patients with advanced HCC. A multicenter, real-world study was conducted to explore the efficacy and safety of TACE in combination with lenvatinib as initial treatment for unresectable HCC patients in a real-world setting (PROLONG study, NCT04560751).

Methods: This real-world study was conducted at 7 centers in China. Eligible patients were aged more than 18 years old, with HCC, CNLC stage IIb-IIIb with unresectable diseases, Child-Pugh ≤7, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, no prior systemic therapy. All patients received TACE combined with lenvatinib, with or without immune checkpoint inhibitors. The primary endpoint was objective response rate (ORR), which was evaluated according to mRECIST, and secondary endpoints included organ-specific objective response rate, progression-free survival (PFS), AFP response rate and time to progression (TTP).

Results: A total of 197 patients were enrolled from August 2020 to February 2023, with 145 patients evaluable for efficacy. The ORR was 48.3% evaluated according to mRECIST, with a complete response (CR) rate of 8.3%, partial response (PR) rate of 40%. The disease control rate (DCR) was 86.2%. The median PFS was 10.2 months (95%CI, 5.9-14.5), and the median OS has not been reached. The most common adverse events (AE) were fever, elevated transaminases, and decreased platelets. No treatment-related grade 5 AE occurred.

Conclusions: Combination therapy based on TACE plus lenvatinib in patients with unresectable hepatocellular carcinoma showed promising efficacy in the real-world setting. No unexpected adverse events were observed.

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953P Tislelizumab plus regorafenib as second-line therapy for unresectable hepatocellular carcinoma (uHCC): A single-arm, phase II trial

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Background: Second-line treatment options for patients with unresectable hepatocellular carcinoma (uHCC) are limited. Monotherapy with regorafenib or tislelizumab (an anti-PD-1 antibody) has shown clinical benefit for uHCC in the second-line setting. The present study explored the safety and efficacy of the tislelizumab plus regorafenib as second-line therapy for uHCC.

Methods: This was a single-arm, investigator-initiated phase II trial. Patients with confirmed uHCC were enrolled to receive tislelizumab (200mg, q3w) plus regorafenib (80mg-160mg, daily, 3 weeks on/1 week off, every 4 weeks). The primary endpoint was safety and tolerability; Secondary endpoints included overall response rates (ORR), progression-free survival (PFS), and disease control rate (DCR) per mRECIST.

Results: A total of 28 patients were enrolled with median age of 59 years (range: 40-76) and 96% were men. Most common etiology of HCC was hepatitis B (n=26, 93%). 54% of patients were Barcelona Clinic Liver Cancer stage C. 67.9% of patients received prior treatment with tyrosine kinase inhibitors (TKIs; sorafenib [50%] or lenvatinib [17.9%]), and 21.4% received TKIs plus PD-1 antibody. ORR was 28.6% and DCR was 71.4%, with 3 pts having CR, 5 PR, and 12 SD. At the data cut-off date, the median PFS of the 28 pts was 6.4 months (95%CI 90%, NA)), and the median OS was not reached. The most common treatment-related adverse events at any grade were rash (6/28;21%), hypertension (9/28;32%), hand-foot syndrome (18/28;64%) and fatigue (7/28;25%), which were mostly grade 1 or 2 in severity.

Conclusions: This study indicated that tislelizumab plus regorafenib is an effective and well-tolerated therapeutic option for patients with uHCC.

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Disclosure: All authors have declared no conflicts of interest.

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954P Radiotherapy combined with tislelizumab plus anlotinib as first-line treatment for hepatocellular carcinoma: A single arm, phase II clinical trial

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Background: The combination of PD-1 blockades with antiangiogenic drugs is the main therapeutic regimen for advanced hepatocellular carcinoma (HCC). Radiotherapy has generally been used to treat HCC with improved long-term outcome. The combination of radiotherapy and other therapies is considered to be a promising treatment for HCC. The objective of this study is to investigate the feasibility and safety of radiotherapy combined with tislelizumab plus anlotinib in advanced HCC.

Methods: In this single-center, open-label, phase II clinical trial, 45 patients(pts) with previously untreated, advanced HCC, with an age ranging from 18-75 years old, and an ECOG performance status ≤ 1 were planned to be enrolled. According to mRECIST efficacy evaluation criteria, the efficacy was evaluated by enhanced CT or MRI. RTOG/EORTC criteria was used to evaluate radiation-induced liver injury. Requirements for radiotherapy planning were D95% ≥14.2-46 Gy and ≥12.5-40 Gy for GTV and CTV, respectively. The patients underwent treatment with tislelizumab (200 mg, Q3W) plus

anlotinib (8 mg, Q3W), and radiotherapy until disease progression or intolerance. The primary endpoints were ORR and OS, the secondary endpoints were PFS, DCR and safty.

Results: At data cut-off date of Feb 2023, 45 pts (44 males and 1 female) were enrolled with a median age of 51.5 years (range: 26-75). Of whom, 4 pts achieved complete response, 22 pts obtained partial response, 8 pts were stable disease, illustrating an ORR of 57.8% (95%CI 42.2-72.3) and a DCR of 75.6% (95%CI 60.5-87.1). The median PFS was 7.8 months (95%CI 5.8-9.8). The rate of treatment emerged adverse events (TEAEs) on grade 1/2 were 82.2%, and grade 3/4 were 13.3% (6/45). No grade 5 or radiation-induced liver disease were observed.

Conclusions: Radiotherapy combined with tislelizumab plus anlotinib demonstrated promising efficacy and tolerable safety profile in the treatment of advanced HCC. And this study was still ongoing and further follow-up was required to obtain final survival results subsequently.

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Disclosure: All authors have declared no conflicts of interest.

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955P IMMUNIB trial (AIO-HEP-0218/ass): A single-arm phase II study evaluating safety and efficacy of immunotherapy with nivolumab in combination with lenvatinib in advanced hepatocellular carcinoma

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Background: The field of systemic therapy in hepatocellular carcinoma (HCC) has significantly evolved over the last years, and IO-based combinations therapies are the current standard of care. Nivolumab is a recombinant human IgG4 mAb targeting PD-1 with clinically meaningful activity in about 15-20% of HCC patients. Combinations of anti- angiogenic multikinase inhibitors, including lenvatinib, and PD-1/PD-L1 inhibitors have demonstrated remarkable antitumor activity with manageable toxicity in several tumor types, including HCC. The IMMUNIB trial aimed to evaluate the efficacy of nivolumab in combination with lenvatinib as first line treatment in patients with advanced HCC.

Methods: This investigator-initiated single-armed phase II trial (NCT03841201) recruited 50 patients (pts) at 8 sites in Germany between 06/2019 and 05/2021. Primary efficacy endpoint was objective response rate (ORR) according to investigator assessed RECIST 1.1. Secondary endpoints included time to progression (TTP), progression free survival (PFS), overall survival (OS) and safety.

Results: Out of 50 enrolled pts (24 BCLC B, 18 BCLC C, 7 not evaluable) 49 received at least one dose of the combination treatment. The ORR by RECIST 1.1 was 32% (CR 6%, PR 26%, SD 42%, PD 12%). Median PFS was 9.0 mo. Median TTP was 9.89 mo (0.7 at 6 mo, 0.43 at 12 mo, 0.31 at 18 mo) and median OS was 25.36 mo (24 events). Of note, at EOS 26 pats were still alive, of whom 13 pats were without progression. 47 (96%) pts experienced at least one TRAE, of which 29 pts (59%) encountered at least one TRAE $\geq$ grade 3. 16 (32.7%) pts had at least one SAE related to the study medication, whereof 14 pts (29%) experienced at least one treatment related SAE $\geq$ grade 3.

Conclusions: No new safety signals were observed for the combination of nivolumab and lenvatinib. Although the study failed to reach its prespecified ORR of at least 43%, the high activity in all efficacy endpoints with a mOS of more than 25 mo supports the further investigation of the combination in HCC.

Clinical trial identification: EudraCT 2018-001480-23, NCT03841201.

Legal entity responsible for the study: Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest.

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956P Phase II study of adjuvant tislelizumab combined with interferon-α and active surveillance in hepatocellular carcinoma patients with microvascular invasion

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Background: Microvascular invasion (MVI) is closely associated with high risk of recurrence and poor long-term survival in HCC patients. For these patients, active and effective adjuvant therapy is of great significance to improve the prognosis. Therefore, we explored the efficacy and safety of interferon-α (IFN-α) combined with PD-1 monoclonal antibody (tislelizumab, TIS) as adjuvant therapy for HCC patients with MVI.

Methods: In this phase 2 study, histologically confirmed HCC patients who had undergone curative resection with MVI, Child-Pugh A, and an ECOG PS $\leq$1 were enrolled. Patients separately received TIS (200 mg IV Q3W) plus IFN-α (30 μg BIW) or active surveillance until disease progression, intolerable toxicity or withdrawal of consent. The primary endpoint was recurrence free survival (RFS). Secondary endpoints included overall survival (OS) and safety.

Results: From January 2021 to December 2021, TIS plus IFN-α group and active surveillance group enrolled 24 and 14 patients, respectively. Baseline characteristics were generally comparable between two groups, including MVI grade (M1: 90.0% vs 85.7%; M2: 10.0% vs 14.3%) and any tumours diameter $>$ 5cm (65.0% vs 50.0%) in TIS plus IFN-α, respectively. At data cutoff (17 Apr 2023), RFS was not reached in TIS plus IFN-α group (95%CI: 9.8-NE), whereas in active surveillance group was 17.09 month (95%CI: 4.8-NE). 1-year RFS rate in TIS plus IFN-α and active surveillance group was 79.2% (95%CI: 0.5-0.9) and 50.0% (95%CI: 0.2-0.7), separately. Median OS was not reached in either group. No severe postoperative complications were observed. In TIS plus IFN-α group, Grade 1 or higher AEs were mainly rash (20.0%), pyrexia (15.0%), pruritus (10.0%) and diarrhea (10.0%).

Conclusions: These results suggested that HCC patients with MVI may benefit from adjuvant tislelizumab plus IFN-α, which can be tested in a future confirmatory trial. We will continue follow-up and update the data further. In the meantime, related basic experiments are underway.

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957P Interim report of Notable-HCC: A phase Ib study of neoadjuvant PD-1 with stereotactic body radiotherapy in patients with resectable hepatocellular carcinoma (HCC)

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Background: So far there is no neoadjuvant therapy recommended by major hepatocellular carcinoma (HCC) guidelines. In other malignancies, ICIs in the neoadjuvant setting have shown better outcomes than in the adjuvant setting, and the combination of radiation therapy to ICIs incrementally improves the systemic response to ICIs. Neoadjuvant therapy of ICIs plus stereotactic body radiotherapy (SBRT) has shown promising results in several types of solid tumours but not HCC.

Methods: This is a phase Ib clinical trial of neoadjuvant SBRT plus PD-1 (tislelizumab) in HCC patients (pts). Prior to resection, pts receive 8 Gy $\times$ 3 SBRT with 2 cycles of PD-1. HCC resection is scheduled 4 weeks after the second PD-1, followed by adjuvant

Table: 957P

Pt #	age (Y)	gender	tumor size (cm)	BCLC stage	RECIST	mRECIST	interval between 2nd PD-1 and surgery	pCR (Y/N)	TARE over grade 3(Y/N)	survival
1	70	F	S7:2.4×2.2	A	SD	SD	31	N	N	Recurrence/RFA
2	74	M	S4a:1.6; S2:1.2	A	SD	S4a:CR; S2:SD	28	S4a: Y; S2:N	No	DFS
3	64	M	S8:1.8×1.6	A	SD	SD	28	N	Y	DFS
4	51	M	S7/8:6.0×6.1	A	PR	PR	26	Y	Y	DFS
5	70	M	S4/5:3.7×4.1	A	SD	PR	40	N	N	DFS
6	52	M	S6/7:4.1×4.0	A	SD	CR	28	N	Y	DFS
7	70	F	S6:3.3	A	SD	SD	34	N	N	DFS
8	48	F	S8:2.2×1.7	A	PR	CR			N	
9	56	M	S6:2.9×2.4	A					N	
10	54	M	S6:4.8×3.3; S8:2.2×1.8	A					N	

PD-1 for up to 1 year. We plan to enrol 20 participants in this trial. The primary study endpoints include the surgery delay over 6 weeks or later, ORR on pre-resection imaging, pathologic response (pCR) rate, safety and tolerability of the sequential SBRT/PD-1. The secondary endpoints are DFS and OS rates every 3 or 6 months after the hepatic resection.

Results: By 10th May 2023, 11 pts were enrolled, all were BCLC A stage. One pt was excluded due to the protocol violation, in other 10 pts, one just starts the adjuvant therapy, two have completed the neoadjuvant therapy and waiting for the scheduled resection, all other 7 pts have completed the resection, and no surgery delay accrued; DCR reached 100% (RECIST: 1 PR, 6 SD; mRECIST: 1 CR, 2 PR, 3 SD, 1 CR+SD); pCR was confirmed in two tumors; So far the safety of neoadjuvant SBRT+PD-1 was satisfied, grade 1 to 2 TRAEs, mainly anemia and white blood cell decreasing were common; grade 3 TRAE occurred in 3 pts (1 granulocytopenia and 2 elevated transaminase), but all well-tolerated. One pt developed recurrence 9 months after surgery (RF ablation), all other 6 pts are still in DFS.

Conclusions: The safety and clinical significance of radiotherapy plus PD-1 as the neoadjuvant therapy in HCC needs further exploration.

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Legal entity responsible for the study: The authors.

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958P Preliminary results of radiotherapy (RT) combined with sintilimab (Sin) and bevacizumab (Bev) in advanced hepatocellular carcinoma (HCC) previously treated with immune checkpoint inhibitors (ICIs): A prospective phase II study

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Background: ICIs have become the critical systematic drugs in advanced HCC, but most patients (pts) will be resistant to it. Evidence of the subsequent regimen for previously ICI-treated HCC pts is little. RT has shown synergistic effect with ICIs and may overcome ICIs resistance. Therefore, this study was designed to evaluate the efficacy and safety of RT combined with PD-1 inhibitor (Sin) and antiangiogenic drug (Bev) in advanced HCC pts who had previously received PD-(L)1 inhibitors.

Methods: This phase II trial study followed Simon's two-stage design. A total of 21 HCC pts who had previously received ICIs will be enrolled. Pts will receive RT (30-40Gy/5-8F) combined with Sin(200mg iv. q3w) and Bev (15mg/kg iv. q3w). Sin and Bev will maintain until disease progression or intolerable toxicity, Sin up to 2 years. The primary endpoint was investigator evaluated objective response rate (ORR) per RECIST1.1. If more than 1 of 9 pts achieved objective response in stage I, the study will enter stage II.

Results: Between March 11, 2022 and April 15, 2023 (data cutoff), the median follow-up was 6.3 months (mo) (range: 2.3—13.2), 10 pts who previously received ICIs + TKIs had been enrolled and received study therapy. 90% (9/10) were BCLC-C. 6 pts previously received one line therapy and 4 pts received two lines. 6 pts received last line immunotherapy less than 6 mo, and 4 pts $\geq$ 6 mo. All 10 pts received at least one radiological evaluation after baseline. 4 pts achieved partial response (PR) with an ORR of 40% (95% CI, 16.8%-68.7%) and a disease control rate (DCR) of 80% (95% CI, 49.0%-94.3%). Median progression-free survival (mPFS) was 7.4 mo (95% CI: 1.5—NA); Median overall survival (mOS) was not reached. Grade $\geq$ 3 treatment-related-adverse events (TRAEs) were reported in 3(30%) pts. Frequently occurring adverse events were grade 1-2, including abdominal distension (40%), hypertension (30%) and ALT, AST elevation (20%).

Conclusions: RT combined with Sin and Bev exhibited promising efficacy and favorable safety for HCC previously treated with ICIs. The trial is still recruiting, more data would be further analyzed and reported.

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959P Combination therapy of envafolimab and suvemcitug in patients with hepatocellular carcinoma (HCC): Results from a phase II clinical trial

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Background: The efficacy of immune checkpoint inhibitors combined with anti-vascular agents has been demonstrated in a variety of solid tumors including HCC. Suvemcitug, selectively binds to and blocks VEGFA from binding to VEGFR1 and 2, thereby inhibiting its activities and preventing tumour angiogenesis and ultimately suppressing tumour growth and metastasis. Envafolimab is a humanized single-domain anti- PD-L1 antibody which is administered subcutaneously (SC). This study aims to assess the efficacy and safety of the combination of suvemcitug and envafolimab as second-line or later therapy in patients (pts) with advanced HCC.

Methods: This was an open-label, multi-cohort, multicenter, phase II trial conducted in China. In Cohort B, eligible pts had received at least one prior line of treatment for HCC and were treated with suvemcitug (2 mg/kg IV Q3W) plus envafolimab (300 mg SC Q3W) until disease progression or unacceptable toxicity was observed. The primary endpoint was objective response rate (ORR) assessed by investigator review using RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of overall response (DoR), progression-free survival (PFS) and safety.

Results: As of March 31,2023, a total of 20 patients were treated with envafolimab and suvemcitug. 80.0% pts (16/20) received one prior therapy and 40.0% pts (8/20) were prior treated with immunotherapy. After a median follow up of 7.4 (5.0, 9.3) months, in 18 efficacy-evaluable patients, the confirmed ORR was 11.1% (2/18), and the DCR was 72.2% (13/18). The median PFS was 4.3 (95% CI 1.4-8.1) months. The most common grade 3 or greater treatment-related adverse events were proteinuria (20.0%,4/20), hypertension (5%,1/20), platelet count decreased (5%, 1/20), blood bilirubin increased (5%, 1/20), γ-glutamyl transferase increased, oesophagitis (5%, 1/20) , and oral ulcer (5%, 1/20). No treatment-related death was reported.

Conclusions: The use of envafolimab and suvemcitug did not result in increased safety concerns. Suvemcitug and envafolimab demonstrated antitumor activity and manageable safety profile in pts with prior treated HCC. Research Sponsor: Shanghai Xianxiang Medical Technology Co., Ltd. and 3D Medicines Inc.

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960P Personalized circulating tumor DNA (ctDNA) monitoring for recurrence detection and treatment response assessment in hepatocellular carcinoma (HCC)

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Background: HCC is an aggressive malignancy, accounting for ∼90% of primary hepatic cancers. While surgical resection and liver transplantation (Tx) can be curative, 8-20% of post-Tx and 40-70% of post-resection patients recur. Here we sought to analyze the utility of longitudinal testing with ctDNA in patients (pts) with HCC.

Methods: This multicenter study retrospectively analyzed 227 plasma samples from 66 pts with HCC. The curative-intent surgeries included liver Tx (41/66, 62%) and hepatectomy (23/66, 34%); two pts (3%) who were inoperable received liver directed and systemic targeted therapy. Five of the 41 post-Tx pts received additional resection for oligometastatic recurrence prior to ctDNA testing. The cohort was analyzed based on 3 mutually exclusive sub-cohorts: Cohort A (N=34): recurrence monitoring after curative liver Tx; Cohort B (N=25): recurrence monitoring after curative-intent surgical resection; Cohort C (N=7): pts with known recurrence monitored for treatment response/disease progression. Longitudinal ctDNA testing was performed using the Signatera™ bespoke mPCR NGS assay.

Results: The cohort distribution included: 28 (42.4%) / 21 (31.8%) / 7 (10.6%) / 9 (13.6%) stage I/II/III/IV pts with a median age of 67 years (range: 21-84); median follow-up of 584 days (range: 79 - 1537). In cohort A, all patients were ctDNA-negative and remained recurrence-free.In cohort B, postsurgical ctDNA was detected in 9 (36%) patients, 6 experienced clinical recurrence and 3 had limited follow-up. The median lead time of ctDNA detection over clinical recurrence was 52 days (range: 0-262). Among the ctDNA-negative patients (N=16), only one pt experienced clinical recurrence; this was >1 year after the last ctDNA test. In cohort C, on-treatment ctDNA dynamics were concordant with treatment response in 4 pts as measured by imaging. The remaining 3 pts were persistently ctDNA-negative on/shortly after systemic therapy.

Conclusions: Longitudinal testing with ctDNA is critical in identifying early recurrence post surgical resection. Similarly, monitoring treatment response in the palliative setting can help resolve ambiguous imaging results.

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961P Blood circulating Galectin-3 is a prognostic biomarker in hepatocellular carcinoma

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Background: Galectin-3 plays critical roles in the adhesion, proliferation, and differentiation of tumor cells. Recent data has suggested that galectin-3 plays a role in the development of hepatocellular carcinoma (HCC), however, its prognostic value has not been validated. The aim of our study was to evaluate the clinical and prognostic value of galectin-3 in HCC patients.

Methods: We prospectively enrolled and collected clinicopathologic data and serum samples from 767 HCC patients between 2001 and 2014 at The University of Texas MD Anderson Cancer Center. The cut-off value for low versus high galectin-3 levels was established using ROC curve analysis. The Kaplan-Meier method was used to estimate overall survival (OS) distributions.

Results: The median OS in this cohort was 14.2 months (95% confidence interval [CI]: 12, 16.1 months). OS was significantly associated with clinicopathologic features, including tumor-node-metastasis (TNM) staging ($p<0.001$), Child-Pugh Score (CPS) ($p<0.001$), cirrhosis ($p<0.001$), metastasis ($p<0.001$), and alpha-fetoprotein (AFP) level ($p<0.001$). At the time of analysis, the one-year OS rate was 45% (95% CI: 0.4, 0.51) among patients with high galectin-3 levels, and 59% (95% CI: 0.54, 0.63) among patients with low galectin-3 levels. OS was significantly inferior in patients with high galectin-3 levels compared to patients with lower galectin-3 levels (median OS: 10.12 vs 16.49 months; $p=0.0022$). Higher galectin-3 levels were significantly associated with a higher risk of death (HR =1.29, 95% CI: 1.1, 1.53). Comparison between low ($n = 464$ patients) and high ($n = 302$ patients) galectin-3 levels showed that mean serum galectin-3 levels were significantly higher in HCC patients with HCV ($p=0.0001$), viral-induced hepatitis ($p=0.0002$), higher Child-Pugh Score (CPS) ($p=0.0009$), and higher Cancer of the Liver Italian Program (CLIP) score ($p=0.0015$).

Conclusions: In conclusion, our study shows that serum galectin-3 level is a valid prognostic biomarker candidate and a potential target for therapy in HCC.

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962P SBRT improves the efficacy of immuno-checkpoint inhibitors for hepatocellular carcinoma through the activation of IL-6/JAK1-STAT3/PD-L1 axis mediated by MBD3 degradation

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Background: Stereotactic radiotherapy (SBRT) has shown promising for unresectable hepatocellular carcinoma (HCC) due to its ability to modulate the tumor immune microenvironment. Methyl-CpG binding domain protein 3 (MBD3) is highly expressed in HCC and negatively correlated with prognosis. However, the role of MBD3 in the radioimmunology of SBRT in HCC remains unclear.

Methods: The expression and correlation of MBD3 and programmed cell death ligand 1 (PD-L1) were analyzed in HCC tissues before and after SBRT by immunohistochemistry (IHC). The mechanic regulations of MBD3 in the radioimmunology of SBRT in HCC were investigated both *in vitro* and *in vivo* studies.

Results: We observed a significant increase of PD-L1 in HCC after SBRT, which was associated with decreased MBD3 expression. As the radiation dose increased, MBD3 gradually degraded, while PD-L1 gradually upregulated in human and murine liver cancer cells. Through RNA sequencing, KEGG enrichment analysis and *in vitro* experiments, we identified that IL-6 was massively activated and released, leading to the activation of the JAK1/STAT3 signaling pathway, and ultimately resulted in the upregulation of PD-L1, which were induced by MBD3 degradation in liver cancer cells by irradiation. *In vivo* experiments showed that the combination of SBRT and PD-L1 blockade significantly enhanced the antitumor efficacy in the murine orthotopic model of HCC, partly dependent on the increased infiltration of $IFN\gamma^{+}CD8^{+}T$ cells in the tumor. We also found that SBRT reactivated proteinase-activated receptor 2 (PAR2) to promote the release of IL-6, activating the JAK1/STAT3 signaling pathway, leading to the upregulation of PD-L1 through relieving the inhibition of *F2RL1* (encoding PAR2) mediated by the deacetylation of the MBD3/NuRD complex. Our findings were further confirmed by IHC analysis of the above proteins in HCC tissues before and after SBRT.

Conclusions: Our study suggests that SBRT can reprogram the tumor immune microenvironment by activating the PAR2/IL-6/JAK1/STAT3 axis through MBD3 degradation, leading to PD-L1 upregulation, which may help develop new therapeutic strategies targeting PD-L1 to improve the efficacy of SBRT in HCC.

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963P Discovery and validation of cfDNA methylation, AFP and ctDNA mutation for the early detection of hepatocellular carcinoma: A multicenter prospective study (ASCEND-Hep)

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Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Early detection of HCC is critical for timely treatment and a better prognosis. In this prospective study (ASCEND-Hep, NCT04835675), we aimed to explore multi-omics including cell-free DNA (cfDNA) methylation, mutation, and α-fetoprotein (AFP) in early detection of HCC.

Methods: This multicenter study prospectively collected blood samples from patients with HCC and benign liver diseases. Age-matched non-cancer controls were obtained from a previous study. Methylation and mutation were detected through a methylation panel of 161,984 CpG sites and a cancer-associated 168-gene panel, respectively. Models were developed in a training set (cancer: 172; non-cancer: 206) and tested in a validation set (cancer: 117; non-cancer: 140). Then the locked models were validated in an independent validation set (cancer: 158; non-cancer: 637).

Results: In the training set, cfDNA methylation model had a higher area under curve than AFP and mutation alone ($P<0.05$). In the validation set, the methylation model yielded an overall sensitivity of 92.3% (95% CI, 85.9%—96.4%) at a specificity of 95.0% (90.0%—98.0%). Meanwhile, AFP >400 ng/mL had a sensitivity of 27.3% (18.8%—37.2%) with a specificity of 100.0% (96.5%—100.0%). Combining cfDNA methylation and AFP showed a better performance with a sensitivity of 94.0% (88.1%—97.6%) and a specificity of 95.0% (90.0%—98.0%), while the addition of mutation did not further improve the performance. Consistent results were observed in the independent validation set that the combined model achieved a sensitivity of 90.5% (84.8%—94.6%) at a specificity of 97.3% (95.8%—98.4%). The sensitivity of the combined model in Barcelona Clinic Liver Cancer Classification 0—A was 87.1% (78.0%—93.4%).

Conclusions: cfDNA methylation yielded superior performance than AFP and mutation alone. Our study highlights a potential clinical utility of combining cfDNA methylation and AFP for HCC early detection.

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965P C14orf159 mutations are associated with shorter relapse-free survival and overall survival after liver transplantation in hepatocellular carcinoma patients meeting Hangzhou criteria

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Background: At present, the long-term curative effect of liver transplantation (LT) in patients with hepatocellular carcinoma (HCC) is better than that of comprehensive treatment, but the overall 5-year survival rate after surgery is only 60%～70%. Postoperative HCC recurrence is one of the main causes of death in LT recipients. Therefore, It's urgent need to explore biomarkers of recurrence and metastasis of HCC after LT, which is of great significance for guiding postoperative reexamination and treatment of recipients.

Methods: This study retrospectively and continuously collected 37 patients with HCC who met the Hangzhou criteria (HC) and had undergone LT from January 2019 to January 2021. All tissue and blood samples were performed by whole exome sequencing (WES). After investigating similar studies and combining our clinical observations, we chose 12 months as the recurrence threshold of patients in this study. 37 patients classified into the recurrence group (n=14) and non-recurrence group (n=23). We analyzed the differences in clinical factors and genomic characters between the two groups.

Results: We firstly present the genomic mutation spectrum of such patients. A total of 11713 genomic alterations were detected and15 genes with a mutation frequency of more than 30%. *BCLAF1* (73%), *MUC4* (57%) and *TP53* (49%) were the top 3 mutated genes. Interestingly, all *C14orf159* mutations occurred in the rerecurrence group (p=0.046). Subsequently, the patients were divided into *C14orf159* mutant type (MT) group and *C14orf159* wild type (WT) group. *C14orf159*-MT group had significantly shorter relapse-free survival (RFS) (p=0.026) and overall survival (OS) (p=0.004). We performed a multivariate analysis showed the *C14orf159*-MT group had shorter RFS (p<0.01; HR=29.33; 95%CI: 4.614-186.5) and OS (p=0.011; HR=11.12; 95%CI: 1.724-71.669).

Conclusions: For the first time, we found that *C14orf159* mutations are associated with shorter RFS and OS after LT in HCC patients meeting HC. It's necessary to design relevant prospective clinical trials with a larger sample to verify this conclusion.

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966P Potential role of neuropilin-1 in the prognosis, development and risk of invasion in hepatocellular carcinoma patients

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Background: Hepatocellular carcinoma (HCC) represents the third most deadly cancer worldwide with still high therapeutic failure and recurrence rates mainly associated with the late diagnosis and the molecular heterogeneity of this liver tumor. The transmembrane glycoprotein neuropilin-1 (NRP1) has shown a key role in the modulation of tumor-associated signaling pathways and processes by interacting with key receptor tyrosine kinases. Nonetheless, few studies have evaluated the potential value of NRP1 as a tumor biomarker or therapeutic target in HCC. For this reason, we aimed at assessing the clinical significance of the receptor NRP1 in the prognosis, diagnosis and other tumor-associated features in HCC patients.

Methods: We conducted a systematic review with meta-analysis including all the articles published up to May 31st 2022 that evaluated the clinical correlation of NRP1 overexpression with tumor prognosis, development and/or other clinicopathological features in patients diagnosed with HCC. An exhaustive literature search was performed in five online databases, selecting potential papers to be included based on predefined eligibility criteria. Data from included studies were extracted or estimated by Parmar method and meta-analyzed employing the STATA 16 software.

Results: A total of 1305 patients from seven studies were included in the quantitative analysis, showing approximately 53.81% of patients NRP1 overexpression. After meta-analysis, higher levels of NRP1 proved to be significantly correlated to poor prognosis, represented by lower overall survival (OS). Moreover, a significant association with tumor pathogenesis was also found by observing higher NRP1 expression in tumor tissue samples from 692 HCC patients. Finally, a marked correlation was obtained between increased NRP1 expression and patient's age, younger than 50 years old, and a higher risk of venous invasion, highlighting the potential of NRP1 as a tumor biomarker in HCC.

Conclusions: Overall, these results suggest that NRP1 have a potential role for prognosis, development and risk of invasion, and, therefore, could constitute a valuable biomarker in patients diagnosed with HCC.

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967P The effect of prognosis value of EZH2 (Enhancer Of Zeste Homologue) staining in hepatocellular cancer

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Background: HCC is a primary malignant liver disease usually presenting with single or multiple nodules developing from underlying chronic hepatitis or cirrhosis. The Polycomb group (PcG) proteins and DNA methylation systems are epigenetic systems involved in hereditary gene activation inhibition. These epigenetic systems are involved in regulating gene expression and are closely related to the development of HCC. EZH2 is a functional enzymatic component of Polycomb Repressive Complex 2

(PRC2). The inhibition of tumor suppressor genes by EZH2 has been observed, and impeding the activity of EZH2 has been shown to decelerate tumor growth. According to some studies, EZH2 expression is associated with aggressive tumor behavior, a poor prognosis, and a poor response to treatment. The goal was to determine if EZH2 expression levels in HCC are of prognostic significance.

Methods: We picked 103 patients who had pathological diagnoses between 2011-2019. Retrospective screenings were done. EZH2 was checked with immunohistochemistry. Survival and treatment responses were analyzed statistically.

Results: 89 (86.4%) patients were male, and 14 (13.6%) were female. The median age of the patients was 68 (min19- max 89). 1% and above was considered positive. Immunohistochemically, EZH2 showed positive staining in 45 (43.7%) patients, and no staining was observed in 58 (56.3%) patients. The patients' median progression-free survival (mPFS) in the positive group was 5 months, while the mPFS of the negative group was 9 months (p=0.012). Based on comprehensive survival analysis, 35 of 45 patients in the positive group had died, and 10 were still alive. In the negative group, 36 patients died, and 22 survived. In the positive group, the median overall survival (mOS) was 8 months; in the negative group, it was 27 months (p=0,007). In our study, EZH2 had prognostic significance for progression-free and overall survival. Furthermore, an increase in EZH2 expression level was associated with a poor prognosis.

Conclusions: We established the prognostic significance of EZH2 for HCC. These findings could lead to new therapeutic strategies (e.g. tazemetostat) for treating and managing HCC. A greater understanding of EZH2's role in HCC requires further research.

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968P High sensitivity routine blood based detection of HCC: An AI model from 220k patients

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Background: Current guidelines for hepatocellular carcinoma (HCC) screening in patients with chronic liver disease (CLD) recommend ultrasound with or without alpha-fetoprotein (AFP) every 6 months. The sensitivity of AFP and USG are low for early stage HCC. Following our previous study which identified a novel routine blood test signature for HCC, this study aims to develop a high-dimensional data classifier which accounts for the intricate interactions between these blood parameters for the detection of HCC. Its performance is then compared with AFP.

Methods: Records from 2000 to 2018 were retrieved from a population-based clinical database of >200k patients, the Hong Kong Hospital Authority Data Collaboration Laboratory. CLD (hepatitis/ cirrhosis) patients with and without HCC were identified with ICD codes, antiviral drug history, virology test and radiology reports. Decompensated cases were excluded. Blood records within one month before the diagnosis of HCC and CLD patients were retrieved. The records retrieved included all components of CBC, LFT, RFT and clotting profile. Data from 2000-2015 were split into training and testing cohorts in an 8:2 ratio while data from 2016-2018 were used as the validation set. Machine learning models were applied and their performances were compared with AFP.

Results: The cohort yielded 223,862 patients including 31,149 with HCC (45.9% hepatitis-associated) and 192,713 without. Results from the test set (n = 12528; 3279 HCC) showed promise in safely excluding non-HCC patients with a sensitivity of 90% and negative predictive value of 97%. The model's high sensitivity maintained steady from late to early stage HCC while that of AFP halved. Our model increases HCC detection rate via USG from 19% to 50% compared to current protocol, indicating potential use in imaging prioritization and cost-saving in HCC surveillance.

Conclusions: An AI classifier for HCC detection is developed from routine blood test patient data. Its performance tested using an ultra-large cohort is consistently high without degradation across all stages with marked superiority to AFP for early stage HCC detection. Currently, multicenter prospective validation is being performed in Hong Kong.

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969P Establishing a novel routine blood component signature for Hepatocellular Carcinoma (HCC) screening with big clinical data

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Background: Alpha-fetoprotein (AFP) is widely used for HCC screening in at-risk populations, but its performance is suboptimal. Routine blood test panels provide insights on multiple cancer-related conditions and have shown to improve detection in other cancers. Hence, we explore the foundation for a new high-dimensional data approach taking multiple routine laboratory parameters and their intricate interactions into consideration with AI. In this study, a routine blood test signature for HCC derived from big clinical data is described

Methods: This is a population-based retrospective study. Patient records from 2000 to 2018 were retrieved from the Hong Kong Hospital Authority Data Collaboration Laboratory. CLD patients with and without HCC were identified based on ICD codes, antiviral drug history, virology test and radiology reports. Patients with decompensated CLD were excluded. Routine blood tests retrieved included CBC, LFT, RFT and clotting profile. Blood records within one month before the diagnosis of HCC and CLD patients were retrieved. Statistical analysis included descriptive statistics and Mann-Whitney U (MWU) test.

Results: The cohort yielded 223,862 patients including 31,149 patients with HCC (13.9%) and 192,713 without. Statistical test results showed a distinctive spectral signature for HCC patients compared to those without HCC. It is characterized by the concurrent presence of more significant liver function derangement (raised ALT, ALP, bilirubin, AST and decreased albumin), tendency for systemic inflammation (lower lymphocyte and RDW), tendency for bleeding (prolonged PT and APTT, low platelet) and suggestions of cachexia (lower albumin, creatinine and urea), all were statistically significant ($P<0.05$, MWU test)

Conclusions: This is the first study to describe a routine blood signature for HCC detection established by big clinical data. The spectral characteristics of HCC separated well from CLD controls. The novel spectrum provides solid clinical ground for the use of advanced machine learning to generate an interactive classification model to detect HCC. In a companion abstract, we describe the development of the proposed signature, which is shown to be superior to AFP in HCC screening.

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970P Real-world multi-center study of systemic treatment after first-line atezolizumab plus bevacizumab for advanced hepatocellular carcinoma in Asia-Pacific countries

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Background: Atezolizumab plus bevacizumab (AB) is one of the commonly used 1st-line regimen for advanced hepatocellular carcinoma (HCC) after its superior outcomes compared to sorafenib in IMbrave150 trial. However, the optimal treatment options for pts with HCC who progressed on the 1st-line AB remain unclear. This real-world study aims to compare efficacy of different systemic 2nd-line treatments in pts with HCC who progressed on 1st-line AB.

Methods: This multi-national, multi-institutional, retrospective study included pts with advanced HCC from 22 centers in 5 Asia-Pacific countries (Korea, Singapore, Hong Kong, Thailand, and Taiwan) who were treated with the 1st-line AB and stopped due to any reasons, including disease progression or toxicity. The endpoints of this study included PFS or OS per 2nd-line regimen.

Results: From June 2016 to January 2023, a total of 673 pts with HCC were treated with 1st-line AB, out of which 369 pts (54.8%) started the subsequent treatment. For the main analysis population treated with 2nd-line systemic therapy (n=340), 18.5% (n=63) of pts were Child-Pugh class B. Sorafenib and lenvatinib were the most commonly used 2nd-line regimen (57.1% and 24.5%, respectively). Overall, the median PFS and OS were of 2.9 (95%CI 2.5-3.1) and 8.0 months (95%CI 7.2-9.3), respectively. Lenvatinib showed longer PFS than sorafenib (3.7 vs 2.1 months, $P<0.0001$), but no significant difference in OS (8 vs 7.2 months, $P=0.094$). Pts treated with various combinations of TKI plus ICI (n=32, 9.4%) showed PFS and OS of 6.4 (95%CI: 3.7-NR) and 18.9 (95%CI: 9.8-NR) months, respectively. Additional analyses showed that pts with shorter PFS of AB had shorter 2nd-line PFS compared to patients who achieved longer 1st-line PFS. 54.9% (161/293) of pts were treated with subsequent systemic treatment after progression on 2nd-line therapy.

Conclusions: In pts with HCC progressed on the 1st-line AB, sorafenib and lenvatinib were the most commonly used 2nd-line regimen with comparable OS. The combination of 2nd-line TKI plus ICI showed promising results, suggesting a potential role for continuing ICIs beyond progression. Further updated data with more pts will be presented.

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971P Effect of preoperative frailty on surgical outcomes following hepatic resection for elderly patients with hepatocellular carcinoma: A multicenter retrospective cohort study from China

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Background: The growing demand for hepatic resection in elderly hepatocellular carcinoma (HCC) patients highlights the need to understand the impact of preoperative frailty on surgical outcomes. This multicenter retrospective cohort study aimed to investigate the association between frailty and short-term and long-term outcomes following hepatic resection in elderly HCC patients.

Methods: We conducted a multicenter retrospective cohort study on elderly patients ($\geq$70 years) who underwent curative-intent hepatic resection for HCC at 10 Chinese hospitals in China from 2012 to 2021. Frailty was assessed using the Clinical Frailty Scale (CFS), with frailty defined as CFS $\geq$ 5. Primary outcomes included overall survival (OS) and recurrence-free survival (RFS); secondary outcomes encompassed postoperative 30-day morbidity, 30-day mortality, and 90-day mortality. We compared these outcomes between patients with and without preoperative frailty.

Results: Of the 488 elderly patients, 148 (30.3%) were considered frail. Frail patients experienced significantly higher postoperative 30-day morbidity (68.9% *vs.* 43.2%), 30-day mortality (4.1% *vs.* 0.6%), and 90-day mortality (6.1% *vs.* 0.9%) than non-frail patients (all $P<0.05$). During a median follow-up of 37.7 months (IQR: 20.4-57.8), frail patients demonstrated significantly worse median OS (41.6 months [95% CI, 32.0-51.2] *vs.* 69.7 months [95% CI, 55.6-83.8]) and RFS (27.6 months [95% CI, 23.1-32.1] *vs.* 42.7 months [95% CI, 34.6-50.8]) compared to non-frail patients (both $P<0.01$). Multivariate Cox-regression analysis revealed frailty as a significant predictor for OS (HR 1.61, 95% CI 1.22-2.13, $P=0.001$) and RFS (HR 1.32, 95% CI 1.03-1.70, $P=0.028$).

Conclusions: Frailty was significantly associated with adverse short-term and long-term outcomes in elderly HCC patients undergoing hepatic resection. Our findings suggest that frailty assessment should be incorporated into perioperative and postoperative prognosis evaluation, and particular attention should be given to frail elderly patients undergoing this procedure.

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972P Sequential therapies after atezolizumab plus bevacizumab or lenvatinib first-line treatments in advanced hepatocellular carcinoma

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Background: Today the most used first-line treatments in hepatocellular carcinoma (HCC) patients are lenvatinib (L) and atezolizumab plus bevacizumab (AB). All the data available about second-line therapies derive from trials conducted in patients who

progressed to first-line sorafenib therapy. The aim of this retrospective proof-of-concept study is to compare different second-line drugs for HCC patients progressed to first-line L or AB.

Methods: The overall cohort included 2225 consecutive patients from 5 countries (Italy, Germany, Portugal, Japan, and Republic of Korea). A total of 1381 patients had progressed disease (PD) at first-line therapy. 917 patients were in L first-line arm, and 464 patients were in AB first-line arm.

Results: 49.6% of PD patients received a second-line therapy without any statistical difference in OS between L (20.6 months) and AB first-line [15.7 months; $p = 0.12$; hazard ratio (HR) = 0.80]. After L first-line, there wasn't any statistical difference between second-line therapy subgroups ($p = 0.27$; sorafenib HR: 1; immunotherapy HR: 0.69; other therapies HR: 0.85). Patients who underwent TACE had a significative longer OS than patients who received sorafenib (24.7 vs. 15.8 months, $p < 0.01$; HR = 0.64). After AB first-line, there was a statistical difference between second-line therapy subgroups ($p < 0.01$; sorafenib HR: 1; L HR: 0.50; cabozantinib HR: 1.29; other therapies HR: 0.54). Patients who received L (17.0 months) and those who underwent TACE (15.9 months) had a significative longer OS than patients treated with sorafenib (14.2 months; respectively, $p = 0.01$; HR = 0.45, and $p < 0.05$; HR = 0.46).

Conclusions: Approximately half of patients receiving first-line L or AB access second-line treatment. Our data suggest that in patients progressed to AB, the systemic therapy able to achieve the longest survival is L, while in patients progressed to L, the systemic therapy able to achieve the longest survival is immunotherapy.

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973P Clinicopathologic and treatment outcome data in 165 fibrolamellar carcinoma patients

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Background: Fibrolamellar carcinoma (FLC) is a rare subtype of liver cancer that primarily affects young adults and adolescents. The main objective of this study is to evaluate the association between survival outcomes and clinical factors of patients with FLC.

Methods: We retrospectively collected clinicopathologic and treatment outcome data from 88 male and 77 female patients with a pathologic diagnosis of FLC. Median overall survival (OS) was calculated using Kaplan-Meier curves. Log rank test, univariable and multivariable Cox models were applied to evaluate the association between clinical outcomes and patients' characteristics.

Results: Mean age at diagnosis was 27.4 years (age range: 9, 76), median OS was 42.6 months (95% CI: 36.5, 59.2). 50.3% of patients in our study were AJCC Stage IV at the time of presentation, with 67.5% having vascular invasion at diagnosis. 5% of patients had liver cirrhosis. 68.5% of patients received surgery, including metastasectomy. 30.9% received radiation therapy, and 77.5% received systemic therapy. Combination of 5-fluorouracil and interferon-alpha2 was the most frequently used systemic therapy (83 patients), with 45 patients receiving other forms of chemotherapy. The median OS of patients who underwent surgery was 59.2 months (95% CI [49.51, 89.68]) versus 20.34 months (95% CI [15.37, 26.02] in patients who did not. Of those who did not have surgery, 94.2% (49 patients) had AJCC stage >II. Higher tumor stage(>II) (HR=2.841; 95% CI [1.309, 6.165]), lack of surgery (HR=3.47; 95% CI [2.193, 5.488]) and lack of receipt of radiation therapy (HR=1.685; 95% CI [1.059, 2.68]) were positively associated with worse OS.

Conclusions: We identified prognostic factors in FLC. The associations of receipt of surgery and radiation with prolonged OS suggest that local control and cancer debulking in this disease is paramount.

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974P The barthel index predicts surgical textbook outcomes following hepatectomy for elderly patients with hepatocellular carcinoma: A multicenter cohort study from China

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Background: The burgeoning demand for hepatectomy in elderly patients with hepatocellular carcinoma (HCC) necessitates improved perioperative care. Geriatric populations frequently experience functional decline and frailty, predisposing them to adverse postoperative outcomes. The Barthel Index serves as a reliable measure for assessing functional capacity, and this study evaluates its impact on surgical textbook outcomes (TOs) as composite quality indicators following hepatectomy in elderly HCC patients.

Methods: A multicenter retrospective cohort study analyzed elderly patients (≥70 years) who underwent hepatectomy for HCC between 2013 and 2021 at 11 Chinese hospitals. Utilizing a Barthel Index cut-off value of 85, patients were divided into two groups: with and without preoperative functional decline and frailty. The primary outcome was TO, encompassing seven criteria. TO rates were compared between groups, and multivariate logistic regression analyses identified independent risk factors for achieving TOs.

Results: Of 497 elderly HCC patients, 157 (31.6%) exhibited preoperative functional decline and frailty (Barthel Index score <85). The overall TO rate was 58.6%. Patients with preoperative Barthel Index score <85 had significantly lower TO rates compared to patients with preoperative Barthel Index score ≥85 (29.3% vs. 72.1%, $P<0.001$). Similar differences emerged regarding perioperative blood transfusion, postoperative major morbidity, prolonged hospital stays, 30-day readmission, and 90-day mortality rates. Multivariate analysis revealed preoperative Barthel Index score <85 as an independent risk for achieving TO (odds ratio 3.413, 95% confidence interval 1.879-6.198, $P<0.001$). Comparable results were observed in subgroup population of patients undergoing open and laparoscopic hepatectomy, respectively.

Conclusions: Preoperative Barthel Index-based assessment of functional decline and frailty significantly predicts TOs following hepatectomy in elderly HCC patients, enabling identification of high-risk patients and informing preoperative management and postoperative care within geriatric oncology.

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975P The clinical impact of urinary protein creatinine ratio and AFP at six weeks in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab

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Background: In systemic therapy for unresectable HCC (u-HCC), atezolizumab plus bevacizumab (Atez+Bev) has become a standard first-line therapy. Although previous studies already reported predictive biomarkers, including neutrophil-lymphocyte ratio (NLR), CRP, and IL-6, there are no established markers in real-world practice. Urinary protein creatinine ratio (UPCR) was reported to be associated with IL-6. We investigated universal predictive markers in the early phase after the administration of Atez+Bev.

Methods: A total of 134 patients who received Atez+Bev at our institution between Oct 2020 and Mar 2023 were enrolled. Tumor assessments by RECIST v1.1 were done using dynamic CT or MRI every 6-12 weeks. Blood and urine examinations, including UPCR and AFP, were performed every 3 weeks. All clinical information was analyzed retrospectively.

Results: The median age of the patients was 74 years, and the median ALBI score was -2.24. The line of treatment was 1st (n=84) and 2nd or later line (n=50). Seventy-eight (58%) patients were BCLC stage B, and 56 were stage C. The median follow-up duration was 11.2 months. The median overall survival (OS) was 24.5 months in 1st line and 21.8 months in 2nd or later line. The median progression-free survival (PFS) was significantly longer in 1st line than in 2nd or later line (8.2 vs. 4.2 months, p=0.01). The independent factors significantly associated with OS were pretreatment

ALBI score (HR 4.8, 95%CI 2.2-10.4, p<.0001) and AFP ≥ 400ng/mL (HR 2.6, 95%CI 1.4-5.0, p=0.003). The independent factors associated with PFS in 1st line were AFP decrease at 6 weeks (HR 0.41, 95%CI 0.2-0.9, p=0.03) and UPCR at 6 weeks (HR 1.3, 95%CI 1.3-2.8, p=0.002). Among the 1st-line patients with stable disease at 6-12 weeks (n=36), the patients with low UPCR (<0.24) at 6 weeks (N=27) had significantly longer PFS than those with high UPCR (11.3 vs. 4.6 months, p=0.02). The dose of Bev within 12 weeks was not significantly different between the two groups.

Conclusions: The assessments of early changes in UPCR and AFP during Atez+Bev were valuable. The therapeutic strategies for patients with stable disease at 6-12 weeks would be considered based on the changes in UPCR and AFP at 6 weeks.

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976P Overall survival in advanced hepatocellular carcinoma treated with concomitant systemic therapy and stereotactic radiation therapy or systemic therapy alone

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Background: First-line systemic therapy (ST) options in advanced hepatocellular carcinoma (HCC) include tyrosine kinase inhibitors and immunotherapy (IO). Evolving data suggest prolonged overall survival (OS) when ST approaches are combined with stereotactic radiation therapy (SRT), although evidence is limited in HCC populations. We hypothesized that advanced HCC patients in the United States National Cancer Database (NCDB) would have improved OS when receiving ST+SRT vs ST alone.

Methods: Stage III/IV HCC patients diagnosed from 2010-2020 and treated with first-line ST±SRT were identified from the NCDB. The primary endpoint was OS from date of diagnosis stratified by the receipt of SRT (ST+SRT vs ST alone). Survival was estimated using Kaplan-Meier methodology and compared via log-rank. Multivariate analysis (MVA) was performed by Cox regression.

Results: Of 10,505 eligible patients with stage III disease, 115 (1.1%) received ST+SRT and 10,390 (98.9%) received ST alone. Of 9,617 eligible patients with stage IV disease, 127 (1.3%) received ST+SRT and 9,490 (98.6%) received ST alone. Median follow-up time was 6.8 months. Baseline characteristics were similar between cohorts. Patients with stage III disease receiving ST+SRT had improved median OS (12.62 months vs. 8.38, log-rank P=0.0054) and higher rates of survival at 1-year (53.0% vs. 38.7%) and 2-years (27.0% vs. 20.7%) compared to those receiving ST alone. Similarly, patients with stage IV disease receiving ST+SRT had improved median OS (11.79 months vs 5.72 months, log-rank P<0.0001) and higher rates of survival at 1-year (49.6% vs 26.2%) and 2-years (23.6% vs. 12.0%). On MVA, receipt of SRT predicted for improved OS (HR=0.748, P=0.0178) and receipt of IO trended towards improved OS (HR=0.859, P=0.0538). Predictors of poor OS included stage IV disease (HR=1.509), primary tumor size > 5 cm (HR=1.354), and Charlson-Deyo Score >0 (HR=1.106) (P=<0.0001).

Conclusions: In patients with stage III/IV HCC, concomitant ST+SRT improved OS compared to ST alone. Prospective clinical trials are warranted to better identify HCC populations which may benefit from combined modality therapy.

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977P Hepatic arterial infusion chemotherapy (HAIC) combined with Regorafenib and PD-1 inhibitors versus Regorafenib combined with PD-1 inhibitors for second-line treatment Hepatocellular carcinoma (HCC)

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Background: Hepatocellular carcinoma (HCC) is a prevalent malignant tumor globally, Hence, there is an urgent need for safer and more effective options to improve the survival rates of HCC patients. This study aims to evaluate the viability, efficacy, and safety of HAIC and Regorafenib combined with PD-1 inhibitors for treating advanced HCC patients.

Methods: This is a multicenter, randomized controlled clinical study of hepatocellular carcinoma. Eligible individuals with unresectable HCC were randomized into either the HAIC combined with regorafenib and PD-1 inhibitors group (HAIC+REG+ICIs group) or the regorafenib combined with PD-1 inhibitors group (REG+ICIs group). The primary endpoint is the objective response rate (ORR). Secondary endpoints include PFS, OS, DCR (all assessed by BICR per RECIST v1.1), and safety.

Results: Up to April 24, 2023, a total of 45 patients were enrolled and all patients are available for analysis. The HAIC+REG+ICIs group and the REG+ICIs group included 28 and 17 patients, respectively.The median age were 52.5 years (range, 32-68) and 47.0 years (range, 24-79), 92.9% and 94.1% were male for each group, the proportions of child-pugh A/B were 64.3%/35.7% vs. 88.2%/11.8%; and the patients with China Liver Cancer Staging (CNLC) Ib/IIa/IIb/IIIa/IIIb/IV stage were 0.0%/3.6%/35.7%/21.4%/32.1%/7.1% vs. 5.9%/11.8%/47.1%/11.8%/17.6%/5.9%, respectively. All patients were infected with HBV. The median follow-up time was 16.6 months (1-21.2). The ORR was 39.3% (11/28) and 29.4%(5/17) for HAIC+REG+ICIs group and the REG+ICIs group, P=0.502. DCR was 82.1%(23/28) and 52.9%(9/17) respectively, P=0.036. The median OS of HAIC+REG+ICIs group was significant longer than REG+ICIs group (19.1 vs. NA months, P=0.03; HR=0.039 95% CI: 0.101-0.941). This study is currently ongoing.

Conclusions: HAIC combined with Regorafenib and PD-1 inhibitors compared with Regorafenib and PD-1 inhibitors showed a better tumor response rate, but there was no significant difference. However HAIC combined with regorafenib and PD-1 inhibitors can significantly prolong the overall survival of second-line HCC patients.

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978P Post-progression outcomes of advanced HCC patients (aHCC pts) treated with first-line atezolizumab/bevacizumab (A/B)

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Background: The optimal treatment (Tx) strategy for aHCC pts who have progressed on frontline A/B is undefined. We evaluated 2nd line Tx patterns and clinical outcomes of aHCC pts following progression on A/B to identify factors associated with post-progression survival (PPS).

Methods: Real world patient data were retrieved from an international HCC database. PPS was from first radiographic progression on A/B to death. Kaplan-Meier median survivals and 95%CI were compared with univariate Cox-regression analysis. Univariate (UVA) and multivariate (MVA) Cox-regression analyses assessed the impact of baseline clinical factors on PPS.

Results: We identified 406 pts alive with progression on A/B. 220 continued active systemic Tx: 203 received 1 further line, 155 with tyrosine kinase inhibitors (TKIs), 45 with immunotherapy, and the remainder had missing data. Median duration of 2nd line Tx was 2.2 months (mo) (IO: 2.3 mo, TKI; 2.1). Compared to pts who received best supportive care (BSC; n=186), pts on active Tx were younger, Child Pugh class (CP) A , ECOG <2 when A/B stopped, had viral etiology, no extrahepatic disease, and had disease control during A/B. Median follow-up from A/B progression was 7.5 mo (95% CI 6.3-8.6). mPPS for all pts was 6.0 mo (95%CI 5.2-7.2). Continued active Tx was associated with prolonged mPPS compared to BSC (9.7 vs 2.0 mo; HR: 0.30; 95%CI 0.2-0.4, p$<$0.001). mPPS was longer with IO (11.8 mo; 95%C: 6.4-NA) than with TKIs (8.1 mo; 95%CI 6.3-10.4) or BSC (2.0 mos ;95%CI 1.5-2.9). Male sex, ECOG $\geq$2 at time of A/B interruption, CP B/C, portal vein tumor thrombosis (PVTT), and primary progression on A/B were associated with increased risk of death in UVA. In MVA, PVTT, ECOG $\geq$2 and BSC independently predicted poor PPS. Active tx was associated with longer mPPS (8.6 mo, 95%CI 6.3-13.0 vs 2.5, 95%CI 2.1-4.4; HR:0.40, 95%CI 0.28-0.58) after performing propensity score matching for confounding factors (ECOG at A/B stop, PVTT, CPS, DCR during A/B).

Conclusions: In addition to known disease related factors, continuation of systemic Tx instead of BSC following progression on A/B is independently associated with improved PPS in pts with aHCC. mPPS was nearly 1 year with IO-based Tx, suggesting a potential role for IO beyond progression after A/B.

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979P Safety interim analyses of first-line systemic therapy with atezolizumab plus bevacizumab (ATZ+BEV) in patients from Spain with unresectable hepatocellular carcinoma (HCC): Phase IIIb ATHECA

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Background: HCC progression is associated with an immunosuppressive tumour microenvironment enhanced by vascular endothelial growth factor (VEGF). ATZ+BEV, synergistically targeting programmed death ligand 1 (PD-L1) and VEGF, was approved as first-line systemic treatment for unresectable HCC after showing efficacy and acceptable safety profile in the pivotal IMbrave150.

Methods: This study evaluates safety and efficacy of 3-week intravenous cycles of first-line ATZ+BEV (1200 mg+15 mg/kg) in patients (pts) with unresectable HCC not previously treated with systemic therapy and with preserved liver function (Child-Pugh A). Here are presented safety interim results of the incidence and severity of treatment emergent adverse events (TEAE) grade (G) $\geq$3 leading to ATZ and/or BEV treatment discontinuation (primary objective) and other safety endpoints (secondary objectives).

Results: In 26 Spanish centres, 100 eligible pts (86 males, median age 66 years), received ATZ+BEV. At a median follow-up of 11.4 months, 63 pts had discontinued either BEV (63 pts) or ATZ (58 pts). TEAE G3 were reported in 44% pts, TEAE G4 in 1%, TEAE leading to death in 5% pts and serious TEAE in 32% pts. Treatment-related adverse events (TRAE) G3 occurred in 26% pts, mainly high levels of bilirubin and liver/pancreatic enzymes (9% pts), gastrointestinal-haemorrhagic disorders (4% pts) and arterial hypertension (7% pts). TRAE G4 was oesophageal varices haemorrhage in 1% pts. Serious TRAE occurred in 10% pts and immune-mediated TRAE G3 in 3% pts. TEAE leading to treatment discontinuation (G3: 9 pts; G4: none) were mainly gastrointestinal-haemorrhagic (4%) and liver biochemistry (2%) disorders. The 6 TEAE leading to death were hepatitis (the only TRAE), abdominal sepsis, aspiration pneumonia, haemoperitoneum, jaundice and hepatic encephalopathy (these last two events occurred in the same patient).

Conclusions: ATHECA preliminary safety data of first-line ATZ+BEV for unresectable HCC showed a TEAE profile similar to previous studies and consistent with the underlying disease and known safety profile of each agent.

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980P Neutrophil count predicts the complete response after transarterial chemoembolization related to favorable outcome in hepatocellular carcinoma

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Background: Systemic inflammatory markers have emerged as novel prognostic biomarkers associated with prognosis for tumors. This study aims to investigate the predictive value of systemic inflammatory markers for complete response (CR) in patients with hepatocellular carcinoma (HCC) who undergo transarterial chemoembolization (TACE).

Methods: This retrospective study enrolled 575 treatment-naïve patients with HCC who underwent TACE. Survival outcomes were evaluated based on tumor response, and the analysis was conducted using a Kaplan-Meier curve. Predictive factors for achieving a CR after the initial TACE were analyzed by univariate and multivariate analysis in a Cox regression model.

Results: After the initial TACE, 246 of 575 (37.0%) patients achieved CR. During a median of 60 months follow-up, CR group had better overall survival than non-CR group (median: 82.3 vs. 51.6 months, P<0.001). Pre-TACE neutrophil count was associated with tumor response (P=0.06). Multivariate analysis showed that hepatitis B virus infection (hazard ratio [HR]=0.585, 95% CI=0.360-0.952, P =0.031) and pre-TACE neutrophil count (HR=2.854, 95% CI=1.115-7.307, P=0.029) were independent predictive factors for CR after the initial TACE. Additionally, high pre-TACE neutrophil count was associated with male gender (P<0.001), large tumor size (P<0.001), advanced Barcelona Clinic Liver Cancer stage (P=0.003) and high PIVKA-II level (P<0.001).

Conclusions: Patients who achieved CR after the initial TACE showed a favorable prognosis. Pre-TACE neutrophil count was found to be an independent predictor of CR. These findings offer valuable insights for identifying patients who would derive the greatest benefit from TACE and for distinguishing those who may require alternative treatment approaches for HCC.

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981P The response of portal vein tumoral thrombosis to moderately hypo-fractionated radiotherapy using intensity modulated radiotherapy

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Background: Hepatocellular carcinoma (HCC) has a high incidence and mortality worldwide, particularly in Africa and East Asia, due to the widespread hepatitis B and C viral infections (1). Locally advanced HCC is frequently associated with vascular invasion, commonly affecting the portal vein, with an incidence of portal vein tumor thrombosis (PVTT) ranging from 31.4 to 34% (2). PVTT is associated with poor clinical outcomes, including deterioration of hepatic function, tumor dissemination, and shorter overall survival (3). Treatment options for HCC with PVTT are limited. Radiation therapy (RT) has an important role in the management of HCC, from palliative to curative intent. (4).

Methods: Fifty patients with PVTT in HCC were prospectively treated with IMRT using moderately hypofractionated doses. A statistical analysis of the patient's survival and radiotherapy (RT) response was done. Potential prognostic factors for response to RT and survival were assessed.

Results: The median survival for 50 patients was 10 months, with a 1-year survival rate of 36% and a response rate of 36%. Response to treatment, Eastern Cooperative Oncology Group Performance Status (ECOG PS), hepatic focal lesion size, and Child-Pugh score were statistically significant prognostic factors for survival in univariate analysis (P = <0.001, P = 0.001, P = 0.007, and P = <0.001, respectively). Among these factors, Child-Pugh score, ECOG PS, and response to treatment were significant for patient prognosis in multivariable analysis (P = 0.003, P = 0.012, and P = 0.023, respectively).

Conclusions: As patients with PVTT usually have a poor prognosis and short survival, using hypofractionated RT regimens with short-course treatment can improve survival in these patients. RT responders can be elected for treatment with another local treatment modality with a chance for better overall survival.

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982P Transarterial chemoembolization with idarubicin versus epirubicin for hepatocellular carcinoma: An interim analysis of a multicentre, randomized controlled phase III trial

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Background: Transarterial chemoembolization (TACE) is a treatment option for hepatocellular carcinoma (HCC), but the optional agent for TACE is limited. We compared the efficacy and safety of TACE with idarubicin versus epirubicin in HCC patients.

Methods: This is a non inferiority randomized controlled trial registered in clinicaltrials.gov with NCT05053386. 186 patients was needed according to calculation. Patients with liver-confined HCC, Eastern Cooperative Oncology Group (ECOG) score 0-1, Child-Pugh class A/B, and Barcelona Clinic Liver Cancer (BCLC) Stage A-C were randomly assigned in a 1:1 ratio to receive TACE with 10mg idarubicin (experimental group) or 50mg epirubicin (control group). The primary endpoint was objective response rate (ORR). The secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety.

Results: 110 patients were recruited from October 2021 to April 2023 at 14 centers in China and randomly assigned to undergo TACE with idarubicin (n=55) or epirubicin (n=55). The median age was 63 years (range 35, 79), most were male (83.6%), ECOG score 0 (85.5%), Child-Pugh A (90.9%), hepatitis B (81.8%), there were no significant differences between groups in baseline characteristics (p>0.05). The experimental group has a good tumor response, as shown by higher ORR (66.0% vs 59.5%, p=0.530) and DCR (89.4% vs 81.0%, p=0.262) versus control group. The median PFS and median OS were not observed yet. No significant differences were found between groups in postembolization syndrome and liver toxicity (p>0.05). The incidence of thrombocytopenia was higher in control group than in experimental group (9.8% vs 25.0%, p=0.046). Grade 3 or 4 adverse events mainly included increased ALT/AST (ALT, 14.8% vs 22.2%, p=0.350; AST, 23.0% vs 19.4%, p=0.686).

Conclusions: Our interim results suggest that idarubicin could be a safe and effective treatment option for lipiodol TACE of HCC. This trial will progress as planned.

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983P Safety and efficacy of durvalumab plus hepatic artery infusion chemotherapy in HCC with severe portal vein tumor thrombosis (Vp3/4) – the DurHope study

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Background: The HIMALAYA trial demonstrated that the efficacy of durvalumab (an PD-L1 inhibitor) is comparable to that of sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC), and its safety profile is more acceptable. The FOHAIC-1 study indicated that hepatic arterial infusion chemotherapy (HAIC) achieves better survival than sorafenib in advanced HCC with intrahepatic high-risk factors (i.e., Vp4 portal vein tumor thrombosis [PVTT]). This study aimed to evaluate the safety and efficacy of durvalumab plus HAIC as first-line therapy in pts with HCC with Vp3/4 PVTT.

Methods: The DurHope study was a single-arm, phase 2 trial. Eligible pts had HCC with Vp3/4 PVTT with no previous systemic treatment. Pts received HAIC of FOLFOX regimens (oxaliplatin 130 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400 mg/m^2, and fluorouracil 2,400 mg/m^2) on day 1–3 plus durvalumab (1120 mg) intravenously on day 7 (±2) of each 21-day cycle for 8 cycles, followed by maintenance with durvalumab (1500 mg) every 28 days until disease progression, unacceptable toxicity, or death. The primary endpoint was 1-year overall survival (OS) rate. Secondary endpoints were progression-free survival (PFS), objective response rate (ORR) per RECIST v1.1, and safety.

Results: In this interim analysis, as of March 20, 2023, 19 pts who received at least one cycle of durvalumab and HAIC were included. The ORR was 47.4% (9/19) with 1 complete response and 8 partial response. The median time to response was 1.3 months (95% CI, 1.3–2.7), and the median duration of response was 5.4 months (95% CI, 3.7–5.8). The most common treatment-emergent adverse events (TEAEs) were hypoalbuminemia (18 [94.7%]), anaemia (17 [89.5%]), and neutropenia (16 [84.2%]). Grade 3/4 TEAEs occurred in 13 pts (68.4%). Two pts (10.5%) experienced grade 4 upper gastrointestinal bleeding.

Conclusions: Combination treatment with durvalumab and HAIC showed promising antitumor activity with ORR of 47.4% in HCC with Vp3/4 PVTT. Prophylactic gastrointestinal endoscope might be necessary to decrease the risk of gastrointestinal bleeding in such pts. Enrollment is ongoing and longer follow-up is needed to evaluate the survival data.

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984P Comparative study of scoring systems predicting outcome of transarterial chemoembolization for hepatocellular carcinoma: A nationwide cohort study

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Background: Several scoring systems have been proposed to predict the outcome of transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). However, the application of the albumin-bilirubin (ALBI) grades to TACE candidates is poorly validated. Evaluation of the applicability of prognostic factors for patients performing TACE is necessary. We aimed to develop new scoring system including ALBI grade.

Methods: 2,632 patients with unresectable HCC, child class A/B and ECOG 0-1 performing TACE were included from national cohort of the Korean Central Cancer Registry between 2008 to 2017. Patients were randomly divided into training (n=1,304) and validation cohort (n=1,328). A prognostic model was developed and validated. We compared with previous scoring models.

Results: In entire cohort, the patient's mean age was 63 years. The patients were hepatitis B virus (57.1%) and child class A (83.2%). The prognostic model of TACE was "largest tumor diameter+ tumor number, AFP, and ALBI grade", which consistently outperformed other currently available models in both training and validation datasets. Patients were assigned points according to sum of tumor burden (≤5, 5-10, ≥10), AFP or ALBI grade. Patients were divided into four risk groups based on their TACE-prognostic (TP) scores: A, B, C and D. The median survival for the groups A, B, C and D was 85.9, 67.3, 52.8 and 33.0 months, respectively.

Conclusions: This new TP scoring system may prove a favorable tool to stratify ideal candidates of TACE and predict OS with favorable performance and discrimination. Further external validation is needed.

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985P Characteristics and outcomes in patients (pts) with unresectable hepatocellular carcinoma (uHCC) who initiated second-line (2L) therapy after receiving first-line (1L) atezolizumab plus bevacizumab (atezo+bev) and in those who did not

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Background: Atezo+bev is a standard of care 1L treatment for uHCC. Currently, there is no evidence to guide treatment decision-making after discontinuation of 1L atezo+bev. Therefore, we aimed to describe the real-world characteristics and outcomes in pts with uHCC who initiated 2L therapy after receiving 1L atezo+bev vs those who did not.

Methods: Oncologists from a US nationally representative network extracted electronic medical chart data for pts with uHCC who received 1L atezo+bev between June 1, 2020 and March 6, 2023. Pts were stratified into two groups based on whether they started 2L therapy within 8 weeks of 1L atezo+bev discontinuation. Pt demographic and clinical characteristics, duration of 1L treatment (DOT), and overall survival (OS) were assessed.

Results: We identified 484 eligible pts (median age, 66 years; 64.9% male; 62.6% White). At baseline, most had good performance status (ECOG PS 0–1, 79.5%) and liver function (Child-Pugh [CP]-A, 81.4%). A higher proportion of pts in the 2L (n=141) vs no 2L (n=40) cohort were White (69.5% vs 52.5%), non-Hispanic (78.0% vs 60.0%), and had Medicare/Medicaid insurance (72.3% vs 45.0%). Between 1L and 2L initiation, liver function deteriorated (CP-A, 74.5% to 52.5%) as did performance status (ECOG PS ≥2: 8.5% to 45.3%). Pts who did not initiate 2L therapy had worse performance status (ECOG PS ≥2, 52.5% vs 8.5%) and liver dysfunction (CP-B or C, 40.0% vs 25.5%). Although median 1L DOT was similar between the 2L and no 2L cohorts (6.9 vs 7.8 months), median OS from 1L initiation was nearly twice as long among 2L (26.0 months [95% CI 21.3, 27.2]) vs no 2L (14.3 months [95% CI 10.2, 24.8]) cohort pts.

Conclusions: This study provides real-world data for sequential therapy in uHCC following atezo+bev. The findings showed differences between pts initiating 2L therapy and those who did not, highlighting the need for better pt selection at the start of 1L atezo+bev and the potential benefit of timely switching from 1L atezo+bev to subsequent therapies.

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987P Safety and efficacy of lenvatinib in patients with unresectable hepatocellular carcinoma (uHCC) in real-world practice in Korea

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Background: We aimed to evaluate the safety and efficacy of lenvatinib in Korean population under real-world practice.

Methods: Patients were prospectively entered at 29 clinical sites through an observational post-marketing study in Korea, funded by Eisai. Patients were treated with lenvatinib according to the approved indication of uHCC. For safety analysis, Adverse Drug Reactions (ADRs) were collected. ADR was defined as AEs where the causal relationship with lenvatinib was not 'unlikely'. The efficacy was assessed by investigators as completed response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as CR or PR in the efficacy analysis set. Statistical analysis was conducted to identify which demographic and clinical factors were related to ORR.

Results: 658 patients were included in the safety analysis set. The mean daily dose was 7.8mg/day and 10.1mg/day in patients with a body weight of $<$ 60kg and $\geq$ 60kg. The relative dose intensity related to tolerance was 97% and 84%, respectively. ADRs $>$ grade 3 were reported in 1% (8/658). The most common ADRs $>$ grade 3 were 'palmar-plantar erythrodysaesthesia syndrome' (0.3%, 2/658). In the efficacy analysis set, 513 patients were included. The results were as follows: CR, 1% (5/513); PR, 13% (66/513); SD, 45% (231/513); and PD, 41% (211/513). Among the demographic and clinical factors, ORR was significantly different depending on the total treatment duration (p $<$0.001).

Table: 987P

	Objective response rate n (%)	No. of Subjects n (%)	p-value
Total treatment duration			
$<$ 3 months	12 (6)	191 (38)	$<$0.001
3 months $\sim$ $<$ 6 months	21 (13)	165 (32)	
6 months $\sim$ $<$ 9 months	15 (19)	78 (15)	
9 months or above	23 (30)	76 (15)	
Total	71 (14)	510 (100)	

Conclusions: Lenvatinib in Korean patients with uHCC was generally well tolerated. The efficacy of treatment varied significantly with regards to the total treatment duration. Patients with longer treatment duration showed higher ORR.

Clinical trial identification: E7080-M082-509

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988P Burden of primary liver cancer in the Middle East and North Africa Region from 1990 to 2019

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Background: Liver cancer is a leading cause of cancer-related mortality worldwide. There is a literature gap regarding its burden in the Middle East and North Africa (MENA) region. Therefore, we aimed to investigate the epidemiological trends of primary liver cancer in the MENA region from 1990 to 2019.

Methods: The Global Burden of Disease database was used to extract the age-standardized rates per 100,000 population for prevalence (ASRP), incidence (ASRI), and years lived with disability (YLDs) of primary liver cancer in the MENA region between 1990 and 2019. Data were analyzed to identify regional distribution patterns across different countries and demographic groups using Wilcoxon signed-rank test.

Results: ASRP for liver cancer in the MENA region was significantly higher in 2019 compared to 1990 (median of 4.34 and 5.38 in 1990 and 2019, respectively; P= 0.002). The major causes of primary liver cancer were hepatitis C virus, followed by hepatitis B virus, nonalcoholic steatohepatitis, and alcohol use. In 2019, the highest ASRP was observed in Qatar (24.894; 95% confidence interval (CI): 18.34-33.24) and Egypt (22.575; 95% CI: 16.20-30.90), while Morocco had the lowest one (2.21; 95% CI: 1.68-2.70). On the other hand, no significant increase was observed from 1990 to 2019 for the ASRI (median of 4.26 and 4.49 in 1990 and 2019, respectively, $P = 0.498$) and YLDs (median of 0.96 and 1.04 in 1990 and 2019, respectively, $P = 0.079$).

Conclusions: The prevalence of liver cancer shows a rising trend in the MENA region from 1990 to 2019. Adopting regional programs to address the major risk factors should be considered.

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989P Disease etiology and efficacy outcomes with atezolizumab plus bevacizumab (atezo-bev) in patients (pts) with unresectable hepatocellular carcinoma (uHCC): Multinational retrospective analysis

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Background: Atezo-Bev is the one of the standard first-line treatments for pts with uHCC. There have been controversies that the efficacy of immune checkpoint inhibitors might be affected by the etiology of HCC. We performed a multinational retrospective study to investigate the impact of disease etiology on the efficacy outcomes with atezo-bev and prognostic factors in real-world uHCC pts treated with first line atezo-bev.

Methods: A total of 161 pts with Child A liver function who received first-line atezo-bev were included in the current analysis from Asan Medical Center (Seoul, Korea), and National Cancer Centre Singapore (Singapore), between July 2016 and July 2022. Pts with Child B liver function or prior systemic therapy were excluded. Tumor response was assessed per RECIST v1.1.

Results: The median age of the pts was 63 years (range, 16-90) and 136 pts (84.5%) were male. The most common etiology was hepatitis B virus (67.0%), followed by non-alcoholic fatty liver disease (NAFLD) (13.0%), alcohol (7.4%) and hepatitis C virus (4.3%). The objective response rate (ORR) of all pts was 23.6%. There was no difference in ORR based on etiology (viral vs non-viral, 22.1% vs 23.1%; NAFLD vs others, 21.1% vs 23.9%). With a median follow-up of 10.9 months(mo) (95% CI, 9.7-13.1), the median progression-free survival (PFS) and overall survival (OS) were 4.1 mo (95% CI, 3.1-6.9) and 14.0 mo (95% CI, 11.2-18.5), respectively. Median PFS and OS did not differ based on etiology (viral vs non-viral; PFS 4.4 vs 4.4 mo and OS, 14.0 vs 13.1 mo; NAFLD vs others; PFS 3.1 vs 4.1 mo and OS, 14.2 vs 14.0 mo). In the multivariable analysis, higher baseline NLR ($\geq$2.5 [median]) was significantly associated with poorer PFS (median 3.8 vs 9.5 mo, HR 2.2, p=0.003) and OS (median 8.8 vs 27.0 mo, HR 5.0, p$<$0.001) compared to baseline NLR $<$ 2.5. The most common adverse events (any grade) was hypertension (27.3%), followed by thrombocytopenia (16.9%), proteinuria (11.5%), and hemorrhage (11.5%).

Conclusions: Current study showed that disease etiology was not associated with the efficacy outcomes with first line atezo-bev in pts with uHCC, while higher NLR was a significant poor prognostic factor for these patients.

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990P Prognosis prediction for unresectable hepatocellular carcinoma undergoing hepatic arterial infusion chemotherapy using convolutional neural network model

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Background: Hepatic arterial infusion chemotherapy (HAIC) is known to be more effective than conventional systemic chemotherapy, showing great potential in treating unresectable hepatocellular carcinoma (HCC) patients. However, there is still unclear which group can benefit more from HAIC.

Methods: 191 patients with unresectable HCC undergoing HAIC from Zhongshan Hospital between May 2019 and March 2022 were retrospectively recruited. Radiomics scores were calculated based on enhanced-T1-weighted, enhanced-T2-weighted, arterial phase and delayed phase images. Clinical factors related to OS and PFS were identified by Cox regression analysis. Three different CNNs of AlexNet, ResNet, and Inception architectures were constructed on 70% of the data set and tested on the remaining 30%. Radiomics scores and clinical factors were reflected to a model eventually. Mean squared error (MSE) and time-dependent receiver operating characteristic curve were calculated for the models.

Results: The OS model included radiomics score with No. of HAIC cycles, tumor thrombus, PIVKA-II, neutrophil-lymphocyte ratio (NLR), aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (γ-GT) and C-reactive protein. And the PFS model included radiomics score with No. of HAIC cycles, tumor thrombus, NLR and γ-GT. The AlexNet-OS model, ResNet-OS model, and Inception-OS model achieved the best MSE of 1.0068, 0.9023 and 0.8506, respectively. The AlexNet-PFS model, ResNet-PFS model, and Inception- PFS model achieved the best MSE of 0.6658, 0.6819 and 1.1012, respectively.

Conclusions: The present models which integrated radiomics information and clinical factors helped predict OS and PFS of unresectable HCC patients undergoing HAIC treatment.

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991P Real-world comparison of trans-arterial chemoembolization and bland embolization for the treatment of hepatocellular carcinoma: A propensity score analysis

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Background: Although Trans-Arterial Chemoembolization (TACE) is the most common procedure for the treatment of intermediate stage hepatocellular carcinoma (HCC), scarce data have demonstrated the superiority of this approach over bland embolization (TAE). In this study we aimed to compare the effectiveness and liver-related complications of these two procedures through a propensity score matching (PSM) analysis.

Methods: We retrospectively reviewed a cohort of patients with intermediate stage HCC treated with first-line TAE (using Lipiodol) or TACE (using either drug-eluting beads or a chemotherapy-lipiodol emulsion) in three referral centers in San José, Costa Rica, between 2019 and 2021. The primary outcome was overall survival (OS). Secondary outcomes included time to systemic treatment, time to liver transplantation, and liver-related complications. A Cox proportional hazard model was used to identify predictors for OS after adjustment using a PSM (1:1 greedy nearest-neighbour matching).

Results: A total of 114 patients were analyzed, with 73 and 41 of them receiving TACE or TAE, respectively. All included patients had diagnosis of advanced chronic liver disease with a Child-Pugh score A in 72.8% of cases. After a median follow-up time of 15.8 months and PSM adjustment, no difference in terms of OS (Hazard Ratio: 1.25; 95% Confidence Interval 95%: 0.69 − 2.23; p = 0.45), time to systemic treatment (HR: 1.52; 95%CI: 0.52 − 4.41; p = 0.44), and transplantation-free survival (HR: 0.34; 95% CI: 0.22 − 2.84; p = 0.30) was observed between patients receiving TACE or TAE. After multivariate analysis only the Child-Pugh score was independently associated to OS (Table). The frequency of liver-related complications was similar among both groups (5 vs 7.5%; p=0.17).

Table: 991P Multivariate analysis for Overall Survival after PSM adjustement

Variable	Hazard ratio (95% Confidence Interval)	p value
Sex (female vs male)	0.95 (0.49-1.84)	0.876
ECOG performance status (0-1 vs 2)	0.52 (0.18-1.55)	0.235
Child-Pugh score (A vs B)	0.32 (0.15-0.66)	0.002*
Type of treatment (TACE vs TAE)	1.68 (0.84-3.33)	0.138

* Statistically significant at p<0.05

Conclusions: TAE and TACE provide similar long-term outcomes and liver-related complications in patients with intermediate HCC.

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992P Analyzing effectiveness and safety of standard-dose and low-dose bevacizumab combination with atezolizumab in patients with unresectable hepatocellular carcinoma: a multi-institutional study in Taiwan

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Background: IMbrave150 trial confirmed the better clinical benefits with 1200 mg of atezolizumab plus 15 mg/kg of bevacizumab (Atezo/Bev) than with sorafenib for patients with unresectable hepatocellular carcinoma (HCC). However, effectiveness and safety with low-dose bevacizumab still remained uncertain in real-world practice. Our study aimed to investigate this issue.

Methods: We conducted a retrospective cohort study by using the Chang Gung Research Database, a multi-institutional electronic medical records database in Taiwan. The eligible patients were locally advanced metastatic and/or unresectable HCC with newly prescribed Atezo/Bev as first-line treatment between January 1, 2020 and December 31, 2022. The index date was the time Atezo/Bev initiation. We classified patients into: (1) the standard-dose group (15 mg/kg bevacizumab), and (2) the low-dose group (< 15 mg/kg bevacizumab). The primary outcome was overall survival (OS) and secondary outcomes included progression-free survival (PFS) and bleeding events. We applied Kaplan-Meier curve to estimate median OS and PFS. Moreover, we used Cox regression model to analyze hazard ratio (HR) and 95% confidence interval (CI) between two group.

Results: We enrolled total 151 patients in our analysis, with 15 patients newly receiving standard-dose bevacizumab (mean [SD] age: 58.5 [10.8]; male: 60.0%) and 136 patients receiving low-dose bevacizumab (mean [SD] age: 61.9 [11.6]; male: 77.9%). With a median 10.1 months of follow-up, the median OS was 14.9 months (95% CI: 1.4 to not reached [NR]) for standard-dose group and 11.2 months (95% CI: 8.8 to 14.3) for low-dose group (HR: 0.78, 95% CI: 0.38-1.56, P=0.48). Also, the median PFS (8.4 vs. 5.7 months, P=0.59) and the rate for bleeding events (20.0% vs. 25.0%, P=0.23) were similar in both groups.

Conclusions: Our study demonstrated no significant difference in OS, PFS and bleeding events between patients receiving standard-dose and low-dose bevacizumab in combination with atezolizumab in real-world clinical practice. Further large scale study was suggested to confirm our findings.

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993P Thyroid dysfunction after atezolizumab and bevacizumab is associated with favorable outcomes in hepatocellular carcinoma (IMbrave150 and Korean patients cohorts)

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Background: The combination of atezolizumab and bevacizumab (Ate/Bev) has become the new standard of care as first-line systemic therapy for unresectable hepatocellular carcinoma (HCC). Although several studies have reported thyroid dysfunction after treatment with immune checkpoint inhibitors, the clinical and immunological significance of thyroid dysfunction in patients with Ate/Bev has not been comprehensively addressed. In this study, we aim to comprehensively evaluate the clinical and immunological implications of thyroid dysfunction in unresectable HCC patients treated with Ate/Bev.

Methods: This study enrolled 208 patients with unresectable HCC treated with Ate/Bev from three Korean cancer centers. Thyroid adverse events (AEs) were reviewed, and cytokines and T cells in the blood samples were analyzed at baseline. For external validation, we analyzed clinical outcomes according to thyroid AEs in patients treated with Ate/Bev in the IMbrave150 study.

Results: Forty-one (19.7%) out of 208 patients experienced thyroid dysfunction (hypothyroidism [17.3%] and thyrotoxicosis [5.8%]) after Ate/Bev treatment. The median time to onset of hypothyroidism and thyrotoxicosis after Ate/Bev treatment were 3.5 months and 1.3 months, respectively. Patients with thyroid AEs demonstrated significantly better results in terms of progression-free survival, overall survival, and objective response rate than those without thyroid AEs. These findings were still consistent even after adjusting for confounding factors. Furthermore, favorable survival outcomes in patients with thyroid AE were also validated in a cohort of IMbrave150 patients. While patients with thyrotoxicosis showed significantly lower level of baseline IL-6, patients with hypothyroidism did not show significant differences in circulating cytokine levels and $CD8^+$ T cell fractions.

Conclusions: A fraction of patients with HCC treated with Ate/Bev experienced thyroid dysfunction, and the development of thyroid AEs was associated with favorable clinical outcomes.

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994P Regorafenib (REG) in patients (pts) with unresectable hepatocellular carcinoma (uHCC) in real-world (RW) practice: Final analysis of the prospective, observational REFINE study by prior liver transplantation (PLT)

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Background: In the final analysis of pts with uHCC from the observational REFINE study (NCT03289273), treatment-emergent adverse events (TEAEs) were consistent with the global, phase 3 RESORCE trial (Kim YJ, ILCA 2022). Median overall survival (OS) in the overall cohort was 13.2 months. Pts with PLT are typically excluded from phase 3 clinical trials in HCC, including RESORCE. Here, we present the final analysis of pts with PLT in REFINE.

Methods: REFINE is an international, prospective, multicenter study that enrolled pts with uHCC for whom the decision to treat with REG was made by their physician before enrollment, according to the local health authority approved label. The primary aim was safety, including incidence of TEAEs (MedDRA v25) and dose modifications due to TEAEs. Secondary endpoints included OS and duration of treatment (DoT).

Results: Of the 1005 evaluable pts, 25 (2%) had PLT (median age, 60 [range 40—69] years; 60% Asian, 96% male). Most pts had ALBI grade 1 (60%), Child-Pugh A status (64%), ECOG performance status 0—1 (80%), and received prior sorafenib (92%); while none received prior immunotherapy. Furthermore, the most common HCC etiology was hepatitis B (68% vs 37% in pts with no PLT). Transarterial chemoembolization was the most common additional prior non-systemic treatment in the PLT subgroup (56%). Median DoT was numerically longer in the PLT vs non-PLT subgroup (5.5 [range 0.6—16.8] vs 3.7 [range <0.1—38.9] months). The most common TEAEs in the PLT subgroup were hand—foot skin reaction (52%), diarrhea (32%), and fatigue (24%). There were no grade 5 drug-related TEAEs in the PLT subgroup. Drug-related TEAEs leading to dose modification or permanent discontinuation were comparable in the PLT and non-PLT subgroups (44% vs 37% and 12% vs 16%, respectively). Median OS from start of REG treatment was similar in the PLT (15.8 months; 95% CI 10.1, 25.4) and non-PLT (12.8 months; 95% CI 11.4, 14.6) subgroups, and with the overall cohort.

Conclusions: Final data from the REFINE study confirm the safety and effectiveness of REG in pts with uHCC and PLT, consistent with findings from the overall cohort.

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995P Real-world treatment patterns, survival and costs in advanced hepatocellular carcinoma (aHCC) in Ontario, Canada

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Background: Our real-world study aimed to assess the current treatment landscape of aHCC in Ontario, Canada.

Methods: This retrospective cohort study used provincial-level databases from Ontario, Canada to identify patients diagnosed with aHCC between April 2010 and March 2019 with follow-up data available until March 2020. De novo stage IV disease and/or receipt of first line (1L) systemic therapy (ST) was used to establish an aHCC diagnosis. Baseline characteristics, treatment patterns, clinical outcomes, health care resource utilization and costs (in 2020 Canadian dollars) were determined.

Results: A total of 7,322 patients were identified using HCC diagnosis codes, of which 802 met the aHCC diagnosis criteria (82% male, median age 66 years). More than half (N=427) received 1L STs (98% sorafenib; <2% lenvatinib), a quarter (N=195) were untreated, and 9% (N=72) were given locoregional therapy without use of ST. Only 4% (N=19) of 1L treated patients were given a 2L treatment. The median time from diagnosis to 1L ST initiation was 2.3 months and median time on 1L ST was 2.4 months. Median overall survival (mOS) from diagnosis was 9.0 months (95% confidence interval [CI]: 7.8-10.3) and 2.7 months (95% CI: 2.3-3.3) for the treated and untreated cohorts, respectively. The mean total cost per 1L treated patient was $49,640, with oral medications as the main cost driver followed by inpatient hospitalizations.

Conclusions: Our study confirmed guarded prognosis of aHCC despite treatments with sorafenib, in keeping with mOS observed in clinical trials. Low uptake of 1L ST and subsequent uptake of 2L underscores high attrition rates likely related to the frailty of aHCC patients and lack of adequate ST options. Future studies will inform whether immunotherapy-based treatments in the latest years will improve ST uptake, attrition rates and health outcomes.

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996P Transarterial chemoembolization combined donafenib with/without programmed death-1 inhibitors for initially unresectable hepatocellular carcinoma in a multicenter retrospective study

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Background: For unresectable hepatocellular carcinoma (uHCC), the efficacy of transarterial chemoembolization (TACE) monotherapy is not satisfactory. Some studies have shown that TACE combined with molecular targeted drugs and programmed death-1 (PD-1) inhibitors shows potential synergistic effects that can prolong the overall survival (OS) of patients with uHCC. Donafenib is a new generation of multi-kinase inhibitor which is approved as the first line treatment for uHCC. This study aimed to evaluate the efficacy and safety of TACE combined with donafenib plus PD-1 inhibitor (TACE+DP) and of TACE combined with donafenib (TACE+D) for uHCC in a multicenter retrospective study.

Methods: The clinical data of patients with uHCC who had received TACE+DP or TACE+D as first-line treatment from six Chinese academic centers, from July 2021 to July 2022, were collected and retrospectively analyzed. In the TACE+DP group, patients received intravenous administration of PD-1 inhibitor every three weeks and oral donafenib (0.2 g) twice daily until intolerable toxicity or disease progression. In the TACE+D group, patients received the same dose of donafenib 3-5 days after TACE. Overall survival (OS), progression-free survival (PFS), and tumor responses were evaluated between the two groups according to the modified RECIST criteria.

Results: A total of 157 patients in the TACE+D group and 166 patients in TACE+DP group were included in this study. Patients in the TACE+DP group had longer median OS (18.1 vs 13.2 months, P<0.001) and longer median PFS (10.6 vs 7.9 months, P<0.001) than those in the TACE+D group. Patients in the TACE+DP group achieved a higher ORR (50.6% vs 41.4%, P=0.019) and a higher disease control rate (DCR) (89.2% vs 82.8%, P=0.010) than those in the TACE+D group. There was no significant difference in the incidence and severity of adverse events in the TACE+DP and TACE+D groups (any grade, 92.9% vs. 94.6%, P=0.270; grade 3 or 4, 33.8% vs. 37.3%, P=0.253).

Conclusions: With favorable safety and tolerability, TACE combined donafenib with PD-1 inhibitors significantly improves PFS, OS, and ORR over TACE combined with donafenib.

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997P A practical risk classification of early recurrence and long term survival outcomes in hepatocellular carcinoma patients with microvascular invasion after curative hepatectomy: A decision tree analysis

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Background: Microvascular invasion (MVI) is an independent poor factor for early recurrence (ER) and long-term outcomes in hepatocellular carcinoma (HCC) after hepatectomy. A practical, convenient, and accurate risk classifications is urgently needed to predict ER risk in HCC patients with MVI and to guide those patients to choose suitable adjuvant therapies to reduce postoperative recurrence risks and prolong long-term survival.

Methods: Data of 440 HCC patients with MVI after curative hepatectomy were retrospectively reviewed. They were randomly divided into a training set and a validation set. Kaplan-Meier curves and Cox regression analyses were used to identify independent prognostic factors of ER. Classification and regression tree (CART) analysis was used to develop ER risk classification in the training set and verified in the validation set.

Results: Multivariate analysis revealed that seven factors, namely, hepatitis B virus deoxyribonucleic acid load, tumor size, Edmondson-Steiner grade, MVI classification, satellite nodules, Ki67 positive index, and cytokeratin 19 expression were independent risk indexs for ER in HCC patients with MVI. The CART strategy showed a good concordance statistics of 0.77 in predicting ER risk, and had a better net benefit and a wider threshold probability range, as well as had a good agreement between the predicted value and actual observed value. The area under the time-dependent receiver operating characteristic curve of the CART strategy in predicting 1-, 3-, and 5-years recurrence-free survival (RFS) were 0.75, 0.78, and 0.84, respectively, and the corresponding overall survival (OS) were 0.74, 0.74, and 0.72, respectively, which were all significantly higher than other eight commonly classic HCC system stages (BCLC stage, Okuda stage, TNM stage, CNLC stage, French stage, CLIP score and JIS score). The ER, RFS and OS were greatly discrepancies between patients that had been stratified into three risk groups. Similar results were obtained in the validation set.

Conclusions: The CART strategy achieved optimal prediction for ER, RFS and OS for HCC patients with with MVI after curative hepatectomy.

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998P Efficacy and safety of curative hepatectomy after conversion therapies for initial unresectable hepatocellular carcinoma: A multicenter propensity score matching study

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Background: Conversion therapy potentially converts the intermediate/advanced Barcelona Clinical Liver Cancer stage hepatocellular carcinoma (HCC) and unresectable HCC become resectable HCC. Patients have chronic liver injury caused by chronic liver diseases and conversion therapies and acute liver injury after hepatectomy. This study evaluated the efficacy and safety of curative resection for HCC after conversion therapy.

Methods: 1220 HCC patients underwent initial curative resection and 142 patients received conversion therapies following curative resection were recruited from Guangxi Medical University Cancer Hospital and Eastern Hepatobiliary Surgery Hospital and divided into initial resected HCC (ir-HCC) group and converted resected (cr-HCC) group. Conversion strategies were detailed in the table. Covariate differences between the two groups were balanced by one-to-one propensity score matching (PSM). Overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups. Risk factors of OS, RFS and severe post-hepatectomy liver failure (sPHLF) were determined.

Table: 998P Conversion therapeutic strategies

Conversion therapy	Patients (n = 142)
TACE	34
TACE+Radiotherapy	9
HAIC	3
Radiotherapy	1
TKI+ICIs	2
HAIC+TKI	1
HAIC+TKI+ICIs	6
HAIC+TAE+TKI	1
HAIC+TAE+TKI+ICIs	2
HAIC+Radiotherapy+TKI+ICIs	1
TACE+TKI	6
TACE+ICIs	5
TACE+TKI+ICIs	49
TACE+Radiotherapy+TKI+ICIs	8
TACE+Radiotherapy+TKI	2
Radiotherapy+ICIs	1
Radiotherapy+TKI+ICIs	12

Results: 131 pairs were matched in ir-HCC group and ir-HCC group by PSM. The cr-HCC group had better mean RFS than ir-HCC group (16.2 *vs.* 12.7 months, *P*=0.011), but not mean OS (19.8 *vs.* 19.3 months, *P*=0.181). SPHLF rate was higher in cr-HCC

group (34.4% *vs.* 19.1%, P=0.005). 90-day mortality showed no differences between the two groups (3.1% *vs.* 3.8%, P=0.734). Conversion therapy independently related to RFS and sPHLF, but not OS. Regional therapies increased the risk of sPHLF in cr-HCC group than ir-HCC group ($P<0.05$). There was no difference in sPHLF between regional therapy with and without systematic regimens in cr-HCC group.

Conclusions: cr-HCC patients after curative resection had prolonged RFS but prone to sPHLF. Regional therapies was mainly responsible for sPHLF regardless combined systematic regimens.

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999P Donafenib combined with hepatic artery infusion chemotherapy (HAIC) and sintilimab for unresectable hepatocellular carcinoma (uHCC): A prospective, single-arm phase II trial (DoHAICs study)

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Background: Both donafenib and anti-PD-1 antibodies are indicated for uHCC, HAIC significantly improved treatment response over TACE in patients (pts) with large uHCC in a phase III trial. Considering the different mechanisms, this study aimed to investigate the safety and efficacy of donafenib combined with HAIC and sintilimab in pts with uHCC.

Methods: This is a prospective, single-arm phase II study. Pts with histologically diagnosed uHCC, no previous systemic treatment, Child-Pugh A5-B7, ECOG performance status (PS) of 0 or 1 were eligible for inclusion. Enrolled pts received donafenib (200 mg, bid), sintilimab (200 mg, q3w) and HAIC (oxaliplatin 85 mg/m^2 2h, leucovorin 400 mg/m^2 2h, fluorouracil bolus 400 mg/m^2 in the first 10 minutes, and fluorouracil infusion 1200 mg/m^2 for 23 hours, q3w) until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR).

Results: From Dec 2021 to Apr 2023, 30 pts were enrolled: BCLC stage A/B/C: 4/10/16; Child-Pugh class A/B: 29/1; ECOG PS 0/1: 29/1. The median tumor size was 7.9 cm, 46.7% pts presented macro vascular invasion, 10.0% had extrahepatic metastasis. As of May 6, 2023, the median follow-up time was 102 days, the median number of HAIC was 3 times (range, 1-8). Based on mRECIST, the ORR was 82.1% (95% CI, 63.1% - 93.9%) with 4 (14.3%) complete responses (CR) and 19 (67.8%) partial responses (PR). The disease control rate (DCR) was 96.4% (95% CI, 81.7% - 99.9%). Of 28 pts evaluable for response, the conversion success rate was 64.3% (18/28), 13 of them received hepatectomy, 5 cases (38.5%) achieved complete pathological response and 6 cases (46.2%) achieved major pathological response. The median time to response (TTR) was 2.1 months. The median progression-free survival (PFS) was 10.2 months (95% CI, NR). The most common treatment-emergent adverse events (TEAEs) were thrombocytopenia, anemia and neutropenia. Grade 3-4 TEAEs occurred in 33.3% of pts. No grade 5 TEAEs were observed.

Conclusions: Combination treatment with donafenib and HAIC plus sintilimab showed promising clinical benefits and acceptable toxic effects in pts with uHCC. The enrollment and follow-up are continuing.

Clinical trial identification: NCT05166772.

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1000P Real-world clinical outcomes of cabozantinib (cabo) as a second-line (2L) treatment for advanced hepatocellular carcinoma (aHCC)

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Background: Cabo is approved in aHCC patients (pts) with prior sorafenib use. With rapid changes in the first-line (1L) treatment landscape, including use of immuno-oncology (IO) based regimens, this study aims to understand the real-world clinical outcomes of 2L cabo following different 1L therapies in aHCC.

Methods: This retrospective analysis used Komodo Health, Inc. data and included adult pts with aHCC in the US who initiated a 1L regimen between Jan 2017 and Oct 2022 and received 2L cabo. Pts were assigned to 3 cohorts based on 1L therapies: (1) tyrosine kinase inhibitor (TKI) monotherapy (mono), (2) IO+non-IO combination (combo), and (3) IO mono or IO+IO combo. Time to discontinuation (TTD) and time to next treatment or death (TNTD) for 2L cabo were evaluated for each cohort using the Kaplan−Meier method and compared using the log-rank test. Starting dose, dose reduction, and adverse events (AEs) of 2L cabo were described.

Results: 160 pts with 2L cabo were included, among whom 68 (42.5%) received 1L TKI, 62 (38.8%) 1L IO+non-IO, and 30 (18.8%) 1L IO mono or IO+IO. Baseline characteristics reflected the real-world aHCC population. The most common regimens were lenvatinib (61.8%) in the TKI cohort, atezolizumab + bevacizumab (91.9%) in the IO+non-IO cohort, and nivolumab (73.3%) in the IO mono or IO+IO cohort. The median (95% CI) TTD for 2L cabo was 3.8 (2.9, 4.9) months in the TKI cohort, 2.9 (2.1, 4.5) in the IO+non-IO cohort, and 2.8 (2.0, 6.8) in the IO or IO+IO cohort. The median (95% CI) TNTD for 2L cabo was 6.5 (5.6, 13.4), 8.6 (5.6, not estimated [NE]), and 10.7 (7.6, NE) months, respectively. The differences in TTD and TNTD among cohorts were not statistically significant (p=0.23 and 0.43, respectively). Among all pts, 74 (46.3%) started cabo at 60 mg and 29 (39.2%) reduced dose, while 60 (37.5%) started at 40 mg and 11 (18.3%) reduced dose. Observed AE rates were as expected with cabo use in previous studies.

Conclusions: This study demonstrates the real-world effectiveness and safety of cabo in 2L aHCC following prior TKIs or IO-based regimens. TNTD, a proxy of progression-free survival, was consistent across different 1L therapies.

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1001P Patients' prioritization of treatment goals in hepatocellular carcinoma (HCC): A global qualitative observational study (PERIDOT)

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Background: Patients with cancer have reported an unmet need regarding education of all treatment options available to them and their impact on survival and quality of life (QoL). This is especially true for patients with HCC in a time of new treatment options like immunotherapy. This study qualitatively explored patients' prioritized treatment goals and cross-referenced them to those of treating physicians.

Methods: Qualitative semi-structured interviews were conducted with patients with HCC and physicians who managed their care in the US, Germany, France, and Japan. Interviews were conducted with physicians (n=12, n=3 per country) and patients (n=51 [10-15/country]) with early (n=20), intermediate (n=15), or advanced (n=16) HCC. Qualitative data were analyzed using directed content analysis techniques and quantitative demographic data were descriptively summarized.

Results: Patients shared a wide range of physical and emotional impacts when describing their HCC journey including fatigue, nausea, appetite loss, diarrhea, and pain. Patients described their role in treatment decision-making as passive but most felt well-informed and involved. Patients described that overall survival (OS) and QoL were most important, in addition to avoiding relapse and disease progression, and were generally similar across the three stages of HCC. Patients did not refer to side effects/safety of treatment as specific treatment considerations but prioritized their overall QoL as an important factor in their treatment decision-making. Physicians identified OS, progression-free survival, and safety/tolerability as important treatment goals and reported that they discussed realistic goals with patients. Treatment pathways and physician decision-making were mainly based on country-specific guidelines and multidisciplinary tumor board recommendations.

Conclusions: Extending survival and improving QoL were important treatment goals for patients. Discussing the benefits and risks of available treatment options with patients is important to ensure they have the opportunity to achieve outcomes aligned to their treatment goals.

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1002P Efficacy and safety of tislelizumab combined with TKIs and FOLFOX4-HAIC in conversion therapy of unresectable hepatocellular carcinoma

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Background: TKIs,ICIs and FOLFOX-HAIC has shown high conversion success rates in unresectable hepatocellular carcinoma(uHCC) patients. This study aimed to evaluate the efficacy and safety of tislelizumab combined with TKIs and FOLFOX4-HAIC as first-line conversion therapy in this population.

Methods: Between April, 2021, and March, 2023, we retrospectively analyzed clinical data of patients with uHCC who underwent tislelizumab ,TKIs(Lenvatinib, Donafenib) and FOLFOX4-HAIC. The primary outcome included ORR, DCR, conversion resection rate (CRR) and TRAEs. Data were expressed as median (range).

Results: A total of 31 patients (27 male, 4 female) completed conversion therapy assessment until the last follow-up time (April 27, 2023). Lenvatinib was administered in 23 patients and donafinib in 8 patients. The patients were characterized with a median age of 54.2 years (34-75), 6 patient with BCLC stage B, 24 patients with BCLC stage C, and 1 patient with HCC postoperative recurrence with intrahepatic metastasis. According to mRECIST criteria, tumor shrinkage was observed in 30 patients, with an ORR of 93.5% (29/31, including 61.3%[19/31] complete response), DCR of 96.8%(30/31), and median time to response(mTTR) of 1.35months (0.7-3.0). Successful conversion was observed in 24 (77.4%) of 31 patients per mRECIST. As of cut-off date, the actual CRR and pathological complete response(pCR) were 29.0%(9/31) and 66.7% (6/9), respectively. There was no operative death, and 1 recurrence after operation. With a median follow-up time of 16.2 months, median progression-free survival(PFS) and overall survival(OS) were not reached. During the follow-up period, 9 patients developed disease progression with a median time to progression(mTTP) of 6.3 months (1-17.8), of whom 5 died due to disease progression. Most common TRAE was aspartate aminotransferase(AST) increased (26 patients, 83.8%).Grades 3 TRAEs occurred in 19 patients (61.3%). All TRAES were tolerable and manageable.

Conclusions: Tislelizumab combined with TKIs and FOLFOX4-HAIC showed high conversion rate and acceptable toxicity in the treatment of uHCC, suggesting that this combination could be considered as a new conversion strategy in this population.

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Disclosure: All authors have declared no conflicts of interest.

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1003P Efficacy and safety of triple combination therapy with transarterial chemoembolization (TACE), tyrosine kinase inhibitor (TKI), and immune checkpoint inhibitor (ICI) versus dual combination therapy in unresectable hepatocellular carcinoma (uHCC): A systematic review and meta-analysis

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Background: Multimodal approach, a combination of various treatment modalities, has emerged as a potential approach for treating uHCC. It is utilized to help relieve tumor burden, slow progression, and provide survival benefits to patients. However, controversies remain in using a multimodal approach in the management of uHCC, and is still debatable. This study aims to evaluate the efficacy and safety of triple combination therapy composed of Transarterial chemoembolization (TACE), TKI, and ICI compared to dual combination therapy (TACE+TKI, TKI+ICI).

Methods: Eligible studies published before March 30, 2023 were retrieved. Outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and occurrence of adverse events (AEs). Literature search was done using through PubMed, Embase, and Cochrane Library. Risk of bias assessment was done using ROBINS-I tool.

Results: Thirteen retrospective studies were included representing 1005 patients with uHCC. There was low to moderate bias among the studies. Triple combination therapy was associated with a significant improvement in survival compared to dual combination therapy: median OS, pooled HR 0.46 (95% CI: 0.39-0.54, $p<0.00001$) and median PFS, pooled HR 0.41 (95% CI: 0.28-0.61, $p<0.00001$). Triple combination therapy was also associated with a significant increase in tumor response compared to dual combination therapy: ORR, pooled RR 1.76 (95% CI: 1.51-2.06, $p<0.00001$), and DCR, pooled RR 1.36 (95% CI 1.24-1.49, p-<0.00001). However, triple combination therapy had a higher risk of adverse events compared to dual combination therapy, pooled RR 1.49 (95% CI: 1.19, 1.86, $p=0.0004$). There was no significant heterogeneity found among the studies included.

Conclusions: Triple combination therapy was associated with significantly better outcomes but higher risk of adverse events than dual combination therapy in patients with uHCC so careful consideration of the risks and benefits must be done before initiating treatment.

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1004P Comparative efficacy of systemic sequential regorafenib after sorafenib or lenvatinib treatment failure for advanced hepatocellular carcinoma: A retrospective, multi-center, real-world study

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Background: Regorafenib is an oral multikinase inhibitor and has been approved as the 2nd-line systemic treatment for advanced hepatocellular carcinoma (HCC) based on the RESORCE trial. However, the efficacy of systemic sequential regorafenib after lenvatinib treatment failure in advanced HCC patients remains unclear.

Methods: A total of 94 patients with advanced HCC who failed sorafenib or lenvatinib treatment and received regorafenib from three cancer centers were included between January 2019 and December 2022. The 1st-line therapeutic plans, disease control rate (DCR) (defined by the RECIST 1.1), and progression-free survival (PFS) were recorded and compared.

Results: A higher percentage of patients with BCLC C stage was observed in the 1st-line lenvatinib group (n=50) than in the sorafenib group (n=44) when we compared the clinical characteristics before regorafenib treatment (81% *vs.* 41%, $p = 0.002$). The median treatment duration of regorafenib was 4.73 months in the sorafenib group and 2.60 months in the lenvatinib group. The intrahepatic, extrahepatic, and overall DCRs of sequential regorafenib after sorafenib or lenvatinib treatment failed were 0.82 and 0.67 ($p = 0.20$), 0.69 and 0.72 ($p = 0.50$), 0.76 and 0.63 ($p = 0.20$), respectively. The overall DCRs of regorafenib were 0.73 and 0.67 in those with and without a combination of immune checkpoint inhibitor (ICI) treatment ($p = 0.20$), respectively. Survival analysis indicated that the median PFS (mPFS) were 4.13, 2.78, and 3.53 months in the 1st-line sorafenib, lenvatinib, and entire groups, respectively ($p = 0.30$). No survival differences were observed between the patients who received 1st-line treatment with or without a combination of ICI reagents (mPFS: 3.2 and 3.7, $p = 0.07$, respectively).

Conclusions: This retrospective, multi-center, real-world study demonstrated that regorafenib could improve the prognosis of patients after lenvatinib treatment failure. Combined ICIs or not in the 1st-line treatment may not affect the short-term efficacy of 2nd-line regorafenib treatment. This study is ongoing, and further conclusions related to overall survival are expected to be published in the future.

Legal entity responsible for the study: All authors in this study.

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1005P Atezolizumab plus bevacizumab combined with transarterial chemoembolization and hepatic arterial infusion chemotherapy for unresectable hepatocellular carcinoma with high tumor burden

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Background: Despite the availability of effective systemic therapies such as atezolizumab plus bevacizumab (A+B), the response rate remains unsatisfactory for patients with unresectable hepatocellular carcinoma with high tumor burden (uHTB-HCC). Our previous studies indicated that transarterial chemoembolization (TACE) combined with FOLFOX-based hepatic arterial infusion chemotherapy (HAIC) showed favorable results for HCC. This study aims to evaluate the efficacy and safety of A+B combined with TACE-HAIC for uHTB-HCC.

Methods: This retrospective study included uHTB-HCC (meeting at least one of the following criteria: beyond up-to-11, VP 3-4, extrahepatic metastases) pts who received TACE-HAIC followed by atezolizumab (1200mg IV) and bevacizumab (15mg/kg IV q4w) between March 2022 and December 2022. Efficacy was evaluated based on tumor response and survival rates, while safety was assessed by adverse events (AEs).

Results: Thirty-five uHTB-HCC pts received A+B combined with TACE-HAIC. Based on mRECIST criteria, the objective response rate (ORR) was 68.6%, with 8 (22.9%) pts achieved complete response, 16 (45.7%) partial response, 4 (11.4%) stable disease, and 7 (20.0%) progression disease. Additionally, 5 (14.3%) pts underwent curative hepatectomy after being converted to resectable HCC. The 1-year overall survival and progression-free survival rates were 94.3% and 71.4%, respectively. Of the 32 (91.4%) pts who experienced treatment-related adverse events (AEs), 13 (37.1%) had grade 3-4 AEs, but no treatment-related deaths occurred.

Table: 1005P

	RECIST 1.1 (%)	mRECIST (%)
CR	0 (0)	8 (22.9)
PR	22 (62.9)	16 (45.7)
SD	6 (17.1)	4 (11.4)
PD	7 (20)	7 (20.0)
ORR	22 (62.9)	24 (68.6)

Conclusions: The results suggested that A+B combined with TACE-HAIC was a promising treatment option for uHTB-HCC pts, given its excellent therapeutic efficacy and manageable adverse events.

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1006P Associations of online search trends and prescription trends for hepatocellular carcinoma drugs

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Background: Hepatocellular Carcinoma (HCC) is a major contributor to cancer-related deaths globally. Advancements in immune and molecular therapies have led to more targeted and safer systemic treatments for advanced and unresectable HCC, replacing the use of non-specific chemotherapies. This study aims to provide an overview of online search and prescription activity of drugs used for HCC.

Methods: Data from IQVIA National Prescription Audit, a comprehensive audit of nearly all monthly US prescription information, was collected from 2017 to 2022 for FDA-approved HCC drugs. Online searches for these drugs were analyzed for visual and quantitative (Spearman's) correlation.

Results: Online searches for HCC drugs in the US increased 1.17-fold between the first quarter(Q1) 2017 and Q4 2022, while prescriptions increased 5.93-fold during this period. Across first line therapies, lenvatinib was most used with a 27.62-fold increase(Q1 2019-Q4 2022), paralleled by a 1.52-fold increase in online searches. Sorafenib use, however, steeply declined by 17.56-fold(Q1 2019-Q4 2022). For second-line and later treatments, cabozantinib was most frequently applied with 3.04-fold increase and 1.62-fold rise in online searches(Q1 2017-Q4 2022). Immunotherapy prescriptions and online searches for pembrolizumab have surged from Q1 2017-Q4 2022, with an increase of 8.03-fold and 1.37-fold, respectively. Lenvatinib (r=0.90), cabozantinib (r=0.67), and pembrolizumab (r=0.54) had the highest correlations between online searches and prescriptions, and all three showed increasing trends. Oncologists(72.40%) were the largest users of the across specialties in 2022, followed by physician assistants/nurse practitioners(16.53%).

Conclusions: Over a 5-year period, the utilization of HCC drugs in the US increased and prescription patterns changed due to positive trial results and guideline changes. There was a positive correlation between online searches and prescription trends for HCC drugs.

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1007P Network meta-analysis (NMA) of lenvatinib vs key comparators in first-line unresectable hepatocellular carcinoma (uHCC)

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Background: This research compared the relative efficacy of lenvatinib monotherapy (mono), a standard of care for treatment of uHCC, versus approved / anticipated comparators. Using inverse probability of treatment weighting (IPTW) and an NMA, updated evidence for lenvatinib mono from LEAP-002, in addition to evidence from REFLECT, were included in the analyses.

Methods: Randomized controlled trials (RCTs) were identified via systematic literature review. REFLECT and LEAP-002 investigated lenvatinib mono in uHCC, with patient-level data available for each, however, only REFLECT had a comparator arm of interest. To utilise all available lenvatinib data, the lenvatinib arm from LEAP-002 was adjusted to match aggregate data for confounding factors from REFLECT using IPTW.

Weighted Cox regression including matching variables as covariates were used to derive hazard ratios (HRs) for OS and progression-free survival (PFS) comparing lenvatinib and sorafenib. The estimated HRs were included in fixed-effects Bayesian NMAs to compare lenvatinib and comparators. Scenario analyses explored alternative choices for IPTW estimators.

Results: Eight RCTs (including REFLECT) and adjusted data from LEAP-002, were included in the NMA. Lenvatinib demonstrated a significant improvement in OS compared with sorafenib, and significant improvement in PFS compared with sorafenib, tremelimumab + durvalumab, tislelizumab and durvalumab (Table).

Table: 1007P NMA results for OS and PFS — lenvatinib vs comparator

Comparator	OS; median HR (95% CrI)	PFS; median HR (95% CrI)
Sorafenib	**0.75 (0.66, 0.86)**	**0.57 (0.49, 0.66)**
Durvalumab	0.88 (0.71, 1.08)	**0.55 (0.45, 0.69)**
Tislelizumab	0.88 (0.71, 1.11)	**0.51 (0.41, 0.65)**
Tremelimumab 300 mg + durvalumab	0.97 (0.77, 1.20)	**0.63 (0.51, 0.78)**
Atezolizumab + bevacizumab	1.14 (0.86, 1.51)	0.87 (0.67, 1.13)
Camrelizumab + apatinib	1.21 (0.92, 1.60)	1.09 (0.82, 1.44)

Bold = significant result
Abbreviations: CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival

Conclusions: These results suggest that patients with uHCC treated with lenvatinib mono have similar or significantly improved OS and PFS when compared with other therapies.

Legal entity responsible for the study: Eisai Inc.

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1008P The safety and efficacy of PD-1 inhibitor (Sintilimab) combined with conventional transarterial chemoembolization (cTACE) for the initial treatment of the stage BCLC B hepatocellular carcinoma (HCC) beyond up-to-seven criteria

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Background: TACE is the first choice for patients (pts) with intermediate-stage HCC. Numerous studies have demonstrated the limited survival benefit of TACE alone in pts with stage BCLC B, particularly in tumor beyond up-to-seven criteria. Single immunotherapy agent showed a certain effect for unresectable HCC pts, but still with unsatisfactory. This study was designed to explore the efficacy and safety of sintilimab plus cTACE for HCC with stage BCLC B (or stage CNLC IIa-IIb) beyond up-to-seven criteria.

Methods: This is a single-arm, phase II study(NCT04842565). Eligible HCC pts were treated cTACE and sintilimab (200mg, IV, Q3W). The first sintilimab dose was given after the first cTACE, and then every 3 weeks. The primary objectives were safety and progression-free survival (PFS). Secondary objectives included ORR assessed by both RECIST v1.1 and mRECIST v1.1, overall survival (OS), and disease control rate (DCR).

Results: From Oct 2020 to Feb 2023, 20 pts were enrolled with a median age of 62 years. All pts were BCLC stage B, and 45.0% (9/20) were CNLC IIa stage, 55.0% (11/20) were IIb stage. At median follow-up duration of 9.0 months, the ORR was 30.0%(95% CI: 14.6%-51.9%) per RECIST, and 60% (95%CI: 38.7%-78.1%) per mRECIST. The DCR was 95.0% (95% CI: 76.4%-99.1%) per both RECIST and mRECIST. Median PFS(by both RECIST and mRECIST) was 7.95 months (95% CI: 2.7-NA), and the median OS was not reached. Four pts converted to curative surgical resection. The optimal cut-off value of PLR(platelet-to-lymphocyte ratio) predicted tumor shrinkage was 100. Low PLR were associated with more tumor shrinkage. The most common TRAEs were hypothyroidism (37.5%), elevated aspartate aminotransferase (10.0%), rash(5.0%). Only one patient experienced grade 3 TRAE(myocarditis) and no treatment-related deaths were reported.

Conclusions: Combination of Sintilimab and cTACE showed promising antitumor activity and manageable toxicity in pts with HCC with BCLC stage B (CNLC stage IIa-IIb) beyond up-to-seven criteria. The PLR is promising predictor for tumor shrinkage in HCC. These strategy should be validated in a large randomized controlled trial.

Clinical trial identification: NCT04842565.

Legal entity responsible for the study: Zhongshan hospital affiliated to Fudan University.

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1009P Network meta-analysis of first-line systemic therapies for advanced hepatocellular carcinoma: A comparison of objective response rates

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Background: Advanced hepatocellular carcinoma (HCC) is a highly lethal disease with limited treatment options. The use of first-line (1L) systemic therapies showcase improved overall survival and quality of life. This study aimed to compare the objective response rate (ORR) of various systemic therapies for advanced HCC in 1L setting using a network meta-analysis.

Methods: A systematic literature review (SLR) and network meta-analysis (NMA) of randomized controlled trials (RCTs) was conducted to assess the efficacy of 1L systemic therapies for advanced HCC. Multiple databases, including PubMed, Embase, and the Cochrane Library were searched for relevant studies. The primary outcome of interest was the ORR of each therapy compared to placebo. The results were obtained for both fixed and random-effect models to estimate each therapy's relative risk (RR) and 95% credible intervals (CrI).

Results: A total of 12 RCTs met the inclusion criteria. The combination therapy of sintilimab + IBI305 had the highest ORR, with an RR of 13.6 (95% CrI: 3.69, 55.67) using fixed-effect and RR of 14.13 (95% CrI: 0.82, 120.1) using random-effect models. SUCRA values ranged from 0.075 for placebo to 0.761 for sintilimab + IBI30. SUCRA rankings were generally better for combination therapies followed by mono-therapies and placebo.

Conclusions: The NMA revealed that the combination therapies had the highest ORR among the systemic therapies in the 1L setting. The SUCRA values confirmed the high probability of these treatments ranking higher in terms of ORR and can be used to support treatment decision-making in clinical practice.

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1010P A parametric network meta-analysis of first-line systemic therapies for advanced hepatocellular carcinoma related to overall survival

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Background: Advanced hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Several first-line systemic therapies have been developed to treat advanced HCC, but their comparative effectiveness remains unclear. This study aimed to conduct a parametric network meta-analysis of first-line systemic therapies for advanced HCC related to overall survival.

Methods: We conducted a systematic literature review of randomized controlled trials assessing first-line systemic therapies for treating adults with locally advanced or metastatic unresectable HCC. The data sources included biomedical databases (Embase, MEDLINE, and CENTRAL), relevant conferences, and grey literature searches. We used the Bayesian framework to perform the analysis, and the distribution of the survival data was modeled using five different parametric distributions. We used deviance information criteria (DIC) to evaluate the goodness of fit of each model. The proportional hazards (PH) assumption was also tested.

Results: The parametric network meta-analysis included 9 randomized controlled trials involving 10 treatments. The log-normal distribution provided the best fit to the survival data, with a DIC value of 3558.4. At 12 months, the highest overall survival rate was seen in the Durvalumab group, with 43% of patients still alive. This was followed by Atezolizumab + bevacizumab, STRIDE, Nivolumab, Donafenib, and sintilimab plus IBI30. The lowest overall survival rates were seen in the Placebo group (17%) and Sorafenib group (28%). At 60 months, the overall survival rate was salmost same among the active treatments.

Conclusions: Parametric NMA is the most preferred method in case of violation of the proportional hazard assumption. Durvalumab and atezolizumab plus bevacizumab were the most effective first-line systemic therapies for advanced HCC in terms of overall survival. These findings can inform treatment decisions for patients with advanced HCC. However, additional studies are needed to confirm these findings and to evaluate the long-term efficacy and safety of these treatments.

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Disclosure: All authors have declared no conflicts of interest.

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1011P A prospective study of TACE combined with lenvatinib plus sintilimab for HCC with portal vein tumor thrombus

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Background: Portal vein tumor thrombus (PVTT) has a high incidence and poor prognosis in hepatocellular carcinoma (HCC) patients, and the treatment demand for such patients is currently unmet. This study aimed to evaluate efficacy and safety of transarterial chemoembolization (TACE) combined with lenvatinib and sintilimab in HCC with PVTT.

Methods: In this prospective study, eligible participants were enrolled and randomized (1:1) into TACE combined with lenvatinib and sintilimab (TACE-LEN-SIN) group and TACE combined with lenvatinib (TACE-LEN) group. The primary endpoint was progression-free survival (PFS), and the secondary endpoints included overall survival (OS), objective response rate (ORR) and disease control rate (DCR) according to mRECIST, and safety.

Results: 116 patients were enrolled from January 2022 to December 2022, 58 patients in each group. Patients had a median age of 50 (range, 51-64.2) years and mostly were male (80.2%). Hepatitis B virus infection was the main cause of HCC (85.3%). 37 (31.9%) patients had extrahepatic metastases. As of April 2023, 49 (84.5%) patients in the TACE-LEN group had disease progression and 38 (65.5%) died, while 37 (63.8%) patients in the TACE-LEN-SIN group had disease progression and 16 (27.6%) died. Both median PFS (4.17 vs. 3.33 months, $P = 0.01$) and median OS (not reached (NR) vs. 8.53 months, $P = 0.003$) in the TACE-LEN-SIN group were significantly longer than those in the TACE-LEN group. ORR (22.4% vs. 12.1%, $P = 0.219$) and DCR (69.0% vs. 53.4%, $P = 0.127$) were slightly higher in the triple group than in the dual group. The results of multivariate Cox regression also found that TACE-LEN-SIN treatment was an independent protective factor for PFS (HR: 0.62, 95% CI: 0.40 − 0.95, $P = 0.028$) and OS (HR: 0.45, 95% CI: 0.25 − 0.82, $P = 0.008$). The most common adverse events (AEs) were hypertension, diarrhea and fatigue. And no significant differences in the incidence of AEs between the two groups, except for those related to Sintilimab.

Conclusions: TACE combined with lenvatinib and sintilimab improved survival outcomes without increasing the unpredictable safety profile compared with TACE combined with lenvatinib for HCC with PVTT.

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1012P First-in-human study of ABSK-011, a novel, highly selective fibroblast growth factor receptor (FGFR) 4 inhibitor for treating advanced hepatocellular carcinoma (HCC) with FGF19 overexpression

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Background: FGF19 overexpression (+) is in ∼ 30% of HCC with poor prognosis, and studies suggested FGF19/FGFR4 signaling axis could be a therapeutic target for HCC. ABSK-011 is an oral, highly selective, and potent FGFR4 inhibitor for treating FGF19+ HCC.

Methods: The ongoing phase I study (NCT04906434) is to evaluate the safety, PK, PD, and preliminary efficacy of ABSK-011. ABSK-011 was given QD or BID orally in 28-day cycles.

Results: As of 30 JUN 2023, 75 patients (pts) were dosed with ABSK-011 ranging from 60 mg to 400 mg QD (N=48), and 160 mg to 220 mg BID (N=27); median age 53.0 y, 82.7% male, 69.3% ECOG PS 1. 72 pts were HCC, 95.8% with prior therapies, 79.2% FGF19+. 160 mg BID and 220 mg BID were selected as recommended doses of expansion (RDE) and all BID pts were FGF19+. Dose-limiting toxicities were observed in 2 pts (both 400 mg QD): diarrhea, ALT increased (↑), AST↑ and hyperbilirubinemia in 1 pt, hypokalemia in 1 pt. Most common treatment-related adverse events (TRAE) (any grade/≥G3) were diarrhea (72.0%/5.3%), ALT↑ (70.7%/10.7%), AST↑ (57.3%/9.3%), hyperphosphataemia (41.3%/0), blood bilirubin↑ (30.7%/1.3%), total bile acids↑ (21.3%/0). G3/4 TRAEs occurred in 29.3% of all pts (14.8% in BID). No G5 TRAE. One complete response (CR) and 12 partial responses were reported by investigator assessment per RECIST 1.1 (including unconfirmed) among the 65 evaluable HCC pts with prior therapies. Longest duration of response (DoR) was 13.1 m and mDoR is not yet mature, with majority of responses ongoing. BID dosing showed encouraging efficacy with an overall response rate (ORR) of 43.5% (10/23, 1 CR), including 6 responders in 160 mg BID (6/18, 33.3%) and 4 in 220 mg BID (4/5, 80.0%). ABSK-011 demonstrated a favorable PK property approximately linear and time-invariant with higher C_{trough} and lower C_{max} at BID vs QD with comparable total daily dose. Pathway inhibition was observed by increased C4, total bile acids, FGF19, and decreased total cholesterol at all dose levels.

Conclusions: The promising response rate and manageable safety profile from this phase I study suggest that ABSK-011 may have clinical benefit for HCC pts with prior therapies through biomarker selection of FGF19.

Clinical trial identification: NCT04906434.

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1013TiP Refinement and validation of a comprehensive clinical diagnostic model (GAMAD) for early detection of hepatocellular carcinoma: A multicenter, prospective study protocol

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Background: Prompt detection of hepatocellular carcinoma (HCC) in patients with chronic liver diseases is critical for enhancing prognosis. Existing imaging techniques and serum markers fall short of clinical needs. This study aims to establish a non-invasive GAMAD test model for early HCC detection by incorporating demographic data (Gender and Age), circulating tumor DNA (ctDNA) Methylation signature in blood, and commonly utilized serum biomarkers [alpha-fetoprotein (AFP), des-γ-carboxy-prothrombin (DCP)]. Additionally, the study will evaluate the model's effectiveness among HCC patients at various stages and/or high-risk HCC groups.

Trial design: This prospective, multicenter, non-interventional study will enroll 2,000 participants, including HCC patients, those with chronic liver diseases (hepatitis, cirrhosis, and benign liver space-occupying lesions), and healthy individuals. Blood samples from all participants will be divided into training and validation sets (1,400 and 600 cases, respectively) for the development and blind validation of the GAMAD (Gender + Age + Methylation + AFP + DCP) HCC-discriminating classifier. The classifier's accuracy and utility will be further assessed in the entire cohort (training and validation cohort). Primary outcome endpoints include sensitivity, specificity, and accuracy [ROC curves; area under the curve (AUC) value] of GAMAD for HCC (in early and each stage) and/or high-risk HCC groups. Secondary outcome endpoints involve comparing GAMAD with the established GALAD model and individual blood indices (AFP, DCP, and methylation testing) to evaluate: (1) GAMAD's clinical utility and

significance for HCC patients in early and other stages (according to different staging systems: TNM staging, the Milan criteria, and the BCLC staging criteria); (2) GAMAD's discrimination ability for patients in various subgroups, including liver cirrhosis (LC) related HCC and LC, HBV related HCC and HBV, HCV related HCC and HCV, and nonalcoholic fatty liver disease (NAFLD) related HCC and NAFLD.

Clinical trial identification: NCT05626985.

Legal entity responsible for the study: Eastern Hepatobiliary Surgery Hospital and The First Hospital of Jilin University.

Funding: Singlera Genomics Inc.

Disclosure: T. Yang: Financial Interests, Institutional, Principal Investigator: Eastern Hepatobiliary Surgery Hospital. H. Liu, H. Wang, S. Zhou, Z. Zheng, R. Liu: Financial Interests, Institutional, Full or part-time Employment: Singlera Genomics Inc. F. Shen: Financial Interests, Institutional, Principal Investigator: Eastern Hepatobiliary Surgery Hospital. G. Lv: Financial Interests, Institutional, Principal Investigator: First Hospital of Jilin University. All other authors have declared no conflicts of interest.

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1014TiP Efficacy and safety of recombinant human adenovirus type 5 injection combined with transhepatic arterial embolization sequential thermal ablation for medium-and high-risk recurrent liver cancer: a prospective, open-label, randomized controlled study

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Background: Currently, 70%-80% of liver cancer patients have recurrence within 5 years after radical surgery. Therefore, determining effective treatment methods for liver cancer is still a major issue of global concern. Recombinant human adenovirus type 5 (rAd5, H101) is the world's first approved oncolytic virus product in China, rAd5 and transarterial chemoembolization (TACE) has significant anti-tumor effect in treatment of liver cancer. Compared with TACE, transhepatic arterial embolization (TAE) sequential thermal ablation may significantly improve the overall survival (OS) rate of liver cancer patients. This study aims to explore the efficacy and safety of rAd5 combined with TAE sequential thermal ablation in treatment of liver cancer, and to further explore the local and systemic immunological changes in patients.

Trial design: This is a prospective, open-label, randomized, parallel controlled study, 110 patients with medium- and high-risk recurrent liver cancer are expected to enroll. Key inclusion criteria are: age $\geq$18 and $\leq$70; ECOG performance status of 0-1; Child-Pugh score $\leq$7; and the expected survival time $\geq$3 months. All participants are randomized 1:1 to receive rAd5 combined with TAE and thermal ablation (experimental group) or TAE and thermal ablation (control group). Before, 10 mg dexamethasone was intravenously administered. rAd5 (H101) will be intratumorally injected into the hepatic segmental artery, the dosage is adjusted according to the maximum diameter of lesions: $\leq$10 cm, 1.0×10^{12} vp/day; $\geq$10 cm, 1.5×10^{12} vp/ day, 28 days for a cycle (4 cycles totally). 1-3 weeks after rAd5 injection and TAE or TAE, thermal ablation treatment will be performed if patients have residual tumor. Patients will be followed up at 1, 3, 6 and 12 months after treatment. The primary endpoint is objective response rate. Secondary endpoints include progression free survival, disease control rate, one-year OS and quality of life score. Exploratory endpoints are the changes from baseline in CD4+, CD8+, Treg, Th1 and Th2. The adverse events will be monitored.

Clinical trial identification: ChiCTR2300067319 (http://www.chictr.org.cn/); Release date, January 04, 2023.

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Disclosure: All authors have declared no conflicts of interest.

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1015TiP A Prospective, phase II clinical study of tislelizumab monotherapy or in combination with lenvatinib for neoadjuvant treatment of resectable hepatocellular carcinoma

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Background: Surgery is the main radical treatment for hepatocellular carcinoma (HCC), but the high postoperative recurrence rate makes the survival benefit of patients limited. Some studies have shown that PD-1 antibody alone as neoadjuvant therapy induced significant tumor necrosis. In our center, Tislelizumab in combination with Lenvatinib as neoadjuvant therapy was well tolerated and significantly induced pathological and clinical response without significant surgical delay (NCT04834986). These results suggest that immunotherapy has good potential as neoadjuvant therapy in resectable liver cancer, but the characteristics of patients targeted by different regiments are not clear. This study aims to explore the factors that influence the efficacy of Tislelizumab monotherapy or in combination with Lenvatinib and accurately screen patients to further improve the safety and efficacy of neoadjuvant treatment.

Trial design: This single-center, two-arm phase II study (NCT05807776) will enroll 50 patients. The key inclusion criteria include confirmed resectable HCC, BCLC A, Child-Pugh A, ECOG PS 0-1, no prior systemic therapy. All patients will undergo pretreatment biopsy and subsequently receive 2 cycles of treatment with 200mg Tislelizumab. Tumor assessment performs in accordance with mRECIST. Patients who achieve partial response(PR) or reduced stable disease(SD) will be assigned to arm 1 and directly undergo surgical resection, start adjuvant treatment 4-8 weeks after surgery with Tislelizumab for 3-6 months. Patients who achieve progressive disease(PD) or increased SD will be assigned to arm 2, undergo second biopsy and receive Tislelizumab and Lenvatinib(8mg/kg) for 2 cycles, followed by surgical resection depends on the patient's physical condition and tumor condition, start adjuvant treatment with Tislelizumab in combination with Lenvatinib for 3-6 months. The primary endpoint is major pathologic response rate (MPR, tumor necrosis $>$70%), secondary endpoints are 1 and 2 years DFS rate, ORR, surgical delay rate (time from the end of last neoadjuvant treatment cycle to surgery $>$ 28 days) and safety. Study enrollment has begun in April 2023.

Clinical trial identification: NCT05807776.

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ANNALS OF ONCOLOGY driving innovation in oncology

INVESTIGATIONAL IMMUNOTHERAPY

1016O Autoimmunity against surfactant protein B drives immune checkpoint inhibitor-related pneumonitis in patients with NSCLC

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Background: Immune checkpoint inhibitor (ICI)-related pneumonitis is a common and serious immune-related adverse event (irAE) in patients with non-small cell lung cancer (NSCLC). The factors driving the development of ICI-related pneumonitis in some patients and not others are poorly understood.

Methods: A prospective cohort of patients with stage IV NSCLC and stage IV melanoma who received ICI treatment was established across four clinical centers in Switzerland. Patient blood was drawn pre-treatment, at every cycle of treatment and, where possible, at the time point of irAE onset. Lung tumor/pneumonitis biopsies were available from some patients. Serum samples were used to perform a high-throughput proteomics analysis as well as ELISAs. Biopsies were used to perform immunohistochemistry and mass spectrometry-based HLA immunopeptidomics analyses. PBMCs were isolated from blood and used to perform *in vitro* T cell stimulation assays followed by flow cytometric cell acquisition. Lastly, PBMCs were also used to perform cell sorting and single cell RNA sequencing.

Results: Using longitudinal samples from a prospective cohort of 144 ICI-treated patients with NSCLC we uncovered important differences between patients with pneumonitis and those without: pre-treatment, patients with pneumonitis showed significantly higher levels of IgG autoantibodies targeting surfactant protein B (SP-B); while, at the onset of pneumonitis, these patients exhibited significantly higher frequencies of $CD4^+$ IFN-γ^+ SP-B-specific T cells in their blood. At the onset of pneumonitis patients also expressed a distinct serum proteomic profile including well-known inflammation-associated immune mediators. Finally, they harbored higher frequencies of T cell clonotypes likely to recognize SP-B in their blood than control patients without pneumonitis.

Conclusions: Our data suggest that the co-occurrence of SP-B-specific IgG autoantibodies and SP-B-specific $CD4^+$ T cells leads to the development of ICI-related pneumonitis in patients with NSCLC. Our data also indicate that the pre-treatment level of SP-B-specific IgG may be used as a potential biomarker to identify patients at higher risk of developing ICI-related pneumonitis.

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1017O NTC-001: A phase I study to test safety and efficacy of BNT221, a non-engineered neoantigen-specific T cell product, in patients with advanced or metastatic melanoma

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Background: Neoantigens are tumor-specific antigens derived from somatic mutations and have been shown to elicit antitumor immune responses. The interim results of a phase I study (NCT04625205) testing a personalized, non-engineered, neoantigen-specific T cell product (BNT221) targeting multiple neoantigens are presented.

Methods: Nine patients with checkpoint- and, if applicable, BRAFi-resistant metastatic melanoma were treated with BNT221. Up to sixty immunogenic MHCI- and MHCII-restricted neoantigens were selected using our RECON® bioinformatics platform and used in an *ex vivo* induction process (NEO-STIM™) to prime, activate and expand memory and de novo T-cell responses from both the $CD4^+$ and the $CD8^+$ T cell compartment, using PBMCs collected via leukapheresis. Two BNT221 doses ($\geq 1 \times 10^8$ cells to $\leq 1 \times 10^9$ cells and $>2 \times 10^9$ cells to $\leq 1 \times 10^{10}$ cells) were evaluated in a 3+3 escalation design, with primary (safety and determination of highest tolerable dose), secondary (efficacy, per RESIST 1.1) and exploratory endpoints. Patients were treated with lymphodepleting chemotherapy prior to infusion. Peripheral blood and biopsies were collected for immune monitoring.

Results: BNT221 was well-tolerated. No dose-limiting toxicities were observed, with grade 3-4 toxicities post infusion limited to hematologic toxicities from lymphodepletion. Seven patients showed stable disease as best overall response (12-36+ weeks). Of those, two patients showed tumor reductions at cutaneous and visceral disease sites and reported quality of life improvements. For all patients, drug products were generated with multiple neoantigen specific CD8+ and CD4+ T cell responses, also detected up to 6 weeks post infusion. Evidence of tumor infiltration was observed through TCR sequencing analysis in one patient tested.

Conclusions: In this first in human study, BNT221 as a single infusion therapy demonstrated a tolerable safety profile, product persistence, prolonged stable disease, and tumor regressions in patients with checkpoint inhibitor-resistant metastatic melanoma. Additional study is warranted and BNT221 combination with anti-PD-1 is currently underway.

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1018O Phase I study of GCC CAR-T therapy IM96 in patients with advanced colorectal cancer

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Background: The clinical outcomes of metastatic colorectal cancer (mCRC) therapies are limited. Guanylyl cyclase 2C (GCC) is ectopically expressed in mCRC and intestinally-restricted. A GCC-targeted CAR-T (IM96) was developed and phase I study was conducted to evaluate the safety and efficacy (NCT05287165).

Methods: In this open-label, 3+3 dose-escalation study, IM96 was evaluated in GCC-positive mCRC patients (pts) failed to ≥3 lines of therapies. Bridging therapies were allowed. Pts were pre-treated with fludarabine and cyclophosphamide, and received a single infusion of IM96 at the dose of 3×10^8 (DL1), 6×10^8 (DL2), 12×10^8 (DL3), or 20×10^8 (DL4) CAR-T cells. The primary objectives were safety and toxicity, and the secondary objectives were efficacy and pharmacokinetic profile.

Results: As of December 2022, 9 pts were enrolled and infused with IM96. The median age was 52.6, and 5/9 cases were male. Bridging therapies were used in 8 pts. Neurotoxicity and ≥grade 3 cytokine release syndromes (CRS) were not observed. Grade 1-2 CRS occurred in 5/9 pts (55.6%) with dramatic increase of interleukin-6. In 4/9 pts (44.4%), grade 1-3 diarrhea and rash were observed. Grade 3 diarrhea occurred in 2/9 pts (22.2%), and grade 2-3 oral mucositis occurred in 3/9 pts (33.3%), only in DL2 and DL3 groups. Dose-limiting toxicity and maximum tolerated dose were not achieved. The disease control rate (DCR) was 66.7%, and the objective response rate (ORR) was 11.1%. After CAR-T infusion, 5/9 (55.6%) patients showed a significant decrease in CEA level which was aberrantly high in all pts at baseline. CAR-T proliferated in all pts and reached peak at 7-10 days after infusion. Two pts showed persisting tumor reduction and declination of CEA level within 3 months, coinciding with CAR-T expansion to 10^8/L. The response in pts with moderate-to-strong GCC expression in ≥30% of tumor cells was 100% DCR, and with this prerequisite, tumor reduction was observed in 100% pts when the IM96 dose was $\geq6\times10^8$.

Conclusions: IM96 was well tolerated and showed encouraging efficacy. The clinical response is correlated with tumor GCC expression, infusion dose, and CAR-T expansion level. This study is ongoing, and dose extensive investigation will also be performed.

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1019O Clinical and translational data from the phase I SURPASS trial of ADP-A2M4CD8 T cell receptor (TCR) T cell therapy alone or combined with nivolumab in solid tumors

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Background: ADP-A2M4CD8 is a TCR T-cell therapy targeting melanoma-associated antigen A4 (MAGE-A4), modified with a CD8α coreceptor, to treat human leukocyte antigen A*02−eligible patients (pts) with unresectable/metastatic solid tumors. ADP-A2M4CD8 monotherapy has demonstrated an acceptable benefit-to-risk profile and encouraging anti-tumor activity in the ongoing phase 1 SURPASS trial. Nevertheless, inhibition of immunosuppressive pathways may improve anti-tumor responses; therefore, new SURPASS cohorts include ADP-A2M4CD8 combined with nivolumab or pembrolizumab. We report data from pts receiving monotherapy and nivolumab combination therapy.

Methods: T-cells are obtained by leukapheresis, transduced with a lentiviral vector carrying the TCR and CD8α coreceptor genes, expanded ex vivo, and infused back to the pt following lymphodepleting chemotherapy. ∼Four weeks after ADP-A2M4CD8 infusion, a subset of pts also received nivolumab 480 mg every 4 weeks until unacceptable toxicity/disease progression. Primary and secondary objectives are safety and anti-tumor activity, respectively.

Results: As of March 9, 2023, 51 pts with a median age of 60 years (range: 31−75) mainly with melanoma, non-small cell lung, ovarian, gastroesophageal, head and neck, or urothelial cancers received $1.02-9.95\text{x}10^9$ ADP-A2M4CD8 T-cells. Median (range) number of prior lines of therapy was 3 (1−8) and MAGE-A4 expression H-score was 250 (90−300). The four most common adverse events related to T-cell therapy were cytokine release syndrome (n=38 [74.5%]; 7 [13.7%] were Grade≥3), neutropenia (27.5%), pyrexia and fatigue (each 21.6%). Overall response rate per RECIST v1.1 by investigator review in monotherapy pts (n=45) was 35.6% (2 complete response, 14 partial response [PR]). Median duration of response was 20.79 weeks (95%CI: 11.6, 30.9). In pts assigned to nivolumab combination (n=6), there was 1 PR, 3 stable disease, and 2 not evaluable (2 pts have not received nivolumab and have no post-baseline RECIST assessment). Data from additional pts treated by August 2023 will be presented.

Conclusions: ADP-A2M4CD8 continues to show an acceptable benefit-to-risk profile, including in pts receiving nivolumab combination therapy.

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1020MO AdvanTIG-203: Phase II randomized, multicenter study of ociperlimab (OCI) + tislelizumab (TIS) in patients (pts) with unresectable, locally advanced, recurrent/metastatic esophageal squamous cell carcinoma (ESCC) and programmed cell death-ligand 1 (PD-L1) positivity

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Background: Prognosis of unresectable ESCC is poor, with median overall survival (OS) in 2nd line (2L) of ∼10 months. Anti-PD-1 agents, including TIS, have demonstrated an OS increase, albeit still unsatisfactory, in unresectable ESCC pts. In preclinical studies and clinical studies of other tumors, coinhibition of T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) and PD-1 enhances antitumor activity of anti-PD-1. AdvanTIG-203 (NCT04732494) is investigating efficacy/safety of TIS +/- OCI (anti-TIGIT) in advanced ESCC pts, progressing on/after 1st line (1L) systemic therapy.

Methods: Adult ESCC pts with PD-L1 tumor area positivity (TAP) ≥10% and progression on/after 1L systemic therapy were randomized (1:1) to OCI 900 mg + TIS 200 mg (O+T) or placebo + TIS (P+T) every 3 weeks until progression, unacceptable toxicity, or withdrawal. Primary endpoint was investigator (INV)-assessed objective response rate (ORR). Secondary endpoints included progression free survival (PFS).

Results: As of 1 Feb 2023, 125 pts (median age 64 years; 88.8% male) were randomized to O+T (n=62) or P+T (n=63). INV-assessed ORR was 30.6% with O+T vs. 20.6% with P+T; hazard ratio (HR) of INV-assessed PFS was 0.93 (95% CI: 0.61, 1.43) (Table). Incidence of pts with ≥1 any adverse event (AE) was comparable between O+T (93.5%) and P+T (95.2%); most common AE was anemia (O+T: 25.8%; P+T: 28.6%). Respective AE rates for O+T and P+T were 41.9% and 41.3% grade ≥3 AEs, 41.9% and 39.7% serious AEs, 9.7% and 15.9% AEs that led to treatment discontinuation, 45.2% and 30.2% immune-related AEs, and 0% and 3.2% treatment-related fatal AEs.

Conclusions: In 2L therapy of advanced ESCC pts with PD-L1 TAP ≥10%, O+T showed tolerable safety profile and trend toward better ORR, but similar PFS vs. P+T.

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1021MO Safety and efficacy of etigilimab (anti-TIGIT) with nivolumab (anti-PD1) in recurrent/advanced solid tumors

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Background: Etigilimab (etig), a humanized IgG1 mAb, blocks TIGIT interaction with PVR (poliovirus receptor) resulting in immune cell activation with tumor cell killing. ACTIVATE, an open-label phase 1b/2 study is evaluating further efficacy, safety, tolerability, and PK/PD of etig+nivolumab (nivo). This is an additional update in select cohorts from ACTIVATE, for tumors less responsive to anti-PD-(L)1 monotherapy.

Methods: Subjects with advanced/metastatic solid tumors and no curative/standard of care therapies are given IV etig+nivo Q2W. Cohorts enrolled include gynecological malignancies: endometrial cancer (EC post-front-line platinum), EC (2-3 prior lines), PD-(L)1+ checkpoint-inhibitor-naïve (CPI-n) cervical cancer, rare cancers (germ cell

Table: 1020MO Efficacy

	O+T (n=62)	P+T (n=63)	
ORR[a], % (95% CI)			
INV[b]	30.6 (19.6, 43.7)	20.6 (11.5, 32.7)	$P^{c,d}$=0.2114
IRC[e]	32.3 (20.9, 45.3)	25.4 (15.3, 37.9)	$P^{c,d}$=0.4209
OS[e,f] (months), median (95% CI)	10.1 (7.1, NE)	9.3 (6.0, NE)	HR[c] (95% CI): 0.93 (0.55, 1.58) $P^{c,g}$=0.3977
PFS[e] (months), median (95% CI)			
INV	3.4 (1.8, 5.1)	3.5 (1.9, 4.1)	HR[c] (95% CI): 0.93 (0.61, 1.43)
IRC	3.6 (2.7, 5.1)	2.8 (1.9, 6.9)	HR[c] (95% CI): 1.01 (0.64, 1.59)

Median follow-up was 7 months. IRC, independent review committee; NE, not estimable [a]Confirmed per RECIST v1.1
[b]Primary endpoint [c]Stratified [d]2-sided; by Cochran-Mantel-Haenszel method [e]Secondary endpoint [f]Still immature (event rate 45.6%) [g]1-sided; by log-rank test

Table: 1021MO Best Observed Response (BOR)[1] - Days on study

Cohorts -n	Complete Response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
CPI-n Cervical Cancer - 8 CPS>1%	3 pts — 163, 365, 386		2 pts — 174, 241	3 pts
CPI-n Uveal Melanoma - 8		2 pts — 228, 608	2 pts — 175, 294	4 pts
Dedifferentiated Liposarcoma - 10		1 pt — 512	4 pts — 162, 167, 191, 216	5 pts
EC — CPI-n - 10		3 pts — 168, 288[2], 394	3 pts — 120, 131, 378	4 pts
GCT - 4		1 pt — 372[2]		3 pts
Total = 40 (%)	3 pts (7.5)	7 pts (17.5)	11 pts (27.5)	19 pts (47.5)

tumor (GCT), sarcoma, uveal melanoma) and ovarian cancer (post-front-line platinum). The primary endpoint is investigator assessed ORR by RECIST 1.1. Secondary endpoints include response duration and safety.

Results: Of 76 safety evaluable subjects, eight subjects showed treatment related adverse events (TRAEs) > than Grade 2. Only one TRSAE was observed. There were no treatment related deaths. See Table for efficacy data for select cohorts. Of 40 evaluable patients presented, 3 CRs, 7 PRs and 11 SDs beyond 120 days were noted. Seven subjects showed clinical benefit for ≥ 1 yr. 1. BOR at treatment termination or by 4 May 2023 for on study patients. 2. mixed response, continued treatment, PD-RECIST 1.1.

Conclusions: Etig in combination with nivo is safe and well tolerated. Preliminary efficacy data of prolonged on study duration with clinical benefit in immune resistant tumors supports continued evaluation in tumor types not typically responsive to anti-PD(L)1 monotherapy.

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1022MO Predicting overall survival of patients with melanoma and NSCLC treated with immunotherapy using AI combining total tumor volume and tumor heterogeneity on CT-Scans

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Background: Using total tumor volume and AI tumor heterogeneity from CT scans, it may be possible to predict the prognosis of oncology patients, identify those who could benefit from immunotherapy, and provide valuable guidance for treatment.

Methods: This retrospective study included 607 patients treated from 2014 to 2019. Baseline CT-scans were collected. All visible lesions were outlined on the largest diameter axial slice by 2 senior radiologists with double reading. The total tumor volume (TTV) was computed by adding estimated lesion volumes. Patients were randomly split into train, test and validation sets with a 56-14-30 ratio stratified by cancer type. Texture features were extracted using either radiomics or a neural network. Two heterogeneity signatures were obtained using PCA followed by random survival forests fit to predict overall survival (OS): radiomics heterogeneity risk (RadH) and AI risk (AiH). These were combined with TTV using a Cox model to establish 2 imaging scores (TTV-RadH, TTV-AiH). Cutoffs were determined using maximally selected rank statistics on the train set. Two populations (low risk-high risk) were evaluated using Kaplan-Meier and Log-Rank tests. Correlations were studied using the Pearson correlation coefficient.

Results: In total, 19877 lesions were annotated. The train, test and validation sets contained 339, 85 and 183 patients. Preliminary results were computed on the train and test sets. The cut-off for TTV was 102 cm3. On the test set, TTV-RadH low and high risk groups had median OS of 3.09 and 16.29 months, while TTV-AiH had median OS of 3.09 and 19.04 months. All Log-Rank tests were statistically significant ($p<0.001$). The correlation was strong between TTV and RadH ($\rho=0.67$), moderate between AiH and RadH ($\rho=0.40$), and weak between TTV and AiH ($\rho=0.27$).

Conclusions: This study developed new prognostic imaging signatures based on baseline CT-scans. These combine both TTV and heterogeneity indexes, extracted using radiomics or a novel method based on self-supervised learning. These methods were able to predict survival of cancer patients treated with immunotherapy in both train and test sets. RadH was more correlated than AiH with volume.

Legal entity responsible for the study: The authors.

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1023MO Decoding immunotherapy resistance: A novel multiparametric magnetic resonance imaging approach to stratify cancer patient outcomes

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Background: This prospective study evaluated the use of multiparametric MRI (mpMRI) in non-invasively assessing the tumor microenvironment and predicting response to immune checkpoint inhibitors (ICIs) in patients with advanced solid tumors, as biomarkers are needed to improve patient selection for ICIs.

Methods: 146 lesions from 40 patients were analyzed at baseline using joint diffusion-T2-relaxation imaging (DRI) and dynamic contrast-enhanced (DCE) imaging to obtain 11 parameters describing tumor microstructure. In addition, 23 baseline biopsies were evaluated using a next-generation immunohistochemistry panel, including PDL1, CD163, CD3, CD8, FOXP3, CD31 and Ki67. The best overall response rate (ORR) was evaluated as per RECIST 1.1. Dichotomized outcome was defined as progression (PD) vs no progression (SD/PR) at best response. LASSO was used to select mpMRI variables, and univariate and multivariate logistic regression models were fitted to predict the outcome.

Results: The ORR was 10% (4 out of 40 patients). Higher density of CD8 cytotoxic cells was independently associated with lower progression rate (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.08—0.77). In multivariate analysis, higher tissue kurtosis representing complex tissue microstructure (OR 5.13, 95%CI 1.33—30.5), low T2 of the tissue indicating lower water content (OR 0.14, 95%CI 0.03—0.51) and higher volume fraction of the extracellular space from DCE (OR 3.32, 95%CI 1.17—12.3) were associated with progression. The multivariate mpMRI model showed promising results with an AUC [95%CI] of 0.85 [0.73, 0.97], which was evaluated using calibration and bootstrapping (AUC of 0.80 [0.69, 0.92]). Statistically significant differences in PFS between High vs Low mpMRI signature score groups were observed (log rank test: p=0.005).

Conclusions: mpMRI provides valuable information about advanced solid tumor microstructure and may serve as a useful tool for patient selection for treatment with ICIs. Biomarker discovery in phase 1 trials is challenging, but mpMRI could identify a subset of progressing patients resistant to ICIs. Further studies are warranted to validate these findings.

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1024MO Interpretable AI-identified spatial tumor microenvironment (TME) neighborhoods associate with severe immune-related adverse events (irAE) and progressive disease (PD) in patients with melanoma treated with anti-PD-1-based therapy

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Background: Among patients with advanced melanoma who receive standard-of-care immune checkpoint inhibitors (ICI; e.g., anti-PD-1 +/- anti-CTLA-4), only ~50% experience tumor response, and ~10-55% experience grade ≥3 irAEs. Pre-treatment biomarkers that can help predict efficacy and toxicity outcomes are highly desirable.

Methods: Pre-treatment tumor specimens from 53 patients with advanced melanoma who received ICI were stained with two multiplex immunofluorescence (mIF) panels: Panel 1 (PD-L1, CD8, FOXP3, PD1, CD163, Sox10/S100); Panel 2 (PD1, CD8, GZMB, TBET, EOMES, and LAG3). We used NaroNet, a deep learning artificial intelligence (AI) framework, to identify spatial cellular neighborhoods (125x125μm^2 image-patches) within the TME. Every morphology, marker expression texture, and interaction was extracted from the images. Toxicity outcomes (grade ≥3 irAEs) and objective response data per RECIST v1.1 were incorporated into the AI algorithm. The AI-identified neighborhoods were visualized and interpreted using the AstroPath platform and tested for an association with clinical covariates.

Results: For each mIF panel, we identified a single neighborhood associated with grade 3/4 irAEs. The first (Panel 1) contained intratumoral CD163+, PDL1(-) cells and lacked FOXP3, PDL1, PD1, and CD8 expression (p=0.008). The second (Panel 2) had PD1+, EOMES+ intratumoral cells without TBET, LAG3, CD8, and PDL1 expression (p=0.04). Notably, these neighborhoods were also associated with PD (p=0.009; p=0.04, respectively). When combined, these two neighborhoods had an AUC of 0.85 (n=8 with PD and severe irAE vs n=45 other), which was irrespective of age, sex, and therapy type (i.e., anti-PD-1 monotherapy or anti-PD-1+CTLA-4).

Conclusions: Our findings suggest that AI-identified, distinct TME neighborhoods could serve as potential biomarkers to identify the subset of patients likely to experience serious irAE and PD after anti-PD-1-based therapy, allowing for consideration of an alternate therapeutic regimen. Additional studies are needed to validate these findings.

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1025MO Preliminary safety, pharmacokinetics and immunomodulatory activity of RBS2418, an oral ENPP1 inhibitor, alone and in combination with pembrolizumab in patients with solid tumors

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Background: ENPP1 is a nucleotide pyrophosphatase and phosphodiesterase and its overexpression is associated with poor prognosis in cancer. ENPP1 inhibition protects cGAMP and ATP from hydrolysis, reduces adenosine levels in the TME, activates APCs and increases T-cell infiltration promoting antitumor immunity. RBS2418, a first-in-class oral ENPP1 inhibitor, is in an ongoing phase I clinical trial in solid tumors.

Methods: Phase 1 dose escalation (3+3 design) with 100, 200, 400 and 800 mg BID dose cohorts of RBS2418 alone or in combination with pembrolizumab (200 mg IV q3w) in patients who have previously failed all SOC therapies. Primary endpoints are safety and PK. On-treatment tumor biopsy and blood samples are collected to determine PK/PD and immune profiles using LC/MS, ENPP1 inhibition, IF, IHC, flow cytometry, and TCR/RNAseq analysis.

Results: The first 3 dose levels evaluated to date in 19 patients were safe and well tolerated with no DLTs. Median plasma concentrations of RBS2418 increased in a dose-dependent manner. Plasma and tumor concentrations of RBS2418 were above the EC90 level of ENPP1 inhibition in all patients at all time-points tested. IHC analyses show baseline ENPP1 and cGAS co-expression in tumors correlating with RBS2418 treatment associated prolonged disease stabilization (SD duration >180 days) and peripheral T-cell activation, increased tumor-infiltrating T-cells and M2 to M1 macrophage repolarization, consistent with the drug's mechanism of action.

Conclusions: Oral RBS2418 alone or with pembrolizumab has been safe and well tolerated at all dose levels studied to date in the ongoing dose escalation study. The PK profile showed plasma levels enabling complete ENPP1 inhibition. Preliminary analyses support the hypothesis that ENPP1 and cGAS co-expression in tumors correlates with RBS2418 treatment associated immune activation and prolonged disease stabilization suggestive of clinical benefit in multiple patients with refractory malignancies including MSS CRC and HCC **(NCT05270213)**.

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1026MO A phase Ib/II study of SHR-1701 (a bifunctional anti-PD-L1/TGF-βRII agent) in combination with bevacizumab (BEV) in patients with advanced solid tumors

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Background: Accumulative evidence demonstrates that anti-angiogenesis plus immune checkpoint inhibitor (ICI) has a synergistic antitumor effect in various types of tumors. Thus, we assessed the safety and efficacy of SHR-1701 plus BEV in patients (pts) with advanced solid tumors.

Methods: This is a multicenter, open-label, phase 1b/2 study. The primary objective of phase 1b part was to determine the recommended phase 2 dose (RP2D) in pts with advanced solid tumors. Phase 2 part enrolled: 1) pts with advanced gastric and gastroesophageal junction cancer (GC/GEJC), PD-L1 CPS ≥1, HER2 negative, who had not received prior systemic therapy (1L); 2) pts with advanced GC/GEJC who had received ≤2 prior systemic therapies; 3) pts with recurrent or metastatic non-squamous non-small cell lung cancer (nsqNSCLC) who had failed ≤2 lines of systemic treatment (including platinum-based chemotherapy and ICI), driver gene-negative. SHR-1701 and BEV were given once every 3-week cycle. Primary endpoint of phase 2 part was objective response rate (ORR).

Results: As of Mar 31, 2023, a total of 67 pts with advanced solid tumor were enrolled, including 19 systemic treatment-naïve GC/GEJC pts, 27 pre-treated GC/GEJC pts, and 10 nsqNSCLC pts. No DLT was observed in phase 1b part. The RP2D was determined to be SHR-1701 30 mg/kg plus BEV 15 mg/kg, Q3W. With a median follow-up of 8.4 mos, the ORR was 21.1%, 33.3%, and 10.0% in the three cohorts, respectively (Table). Treatment-related adverse events (TRAEs) occurred in 94.0% of pts. Grade 3 TRAEs were reported in 29.4% of pts, with the most common ones being anemia (5.8%), increased ALT (2.9%), and increased AST (2.9%). No grade 4/5 TRAEs were reported.

Conclusions: SHR-1701 plus BEV showed encouraging antitumor activity with a favorable safety profile in pts with advanced GC/GEJC and nsqNSCLC.

Clinical trial identification: NCT04856774.

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1027P An open-label, multicenter, phase I/II study of GI-101, CD80-IgG4 Fc-IL2v, in advanced solid tumors (Part A of GII-101-P101; KEYNOTE-B59)

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Background: GI-101 is a novel immunocytokine containing CD80 and IL-2v. GI-101 monotherapy and with pembrolizumab have demonstrated early signs of anti-tumor activities in the ongoing GII-101-P101 study[1]. Here we report clinical outcomes from Part A (GI-101 monotherapy) of the study with additional patients (pts) treated.

Methods: GII-101-P101 study is a 4-part, first-in-human, phase 1/2 study of GI-101 monotherapy and in combination with various agents in pts with advanced solid tumors. In Part A, dose escalation with 3+3 design established the recommended phase 2 dose (RP2D) and is followed by expansion cohort. Primary endpoints include safety, tolerability and investigator-assessed objective response.

Results: At the data cut-off of 20 Apr 2023, 57 pts received GI-101 monotherapy (19 in escalation and 38 in expansion cohorts). The median number of prior therapies were 3 [1—11] and 47% were previously experienced immunotherapy. No dose-limiting toxicities (DLTs) were reported in escalation cohort (0.002∼0.3 mg/kg) and maximum tolerated dose (MTD) was not reached. The dose of 0.3 mg/kg GI-101 Q3W was established as the RP2D. Treatment-emergent adverse events (TEAEs) occurred in 55 pts (96%); the most common (>30%) were pyrexia (67%) and transient AST increase (37%). Objective responses were observed in 3/50 evaluable pts regardless of prior anti-PD-(L)1 therapy; 1 confirmed CR (cervical cancer), 1 confirmed PR (UBC) and 1 unconfirmed PR (NSCLC) with 1 CR is ongoing (144+ days). Disease control rate is 46% and median PFS [min-max] was 41 [21-294] days. Meaningful target lesion reduction at 54W (-53%; on-treatment > 429+ days) was observed in MSS CRC with liver metastasis. GI-101 resulted in robust expansion of peripheral lymphocyte at

Table: 1026MO Efficacy outcomes

Variables	GC/GEJC (1L)		GC/GEJC (≥2L)		nsqNSCLC
	All (n=19)	CPS≥5 (n=15)	All (n=27)	CPS≥5 (n=9)	All (n=10)
Best overall response, n (%)					
CR	0	0	1 (3.7)	1 (11.1)	0
PR	4 (21.1)	4 (26.7)	8 (29.6)	6 (66.7)	1 (10.0)
SD	7 (36.8)	5 (33.3)	5 (18.5)	1 (11.1)	5 (50.0)
PD	7 (36.8)	5 (33.3)	12 (44.4)	1 (11.1)	3 (30.0)
NE	1 (5.3)	1 (6.7)	1 (3.7)	0	1 (10.0)
ORR, % (95% CI)	21.1 (6.1, 45.6)	26.7 (7.8, 55.1)	33.3 (16.5, 54.0)	77.8 (40.0, 97.2)	10.0 (0.3, 44.5)
DCR, % (95% CI)	57.9 (33.5-79.7)	60.0 (32.3, 83.7)	51.8 (32.0, 71.3)	88.9 (51.8, 99.7)	60.0 (26.2, 87.8)
mPFS, months (95% CI)	4.1 (1.3-NR)	4.1 (1.4-NR)	4.0 (1.4-NR)	10.3 (1.3-NR)	6.2 (1.3-9.9)

RP2D, median 3.4-fold [2.0-8.4], primarily CD8+ T, NK, effector and central memory T cells, but not Tregs. Lymphocyte expansion was correlated with increased PFS (P=0.00515).

Conclusions: GI-101 was well tolerated as monotherapy. Monotherapy activity was seen regardless of previous immunotherapy experience, with a favorable benefit to risk profile. The other parts of the trial with pembrolizumab, lenvatinib and radiation continue to enroll.

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Legal entity responsible for the study: GI Innovation, Inc.

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1028P Preliminary phase I results from a first-in-human study of EMB-02, a PD-1xLAG-3 bispecific antibody, in patients (pts) with advanced solid tumors

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Background: Co-inhibition of LAG-3 and PD-1 pathways has been shown to yield better efficacy than PD-1 blockade alone in pts with previously untreated metastatic melanoma. EMB-02 is a tetravalent PD-1×LAG-3 bispecific antibody developed based on EpimAb Biotherapeutics' proprietary Fabs-In-Tandem-Immunoglobulin (FIT-Ig®) platform. In preclinical studies, EMB-02 demonstrated the ability to concomitantly or independently engage immune cells expressing PD-1 and LAG-3 to restore T cell effector function, and induced transient co-degradation of PD-1 and LAG-3 which led to more efficient PD-1 depletion on activated T cells.

Methods: EMB02x101 is an open-label, first-in-human, phase I/II study of EMB-02 in pts with advanced solid tumors. The phase I dose escalation portion evaluated 6-900mg doses of EMB-02 (weekly i.v.), guided by the Bayesian optimal interval (BOIN) design. The primary objectives were to investigate safety and tolerability and determine the MTD and/or the RP2D(s). Secondary objectives included pharmacokinetics (PK), immunogenicity, and preliminary anti-tumor activity.

Results: As of January 31, 2023, EMB-02 was administered to 47 pts during the dose escalation portion (45% had ≥3 prior lines of systemic treatment, and 43% had prior checkpoint inhibitor treatment). Treatment related adverse events occurred in 66% of pts, and 15% were grade 3/4. One DLT of grade 4 immune mediated hepatitis was observed at the 900mg dose. EMB-02 showed dose proportional PK across 6-900mg doses, and PK/PD modeling and simulation indicated at least 90% of pts at ≥180mg doses had complete peripheral PD-1 receptor occupancy. Among 47 efficacy evaluable pts, 2 CRs, 1 PR, and 18 SDs were observed per RECIST 1.1. All 3 responders were still under follow up with no PD observed as of the data cut-off date. CBR-24 (CR+PR+ durable SD [≥24wks]) was 19% (9/47).

Conclusions: EMB-02 has demonstrated a tolerable safety profile and encouraging anti-tumor activity during the dose escalation phase, warranting further development. Expansion cohorts in select advanced solid tumours are ongoing.

Clinical trial identification: NCT04618393.

Legal entity responsible for the study: Shanghai EpimAb Biotherapeutics Co., Ltd.

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1029P Dazostinag (TAK-676) alone and in combination with pembrolizumab (pembro) in patients (pts) with advanced or metastatic solid tumors: Preliminary safety, PK/PD, and anti-tumor activity in a phase I dose escalation study supporting a recommended dose for expansion (RDE)

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Background: Dazostinag (TAK-676) is a novel, IV, small molecule synthetic STimulator of INterferon Genes (STING) agonist, which acts as an innate immunity enhancer. In preclinical models, dazostinag induced dose-dependent cytokine production and activation/proliferation of immune cells. We present data from Part 1 of iintune-1 (NCT04420884), a phase 1 study of single agent (SA) dazostinag and combined with pembro in advanced or metastatic solid tumors.

Methods: Part 1 comprised a single-pt safety lead-in with SA dazostinag 0.1 mg IV, followed by dose escalation using Bayesian Logistic Regression Model design. Dose escalation in the combination arm began after no dose-limiting toxicities (DLTs) were seen with ≥2 SA doses. Pts receive dazostinag IV (Days 1, 8, 15) +/- pembro 200 mg IV (Day 1) in 21-day cycles.

Results: As of May 2023, 36 and 43 pts have received SA dazostinag and with pembro, respectively. There have been no DLTs up to 7 mg SA and 5 mg with pembro. The most common adverse events were fatigue (33%), nausea (29%), and pyrexia (22%). Dazostinag had linear PK across the dose range tested and was not affected by combination with pembro; elimination profile was bi-phasic with a terminal half-life of 0.5—1.7 hrs. Exposure-safety analysis indicated increasing incidence of fever or cytokine release syndrome with dazostinag Cmax. PK/PD analysis for all pts indicated dose/concentration-dependent increases in a blood 24-gene STING signature score, and plasma IFN-γ and IP-10. Dazostinag achieved a >3.5-fold induction of STING signature score across multiple dose levels. For dazostinag 5 mg with or without pembro, a >2-fold increase in IFN-γ and other cytokines (including IP-10) and increased peripheral Ki67+CD8+ T cell proliferation were observed. Three pts had objective confirmed clinical responses with dazostinag plus pembro.

Conclusions: Preliminary safety, PK/PD data, and anti-tumor activity support the declaration of the RDE of dazostinag 5 mg + pembro 200 mg. Expansion cohorts in colorectal and head and neck cancer are enrolling.

Clinical trial identification: NCT04420884.

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1030P Phase I, first-in-human trial evaluating the STING agonist BI 1387446 alone and in combination with ezabenlimab in solid tumors

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Background: Engagement of the STING pathway is involved in spontaneous and treatment-induced anti-cancer immunity. Activation of STING with a specific agonist, as a monotherapy or in combination with anti-PD1 therapy, may be a promising novel anticancer strategy. Here we report the first-in-human results for the STING agonist BI 1387446 alone (Arm A) and in combination with ezabenlimab (Arm B).

Methods: The phase 1, open-label, multicenter, dose-finding study 1426.1 (NCT04147234) evaluated BI 1387446 ± ezabenlimab in patients with advanced or metastatic solid tumors. In Arms A and B, BI 1387446 was given intratumorally starting at 50 µg (Cycles 1–3: Days 1, 8, 15; Cycle ≥4: Day 1). Patients in Arm B received ezabenlimab 240 mg intravenously on Day 1 in 21-day cycles. Dose escalation was guided by a Bayesian logistic regression model with overdose control. Eligibility criteria included: ECOG PS 0 or 1, ≥1 lesion suitable for injection, and exhausted standard treatment options. Primary endpoint was maximum tolerated dose (MTD) based on number of dose-limiting toxicities (DLTs). Secondary and further endpoints included safety, efficacy, pharmacokinetics, and pharmacodynamics.

Results: Overall, 41 patients were treated (Arm A n=26; Arm B n=15). In Arm A, median age was 63 years and 46.2% had ECOG PS 1. In Arm B, median age was 56 years and 73.3% had ECOG PS 1. Maximum BI 1387446 dose was 400 µg in Arm A and 200 µg in Arm B. Median duration of BI 1387446 treatment was 1.8 months and 2.4 months in Arms A and B, respectively. DLTs were reported in 1 patient in Arm A receiving BI 1387446 200 µg (grade 3 fatigue and myalgia). No DLTs were reported in Arm B. The MTD was not reached. Safety and efficacy are summarized in the Table. Best response was stable disease (per RECIST v1.1 Arm A 46.2%, Arm B 53.3%).

Conclusions: BI 1387446 monotherapy and in combination with ezabenlimab was well tolerated. MTD for either regimen could not be determined. Table (334/600).

Table: 1030P

	Arm A n=26	Arm B n=15
AEs, n (%)		
Any	25 (96.2)	15 (100)
Immune-related	1 (3.8)	0
DLTs	1 (3.8)	0
Leading to BI 1387446 dose reduction	0	0
Leading to BI 1387446 discontinuation	1 (3.8)	2 (13.3)
BI 1387446-related AEs, n (%)		
Any grade	14 (53.8)	9 (60.0)
Injection site pain	4 (15.4)	0
Fatigue	3 (11.5)	1 (6.7)
Pyrexia	3 (11.5)	1 (6.7)
Asthenia	1 (3.8)	4 (26.7)
Hyperthyroidism	0	1 (6.7)
Grade 3	3 (11.5)	0
Grade 4 or 5	0	0

Clinical trial identification: NCT04147234.

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1031P ANV419, a selective IL-2Rβ/γ agonist in patients with relapsed/refractory advanced solid tumors

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Background: ANV419 is a potent and selective IL-2Rβ/γ selective agonist, designed to enable the delivery of high-dose IL-2 in a safe way. ANV419 leads to preferential expansion of CD8+ T and NK cells over Treg cells. ANV419-001 is an open-label, phase 1 dose escalation study of intravenous single-agent ANV419 in patients with relapsed/refractory advanced solid tumors.

Methods: A 3+3 dose escalation design was applied. Primary objective was to evaluate the safety and tolerability of ANV419. Secondary objectives include efficacy using RECISTv1.1, characterization of pharmacokinetics (PK), pharmacodynamics (PD)

and immunogenicity of ANV419. The DLT observation period was two weeks. ClinicalTrials.gov Identifier: NCT04855929.

Results: At the data cutoff (22 Mar 2023), 40 pts received ANV419 at 3, 6, 12 (n=1 each), 24 (n=5), 48 (n=3), 72 (n=3), 108 (n=6), 162 (n=3), 243 (n=6) and 364 µg/kg (n=5) Q2W and at 243 µg/kg Q3W (n=6). Patients were generally heavily pretreated (1-8 lines) and 75% received immune checkpoint inhibitors. Two DLTs (CRS G3, pemphigoid G3) occurred in 2 pts at 364 µg/kg. ANV419-related AEs occurred in 97.5% of pts;. 35% ≥G3, transient, self-limiting and allowing treatment continuation. The only G4 AEs were transient lymphopenia, no G5 AEs occurred. No AEs led to treatment discontinuation. The most frequent ANV419-related AEs (≥ 10% of pts) were pyrexia, chills, vomiting, nausea, CRS, increased liver enzyme levels, fatigue, diarrhea, hypotension, myalgia, rash and thrombocytopenia, mainly G1 and G2. PK data showed half-life up to 12 hrs at RP2D. ANV419 induced a dose-dependent preferential expansion of Ki67+ CD8+ T and NK cells over Ki67+ Treg cells. Among 39 pts evaluable for tumor response, SD according to RECIST v1.1 was demonstrated in 21 pts (52.5%), prolonged PR in one pt with advanced immunotherapy-resistant NSCLC.

Conclusions: Overall, ANV419 was well-tolerated. All events were self-limiting, reversible, or manageable with standard supportive care. ANV419 at a dose of 243 µg/kg was determined as MTD and RP2D. Preliminary anti-tumor activity was observed including durable response in NSCLC. Further studies assessing the anti-tumor activity of ANV419 in melanoma and myeloma are ongoing.

Clinical trial identification: NCT04855929.

Legal entity responsible for the study: ANAVEON AG.

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1032P A phase II study of sintilimab plus IBI310 for Epstein-Barr virus (EBV)-associated gastric cancer

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Background: EBV is associated with about 10% of gastric cancers. Preliminary data has indicated that patients(pts) with EBV-associated gastric cancer (EBVaGC) could benefit from immunotherapy. The purpose of this study is to evaluate safety and efficacy of sintilimab (anti-PD-1) plus IBI310 (anti-CTLA-4) for EBVaGC. The preliminary results of first-line (cohort B) and ≥ 2 line (cohort C) settings were reported. The study is still recruiting.

Methods: Adult pts with EBV+ (in situ hybridization, ISH), unresectable locally advanced or metastatic, histopathologically confirmed GC/GEJC (cohort B: pts with treatment-naïve; cohort C, pts who had failed at least one standard treatment regimen) were enrolled. Pts in both cohorts received sintilimab 3mg/kg (200mg for weight≥60kg) IV Q3W plus IBI310 1mg/kg IV Q6W combination regimen for 1-3 cycles, and sintilimab monotherapy maintenance thereafter until disease progression, unacceptable toxicity or for up to 24 months. The endpoints include ORR per RECIST v1.1 by investigator, other efficacy measures and safety profile in both cohorts.

Results: As of Feb 22, 2023, 49 pts were enrolled (28 in cohort B and 21 in cohort C). Any and grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 38 (77.6%) and 10 (20.4%) pts, respectively. No TRAE leading to drug discontinuation or death. Any and grade ≥ 3 immune related adverse events (irAEs) occurred in 33 (67.3%) and 7 (14.3%) pts, respectively. In cohort B, for 26 efficacy evaluable pts, the confirmed ORR were 61.5% (95% CI, 40.6-79.8), and DCR was 80.8% (95% CI, 60.7-93.5). The median DoR was 8.3 months (95% CI, 4.0-15.1). With a median follow-up of 13.3 months, the median PFS and OS were 5.5 months (95% CI, 2.8-9.7) and 24.6 months (95% CI, 10.3-28.8), respectively. In cohort C, for 17 efficacy evaluable pts, the confirmed ORR was 47.1% (95% CI: 23.0-72.2) and the DCR was 76.5% (95% CI, 50.1-93.2). The median DoR was 5.6 months (95% CI, 1.4-NR). With a median follow-up of 21.1 months, the median PFS and OS were 5.4 months (95% CI, 1.3-8.4) and 12.8 months (95% CI, 4.1-NR), respectively.

Conclusions: Sintilimab in combination with IBI310 were well tolerated, and shown promising anti-tumor efficacy both in first-line and ≥ 2 line locally advanced or metastatic EBV-associated gastric cancer.

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1033P First-in-human study of MALT1 inhibitor MPT-0118: Results from monotherapy dose escalation in advanced or metastatic refractory solid tumors

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Background: MALT1 protease inhibition reprograms tumor-resident regulatory T cells (Treg), inducing interferon-gamma (IFN) expression and loss of immunosuppressive function. MPT-0118 is an orally bioavailable MALT1 inhibitor undergoing phase 1 clinical evaluation.

Methods: Part A enrolled eligible patients (pts) into escalating dose cohorts of MPT-0118. Primary study objectives were safety, tolerability, and assessment of the recommended phase 2 dose (RP2D). Other objectives were the assessment of pharmacokinetics (PK), biomarkers, and objective response rate (ORR) per RECIST v1.1 and

Table: 1033P

MPT-0118 dose level (mg/day)	Number of Pts	DLTs	Pts with Grade ≥3 TRAE	Number of Pts with most common TRAEs*
50	1	0	0	1
100	1	0	1 (neutrophil and white blood cell count decreased)	1
150	4	0	0	1
200	7	0	2 (febrile neutropenia, hepatitis)	4
300	4	0	0	3
Total	**17**	**0**	**3**	**10**

*Dizziness (5), vision blurred (4), fatigue (4), dry mouth (3), tremor (3), representing all observed AEs with frequency ≥ 3 Note: AEs were graded according to the NCI-CTCAE version 5.0.

iRECIST. Paired biopsies were obtained during screening and after 8 days of treatment.

Results: 17 pts were treated (median age 54 years (32-77), 59% male, median 4 prior lines of therapy, 35% prior immunotherapy). No dose-limiting toxicities (DLT) were observed, and all treatment-related adverse events (TRAE) were reversible.

The RP2D was at 200 mg/day based on PK and clinical observations. Among 13 response-evaluable pts, 5 had stable disease (SD) (38%) after ≥2 treatment cycles, of which 3 had tumor shrinkage, including chordoma, gastric and breast cancers. In an immunotherapy naïve MSS gastric cancer pt, tumor size decreased by 20% with a concurrent improvement of ascites and doubling of tumor-infiltrating CD8+ T cells. MPT-0118 *ex vivo* incubation of gastric cancer ascites collected outside the study resulted in Treg reprogramming. In the other SD pts, median CD8 T-cells, IFN, or PD-L1 markers increased. PK data showed a dose-proportional increase in plasma drug concentrations.

Conclusions: In this first human trial of a MALT1 inhibitor in solid tumor pts, MPT-0118 demonstrated good tolerability with no immune-related toxicities and single-agent activity in cold tumors with poor response to checkpoint inhibitors. The biomarker data are consistent with the purported mechanism. The results warrant advancing to study Part B in combination with pembrolizumab.

Clinical trial identification: NCT04859777.

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1034P Phase I/II dose escalation and dose expansion study of TransCon IL-2 β/γ alone or in combination with pembrolizumab: Determination of recommended phase II dose (RP2D) for monotherapy

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Background: TransCon IL-2 β/γ is a novel prodrug with sustained release of an IL-2 analog (IL-2 β/γ). It is created by permanently attaching a 5 kDa mPEG in the IL-2Rα binding site and transiently attaching this IL-2 β/γ to an mPEG carrier molecule via a TransCon Linker creating a prodrug and improving pharmacokinetics (PK). The key objectives of the IL-Believe trial are to evaluate safety/tolerability, define the maximum tolerated dose and RP2D of TransCon IL-2 β/γ alone or in combination with pembrolizumab.

Methods: Patients age ≥18 with advanced solid tumors receive TransCon IL-2 β/γ IV as monotherapy or in combination with pembrolizumab IV every 3 weeks. Disease is assessed every 9 weeks per RECIST 1.1. Safety, PK, and pharmacodynamics (PD) are evaluated.

Results: As of 28 April 2023, 25 patients were treated with monotherapy (20 to 160 mcg/kg) and 14 in combination (20 to 80 mcg/kg). One Dose Limiting Toxicity of Grade 3 (G3) Cytokine Release Syndrome was reported at 160 mcg/kg monotherapy. No grade 3 or higher treatment related adverse event was reported at the RP2D (120 mcg/kg). PK results showed systemic drug exposure of TransCon IL-2 β/γ with a half-life of at least 35 hours. PD data suggested sustained activation and dose dependent expansion of cytotoxic effector cells while Tregs were expanded minimally. Absolute lymphocyte counts increased in a dose dependent manner while eosinophil counts remained low. Preliminary antitumor efficacy was observed in monotherapy, including 1 unconfirmed partial response (MSI-h CRC, progressed on prior anti-PD1) at 120 mcg/kg and >45 weeks of stable disease in 1 patient with pancreatic cancer at 80 mcg/kg, both continuing with treatment. The monotherapy RP2D was determined to be 120 mcg/kg.

Conclusions: TransCon IL-2 β/γ is generally well-tolerated as monotherapy and in combination with pembrolizumab. The RP2D for monotherapy was determined at 120 mcg/kg IV every 3 weeks while dose escalation continues for combination therapy. PK data indicated a half-life of at least 35 hours and PD data confirm durable activation and expansion of cytotoxic immune cells from TransCon IL-2 β/γ.

Clinical trial identification: NCT05081609.

Legal entity responsible for the study: Ascendis Pharma.

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1035P Phase I dose escalation study of IMC-002, a novel anti-CD47 monoclonal antibody, in patients with advanced solid tumors

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Background: IMC-002 is a fully human IgG4 antibody targeting CD47. IMC-002 induces phagocytosis of tumor cells by macrophages and significantly suppresses tumor growth in preclinical models of hematologic and solid tumors. Here we present preliminary safety, pharmacokinetics (PK), and efficacy data from ongoing phase 1 study of IMC-002 in patients with advanced solid tumors who failed to standard therapy (without priming dose).

Methods: We used a traditional 3+3 design to evaluate dose limiting toxicity (DLT) over 21 days, with 4 doses of IMC-002 (5, 10, 20 and 30 mg/kg). IMC-002 was administered intravenously once every 2 weeks until disease progression or unacceptable toxicity. Tumor assessments were performed every 6 weeks according to RECIST 1.1 criteria.

Results: As of May 2023, we enrolled 12 refractory patients (9 hepatocellular carcinoma, 2 breast cancer, 1 gallbladder cancer) with median age of 55 (range 39-73). Eleven of these patients were at stage IV with multiple distant metastases and high tumor burden. The median number of prior systemic therapy was 3 (range 1-3) and 4 patients received anti-PD-(L)1 antibody. The median interval between the last dose of previous therapy and IMC-002 was 1 month (range 1-4). No DLTs were observed across 4 dose levels. The majority of treatment related adverse events (TRAEs) were grade 1-2 (92%) and most of these events occurred during the first cycle (95%). TRAEs observed in more than 2 patients included transient vitreous floaters, skin rash, anemia and nausea. No infusion related reactions, thrombocytopenia, or neutropenia were reported. The serum exposure of IMC-002 (C_{max} and AUC) increased with dose, and the predicted trough concentration exceeded the minimum efficacious concentration for IMC-002 when administered at a dose of over 10 mg/kg once every 2 weeks. Among the 11 efficacy evaluable patients, 5 had stable disease with a median treatment duration of 6 cycles (range 5-12). Among them, 4 had HCC and 1 had breast cancer.

Conclusions: IMC-002 demonstrated a favorable safety profile when administered intravenously every 2 weeks up to 30 mg/kg and showed preliminary efficacy in patients with advanced solid tumors. Based on safety and PK profile, we determined the recommended phase 2 dose as 20 mg/kg.

Clinical trial identification: NCT05276310.

Legal entity responsible for the study: ImmuneOncia Therapeutics, Inc.

Funding: ImmuneOncia Therapeutics, Inc.

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1036P A phase I/IIa first-in-human study of PM1003 (anti-PD-L1 x 4-1BB bispecific antibody) in patients with advanced solid tumors

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Background: PM1003 is a VHH-based anti-PD-L1 x 4-1BB bispecific antibody that exhibits PD-L1 expression-dependent 4-1BB agonism, with excellent anti-tumor activity and safety in preclinical studies.

Methods: The safety and tolerability of PM1003 in patients (pts) with advanced solid tumors were assessed during dose escalation, and pts with advanced solid tumors positive for PD-L1 expression have been enrolled for assessing anti-tumor activity during dose expansion.

Results: At the data cut-off up to Apr. 19, 2023, 23 pts had been enrolled, with 19 pts for dose escalation (3 pts for each of the 0.02, 0.1, 1, 3, 10 mg/kg dose levels and 4 pts for the 6 mg/kg dose level). All pts had prior 1-6 lines of systemic treatment. Dose-limiting toxicity (DLT) was assessed over 21 days after the first dose followed by dosing Q2W. 4 pts were enrolled for dose expansion (2 pts in 1 mg/kg, 1 patient in each of the 3 and 6 mg/kg dose levels, Q2W). No DLTs were observed during dose escalation. Treatment-related adverse events (TRAEs) occurred in 22 pts (95.7%). The most common TRAEs in pts included anemia (39.1%, Grade≥3 0%), aspartic acid aminotransferase increased (30.4%, Grade≥3 4.3%), white blood cell count decreased (30.4%, Grade≥3 8.7%) and platelet count decreased (30.4%, Grade≥3 0%). For the 1 - 10 mg/kg cohorts, $T_{1/2}$ was 6.3 - 15.3 days after the first dose. PD-L1 target occupancy approach to saturation at 7 days after the first dose and maintained stable. 18 pts were evaluable for efficacy. The objective response rate was 5.6% and the disease control rate was 44.4%. Preliminary antitumor activity was observed in one PD-L1 positive gastric cancer patient (1 mg/kg, Q2W; TPS=5%, CPS=30) who was heavily treated with chemotherapy, anti-PD-1 and anti-HER2-ADC after surgery. 87.8% of tumor shrinkage was achieved in the target lesion at the first efficacy evaluation (7 weeks) after PM1003 treatment. Partial Response was confirmed at subsequent visits.

Conclusions: PM1003 was well-tolerated at doses up to 10 mg/kg and preliminary antitumor efficacy was observed in a patient with prior anti-PD-1 treatment. Expansion cohorts to evaluate efficacy and further safety in PD-L1-positive pts are ongoing.

Clinical trial identification: ChiCTR2100052887.

Legal entity responsible for the study: Biotheus Inc.

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1037P Phase I dose-escalation trial with tumor-targeted interleukin-12 (IL12-L19L19) in patients with solid tumors

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Background: Interleukin-12 (IL12) is a potent immunostimulatory cytokine that enhances T- and NK-cell-mediated anti-tumor immunity. The targeted delivery of IL12, by conjugation to the tumor-targeting antibody L19, increased the therapeutic index and showed a potent anti-tumor effect in mouse models. The L19 antibody binds to the alternatively spliced extra domain B (EDB) of fibronectin, an abundant component of the stroma of most solid tumors, which is undetectable in most healthy adult tissues. The promising preclinical results with EDB-targeted IL12 provided the motivation to study IL12-L19L19 in a phase I clinical trial.

Methods: Eligible patients (pts) have progressive metastatic solid cancers and transiently benefited from prior immune checkpoint inhibitors. The treatment consists of weekly intravenous administrations of IL12-L19L19 up to a maximum of eight infusions, followed by bi-weekly maintenance until disease progression, unacceptable toxicity, withdrawal of consent, or the investigator's decision. During the Dose Escalation part, patients are sequentially assigned to 9 dose levels (0.1 μg/kg to 32 μg/kg). The Dose Escalation continues until the Dose Limiting Toxicity (DLT) rate reaches 33% in a cohort of 2 — 6 pts. Once the Recommended Dose (RD) is defined, 40 additional pts will be treated in the Dose Expansion part.

Results: A total of 14 pts (median age 62 years [37-72], 9 male, 5 female) have completed the DLT observation window in cohorts 1 — 5. The most common tumor types are NSCLC (4 pts) and melanoma (3 pts). One patient in cohort 3 (0.5 μg/kg) developed a DLT (G3 transient AST/ALT increase). None of the pts in cohorts 1 (0.1 μg/kg), 2 (0.25 μg/kg), 4 (1 μg/kg), and 5 (2 μg/kg) developed a DLT. The most common treatment-related adverse events (TRAEs) of any grade were fever (88%), fatigue (41%), and lymphocyte count decrease (41%). The most common CTCAE G3 TRAE was pyrexia (12%). 8 of 14 pts had Stable Disease, and one patient suffering from metastatic TNBC achieved a Partial Response at week 8. The Dose Escalation part of the trial is still ongoing.

Conclusions: Intravenous infusion with IL12-L19L19 treatment has been tolerated up to 2 μg/kg. The RD of IL12-L19L19 is still to be defined. Initial signs of activity have been observed.

Clinical trial identification: EudraCT 2019-000613-36, NCT04471987.

Legal entity responsible for the study: Philogen S.p.A.

Funding: Philogen S.p.A.

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1038P A phase II trial of the IO102-IO103 vaccine plus pembrolizumab: preliminary analysis for first-line (1L) treatment of non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head and neck (SCCHN)

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Background: The IO102-IO103 vaccine is an investigational first-in-class, dual-antigen, immune-modulatory therapy that stimulates activation of T cells against IDO+ and/or PD-L1+ cells in cancer, resulting in potentially increased susceptibility to anti-PD-1 blockade. Treatment with IO102-IO103 plus nivolumab in anti-PD-1 naïve metastatic melanoma shows high clinical activity and is well tolerated (Kjeldsen, Nat Med 2021). Thus, there is strong rationale for combining IO102-IO103 and anti-PD-1 therapy in 1L treatment of NSCLC and SCCHN.

Methods: This is a phase 2, non-comparative, open-label, multi-cohort trial (EudraCT No. 2021-003026-69; ClinicalTrials.gov No. NCT05077709). Patients (pts) with no prior treatment for metastatic disease are being enrolled: metastatic NSCLC, with PD-L1 tumor proportion Score $\geq$50% (Cohort A); recurrent or metastatic SCCHN with PD-L1 combined positive scores $\geq$20 (Cohort B). Pts receive 3-week cycles of subcutaneous IO102-IO103 (85-85 µg on Day [D] 1 and 8 of Cycle 1 and 2, then D1 only) plus intravenous pembrolizumab (200 mg on D1), for $\leq$2 years. Primary endpoint is overall response rate by RECIST 1.1., with secondary endpoints including safety.

Results: At data cut-off (April 12, 2023) 15/22 and 4/6 enrolled pts were efficacy evaluable ($\geq$2 full cycles of treatment and $\geq$1 scan) in Cohorts A and B, respectively. Eleven and two patients had 2 or more scans in Cohort A and B. In Cohort A, 8 pts (53.3%) had a partial response (PR; 4 confirmed), while 5 had stable disease; 2 pts had progressive disease (PD). In Cohort B, 2 pts (50%) had a PR (1 confirmed) and 2 pts had PD. For the 28 treated pts, any grade treatment-related adverse events (TRAEs) occurred in 17 (60.7%) with 1 (3.6%) being serious. Most common TRAE reported was injection site reactions (n=8; 28.6%).

Conclusions: This preliminary analysis suggests combining IO102-IO103 and pembrolizumab in pts with metastatic NSCLC and recurrent/metastatic SCCHN is tolerable, with encouraging clinical activity, and supports further development. Enrollment is ongoing. Additional clinical and biomarker data from trial patients are planned to be presented at the meeting.

Clinical trial identification: EudraCT: 2021-003026-69 Start date: 2022-05-09 (date of competent authority decision) Date on which this record was first entered in the EudraCT database: 2021-12-14 ClinicalTrials.gov Identifier: NCT05077709.

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1039P First-in-human phase I study of givastomig, a novel Claudin 18.2/4-1BB bispecific antibody in advanced solid tumors

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Background: Givastomig is a first-in-class bispecific antibody designed to target tumors with a wide range of Claudin 18.2 (CLDN18.2) expression and engage 4-1BB through a unique conditional activation mechanism at the tumor sites to avoid systemic toxicities.

Methods: This study evaluates safety, clinical response (RECIST v1.1), pharmacokinetics (PK), soluble 4-1BB (s4-1BB) levels, serum cytokines and immunophenotypes. Givastomig was administered intravenously every 2 weeks (Q2W) across 8 dose levels (0.1-15mg/kg) in patients with advanced solid tumors. The Bayesian Optimal Interval design was utilized during dose escalation without CLDN18.2 preselection. Additionally, 6 CLDN18.2+ patients per dose level were enrolled at 5, 8, and 12mg/kg in parallel expansions. CLDN18.2+ is defined as ≥1% of tumor cells with ≥1+ intensity by immunohistochemistry.

Results: As of 18 April 2023, 50 patients were enrolled (32 in the dose escalation and 18 in the parallel expansions) with a median age of 66 years, ECOG 0/1 (34%/66%), and a median of 3 prior lines of therapy. No dose-limiting toxicity was observed up to 15 mg/kg, and maximum tolerated dose was not reached. The most common treatment-related adverse events (TRAEs) were Grade 1/2 nausea (22%), fatigue (14%), and vomiting (12%) with 7 sporadic Grade 3 TRAEs, and no Grade ≥4 TRAEs. Givastomig exhibited a linear PK at doses ≥5 mg/kg and a dose-dependent increase of s4-1BB levels reaching a plateau at doses ≥8 mg/kg. Among 18 efficacy-evaluable patients with CLDN18.2+ gastroesophageal cancer (GEC) at 5, 8, and 12mg/kg, partial response (PR) in 1 patient each at 5 and 8 mg/kg, unconfirmed PR in 2 patients at 12 mg/kg, and stable disease in 2 patients were observed. An additional PR was observed in 1 patient with head and neck cancer at 12mg/kg. CLDN18.2 expression among the responders ranged from 11% to 100%.

Conclusions: Givastomig is well tolerated up to 15 mg/kg Q2W. Encouraging monotherapy activity was observed in heavily pre-treated GEC patients with a wide range of CLDN18.2 expression, including low CLND18.2 tumors. The PK profile, s4-1BB induction, and efficacy signal support 12 mg/kg as an optimal dose. Further development of givastomig mono- and combo- therapy in GEC and other cancers is planned.

Clinical trial identification: NCT04900818.

Legal entity responsible for the study: I-Mab Biopharma.

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1040P Phase I study of IL-8 inhibitor AMY109 plus atezolizumab (atezo) in patients (pts) with advanced solid tumours

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Background: AMY109 is a humanised monoclonal antibody that binds to IL-8. IL-8 plays a role in immunosuppression, fibrosis and epithelial-to-mesenchymal transition in the tumour microenvironment (TME). Combining AMY109 with atezo (anti-PD-L1) may enhance its anti-tumour effects by making the TME more favourable to PD-L1 inhibition.

Methods: This multicentre, open-label, dose-escalation study evaluated the safety, tolerability and pharmacokinetics (PK) of AMY109 (2—45 mg/kg) plus atezo (1200 mg) IV q3w in Part 1, and AMY109 (15—45 mg/kg) plus atezo (1200 mg) IV q3w in Part 2 in pts with previously treated advanced solid tumours and ECOG PS 0—1. Primary endpoints were AMY109 and atezo PK, safety and dose-limiting toxicity (DLT) in Part 1, and safety and anti-tumour activity in Part 2.

Results: Thirty-eight pts (18 in Part 1, 20 in Part 2) were enrolled (Table). Part 1 showed no DLTs and a dose-proportional increase in AMY109 exposure over 2—45 mg/kg, with no apparent change in mean atezo serum concentrations (94—115 µg/mL at Cycle 2 pre-dose across AMY109 dose groups). In Part 2, a total of 4, 12 and 4 pts received 15, 30 and 45 mg/kg AMY109, respectively. Accumulation of plasma IL-8 concentration after starting AMY109 was seen in all dose cohorts. The table shows safety data and anti-tumour activity. No adverse events led to treatment withdrawal. Overall, the objective response rate was 5%; the disease control rate was 29%. The two pts with partial responses had uterocervical and pancreatic cancer, respectively, and had been treated for >500 days at the cut-off date (22 July 2022): one received 45 mg/kg AMY109 throughout, and the other received 30 mg/kg AMY109 until cycle 6, and 45 mg/kg thereafter. Exploratory biomarker results will be presented.

Table: 1040P

	Part 1					Part 2
AMY109 dose, mg/kg	2	6	15	30	45	15—45
Patients, n[a]	3	3	3	3	6	20
Safety, n (%)						
TRAE	3 (100)	1 (33)	3 (100)	0	6 (100)	8 (40)
Grade 3—4 TRAE	1 (33)	0	0	0	1 (17)	3 (15)
Confirmed best response, n (%)						
Responders	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (5)
Partial response	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (5)
Disease control rate	2 (67)	0 (0)	0 (0)	1 (33)	2 (33)	6 (30)

TRAE, treatment-related adverse event (related to any treatment). [a]Patients had oesophageal, colorectal, head and neck, pancreatic, breast, uterine, ovarian and other cancers.

Conclusions: AMY109 showed dose-proportional increases in exposure. With no DLTs, AMY109 plus atezo was well tolerated in pts with advanced solid tumours, with no new safety signals. The partial responses were durable.

Clinical trial identification: jRCT2080225101.

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1041P Phase I open-label, dose escalation and expansion study of YH003, an anti-CD40 agonist monoclonal antibody in combination with toripalimab in patients (pts) with advanced solid tumours

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Background: Agonistic CD40 antibodies have been shown to promote anti-tumour T cell responses and promising activity has been observed in advanced solid tumours. Here we report the results of a multicenter, open-label study of YH003 + Toripalimab in dose escalation for pts with advanced solid tumours.

Methods: This was a phase I dose-escalation and expansion study. Part 1 was dose-escalation stage using an accelerated "3+3" design. The primary objective of Part 1 was safety and tolerability and to identify a maximum tolerated dose (MTD). Patients with advanced solid tumours received YH003 by IV administration Q3W as monotherapy at 0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg for the first cycle (21 days), then in combination with fixed-dose Toripalimab at 240 mg Q3W from cycle 2. Patients tolerating treatment and deriving benefit could continue treatment for up to 1 year.

Results: Between 29 Jul 2020 and 26 May 2022, 20 pts were treated in Part 1. A DLT (dose-limiting toxicity) was observed at 1.0 mg/kg dose level (grade 3 transaminitis) in 1 pt. The MTD was not reached. Among Part 1 pts, 13 (65%) had any grade treatment related adverse events (TRAEs). The most common ($\geq$ 10%) TRAEs were infusion related reactions, pyrexia, fatigue, nausea, elevated AST/ALT. No Grade 3-5 TRAEs and treatment-related SAEs occurred. 8 pts had received prior immunotherapy (PD-1/PD-L1 or PD-1+CTLA-4). Among 16 pts assessable for response, 1 pt achieved a complete response (CR), another pt achieved a partial response (PR) and 3 pts achieved stable disease (SD). A pt with anti-PD1/anti-CTLA4 refractory ocular melanoma with liver metastases (0.1 mg/kg dose level) achieved PR at the first tumour assessment in week 10 and ultimately a CR after nearly 2 years of study treatment. YH003 was well tolerated up to 3.0 mg/kg dose levels when combined with Toripalimab. Combining safety and preliminary efficacy data, the recommended dose of YH003 for part 2 was 0.3 mg/kg.

Conclusions: YH003 was well tolerated up to 3.0 mg/kg dose levels when combined with Toripalimab, and 0.3mg/kg was deemed the RP2D. YH003 has shown encouraging antitumour activity in patients with advanced solid tumours.

Clinical trial identification: NCT04481009.

Legal entity responsible for the study: Eucure (Beijing) Biopharma Co., Ltd.

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1042P INSIGHT 003 evaluating feasibility of eftilagimod alpha (soluble LAG-3) combined with first-line chemo-immunotherapy in metastatic non-small cell lung cancer (NSCLC) adenocarcinomas

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Background: Stratum C of the INSIGHT platform trial evaluates eftilagimod alpha (efti) combined with standard of care (SOC) 1st line chemo-immunotherapy (IC) in metastatic NSCLC patients (pts). Efti is an MHC class II agonist (soluble LAG-3 protein) activating antigen-presenting cells followed by T-cell (CD4/CD8) activation. Efti aims to enhance efficacy of IC.

Methods: Pts with 1st line advanced or metastatic NSCLC adenocarcinomas (non-squamous) receive carboplatin AUC5 / pemetrexed 500 mg/m^2 q3w 4 cycles followed by optional pemetrexed 500 mg/m^2 q3w maintenance plus pembrolizumab 200 mg q3w combined with s.c. efti (30 mg) (q2w for 24 weeks; thereafter q3w till week 52). Imaging: q8w. Primary endpoint: feasibility (safety / tolerability). Secondary endpoints include ORR (RECIST 1.1.), PFS, OS.

Results: From 02Aug2021 till data cut off 18Apr2023 21 pts were enrolled and received treatment (median age: 65 years; 66.7% male). No occurrence of unacceptable toxicities. 10 SAE (grade 1-2: 3; grade 3: 4; grade 4: 0; grade 5: 3) were reported. 1 pancreatitis was possibly related to efti (or immunotherapy in general) and unexpected. So far, 4 pts completed max. treatment with efti for 52 weeks. The most frequent AEs were anemia in 18 pts (52.4%, grade 1-2 and 33.3%, grade 3), neutropenia in 18 pts (19.0%, grade 2 and 66.7%, grade 3-4), leukopenia in 16 pts (28.6%, grade 1-2 and 47.6%, grade 3-4) and thrombocytopenia in 14 pts (42.9%, grade 1-2 and 23.8%, grade 3-4). 5 AEs with grade 3 and no AE with grade 4 and 5 were considered related to efti. Out of 21 pts, 14 pts (67%) showed partial response, 5 (24%) stable disease, 2 (9%) progressive disease as BOR. Even pts with negative or low PD-L1 status (TPS) showed promising efficacy signals. Median follow up: 8.3 months, median OS: not reached.

Conclusions: To date, 30 mg efti combined with SOC appears to be feasible and safe with promising signals of efficacy, so that the trial was amended for inclusion of further 30 pts.

Clinical trial identification: EudraCT 2016-002309-20, NCT03252938.

Legal entity responsible for the study: Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest, Steinbacher Hohl 2-26, D-60488 Frankfurt, Germany.

Funding: Immutep GmbH.

Disclosure: S. Al-Batran: Financial Interests, Personal, Advisory Board: Lilly, Bristol Myers Squibb, MacroGenics, Immutep, MSD Sharp & Dohme; Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Lilly, AIO Studien gGmbH, MCI Deutschland GmbH; Financial Interests, Personal, Other, CEO/founder: Institute of Clinical Cancer Research IKF at Northwest Hospital; Financial Interests, Institutional, Research Grant: Sanofi, Roche, Celgene, Vifor, Medac, Hospira, Lilly, Eurozyto, Immutep, Ipsen, Bristol Myers Squibb, MSD Sharp & Dohme, AstraZeneca, German Cancer Aid (Krebshilfe), German Research Foundation, Federal Ministry of Education and Research. T.O. Goetze: Financial Interests, Personal, Advisory Role: Lilly, MSD Oncology, Bayer, SERVIER, Roche, Novartis, Incyte, Foundation Medicine, Bristol Myers Squibb; Financial Interests, Personal, Speaker's Bureau: Lilly; Financial Interests, Personal, Research Funding: Deutsche Forschungsgemeinschaft, Gemeinsamer Bundesausschuss; Financial Interests, Institutional, Research Funding: Deutsche Krebshilfe, Lilly, AstraZeneca, Incyte. All other authors have declared no conflicts of interest.

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1043P First-in-human study of TU2218, TGFβRI and VEGFR2 dual inhibitor in patients with advanced solid tumors

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Background: TU2218 is a highly potent, oral dual inhibitor against TGFβ type I receptor (TGFβRI /ALK5) and VEGFR2. VEGF and TGF-β pathways play important roles in the function of TME, especially in immune tolerance inextricably related with poor outcomes of anti-PD-(L)1 therapy. This is a first-in-human study to investigate the safety and tolerability of TU2218 mono- and combination therapy with pembrolizumab.

Methods: This non-randomized, multinational, open-label study has been evaluating the safety, tolerability, PK, and preliminary efficacy of TU2218 mono- and combination therapy with pembrolizumab in advanced solid tumors. The eligible patients were aged ≥ 18 years, ECOG (0 or 1), and had measurable tumors per RECIST 1.1. TU2218 monotherapy was planned at 6 dose levels (30, 60, 105, 150, 195, 270 mg/day) with 2 weeks on and 1 week off in 3-week cycles according to the BOIN method. The starting dose of TU2218 given with pembrolizumab was determined after yielding TRAEs of at least Grade 2 in severity during monotherapy using the traditional 3+3 design.

Results: Seventeen patients with advanced solid tumors received 5 different dose levels of monotherapy. Major demographics, treatment-related adverse events (TRAEs) and PK parameters are summarized in the table.

Table: 1043P

Cohort	1	2	3	4	5
Total Daily Dose (mg)	30	60	105	150	195
N	3	4	4	3	3
Median age (Range)	54 (48-56)	61 (46-78)	70 (52-77)	72 (56-72)	65 (37-75)
Male/ Female	0/3	2/2	1/3	1/2	1/2
TRAE, n (Grade)	0	3 (G2)	2 (G2)	1 (G2)	6 (G2)
* G2 TRAEs were reported from 2 patients of Nausea, Dehydration, Fatigue in Cohort 2, 2 patients of Itching & Platelet Count Decreased in Cohort 3, 1 patient of Nausea in Cohort 4, and 3 patients of Itching, Skin Rash, Myalgia, Anorexia, Arthralgia & Mucositis oral in Cohort 5.					
Mean PK Parameters					
tmax (h)	1	0.7	1.6	1.2	
Cmax (ng/mL)	95	162	374	781	1875
AUClast (ng·h/mL)	200	257	819	1854	3664
t1/2 (h)	2.1	1.7	1.7	2.6	
* For cohort 5, simulated data					

No TRAEs of Grade 3 or higher were reported while all Grade 2 TRAEs were tolerable in TU2218 monotherapy. Systemic exposure to TU2218 increased over-proportionally with the dose-escalation. The starting dose of TU2218 for the combination therapy with pembrolizumab was 105mg/day, with subsequent incremental doses of 150mg/day and 195mg/day. To date, clinical studies of TU2218 are ongoing.

Conclusions: TU2218, a first-in-class oral dual inhibitor against TGFβRI and VEGFR2, was well-tolerated in the monotherapy.

Clinical trial identification: NCT05204862.

Legal entity responsible for the study: TiumBio Co., Ltd.

Funding: TiumBio Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

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1044P A phase Ia first-in-human study of JS007, a novel anti-CTLA-4 monoclonal antibody, in patients with advanced solid tumors

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Background: JS007 is a humanized IgG1 monoclonal antibody that targets cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) with superior binding affinity and anti-tumor activity from the preclinical study. Here we report the results of a first-in-human phase 1a study which assessed the safety, pharmacokinetics, and preliminary efficacy of JS007 in patients (pts) with advanced solid tumor (NCT05049265).

Methods: This open-label, single-arm, multicenter, phase 1a trial enrolled pts with advanced solid tumor who were resistant or intolerant to standard treatment, and included dose escalation and dose expansion phases. In the dose escalation phase, an accelerated titration followed by 3+3 design was used to assess the tolerability and safety of JS007 administered intravenously at doses of 0.03, 0.3, 1, 3 and 10 mg/kg Q3W. In the dose expansion phase, two dose cohorts were selected to enroll additional 6-9 pts per cohort.

Results: As of April 25, 2023, 26 pts had received JS007 (8 pts received > 3 prior lines of standard regimens, and 17 were pretreated with immunotherapy), including gastric adenocarcinoma (n=5) and non-small cell lung cancer pts (n=4). No dose-limiting toxicity was observed and the maximum tolerated dose was not reached. The dose cohorts of 3 and 10 mg/kg were expanded. Seventeen (65.4%) pts experienced treatment-related adverse events (TRAEs), with 8 (30.8%) experiencing grade 3 or higher TRAEs. The most common TRAEs (≥10%) were alanine aminotransferase increased (15.4%, 4/26), hemoglobin decreased (15.4%, 4/26), aspartate aminotransferase increased (11.5%, 3/26), and lipase increased (11.5%, 3/26). Among the evaluable 21 pts, one patient at 3 mg/kg achieved partial response and 11 reported disease stable (SD). One esophageal squamous cancer patient at 1 mg/kg showed SD for 8 months. Pharmacokinetics analysis showed serum exposure of JS007 generally increased with an increasing dose over the assessed dose range.

Conclusions: JS007 is well-tolerated with preliminary promising efficacy in heavily pretreated pts. The dose expansion phase is still ongoing, and the combination of JS007 with the anti-PD-1 antibody toripalimab is planned.

Clinical trial identification: NCT05049265.

Legal entity responsible for the study: Shanghai Junshi Biosciences Co., Ltd.

Funding: Shanghai Junshi Biosciences Co., Ltd.

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1045P Safety and preliminary clinical activity of JNJ-78306358 (JNJ-358), an HLA-G and CD3 bispecific antibody, for the treatment of advanced stage solid tumor

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Background: HLA-G has limited normal tissue expression but is expressed in a variety of human cancers where it may have an immune evasion function. JNJ-6358 is a bispecific antibody that redirects T cells to kill HLA-G-expressing tumor cells.

Methods: This phase 1 dose escalation study evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of JNJ-6358 administered subcutaneously to adult participants (pts) with metastatic or unresectable solid tumors with a high prevalence of HLA-G expression: renal cell carcinoma (RCC), ovarian cancer (OC), and colorectal cancer (CRC). Dose escalation followed a modified continual reassessment method.

Results: As of 09 February 2023, 39 pts (23 with CRC, 10 with OC, and 6 with RCC) were dosed once weekly in 7 cohorts. Premedication included high dose corticosteroids. The majority of pts (54%) had 4 or more prior lines of systemic therapy for metastatic disease. The most common treatment-emergent adverse events were cytokine release syndrome (CRS) (49%), ALT/AST increase (39%), injection site erythema (39%), fatigue (36%), and abdominal pain (26%). CRS was G1 or G2 and responded to tocilizumab. Dose limiting toxicities (DLTs) were reported in 4 pts, 2 with G3 increased transaminases, 1 with G3 pneumonitis, and 1 with recurrent G1 CRS requiring dose reduction. G3 DLTs coincided with CRS. No treatment related

deaths were reported. There were no objective responses per RECIST. Target lesion reduction >10% from baseline was observed in 5 pts. Two pts had stable disease >40 weeks. HLA-G was detected (IHC H-score > 0) in archival tissue from 12 of 25 pts. No relationship between tumor reduction and baseline HLA-G expression was observed. JNJ-6358 exposure levels increased with dose. Anti-drug antibodies (ADA) were observed in 45% of evaluable pts and were associated with loss of detectable exposure.

Conclusions: JNJ-6358 dose escalation was limited by CRS-associated toxicities, which were only partially mitigated by step-up-dosing and premedication. Considering the CRS-related toxicities and the ADA formation, the Sponsor decided to halt dose escalation. No recommended phase 2 dose was determined.

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Funding: Janssen R&D.

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Moreno Garcia: Financial Interests, Personal, Advisory Board: BMS, Janssen, Roche, Basilea, Bayer, AstraZeneca; Financial Interests, Personal, Full or part-time Employment: START; Financial Interests, Institutional, Local PI, AbbVie, AceaBio, Adaptimmune, ADC Therapeutics, Aduro, Agenus, Amcure, Amgen, Astellas, AstraZeneca Bayer BeiGene BioInvent International AB, BMS, Boehringer, Boheringer, Boston, Celgene, Daichii Sankyo, DEBIOPHARM ,Eisai, e-Terapeutics, Exelisis, Forma Therapeutics, Genmab, GSK, Harpoon, Hutchison, Immutep, Incyte, Inovio, Iovance, Janssen, Kyowa Kirin, Lilly, Loxo, MedSir, Menarini, Merck, Merus, Millennium, MSD, Nanobiotix, Nektar, Novartis, Odonate Therapeutics, Pfizer, Pharma Mar, PharmaMar, Principia, PsiOxus, Puma, Regeneron, Rigontec, Roche, Sanofi, Sierra Oncology, Synthon, Taiho, Takeda, Tesaro, Transgene, Turning Point Therapeutics, Upshersmith.: Multiple. All other authors have declared no conflicts of interest.

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1046P Phase I/II open-label study on an anti-GPC3 T cell engager, SAR444200, in patients with advanced solid tumors: Preliminary dose escalation results

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Background: SAR444200 is a novel NANOBODY® T cell engager that simultaneously binds TCR$\alpha\beta$ and glypican-3 (GPC3) to co-engage T cells with GPC3-expressing tumor cells, resulting in T cell-dependent cellular cytotoxicity. Here, we present the preliminary safety, pharmacokinetics (PK) and biomarker data for the first two dose levels (DLs) of SAR444200 in patients with advanced solid tumors in dose escalation cohort (Part 1A) from the study (EudraCT 2021-006623-17/ NCT05450562).

Methods: This ongoing phase 1/2 open-label trial, evaluated intravenously administered SAR444200 in adult patients with GPC3+ solid tumors. Treatment was administered weekly following a lead- in dose administration at two DLs (DL1 and DL1A). Whole blood samples were collected to assess biomarkers and plasma concentrations of SAR444200. PK analysis was performed with ECL-based total PK assay using Meso Scale Discovery platform. A validated multiplex ELISA based assay was used for cytokine analysis.

Results: Tumor tissues from 115 patients were prescreened to identify GPC3-positive tumor cells by immunohistochemistry in a central lab. The positivity rate for hepatocellular carcinoma (HCC) was 18/21 patients (86%), and for non-small cell lung cancer was 3/6 patients (50%). As of 17th January 2023, a total of 8 patients received SAR444200 (DL1: n=4; DL1A: n=4). Most patients (87%) presented with HCC. No dose-limiting toxicities were observed. Six of 8 patients (75%) reported treatment-related adverse events (TRAEs) of any grade (Gr), including one patient with a serious TRAE (prolonged hospitalization due to Gr 2 CRS [cytokine release syndrome]). Gr 1 or 2 CRS was observed in 5 (62%) patients. Infusion-related reaction occurred in 1 (25%) patient. Following lead-in dosing up to Day 15, the maximum observed concentration (C_{max}) of SAR444200 at first two DLs occurred at the end or shortly after the end of infusion. Biomarker analysis showed an increase of cytokines (interleukin-6 and interferon gamma) during Cycle 1. Cytokines declined after Cycle 1.

Conclusions: These preliminary results from the first two DLs suggest that SAR444200 is tolerable at the tested DLs in patients with advanced solid tumors. Dose escalation continues at this time.

Clinical trial identification: EudraCT 2021-006623-17, NCT05450562.

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1047P AXA-042, a systemically administered TLR2/6 agonist, demonstrates target engagement and TLR pathway activation in patients with advanced solid tumors

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Background: AXA-042 is a novel synthetic, pegylated toll-like receptor (TLR) 2/6 agonist in development for the treatment of advanced solid tumors. Nonclinical pharmacology studies have demonstrated that AXA-042 functions through a multicellular mechanism, including activation of the pro-inflammatory innate immune response, reduction in immunosuppressive macrophages at the tumor site, activation of dendritic cells, and release of chemokines to facilitate T-cell recruitment. A first-in-human study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of AXA-042 as monotherapy and in combination with a checkpoint inhibitor in subjects with advanced solid tumors is currently ongoing (ACTRN12622000993796).

Methods: AXA-042 is administered intravenously once every 21 days. After obtaining informed consent, whole blood and plasma samples were collected from patients pre- and post-treatment for assessment of AXA-042 pharmacokinetics and pharmacodynamic biomarkers. The Nanostring nCounter™ PanCancer IO 360 Panel and a 43-marker CYTOF panel were used to identify AXA-042 transcriptomic and immune modulation response signatures in whole blood samples collected 24- and 168-hours post dose. The OLINK Target 48 Cytokine Panel was used for the longitudinal assessment of cytokine modulation.

Results: Preliminary statistical analysis of immunomodulatory effects pre- and post-treatment is consistent with the proposed mechanism of AXA-042. Samples from the initial cohort of patients (n=3-6) displayed consistent transient induction of cytokines and chemokines, that returned to baseline within 2-8 hours post dose. Nanostring analysis confirmed TLR pathway engagement and revealed an induction of pro-inflammatory gene signatures, associated with myeloid cell activation and NFkB signaling. CYTOF characterization of immune subset activation and additional transcriptomic analyses are underway and will be presented.

Conclusions: AXA-042 demonstrates on-target biological activity in patient blood samples. Further biomarker analyses are ongoing and will be correlated with clinical activity in a larger number of patients.

Clinical trial identification: ACTRN12622000993796.

Legal entity responsible for the study: Axelia Oncology.

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Disclosure: A. Latifi, P. Kearney: Financial Interests, Personal, Full or part-time Employment: Axelia Oncology. P. Wabnitz, A. Galkin: Financial Interests, Personal, Financially compensated role: Axelia Oncology. All other authors have declared no conflicts of interest.

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1048P Phase I/II Study of JK08, an IL-15 antibody fusion protein targeting CTLA-4, with unresectable locally advanced or metastatic cancer

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Background: CTLA-4 is a central inhibitory regulator of T-cell activation & a hallmark of T-regulatory cells (Tregs). Emerging evidence suggests anti-tumor activity of CTLA-4 antibodies may be modulated by the local presence of NK cells, which can mediate Treg depletion. IL-15 is a pleiotropic cytokine important in both innate & adaptive immunity. The IL-15/IL-15Rα complex can stimulate adjacent cells through the IL-2Rβ/γ complex, with the highest expression on NK cells & CD8+ T cells. JK08, a fully human monoclonal antibody specific for CTLA-4 with a C-terminal fusion consisting of IL-15/IL-15Rα, is intended to widen the therapeutic window for CTLA-4-targeted therapy & IL-15 targeted therapy. Preclinical studies demonstrate JK08 retains the functionality of the CTLA-4 antibody & the IL-15 fusion domain.

Methods: Patients (pts) with relapsed/refractory solid tumors receive subcutaneous (SQ) JK08 monotherapy once weekly in this phase 1/2 accelerated 3+3 dose escalation study. Pts are evaluated for safety and anti-tumor activity. Secondary endpoints include evaluation of pharmacokinetic parameters & immunogenicity. Exploratory endpoints include PK, proliferation & activation markers of immune cell populations, & changes in cytokine levels. Four expansion cohorts are planned following dose escalation.

Results: Eighteen (18) refractory metastatic solid tumor pts have been treated to date with JK08. A maximal tolerated dose has not been reached. Median (range) age: 66.5 (53 - 80) years. To date, treatment has been well-tolerated, with adverse events consisting primarily of Gr 1 & 2 injection site reactions (ISRs), which recover with NSAIDs & do not worsen with subsequent treatments. Other than ISRs, no Gr 2 or higher adverse events have been observed to date. 11 pts remain on treatment, with the longest continuing therapy for 23 weeks. *Ex-vivo* analyses have shown dose-dependent pharmacodynamic effects.

Conclusions: At the dose levels evaluated to date, JK08 has been well tolerated, demonstrating preliminary disease stability & anticipated modulation of target immune cell populations in aggressive heavily pre-treated solid tumors. These results provide an initial characterization of JK08 biology & activity.

Legal entity responsible for the study: Salubris Biotherapeutics, Inc.

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Disclosure: J. Johnson, J.P. McNally, A. McEwen, S. Murphy, S. Singhal: Financial Interests, Institutional, Full or part-time Employment: Salubris Biotherapeutics, Inc. All other authors have declared no conflicts of interest.

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1049P Phase Ib/II trial of envafolimab, a novel subcutaneous single-domain anti-PD-L1 monoclonal antibody, plus lenvatinib in patients with selected advanced solid tumors

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Background: Envafolimab is the world's first subcutaneously injectable anti-PD-L1 antibody approved by China's National Medical Products Administration with the injection time of less than 20 seconds. Here, we report the results from a phase Ib/II study of envafolimab plus lenvatinib in patients with selected advanced solid tumors.

Methods: This was an open-label, multi-center trial. 6 patients with advanced solid tumors were enrolled in the phase Ib study for safety evaluation first, and then the phase II was divided into two cohorts. Cohort 1, PD-(L)1 inhibitor therapy resistant advanced non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). Cohort 2, treatment naive advanced RCC. The objectives of phase Ib were to assess the safety and determine the recommended phase II dose (RP2D) for envafolimab plus lenvatinib. The primary endpoint of phase II was objective response rate (ORR) per RECIST v1.1.

Results: As cutoff date of March 31 2023, 24 patients were enrolled in phase Ib (n = 6) and the phase II expansion (n = 18). The RP2D was envafolimab 400mg every 4 weeks plus lenvatinib 20 mg/d. In PD-(L)1 resistant NSCLC (n=11), ORR was 27.3 % (95% CI: 6.0% to 61.0%), median duration of response (mDOR) was 4.2 months (95% CI: 3.7 to NE) and median progression-free survival (mPFS) was 8.1 months (95% CI: 1.8 to NE). In treatment naive RCC (n=5), ORR was 80.0% (95% CI: 28.4% to 99.5%), mDOR was NE (95% CI: NE to NE) and mPFS was NE (95% CI, NE to NE). The most common treatment-related adverse events (TRAEs) were proteinuria (75.0%), hypothyroidism (70.8%) and hypertension (62.5%). There were no grade 5 TRAEs and no TRAEs resulted in envafolimab or lenvatinib discontinuation.

Conclusions: Envafolimab in combination with lenvatinib demonstrated a robust preliminary ORR and mPFS in PD-(L)1 resistant NSCLC patients with manageable safety profile. In consistent with the results from other intravenous anti-PD-1 antibody plus Lenvatinib in RCC patients, subcutaneous injection of envafolimab with lenvatinib provided a more convenient dose regimen in this population. Further evaluation of this combination therapy are underway in both populations.

Clinical trial identification: NCT05024214.

Legal entity responsible for the study: 3D Medicines Inc.

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1050P Sensitization to immunotherapy through manipulation of tumor transcription by lurbinectedin

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Background: Despite recent advances in the use of immunotherapy only a minority of cancers respond to immune checkpoint blockade (ICB). Current cytotoxic drug treatments for small cell lung cancer (SCLC) have been known to act by induction of DNA damage. These notable results can be explained by high number of genomic aberrations observed in SCLC combined with rapid cellular proliferation resulting in accumulation of DNA damage and genomic instability. SCLC cells are reliant on DNA damage repair pathways and transcription proficiency. Recent preclinical data have shown that the DDR influences multiple aspects of tumor immunogenicity. We propose the sensitizing of ICB resistant tumors through transcriptional stress by exposure to the RNA Pol II inhibitor lurbinectedin (LUR). 2SMALL is a two-part phase 1/2 study assessing the safety, tolerability and efficacy of LUR in combination with atezolizumab (ATZ) as second line treatment for ES-SCLC.

Methods: 2SMALL phase I was an open-label, single arm, dose exploration trial. ES-SCLC patients received increasing doses of LUR plus a fixed dose of ATZ every 3 weeks following a standard 3+3 dose escalation design. Study endpoints included the definition of the safety profile and the recommended dose. Additional objectives included efficacy (ORR and PFS). A syngeneic immunocompetent mice model for SCLC (Rb-/-p53-/-) has been used to identify the efficacy of LUR in combination with an anti PD-L1 mAb. The role of LUR at inducing DNA sensing pathways was evaluated in several cell lines, PDX derived organoids and ex vivo.

Results: Objective responses were observed in 15 pts (ORR: 57.69%), including complete responses in 2 pts (7.69%), partial response in 13 pts (50%). 6 pts had stable disease (26.92%) and 3 pts progressive disease (11.54%). Disease control rate was 84.61 %, median PFS was 4.93 months (range 3.37 - 7.67 months). Type I IFN pathway, proinflammatory cytokines, chemokines and PD-L1 were upregulated by LUR in SCLC models.

Conclusions: Combination of LUR plus ATZ was well tolerated, with no unexpected toxicities. Preliminary anti-tumor activity is remarkable. Our results show effective tumor-activating IFN type 1, which increases immunity against tumors and provides the rationale to combine DDR inhibitors with ICBs.

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1051P Intratumoral injection of LTX-315 in combination with pembrolizumab in patients with advanced melanoma refractory to prior PD-1/PD-L1 therapy: Interim results from the ATLAS-IT-05 trial

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Background: LTX-315 is an oncolytic peptide of non-viral origin that is in clinical development for the treatment of solid tumors. We investigated whether treatment with LTX-315 in combination with pembrolizumab is safe and efficacious.

Methods: This open-label, single-arm phase II trial includes patients with stage IIIB-stage IVm1b (without liver metastases) metastatic melanoma, who have progressed on or after after PD-1/PD-L1 inhibitor therapy. In Part A, patients receive intratumoral LTX-315 injections (5 mg per injection and up to 40 mg total) on up to 7 treatment days over 5 weeks and pembrolizumab (200 mg i.v.) on Days 1 and 22. In Part B, pembrolizumab (400 mg i.v.) is given every 6 weeks starting at Day 43 until maximum 24 months. The primary objective is antitumor activity assessed by the investigators using RECIST v1.1 criteria. Secondary objectives include safety data.

Results: At the cutoff date of 24 April 2023, 14 of 20 planned patients have been enrolled and treated: 13 patients with metastatic melanoma and 1 patient with advanced acinic cell carcinoma (included under an earlier protocol version). Mean age of enrolled patients was 64 years and 50% had received 2 or more prior systemic anticancer therapies. Preliminary antitumor activity was evaluable in 7 patients who had $\geq$1 post-baseline scan available at the cutoff date. The Overall Response Rate was 14% with 1 patient with partial response. Disease Control Rate was 43%. All 14 enrolled patients had received $\geq$1 LTX-315 injection and $\geq$1 pembrolizumab infusion and were included in the interim Safety Population. Treatment-emergent adverse events (TEAEs) were reported in 11 patients (79%). The most common ($\geq$10%) TEAEs related to LTX-315 were mild to moderate injection site pain (50%) and asthenia (14%). There was no increase in immune-related adverse events.

Conclusions: Intratumoral LTX-315 administration in combination with pembrolizumab appears to be well tolerated and showed preliminary efficacy in patients with advanced melanoma. Updated efficacy and safety data will be presented at the conference.

Clinical trial identification: NCT04796194.

Legal entity responsible for the study: Lytix Biopharma AS.

Funding: Lytix Biopharma AS.

Disclosure: S. Dalle: Financial Interests, Institutional, Advisory Board: MSD, BMS; Financial Interests, Institutional, Research Grant: BMS, MSD. T.U. Marron: Financial Interests, Personal, Advisory Board: Regeneron, AbbVie, Merck, BMS, Boehringer Ingelheim, Atara, AstraZeneca, Genentech, Celldex, Chimeric, Glenmark, Simcere, Surface, G1 Therapeutics, NGMbio, DBV Technologies, Arcus, Astellas; Financial Interests, Personal and Institutional, Research Grant: Regerenor, BMS, Merck, Boehringer Ingelheim. C. Robert: Financial Interests, Personal, Other, Consultancy fees: BMS, ROCHE, PIERRE FABRE, NOVARTIS, SANOFI, MSD, ASTRAZENECA, PFIZER. M.S. Nyakas: Financial Interests, Personal, Speaker, Consultant, Advisor: BMS, MSD, Pierre Fabre, Novartis. K. Bruins Slot: Financial Interests, Personal, Full or part-time Employment: Lytix Biopharma AS. V. Sundvold: Financial Interests, Personal, Full or part-time Employment: Lytix Biopharma. î Rekdal: Financial Interests, Personal, Full or part-time Employment: Lytix Biopharma; Financial Interests, Personal, Stocks/Shares, Lytix Biopharma: Lytix Biopharma. B. Sveinbjornsson: Financial Interests, Personal, Full or part-time Employment: Lytix Biopharma; Financial Interests, Personal, Stocks/Shares: Lytix Biopharma. G. Currie: Financial Interests, Personal, Full or part-time Employment: Pasithea Therapeutics; Financial Interests, Personal, Advisory Role: Lytix Biopharma, Nanotics LLC; Financial Interests, Personal, Stocks/Shares: Regeneron Pharmaceuticals, Gilead; Financial Interests, Personal, Proprietary Information: Rainier Therapeutics. All other authors have declared no conflicts of interest.

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1052P Phase-Ib trial of metformin combined with nivolumab for refractory/recurrent solid tumors

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Background: Our previous findings showed that the addition of metformin to nivolumab achieved remarkable tumor regression and increased the number of tumor-infiltrating T cells in mouse models. Therefore, we conducted a phase Ib study with a combination therapy of nivolumab and metformin for patients with refractory/recurrent solid tumors.

Methods: The study consisted of part 1, evaluating the maximum-tolerated dose (MTD), safety, pharmacokinetics, and efficacy in solid tumors, and part 2, investigating principally safety at the recommended dose limited in thoracic and pancreatic cancers. Metformin and nivolumab were given orally at a dose of 750 mg to 2250 mg/day and biweekly at an intravenous fixed dose of 3mg/kg, respectively. The dose-limiting toxicity (DLT) was evaluated for each patient within the first 4 weeks. Both metformin and nivolumab were continued until confirmed progression or discontinued due to toxicity.

Results: Seventeen and twenty-four patients were enrolled in parts 1 and 2, respectively. The primary lesions were pancreatic cancer in 24 patients, thymic epithelial tumor in three patients, non-small cell lung cancer in two patients, and others in ten patients. The DLT was observed in one of six patients at a dose of 750 mg/day for metformin, one of six patients at a dose of 1500mg/day for metformin, and none of three patients at the maximum dose level of 2250 mg/day for metformin, which did not reach the MTD. Therefore, the dose of 2250 mg/day for metformin was selected in part 2. An objective response was observed in 4 of 41 patients (9.8% [95% confidence interval (CI): 2.7-23.1]. The one-year progression-free and overall survival rates were 9.8% [95% CI: 3.1-21.0] and 56.8% [95% CI: 34.2-74.3], respectively. Two patients have remained alive without progression for more than three years. There was no correlation between blood levels of metformin and treatment efficacy. Grade 1 hypoglycemia was observed in two patients, and Grade 3 lactic acidosis was observed in one patient.

Conclusions: This combination therapy was well tolerated and demonstrated clinically meaningful efficacy in selected patients. In the future, further verification of the mechanism in cases in which treatment was effective is required.

Clinical trial identification: UMIN000028405.

Legal entity responsible for the study: The authors.

Funding: Ono Pharmaceutical Co.Ltd.

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1053P Tumor-restricted delivery of an immune-therapeutic payload by modified macrophages for the treatment of glioblastoma: The TEM-GBM STUDY (NCT03866109)

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Background: The tumor microenvironment (TME) is a dynamic network including factors and host cells influencing cancer progression. TEMs (Tie2-Expressing Monocytes), a subset of tumor-associated myeloid cells transiently recruited to tumors and contributing to its progression, are an attractive target for the design of novel anti-cancer therapy.

Methods: TEM-GBM is an open-label, Phase 1/2a dose-escalation study evaluating safety and efficacy of Temferon in up to 27 newly diagnosed, unmethylated-MGMT GBM patients. The patients are assigned to 8 cohorts and receive a single increasing dose of Temferon. Temferon is a genetically modified, autologous hematopoietic stem cell-based therapy designed to deliver IFNα into the TME via Tie-2 expressing monocytes.

Results: As of February 2023, 4 doses of Temferon (0.5-3.0x106/kg) were tested across 18 patients assigned to 6 cohorts. Follow-up from surgery is 6—36mo (2—32mo after Temferon). To date, no DLTs have been identified. In all patients, there was fast hematological recovery from the sub-myeloablative conditioning regimens used and rapid engraftment of gene modified cells, which persisted, albeit at lower levels, up to 24 mo (longest time of analysis). Median OS is 15mo from surgery. To determine if Temferon therapy leads to a detectable adaptive immune response, T cell immunorepertoire was assessed in the tumor samples, at first and, when performed, second surgery (6 cases), and in peripheral blood cells. TCR analysis suggests a correlation between Temferon doses and T cell populations present in the TME, particularly in patients treated by higher doses of Temferon. The frequency of peripherally expanded clones found in the tumor samples increases by the second surgery, as evidence of a notable crosstalk between the peripheral and tumor repertoires of T cells.

Conclusions: The results provide initial evidence of Temferon's potential to reprogram GBM TME and elicit T cell-mediated immune responses.

Clinical trial identification: NCT03866109.

Legal entity responsible for the study: Genenta Science SpA.

Funding: Genenta Science SpA.

Disclosure: F. Ciceri: Financial Interests, Institutional, Principal Investigator: Genenta Science SpA. B. Gentner: Financial Interests, Personal, Stocks/Shares: Genenta Science SpA; Financial Interests, Personal, Financially compensated role, Advisor: Genenta Science SpA; Financial Interests, Personal, Research Funding: Genenta Science SpA. M. Eoli: Financial Interests, Institutional, Principal Investigator: Genenta Science SpA. S. Mazzoleni: Financial Interests, Personal, Full or part-time Employment: Genenta Science SpA; Financial Interests, Personal, Stocks/Shares: Genenta Science SpA. L. Naldini: Financial Interests, Personal, Stocks/Shares: Genenta Science SpA; Financial Interests, Personal, Financially compensated role, Advisor: Genenta Science SpA; Financial Interests, Personal, Research Funding: Genenta Science SpA. C. Russo: Financial Interests, Personal, Full or part-time Employment: Genenta Science SpA; Financial Interests, Personal, Stocks/Shares: Genenta Science SpA. G. Finocchiaro: Financial Interests, Institutional, Coordinating PI: Genenta Science SpA. All other authors have declared no conflicts of interest.

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1054P A phase Ia study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of a modular CLDN18.2-targeting PG CAR-T therapy (IBI345) in patients with CLDN18.2+ solid tumors

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Background: Chimeric antigen receptor (CAR) T-cell therapy holds great promise for the treatment of solid tumors; however, how to avoid or minimize the "on-target off-tumor" effect of CAR-T therapy remains a major issue, we developed a P329G (PG) modular and switchable CAR technology, in which CAR-T cells bind tumor antigens indirectly via an Fc-silent tumor-targeting human antibody(Ab) containing the PG mutation as an adapter molecule, whose activity is controllable by the PG Ab. Here, we report the first-in-human clinical results of a CLDN18.2-targeting PG CAR-T product (IBI345) for the treatment of CLDN18.2+ solid tumors.

Methods: In this phase 1a study, patients (pts) with CLDN18.2+ advanced solid tumor received an infusion of IBI345 consisting of one dose of PG CAR-T cells at escalating doses of 50, 250×10^6 cells plus $\geq$ 1 dose of CLDN18.2-targeting PG Ab at a fixed dose of 1mg/kg Q3W after lymphodepletion preconditioning. The objectives include safety and tolerability, pharmacokinetics and preliminary efficacy (per RECIST 1.1) of IBI345.

Results: As of Apr 7, 2023, 5 pts were treated with IBI345. All 5 pts experienced TRAEs, and grade $\geq$ 3 TRAE were neutrophil count decreased (n=2) and decreased appetite (n=1). No CRS, ICANS or treatment-related deaths occurred. For 4 efficacy-evaluable pts (Table), 1 EGJC pt achieved PR and 2 pts (1 GC, 1 PC) achieved SD. CAR-T expansion and persistence were detected in all pts, with a median peak of 1,840 copies/µg gDNA (1,500-4,020), a median time to peak of 16 days (9-20), and a median persistence of 45 days (35-127).

Conclusions: IBI345 demonstrated a manageable safety profile and preliminary efficacy in patients with CLDN18.2+ advanced solid tumors. To realize the full potential of this modular CAR-T cell product, the dose and regimen of the P329G Ab and CAR-T cells requires further exploration.

Clinical trial identification: NCT05199519.

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Legal entity responsible for the study: Innovent Cells Pharmaceuticals.

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Table: 1054P Overview of clinical and biomarker results for each individual patient

IBI345	Patient	CLDN 18.2 expression	Age (years)	Gender	Tumor Type	Previous lines	Best overall response
IBI345 PG IgG 1mg/kg + PG CAR-T cells 50*10-6	PT01	1+, 12%; 2+,3%; 3+, 0%	69	Male	Esophagogastric junction cancer (EGJC)	2	Partial response
IBI345 PG IgG 1mg/kg + PG CAR-T cells 250*10-6	PT02	1+, 1%; 2+,0%; 3+, 0%	64	Male	Gastric cancer (GC)	2	Stable disease
	PT03	1+, 0%; 2+, 5%; 3+, 90%	60	Male	Pancreatic cancer (PC)	2	Stable disease
	PT04	1+, 0%; 2+, 0%; 3+, 100%	68	Female	Pancreatic cancer (PC)	3	Progressive disease

1055P Safety and Activity of SmarT cells plus PD-1 blocking antibodies in patients with heavily pretreated solid cancers: An open-label and dose-escalation study

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Background: Efficient infiltration of activated T cells into tumors plays an important role in the therapeutic effect of adoptive cell immunotherapy. We previously modified T cells with a tumor-penetrating peptide iRGD (SmarT cells), and demonstrated that SmarT cells promote tumor-specific lymphocyte infiltration and enhanced the anti-tumor efficacy of PD-1 blocking strategy.

Methods: Here we report the interim analysis results of an ongoing phase 1/2 dose-escalation clinical trial of SmarT plus PD-1 mAb in patients with previously treated solid cancers (ChiCTR2200061306). The primary objective was safety for the combination of SmarT cells, low dose radiation and PD-1 mAb; secondary objectives included efficacy and dose-finding of SmarT cells. We treated 10 patients with three SmarT doses: 1.0×10^9, 5.0×10^9 or 1.0×10^9 cells. The low dose radiation (1Gy) was carried out 24 hours before SmarT injection.

Results: Three patients experienced a grade 2 fever. Two patients experienced a grade anemia. No cytokine release syndrome (CRS) occurred. No grade 3 or higher treatment-related adverse events or deaths were reported. A total of three patients had stable disease (SD) and seven patients had a progressive disease (PD). The disease control rate (DCR) reached 30.0%. The median progressive free survival time (mPFS) was 71 days and the median overall survival time (mOS) was 201 days.

Conclusions: These initial results suggest that SmarT cells has promising efficacy with an acceptable safety profile in patients with heavily pretreated, solid cancers.

Clinical trial identification: The trial protocol number is ChiCTR2200061306 and the release date 20 June 2022.

Legal entity responsible for the study: The Ethics Committee of Nanjing Drum Tower Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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1056P Efficacy of spartalizumab across multiple cancer types in patients with PD1-high mRNA expressing tumors (SOLTI-1904 ACROPOLI)

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Background: Building upon our earlier findings (Paré et al. Ann Oncol 2019), we hypothesized that anti-PD1 monotherapy is active across multiple cancer-types in *PD1*-high mRNA expressing tumors.

Methods: ACROPOLI is a phase II, open-label, non-randomized, multicentric trial in Spain, evaluating the efficacy of spartalizumab (anti-PD1) monotherapy for advanced *PD1*-high mRNA expressing solid tumors. *PD1*-high was defined by a pre-specified cutoff from FFPE tumor samples. Pts received spartalizumab 400 mg 4-weekly, and the primary objective was overall response rate (ORR) according to RECIST v1.1. Secondary objective was clinical benefit rate (CBR), defined as non-progressive disease for $\geq$6 months. Here, we report the early efficacy results of a prespecified interim analysis (IA) after the first 50 pts enrolled. A succesfull IA was defined as an ORR of $\geq$14%. Additionally, we report updated efficacy and safety data (n=58).

Results: From Apr2021 to May2022, 916 tumors were analyzed and 10.8% were *PD1*-high. Median of TILs in *PD1*-high tumors was significantly higher than in the rest of tumors (15% vs. 4%, $p<0.001$). Across 10 clinical sites, 58 pts (35 women) were enrolled with 20 different tumor histologies and a median of 2 prior treatments for advanced disease (range 0-13). Regarding the IA (data cutoff Apr2022), the ORR was 16% (8/50) and the Clinical Benefit Rate (CBR) was 28% (14/50). Regarding the updated efficacy results (data cutoff May2023), ORR was 17.2% (10/58) and CBR 29.3% (17/58). Clinical responses were observed in different cancer-types, including mesothelioma, sarcoma, carcinoma of primary unknown, cholangiocarcionoma, colorectal, ovarian, gastric and pancreatic cancers. 5 patients (8.6%) experienced grade 3-4 toxicities related to spartalizumab, with one fatal event.

Conclusions: Spartalizumab monotherapy demonstrated promising efficacy data and a favorable safety profile in heavily treated patients with immune-inflamed solid tumors expressing high levels of *PD1* mRNA. Premature discontinuation of the trial's recruitment occurred due to the termination of the spartalizumab development program. Nevertheless, the trial will begin enrolling a new cohort of 111 patients with *PD1*-high tumors with tislelizumab.

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Research; Financial Interests, Personal, Advisory Board: AstraZeneca, 1TRIALSP, S.L.; Financial Interests, Personal, Member of Board of Directors, Leadership role: Reveal Genomics, SL.; Financial Interests, Personal, Stocks/ Shares: Reveal Genomics, Oncolytics Biotech; Financial Interests, Personal, Royalties: Reveal Genomics, INTERNATIONAL ONCOLOGY BUREAU, S.L.; Financial Interests, Institutional, Local PI: Roche, AstraZeneca; Financial Interests, Personal and Institutional, Steering Committee Member: Daiichi Sankyo; Financial Interests, Institutional, Coordinating PI: Novartis; Non-Financial Interests, Institutional, Other, Leadership roles: Patronage committee: SOLTI Foundation, Actitud Frente al Cáncer Foundation; Non-Financial Interests, Personal, Other, Asociación Española de Investigación sobre el Cáncer: ASEICA. T. 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1057P Long-term follow-up of a phase II study of tislelizumab (TIS) monotherapy in patients (pts) with previously treated, locally advanced, unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors

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Background: TIS is an anti-programmed cell death protein 1 monoclonal antibody engineered to minimize FcγR binding. Primary results from this single-arm, multicenter, open-label, phase 2 study (NCT03736889) evaluating TIS in pts with MSI-H/dMMR solid tumors showed a clinically meaningful objective response rate (ORR). Here, we report updated analysis with longer follow-up.

Methods: Eligible adult participants had previously treated, locally advanced, unresectable/metastatic solid tumors with centrally confirmed MSI-H/dMMR, ≥1 measurable lesion (RECIST v1.1), and an ECOG performance status ≤1. Pts received TIS 200 mg intravenously once every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint was Independent Review Committee (IRC)-assessed ORR (RECIST v1.1). Secondary endpoints included overall survival (OS), IRC-assessed duration of response (DoR), progression-free survival (PFS), and disease control rate, and safety.

Results: Of 80 pts enrolled and treated in the study, 75 had measurable disease per IRC at baseline and were included in the efficacy-evaluable population. At data cutoff (Dec 5, 2022), median study follow-up was 28.9 months; minimum follow-up from last patient in to data cutoff was 28.1 months. Efficacy results are shown in the Table. ORR was 49.3%; median DoR, PFS, and OS were not reached. Treatment-emergent adverse events (TEAEs) ≥grade 3 occurred in 48 pts (60.0%); the most common was anemia, occurring in nine pts (11.3%). TEAEs leading to treatment discontinuation occurred in six pts (7.5%).

Conclusions: With a minimum of 28.1 months' follow-up, TIS-treated pts with previously treated MSI-H/dMMR solid tumors demonstrated a higher ORR compared with previous analysis, and durable improvements in DoR, PFS, and OS, with no new safety signals.

Table: 1057P Tumor Response in the Efficacy-evaluable Population

	All tumor types (N=75)
ORR, n (%)	37 (49.3)
95% CI	37.6, 61.1
Best overall response, n (%)	
Complete response	10 (13.3)
Partial response	27 (36.0)
mDoR,[a] mo (95% CI)	NR (NE, NE)
24-month DoR rate, % (95% CI)	97.0 (80.4, 99.6)
mPFS,[a] mo (95% CI)	NR (7.5, NE)
24-month PFS rate, % (95% CI)	56.7 (44.1, 67.4)
mOS, mo (95% CI)	NR (33.3, NE)
24-month OS rate, % (95% CI)	68.6 (56.6, 77.9)

[a]IRC-assessed per RECIST v1.1 OS analysis is based on safety analysis population (N=80). CI, confidence interval; m, median; mo, months; NE, not estimable; NR, not reached.

Clinical trial identification: NCT03736889 (first posted November 9, 2018).

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1058P Intraperitoneal nivolumab for malignant ascites in patients with advanced gastrointestinal or pancreaticobiliary tract cancer

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Background: Malignant ascites occur in 10 − 15% of patients with cancers from gastrointestinal tract, and it leads to impaired quality of life and declined performance. The abundance of immune cells in the peritoneum and ascites, as well as the immune escaped circumstance created by cancer cells in the peritoneum, suggest the potential use of intraperitoneal (IP) immune checkpoint inhibitors to control malignant ascites.

Methods: Patients with cancers from gastrointestinal or pancreaticobiliary tract who had cytologically confirmed malignant ascites were enrolled. Twenty mg of nivolumab diluted in 100 ml of saline was infused into the peritoneal cavity in 10 minutes after paracentesis. IP therapy was repeated after each paracentesis until ineffectiveness of therapy judged by physician, unacceptable toxicity, or patient's refusal. The clinical response and adverse effects were recorded. The cellular components of malignant ascites sampled prior each paracentesis were analyzed by flow cytometry.

Results: Totally, 9 patients with a median age of 55 years were treated with IP nivolumab. The cancer types were pancreatic cancer in 4, biliary tract cancer in 3, and gastric cancer in 2 patients. Systemic anticancer treatments were given for 3 lines in 2, 2 lines in 2, and 1 line in 4 patients before the administration of IP nivolumab. After a median of 3 (2 − 5) cycles of treatment, 7 (77%) patients had clinical response as evidenced by reduced ascites and less frequent paracentesis. The change of tumor cell number in serial ascites, instead of the change of lymphocyte counts and lymphocyte percentage, correlated with the clinical response. There was only grade 1 tenderness over the puncture site as the adverse effect. The reasons of stop IP were death due to disease progression in 5, patient's wish in 2, and clinical unresponsiveness in 2 patients, respectively.

Conclusions: IP administration of nivolumab was a safe and effective method to control malignant ascites from gastrointestinal or pancreaticobiliary tract cancer. Further validation of the application in larger population and other types of cancer, as well as biomarkers study are needed.

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1059P Tertiary lymphoid structures localization and maturation heterogeneities correlate with divergent clinical outcomes and immune responses of clear cell renal cell carcinoma

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Background: Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that form postnatally in non-lymphoid tissues and arise under pathological conditions. However, the clinical implications of localization and maturation stage of TLS in clear cell renal cell carcinoma (ccRCC) remain to be elucidated.

Methods: Immunohistochemistry and multispectral fluorescent were used to evaluate the TLS heterogeneity along with TME cell-infiltrating characterizations. We comprehensively assessed the prognostic and immunological implications of the TLS heterogeneity in 625 patients with ccRCC from multiply cohorts. Associations between TLS heterogeneity and immunologic activities were assessed by the quantification of immune cells infiltration.

Results: TLS typically comprises B-cell follicles with germinal centers and are surrounded by T-cell zones and dendritic cells. TLS infiltrates were identified in 34.2% of the ccRCC samples. A higher proportion of early TLS was found in peritumoral TLS, while intratumoral TLS mainly comprised secondary follicle-like. Kaplan-Meier analyses indicated that the presence of intratumoral TLS markedly correlated with both superior progression-free survival PFS and OS, while the presence of peritumoral TLS showed the opposite predictive trends for outcomes. Notably, presence of TLS, especially intratumoral TLS and mature TLS (namely SFL-TLS, with $CD23^+$ germinal center) significantly correlated with better clinical outcomes and objective reflection rate for ccRCC patients receiving immunotherapies. Interestingly, in ccRCC samples with the presence of peritumoral TLS enriched with primary follicle-like TLS, the proportion of $PD\text{-}L1^+$ tumor-associated macrophages and Treg infiltration in the peritumoral regions increased prominently, showing a typical suppressive TME characterizations.

Conclusions: In conclusion, this study for the first time revealed the implications of TLS localization and maturation heterogeneity on the clinical outcomes and immunological status and responses of ccRCC, allowing the identification of immunophenotypes and the improvement of immunotherapeutic effectiveness for ccRCC.

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1060P Balance of CD36+ and CD16+ monocytes controls TLR-mediated cytokine release syndrome and MHC-dependent antitumor responses in EpCAM CAR T cell therapy for gastrointestinal cancers

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Background: EpCAM is a prominent cancer antigen expressed in gastrointestinal cancers. Our clinical trial (NCT05028933 and ChiCTR2100047129), comprising 12 patients, provides the first evidence that EpCAM CAR-T cells display promising efficacy against gastric cancer (disease control rate: 66.7%). During the trial, varying grades of cytokine release syndrome (CRS),occurred in 66.7% of patients. Nevertheless, the current understanding of the mechanism of CRS is limited. As the severity of CRS varies among patients receiving CAR-T therapy, identifying immunological profiles that are relevant to CRS may provide opportunities to screen patients at lower risk to improve the safety of CAR-T treatment. Targeting monocytes could offer novel perspectives for managing CAR-T therapy-induced CRS. However, the specific monocyte subsets and underlying mechanisms responsible for CRS-associated cytokine production are not yet fully understood.

Methods: Human peripheral blood mononuclear cells (PBMCs) were isolated from 2ml whole blood using Ficoll density gradient centrifugation. A Single-cell sequencing was performed using the GemCodeTM single-cell platform and Chromium Single Cell 5′ Reagent Kit (10× Genomics). Hu-PBL NOG mice were generated by injecting 10 million human peripheral blood mononuclear cells into NOG-MHCI/II-2KO mice. CAR-T cells were administered via tail vein when tumor volume reached 100 mm^3.

Results: $CD36^+$ monocyte cell numbers were significantly increased in CRS patients while $CD16^+$ monocytes increased in response patients. Our data indicated activation of the antigen presentation in $CD16^+$ monocytes or Toll-like receptor signaling in $CD36^+$ monocytes may determine cytokine release syndrome and adaptive immune responses in CAR T-cell therapy.

Conclusions: We present valuable insights into the pathophysiology of CRS and suggest that TLR4 on $CD36^+$ monocytes is a promising target for managing CRS, which offers a new strategy for mitigating the side effects of CAR-T therapy. We also highlight the role of innate immune components, particularly $CD16^+$ monocytes, in achieving optimal CAR-T treatment efficacy through antigen processing and presentation.

Clinical trial identification: The study had a classic 3+3 design for each indication trial, with separate EpCAM CAR-T cell (IMC001) dose escalations for monotherapy. We report the first dosage group in advanced colon cancers (NCT05028933) and gastric cancers (ChiCTR2100047129).

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1061P Association of transcriptomic mapping of tumors with high expression of Tregs to identify surfaceome gene signatures with efficacy to check point inhibitors

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Background: Immune cell populations within the tumor microenvironment modulate the host immune response against tumors. An example is the population of regulatory CD4+ T cells (Tregs) that produces an inhibitory effect against effector immune cells. In the present work we interrogated publicly available genomic datasets, to explore the transcriptomic profile of breast tumors with high expression of Tregs.

Methods: We used breast cancer datasets to identify genes whose expression correlated with high presence of regulatory T-cells infiltration. Immune cell infiltration was determined by using the normalized RNA-seq based transcriptome-wide gene expression data and the xCell algorithm. TIMER platform was employed to analyze the association between expression and the presence of tumor immune infiltrates. Datasets from patients treated with check point inhibitors were interrogated to evaluate response to immunotherapy.

Results: Only 0.5% of the total transcriptome correlated with the presence of Tregs and only four transcripts, *BIRC6, MAP3K2, USP4* and *SMG1*, were commonly shared among the different breast cancer subtypes. Ten up-regulated genes (*MSR1, CD80, OLR1, ABCA1, ADAM17, ANO6, TMEM245, ITGAV, CLEC5A* and *ATP13AE*) coded for proteins expressed at the cell membrane. A statistically significant correlation was observed between the presence of *CD80, ORL1* and *MSR1* and the expression of PDL1 and PD1 in basal-like subtype. A similar association was observed between *MSR1* and *CD80* with macrophage presence in basal-like tumors and between OLR1, *ABCA1, ITGAV,* and *CLEC5A* and macrophages in HER2+ tumors. Some of the identified genes was linked with favorable outcome and response to checkpoint inhibitors. *MSR1, CD80, OLR1, ABCA1, TMEM245,* and *ATP13A3* predicted outcome to anti-PD(L)1 and anti CTLA4 therapies. The activity, in terms of clinical response, of each single transcript was further confirmed, for some of them, using an additional cohort of patients treated with immune-based therapies.

Conclusions: In summary, we identify genes expressed in a subset of immune cells that predict efficacy to checkpoint inhibitors. Further prospective studies are ongoing to confirm these findings in patients.

Legal entity responsible for the study: The authors.

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1062P Anti-PD1 efficacy in European patients with advanced MSI-H/MMRd non-colorectal cancers

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Background: Anti-PD1 immunotherapy is approved by the US FDA since 2017 for the treatment of adult & pediatric unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (MMRd) advanced solid tumours. In Europe, the EMA has approved anti-PD1 immunotherapy for MSI-H/MMRd cancers in 2022 for only 5 tumour indications, including colorectal cancers (CRC). Here we report the results of nivolumab, an anti-PD1 immunotherapy, in European non-CRC MSI-H/MMRd cancer patients.

Methods: AcSé nivolumab is a multi-centre, single arm, phase II basket trial launched by the French National Cancer Institute (INCa) and sponsored by Unicancer, testing the anti-PD-1 nivolumab in rare advanced and unapproved tumour indications. Here we report the results of the MSI-H/MMRd cohort. Nivolumab was administered at 240 mg IV q2w until disease progression or toxicity for a maximum of 2 years. The primary endpoint was the RECIST 1.1 objective response rate (ORR) at 12 weeks. Updated results with a mean follow-up of 21 months and a specific focus on non-EMA (European Medicines Agency) approved indications are reported.

Results: From July 2017 to October 2018, 50 patients (mean age 63 years) were enrolled. Primary locations were endometrial (19), gastric (10), small bowel (6), biliary (4), Genito-Urinary (GU) (3), breast (2), pancreas (5), and anal (1). 94% of patients were previously treated and 42% had $\geq$2 previous lines. The mean number of 2 weeks cycles was 28/patient. The ORR at 12 weeks was 34% (95%CI, 21.2 to 48.8) with a best overall ORR of 50% (95%CI, 35.5 to 64.5) and a median time to response of 5.5 months. Median progression-free survival was 29.7 months (95%CI, 4.6 to NA). Among the 17 responders at 12-weeks, 12 (70%) were still responding after 24 months of treatment. 6-month overall survival rate was 77.9% (95%CI, 67.1 to 90.3%). Among the 11 patients with rare MSI primary cancer (pancreas, breast, anal, GU), the overall ORR was 36% (4 patients). No new safety signals has been observed.

Conclusions: This study confirms the anti-PD1 nivolumab efficacy in non-colorectal MSI patients, even in rare MSI tumours of European patients. A MSI-H/MMRd tumour agnostic approval of anti-PD1 immunotherapy should be considered by the EMA.

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Legal entity responsible for the study: Unicancer.

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Disclosure: C. Tournigand: Non-Financial Interests, Leadership Role: GERCOR; Non-Financial Interests, Advisory Role: Fondation APHP. S. Oudard: Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Financially compensated role, Honoraria: AZ, Astellas, Bayer, BMS, Janssen, Merck, MSD, Novartis, Pfizer, Sanofi, IPSEN; Financial Interests, Personal, Financially compensated role, Travel Accommodations/Expenses: EISAI, Roche. E.B. Saada: Financial Interests, Personal, Project Lead: AstraZeneca, Merck Serono. D. Pouessel: Financial Interests, Personal, Invited Speaker: Ipsen, Bristol-Myers-Squibb, AstraZeneca, Astellas Pharma, MSD Oncology, Pfizer / Astellas; Financial Interests, Personal, Advisory Board: Astellas Pharma, Pfizer, MSD Oncology, Bristol-Myers-Squibb, Merck; Financial Interests, Institutional, Local PI: Merck Sharp & Dohme, Roche, Bristol-Myers-Squibb, AstraZeneca, Seagen. C. Le Tourneau: Financial Interests, Personal, Advisory Board: BMS, MSD, Merck Serono, Nanobiotix, Roche, Rakuten, Seattle Genetics, GSK, Celgene, ALX Oncology, Exscientia. P. Augereau: Financial Interests, Personal, Financially compensated role, Honoraria: GSK, AZD DAICHI, PFIZER, NOVARTIS. J. Soria: Financial Interests, Personal, Full or part-time Employment, From Sept 2017 to Dec 2019: AstraZeneca; Financial Interests, Personal, Member of Board of Directors, 2019-2021: Hookipa Pharmaceuticals; Financial Interests, Personal, Full or part-time Employment, SVP Amgen since August 2021: Amgen; Financial Interests, Personal, Stocks/Shares: Gritstone, Relay Therapeutics. T. André: Financial Interests, Personal, Advisory Board, Advosiry Board on February 12, 2021: Astellas pharma; Financial Interests, Personal, Advisory Board, Advisory Board on February 2021: Kaleido Biosciences; Financial Interests, Personal, Invited Speaker, and advisory board 2021: Amgen; Financial Interests, Personal, Invited Speaker, Ivited speaker in a symposuim december 2020: AstraZeneca; Financial Interests, Personal, Advisory Board, and consultant fees and consultant contract 2021 and 2022: Bristol Myers Squibb; Financial Interests, Personal, Advisory Board, Advisory board in Janaury 2020 : Clovis; Financial Interests, Personal, Advisory Board, Advisory board in january 2020: Gritstone Oncology; Financial Interests, Personal, Advisory Board, Advisory board 2020: Haliodx; Financial Interests, Personal, Advisory Board, and consultant fees/consultant contract and invited speaker: MSD Oncology; Financial Interests, Personal, Invited Speaker, and other: Pierre Fabre; Financial Interests, Personal, Invited Speaker, in an symposuim in 2020: Roche; Financial Interests, Personal, Invited Speaker, in a meeting in 2019: Ventana; Financial Interests, Personal, Invited Speaker, In a educational meeting in 2019: Sanofi; Financial Interests, Personal, Advisory Board, in a symposuim in 2020: Servier; Financial Interests, Personal, Advisory Board, Consultant with personnal fees and invited speaker: Servier; Financial Interests, Personal, Advisory Board, in 2019: GSK; Financial Interests, Personal, Invited Speaker, in 2020 and 2021: GSK; Financial Interests, Personal, Invited Speaker, Virtual symposuimLecture: 1 MSI-H CRC: Implementation of Immunotherapy in clinical practice (30 minutes) — (this will be pre-recorded)Q&A — Live Q&A — (10 minutes) (on July 2, 2021): MSD Oncology; Financial Interests, Personal, Invited Speaker, June 2022 : Sanofi; Financial Interests, Personal, Advisory Board, Contract 2021, 2022, 2023: Merck & Co., Inc; Financial Interests, Personal, Advisory Board, Contrat 2019, 2020, 2021, 2022: BMS; Financial Interests, Personal, Advisory Board, Contract 2021: Gritstone Oncologie; Financial Interests, Personal, Invited Speaker, June 2022 and June 2023 during ESMO GI meeting: Seagen; Financial Interests, Personal, Writing Engagement, Contract of consulting 2021 and 2022 and 2023: MSD Oncology; Financial Interests, Personal, Advisory Board, September 2022: GSK, Seagen; Financial Interests, Personal, Writing Engagement, Contract of consulting 2022 and 2023: GSK; Financial Interests, Personal, Writing Engagement, Contract of consulting 2022: Nordic Pharma; Financial Interests, Personal, Invited Speaker, October 2022: Merck Serono; Financial Interests, Personal, Other, Educationnal in 2022: Roche; Financial Interests, Personal, Other, Contract of consulting 2020, 2021, 2022, 2023: Servier; Financial Interests, Personal, Advisory Board, 2023: Aptide Health, Glilead; Financial Interests, Institutional, Other, Investigator and scientific comitee president: Gercor Academic group; Financial Interests, Institutional, Coordinating PI, PI Garnet study: GSK; Financial Interests, Institutional, Coordinating PI, Keynote 164 and 171 and 811 and C08: MSD; Financial Interests, Institutional, Coordinating PI, BMS CA209-8HW, BMS CA209-142, BMS CA209-577: BMS; Financial Interests, Institutional, Coordinating PI, SPOTLIGHT study: Astellas; Financial Interests, Personal, Steering Committee Member, and internationnal PI (trial chair Solstice study): Servier; Financial Interests, Personal, Steering Committee Member, MOUNTAINEER and MOUNTAINEER-03 study (PI for France) 2022, 2023: Seagen; Non-Financial Interests, Member of Board of Directors, Investigator: Gercor group; Non-Financial Interests, Member of Board of Directors, President since october 2022: ARCAD Foundation. A. Marabelle: Financial Interests, Personal, Advisory Board: Gritstone, Innate Pharma, Neogene, Deka Biosciences, Hotspot Therapeutics, Johnson & Johnson, Depth Charge, Bioline Rx, Clover Biopharmaceuticals, Grey Wolf Therapeutics, Lytix Biopharma, RedX Pharma, HiFiBiO Therapeutics, ImCheck Therapeutics, Shattuck Labs, Marengo Therapeutics, PegaOne; Financial Interests, Personal, Other, Associate Editor: European Journal of Cancer; Financial Interests, Personal, Stocks/Shares: HiFiBiO Therapeutics, Deka Biosciences, HotSpot Therapeutics, Shattuck Labs; Financial Interests, Institutional, Research Grant: BMS, AstraZeneca, Sanofi; Financial Interests, Institutional, Coordinating PI: IMCheck, SOTIO, Roche/Genentech, MSD, BMS, OSE Immunotherapeutics, EISAI, Pierre Fabre, Adlai Nortye, Molecular Partners; Financial Interests, Steering Committee Member: Roche; Financial Interests, Institutional, Funding: Transgene; Non-Financial Interests, Other, Associate Editor: IOTECH Journal; Non-Financial Interests, Institutional, Product Samples: BMS, IDERA, MSD, Transgene; Non-Financial Interests, Leadership Role: Société Française d'Immunothérapie des Cancers; Non-Financial Interests, Member: Society for Immunotherapy of Cancer, American Association for Cancer Research, American Society for Clinical Oncology; Other, Other, Consultant: Third Rock Ventures, Guidepoint; Other, Other, Advisor: Medicxi. 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1063P Differential tumor responses are a poor prognostic factor in patients receiving immune checkpoint inhibitors

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Background: Radiological assessment of tumor response to immune checkpoint inhibitors (ICI) can be challenging. This retrospective study aimed to identify patterns of dissociated response (DR) to treatment and correlate them to clinical outcome.

Methods: We analyzed CT imaging data from 257 metastatic patients receiving ICI, who underwent imaging at baseline and on-therapy. Up to 10 lesions per organ were segmented using 3DSlicer at baseline and best response by RECIST 1.1. Changes in tumor diameter from baseline to best response were assessed. DR was defined as the co-existence of lesions with an increase and decrease in diameter (-10% / +10%,

based on an internal variability study) or a decrease in diameter of one or more lesions with the appearance of new lesions.

Results: This cohort comprised 257 patients (63% male) with different tumor types including lung, melanoma, breast, colorectal and others. According to the RECIST classification 6.6% (17/257) of patients had CR, 20.2% (52/257) PR, 35.4% (91/257) SD and 37.7% (97/257) PD. DR was identified in 13% (34/257) patients at the time of best response by RECIST. 21/34 patients with DR were classified as SD or PR by RECIST1.1; their overall survival was significantly lower than SD/PR patients without DR (n=140) (median OS 11.96 vs 20.01 months, p-value <0.02). The incidence of DR was not associated with tumor type or burden of disease. A higher number of organs affected at baseline was significantly associated with presence of DR (p<0.001). Liver metastasis were a poor prognostic factor irrespective of DR (median OS 7.3 vs 15 months, p-value<0.005).

Conclusions: Dissociated responses to ICI are common across tumor types and associate with poor clinical outcome. DR probably reflects underlying intra-patients' biological heterogeneity both at the tumor and tumor micro-environment level and can be captured through individual lesion assessment in standard of care imaging.

Legal entity responsible for the study: The authors.

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1064P Performance of low dose immunotherapy (IO) and standard dose IO in microsatellite-instability−high (MSI-H) metastatic colorectal cancer (mCRC): Real-world data

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Late withdrawal

1065P Prospective assessment of nutritional status in patients with advanced non-small cell lung cancer and renal cell carcinoma treated with immune checkpoint inhibitors

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Background: The nutritional status of patients with advanced cancer seems to affect the immune activity against tumor cells. We investigated the prognostic role of nutritional status in patients with advanced non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) treated with immune checkpoint inhibitors (ICIs).

Methods: We prospectively enrolled patients with advanced NSCLC and RCC receiving ICIs from June 2021. Patient nutritional status at baseline and after three months of treatment (T1) was evaluated using the controlling nutritional status (CONUT) score (serum albumin, total cholesterol, and lymphocyte count) and body composition (BC), assessed by trained dietitians through bioelectrical impedance analysis (BIA). Data were correlated to disease control rate (DCR) and progression-free/overall survival (PFS/OS).

Results: Among 69 patients enrolled, 71% (N=49) had NSCLC**,** 78% (N=54) were treated in first line and 58% (N=40) with ICIs as monotherapy. At a median follow up of 11 months (95%CI 8.2-15.9), patients with a low CONUT score (score value lower than or equal to 4), meaning a good nutritional status, had higher DCR (74% vs 38%, p=0.004), longer PFS (HR: 0.28, 95%CI 0.14-0.55, p<0.001) and longer OS (HR 0.33, 95%CI 0.14-0.80, p=0.01) compared to those with high CONUT score (score value > 4), characterized by poor nutritional status. Among BC parameters, skeletal muscle index (SMI: skeletal muscle mass/height^2) predicted clinical outcomes: patients with high SMI (>8.9 for male, > 6.4 for female) showed higher DCR (74% vs 40%, p=0.02), longer PFS (HR: 0.40, 95%CI 0.17-0.92, p=0.03) and longer OS (HR 0.20, 95% CI 0.07-0.56, p=0.002), compared to those with low SMI, defined as sarcopenic patients. Patients with any grade of SMI drop at T1 had shorter PFS (HR 3.04, 95% CI 1.18-7.79, p=0.02) compared to those with stable or increased SMI.

Conclusions: Nutritional status assessed by CONUT score and BC may predict clinical outcomes in patients with advanced NSCLC and RCC treated with ICIs. The study is ongoing to mature follow up and additional translational analyses are planned to disentangle the immunophenotypic features related to patients' nutritional status.

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Disclosure: R. Berardi: Financial Interests, Personal, Advisory Board: AstraZeneca, BMS, Boehringer Ingelheim, EISAI, Novartis, MSD, Otsuka, Eli Lilly, Roche, Italfarmaco, Seagen. All other authors have declared no conflicts of interest.

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1066P Negative impact of steroids on the efficacy of immunotherapy in a multi-tumor cohort of patients: time and dose-dependent

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Background: Previous data suggest a negative impact of steroids (ST) in patients (pts) treated with immune checkpoint inhibitors (ICI), due to their immunosuppressive properties. How dosage and time of administration modulate this effect is yet to be clarified.

Methods: Retrospective study of pts who received ICI alone in a tertiary university hospital (2016-2022). For each pt, the daily dose of ST was collected (equivalent in mg/kg of prednisone) until progression of disease (PD) or death: 30 days before the 1st cycle (C1) (-30D), 30 days from C1 (D1-30), 3 months from C1 (D1-90) and after 6 months (m) from C1 (>D6m). We evaluated the impact of the cumulative dose (CD) of ST on the objective response rate (ORR), the disease control rate (DCR) and progression-free survival (PFS).

Results: We evaluated 475 pts (median age: 67.5) with advanced solid tumors (NSCLC: 33.9%; urothelial: 17.3%; renal: 13.7%; melanoma: 11.2%; head and neck: 11.0%; others: 12.9%) treated with anti-PD1 (64.4%), anti-PDL1 (20.4%), anti-PD1 plus anti-CTLA4 (13.3%) or anti-CTLA4 (1.9%); 42.1% in 1st line, 43.1% in 2nd line, 14.8% in further lines. Performance status (PS) prior to C1 was: 0 (31.0%), 1 (53.6%), ≥2 (15.4%). 48.2% of pts received ST during therapy with ICI (17.3% in -30D; 32.6% in D1-D90; 16.6% in >D6m). The ORR was significantly lower in pts who received ST in -30D

(20.3% [95% CI 11.4-29.1%] vs 36.7% [95% CI 31.8-41.5%]; $p<0.01$) and in D1-90 (25.7% [95% CI 18.6-32.7%] vs 37.7% [95% CI 32.3-43.1%; $p=0.01$]). The negative impact of ST was confirmed by a multivariate analysis including PS, type of tumor, disease burden, type of ICI and line of treatment. There was an inverse correlation between the CD of ST in -30D and the DCR (no ST: 52.1%; Q1: 45%; Q2: 30.0%; Q3: 15.8%; Q4: 25%) ($p<0.01$). The impact of CD was confirmed in D1-30, but not in D1-90 and >D6m. Among pts without PD at 6 months, PFS tended to be longer in those who received ST (23.2 vs 17.6 m; $p=0.065$).

Conclusions: Our results demonstrate the negative impact of ST on the outcomes of ICI, even at low doses. This effect seems time and dose-dependent, prevailing in pts with an early exposure to ST (<3m) and proportional to cumulative dose only around the initiation of ICI (from -30D to D30).

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1067P The interchangeability of Immune checkpoint inhibitors

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Background: Immune checkpoint inhibitors (ICIs) are used for the treatment of various tumours. They are amongst the best-selling cancer drugs. The introduction of several new ICIs in the past few years has not resulted in price competition. From clinical and societal perspectives, it is worthwhile to investigate whether the six available ICIs are therapeutically interchangeable. If so, this may facilitate use and stimulate price reduction by competition.

Methods: We investigated by means of a literature review, whether the ICIs for the indications with the greatest expenditure and number of patients, namely lung cancer and melanoma, are being interchangeable. Due to the lack of direct comparative studies we conducted a systematic search in PubMed, Embase en de Cochrane Library to identify all eligible (network)meta-analyses (NMA) until November 2022. Literature search terms used were "network meta-analysis" 'PD[L] 1" AND non small lung carcinoma AND melanoma. Only NMA's including randomized clinical trials that compared the efficacy (overall survival and progression free survival) and safety (treatment related side-effects) of the PD-(L)1 inhibitors nivolumab, pembrolizumab, atezolizumab, durvalumab and/or cemiplimab with or without chemotherapy to chemotherapy were eligible.

Results: A total of 3 NMA's involving patients with advanced NSCLC were included, and one NMA involving not-previously treated patients with advanced melanoma. Where indications do overlap - mainly monotherapy — no studies with head-to-head comparisons of ICIs have been conducted. By indirect comparison of evidence, no clinically relevant differences in effectiveness and safety are apparent. However, the validity of these indirect comparisons have strong limitations, due to the differences in inclusion criteria and patient characteristics.

Conclusions: We conclude that the determination of interchangeability of ICIs is complicated due to the limited overlap in authorized indications and lack of direct comparison between ICIs. Where indications do overlap, we expect that any differences will have limited clinical significance. We call for (publicly funded) randomized multi-cancer trials for a direct head-to-head comparison of ICIs. Such direct comparative evidence is needed to reach a competitive field.

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1068P Fasting mimicking diet reduces anti-OX40/anti PD-L1 and anti-PD-1/anti-CTLA-4 cardiovascular side effects in melanoma and lung cancer models

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Background: Several strategies based on immune checkpoint inhibitors (ICIs) have been developed or are investegated in clinical trial to assess their benefits in prolonging overall survival in cancer patients. However, ICIs-induced side effects ranging from autoimmune endocrine disorders to mucositis and to a rare but clinically significant cardiotoxicity with high rate of mortality represent important limitations. Cardiovascular complications in ICIs-treated patients includes myocarditis, vasculitis, arrhythmia, fibrosis and heart failure. Moreover, both the limited efficacy in a large portion of patients and the acquisition of resistance represent additional limitations for ICIs, underlining the need for new immunotherapy strategies. Fasting mimicking diets (FMDs) applied for several days periodically are emerging as highly promising enhancers of a wide variety of cancer therapies including immunotherapy.

Methods: A preclinical study in melanoma and lung tumor-bearing mice treated with two combinatorial ICIs therapies (anti-OX-40/PDL-1 or antiCTLA-4/anti-PD-1) during a standard or FMD was performed.

Results: FMD is highly effective in inhibiting the growth of melanoma, unlike anti-PD1/anti-CTLA4 and anti-OX40/anti-PD-L1 immunotherapy which are ineffective against both melanoma and lung cancer. However, FMD in combination with anti-OX40/anti-PD-L1 seems tofurther delay melanoma and lung cancer growth, although this trend is not statistically significant. On the other hand, cardiac fibrosis, necrosis and hypertrophy were reduced in the FMD *vs* standard diet group in both cancer models. Immune infiltration of $CD3^+$ and $CD8^+$ cells in myocardial tissues was reduced in FMD indicating myocarditis inhibition effects of the dietary intervention. Systemic and myocardial IL-1α, IL-1β, IL-6, IL17-α, G-CSF, and GM-CSF levels were also reduced in the FMD vs standard diet group.

Conclusions: These results indicate that FMD cycles applied to mouse models of melanoma and lung tumor reduce biomarkers involved in cardiovascular disease and resistance to immune-dependent activity without interfering with ICIs therapies.

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1069P Potential biomarkers for predicting severe immune-related adverse events during checkpoint immunotherapy: T Cell receptor and whole exome sequencing findings from a prospective multicenter study

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Background: Grade 3/4 immune-related adverse events (severe irAEs), caused by anti-PD-1/PD-L1 antibodies, can lead to fulminant and even fatal consequences. However, the identification of biomarkers for irAEs prediction is lacking. Previous studies have suggested that germline mutations and T-cell receptor (TCR) diversity are associated with the development of irAEs during cancer immunotherapy. Here, our study aims to explore promising biomarkers for predicting severe irAEs.

Methods: Patients who received immune checkpoint inhibitors (ICIs) treatment between November 2021 and December 2022 were enrolled in a study with follow-up. Blood samples were collected at baseline and from those with severe irAEs during or after treatment. Blood samples underwent whole exome sequencing and TCR sequencing. Germline mutations were compared between severe irAEs and non-severe irAEs groups, with additional TCR analysis including diversity index and cluster analysis.

Results: The study enrolled 128 patients, among whom 12 (9.38%) developed serious irAEs. Germline mutations in 10 immune-related genes (MMEL1, MDM4, GPR35, LPP, BACH2, EGFR, JAK2, PTEN, SMAD3, TYK2) were significantly different between severe

and non-severe irAEs groups ($p < 0.05$). TCR sequencing analysis revealed that 3 motifs in the severe irAEs group and 7 motifs in the non-severe irAEs group were also significantly different ($p < 0.05$). A PLS-DA analysis combining biomarkers, genes, and motifs successfully distinguished between the two groups. Additionally, we observed a significant decline in CDR3 counts from baseline to post-severe irAEs in TCR.

Conclusions: Study results indicated that germline mutations and changes in TCR characteristics may predict severe irAEs in cancer immunotherapy, emphasizing the need for further research and personalized management of these adverse events.

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1070P Patterns of adverse reactions for immune checkpoint inhibitors in cancer patients with central nervous system metastases

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Background: Immune checkpoint inhibitors (ICIs) have yielded promising results in the treatment of cancer patients with central nervous system (CNS) metastases. However, due to a dearth of clinical research, it is necessary to further elucidate the side effects of ICIs in patients with CNS metastases.

Methods: We identified patients with CNS metastases treated with ICIs from Q1 2013 to Q2 2022 by scrutinizing the FDA Adverse Event Reporting System (FAERS) database. Following removal of duplicate data, the study collected 511 cases. Subsequently, disproportionality analysis was performed. Risk factors were explored using univariate and multivariate logistic regression. Moreover, the influence of clinical factors on the time to onset of adverse reactions was examined.

Results: The study revealed a higher susceptibility to psychiatric complications, including confusion state, insomnia, mania, and memory impairment, following ICIs treatment in CNS metastasis patients. Furthermore, rare but severe retinal detachment may arise due to anti-PDL1 drug usage, whereas co-administration of anti-PD1 and anti-CTLA4 drugs may produce nephrotoxicity concerns. Multivariate logistic regression analysis demonstrated that the combined therapy of anti-PD1+anti-CTLA4 therapy was an independent risk factor for adverse nephrotoxic reactions in CNS metastasis patients (OR: 2.75, 95%CI: 1.37-5.46, $P<0.05$). The onset time of complications differed depending on the immunotherapeutic strategy. Anti-PD-L1 therapy had a later onset time of complications (Median: 67 days, IQR: 28.75-114.25) compared to that of anti-PD1 (Median: 33 days, IQR: 10-90) and anti-CTLA4 therapy (Median: 29 days, IQR:10.5-52.5), respectively. Furthermore, our study indicated that younger patients exhibited a higher probability of fatal complications (OR: 0.97, 95% CI: 0.95-0.99, $P=0.02$) and experienced a shorter time to onset of complications ($r=2.27$, $P=0.007$).

Conclusions: This study employed a massive database to investigate the spectrum of adverse reactions resulting from ICIs therapy administered to CNS metastasis patients, thereby providing vigilance data for broader clinical applications.

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1071P Analysis of pulmonary adverse events associated with immune checkpoint inhibitors based on FAERS and VigiBase database

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Background: The utilization of immune checkpoint inhibitors (ICIs) has become increasingly prevalent in cancer treatment. However, ICIs may also precipitate a spectrum of immune-related adverse events, which can target various organ systems. Among these, pulmonary immune-related adverse events (pirAEs) are the leading cause of ICI cessation and mortality.

Methods: Individual Case Safety Reports (ICSRs) were obtained from FAERS and VigiBase. We identified reports pertaining to eight ICIs for the purposes of this study, namely nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab, ipilimumab, and tremelimumab. Subsequently, we utilized expert consensus to select 52 significant pirAEs with high incidence or of clinical significance and then evaluated the incidence and mortality of pirAEs across varying time periods following the initiation of ICIs therapy.

Results: 16,372 and 7,943 ICSRs were collected using FAERS and VigiBase, respectively. More than 50% of pirAEs occurred within 60 days after treatment with ICIs (FAERS:70.0%,VigiBase:55.7%), and their mortality was higher than that after 60 days (15% vs 12%, 12% vs 7%). In each period after the use of ICIs, pirAEs with the highest incidence were interstitial lung disease (14.6%,26.4%), dyspnoea (18.4%,17.0%)and pneumonitis (13.0%,17.0%). The all-cause mortality of respiratory failure (30%, 58%), pulmonary hemorrhage (28%,57%), acute interstitial pneumonitis (75%, 27%), and stridor (31%, 30%)was over 25%. The mortality of respiratory failure remained stable at a high level in each period after initiation of immune therapy (24-40%, 42-69%).

Conclusions: Using data from the FAERS and VigiBase, we conducted an analysis of the frequency and incidence of pirAEs during varied periods after the onset of ICIs therapy. We offer a groundbreaking revelation, identifying the occurrence of pirAEs which manifest early on, within the initial 60 days of treatment, and exhibit a high incidence and mortality rate. Among pirAEs, interstitial lung disease, dyspnea, and pneumonitis were most frequently reported with respiratory failure being a consistently fatal adverse event highlighting the necessity of heightened physician vigilance.

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1072P DuoBody-EpCAMx4-1BB mediates conditional T cell co-stimulation and promotes antitumor activity in preclinical models

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Background: While 4-1BB has shown preclinical promise as an immuno-oncology target, classical 4-1BB agonists have demonstrated limited success in clinical trials due to modest efficacy or severe hepatotoxicity. EpCAM is homogeneously expressed on the surface of cancer cells in many solid tumor indications. DuoBody-EpCAMx4-1BB (BNT314/GEN1059) is an Fc-inert immunomodulatory bispecific antibody (bsAb) designed to boost antitumor immune responses through EpCAM-dependent 4-1BB agonistic activity.

Methods: Target binding and functional activity of DuoBody-EpCAMx4-1BB was assessed by flow cytometry, cell-based reporter assays, and primary human lymphocyte/tumor cell-co-culture assays. Proof-of-principle *in vivo* studies were conducted using the murine MC38 tumor model. Non-clinical safety was assessed in cynomolgus monkeys.

Results: DuoBody-EpCAMx4-1BB bound to EpCAM on tumor cells and 4-1BB on activated T cells. By cross-linking target-expressing cells, DuoBody-EpCAMx4-1BB induced 4-1BB agonistic activity, which was conditional on binding to EpCAM due to its inert IgG1 Fc domain. In co-culture with $EpCAM^+$ tumor cells, DuoBody-EpCAMx4-1BB dose-dependently enhanced activation of $CD4^+$ and $CD8^+$ T cells in anti-CD3-stimulated PBMCs from both healthy donors and cancer patients. Furthermore, DuoBody-EpCAMx4-1BB enhanced proliferation and cytokine secretion of activated healthy donor T cells and increased $CD8^+$ T-cell mediated killing of $EpCAM^+$ tumor cells *in vitro*. In *ex vivo* assays using tissue samples of patient-derived lymphocyte-infiltrated $EpCAM^+$ tumors, DuoBody-EpCAMx4-1BB enhanced $CD8^+$ T-cell and NK-cell expansion. An Fc-inert EpCAMx4-1BB bsAb exhibited antitumor activity in mice. DuoBody-EpCAMx4-1BB was well-tolerated in cynomolgus monkeys at doses up to 50 mg/kg (QWx5).

Conclusions: Through conditional 4-1BB agonistic activity, DuoBody-EpCAMx4-1BB enhanced T-cell activation, proliferation, and effector functions *in vitro* and *ex vivo*. In a murine model, an Fc-inert EpCAMx4-1BB bsAb promoted antitumor activity *in vivo*. It is intended to investigate the clinical safety and preliminary antitumor activity of DuoBody-EpCAMx4-1BB in patients with solid tumors in a first-in-human trial.

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1073P Overcoming resistance to immunotherapy with FGFR inhibition in GU cancer models

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Background: Despite the encouraging success of checkpoint inhibitors, approximately 70% of tumors can eventually become resistant over time. The tumor microenvironment, in particular cancer-associated fibroblasts (CAFs), is one of the important mechanisms of resistance. OM-RCA-01, a anti-FGFR1 humanized antibody, and alofanib, a FGFR2 allosteric inhibitor showed promising results in previous studies.

Methods: Renal cancer cells (Renca; 5×10^5) were implanted by subcutaneous (sc) injection into C57BL/6 mice. Additional Renca cells and human kidney CAFs (1.5×10^6) were premixed in Matrigel and implanted sc in second cohort of C57BL/6 mice. Treatment with ipilimumab (ipi, 200 mcl on days 7, 10, and 13) was initiated in both cohorts when tumor volumes reached 70 mm^3. Treatment with OM-RCA-01 (30 mg/kg every 3 days) or IgG2a isotype control was initiated after ipi when tumor volumes reached 1,500 mm^3. Prostate cancer cells (DU-145; 4×10^6) were implanted sc in female BALB/c mice. Treatment with human anti-LAG3 antibody (1 mg/kg, biweekly) or control was initiated when tumor volumes reached 150 mm^3. Treatment with alofanib (116 mg/kg, iv daily) or control was initiated when tumor volumes reached 1,900 mm^3. Tumor growth was monitored by caliper measurement every 3 days. The primary endpoint was tumor growth delay (TGD) from the initiation of immunotherapy.

Results: Treatment with OM-RCA-01 resulted in higher levels of IFNγ release by 43% and increased IL-2 secretion by 65% over control. IHC showed a significantly lower number of α-SMA/FSP/vimentin-positive CAFs in the OM-RCA-01 cohort. The table summarizes the results of in vivo studies.

Table: 1073P

Comparison between groups	TGD, % (P-value)
Ipilimumab, CAFs- vs. CAFs+ cohorts	44.0 (0.027)
Renal cancer, CAFs+, OM-RCA-01 vs. IgG2a	96.1 (<0.001)
Renal cancer, CAFs-, OM-RCA-01 vs. IgG2a	74.5 (<0.001)
Prostate cancer, anti-LAG3 vs. control	19.4 (0.035)
Prostate cancer, alofanib iv vs. control	69.4 (0.012)

Conclusions: Inhibition of FGFR1 and FGFR2 following immunotherapy resulted in a twofold suppression of tumor growth, especially in the CAFs+ cohort.

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1074TiP A phase I/II, open label, first-in-human, dose escalation and expansion study of SAR445877 administered as monotherapy in adults with advanced solid tumors

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Background: SAR445877 (SAR'877) is a fusion protein of high affinity anti-programmed cell death protein 1 (PD1) antibody combined with a detuned interleukin 15 (IL15) (complexed with IL15 receptor sushi domain). SAR'877, via its anti-PD1 moiety, binds to PD-1-expressing T and natural killer (NK) cells and potentially allows for a targeted expansion and activation of CD8+ T and NK cells expressing both PD1 and IL2/15Rβγ. Nonclinical studies have demonstrated SAR'877 as an immune-modulatory agent.[1]

Trial design: This is a first in human, open-label, multicenter, dose escalation and expansion phase 1/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-tumor activities of SAR'877 administered intravenously as a single agent in adult participants with advanced unresectable or metastatic solid tumors (EudraCT 2022-001239-95/NCT05584670). The study is conducted in 2 parts. The Part 1 (dose escalation) will determine the maximum tolerated dose or maximum administered dose per occurrence of dose limiting toxicities in the first 28-days (cycle 1 and 2), recommended dose(s), and the overall safety and tolerability profile of SAR'877. A multicohort Part 2 (dose expansion) would assess the safety and preliminary efficacy of SAR'877 (2 dose levels in at least 1 indication, as applicable) and will include cohorts with advanced solid tumors regardless of the tumor proportion score/combined positive score and cohort with a negative expression of the PDL1. Approximately, 240 participants will be enrolled of which nearly 75 participants will be enrolled in the Part 1 (dose escalation) and 165 participants in the Part 2 (dose expansion). Adverse effects will be assessed per National Cancer Institute, Common Terminology Criteria for Adverse Events version 5.0 and American Society for Transplantation and Cellular Therapy consensus grading. Tumor response will be determined according to Response Evaluation Criteria in Solid Tumors criteria. Dose escalation Part 1 is conducted in US, Spain and Netherlands. The study is enrolling participants. Lu D et al, J Immunother Cancer (2020);8(Suppl 3):573.

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1075TiP A phase I/Ib open-label, first-in-human, single agent, dose escalation and expansion study of a HER2-targeted T cell engager (SAR443216) in patients with relapsed/refractory HER2-expressing solid tumors

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Background: Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor overexpressed in multiple cancers and is a clinically validated target for cancer treatment with several approved HER2-targeted therapies. SAR443216 is a novel trispecific antibody T cell engager (TCE) that has shown preclinically to target HER2-expressing tumors by co-engaging tumor cells via HER2, and T cells via CD3 and CD28, resulting in T cell activation and tumor cytolysis. SAR443216 utilizes T cells of the adaptive immune system to eradicate HER2-expressing cancers, unlike other HER2 therapies.[1]

Trial design: This is a first-in-human, open-label, multicenter, dose escalation and expansion phase 1/1b study evaluating safety, pharmacokinetics (PK), pharmacodynamics, and preliminary clinical efficacy of SAR443216 administered intravenously (IV) or subcutaneously (SC) as a single agent in patients with HER2-expressing solid tumors (EudraCT 2021-00008632/NCT05013554). The study is conducted in 2 parts: The dose escalation part (n=∼70 dose limiting toxicity [DLT] evaluable patients) will assess safety and dose findings of SAR443216 using Bayesian-CRM model, in patients with HER2-expressing solid tumors who have exhausted all standard of care therapies. Dose expansion part (n=∼130 in 4 cohorts) will assess the safety and efficacy of SAR443216 at the recommended dose for expansion in cohorts defined by HER2-expression (1+, 2+ or 3+ by IHC) and/or HER2-activating mutations. Adverse events (AEs) are assessed per NCI CTCAE v5 and tumor response as per RECIST 1.1. Primary endpoints are DLTs, treatment-emergent AEs, serious AEs, and laboratory abnormalities for dose escalation; objective response rate (ORR) and duration of response (DOR) for dose expansion. Key secondary endpoints include ORR, DOR, PK, and incidence of antidrug antibodies in all patients. Dose escalation recruitment is ongoing in South Korea, Spain, Taiwan, and USA. As of April 2023, 29 patients have been enrolled. 1. Seung E, et al. Nature. 2022;603:328-334.

Clinical trial identification: EudraCT 2021-00008632, NCT05013554.

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1076TiP First-in-human study of ABBV-514 as monotherapy and in combination with budigalimab in patients with advanced solid tumors

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Background: Regulatory T-cells (Tregs) are specialized T-cells that can inhibit anti-tumor immune responses, and high intratumoral Treg levels have been associated with negative outcomes in cancer. Chemokine receptor (CCR)8 is preferentially expressed on tumor-infiltrating Tregs, relative to peripheral blood Tregs and effector T cells. ABBV-514 is an afucosylated monoclonal antibody that binds CCR8 and is designed to enhance antibody-dependent cellular cytotoxicity to deplete tumor-infiltrating Tregs. This first-in-human trial evaluates safety, pharmacokinetics (PK), and preliminary efficacy of ABBV-514 as monotherapy and in combination with budigalimab (BDG), a PD-1−blocking antibody.

Trial design: This is a multicenter phase 1 dose-escalation/expansion study (NCT05005403). Eligible patients (≥18 years) have evaluable or measurable disease per RECIST v1.1 and ECOG performance status ≤1. Primary objectives are to assess safety, tolerability, and PK and to determine the maximum tolerated/maximum administered dose of ABBV-514 as monotherapy and in combination with BDG. Secondary and exploratory objectives are to evaluate immunogenicity of ABBV-514 as mono- or combination therapy, to assess preliminary efficacy (objective response rate per RECIST v1.1 criteria, clinical benefit rate, duration of response, progression-free survival), and to evaluate pharmacodynamics and predictive biomarkers. Patients are

treated until disease progression or intolerable toxicity. Dose escalation will be guided by a Bayesian optimal interval design. Planned enrollment is 176 patients: up to 140 in dose escalation and 36 in dose expansion. In dose escalation, patients with relapsed/refractory (R/R) solid tumors will be enrolled in ABBV-514 monotherapy (N≤55) or ABBV-514 + BDG (N≤55) cohorts; up to 30 additional patients will be included in paired biopsy cohorts. In dose expansion, patients with R/R non-small cell lung cancer will be enrolled in ABBV-514 monotherapy (N=12) and ABBV-514 + BDG (N=12) cohorts, and patients with R/R head and neck squamous cell carcinoma in an ABBV-514 + BDG (N=12) cohort. Enrollment initiated in November 2021, with 30 patients enrolled as of April 2023.

Clinical trial identification: NCT05005403.

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1077TiP TAK-500 as a single agent and in combination with pembrolizumab in patients (pts) with advanced solid tumors: Rationale and design of a phase I/II study

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Background: TAK-500 is a novel immune-cell-directed antibody drug conjugate comprising the STING agonist TAK-676 conjugated to a human IgG1 anti-C-C chemokine receptor 2 (CCR2) antibody. In preclinical models, treatment with the TAK-500 murine surrogate resulted in activation of innate and adaptive immunity and antitumor activity, which was increased when combined with an anti-PD-1 antibody. Based on these data, a phase 1/2 open-label, dose-escalation and expansion study was designed to determine safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of TAK-500 as a single agent and in combination with pembrolizumab in CCR2-enriched solid tumors (NCT05070247). Phase 1 has been previously described (Diamond et al, ASCO, 2022), here we present the phase 2 design.

Trial design: Approximately 231 patients with treatment-refractory, advanced or metastatic non-squamous non-small cell lung cancer (NS NSCLC), pancreatic adenocarcinoma (PDAC), or renal clear cell carcinoma (RCC) will be enrolled. Eligible patients will receive TAK-500 intravenously as a single agent or with pembrolizumab 200 mg every 3 weeks. Randomized comparisons of two dose levels of TAK-500 (DL1 and DL2) as a single agent and in combination with pembrolizumab will be carried out as follows: patients with 2nd-line NS NSCLC will be randomized 2:1 to receive TAK-500 at DL1 or DL2 with pembrolizumab while patients with 3rd-line NS NSCLC will be randomized 1:1 to receive single-agent TAK-500 at DL1 or DL2. Patients with 2nd-line PDAC will be randomized 1:1 to TAK-500 at a single dose level alone or with pembrolizumab. A single cohort of patients with 3rd-line RCC will receive single-agent TAK-500 with pembrolizumab at DL1. A Simon's 2-stage design with futility analyses based on response per RECIST v1.1 will be used for 2nd-line NS NSCLC and 2nd-line PDAC. A single-stage statistical design will be utilized for 3rd-line NS NSCLC and RCC. As of May 2023, 6 sites in the United States are recruiting; the global phase 2 is planned to start in 2024.

Clinical trial identification: NCT05070247.

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1078TiP Phase I/II, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of SNS-101 (anti-VISTA) as monotherapy and in combination with cemiplimab in patients (pts) with advanced solid tumors

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Background: SNS-101 is a novel monoclonal antibody, selectively targeting the active/protonated form of V-domain Ig suppressor of T-cell activation (VISTA) found in the low pH of the tumor microenvironment. SNS-101 selectively binds with high affinity to VISTA at pH 6.0 and blocks the interaction between its receptor, the T-cell checkpoint P-selectin glycoprotein ligand-1. Based on preclinical data, SNS-101, either as monotherapy or in combination therapy with a PD-1 blocker, cemiplimab, is expected to exhibit an acceptable tolerability profile and demonstrate anti-tumor activity in pts with advanced solid tumors.

Trial design: This is a first in human, open-label, multi-center, dose escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of SNS-101, as monotherapy or in combination with cemiplimab in pts with advanced solid tumors. This study is being conducted in 3 parts: Part A (∼25 pts): Phase 1 (P1) Monotherapy Dose Escalation (SNS-101 alone) Part B (∼24 pts): P1 Combination Dose Escalation (SNS-101 + cemiplimab) Part C (∼80 pts): Phase 2 (P2) Expansion Cohorts (SNS-101 ± cemiplimab) Dose escalation/de-escalation will proceed following the Bayesian Optimal Interval Design until the Maximum Tolerated Dose (MTD)/Recommended phase 2 Dose (RP2D) is determined. Tumor imaging will be performed every 6 weeks. All pts will receive SNS-101 ± cemiplimab as intravenous infusion(s) every 3 wks and may continue until confirmed progressive disease or unacceptable toxicity. Primary objectives include safety, tolerability and RP2D/MTD (P1); and to evaluate anti-tumor activity (P2). Key eligibility includes histologically or cytologically locally advanced, unresectable or metastatic solid tumor, measurable disease, Eastern Cooperative Oncology Group ≤1 and pre-treatment/on-treatment tumor biopsy samples. Tumor types for P2 will be determined based on data from P1 and emerging results from preclinical studies/scientific data. The IND cleared in April 2023 and the study is open for enrollment.

Clinical trial identification: SNS-101-2-1.

Legal entity responsible for the study: Sensei Biotherapeutics.

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1079TiP A phase I first-in-human study of PRTH-101, an IgG1 monoclonal antibody targeting DDR1, as a monotherapy and combined with pembrolizumab in patients with advanced solid malignancies

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Background: Discoidin domain receptor 1 (DDR1) is a collagen receptor that represents a promising therapeutic target due to its role in excluding lymphocytes from the tumor microenvironment (TME) by aligning collagen fibers. DDR1 expression is high in multiple cancer types and associated with worse survival. DDR1 activity-driven RNA signatures are associated with poor responses to PD-1 inhibition. PRTH-101 is a humanized IgG1 antibody that binds to the extracellular domain of both membrane-bound and soluble DDR1. In preclinical models, PRTH-101 monotherapy resulted in disruption of aligned collagen fibers in the tumor stroma, increased infiltration of lymphocytes, and tumor growth inhibition. When PRTH-101 is combined with PD-1 inhibition, activated T cell infiltration is increased compared to PRTH-101 alone. These data provide a strong rationale for evaluating PRTH-101 as monotherapy and in combination with PD-1 blockade in multiple indications.

Trial design: This is a phase 1, first-in-human study that will evaluate intravenous PRTH-101 +/- pembrolizumab in patients with advanced solid tumors, The first part seeks to identify the maximum tolerated dose (MTD) or optimal biologic dose (OBD), of PRTH-101 to determine the recommended phase 2 dose (RP2D). Biomarker backfill cohorts of 10 additional patients each are planned for the two highest dose cohorts to aid biomarker correlation with dose and response. The second part seeks to identify the MTD or OBD of PRTH-101 in combination with pembrolizumab to determine the PRTH-101 combination RP2D. Both parts will use a Bayesian Optimal Interval design. A third part consists of dose expansion in disease-directed cohorts to assess the anti-tumor efficacy of PRTH-101 monotherapy and/or combination therapy in up to 40 patients per cohort in a Bayesian Optimal Phase 2 design with prespecified stopping boundaries based on objective response rates. Safety, efficacy, pharmacokinetic, and pharmacodynamic endpoints will be monitored and reported. DDR1 expression levels on tumors, circulating DDR1, molecular and cellular changes in the TME, and changes on CD8 PET imaging will also be assessed.

Clinical trial identification: NCT05753722, 03MAR2023.

Legal entity responsible for the study: Parthenon Therapeutics.

Funding: Parthenon Therapeutics.

Disclosure: S. Sen: Financial Interests, Institutional, Local PI: Parthenon Therapeutics. A.I. Spira: Financial Interests, Personal, Other, Consulting or Advisory Role: Incyte, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Janssen Research & Development, Mersana, Gritstone Bio, Daiichi Sankyo/AstraZeneca, Array Biopharma, Blueprint Medicines; Financial Interests, Personal, Other, Consulting or Advisory Role / Honoraria: Amgen, Novartis, Takeda, AstraZeneca/MedImmune, Merck, Bristol Myers Squibb; Financial Interests, Personal, Other, Honoraria: CytomX Therapeutics, Janssen Oncology, Bayer; Financial Interests, Institutional, Officer, CEO: NEXT Oncology Virginia; Financial Interests, Personal, Stocks/Shares: Eli Lilly; Financial Interests, Institutional, Local PI: LAM Therapeutics, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Newlink Genetics, Incyte, AbbVie, Ignyta, Trovagene, Takeda, Macrogenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen Oncology, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Kezar, Revolution Med. D. Sommerhalder: Financial Interests, Personal, Other, Ad-hoc advisory role: Syneos SAG; Financial Interests, Personal, Other, Medical consulting: Guidepoint; Financial Interests, Institutional, Full or part-time Employment, Employed as a physician by Texas Oncology, a for-profit entity.: Texas Oncology/US Oncology; Financial Interests, Institutional, Local PI: Astellas, Biomea Fusion, Boehringer Ingelheim, BJ Biosciences, BioNTech, Fate Therapeutics, Gilead Sciences, Immuneering, Kura Oncology, Monopteros Therapeutics, Navire, Nimbus Saturn, NGM Biopharmaceuticals, Parthenon, Pfizer, Revolution Medicines, Mirati Therapeutics, Symphogen, Teon Therapeutics, MediLink Therapeutics, ZielBio. F. Meric-Bernstam: Financial Interests, Personal, Other, Consultant: AstraZeneca, F. Hoffman-La Roche Ltd., Zymeworks, OnCusp Therapeutics; Financial Interests, Personal, Advisory Board, Advisory Board/Consultant: Seagen; Financial Interests, Personal, Advisory Board: Zentalis, Karyopharm, Biovica, Eisai, Protai, TheraTechnologies; Financial Interests, Personal, Other, Consulting: Tallac Therapeutics, Lengo Therapeutics, Loxo-Oncology, Black Diamond, Infinity Pharmaceuticals, AbbVie, GT Aperion, Ecor1; Financial Interests, Personal, Other, Consutling: Menarini Group; Financial Interests, Institutional, Other, Local PI / Research Grant: Aileron Therapeutics, Bayer Healthcare, CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., eFFECTOR Therapeutics, Taiho Pharmaceutical Co.; Financial Interests, Institutional, Other, Local PI / Research Grant / Coordinating PI: AstraZeneca; Financial Interests, Institutional, Local PI: Calithera Biosciences, Curis Inc., Debiopharm International, Guardant Health Inc., Klus Pharma, Novartis; Financial Interests, Institutional, Other, Local PI / Steering Committee Member: Genentech Inc.; Financial Interests, Institutional, Research Grant: Takeda Pharmaceutical Co., Puma Biotechnology Inc., Repare;

Other, Other, Travel support: European Organisation for Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO); Other, Other, Travel Support: Cholangiocarcinoma Foundation. J.D. Berlin: Financial Interests, Personal, Advisory Board: Merck KGA, mirati, merus, bristol Meyers, bexion, ipsen, merck, sharp, dohme, biosapien, insmed, Oxford biotherapeutics; Financial Interests, Institutional, Local PI: Astellas, atreca, bayer, BMS, dragonfly, I-MAB, transient therapeutic, totus, Tyra, Sumitomo Dainippon Pharma Oncology, 23 and Me, strata, Eli Lilly, hibercell; Other, Other, DSMB member: AstraZeneca, novocure, I-SPY. M. Cecchini: Financial Interests, Personal, Advisory Board, Honoraria for advisory board: Eisai Co, Agios Pharmaceuticals, DAVA Oncology, BAYER Pharmaceuticals, Seattle Genetics, Macrogenics, Taiho, Daiichi Sankyo, AstraZeneca; Financial Interests, Personal, Stocks/Shares, Stock options for advisory role: Parthenon Therapeutics. R.E. Sanborn: Financial Interests, Personal, Advisory Board: AstraZeneca, EMD Serono, Daiichi Sankyo, Lilly Oncology, Janssen Oncology, Macrogenics, Sanofi Aventis, Regeneron, Mirati Therapeutics, GSK, G1 Therapeutics; Financial Interests, Personal, Invited Speaker: Illumina; Financial Interests, Personal, Steering Committee Member: GSK, Janssen Oncology; Financial Interests, Institutional, Funding, Funding for investigator-sponsored trial: Merck, AstraZeneca; Financial Interests, Institutional, Other, Institutional research support: BMS; Financial Interests, Institutional, Funding, Clinical trial funding: Jounce. G.E. Peoples: Financial Interests, Personal and Institutional, Advisory Role: Parthenon Therapeutics. T. Schürpf: Financial Interests, Personal, Full or part-time Employment: Parthenon Therapeutics. L.A. Dillon: Financial Interests, Personal, Full or part-time Employment: Parthenon Therapeutics. G.T. Clifton: Financial Interests, Personal, Full or part-time Employment: Parthenon Therapeutics. J.P. Eder: Financial Interests, Personal, Full or part-time Employment: Parthenon Therapeutics. A.W. Tolcher: Financial Interests, Personal and Institutional, Coordinating PI: Parthenon Therapeutics. All other authors have declared no conflicts of interest.

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1080TiP An investigator-initiated phase I study to assess the safety and tolerability of ex vivo next-generation neoantigen-selected tumor-infiltrating lymphocyte (TIL) therapy in advanced immune checkpoint blockade (ICB) resistant solid tumors (NEXTGENTIL-ACT)

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Background: Lymphocytes play a crucial role in cancer immunity and patient survival, representing an attractive treatment option for melanoma and diverse epithelial tumors. Neoantigen-reactive TILs can recognize and kill cancer cells, inducing tumor regression and potentially increasing the efficacy of adoptive cell therapies (ACT). NEXTGENTIL-ACT consists of TIL selected based on identifying somatic non-synonymous mutations or viral neoantigens encoded in tandem minigenes and presented by autologous peripheral B cells.

Trial design: This is an investigator-initiated phase 1, single-center, open-label study assessing the safety, tolerability, and anti-tumor activity of single-dose NEXTGENTIL with high-dose IL-2 (720.000 IU/kg) following non-myeloablative lymphodepleting chemotherapy in adults with confirmed metastatic or unresectable advanced ICB-resistant solid tumors. The NEXTGENTIL product contains a polyclonal autologous lymphocyte population of TILs ranging from 5x108 to 1.11x1011 cells expanded from core tumor biopsies and selected based on neoantigen recognition using a high-throughput personalized screening approach. A bridge treatment during TIL expansion and screening for neoantigen recognition is allowed. The primary objectives are to evaluate the safety, tolerability, feasibility, and initial clinical activity. Four more patients will be included if a maximum of one treatment-limiting toxicity is observed in the first six patients. The preliminary anti-tumor activity will be assessed by RECIST v1.1. Patients must be at least 18 years old, have ECOG 0-1, and have received standard therapy (including ICB when indicated). One target lesion must be accessible for a biopsy/resection that allows TIL generation, and another must meet RECIST criteria. Patients must be medically fit enough to undergo all study procedures and interventions and have adequate cardiovascular and pulmonary functions. Patients with an autoimmune disease requiring immunosuppressive treatments will be excluded.

Clinical trial identification: EudraCT 2020-005778-90 (27.01.2021), NCT05141474.

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology.

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J. Tabernero: Financial Interests, Personal, Advisory Board, scientific consultancy role: Orion Biotechnology, Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daichii Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc., HalioDX SAS, Ikena Oncology, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Seattle Genetics, Servier, Taiho, Tessa Therapeutics, TheraMyc, Hutchinson MediPharma International, Scandion Oncology, Ona Therapeutics, Sotio Biotech, Inspirna Inc, Scorpion Therapeutics, Tolremo Therapeutics; Financial Interests, Personal, Invited Speaker, educational collaboration: Medscape Education, Physicians Education Resource (PER), PeerView Institute for Medical Education, Imedex / HMP; Financial Interests, Personal, Invited Speaker, educacional collaboration: MJH Life Sciences; Financial Interests, Personal, Advisory Board: Cardiff Oncology; Financial Interests, Personal, Stocks/Shares: Oniria Therapeuics; Financial Interests, Institutional, Research Grant, ACRCelerate: Colorectal Cancer Stratified: Fundación Científica de la Asociación Española Contra el Cáncer; Financial Interests, Institutional, Research Grant, OPTIMISTICC: Opportunity to Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer: Cancer Research UK; Financial Interests, Institutional, Funding, Clinical Trials & Research: Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb International Corporation, Celgene International SARL, Debiopharm International SA, F. Hoffmann-La Roche Ltd, Genentech Inc, Janssen-Cilag International NV, Merck Health KGAA, Merck, Sharp & Dohme de España, SA, Novartis Farmacéutica SA, PharmaMar SA, Sanofi-Aventis Recherche & Développement, Servier, Taiho Pharma USA, Inc, BeiGene, Boehringer Ingelheim, HalioDX SAS, Hutchinson Medipharma, MedImmune, Menarini, Merus N V, Pfizer, Mirati; Non-Financial Interests, Member of Board of Directors, Board of Directors: Cancer Core Europe, Spanish Association Against Cancer -AECC; Non-Financial Interests, Member of Board of Directors, General Assembly: Horizon Europe Cancer Mission; Non-Financial Interests, Leadership Role, External Scientific Committee: Institute for Health Research INCLIVA — Clinical Hospital of Valencia, IdiSNA —Universidad de Navarra; Non-Financial Interests, Leadership Role, Scientific Advisory Board: Spanish National Cancer Research Centre (CNIO); Non-Financial Interests, Advisory Role, International Scientific Evaluation Committee: Bosch Health Campus (BHC); Non-Financial Interests, Advisory Role, Review Board: National Decade Against Cancer (NCT) - German Consortium for Translational Cancer Research (DKTK); Non-Financial Interests, Advisory Role, Scientific Advisory Board: Karolinska Comprehensive Cancer Centre; Non-Financial Interests, Advisory Role, International Review Committee (IRC): Oncode Institute; Non-Financial Interests, Advisory Role, Scientific Advisory Board (SAB): Oslo University Hospital Comprehensive Cancer Centre (OUH CCC); Non-Financial Interests, Principal Investigator, Clinical Trials & Research: AstraZeneca Pharmaceutics LP, Array Biopharma Inc., BeiGene, Boehringer Ingelheim, Debiopharm International SA, Bristol Myers Squibb International Corporation, Celgene International SARL, F. Hoffmann-La Roche Ltd, Genentech Inc., HalioDX SAS, Hutchinson Medipharma, Menarini, Janssen-Cilag International NV, MedImmune, Merck Healthcare KGAA, Merck, Sharp & Dohme de España SA, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Sanofi-Aventis Recherche & Développement, Servier, Taiho Pharma USA Inc; Non-Financial Interests, Leadership Role, Governance Advisory Committee: European Organization for Research and Treatment of Cancer -EORTC; Non-Financial Interests, Leadership Role, Vice Chairman: World Innovative Networking (WIN) Consortium in Personalized Cancer Medicine; Non-Financial Interests, Other, Coordinating PI & Steering Committee Member. Clinical Trials & Research: Array Biopharma Inc., AstraZeneca Pharmaceutical LP, Boehringer Ingelheim, MedImmune, Menarini, Merck Healthcare KGAA, Merck, Sharp & Dohme de España SA, Pfizer, Servier; Non-Financial Interests, Other, Steering Committee Member. Clinical Trials & Research: Debiopharm International SA, F. Hoffmann-La Roche Ltd, Genentech Inc., HalioDX SAS, Hutchinson Medipharma, Janssen-Cilag International NV, Merus NV, Taiho Pharma USA Inc; Non-Financial Interests, Other, Coordinating PI. Clinical Trials & Research: Mirati; Non-Financial Interests, Member: AACR, ASCO, EACR, EORTC, SEOM; Other, Other, President: Oncology Master Plan — Catalonia Department of Health; Other, Other, Advisory Committee: Advisory Committee on Pharmaceutical Provision Financing under the Spanish National Health System. A. 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MELANOMA AND OTHER SKIN TUMOURS

1081O ctDNA reduction and clinical efficacy of the darovasertib + crizotinib (daro + crizo) combination in metastatic uveal melanoma (MUM)

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Background: MUM has limited effective therapies. Driver mutations in *GNAQ/11* occur in >95% of MUM, activating protein kinase C (PKC) signaling. Darovasertib (IDE196), an oral PKC inhibitor, has clinical activity in MUM (*Br J Cancer.* 2023;128(6):1040-1051). Crizotinib, an oral c-MET inhibitor, showed synergy with Daro pre-clinically. This phase 1/2 study evaluated the combination in first line (1L) and pretreated MUM.

Methods: Eligibility included RECIST 1.1 measurable disease, ECOG 0-1 and adequate organ function. Dose escalation used a 3 + 3 design with 3 escalation cohorts, followed by expansion at 300 mg BID Daro + 200 mg BID Crizo. Safety, efficacy, and circulating tumor (ct) DNA were assessed.

Results: At 08Mar2023 data cut-off, of 68 MUM pts treated at the expansion dose (safety population (SP)) as of September 2022, 63 were evaluable for response (per-protocol efficacy population (PPEP)). The PPEP had a large tumor burden: 66% with largest metastatic lesion > 3cm, 64% with hepatic + extrahepatic disease, & 60% with elevated LDH. HLA-A2*02:01 status (n=51 tested): 63% neg., 37% pos. In the SP, the most common drug-related adverse events (AEs) (>30%) were diarrhea, nausea, edema, fatigue, hypotension & rash. AEs were largely Grade 1-2. Related Serious AEs were seen in 6 (9%) pts and AEs leading to discontinuation in 4 (6%) pts. In the PPEP, 30% had a confirmed partial response (cPR) with 92% of patients having tumor shrinkage. First-line (1L) pts (n=20) had a cPR of 45% with 95% of patients having tumor shrinkage. Median PFS (mPFS) in both PPEP and 1L pts was ∼7 months. In pts with hepatic only disease (n=20 pts, 1L and pretreated), an ORR of 35% and mPFS was 11 months. Clinical efficacy was seen in both HLA-A2 pos. and neg. pts. There were deep & sustained ctDNA molecular responses in the majority of pts.

Conclusions: Initial evaluation of Daro + Crizo in both 1L & pretreated pts with MUM showed a manageable safety profile and clinical efficacy that appears superior to current standards of care. ctDNA was reduced in almost all pts. These data support the registrational phase II/III study for potential accelerated approval in 1L HLA-A2 neg. MUM, where there are no FDA approved therapies.

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Funding: IDEAYA Biosciences.

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Mckean: Financial Interests, Institutional, Other, Consulting: Pfizer, Castle Biosciences, Eisai, IQVIA, Merck, Moderna; Financial Interests, Personal, Other, Consulting: iTeos; Financial Interests, Institutional, Research Grant: Ascentage Pharma Group, Bicycle Therapeutics, Dragonfly Therapeutics, Epizyme, Exelixis, Genentech, GSK, IDEAYA Biosciences, Ikena Oncology, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Moderna, NBE Therapeutics, Novartis, Oncorus, Plexxicon, Prelude Therapeutics, Regeneron, Sapience Therapeutics, Seattle Genetics, Tizona Therapeutics, Tmunity Therapeutics, TopAlliance Biosciences, Aadi Biosciences, Alpine Immune Sciences, Arcs Biosciences, Bayer, Arvinas, ASCO, Astellas, BioMed Valley Discoveries, BioNTech, C4 Therapeutics, EMD Serono, Erasca, Foghorn Therapeutics, G1 Therapeutics, Gilead Sciences, ImmVira Pharma, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Nektar, OncoC4, PACT Pharma, Pfizer, Poseida, Pyramid Biosciences, Scholar Rock, Synthrox, Takeda Pharmaceuticals, Teneobio, Tempest Therapeutics, Xilio. 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1082O Concurrent intrathecal (IT) and intravenous (IV) nivolumab (N) for melanoma (MM) patients (pts) with leptomeningeal disease (LMD)

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Background: Pts with LMD have dismal prognosis and few clinical trial options. We previously reported safety and efficacy of the dose escalation (DE) phase of an open label, single arm, single center phase I/IB trial (NCT03025256) for MM pts with LMD. Concurrent IT/IV N was well tolerated, no new or unexpected CNS toxicities. 50mg IT N was the recommended dose (RD) for expansion accrual. Here we report the updated safety and efficacy results for the escalation and expansion cohorts.

Methods: Study design methods were previously reported (Glitza, *Nat Med,* 2023). Primary objectives were to determine safety and RD of IT/IV N and safety in RD expansion cohort. Secondary objectives included overall survival (OS).

Results: Fifty pts total were treated (48 pts with MM, 2 pts with NSCLC), including 31 pts with IT N 50 mg. Median age at LMD diagnosis was 49 (19-74); 27 pts are male. All pts had radiographic evidence of LMD; 26 pts had positive CSF cytology at baseline. Median follow-up and OS is shown in the table. Safety profile remained consistent with prior reports: 9 pts (18%) experienced gr 3 AEs, none had gr 4 or 5. Nausea (46%), rash (40%), vomiting (34%), diarrhea (20%), and dizziness (20%) were the most common AEs. Thirty pts (60%) experienced AEs after IT N administration, including 2 gr 3 (vasogenic edema, elevated ALT); remainder were gr 1/2.

Table: 1082O

	Med follow up wks (range)	Median OS Wks (95% CI)	OS 13 wks	OS 26 wks	OS 52 wks
All	27.3 (2, 251)	30 (19, 64)	68%	54%	35%
<50 mg	25 (5, 251)	25 (15, 143)	68%	47%	26%
50 mg	30 (2, 140)	41 (13, 65)	68%	58%	43%

Conclusions: This updated analysis confirms the safety of IT (50mg)/IV N. There were no significant differences in OS between the tx groups and no unexpected toxicities were observed at RD. These results support further evaluation of IT immunotherapy strategies for pts with LMD. Insights gained from translational studies on CSF samples will aid in the development of future IT immunotherapy strategies for these patients.

Clinical trial identification: NCT03025256.

Legal entity responsible for the study: The authors.

Funding: Bristol Myers Squibb.

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1085O Atezolizumab, bevacizumab, and cobimetinib (TACo) in patients (pts) with PD1 refractory melanoma brain metastases (MBM)

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Background: Combination immune checkpoint blockade (ICB) achieves frequent durable responses in pts with untreated MBM. However, systemic treatments (tx) after ICB failure are limited, especially in BRAF wild-type pts. We investigated the novel TACo regimen in ICB- refractory MBM based on biological insights that (1) VEGF can drive ICB resistance, and (2) MEK inhibition can increase MHC I expression and T cell infiltration to potentially synergize with ICB. We hypothesized this regimen would be safe and demonstrate efficacy in pts with MBM.

Methods: In this single-center phase II study evaluating TACo in pts with MBM (NCT03175432), primary objectives included safety and efficacy (intracranial response rate (ICRR) by modified RECIST 1.1). Secondary objectives included IC clinical benefit rate (ICCBR), progression free (PFS) and overall survival (OS), and duration on tx (DoT). Prior PD1 tx and $\geq$1 non irradiated lesion (5-30mm) were required. BRAF mutated pts were allowed after BRAF/MEK tx (3-month washout). Pts on $\leq$4m/day PO of dexamethasone or equivalent were allowed. Tx schedule: atezolizumab 840mg IV every 2 weeks (wks), bevacizumab 5mg/kg every 2 wks, cobimetinib 60mg PO daily for 3 wks followed by 1 wk off. MRIs were obtained prior to cycles 1-3, and 5.

Results: Of the 20 pts treated, 70% were male, median age 59.5 yrs (34-78), and 2 pts were BRAFV600E mutated. 11 pts had $\geq$ 1 prior tx for MBM. Median follow up was 8.2 mos (0.4-39.2). Median DoT was 8 wks (0.6-63.8). 18 pts experienced tx related adverse events (AEs), most commonly rash (70%), diarrhea (D) (55%), hypertension (HTN) (25%), proteinuria (25%). 35% pts had gr 3/4 AEs: HTN (15%), D (10%) were most common. 2 pts stopped tx due to toxicity. 18 pts were evaluable for IC response: ICRR was 39% (1 CR, 6 PR) and ICCBR was 56% (+SD). Median PFS was 2.7 mos (95% CI 0.9,7.3) and median OS was 9.3 (95% CI 3.8,20.9). 7 (35%) pts continued on tx post progression for $\geq$ 3 wks (3-55 wks).

Conclusions: In this heavily pretreated MBM pt population with no available standard systemic therapy options, TACo regimen was tolerable, demonstrated IC clinical benefit, and provided clinical benefit beyond progression, warranting further evaluation.

Clinical trial identification: NCT03175432.

Legal entity responsible for the study: MD Anderson Cancer Center - PI Hussein Tawbi.

Funding: Genentech.

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1083MO Brain metastases and survival evaluation in the SECOMBIT trial

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Background: Despite the availability of effective systemic therapies, a significant number of advanced melanoma patients develop brain metastases. In the SECOMBIT study patients received the combination of encorafenib/binimetinib (E+B) as targeted therapy (T-T) or the combination of ipilimumab/nivolumab (I+N) as immunotherapy (I-O). In the present analysis, we updated survival outcomes and investigated if the incidence of and timing to brain metastasis onset were significantly different in patients receiving T-T (Arm A) or I-O (Arm B) as first line with switch at progression, as well as the "sandwich" strategy with T-T first preplanned switched to combo I-O after 8 weeks, returning back to T-T after progression (Arm C). In our previous reports, 4-year survival outcomes confirmed long-term benefit in ARM B and C pts. We also described preliminary biomarkers analyses where the loss-of-function affecting JAK or low baseline levels of serum interferon gamma (IFNy) are correlated to PFS and OS.

Methods: From Nov 2016 to May 2019, of 251 pts enrolled, 69 were randomized in ARM A, 71 pts in ARM B and 69 pts in ARM C. BMFS (Brain Metastasis Free Survival) was defined as time from start of first systemic therapy until new brain metastasis detection or last pts contact (censored BMFS). The Kaplan-Meier method was used to estimate OS and PFS. The median follow up was 43 months (IQR: 37-51).

Results: Pts treated in arm B and C had a lower risk to develop brain metastasis compared to pts in arm A. Brain metastasis occurred during first line treatment, in 17, 6, and 8 patients, respectively, treated in ARM A, B and C. During the study, an intracranial progression was detected in a total of 23, 11 and 9 patients in ARM A, B and C. The exploratory HR for BMFS was of 0.51 (0.25-1.04) for ARM B vs ARM A, and 0.37 (0.17-0.81) for ARM C vs ARM A. In the biomarker analysis, pts with high tumor mutational burden (TMB, $\geq$10 mut/mb) had an improved BMFS compared with pts with low TMB [HR 0.20 (0.05-0.95)]. JAK mutated pts had a better BMFS compared to wild type pts [HR 0.26 (0.06-1.12)].

Conclusions: Patients in ARM B and C had a longer BMFS compared with pts who started treatment with T-T. BMFS rate at 4 years was better in TMB high and in JAK mutated pts. At the time of the meeting it will also be reported the 5-years OS data.

Clinical trial identification: NCT02631447.

Legal entity responsible for the study: Fondazione Melanoma.

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1084MO Nivolumab plus ipilimumab in melanoma patients with asymptomatic brain metastases: 7-year outcomes and quality of life from the multicenter phase III NIBIT-M2 trial

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Background: The phase III NIBIT-M2 study showed a 41% 5-year overall survival (OS) of melanoma patients (pts) with asymptomatic brain metastases (BM) treated with ipilimumab (I) plus nivolumab (N) (I+N) (*Di Giacomo AM, CCR 2021*). In spite of the significant efficacy of I combined with N, no data are available on long-term survival, and patient-reported outcomes (PROs) and quality of life (QoL) in this patient population. Here, we report the 7-year efficacy outcomes and HRQoL analyses of the NIBIT-M2 study.

Methods: The NIBIT-M2 study recruited melanoma pts with active, untreated, asymptomatic BM from 9 Italian Centers that were randomized (1:1:1) to fotemustine (F) (Arm A), I+F (Arm B), or I+N (Arm C). Primary endpoint was OS; among secondary endpoints were intracranial progression-free survival (iPFS) and HRQoL. PROs were assessed at week (W) 1 and W12 using the EORTC Quality of Life Questionnaire (QLQ)-C30 Version 3.

Results: From Jan 2013 to Sept 2018 , 80 pts were enrolled: 76 received F (23), I+F (26), or I+N (27). As of May 1, 2023, at a median follow-up of 67 months (mo), median OS was 8.5 (95% CI: 6.6-10.3), 8.2 (95% CI: 2.1-14.3) and 29.2 (95% CI: 0-69.9) mo for Arm A, B, and C respectively. The 7-y OS rate was 10.0% (95% CI: 0-22.5) in Arm A, 10.3% (95% CI: 0-22.6) in Arm B, and 42.8% (95% CI: 23.4-62.2) in Arm C. Median iPFS was 3.0 (95% CI: 2.3-3.6), 3.3 (95%CI: 1.2-5.4) and 8.7 (95% CI: 0-19.9) for Arm A, B, and C, respectively. The 7-year iPFS rate was 4.3% (95% CI: 0-12.7) in Arm A, 7.7% (95% CI: 0-17.9) in Arm B, and 28.6% (95% CI: 11.2-46.0) in Arm C. Seventy-two pts (compliance 95%) and 34 pts (compliance 45%) completed the baseline and the W12 QLQ C-30 assessment. HRQoL was preserved in all treatment arms; no significant differences were observed in global health score. Most functional scales evaluated were preserved from baseline to W12, with a lower mean score decrease in pts receiving I+N.

Conclusions: The 7-year results of the NIBIT-M2 study, with the longest follow-up available to date in melanoma pts with asymptomatic BM treated with I+N, continue to show persistent therapeutic efficacy. HRQoL was preserved in all treatment arms and I+N induced a lower decrease in mean functional scales.

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1086MO Lifileucel tumor-infiltrating lymphocyte (TIL) cell therapy in patients (pts) with advanced mucosal melanoma after progression on immune checkpoint inhibitors (ICI): Results from the phase II C-144-01 study

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Background: Advanced mucosal melanoma is rare and difficult to treat, with worse outcomes after anti−PD-1 therapy than nonmucosal melanoma (median ORR: 19%−23%; median OS: 11.3−13.4 mo in large pooled analyses [D'angelo *JCO* 2017 , Mignard *J Oncol* 2018 , Hamid *Br J Can* 2018]). Lifileucel, a one-time autologous TIL cell therapy, had an ORR of 31.4% in 153 pts with heavily pretreated advanced melanoma (only uveal excluded) in the C-144-01 study (NCT02360579; Chesney *JITC* 2022). We report outcomes of pts with advanced mucosal melanoma treated with lifileucel in C-144-01.

Methods: Pts (coh 2+4) must have progressed after anti−PD-1/PD-L1 therapy. Pts had ≥1 lesion resected for lifileucel manufacturing, then received lymphodepleting chemotherapy (cyclophosphamide 60 mg/kg/d × 2d; fludarabine 25 mg/m^2/d × 5d), a single lifileucel infusion, and up to 6 doses of high-dose IL-2. Responses were assessed by IRC per RECIST v1.1.

Results: Fifteen pts with mucosal melanoma were enrolled; lifileucel was manufactured for all 15 (100%), and lymph nodes were the most common source (47%). Twelve pts received lifileucel (median target lesion SOD: 118.9 mm; median prior lines of therapy: 2 [range: 1−6]; LDH >ULN: 42%; liver and/or brain metastases: 42%). Median number of TIL infused was 26 × 10^9 cells. ORR was 50% (95% CI: 21%−79%). At median study follow-up of 35.7 months, median DOR was not reached (NR; 95% CI: 12.5 mo−NR), median PFS was NR (95% CI: 1.4 mo−NR), and median OS was 19.4 mo (95% CI: 7.9−NR). TEAEs were consistent with known safety profiles of lymphodepleting chemotherapy and IL-2. The most common (≥30%) G3/4 non-hematologic TEAEs were febrile neutropenia (58%) and hypotension (33%). Translational data will be presented.

Conclusions: In C-144-01, the activity of lifileucel in this small subset of pts with the difficult-to-treat mucosal melanoma subtype was clinically meaningful and durable (ORR: 50%; median DOR: NR) with anti-tumor activity that was consistent with the overall post-anti−PD-1/PD-L1 advanced melanoma population. These data further support the potential benefit of lifileucel as a one-time treatment that is differentiated from other immunotherapies.

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1087MO A single arm phase II, multicenter trial to evaluate the clinical activity and safety of avelumab plus cetuximab in unresectable stage III or IV cutaneous squamous cell carcinoma: First results from the AliCe study

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Background: In cutaneous squamous cell carcinoma (cSCC), both PD-1 and EGFR-inhibitors are effective, but durable tumor control, especially in anogenital cSCC, is still limited. For the latter, and refractory patients (pts), there is an unmet medical need.

Methods: Pts with unresectable stage III/IV cSCC were treated with PD-L1 inhibitor avelumab (10 mg/kg q2w) plus EGFR-inhibitor cetuximab (500 mg/m^2 q2w) for up to 1 year. The Safety Analysis (SAF) set was defined as pts who received at least 1 administration of study treatment, the per protocol (PP) set if treated for at least 12 weeks.

Results: 54 pts were registered (SAF Set: 51 pts; PP Set: 37 pts). Two-thirds of pts had prior systemic treatment for cSCC, i.e. chemotherapy or PD-1 inhibition. 31.4% (SAF) and 21.6% (PP) of primaries were anogenital cSCC. Within a median follow up of ∼ 2.5 years, median PFS/OS were 8.4/17.4 months in the SAF and 9.2/25.4 months in the PP set, respectively. No significant differences in PFS and OS were observed when subgroups for tumor stage (III vs. IV), location of primary (anogenital vs. elsewhere), or prior treatment (yes vs. no) were analyzed. Adverse events (AE) >= grade 3 were common, but adverse drug reactions (ADR) >= grade 3 occurred only in ∼ 20% of pts, which is explained by the frailty of pts with advanced cSCC. Only two pts discontinued treatment due to ADR (abnormal ECG, sarcoid-like lesions).

Table: 1087MO

Baseline characteristics and outcome data	SAF set (n=51)	PP set (n=37)
Mean age (years)	71.8	73.2
Sex female	33.3%	32.4%
ECOG > = 1	37.3%	43.2%
Stage (III/IV)	21.6%/78.4%	24.3%/75.7%
Anogenital primary	31.4%	21.6%
Prior systemic treatment	66.7%	67.6%
Response rate	45.1%	56.8%
Median PFS (95% CI), months	8.4 (4.5-10.2)	9.2 (8.3-12.5)
Median OS (95% CI), months	17.4 (11.1-33.1)	25.4 (13.9-NR)
AE > = grade 2	43 (84.3%)	32 (86.5%)
Adverse drug reactions (ADR) > = grade 3	10 (19.6%)	6 (16.2%)

Conclusions: Avelumab plus cetuximab is a feasible treatment option in patients with cSCC. This combination shows remarkable activity even in patients in whom PD-1 blockade has low efficacy, such as anogenital cSCC, or after failure of anti-PD-1 monotherapy.

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1088MO A phase II study of neoadjuvant cemiplimab for stage II to IV cutaneous squamous cell carcinoma (CSCC): One-year follow-up

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Background: We previously reported a high rate of pathologic complete response (pCR) or major pathologic response (MPR) to neoadjuvant (neoadj) cemiplimab (anti-programmed cell death-1) among 79 patients (pts) with locoregionally advanced, resectable CSCC. Here, we present 1-year follow-up data, with event-free, disease-free and overall survival (EFS, DFS, OS; NCT04154943).

Methods: This non-randomised multicentre phase II study had 2 parts. In part 1, pts with resectable stage II–IV (M0) CSCC received neoadj cemiplimab 350 mg every 3 weeks (Q3W) for up to 4 doses followed by curative-intent surgery. In Part 2, per investigator discretion, pts received adjuvant cemiplimab for up to 48 weeks or radiotherapy (RT) or observation only. EFS (time from first dose of neoadj cemiplimab to progressive disease precluding surgery, inability to undergo complete resection, disease recurrence, or death due to any cause); DFS (time from surgery until CSCC recurrence or death due to any cause) and OS were summarised by the Kaplan-Meier method.

Results: At December 1, 2022 data cut-off, median duration of follow-up was 18.7 months (range: 1.3–30.4) for all 79 pts. Among 70 pts who had surgery, the most common choices for subsequent care were observation only (n=29), cemiplimab (n=16), or RT (n=12) or other (Table). None of 40 pts with pCR and 1 of 10 pts with MPR experienced recurrence. Estimated 12-month EFS was 89% (95% confidence interval [CI]: 79–94%) for all pts and 95% (95% CI: 81–99%) for pts with pCR. Of 70 pts who completed surgery, 12-month DFS was 92% (95% CI: 82–97%). For all 79 pts: estimated 12-month OS rate was 92% (95% CI: 83–96%). Of 16 pts who received cemiplimab in part 2, there were 2 serious adverse events: grade 3 cardiomyopathy and grade 3 hypophysitis.

Table: 1088MO

	Pathology response by independent central pathology review		
n (%)	**pCR (n = 40)**	**MPR (n = 10)**	**Non-pCR/non-MPR (n=20)**
Adjuvant treatment in part 2			
Cemiplimab	12 (30)	1 (10)	3 (15)
Radiotherapy	1 (3)	5 (50)	6 (30)
Observation only[a]	24 (60)	3 (30)	2 (10)
Other			
Survival follow up	0	0	2 (10)
Imaging only[b]	0	0	6 (30)
Not applicable[c]	3 (8)	1 (10)	1 (5)
CSCC recurrence	0 (0)	1 (10)	2 (10)

[a]Patients in the "observation only" group had 4 doses of cemiplimab in Part 1. [b]Patients in the "imaging only" group had <4 doses of cemiplimab due to progressive disease in Part 1. [c]Included: lost to follow up (n=2), withdrawal of consent (n=1), fatal post-op COVID pneumonia (n=1), post-op death prior to starting Part 2 (n=1).

Conclusions: In pts with resectable stage II–IV CSCC, neoadj cemiplimab demonstrated favourable EFS, DFS and OS rates, and no recurrences in pts with pCR at a median follow-up of 18.7 months. There were no new safety signals with cemiplimab.

Clinical trial identification: NCT04154943.

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1089P Adjuvant nivolumab (NIVO) vs ipilimumab (IPI) in resected stage III/IV melanoma: 7-y results from CheckMate 238

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Background: In the phase III CheckMate 238 trial, NIVO showed improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs IPI in pts with high-risk, resected stage IIIB—C or IV melanoma, sustained for 5 y; no significant difference was observed in OS. Updated 7-y results are presented.

Methods: Pts aged > 15 y (stratified by disease stage and PD-L1 status) were randomized 1:1 to NIVO 3 mg/kg Q2W (n = 453) or IPI 10 mg/kg Q3W for 4 doses then Q12W (n = 453), for up to 1 y or until disease recurrence/unacceptable toxicity. Endpoints included RFS, OS, DMFS in stage III pts, and safety. Progression-free survival through next-line therapy (PFS2) and melanoma-specific survival (MSS) are post hoc analyses presented here for the first time.

Results: At 7-y, RFS remained superior with NIVO vs IPI (HR 0.74; 95% CI 0.62—0.88) with DMFS and PFS2 also favoring NIVO (Table). New recurrence events since 5 y included 12 new events (2 regional, 7 distant, 2 new primary, 1 death) for NIVO and 7 new events (1 local, 2 distant, 4 deaths) for IPI; 6% and 5% of at-risk pts relapsed after yr 5. For NIVO vs IPI respectively, there were a total of 13 and 12 new deaths overall (8 and 10 due to melanoma). Subsequent systemic therapy was less frequent with NIVO than IPI (36% vs 44%), including subsequent immunotherapy in 26% vs 36% of pts. No new voluntarily reported late-emergent treatment-related adverse events were reported since the 4-y database lock, and overall rates remain low.

Conclusions: At 7-y follow-up, the longest follow-up of any anti—PD-1 therapy in this setting, NIVO showed superior long-term RFS vs IPI in pts with stage IIIB—C or IV resected melanoma. DMFS and PFS2 also favored NIVO, and OS and MSS rates were high in both arms, with no significant difference between arms. The additional recurrences at 7-y vs 5-y follow-up may indicate a clinical consideration for imaging and follow-up visits beyond 5 y.

Table: 1089P

	NIVO (n = 453)	IPI (n = 453)
	7-y rates, % (95% CI) HR[a] (95% CI)	
RFS	45 (40—50) 0.74 (0.62—0.88)	38 (33—42)
OS	71 (66—75) 0.89 (0.70—1.14)	69 (64—73)
MSS	75 (70—79) 0.89 (0.68—1.16)	72 (68—76)
DMFS[b]	54 (48—60) 0.82 (0.66—1.01)	50 (44—55)
PFS2	59 (54—64) 0.76 (0.62—0.93)	52 (48—57)

[a]NIVO vs IPI (Stratified Cox proportional hazards model). [b]In stage III patients (NIVO = 307; IPI = 366).

Clinical trial identification: NCT02388906.

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1090P Outcome impact of time from complete resection to start of adjuvant immunotherapy in stage III-IV melanoma patients

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Background: Adjuvant therapy with immune checkpoint inhibitors improves outcomes in patients with resected melanoma. However, clinical trials included patients that started treatment within a maximum of three months after complete resection. The objective of this study is to analyze whether starting adjuvant therapy beyond 3 months after surgery could impact on efficacy.

Methods: This is a multicenter retrospective study of patients with completely surgically resected stage III to IV melanoma that have been treated with PD-1 inhibitors (either alone or in combination). We compared efficacy and pattern of recurrence according to the period of time from last resection to the start of immunotherapy (more -group A- or less -group B- than three months).

Results: We included 214 patients, group A included 31 (14%) patients and group B 183 (86%) patients; baseline characteristics were similar between both groups. With a median follow up of 20 months, 22 (71%) patients in group A and 76 (42%) patients in group B have recurred; the median disease free survival (DFS) was 8,4 months (95% CI 2-14,8) in group A and 43,4 months (95%CI 26-60,7) in group B (log rank p=0,002). After multivariate analysis Hazard Ratio (HR) was 3,8 (95% CI 2,1-6,8, p<0,001). Patients in group A presented higher rate of distant recurrence (86% vs 73%) and visceral non-pulmonary recurrence (18% vs 8%) than group B, without differences in central nervous system (CNS) recurrence (18% vs 15%). For patients with distant recurrence that received systemic therapy (18 in group A and 51 in group B), both groups showed similar overall response rate (40% vs 42%) and DFS (median 6,6 vs 8,9 months, p>0,05). Group A showed a trend to shorter overall survival (OS) than group B (median OS NR in both groups; OS at 18 and 24 months were 81% and 69% in group A vs 91% and 87% in group B, respectively).

Conclusions: Starting adjuvant PD-1 inhibitors after more than 3 months from last resection surgery negatively impacts in DFS in patients with resected melanoma, with a higher proportion of distant recurrence.

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1091P Relapse-free survival with adjuvant dabrafenib/trametinib therapy after relapse on a prior adjuvant checkpoint inhibitor and subsequent surgical resection in patients with BRAF V600-mutated stage III/IV melanoma

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Background: In BRAF mutant resected melanoma, both targeted therapy and immunotherapy have shown durable clinical benefit as 1st line (1L) adjuvant therapy. However, there are no clinical studies evaluating 2nd line (2L) adjuvant targeted therapy in patients with locoregional relapse and complete surgical resection following initial adjuvant immunotherapy.

Methods: This was a retrospective, multicenter chart review study of BRAF V600-mutated stage III/IV melanoma patients in the United States, Australia, and The Netherlands who received 1L adjuvant checkpoint inhibitor therapy, then relapsed locoregionally or distantly, were again resected to NED, and then treated with dabrafenib/trametinib (dab/tram) as 2L adjuvant therapy. The primary endpoint was relapse-free survival (RFS-2) after initiation of dab/tram therapy. Secondary endpoints included overall survival (OS) and distant metastasis-free survival (DMFS). Analyses were descriptive with event time endpoints (RFS-2, OS, DMFS) estimated using the Kaplan-Meier method.

Results: A total of 37 patients were included (median age 51 years, 62% male, 89% stage III, median follow-up of 19 months from dab/tram initiation). Median time to dab/tram initiation after repeat resection to NED was 0.9 months (range: 0.2 – 2.8 months). A majority (73%) had discontinued dab/tram by last follow-up, with median therapy duration of 10.1 months (range: 1 day – 22.7 months). Median (95% confidence interval [CI]) RFS-2 was 18.9 (14.9 – 28.1) months, with 91% and 81% remaining relapse-free at 12 and 18 months, respectively; most patients also remained distant metastasis-free at 6 months (97%) and 12 months (85%). Only 2 patients were deceased at last follow-up, with nearly all patients (97%) still alive at 18 months; median OS was not reached.

Conclusions: More than 80% of patients remained relapse- and metastasis-free for at least 12 months after initiation of dab/tram. Longer follow-up and a larger patient cohort is needed in future studies to confirm efficacy of 2L adjuvant dab/tram in this population.

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1092P Adjuvant treatment with anti-PD-1 in acral melanoma patients: A nationwide study

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Background: Previous studies demonstrate limited efficacy of immune checkpoint inhibitors in patients with irresectable acral melanoma (AM) compared to cutaneous melanoma (CM) in other locations. However, little is known about the outcomes of adjuvant therapy for resectable stage III-IV AM. This study aims to compare clinical outcomes after treatment with adjuvant anti-PD-1 in resectable stage III-IV AM and compare them to CM.

Methods: All patients with stage III-IV AM and CM who received adjuvant anti-PD-1 after complete resection between 2017 and 2022 were included from the prospective nationwide Dutch Melanoma Treatment Registry. We described baseline characteristics and analyzed the recurrence-free survival (RFS). A multivariable Cox regression analysis was performed to account for potential confounders age, performance status (ECOG), AJCC 8th edition disease stage, mutation status. Type of recurrence (locoregional or distant metastases) and toxicity rates will be presented at the conference.

Results: In total, 1977 patients (86 AM and 1891 CM) were included. At baseline, *KIT* mutations were more common in AM patients. In addition, AM patients more often had higher AJCC 8 disease stages. No other significantly different baseline characteristics were identified. Median follow-up was 16.4 months. The median RFS was 14.8 months (95%CI: 11.5-29.7) for the AM cohort and 37.4 months (95%CI: 32.1 - NR) for the CM cohort (p=.002)). After correcting for potential confounders, AM remained associated with higher risk of recurrence than CM (HR_{adj} 1.55; 95%CI: 1.09-2.19; p=.014).

Table: 1092P Baseline characteristics and median RFS stratified by melanoma type.

		AM (n=86)	CM (n=1891)	P-value
Median age (IQR)		65 [54, 72]	64 [54, 73]	.984
Gender (n (%) female)		45 (52.3)	793 (41.9)	.160
AJCC8 stage (n (%))	IIIA	5 (5.7)	130 (6.9)	.001
	IIIB	17 (19.5)	599 (31.7)	
	IIIC	58 (66.7)	713 (37.7)	
	IIID	2 (2.3)	37 (2.0)	
	IV	2 (2.3)	170 (9.0)	
	Unknown	3 (3.4)	241 (12.8)	
Mutation (n (%))	BRAF	23 (26.7)	804 (42.5)	.001
	NRAS	9 (10.5)	441 (23.3)	
	KIT	7 (8.1)	12 (0.6)	
Median RFS (months; 95% CI)		14.8 (11.5-29.3)	37.4 (32.1-NA)	.002

Conclusions: This study suggests that AM patients treated with adjuvant anti-PD-1 have shorter RFS than CM patients receiving the same treatment. Longer follow-up is needed to investigate overall survival and distant-metastasis-free survival.

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1093P Neoadjuvant (NeoAd) intratumoral (IT) TAVO-EP (plasmid IL-12 electro gene transfer) in combination with nivolumab (NIVO) for patients (pts) with operable locoregionally advanced melanoma

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Background: IT TAVO-EP (tavokinogene telseplasmid delivered by electroporation) results in localized expression of IL-12 in the tumor microenvironment. This phase II study (NCT04526730) was designed to evaluate NeoAd TAVO-EP in combination with NIVO in subjects with operable, locoregionally advanced melanoma. Pts provided an IRB-approved (Advarra IRB Pro00041794) written informed consent.

Methods: The NeoAd phase comprised up to 3 x4-week cycles of TAVO-EP on days 1, 8 and 15 (optional) concurrently with 480 mg NIVO iv on day 8 of each cycle. Surgery followed and later adjuvant NIVO was initiated. Primary endpoint was pathologic complete response (pCR), secondary endpoints included near pCR (≤10% viable tumor), pathologic major response (pMR; pCR + near pCR) and nonresponse (pNR), among others. Biomaterials were collected at screening, C1D8, C2D1, pre-surgery and during adjuvant phase.

Results: 16 pts (7 female, 9 male, cutaneous primary, age 30 − 88) were treated; 9 Stage IIIB, 5 IIIC, 2 IV (M1a) as clinically assessed. Highest-grade (Gr3) treatment-related adverse events included 1 hyponatremia, 2 diarrhea/colitis, 1 pancreatitis, 1 hypertension. One pt currently in NeoAd phase. Among the 15 pts who completed NeoAd phase, median number of NeoAd NIVO was 3 (range 1 - 3) and TAVO-EP 7 (3 - 9). Preoperative response rate (RECIST, unconfirmed) was 9/15 (60%; 95% CI: 55.7-68.3%); 2 PD, 4 SD, 6 PR, 3 CR. One pt with PR declined surgery and 1 with early distant PD did not have surgery. Among 13 pts who had surgery: 2 pNR, 3 near pCR, 8 pCR; pMR rate was 11/14 (78.6%; 95%CI: 73.7—81.9%). Among those with pMR, there was no melanoma relapse to date with a median follow up of 11.4 months (range 0.9 − 24.6) from surgery. At baseline, many pts had low levels of CD8+ TIL, PD-L1, and IFN-gamma signature scores. Combination therapy induced local and systemic proinflammation changes, including increases in immune-related gene expression profiles, CD8+ TIL and peritumoral T cells.

Conclusions: NeoAd IT TAVO-EP and iv NIVO exhibited promising clinical activity and a favorable safety profile. Enhanced immune activation in responding patients supports the proposed immune mechanisms.

Clinical trial identification: NCT04526730.

Legal entity responsible for the study: Moffitt Cancer Center.

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1094P Relapse free survival (RFS) at 3 years by pathological (path) response to neoadjuvant systemic treatment (NST) in patients (pts) with surgically resectable, high-risk melanoma

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Background: For pts with high-risk, surgically resectable melanoma, NST demonstrated improved outcomes compared to upfront surgery and adjuvant therapy. Outcomes are most improved in pts who achieve a pathologic complete response (pCR) with any NST [targeted therapy (TT) or immune checkpoint blocked (ICB)]. Prior studies in ICB NST suggest improved outcomes associated with any path response. We evaluated updated data from 2 previously reported NST studies for long-term outcomes by path response, determined by percent tumor viability (TV).

Methods: We analyzed 2 trials in for clinical stage III/IV, resectable melanoma: NST [2 months (mo)] + adjuvant (10 mo) dabrafenib + trametinib (DT) (NCT02231775) and ICB, (NCT02519322). ICB trial arms were 8-9 wks of NST: nivolumab (nivo) (Arm A), ipilimumab 3mg/kg plus nivo 1mg/kg (Arm B) both followed by adjuvant nivo for 6 mo, and nivo + relatlimab (2 mos NST, 10 mos adjuvant) (Arm C). RFS was estimated using Kaplan Meier (KM) method and differences by path responses were evaluated by the log-rank test.

Results: 97 pts of 103 treated pts underwent surgery and were evaluable for analysis by detailed path response: 49 pts on DT and 48 on ICB (11 Arm A, 10 Arm B, 28 Arm C). Median follow up for all pts was 34.5 mos (3.8-94.8). Median RFS in mos for any pt with pCR was not reached and 23.7 mos (95% CI: 11.3, 30.5) for pts with <pCR (p<0.001). The table reports 36 mos RFS by NST and path response: >50% TV (pNR), 11-50% TV (pPR), 1 - ≤10% TV near pCR, and 0% TV pCR. Additional clinical data and outcomes will be reported at the meeting.

Table: 1094P 36 mos RFS KM rates

Path response	All pts			TT pts			ICB pts		
	n	Rate		n	Rate		n	Rate	
pCR	42	83%	p < 0.001	17	65%	p < 0.001	25	96%	p = 0.005
near pCR	10	53%		7	36%		3	100%	
pPR	16	24%		12	0%		4	75%	
pNR	29	32%		13	8%		16	49%	

Conclusions: At 3 years, RFS in pts treated with NST TT and ICB with pCR continues to be superior to those with <pCR. Any path response to ICB NST (pCR, near pCR, pPR) is associated with improved RFS, but only pCR predicts durable RFS in TT NST. It is critical to understand associations between NST, path response, and outcomes to support personalization of adjuvant approaches and improve overall outcomes.

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1095P Associations between baseline biomarkers and 3-year survival in the PRADO trial testing neoadjuvant ipilimumab and nivolumab in stage III melanoma

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Background: PRADO tested neoadjuvant ipilimumab plus nivolumab in 99 stage III melanoma patients (pts) followed by omission of therapeutic lymph node dissection (TLND) and adjuvant therapy in pts achieving a major pathologic response (MPR) in their index lymph node, and addition of adjuvant therapy after TLND in non-responding (pNR) pts. Previous analyses of PRADO and its previous OpACIN-neo trial showed that a high interferon-gamma (IFN-γ) signature, PD-L1 expression and tumor mutational burden (TMB) were associated with major pathologic response (PD-L1 expression only in PRADO). Here, we report the association between these biomarkers and 3-year (3y) survival of PRADO.

Methods: The IFN-γ signature, PD-L1 expression and TMB were analyzed on baseline tumor biopsies using mRNA sequencing (n=80), anti-PD-L1 mAb (clone 22C3) (n=76), and whole exome sequencing (n=75). Cutoffs between high and low cohorts were calculated using ROC curves on MPR. Event-free (EFS), relapse-free (RFS), distant metastasis-free (DMFS) and overall (OS) survival curves were generated and compared using the Kaplan-Meier and log-rank method.

Results: Pts with a high baseline IFN-γ signature or a PD-L1 expression of ≥1% had a significantly higher 3y EFS rate than pts with low levels (85% vs 61%, p=0.006 and 91% vs 67%, p=0.005, respectively) (Table). Pts with a high TMB had a numerically higher 3y EFS rate (81% vs 64%, p=0.072). The correlation between baseline IFN-γ signature and PD-L1 expression and EFS translated into a numerical benefit in RFS, DMFS and OS (OS was statistically significant for PD-L1). However, no association with RFS, DMFS or OS was observed for TMB.

Table: 1095P

	3-year survival rate estimate		Log-rank p-value
Registration-to-event analyses			
IFN-γ	High (n=39)	Low (n=41)	
EFS	85%	61%	0.006
OS	95%	80%	0.059
PDL1	≥1% (n=33)	<1% (n=43)	
EFS	91%	67%	0.005
OS	100%	81%	0.010
TMB	High (n=31)	Low (n=44)	
EFS	81%	64%	0.072
OS	87%	86%	0.940
Surgery-to-event analyses*			
IFN-γ	High (n=39)	Low (n=34)	
RFS	85%	70%	0.066
DMFS	90%	73%	0.053
PDL1	≥1% (n=32)	<1% (n=37)	
RFS	91%	78%	0.068
DMFS	94%	84%	0.130
TMB	High (n=29)	Low (n=39)	
RFS	83%	72%	0.210
DMFS	86%	77%	0.320

*Patients with an event prior to surgery (n=6) or who did not undergo surgery (n=1) were excluded.

Conclusions: The IFN-γ signature seems to be the most robust baseline biomarker for long-term (event-free) survival across different cohorts. In contrast to results from the previous OpACIN-neo trial, PD-L1 expression was also associated with survival in PRADO, while TMB was not significantly associated.

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1096P Prolonged follow-up confirms durability of favorable outcomes after neoadjuvant ipilimumab plus nivolumab in melanoma

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Background: A paradigm shift in the treatment of resectable stage III melanoma is expected, given the superior results of neoadjuvant (neoadj) immune checkpoint inhibition (ICI) in the SWOG S1801 trial and with the 1st phase III trial (NCT04949113) on its way. In this rapidly evolving field, long-term outcomes of neoadj ICI are scarce. Here we report the 4- and 6-yr survival update of the OpACIN and OpACIN-neo.

Methods: In the randomized OpACIN trial, 20 patients (pts) with resectable stage III melanoma were treated with ipilimumab (IPI) 3mg/kg + nivolumab (NIVO) 1mg/kg; in the adjuvant (adj) arm 4 cycles after therapeutic lymph node dissection (TLND) and in the neoadj arm 2 cycles before and 2 after TLND. In the OpACIN-neo trial, 86 pts were randomized between neoadj IPI 3mg/kg + NIVO 1mg/kg (2x; arm A), IPI 1mg/kg + NIVO 3 mg/kg (2x; arm B) and IPI 3mg/kg (2x) > NIVO 3mg/kg (2x; arm C), followed by TLND without adj therapy. Event-free survival (EFS) was defined as time from randomization to progression, recurrence or death.

Results: Median follow-up (FU) for OpACIN was 84.0 mo. Estimated 6-yr EFS was 60% for both the adj and neoadj arm, while OS was 70% and 90% respectively. Only 1 recurrence has been observed after the 3-yr landmark. Median FU for OpACIN-neo was 60.7 mo. Estimated 4-yr EFS was 80% (see table for EFS/OS). After the 3-yr

landmark, 1 new recurrence was observed and 1 non-melanoma related death. Major- and partial pathological responders (MPR/pPR) had 4-yr EFS rates of 96% and 92%, versus 33% in non-responders (pNR). Combining data from both trials, the median time to recurrence was 6.2 mo for the 16 pts that relapsed after pNR, while this was 37.7 mo for the 3 pts that relapsed after MPR/pPR.

Table: 1096P

	6-year EFS (95% CI)	6-year OS (95% CI)
OpACIN — adjuvant	60% (36-100)	70% (47-100)
OpACIN - neoadjuvant	60% (36-100)	90% (73-100)
	4-year EFS (95% CI)	**4-year OS (95% CI)**
OpACIN-neo	80% (43-89)	92% (86-98)
Arm A	87% (75-100)	90% (80-100)
Arm B	77% (63-93)	93% (85-100)
Arm C	77% (62-95)	92% (83-100)

Conclusions: Although the EFS rates are similar for the neoadj and adj arms after 6 yrs in the OpACIN trial, the favorable EFS and OS rates observed in the larger OpACIN-neo support the durability of response to neoadj IPI plus NIVO. The pathological response may serve as predictor for long-term outcome.

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1097P Durable relapse-free survival in stage IV melanoma patients (pts) treated with neoadjuvant immune-checkpoint inhibitor (ICI) followed by local procedures

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Background: Achieving a complete response (CR) with ICI is associated with a long term survival in advanced melanoma pts. The long term outcome of pts for which the CR is obtained by a local procedure (LP) such as surgery, radiotherapy or interventional radiology following ICI is not known. We report here long term relapse-free survival (RFS) and overall survival (OS) data of a cohort of pts in this situation.

Methods: RFS and OS of melanoma pts with a CR obtained by ICI + LP were estimated from the time of LP to progression or death using the Kaplan-Meier method. Pts with no viable cells in the resected metastases were excluded.

Results: 40 pts (57.5% males) with a mean age of 52.4 years achieved a CR after receiving ICI combined by an additional LP on 1 to 3 stable or progressing metastatic sites including lymph nodes, skin, lung, liver and brain. Most pts had received previous treatment lines (mean: 2.9). 23 (57.5%) pts were in progression according to RECIST 1.1 before the LP, 5 (12.5%) pts were in partial response, and 1(2.5%) pt in stable disease. 4 (10%) pts had a dissociated response and for 7 (17.5%) pts the response was not evaluable. Median duration between ICI onset and LP was 8.9 months [3.9—16.4]. After a median duration of follow-up of 5.4 years from LP, the median duration of response was not reached, 5 years RFS and OS rates were 58.65% [44.52—77.27] and 88.57% [78.63—99.76] respectively. Median RFS and OS were not reached. Relapses occurred in 14 (35%) pts, most often on a site different from that treated by the LP.

Conclusions: This real life study shows that long term RFS and OS can be achieved when ICI is given before a LP at oligometastatic sites in spite of tumor progression following ICI and suggests that neoadjuvant ICI should be evaluated in stage IV pts.

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1098P Anti-PD1-based neoadjuvant therapy in resectable stage III or IV melanoma patients: A systematic review and meta-analysis

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Background: Neoadjuvant therapy (NAT) with immunotherapy (anti-PD1-based) has shown promising event-free survival (EFS) and pathologic complete response (pCR) in resectable melanoma patients. We performed a systematic review and meta-analysis to evaluate anti-PD1-based NAT for stage III and IV resectable melanoma.

Methods: We searched PubMed, Scopus, and Cochrane Library databases for clinical trials and observational cohort studies. Outcomes of interest were pCR, major pathologic response (MPR), EFS, and overall survival (OS). Subgroups analysis included clinical stages and mucosal and acral melanomas (MM/AM) subpopulation. Heterogeneity was examined with I2 statistics; We used a DerSimonian and Laird random effects model.

Results: Eleven studies were included, comprising nine phase II/Ib clinical trials and two observational cohort studies with 486 patients. Of them, 85% had cutaneous melanoma, and 15% had MM/AM. Overall, 43% received single-agent NAT. In a pooled analysis, the pCR rate was 35.1% (95%CI 25.7-44.4). Stage III patients achieved a pCR of 36.9% (95%CI 28.9-71.5), whereas studies including stages III/IV reported pCR in 34.1% (95%CI 19.9-48.4). Single-agent therapy led to pCR in 30.5% (95%CI 20.2-40.9) of patients, while those treated with combination therapy had a pCR rate of 42.1% (95%CI 25.6-58.5). MPR was reached in 49.0% (95% 39.6-58.5) of patients. 231 (82.4%) remained free-of-events with a minimum follow-up of 14.6 months. OS was 90.1% (95%CI 86.0-93.1) in two years (27 deaths). Overall pathological response (CR+MPR+PR) was seen in 71.2% (95%CI 63.5-79.0) of patients, and the overall radiographic response in 50.8% (95%CI 45.0-56.5). According to pCR, responders had a greater EFS than non-responders with an OR of 0.10 (95%CI 0.02-0.49 p=0.004). Among MM/AM, 19.9% (95%CI 7.8-34.9) of patients had pCR. There were no treatment-related deaths or delays of surgery.

Conclusions: Our study supports anti-PD1-based NAT anti-tumor activity in patients with resectable melanoma. Patients with pCR and stage III seem to benefit most from NAT, while rare melanomas still have a worse response. Other ongoing studies and more mature data are needed to confirm our findings.

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1099P Long-term survival follow-up from the REDUCTOR trial: Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection

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Background: The REDUCTOR trial demonstrated that neoadjuvant dabrafenib (D) plus trametinib (T) allowed radical (R0) resections in 81% of patients with prior unresectable locally advanced BRAF-mutated melanoma. Major pathologic responses were seen in 9/18 patients undergoing surgery. Recurrences were observed in 50% of patients and usually occurred shortly after surgery. Here, we present an update of long-term relapse-free survival (RFS), progression-free survival (PFS) and overall survival (OS).

Methods: In this single-arm phase II trial, 21 patients with unresectable, BRAF-mutated, locally advanced stage IIIC or oligometastatic stage IV melanoma were treated with neoadjuvant D+T for 8 weeks. PET/CT and physical examination were performed to evaluate response. If sufficient downsizing of the tumor was observed, surgical resection was performed. Adjuvant therapy was not routinely given. The primary endpoint was the percentage of patients achieving a R0 resection. Secondary endpoints were RFS, PFS and OS.

Results: At a median follow-up of 80.9 months (IQR 38.6-89.7 months), the median RFS in patients that underwent surgery was 15.4 months (95% CI 8.89-not reached). The median PFS in all patients was 12.4 months (95% CI 8.68-not reached). Recurrences were seen in 10/18 patients undergoing surgery, most of which occurred in the first year after resection (8/10). One patient recurred after 1 year and one after 5 years. The median OS was not reached. The 1-year, 2-year, 3-year and 4-year OS were 100%, 85% (95% CI 70.7-100.0), 85% (95% CI 70.7-100.0) and 75% (95% CI 58.2-96.6), respectively. In total, 1/6 patients (17%) with a pathologic complete response (pCR) developed recurrence, compared to 4/5 patients (80%) with a pathologic non-response (pNR). Late recurrences (after >1 year) were seen in a patient with a near-pCR and a patient with a pNR.

Conclusions: These data confirm favorable long-term survival rates after neoadjuvant D+T and surgical resection without adjuvant therapy in prior unresectable locally advanced BRAF-mutated melanoma patients. Most patients remain disease-free if no recurrence occurs in the first year after treatment.

Clinical trial identification: EudraCT: 2013-002616-28.

Legal entity responsible for the study: Netherlands Cancer Institute, Amsterdam, The Netherlands.

Funding: Netherlands Cancer Institute and Novartis.

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1100P Open-label non-randomized phase IB study to characterize the safety, tolerability and recommended dose of tinostamustin in combination with nivolumab in patients with advanced melanoma (ENIGMA)

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Background: Melanoma patients (pts) progressing after immune checkpoint inhibitors (ICI) and BRAF targeting therapy have a poor prognosis. We explored the feasibility of a combination of the alkylating deacetylase inhibition fusion molecule tinostamustine in sub-chemotherapeutic concentrations and nivolumab.

Methods: This study was initiated to characterize dose-limiting toxicity (DLT) and the recommended phase-2 dose (RP2D) of tinostamustine and nivolumab in pts with advanced melanoma. Tinostamustine was administered at escalating doses of 15 and 30 mg/m^2 in a 3-plus-3 design, nivolumab was added at a dose of 3 mg/kg on day 15, both given i.v. every 2 weeks until toxicity or tumor progression (with the option of treatment-beyond progression).

Results: 17 pts were included into the study including 4 pts treated with tinostamustine 15 mg/m^2 over 60 min and 13 pts treated with tinostamustine 30 mg/m^2 over 60 min. 13/17 pts (77%) received prior ICI, 7/17 pts (41%) had unfavorable melanoma types (acral, mucosal, uveal) and 10/17 pts (59%) elevated baseline lactate dehydrogenase (LDH). No DLT was documented and the RP2D for tinostamustine in combination with nivolumab was defined as 30mg/m^{2}over 60 min. We observed one nivolumab-associated serious adverse event (SAE) of immune-related pneumonitis. Mean treatment duration was 22 weeks; 3 patients received $\leq$4 weeks of study treatment due to early progression. Disease stabilization among 15 evaluable pts was 47%, including 3pts (20%) with a confirmed partial response. Median progression-free survival was 8.3 weeks (95% CI 2.4 to 15.4 weeks), median overall survival 19.1 weeks (95% CI 2.4 to 41 weeks). No severe myelosuppression was observed except a single case of grade 3 leucocytopenia.Ex vivo T-cell stimulation and ELISA from blood samples revealed induction of adaptive T-cell and antibody responses against tumor-associated antigens.

Conclusions: Tinostamustine at an immune-modulatory dose of 30 mg/m^2 over 60 min is safe when co-administered with nivolumab 3mg/kg and resulted in 47% disease stabilization and 20% objective radiological responses in pts with advanced melanoma failing standard ICI treatment.

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Legal entity responsible for the study: Clinical Trial Unit, Cantonal Hospital, 9007 St. Gallen, Switzerland.

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1101P The effect of LNS8801 in combination with pembrolizumab in patients with treatment-refractory cutaneous melanoma

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Background: LNS8801 is an oral G-protein coupled estrogen receptor (GPER) agonist. LNS8801 treatment results in increased melanocytic differentiation, reduced c-Myc protein levels, inhibition of proliferation, and enhancement of immune recognition of cancer cells in the first-in-human study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT04130516). LNS8801 also demonstrated monotherapy activity in cutaneous melanoma (CM) patients, including a patient that is on treatment for over 3 years with no evidence of active or recurrent disease.

Methods: Patients with treatment-refractory CM received LNS8801 (125 mg, QD, PO) and pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective was safety and tolerability. Secondary endpoints include pharmacokinetic, pharmacodynamics, objective response rate (ORR) and disease control rate (DCR, CR+PR+SD). Presence of a consensus, fully-functional, germline GPER coding sequence was assessed as a potential predictive biomarker.

Results: As of 4/15/23, 10 CM patients were treated. All patients received prior PD-1 and CTLA-4 directed ICIs, and were treated with a median of 2.5 prior lines of systemic therapies. 8 of 10 patients had AEs possibly related to study drugs (n=4 with grades 1-2 and n=4 with grade 3), with AST/ALT elevation, diarrhea, or fatigue occurring in more than 1 patient. Regarding efficacy, 2 had partial responses (PR), 4 had stable disease (SD), and 1 patient has not been evaluated, resulting in an ORR of 20% and DCR of 60%. Both patients with PRs remained on treatment for greater than 24 weeks. Consensus germline GPER was present in 7 of 10 sequenced patients. Of patients positive for this biomarker, 2 had PR and 3 had SD, resulting in an ORR of 29% and DCR of 71%.

Conclusions: LNS8801 and pembrolizumab is tolerable and has encouraging activity in patients with treatment-refractory CM, including patients who enrolled immediately after confirmed progression on ICIs. Consensus germline GPER is a promising predictive biomarker, and is associated with improved outcomes in patients treated with LNS8801. These data support further development of LNS8801 in combination with pembrolizumab treat advanced CM patients.

Clinical trial identification: NCT04130516.

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1102P Evaluation of surrogate endpoints for overall survival within the RELATIVITY-047 trial

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Background: Advances in the first-line treatment of metastatic melanoma raised the need for earlier assessment of clinical trials using intermediate endpoints that may reach statistical maturity sooner than overall survival (OS) without being influenced by subsequent treatments.

Methods: We evaluated progression-free survival (PFS), time-to-next-treatment-or-death (TNTD) and objective response rate (ORR) as potential surrogate endpoints (SEs) for OS within the phase II/III RELATIVITY-047 trial (n=714) using patient-level data with $\geq$21 months of follow-up. Individual-level (IL) correlations with OS were derived from copula functions and measured by Spearman's (ρ) and Kendall's (τ) rank

correlation coefficients for PFS and TNTD, and by an odds ratio (OR) for ORR. Patients were clustered in 8 non-overlapping regions according to their country of enrolment for trial-level (TL) surrogacy assessment. Within each region treatment effects on PFS, TNTD and OS were calculated by Cox-proportional-hazards models. TL correlations between the SEs and OS were estimated by weighted linear regression and measured by coefficient of determination (R^2). Sensitivity of the results were tested with respect to alternative geographic clustering.

Results: At the IL, ORR and TNTD were strongly correlated with OS, whereas PFS showed moderate correlation with OS. At the TL, PFS and ORR showed moderate correlation with OS with wide uncertainty whereas TNTD had strong correlation with OS with narrower margin of uncertainty. Alternative geographic clustering of patients had marginal impact on the IL ($\leq$ 0.02 change in all measures for all SEs) and modest impact on TL correlations ($\leq$ 0.08 change in R^2 for all SEs).

Table: 1102P

Correlation	IL		TL
	ρ [95% CI]	τ [95% CI]	R^2 [95% CI]
PFS - OS	0.70 [0.68, 0.72]	0.51 [0.45, 0.58]	0.71 [0.35, 1.00]
TNTD - OS	0.84 [0.81, 0.86]	0.66 [0.63, 0.69]	0.95 [0.87, 1.00]
ORR - OS	**OR** 10.60 [6.77-14.43]		0.64 [0.21, 1.00]

Conclusions: Within the RELATIVITY-047 trial, TNTD-OS surrogacy was stronger and more stable than PFS-OS and ORR-OS surrogacy. The strength of each surrogacy relationship analyzed in this study and their relative order were consistent with those previously reported from other immune-checkpoint inhibitor studies.

Clinical trial identification: Phase II/III study: RELATIVITY-047 (CA224-047), NCT03470922.

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1103P Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year subgroup analyses from RELATIVITY-047

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Background: In RELATIVITY-047 (NCT03470922), NIVO + RELA previously demonstrated a statistically significant improvement in the primary endpoint of PFS per BICR vs NIVO, with a clinically meaningful (non-significant) statistical improvement in OS and a numerically higher ORR (secondary endpoints) in pts with previously untreated metastatic or unresectable melanoma. Post hoc analyses exploring the efficacy of NIVO + RELA vs NIVO according to baseline (BL) sites of metastasis (mets) and the time to development of CNS mets are reported herein.

Methods: Pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg fixed-dose combination (FDC) or NIVO 480 mg intravenously Q4W. Exploratory post hoc analyses were performed for PFS, OS, ORR, and melanoma-specific survival (MSS) by the no. of mets sites and the presence or absence of liver and lung mets. Time to development of new CNS mets per BICR was also assessed in both arms. Follow-up (f/u) brain imaging was not mandated per protocol.

Results: Median f/u was 25.3 mo; 581/714 pts were included in the BL mets analysis (mucosal and acral pts were excluded). Efficacy favored NIVO + RELA over NIVO in the majority of subgroups analyzed (Table). In pts without CNS mets at BL (348 in each arm), 17 pts (5%) in the NIVO + RELA arm and 31 pts (9%) in the NIVO arm developed new CNS mets per BICR over the course of tumor assessment f/u. Median time to the development of new CNS mets per BICR was 11.1 mo (range, 2.0—31.5) with NIVO + RELA and 6.6 mo (range, 0.6—32.7) with NIVO.

Conclusions: Efficacy outcomes generally favored NIVO + RELA over NIVO in pts with BL liver or lung mets and regardless of no. of BL sites of disease. Fewer pts on NIVO + RELA vs NIVO developed new CNS mets (and took a longer time to develop them), suggesting CNS activity with the FDC; however, incidence was low. Activity of NIVO + RELA in pts with CNS mets needs to be confirmed in a dedicated CNS study. Additional analyses will be presented.

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Table: 1103P

	n	PFS HR (95% CI)	OS HR (95% CI)	MSS HR (95% CI)	ORR ORR difference, % (95% CI)
No. of mets sites					
1	184	0.85 (0.57—1.27)	0.92 (0.56—1.52)	0.85 (0.48—1.51)	14.1 (-0.3 to 27.8)
2—3	286	0.71 (0.53—0.95)	0.69 (0.49—0.98)	0.59 (0.40—0.88)	11.5 (0.1 to 22.4)
$\geq$ 4	109	0.91 (0.59—1.42)	0.74 (0.46—1.21)	0.77 (0.46—1.28)	-0.1 (-17.6 to 17.1)
Liver mets					
Present	122	0.81 (0.53—1.23)	0.62 (0.37—1.03)	0.72 (0.41—1.27)	9.4 (-7.7 to 25.6)
Absent	459	0.81 (0.64—1.02)	0.84 (0.64—1.11)	0.72 (0.53—0.99)	9.3 (0.2 to 18.1)
Lung mets					
Present	254	0.77 (0.57—1.05)	0.72 (0.50—1.04)	0.71 (0.47—1.05)	12.8 (0.7 to 24.4)
Absent	327	0.85 (0.64—1.12)	0.84 (0.61—1.17)	0.73 (0.5—1.07)	6.8 (-4.0 to 17.3)

Unstratified HR; NIVO + RELA vs NIVO.

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1104P Efficacy of immune checkpoint inhibition in metastatic or non-resectable melanoma after failure of adjuvant anti-PD1 treatment: A EUMelareg real-world evidence study

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Background: Adjuvant immune checkpoint inhibition (ICI) with anti-PD1 antibodies in high-risk resected melanoma has been shown to improve recurrence-free survival by about 50 percent. It is unclear, whether adjuvant pre-treatment with anti-PD1 antibodies would impair response to ICI in metastatic patients with recurrence after adjuvant ICI.

Methods: From the adjuvant study platform of the European Melanoma Treatment Registry (EUMelaReg) we analysed cases with recurrence following adjuvant anti-PD1 ICI. In those, receiving ICI in the first-line setting, response rates and progression-free survival were compared to patients selected from the EMelaReg database by matching for relevant prognostic factors in the first-line non-adjuvant setting.

Results: A total of 389 melanoma patients with first-line ICI after failure from adjuvant anti-PD1 antibody treatment could be matched 1:1 for several prognostic covariates to first-line ICI cases without adjuvant pre-treatment. Overall response rate was significantly lower after adjuvant anti-PD1 treatment failure (32.9% vs. 40.0%) and progression free survival was 4.6 months for patients with adjuvant pre-treatment as compared to 10.1 months for PD1-naive patients ($p<0.0001$). This contrast was independent from usage of single agent anti-PD1 or combined ICI with anti-PD1 and anti-CTLAE4 in the first-line setting.

Conclusions: Adjuvant pre-treatment with anti-PD1 antibodies was related to an inferior response and progression-free survival in patients with metastatic or non-resectable melanoma receiving ICI in the first-line setting.

Legal entity responsible for the study: The European Melanoma Treatment Registry.

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1105P First-line nivolumab plus ipilimumab in advanced melanoma patients previously treated with adjuvant systemic therapy

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Background: The combination of nivolumab and ipilimumab (NIVO+IPI) is associated with the most durable responses and the highest overall survival rates in patients (pts) with advanced melanoma. However, this regimen is increasingly being used in a different patient population than in clinical trials, namely after prior adjuvant treatment. The objective of this study is to evaluate the efficacy and safety of NIVO+IPI in pts who have relapsed despite adjuvant treatment.

Methods: This retrospective analysis included pts with unresectable stage III and stage IV melanoma treated with NIVO+IPI between 01/2021-10/2022 at 5 cancer centers in Poland according to uniform criteria. All pts received prior adjuvant therapy (immunotherapy or BRAF/MEK inhibitors) for stage III/IV melanoma.

Results: A total of 70 pts were identified. The median age was 53 years, 32% of pts were female, 46% had *BRAF* mutation. At baseline, 18.5% of pts had unresectable stage III disease, 21.2% had stage M1a, 18.2% M1b, 34.8% M1c and 7.6% M1d. Most pts (81.4%) received anti-PD1 in the adjuvant setting. In 70% of pts, the disease relapsed during adjuvant therapy. Median follow-up time was 12.6 months. The objective response rate was 24%. A higher response rate was observed in pts who were immunotherapy-naive (33%) than in pts who received anti-PD1 in the adjuvant setting (22%). Median progression-free survival (mPFS) was 3.9 (95%CI 3.0—9.7) months. Although not statistically significant, a higher median PFS of NIVO+IPI was observed in patients who received BRAF/MEK inhibitors as compared to those who were treated with anti-PD1 antibodies in the adjuvant setting (11.1 vs 3.7 months, p=0.53). Overall survival rate at 12 months was 59% (95%CI 47—74). Treatment-related adverse events (TRAEs) of any grade were observed in 97% of pts and grade 3/4 TRAEs occurred in 24% of pts.

Conclusions: NIVO+IPI shows lower efficacy in advanced melanoma pts who have relapsed despite adjuvant treatment comparing to clinical trial data. The population of pts with a particularly poor prognosis are those previously treated with adjuvant anti-PD-1 antibodies, as disease recurrence indicates some resistance to immunotherapy difficult to overcome by adding anti-CTLA4 antibody to anti-PD-1 therapy.

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1106P Anti-PD-1 (PD1) monotherapy or in combination with anti-CTLA-4 for metastatic melanoma (MM) patients (pts) with liver metastases (mets)

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Background: Liver mets have been associated with poor response and survival in pts with MM treated with PD1 alone or in combination with anti-CTLA-4 (ipilimumab; PD1+IPI). Whether these pts benefit from PD1+IPI over PD1 is unknown. In MM pts with liver metastases, we sought to: a) determine objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) to PD1 vs PD1+IPI, and b) identify clinical predictors of response and survival to PD1+/-IPI.

Methods: MM pts with liver mets treated with 1st line PD1 or PD1+IPI were included. Demographics, patient and disease characteristics, baseline blood parameters and clinical outcomes were examined. Univariate and multivariate (MVA) analyses were performed to identify clinical predictors of response and survival.

Results: Of 533 MM pts treated with 1st line PD1 or PD1+IPI; 284 (53%) had PD1 and 249 (47%) had PD1+IPI. PD1 group had more ECOG PS $\geq$1 (53% vs 34%), but less BRAF V600 mutation (15% vs 33%) and stage M1D (15% vs 31%). Median follow-up from commencement of PD1+/-IPI was 47 months (42—51); ORR was 41%, higher in PD1+IPI (47%) vs PD1 (35%) (p=0.0027). PFS and OS at 1 year were 68% and 40%, respectively; non statistically higher with PD1+IPI (69%/43%) vs PD1 (67%/38%) (p>0.05). However, on MVA with multiple imputation for missing values and adjusting for predefined variables including age, gender, melanoma subtype (cutaneous non-acral, acral and mucosal), mutation status, ECOG PS, LDH and M1 substage

(M1c versus M1d), PD1+IPI was associated with higher ORR (OR 2.21, 1.46 − 3.36; p<0.001), PFS (HR 0.73, 0.57 − 0.92; p=0.009) and OS (HR 0.71, 0.54 − 0.94; p=0.018) compared to PD1. Age (ORR, PFS), ECOG PS (OS), LDH (PFS, OS), M1 substage (ORR, PFS, OS), mutation status (PFS), melanoma subtype (OS) were also independent predictors of response and/or survival. Most pts ceased treatment due to progression (262 [53%]), and more pts stopped treatment due to toxicity in the PD1+IPI (n=77, 31%) vs PD1 (n=36, 14%) group.

Conclusions: In pts with liver metastases, 1st line PD1+IPI showed higher ORR and improved survival compared with PD1 alone. These data will help guide treatment selection for pts with melanoma liver metastases.

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1107P BRAF mutation status does not impact outcomes with tebentafusp in advanced cutaneous melanoma

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Background: Tebentafusp (tebe), a bispecific (gp100 x CD3) ImmTAC, targets gp100 peptide-HLA-A*02:01 complexes overexpressed in melanoma. In a phase (Ph) 1b study (NCT02535078), pts with metastatic cutaneous melanoma (mCM) who relapsed or were refractory to prior anti-PD(L)1 and received tebe combined with durvalumab (durva) with or without tremelimumab (treme) (n=58), had a 1-year (yr) OS of 75%, comparing favorably with recent benchmarks (38%-57%) [1-3]. Nearly half of pts with mCM harbor activating BRAF mutations and sequencing of BRAF inhibitor regimens (BRAFi) with immunotherapies may be important [4]. Here we present tebe efficacy and safety in pts with mCM by BRAF mutation status.

Methods: In the Ph 1b study, HLA-A*02:01+, pre-treated mCM pts received weekly tebe (IV) monotherapy in arm 4 or in combination with durva and/or treme (IV) Q4W (arms 1-3). Primary objective was RP2D. Secondary objectives were safety and efficacy. OS was obtained using Kaplan-Meier methods. Tumor assessments were performed according to RECIST v1.1. This analysis was performed on all pts in arms 1-4 with data cut-off Oct 7 2022 and median follow up of 14.8 months.

Results: 38/112 (34%) pts had an activating V600 BRAF mutation (BRAFm); of whom, 24 (63%) had received a prior BRAFi regimen. Baseline parameters (e.g., ECOG, LDH, anti-PD(L)1 exposure) were similar between the BRAFm and BRAF wild type (BRAFwt) pts. OS and tumor shrinkage were similar in BRAFm and BRAFwt pts with 1-yr OS of 68% and 62% and tumour shrinkage in 42% and 38% of pts, respectively. The safety profile of tebe was similar in BRAFm and BRAFwt pts. Among BRAFm pts, OS trended longer in those who did not receive prior BRAFi versus those who did (1-yr OS 84% vs 59%).

Conclusions: In this study, promising OS was seen in pretreated mCM pts with or without BRAFm, although OS trended longer in BRAFm pts who had not received prior BRAFi compared with those who did. An ongoing trial (NCT05549297) is investigating tebe as monotherapy and in combination with pembrolizumab in pts with previously treated advanced melanoma including both BRAFwt and BRAFm. 1. Zimmer L, et al. Eur J Cancer 75:47−55, 2017 2. Silva IPD, et al. J Clin Oncol 38:10005−10005, 2020 3. Arance AM et al. J Clin Oncol 39:S9504, 2021 4. Atkins MB, et al. J Clin Oncol 41(2):186-197, 2023.

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1108P Outcomes of patients with unresectable or metastatic melanoma after cessation of immunotherapy following complete response or toxicities

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Background: Checkpoint inhibitors (CPI) have changed the treatment paradigm for patients (pts) with advanced melanoma with significant improvements in overall survival. This study evaluated the outcomes of patients with advanced melanoma who were treated with CPI and had cessation of treatment due to either complete response (CR) or toxicities (tox).

Methods: From January 2015 to December 2021, 699 pts with unresectable stage III or stage IV melanoma were treated by a single prescriber across two centres in Brisbane, Queensland. In this retrospective study, we analysed 237 pts who had ceased CPI either due to CR, defined trial protocol or tox. We performed descriptive analyses of outcomes following cessation of CPI and subsequent treatment received after documented disease recurrence.

Results: Of the 237 pts who had ceased CPI, 176 pts had CR, 53 pts had treatment related tox and 8 pts had completed trial protocol. The average age of pts treated with CPI was 63 years old and the mean duration of treatment was 448 days. In this study, 71.3% of pts were BRAF wild-type, 27.4% of pts had a BRAF mutation and 1.3% of pts with uveal melanoma. 59.5% of pts had monotherapy CPI while 40.5% of pts had combination CPI. 182 pts (76.8%) had ongoing CR whilst 55 pts (23.2%) relapsed following cessation of therapy. In the cohort that relapsed, 36 pts had stopped CPI due to CR or defined trial protocol and 19 pts stopped following treatment related tox. The relapse rate was higher in pts stopped CPI due to tox (35.8%) compared to the cohort of pts who ceased due to CR or defined trial protocol (19.6%). Of those 55 pts who had relapsed, 22 were rechallenged with response, 12 were rechallenged with no response, 2 were rechallenged but ceased due to tox, 1 was rechallenged and is awaiting restaging, 7 had local therapy with either radiation therapy or surgery, 3 had different systemic therapy. 8 pts received best supportive cares.

Conclusions: Patients who had ceased CPI following CR had durable responses and a lower rate of relapse compared to pts with treatment related tox. On recurrence, retreatment with immunotherapy demonstrated response and could be considered a viable treatment option.

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1109P Second-line pembrolizumab (pembro) in Chinese patients (pts) with advanced melanoma: Long-term follow-up of the phase I KEYNOTE-151 study

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Background: At the 3-y follow-up of KEYNOTE-151 (NCT02821000), second-line pembro showed manageable safety and clinically meaningful antitumor activity in Chinese pts with advanced melanoma. Results from more than 5 y of follow-up are presented.

Methods: Adults who had histologically confirmed locally advanced or metastatic melanoma, who were of Chinese descent, and whose disease progressed with first-line therapy received pembro 2 mg/kg IV Q3W for $\leq$35 cycles ($\sim$2 y) or until disease progression or unacceptable toxicity. Pts with SD or better who discontinued pembro could receive a second course of pembro ($\leq$17 cycles) upon disease progression. Primary end points were safety and tolerability and ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points were DOR and PFS per RECIST v1.1 and irRECIST by BICR, ORR per irRECIST by BICR, and OS. Safety and OS were analyzed in pts who received $\geq$1 dose of pembro. Other efficacy end points were assessed in pts who received $\geq$1 dose of pembro and had measurable disease per RECIST v1.1 at baseline.

Results: One hundred three pts received pembro (102 with measurable disease at baseline). Median age was 52 y, 57.3% of the pts were female, 51.5% had PD-L1 positive disease, and 14.6% had mucosal melanoma. Median follow-up at data cutoff (Nov 30, 2022) was 73.2 mo (IQR, 67.6-74.8). No new safety signals were reported. Grade 3-5 treatment-related AEs occurred in 12.6% of pts; no pts died of treatment-related AEs. ORR per RECIST v1.1 was 17.6% (95% CI, 10.8-26.4; 1 CR, 17 PR); DCR was 38.2% (95% CI, 28.8-48.4). Median DOR per RECIST v1.1 was 13.8 mo (range, 2.7-69.4+); an estimated 37.7% of pts had DOR $\geq$60 mo. Median PFS was 2.8 mo (95% CI, 2.7-3.5); 60-mo PFS was 5.0%. One additional pt had PR per irRECIST (ORR, 18.6%; 95% CI, 11.6-27.6). Median OS was 13.2 mo (95% CI, 10.4-16.5); 60-mo OS was 13.4%. One pt with PR as the best overall response per RECIST v1.1 received second-course pembro.

Conclusions: After more than 5 y of follow-up, second-line pembro continued to show manageable safety and clinically meaningful antitumor activity in Chinese pts with advanced melanoma. These results support the continued use of pembro in this population.

Clinical trial identification: NCT02821000.

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1110P A phase II clinical trial of SHR-1701 combined with temozolomide for advanced melanoma

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Background: Immune checkpoint inhibitors (ICIs) have limited efficacy in advanced melanoma in Asians, and chemotherapy is still an important option. Temozolomide (TMZ) has been recommended in guidelines for treatment of melanoma. SHR-1701 is a bifunctional fusion protein composed of a mAb against PD-L1 fused to the extracellular domain of TGF-β receptor II. Here, we report the safety and efficacy of SHR-1701 combined with TMZ in advanced melanoma.

Methods: In this single-center, phase II study, patients(pts) with advanced melanoma were eligible. Prior ICIs plus TMZ and progressed within 6 months was not permitted. Pts received SHR-1701(30 mg/kg IV Q3W) combined with TMZ (150 mg/m^2 IV, Days 1-5 Q3W) until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST1.1. Secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. A standard Simon two-stage design was used. If there were more than 5 responses in 21 pts in stage I, the study would continue to 31 pts in stage II.

Results: As of March 31, 2023, 21 pts were enrolled. Various histology subtypes were included (16 acral, 2 mucosal, 2 cutaneous, 1 unknown histology subtype). The median age was 54 years (range, 34-73), most patients were male (52.4%), 18 pts (85.7%) were ECOG PS 1, 15 pts (71.4%) were stage IV. Received previous 0/1/2 lines of systemic treatment were 14(66.7%)/4(19.0%)/3(14.3%) pts. The median follow-up was 4.4 months (range, 0.5 to 12.7 months). At the data cutoff, 12 pts remained on treatment. Of 16 evaluable pts, 7 pts had partial response, and 6 pts had stable disease. The unconfirmed ORR and DCR were 43.8% and 81.3%, respectively. After treatment, 3 pts with solitarily metastatic lesions received curative surgery. Of 21 pts, the incidence of treatment-related adverse events (TRAEs) was 47.6%, most commonly anemia, γ-glutamyltransferase increase and rash (14.3% each). The incidence of grade 3 TRAEs was 14.3%. No grade $\geq$ 4 TRAEs occurred.

Conclusions: SHR-1701 plus TMZ showed promising antitumor activity in advanced melanoma pts, and was generally well tolerated.

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1111P A randomised phase II study of intermittent versus continuous dosing of targeted therapy in patients with BRAFV600 mutant advanced melanoma (INTERIM)

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Background: BRAF+MEK inhibitors extend life expectancy of BRAF V^{600} mutant advanced melanoma patients; acquired resistance limits duration of benefit. Preclinical and case studies suggested that intermittent dosing could enable patients to remain on treatment longer, delay onset of disease progression and offer improved quality of life (QoL). INTERIM was a UK randomised multicentre phase II trial testing an intermittent dosing regimen.

Methods: Patients with BRAFV^{600} mutant advanced melanoma with ECOG PS 0-1 due to start dabrafenib+trametinib were randomised to receive dabrafenib (150mg bid) and trametinib (2mg od) either continuously (CONT) or intermittently (INT; dabrafenib d1-22+trametinib d1—15) on a 28 day cycle. Prior immunotherapy and brain involvement was allowed. Patient recruitment, treatment compliance, QoL and progression-free survival (PFS) were evaluated for the primary endpoint. Secondary endpoints included response rate (ORR), overall survival (OS) and toxicity. The prognostic and predictive value of mutant BRAFV^{600E} ctDNA was measured by droplet digital PCR (ddPCR), using mutant allele frequency of >1% as the detection threshold.

Results: 79 patients (39 INT, 40 CONT) were recruited from Dec '17—Feb '20; median age 67 years, 52% PS 1, 65% AJCC (7th ed) M1c, 29% had brain metastases and 46% had LDH > ULN. With median follow-up of 19 months, INT was inferior in all efficacy measures: median PFS 8.5 vs 10.7mo (HR 1.39, 95% CI 0.79—2.45, p = 0.255); median OS 18.1 mo vs not reached (HR 1.69, 95% CI 0.87—3.28, p = 0.121), ORR 57% vs 77%. INT patients experienced fewer treatment related AEs (76% vs 88%), but a higher proportion of grade >3 AEs (53% vs 42%). QoL at 6 months favoured CONT. 66 patients had baseline plasma collected for ctDNA analysis and 27 (41%) of these had detectable BRAFV^{600E} ctDNA. Detection prior to treatment correlated with worse OS (HR 2.55, 95%CI 1.25-5.21, p=0.01) and higher disease burden (LDH>ULN; p<0.001). A change to undetected during treatment did not significantly predict better OS.

Conclusions: The UK INTERIM study is consistent with other national studies suggesting that intermittent dosing does not improve efficacy of BRAF+MEKi.

Clinical trial identification: Protocol Number: INTERIM17; Final version and date: V4.0 01 August 2019 EudraCT Number: 2016-005228-27; ISRCTN Number: 18183156.

Legal entity responsible for the study: Cambridge University Hospitals NHS Foundation Trust.

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1112P Five-year survival after intermittent targeted therapy and anti-PD1 in stage IV melanoma: An update of the IMPemBra trial

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Background: IMPemBra was the first trial testing intermittent, short-term, dabrafenib and trametinib (DT) plus pembrolizumab (PEM) in patients with stage IV melanoma, with the concept of inducing stronger immune infiltration in the tumor, translating in better long-term outcome. The adverse event (AE) rate of intermittent DT was lower than for continuous triple therapy. While addition of DT only slightly increased the best overall response from 75% to 88%, the 3-year progression free survival (PFS) and overall survival (OS) was higher for the DT+PEM cohorts as compared to PEM only (53% vs 25%, and 64% vs 33%, respectively), no statistically significant differences were found probably due to small patient cohorts. Here we present the updated 5-year PFS and OS data from patients enrolled in the IMPemBra trial.

Methods: 32 treatment-naïve patients with stage IV melanoma harboring a BRAFV600E/K mutated melanoma were enrolled. All patients started with 2 cycles of PEM 200mg (Q3W), followed by randomization to either PEM monotherapy (cohort 1); PEM in combination with either dabrafenib (D) 150 mg BID + trametinib (T) 2mg QD intermittent for 2x1 week (cohort 2), 2x2 weeks (cohort 3) or continuously for 6 weeks (cohort 4). From week 12 and onwards, all cohorts continued PEM for a maximum of in total 2 years.

Results: With a median follow-up of 59.6 months, the estimated 5-year RFS and OS rates were 25% and 50% in cohort 1, 63% and 63% in cohort 2, 38% and 75% in cohort 3, and 60% and 75% in cohort 4, respectively, as shown in the table. We observed no differences in the quantity and type of subsequential therapies between the cohorts. No new safety signals were identified.

Table: 1112P

5-year clinical outcomes

	5-year PFS (95% CI)	5-year OS (95% CI)
All patients (n=32)	46% (32.5-67.3)	66% (51.1-84.3)
Cohort 1 (n=8)	25% (7.5-83.0)	50% (25.0-100)
Cohort 2 (n=8)	63% (36.5-100.0)	63% (36.5-100)
Cohort 3 (n=8)	38% (15.3-91.7)	75% (50.3-100)
Cohort 4 (n=8)	60% (33.1-100)	75% (50.3-100)

Subsequential therapies

	Subsequential treatment	Anti-PD1	Anti-CTLA-4	Anti-CTLA-4 + anti-PD1	Targeted therapy	Surgery	Other
All patients	**18 (56%)**	6 (33%)	2 (11%)	7 (39%)	14 (78%)	2 (11%)	1 (6%)
Cohort 1	**6 (75%)**	1 (13%)	1 (13%)	3 (38%)	5 (63%)		1 (13%)
Cohort 2	**3 (38%)**			2 (25%)	3 (38%)		
Cohort 3	**5 (63%)**	3 (38%)			3 (38%)	1 (13%)	
Cohort 4	**4 (50%)**	2 (25%)	1 (13%)	2 (25%)	3 (38%)	1 (13%)	

Conclusions: This update from the IMPemBra trial confirms the previous findings indicating that the addition of short-term DT to PEM can induce long-lasting responses upon PEM that appears to be superior compared to PEM monotherapy. This improved PFS translated also into a promising increase in 5-year OS compared to PEM in first line therapy.

Clinical trial identification: NCT02625337.

Legal entity responsible for the study: Netherlands Cancer Institute - Antoni van Leeuwenhoek Amsterdam.

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1113P COLUMBUS 7-year update: A randomized, open-label, phase III trial of encorafenib (enco) + binimetinib (bini) vs vemurafenib (vemu) or enco in patients (pts) with BRAF V600−mutant melanoma

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Background: In the randomized, 2-part, multicenter, open-label, phase III COLUMBUS study, enco + bini (approved in the US, EU, and other countries) and enco alone improved PFS and OS rates vs vemu in patients with BRAF V600−mutant metastatic melanoma. Here we report data from the 7-year analysis of COLUMBUS part 1.

Methods: Pts with advanced or metastatic BRAF V600−mutant melanoma were randomized 1:1:1 to enco 450 mg QD + bini 45 mg BID, vemu 960 mg BID, or enco 300 mg QD. Pts were treatment (tx)-naive or had progression after 1L immunotherapy. No prior BRAF/MEKi was allowed. Randomization was stratified by cancer stage (IIIB + IIIC + IVM1a + IVM1b vs IVM1c), ECOG PS (0 vs 1), and prior 1L immunotherapy (yes vs no).

Results: 577 pts were randomized to enco + bini (n=192), vemu (n=191), or enco alone (n=194). Updated analyses were conducted after >93 mo of minimum follow-up (cutoff: Jan 13, 2023). The 7-year PFS and OS rates (95% CI) were 21.2% (14.7, 28.4) and 27.4% (21.2, 33.9) in the enco + bini arm and 6.4% (2.1, 14.0) and 18.2% (12.8, 24.3) in the vemu arm, respectively. TEAEs (≥30% with enco + bini) were nausea, diarrhea, vomiting, arthralgia, and fatigue. Grade 3/4 TEAEs (≥5% with enco + bini) were γ-glutamyltransferase increased, blood CPK increased, hypertension, ALT increased, and anemia. Across arms, 16% to 20% of pts discontinued tx due to AEs. After tx discontinuation, 15% of pts from the enco + bini arm, 42% from the vemu arm, and 28% from the enco alone arm received BRAF/MEKi tx; 42% from the enco + bini arm, 49% from the vemu arm, and 43% from the enco alone arm received checkpoint inhibitors.

Conclusions: With a median duration of follow-up of 100 mo, the 7-year analysis from COLUMBUS part 1 confirms the long-term, sustained efficacy and known safety profile of enco + bini, with no new safety signals emerging, in pts with BRAF V600—mutant metastatic melanoma.

Table: 1113P

By BICR	Enco + bini (n = 192)	Vemu (n = 191)	Enco alone (n = 194)
mPFS, mo (95% CI)	14.9 (11.0, 20.2)	7.3 (5.6, 7.9)	9.6 (7.4, 14.8)
mOS, mo (95% CI)	33.6 (24.4, 39.2)	16.9 (14.0, 24.5)	23.5 (19.6, 33.6)
7-year PFS rate, % (95% CI)	21.2 (14.7, 28.4)	6.4 (2.1, 14.0)	15.8 (9.3, 23.8)
7-year OS rate, % (95% CI)	27.4 (21.2, 33.9)	18.2 (12.8, 24.3)	31.7 (24.9, 38.7)
Best overall response, n (%)			
CR	29 (15.1)	16 (8.4)	17 (8.8)
PR	94 (49.0)	62 (32.5)	83 (42.8)
SD[a]	54 (28.1)	77 (40.3)	63 (32.5)
PD[b]	15 (7.8)	36 (18.9)	31 (16.0)
ORR, % (95% CI)	64.1 (56.8, 70.8)	40.8 (33.8, 48.2)	51.5 (44.3, 58.8)
DCR, % (95% CI)	92.2 (87.4, 95.6)	81.2 (74.9, 86.4)	84.0 (78.1, 88.9)

[a]Includes non-CR/non-PD. [b]Includes best response of unknown or no assessment.

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1114P Encorafenib (E) plus binimetinib (B) in unresectable advanced or metastatic BRAFV600-mut melanoma, real-world evidence in Spain (GEM 2002 - BECARE)

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Background: Combined BRAF/MEK inhibitors have demonstrated efficacy and tolerability in phase III clinical trials, and is standard of care for advanced/metastatic BRAF-mutated melanoma. However there is limited evidence in the real-world.

Methods: BECARE is a retrospective study of EB in unresectable advanced/metastatic $BRAF^{V600}$-mut melanoma in 21 sites from Spain. The study includes melanoma patients (pts) treated according to standard clinical practice with EB in the 1st or after progression to a 1st line with immune checkpoint inhibitors (IT) for advanced or metastatic stage. Previous BRAF- and/or MEK- inhibitor (other than adjuvant ended $\geq$ 6 m before EB) or chemotherapy was not allowed. The primary objective is to characterize the population of pts receiving EB and assess treatment efficacy and tolerability in the real world.

Results: From Sep 2021 to Mar 2023, 117 pts were included. Median age was 59 years (range: 23-89), 59.8% were male, 64.1% had ECOG 0, all pts had metastasis at inclusion, and 21.4% brain metastasis. LDH was elevated in 35.9% of pts. The median follow-up was 13.1 m (95% CI: 11.4-15.1). EB was administered as the 2nd line after IT in 28 (23.9%) pts. The median PFS and OS for pts with brain metastasis treated with EB in the 1st line was 6.3 m (95% CI: 6.2-12) and 10 m (95% CI: 7.4-NR), respectively. Treatment-related adverse events of grade 3-4 were reported in 17 (14.5%) pts, being the most common elevated liver enzymes (6%), diarrhea (2.6%) and fatigue (1.7%). Creatinine was increased in 3 (2.6%) pts, and eye disorders present in 6 (5.1%). EB was administered for a median of 10.7 m (95% CI: 8.2-12.6) and required dose reductions or interruptions due to AEs in 29 (24.8%) and 37 (31.6%) pts, respectively. Treatment was ended due to toxicity in 6 (5.1%) pts.

Table: 1114P

EB treatment	ORR; n (%)	median PFS (95% CI); months	median OS (95% CI); months
1st line	63 (75)	12 (9.4-21.6)	24.6 (14.8-NR)
2nd line after IT	21 (77.8)	12.5 (6.6-NR)	13.9 (10.5-NR)

Conclusions: EB confirmed efficacy in the real-world including pts with worse prognosis than clinical trials. EB is also a feasible option after IT. Toxicity consistent with previous experience.

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1115P Comparison of efficacy and toxicity of dabrafenib/trametinib versus vemurafenib/cobimetinib therapy in routine medical practice: Eight years of BRAF/MEK inhibitor use in routine clinical practice

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Background: BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) significantly changed the prognosis of patients with advanced melanoma. Our aim was to compare long-term treatment outcomes in patients treated with vemurafenib + cobimetinib (V+C) and dabrafenib + trametinib (D+T) in real world practise.

Methods: Consecutive patients with unresectable or metastatic *BRAF*-mutated melanoma started treatment with V+C and D+T between 01/Jan/2014 and 30/Jun/2021 according to national drug reimbursement programme. Clinical factors including age, sex, primary location of melanoma, ECOG performance status, baseline LDH level, metastasis location, response to treatment, adverse events (AEs) were analysed. Survival analyses were performed using the Kaplan-Meier method, Log-rank and chi-square tests were used for comparison between groups.

Results: In total 583 patients were enroled, 178 (31%) received first-line V+C, while 405 (69%) D+T. The patients with V + C were significantly younger (median 56 vs 62; p=0.0001) and had more frequent brain metastases (40% vs 30%, p = 0,023). The estimated median OS (mOS) in *V+C* group was 12.0 month while in D+T - 12.5 months (p=0.79; HR=1.03, Cl 95% 0.8-1.3). The estimated progression free survival (mPFS) group V+C was 7.8 month while in D+T - 7.2 months (p=0.81; HR=1.02, Cl 95% 0.8-1.2). 5- and 7-years OS rates was 21%/19% and 17%/13% and PFS rates 11%/11% and 8%/8% in V+C and D+T group, respectively. In multivariate analysis a significant positive effect on OS and PFS had normal LDH level, no brain metastases and ECOG 0 in both groups, in addition only in D+T group a significant positive effect on OS had age $\geq$ 65 years. The percentage of patients with any grade of AEs was similar in boths groups (p=0,8088). Skin AEs and nephrotoxicity were more frequent in V+C group (p=0.0004 and p=0.01, respectively); fever were more frequent in D+C group (p = 0.035).

Conclusions: The analysis did not show differences in median OS and PFS between patients treated in the first line with *V+C* and *D+T*. In the V+C group there were more skin AEs and nephrotoxicity, and in D+T fever was more common, however the treatment was well tolerated in nonselected patients.

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1116P Long term outcome of complete responders to immune checkpoint inhibitors (ICI) or target therapy (TT) in advanced melanoma

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Background: Achieving a CR with ICI or with TT is associated with long-term survival in advanced melanoma pts. This is a retrospective study of the characteristics and long-term outcome of complete responders to ICI or TT.

Methods: Clinical data were collected between October 2010 and July 2022. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Cox multivariate proportional hazard regression model was applied to analyze association between clinical characteristics and PFS.

Results: A CR was achieved by 197 pts after ICI (anti-PD-1+/-anti-CTLA-4) for 168 (85.3%) and TT (anti-BRAF+/-anti-MEK) for 26 (13.2%) pts respectively. Median follow-up (FU) was 72 months (mos) [range=8;132]. Median duration of treatment (tx) was 11.1 mos [IQR=5.9;19.3] with ICI and 19.4 mos [IQR=8.5;30.4] with TT. Median duration to achieve the 1st CR was 9 mos with ICI and 13.9 mos with TT. Median duration of response was not reached (NR) with ICI and 2.28 mos [95%CI=1.15;NA] with TT. Relapses occurred in 38 (22.6%) and 16 (61.5%) of pts respectively, meaning a significantly higher relapse risk with TT than with ICI (HR=2.58 [95%CI=1.23 ;5.43], p=0.012). Median PFS was NR with ICI and 2.97 mos [95%CI=2.65;NA] with TT. PFS rate at 72 mos was 73.3% with ICI [95%CI=65.84;81.67] and 33.9% with TT [95% CI=18.27;63.21]. Number of lines, LDH, BRAF/NRAS mutation status were not statistically associated with relapse. Relapse occurred during tx in 6 (16.2%) and 8 (53.3%) pts and after tx discontinuation in 31 (83.8%) and 7 (46.4%) pts with ICI and TT respectively. The brain was a site of relapse in 2.9 % and 19.2% of responders to ICI and TT respectively (p: 0.0046, Fisher exact test). Among relapsing pts, 23 pts were rechallenged with ICI and 5 with TT, a new CR occurring in 3 and 2 pts respectively. Median OS was NR in both groups. After a median FU of 72 mos, 87.1% [95% CI=81.38;93.40] pts and 64.6% [95%CI=45.23;92.31] were alive respectively.

Conclusions: In this real life long-term study of patients in CR, 6 year PFS rates were 73.3% with ICI vs 33.9% with TT and 87.2% vs 64.6 % were alive with ICI and TT respectively. Brain relapses were significantly more frequent in the TT responder group than with ICI.

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1117P Overall survival (OS) in patients with metastatic BRAF V600-mutant melanoma treated with encorafenib plus binimetinib (ENCO+BINI): Comparing real-world vs clinical trial data

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Background: ENCO+BINI, a combination BRAF and MEK inhibitor therapy, prolonged OS in patients with BRAF V600-mutant metastatic melanoma in the multinational, phase III COLUMBUS clinical trial. We assessed how the real-world effectiveness of ENCO+BINI compares to efficacy observed in clinical trials after accounting for differences in patient profiles across these settings.

Methods: Patients treated with ENCO+BINI were drawn from the COLUMBUS trial and from Flatiron Health, an EMR-derived database of academic and community cancer clinics in the US. Included patients were adults with metastatic BRAF V600E/K mutated melanoma without central nervous system metastases who were untreated or had prior 1L immunotherapy (IO) and ECOG performance status (PS) of 0/1. OS was compared between ENCO+BINI patients treated in Flatiron vs. COLUMBUS, adjusting for age, sex, race, BMI, ECOG PS, LDH, prior 1L IO, prior medication/surgery, time since metastasis, and time from initial diagnosis to metastasis.

Results: This study included 275 patients treated with ENCO+BINI (192 from COLUMBUS, 83 from Flatiron). At baseline, patients in Flatiron had worse LDH (42% > ULN vs 29%), worse ECOG (46% vs 29% with ECOG PS of 1), and were more likely to have had prior 1L IO (36% vs 9%). Fewer patients in Flatiron had therapies after ENCO+BINI discontinuation (28% vs 43%). Survival at one (75% vs 75%) and 2 years (52% vs 58%) was similar, while median OS was numerically shorter in Flatiron (24.0 vs 33.6 months; p=0.35). OS was not significantly different between Flatiron and COLUMBUS in adjusted analyses (HR: 1.03 [0.62, 1.72]; p=0.90). Adjustments for sites/number of metastases and subsequent therapies, which may impact longer-term OS, may warrant consideration in the future.

Conclusions: Real world data suggests that clinical outcomes, including OS, for patients with metastatic BRAF V600-mutant melanoma treated with ENCO+BINI, are similar to those from trials, after accounting for differences in patient profiles. This indicates that clinical trial efficacy of ENCO+BINI translates to effectiveness in a broader real-world population, including patients treated with prior 1L IO.

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1118P Real-world treatment patterns and outcomes among patients with BRAF+ metastatic melanoma refractory to first-line immunotherapy

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Background: Many patients with BRAF+ metastatic melanoma (MM) experience tumor progression during first-line (1L) immunotherapy (IO). This real-world study evaluated the characteristics, treatment patterns, and outcomes among BRAF+ MM patients who experienced disease progression while on 1L IO.

Methods: This retrospective cohort study used Flatiron Health data from 1/1/2014 to 9/30/2021. Included patients were age ≥18 years with BRAF+ MM and were 1L IO-refractory, defined as having documented disease progression within 6 months of 1L IO initiation. Therapy use post-progression was defined as 2L, regardless of whether it was a new therapy or the same as 1L. Patient characteristics and treatment patterns were evaluated descriptively. The Kaplan-Meier method was used to describe overall survival (OS) and time to progression or death (TTPD) in patients who continued to receive IO (2L IO) and those who switched to targeted therapy (2L TT), from the start of 2L therapy.

Results: A total of 325 patients (mean age 60 years, 65% male) were included. Median time from 1L IO initiation to first disease progression was 64 days. Post-progression, 157 patients (48%) were treated with 2L IO within a median of 0 days and 83 (26%) initiated 2L TT within a median of 13 days. The median duration of 2L therapy for patients treated with 2L IO and 2L TT was 127 vs 182 days, respectively. Patients on 2L IO had improved median OS compared to those who received 2L TT (27.2 vs 10.5 months; p<0.0001) as well as improved time to next progression at 1 (32 vs 11%) and 2 years (23 vs 2%). Median TTPD was similar for patients treated with 2L IO and 2L TT (4.1 vs 4.8 months; p=0.078), despite patients receiving 2L TT having evidence of more severe disease (higher ECOG, elevated lactate dehydrogenase, and more liver metastases).

Conclusions: Outcomes among patients with 1L IO-refractory BRAF+ MM are poor and many patients progress on 2L therapy. While 2L IO appeared to lead to more durable treatment responses for some patients, 2L TT was associated with a similar TTPD despite patients having more severe disease. Earlier use of TT (i.e., 1L TT+IO combinations) should be considered for this group with especially poor prognosis.

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1119P Stage IIIA melanoma with isolated tumor cells in lymph nodes: Time for reviewing the AJCC v8 classification

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Background: The classification of stage III melanoma has significantly changed in the American Joint Committee on Cancer 8th version (AJCC v8). Besides including four new substages, AJCC v8 defines that lymph nodes (LN) with metastatic tumor cells, regardless of the size and the technic used to identify it, should be considered tumor-involved LN. This implies that even thin melanomas with isolated tumor cells (ic) in LN will be classified as stage IIIA, potentially upstaging patients (pts) with good prognosis.

Methods: Patients with cutaneous melanoma diagnosed with stage I-III between 2000-2020 at the Centre of Dermatooncology, University-Hospital of Tuebingen, were included. A cohort of stage IIIA (ic) pts from the DeCOG trial was used as a validation cohort. Relapse-free survival (RFS) and distant metastasis-free survival (DMFS) were evaluated using Kaplan-Meier estimates. Data on pts and tumor characteristics will also be presented.

Results: The Tuebingen cohort included 106 pts with stage IIIA (ic) and 132 pts with stage IIIA with a LN metastasis >0.1 mm (from now on stage IIIA). The validation cohort from the DeCOG trial consisted of 39 pts with melanoma IIIA (ic) and 104 pts with stage IIIA. The median follow-up (mFU) for stage IIIA (ic) and IIIA in the CMMR cohort was 64 and 60 months (95% CI 34-97 and 35-106), respectively. The mFU for stage IIIA (ic) and IIIA in the DeCOG cohort was 64 and 62 months (95%CI 47-95 and 37-86), respectively. In the Tuebingen cohort, 10y RFS rates for stage IIIA (ic) and IIIA

were 82% (95% CI 72-92) and 48% (95% CI 38-58), respectively (p<0.001). The 10y DMFS rates for stage IIIA (ic) and IIIA were 87% (95% CI 79-96) and 55% (95% CI 44-66), respectively; (p<0.001). In the DeCOG cohort, 10y RFS for stage IIIA (ic) and stage IIIA were 88% (95% CI 77-99) and 35% (95% CI 7-62), respectively; (p=0.009). The 10y DMFS for stage IIIA (ic) and IIIA was 88% (95% CI 77-99) and 60% (95% CI 39-80), respectively (p=0.061).

Conclusions: AJCCv8 Stage IIIA (ic) melanoma has a prognosis similar to stage IB, statistically significantly better than Stage IIIA. LN with isolated tumor cells should not be considered tumor-involved LN, and this should be reviewed in the new AJCC edition.

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1120P Development and external validation of a clinical prediction model to predict recurrence-free survival and melanoma-specific survival in patients with melanoma after sentinel lymph node biopsy

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Background: The introduction of adjuvant systemic treatment for patients with high-risk melanoma has increased the importance of adequate melanoma staging. However, inconsistencies in outcomes between disease stages exist, as an increase in stage does not necessarily correspond to improved recurrence-free survival (RFS) or melanoma-specific survival (MSS). Therefore, there is a need for a tool that can predict patient-specific outcomes rather than grouping patients according to outcome.

Methods: A total of 4071 patients who underwent sentinel lymph node biopsy between 1997 and 2013 in four European melanoma centers were included in the development cohort. A prognostic model and nomogram were developed to predict recurrence and melanoma-specific mortality (MSM) on a continuous scale in patients with >pT1a melanomas. From this model, individual values for RFS and MSS were derived. For the purpose of external validation, a cohort consisting of 4822 patients was provided by the Melanoma Institute of Australia. Model performance was assessed by discrimination (C-index) and calibration.

Results: The prediction model for recurrence and MSM contained six prognostic factors: positive sentinel node (SN) status, Breslow depth, ulceration, age, location and SN tumor burden. The C-index for the recurrence model was 0.76, and was 0.79 for the MSM model. External validation showed good calibration for both outcomes with a C-index of 0.74 for recurrence and 0.76 for MSM.

Conclusions: This EORTC-MIA prediction model and nomogram provides patient-specific risk probabilities for recurrence and MSM and consequently RFS and MSS using only readily-available variables. The nomogram can support clinical decision-making for adjuvant treatment in patients with high-risk melanomas.

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1121P Interferon-gamma (IFNγ) gene signature as a predictive biomarker for response in lactate dehydrogenase (LDH) low advanced melanoma patients

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Background: In current clinical practice, LDH level is widely used as decision tool between anti-PD1 monotherapy (LDH low) versus combination of anti-PD1 and anti-CTLA4 (LDH high). However, approximately only 50% of LDH low patients respond to anti-PD1. In stage III melanoma patients (generally LDH low) the interferon (IFN)g signature has been identified as strongest baseline marker for response to neo-adjuvant combination immunotherapy. Therefore, we addressed the question whether an IFNg signature could serve as additional biomarker for treatment decisions in LDH low advanced melanoma patients.

Methods: Advanced melanoma patients participating in biobank study in the Netherlands Cancer Institute (NKI), treated with anti-PD1 monotherapy between April 2014 and June 2016 were retrospectively identified. The IFNg-signature was analyzed on baseline paraffine tumor biopsies using mRNA sequencing. The cutoff between IFNg-high and IFNg-low cohorts was calculated using ROC curves on the objective response (OR).

Results: Forty-nine patients were included: the majority had cutaneous (98%) and BRAF wild type (53%) melanoma and stage M1c disease (39%, AJCC 8th edition). Patients with a high IFNg-signature at baseline showed a higher response rate to anti-PD1 (OR 86% vs 43%; p=0.016) and an improved progression free survival (p=0.046) and overall survival (p=0.064).

Table: 1121P

	IFNg low (n=46)	IFNg high (n=19)
Objective response	15 (43%)	12 (86%)
median PFS (m, IQR)	7.0 (2.0, 23.5)	25.5 (7.0, 72.0)
median OS (m, IQR)	23.0 (12.0, 76.0)	60.5 (37.0, 76.8)
24 m PFS (%)	27% (CI: 15.4-46.8)	50% (CI: 29.6-84.4)
60 m PFS (%)	15% (CI: 6.7-33.4)	43% (CI: 23.4-78.5)
24 m OS (%)	46% (CI: 31.9-65.6)	78% (CI: 59.8-100)
60 m OS (%)	31% (CI: 19.3-51.3)	50% (CI: 29.6-84.4)

PFS, progression free survival; OS, overall survival; m, months; IQR, interquartile range; CI, 95% confidence interval.

Conclusions: Our results suggest that the IFNg-signature could become a biomarker for treatment decisions in LDH low patients directing towards anti-PD1 monotherapy (in IFNg high patients) versus combination therapy, with either anti-LAG3 or anti-CTLA-4 in IFNg low patients. However, confirmation in larger cohorts and in other combination therapies is needed.

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1122P Neutrophil/lymphocyte ratio and systemic inflammatory index as prognostic biomarkers in metastatic melanoma patients under immune checkpoint inhibitors: Could any of them be used?

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Background: Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 are now the standard of care for patients with advanced melanoma, with an improvement in overall survival (OS) and quality of life. Elevated neutrophil to lymphocyte ratio (NLR) and systemic inflammatory index (SII) have been reported associated with poor survival in cancer patients, including those with ICI. The aim of this study was to determine the clinical significance of pre-treatment NLR and SII as prognostic indicator in metastatic melanoma patients treated with ICI.

Methods: Retrospective, multicentric study of metastatic melanoma patients who received ICI between 2016-2022 in two hospitals in Portugal. The SII [platelets x neutrophil/lymphocyte ratio] and NLR were calculated before the beginning of ICI. SII was considered high if $>$ 572 and NLR was considered high if $>$5. Data was collected from clinical records. Statistical analysis was performed with SPSSv26. Progression free survival (PFS) and OS were assessed using Kaplan-Meier plots and log-rank testing.

Results: Eighty-nine patients were enrolled, 57 were male, mean age 68 years old. Seventy-six patients had cutaneous, 10 mucosal and 3 uveal melanoma. The type of ICI was nivolumab in 36 patients, ipilimumab/nivolumab in 34 and pembrolizumab in 19. With a median follow-up of 19 months, the median PFS and OS was 11 and 15 months, respectively. NLR was high in 12 patients. The median PFS was 3 months in NLR high vs 25 months in NLR low patients and OS was 13 months in NLR high vs 32 months. However, these differences were not statistically significant. A total of 53 patients were presented with SII high. In this group, the median PFS was 10 months vs 22 months in SII low patients (p=0.017) and the median OS was 17 months vs 32 months (p=0.032).

Conclusions: The present study suggests that elevated SII may be associated with a worse PFS and OS in metastatic melanoma patients, however, this association was not demonstrated for NLR. Thus, SII could be a prognostic value on advanced/metastatic melanoma in patients under ICI and could be an important tool in the management of these patients.

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1123P Baseline tumor-infiltrating lymphocytes and response to immune checkpoint inhibition in advanced melanoma

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Background: Although the presence of tumor-infiltrating lymphocytes (TILs) in pathological specimens has been associated with prolonged survival in melanoma, it is largely unknown whether TILs can predict response to immune checkpoint inhibition (ICI) in advanced melanoma. Therefore, we investigated the association between treatment response and TILs in the largest cohort to date.

Methods: Patients who received first-line anti-PD1 $\pm$ anti-CTLA4 for advanced cutaneous melanoma were retrospectively identified from nine hospitals in the Netherlands. TILs were scored as absent, non-brisk or brisk on hematoxylin and eosin (H&E) slides of primary melanoma and pre-treatment metastases. The primary outcome was clinical response to ICI according to RECIST 1.1. Univariable and multivariable logistic regression analyses were performed and Kaplan-Meier methods were used for survival analyses.

Results: Metastatic melanoma specimens were available for 676 patients, whereas primary melanomas were available from 436 patients. TILs were absent in 347, non-brisk in 260 and brisk in 69 metastases. Compared to patients with absent TILs, both patients with non-brisk TILs (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.25-2.43) and brisk TILs (OR 3.58, 95%CI 2.01-6.64) had a higher probability of response to ICI. This association remained in multivariable analysis, adjusted for age, sex, disease stage, lactate dehydrogenase level and World Health Organisation performance score (see table). Patients with absent TILs had a shorter median progression-free survival (PFS) compared to patients with non-brisk TILs and brisk TILs (6.2, 10.6 and 19.3 months, respectively [p=0.003]). No significant association was found between TILs in primary melanoma specimens and response.

Table: 1123P Objective response rate (ORR), odds ratio (OR) and adjusted OR for response, median progression-free survival (PFS) and overall survival (OS) in months, stratified by TIL score on 676 pre-treatment metastatic specimens of advanced melanoma patients treated with ICI

	TIL score			
	Absent	Non-brisk	Brisk	*p-value*
ORR	45%	58%	74%	
OR [95% CI] for response (univariable)	REF	1.74 [1.25-2.43]	3.58 [2.01-6.64]	$<$0.001
OR [95% CI] for response (multivariable)	REF	1.61 [1.13-2.32]	3.09 [1.68-5.92]	$<$0.001
Median PFS [95% CI]	6.2 [5.4-9.0]	10.6 [6.4-not reached]	19.3[9.5-not reached]	0.003
Median OS [95% CI]	19.8 [15.4-29.4]	49.4 [25.7-not reached]	40.8[23.5-not reached]	0.003

Conclusions: The presence of non-brisk and brisk TILs in pre-treatment metastatic H&E histopathology specimens is associated with better response to ICI and survival outcomes.

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1124P IL-6 as prognostic factor in adjuvant or metastatic skin cancer patients treated with immunotherapy: A deep biomarker analysis

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Background: The immune checkpoint inhibitors (ICIs) revolutionized cancer therapeutic landscape and substantially improved the survival of patients (pts) with advanced malignancies, especially in skin cancer pts. IL-6 is a key inflammatory molecule secreted by M2 macrophages after polarization, mediating the progression of pancreatic and colorectal cancer. The purpose of this study is to retrospectively investigate the relationships between IL-6 and outcome in skin cancer patients treated with immunotherapy.

Methods: IL-6 levels were analyzed in two independent cohorts, in cohort 1 serum IL-6 were evaluated from 386 consecutive skin cancer pts before start ICIs. IL-6 was measured by Electrochemiluminescence immunoassays (ECLIA) from Cobas C6000 (Roche). In cohort 2 we conducted a gene profile analysis with Nanostring from PBMCs of 121 metastatic melanoma pts. All pts signed informed consent. Patient's characteristics and treatment are listed in the table.

Table: 1124P

Patient characteristics	Cohort 1 N=386	Cohort 2 N=121
Median age	62 (range 23-96)	62 (range 27-91)
Gender: female/male, n (%)	146/240 (38/62)	53/68 (38/62)
BRAF Status, Mutation, n (%)	126 (32)	22 (32)
Line of treatment in mtx pts	N = 288	
1st line treatment, anti-PD1	145 (38)	88 (73)
1st line treatment, anti-CTLA4	15 (4)	33 (27)
1st line treatment, ipi+nivo	28 (7)	36 (30)
1st line treatment, cemiplimab in CSCC	40 (10)	
ORR, n (%)	48 (64)	
Resected stage III/IV melanoma, anti-PD1	N = 98	
Progression disease, n (%)	26 (27)	

Results: Among 507 pts, in cohort 1 lower serum IL-6 was associated with a better Progression Free Survival (PFS) 18.67 months (95% CI 16.6-20.7) versus 10.31 months (95% CI 8.5-12.0), HR = 0.45 (CI 0,3-0,5, p<0.0001); Overall Survival (OS) (27.59 months (95% CI 25.9-29.2) versus 20.12 months (95% CI 17.7-22.4), HR = 0.32 (CI 0,23-0,47, p<0.0001) and Overall Response Rate (ORR) (p<0.001). Similarly, IL-6 and previous therapy are associated with OS and PFS in multivariate analysis (p <0.01). We also confirmed the association between IL-6 and outcomes in all subgroups. In cohort 2 we observed a similar trend in pts with lower IL-6 expression. Moreover, higher IL-6 was associated to MAP3K12, EGFR, SELL, FPR1 genes.

Conclusions: We found that lower levels of both serum and gene expression of IL-6 are associated with better OS, PFS and ORR. Furthermore, IL-6 is associated to higher expression of genes relate to cell cycle, proliferation and metastasis. Further investigations are needed to get additional information.

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1125P Identification of a subset of metastatic melanoma patients demonstrating germline determined insensitivity to immunotherapy

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Background: Long-term clinical outcomes post immune checkpoint blockade (ICB) for metastatic melanoma (MM) are highly variable. Whilst this is in part reflects intertumour heterogeneity, the degree patient germline genetic variation influences ICB responses is poorly characterised. Previous pan-tumour patient cohort studies suggested that homozygosity at Class I MHC alleles is associated with reduced survival post ICB, although these observations have not been reproduced in meta-analyses. Here we explore the relationship between homozygosity at one, two and three alleles at Class I MHC in a longitudinal follow-up cohort of patients receiving ICB for MM, integrating observations with immunological and transcriptomic data at single-cell resolution.

Methods: 232 MM patients receiving standard of care ICB were HLA typed using genome-wide genotyping and followed for up to 9 years. Pre-treatment and on treatment CD8 T cells RNA and T cell receptor (TCR) sequencing of was performed for all samples (n>500), as well as focused single-cell RNA seq. The relationship between homozygosity at HLA-A, HLA-B and HLA-C and survival parameters were explored with results integrated with transcriptomic and immunophenotyping.

Results: 50.9% of patients survived for >5 years. Notably, no effect of homozygosity at either one or two Class I HLA alleles on outcomes was noted (60.5% vs. 49.8% - no homozygosity, P=0.17). However, patients homozygous at three alleles (3.0% cohort) have catastrophic outcomes, independent of tumour features, with 1 year survival 17.8% vs. 75.2%, P<0.0001. Pre-treatment these patients have reduced CD8 TCR diversity, and marked immune dysregulation. Single-cell RNA sequencing demonstrates impaired responses to ICB from treatment initiation.

Conclusions: Understanding ICB resistance is of vital importance in stratifying MM treatments. We find homozygosity at one or two Class I MHC alleles does not impact outcomes. Conversely, we demonstrate a subset of MM patients have homozygosity at all three Class I MHC alleles. They show markedly impaired immunological and transcriptomic responses to ICB, with very poor clinical outcomes. This work marks the first description of germline encoded ICB resistance.

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1126P REtrospective Study of definitive therapy for head and neck mUcosal MElanoma: The RESUME study

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Background: Head and neck mucosal melanoma (HNMM) is a rare clinical subtype of melanoma. The aim of this study was to compare survival following surgery-based treatment (S group) versus radiotherapy-based treatment (RT group) and to assess the efficacy of the addition of adjuvant immune checkpoint inhibitor (adj-ICI) after definitive treatment for locally advanced HNMM patients.

Methods: This was a multi-institutional retrospective study which enrolled patients treated for locally advanced HNMM patients between October 2014 and March 2022.

Treatment efficacy was compared between the S and RT groups and between those with and without adj-ICI.

Results: Among 294 patients, 148 patients were in the S group and 146 in the RT group. In the RT group, 80 patients received proton RT and 43 received carbon ion RT. Patient characteristics between the S and RT groups were mostly similar, except for patients with nasal and paranasal sinus primary sites (77% in S group vs. 91% in RT group) and clinical-T4 stage disease (25% in S group vs. 51% in RT group). Overall, 29 in the S group and 43 in the RT group received adj-ICI. Among patients without adj-ICI, the S group tend to have longer progression-free survival (PFS) than the RT group (hazard ratio [HR] 1.34, 95% confidence interval [CI] 0.98-1.84). However, there was no significant difference in overall survival (OS) between the S and RT groups (HR 1.02, 95% CI 0.64-1.62). Patients with adj-ICI experienced significantly longer PFS than those without adj-ICI (HR 0.68, 95% CI 0.48-0.96) irrespective of definitive treatment (HR 0.65, 95% CI 0.37-1.13 in S group; HR 0.65, 95% CI 0.41-1.03 in RT group). However, OS did not significantly differ between those with and without adj-ICI (HR 0.96, 95% CI 0.59-1.56).

Conclusions: There were no significant differences in PFS and OS between the S and RT groups. Although the addition of adj-ICI yielded longer PFS in locally advanced HNMM patients, adj-ICI might not lead to a benefit in OS.

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1127P Efficacy of immune checkpoint inhibitors (ICIs) in advanced mucosal melanoma (MM): A systematic review and meta-analysis

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Background: Unresectable or metastatic MM has been associated with worse survival and inferior treatment responses than cutaneous melanoma. ICIs are commonly used to treat advanced MM; however, robust conclusions on their efficacy are limited by small studies with heterogeneous patient populations.

Methods: A systematic review and meta-analysis was conducted to benchmark the efficacy of ICIs in advanced MM. PubMed, Medline, Embase, Web of Science and CENTRAL were searched in April 2023 using a combination of ICI and MM search terms, restricted to primary studies with at least 5 patients. Logit-transformed objective response rates (ORR) and adverse event (AE) rates were pooled using a random effects model and the inverse variance methods. Progression-free survival (PFS) and overall survival (OS) Kaplan-Meier curves were digitalised and used to construct summary plots, from which median estimates were derived. Results are reported with 95% confidence intervals.

Results: 28 studies reporting on ICIs in advanced MM were identified (n=2008). 37 treatment types were reported − 10 anti-CTLA4 (n=212), 21 anti-PD1 (n=1428) and 6 anti-CTLA4 plus anti-PD1 (n=368). 62% of patients were treatment-naïve. Pooled ORR was 10% (7-13) for anti-CTLA4, 23% (22-28) for anti-PD1 and 31% (28-35) for anti-CTLA4 plus anti-PD1 ($P<0.001$). Median PFS was 3.5 months (2.7-4.7) for anti-CTLA4, 4.0 months (2.9-5.2) for anti-PD1 and 4.7 months (3.6-6.6) for anti-CTLA4 plus anti-PD1 ($P<0.001$). Median OS was 7.2 months (5.7-10.6) for anti-CTLA, 14.4 months (10.8-17.5) for anti-PD1 and 19.4 (13.8-21.2) for anti-CTLA4 plus anti-PD1 ($P<0.001$). Grade 3 and higher AEs occurred in 36% (1-95) of patients for anti-CTLA4, 14% (11-18) for anti-PD1 and 50% (33-58) for anti-CTLA4 plus anti-PD1.

Conclusions: ICIs are associated with modest activity in patients with advanced MM. Although efficacy is slightly greater with combined anti-CTLA4/anti-PD1 compared to anti-PD1 alone, this was associated with a significantly high risk of grade 3+ AEs. Recommendations for combination ICI therapy should involve a risk-benefit analysis for individual patients. Research to identify predictive molecular biomarkers for ICI efficacy may help with treatment selection for advanced MM.

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1128P A phase I dose escalation and expansion study of FHD-286, a novel BRG1/BRM (SMARCA4/SMARCA2) inhibitor, for the treatment of metastatic uveal melanoma

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Background: The BRG/Brahma-associated factors (BAF) family of chromatin remodeling complexes regulates the chromatin landscape of the genome. Through its ATP-dependent chromatin remodeling activity, BAF regulates the accessibility of gene-control elements, allowing for the binding of transcription factors. FHD-286 is a first-in-class, orally administered compound that potently and selectively inhibits the ATPase components of the BAF complex, SMARCA4 and SMARCA2 (BRG1 and BRM, respectively).

Methods: As of a 31 December 2022 data cutoff, FHD-286 was administered in patients with metastatic uveal melanoma at escalating doses either on a daily dosing regimen ranging from 2.5 mg QD to 10 mg QD or an intermittent regimen of 1-week-on/1-week-off at 10 mg or 15 mg doses. Primary endpoints were safety, tolerability, dose-limiting toxicities (DLTs), and determination of the recommended phase II dose(s) (RP2D). Secondary endpoints included pharmacokinetic (PK) and preliminary efficacy.

Results: At data cutoff, 52 patients had received at least 1 dose of FHD-286. Any grade (Gr) treatment-related adverse events (TRAEs) occurred in 83% of patients, most commonly dysgeusia (39%), fatigue (31%), AST increased (29%), nausea/vomiting (29%), dry mouth (25%) and rash (25%). Gr $\geq$ 3 TRAEs occurred in 25% of patients, most commonly anemia, asthenia, ALP increased, hypokalemia, muscular weakness and rash each occurring in 4% of patients. One patient with Gr 3 keratitis and 2 patients with Gr 3 rash met DLT criteria at the 7.5 mg QD dose level. These AEs were non-serious and improved with dose interruption. No treatment-related deaths occurred. Ongoing PK analysis indicates that FHD-286 accumulates with QD dosing and PK exposure increases with increasing dose. One patient assigned to the 10 mg QD dosing cohort achieved a partial response and remained on treatment for 16 months; prolonged stable disease and reductions in tumor burden have also been observed across dose levels.

Conclusions: FHD-286 has been generally well-tolerated and preliminary anti-tumor activity has been observed. The RP2D(s) has not yet been established. Updated dosing, safety, tolerability, PK and anti-tumor activity data will be shared at the meeting.

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Legal entity responsible for the study: Foghorn Therapeutics Inc.

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Leadership Role: SWOG. M. Mckean: Financial Interests, Institutional, Other, Consulting: Pfizer, Castle Biosciences, Eisai, IQVIA, Merck, Moderna; Financial Interests, Personal, Other, Consulting: iTeos; Financial Interests, Institutional, Research Grant: Ascentage Pharma Group, Bicycle Therapeutics, Dragonfly Therapeutics, Epizyme, Exelixis, Genentech, GSK, IDEAYA Biosciences, Ikena Oncology, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Moderna, NBE Therapeutics, Novartis, Oncorus, Plexxicon, Prelude Therapeutics, Regeneron, Sapience Therapeutics, Seattle Genetics, Tizona Therapeutics, Tmunity Therapeutics, TopAlliance Biosciences, Aadi Biosciences, Alpine Immune Sciences, Arcs Biosciences, Arvinas, ASCO, Astellas, Bayer, BioMed Valley Discoveries, BioNTech, C4 Therapeutics, EMD Serono, Erasca, Foghorn Therapeutics, G1 Therapeutics, Gilead Sciences, ImmVira Pharma, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Nektar, OncoC4, PACT Pharma, Pfizer, Poseida, Pyramid Biosciences, Scholar Rock, Synthrox, Takeda Pharmaceuticals, Teneobio, Tempest Therapeutics, Xilio. S. Piperno-Neumann: Financial Interests, Personal, Advisory Board: Immunocore, Pierre Fabre, Atlanthera. A.N. Shoushtari: Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, Immunocore, Novartis, Erasca; Financial Interests, Personal, Royalties: UpToDate; Financial Interests, Institutional, Local PI: Bristol Myers Squibb, Immunocore, Pfizer, Novartis, Checkmate Pharmaceuticals, Linnaeus Therapeutics, Foghorn Therapeutics, Prelude Therapeutics, Iovance Biotherapeutics; Financial Interests, Institutional, Coordinating PI: Polaris, Xcovery, Targovax ASA; Non-Financial Interests, Member: ASCO. L. Hernandez-Aya: Financial Interests, Personal and Institutional, Advisory Board: BMS, CASTLE Bioscience, Replimune; Non-Financial Interests, Institutional, Principal Investigator: Foghorn Therapeutics, Immatics, Syntrix Pharmaceuticals. M. Orloff: Financial Interests, Personal, Advisory Board: Trisalus, Delcath, Replimune, IDEAYA, Immunocore; Financial Interests, Personal, Speaker, Consultant, Advisor: Immunocore. S. Khan: Financial Interests, Personal, Advisory Board: Castle Biosciences, Replimune Inc. K. Montazeri: Financial Interests, Personal, Speaker, Consultant, Advisor: Immunocore. E. Kapiteijn: Financial Interests, Institutional, Advisory Board: BMS, Novartis, Pierre Fabre, Merck, Delcath, Bayer, Lilly; Financial Interests, Institutional, Coordinating PI: BMS, Pierre Fabre, Delcath. E. Buchbinder: Financial Interests, Personal, Advisory Board: Instilbio, Nektar, Novartis, BMS, Iovance, Merck, Sanofi, Xilio; Financial Interests, Institutional, Coordinating PI: Genentech, Partners therapeutics; Other, Spouse employment: AstraZeneca, Takeda. S. Agresta: Financial Interests, Personal, Full or part-time Employment: Foghorn Therapeutics; Financial Interests, Personal, Stocks/Shares: Foghorn Therapeutics; Financial Interests, Personal, Officer: Foghorn Therapeutics. S. Reilly: Financial Interests, Personal, Full or part-time Employment: Foghorn Therapeutics; Financial Interests, Personal, Stocks/Shares: Foghorn Therapeutics, Adaptimmune Therapeutics, Johnson & Johnson, Procter & Gamble; Financial Interests, Personal, Other, Investor: Luna Genetics. C.M. Patriquin: Financial Interests, Personal, Stocks/Shares: Foghorn Therapeutics, Roche; Financial Interests, Personal, Full or part-time Employment: Foghorn Therapeutics. D. Hickman, L. Granlund, M. Hentemann, J. Piel: Financial Interests, Personal, Full or part-time Employment: Foghorn Therapeutics; Financial Interests, Personal, Stocks/Shares: Foghorn Therapeutics. D. Corrigan: Financial Interests, Personal, Stocks/Shares: Foghorn Therapeutics. P. Martin: Financial Interests, Personal, Full or part-time Employment: Certara. I. Mehmi: Financial Interests, Personal, Speaker, Consultant, Advisor: BMS; Financial Interests, Personal, Advisory Board: AZ.

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1129P Effect of subsequent therapies including checkpoint inhibitors on overall survival in a phase III randomized trial of tebentafusp in first-line metastatic uveal melanoma: Long-term follow-up

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Background: Tebentafusp (tebe) is a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells. Tebe significantly improved overall survival (OS) compared to investigator's choice of pembrolizumab, ipilimumab or dacarbazine (HR 0.51) in first line (1L) mUM [NCT03070392]. Here we evaluated the impact of subsequent therapy on long-term survival.

Methods: Analyses were conducted on HLA-A*02:01+ patients with first line mUM recruited to the randomized phase III study (Study 202, N=378). Crossover to tebe was not permitted until the planned interim analysis demonstrated significant OS benefit. Inverse probability of censoring weighting (IPCW) was used to compare the tebentafusp and investigator's choice (IC) arms by removing the effects of subsequent therapies (any versus CPI only). OS from the start of subsequent therapy was compared between arms using Cox regression models adjusted for prognostic baseline covariates.

Results: After a median follow-up of 37.8 months, a similar percentage of patients, ~ 62%, received subsequent therapy in each arm. Median time to first subsequent therapy was longer for tebe pts (6.4 mo) vs. IC pts (4.5 mo). The most frequent subsequent therapy was CPI in both arms (received by 49% of tebe pts and 34% of IC pts); 17% of IC pts received subsequent tebe. When adjusting for the effect of subsequent therapy (any or CPI), the OS benefit from the ITT analysis was maintained. In an analysis of survival from the start of any first subsequent therapy, prior tebe patients tended to have longer OS compared to prior IC patients, HR (95% CI) 0.75 (0.55, 1.04). This difference was also seen when restricting to patients who received subsequent CPI therapy, HR (95% CI) 0.72 (0.48, 1.09).

Conclusions: Based on IPCW analysis, the OS benefit in first line HLA-A*02:01+ mUM patients is predominantly due to tebentafusp and not due to subsequent therapy. This reinforces the use of tebentafusp in the first line setting. Updated data with a minimum 3 years of follow-up will be presented. 1. Yang J. et al. ASCO 2019 , *J. Clin Oncol* 37:15_suppl, 9592.

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1130P Tebentafusp (tebe) in an ongoing cohort of 72 French patients (pts) with metastatic uveal melanoma (mUM)

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Background: Tebe, a bispecific T-cell engager, showed a benefit in response rate, progression-free survival (PFS) and overall survival (OS) in HLA A*02-01^{pos} mUM pts in the IMCgp100-202 phase III trial. Prior to approval, French Health Authorities allowed an early access to Tebe in May 2021 to mUM pts. We report here our real-world experience with Tebe and analyses of potential prognostic and predictive biomarkers.

Methods: Ongoing ambispective cohort of mUM pts treated with Tebe. Tumor sizes were evaluated according to RECIST 1.1. Circulating tumor DNA (ctDNA) analyses were performed on this cohort and on the 18 pts enrolled in the IMCgp100-202 trial and randomized to Tebe, at Institut Curie. ctDNA was measured by digital droplet PCR (ddPCR) targeting codons 183 & 209 of both *GNAQ* and *GNA11*.

Results: 72 pts were included from May 26th 2021 to December 12th 2022. With a median follow-up of 48 weeks, patients received a median of 22 weeks of Tebe. Out of 60 assessable pts, 33 (55%) showed stable disease and 5 (8%) partial response according to RECIST 1.1. Median PFS (mPFS) was 28 weeks (confidence interval 95% [CI_{95}]: 8-56). OS at 12 months (OS_{12m}) was 72%. No new, unexpected safety event occurred. Elevated baseline LDH was correlated with poorer OS (Spearman rho= -0.26, $p<0.01$). 63 pts had mUM carrying somatic mutations detectable by ddPCR (ie *GNAQ/GNA11* mutations). Of these, 39 pts (62%) had detectable ctDNA at baseline. Pts with detectable ctDNA at baseline had poorer PFS (mPFS 4.0 vs 14.0 months; HR=2.83, CI_{95}[1.48-5.41]) and OS (OS_{12m} of 51.5% vs 95.4%; HR=6.11, CI_{95}[2.04-18.3]) than those with undetectable ctDNA. 22 pts cleared their ctDNA at first assessment (12 weeks) and had numerically better OS_{12m} than those who did not (70% vs 60%; HR = 1.83 CI_{95}[0.92-13.9]).

Conclusions: In this real-world cohort of mUM pts, Tebe is associated with clinical outcomes in lin withthe IMCgp100-202 trial. Baseline ctDNA and LDH are prognostic factors while ctDNA clearance might predict benefit from Tebe. Other analyses are ongoing to identify new predictive biomarkers.

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1131P Management of metastatic uveal melanoma (MUM) patients on tebentafusp in a real-world setting

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Background: Tebentafusp (TEBE), a bispecific T-cell engager targeting HLA-presented gp100 peptide, was approved for treatment-naïve (TN) MUM HLA-A*02:01+ pts. In its pivotal trial, pts attended weekly outpatient (OP) visits and the duration of premedication was not defined. Additional data on drug administration, safety, and efficacy of a tertiary center may provide insight into optimal premedication and an ideal follow-up schedule in the real-world setting.

Methods: We assessed MUM pts treated with TEBE at our center from Jun/2021-Nov/2022. Data on adverse events (AE), OP visits and discontinuation of premedication were analyzed. Efficacy outcomes included OS, PFS, time-to-TEBE discontinuation (TTD), and best response (BOR - clinician's assessment). Survival was estimated using Kaplan-Meier; categorical variables were analyzed using logistic regression, Chi-square/Fisher's exact tests.

Results: We identified 36 pts. Median age was 64 (30-90); 21 (58.4%) were male. At TEBE initiation, 22 (61%) pts had M1a disease. 20 pts (55.6%) had only 1 metastatic site, and 19 (53%) presented with liver-only disease. Extrahepatic involvement occurred in 17 (47%) pts. 25 pts (69.4%) were TN. Tumor reduction (TR) occured in 5 (14%) and disease control (DC) in 23 (64%) pts. The 1y OS was 68% (median: NR). Median PFS and TTD were, respectively, 6 (95%CI 3.8-8.1) and 9 mo (95%CI 4.6-13.3), with 1y PFS and TTD of 14% and 35.4%. Pts whose BOR was TR or SD had longer TTD when compared with those experiencing PD (12 vs 4 mo, $p<0.01$). All pts developed AE, most frequently rash (n=33), fever (n=23), and pruritus (n=14); 30.5% had G3/4 AE, with rash and hypoxemia occurring in 45% and 27%, respectively. M1a stage was associated with higher DC rate ($p=0.03$) and lower incidence of fever ($p<0.01$); rash was the only factor associated with DC in the multivariate analysis ($p<0.01$). The median number of inpatient doses was 4 (3-18). In the OP setting, 19 pts (53%) were switched to q3 week visits after a median of 6 doses (6-39). For 19 pts (53%), premedications were successfully stopped after a median of 7 doses (4-27).

Conclusions: Our data supports the reduction of OP visits and holding premedication after the resolution of AE. The promising activity of TEBE was confirmed in this cohort mostly comprised of TN pts.

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1132P Chemokine expression in uveal melanoma and association with tumor genetics and response to immunotherapy

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Background: Uveal melanoma (UM) is a rare form of melanoma having poor responses to currently available systemic agents. Our goal is to understand differences in chemokine expression in relation to tumor genetics and response to immunotherapy.

Methods: UM patient tumors (N=278, 41 primary, 174 liver mets and 63 other mets) were profiled by NGS DNA/RNA at Caris Life Sciences (Phoenix, AZ). Chemokine expression, high/Low (H/L) defined as samples with $>75^{th}$- or $<25^{th}$-percentile of transcripts per million (TPM). Tumor microenvironment (TME) cell fraction estimated by RNA, with median fold changes (H/L) or proportion of samples with non-zero fraction reported (Table). PDL1+ (SP142) tested by IHC. Survival data obtained from insurance claims.

Results: Primary tumors had increased expression of *CXCR4, CXCR1*, *CXCR2*, *CCL27* and *CXCL13* compared to liver mets (FC range 1.2-4.2), while *CXCL2* expression was increased in liver mets (2.3, $p<0.01$). In liver mets, increased infiltration of immunosuppressive cells was observed for *CXCR4*-H and *CXCL12*-H tumors(Table). Only M1 macrophages, CD8+ T cells and B cells were increased for *CXCR4*-H and *CXCL12*-H primary tumors. PDL1+ rates were increased in *CXCR4*-H tumors overall (H 36% vs L 13%, $p<0.05$). In liver mets, *SF3B1* mutation was associated with lower *CXCL1* and *CXCL2* expression compared to WT (0.35- and 0.47-fold, respectively, p-<0.01). *BAP1*-mutated liver mets showed increased *CXCL1* expression (2.0-fold, p-0.04), whereas *CCR10* expression was increased in *BAP1*-mutated primary tumors (2.6-fold, p-0.02). Among immunotherapy treated patients with liver mets, there was a trend for improved survival for *CXCL12* H (n=13) vs L (n=12) (HR 0.51 (0.21-1.3), p=0.14) and *CXCR4* H (n=13) vs L (n=12) (HR 0.49 (0.20-1.2), p=0.12) though not significant.

Table: 1132P TME (liver mets): CXCR4/CXCL12 median fold change (H/L) (where median is 0, % non-zero H vs L).

Immune Cell	*CXCR4* Median FC (H/L) or non-zero%	p-value	*CXCL12* Median FC (H/L) or non-zero%	p-value
Monocyte	13% vs 0%	0.01	37% vs 11%	0.31
Treg	2.9	<0.01	2.9	<0.01
T cell CD8	70% vs 28%	<0.01	67% vs 34%	<0.01
T cell CD4	32% vs 13%	0.02	37% vs 11%	0.01
NK cell	1.4	<0.001	1.5	<0.001
Macrophage M2	1.3	0.002	1.3	<0.001
Macrophage M1	92% vs 50%	<0.01	96% vs 49%	<0.001
B cell	1.6	<0.01	1.3	0.02

Conclusions: Our results suggest chemokines are differentially expressed in tumors harboring the common alterations associated with medium risk of distant metastases.

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1133P SF3B1 mutation predicts improved overall survival in metastatic uveal melanoma patients: Molecular and clinical correlates

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Background: Metastatic uveal melanoma (MUM) is a rare and lethal disease with varied clinical course. Despite the existence of well-characterized molecular drivers none have been associated with clinical outcomes in MUM. We aimed to study how uveal melanoma genetic alterations affect MUM prognosis.

Methods: From a prospective database of MUM patients, we analysed molecular alterations of primary tumors, including mutations (GNAQ/GNA11 and SF3B1) and chromosomal imbalances (chr3 monosomy (M3),chr8q amplification (+8q), chr8p deletion (-8p),chr8p amplification (+8p), chr1p deletion (-1p), chr6p deletion (-6p), and chr6q amplification (+6q)). Relevant clinical features at the time of MUM diagnosis, such as age, sex, disease-free survival from primary tumor, ECOG score, size of liver metastasis, and levels of LDH, alkaline phosphatase (ALP), bilirubin (BIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) were recorded. Survival analysis was calculated from MUM diagnosis to death or last follow-up.

Results: Molecular data was obtained from 59 of 119 MUM patients treated at our institution from 2007 to 2022. The mutational driver profile was: 46% GNAQ and 40% GNA11; 42% Q209P and 44% Q209L; 19% SF3B1 mutation being 10% R625H, and 9% R625C. Chromosomal alterations were: M3 81%, +8q 60%, +8p 15%, -8p 12%, -1p 30%, -6q 17%, and +6p 17%. The median overall survival (mOS) for the entire cohort was 16 months(m). Among all genetic alterations, only SF3B1 had a significant impact on mOS: 13m (95% CI 10-15) for wild-type (WT) vs 31.6 m (95% CI 16-46) for mutant (MUT), p=0.01, HR=0.32. Survival probability was higher at 12, 24, and 48m for WT vs MUT (57% vs 81%, 17% vs 70%, and 6% vs 37%). SF3B1 mutation was not statistically associated with any clinical variable. In the multivariate analysis using all clinical variables and SF3B1 status, only DFS $\geq$2y (HR=2.3), elevated LDH (HR=3.5), elevated ALP (HR=6.1), and SF3B1 MUT (HR=0.2, 95%CI 0.1-0.8, p=0.02) remained significant.

Conclusions: SF3B1 mutation is independently associated with improved OS in MUM patients. Results may affect MUM care, treatment development, and trial stratification. More research is needed to confirm these findings.

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1134P Safety and efficacy of low dose (LD) ipilimumab (Ipi) + pembrolizumab (pem) in checkpoint inhibitor (CPI) naïve patients (pts) with melanoma brain metastases (MBM)

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Background: The CPI combination of standard dose (SD) Ipi (3mg/kg) and nivolumab 1mg/kg (N) has dramatically improved outcomes in pts with MBM but is associated with frequent grade (gr) 3/4 adverse events (AEs). In pts without MBM, LD Ipi (at 1mg/kg) + anti-PD1 with N or Pem has demonstrated promising efficacy with reduced toxicity. We hypothesized this approach would have activity in pts with MBM.

Methods: We conducted a phase II, single arm and site trial (NCT03873818) evaluating LD Ipi + Pem in pts with MBM. Pts received up to 4 cycles of LD Ipi + Pem, followed by Pem only. At least 1 MBM >/= 5mm was required. CPI naïve (Cohort A) and prior PD-1 (Cohort B) were allowed. Primary objective included intracranial (IC) benefit rate (CBR) − complete response (CR) + partial response (PR) + stable disease (SD) $\geq$ 6 months (mos) by mRECIST 1.1. Secondary objectives were overall (OS) and progression free (PFS) survival. Study was terminated early due to accrual challenges. Here we report the efficacy results of cohort A.

Results: A total 19 of a planned 25 (76%) pts were treated in Cohort A. 58% (11) were male, median age was 63 years (23-88), 7 had BRAF V600 mutation. Median number of MBM was 3 (1-20), median diameter of largest MBM 8 mm (5-28). Pts received a median 4 cycles (1-4) of the combination, median total cycles received was 6 (1-35). IC CBR was 58% (32% CR, 11% PR, 16% SD). At a median follow-up of 14.5 mos (0.5-43), median IC PFS was 8.0 mos (95% CI 1.4- not reached) and median OS has not been reached. 11 (58%) pts in cohort A are alive at time of data lock. 25% (4/16) of pts stopped tx due to progression. 7 pts (37%) stopped tx for AEs. 16 pts experienced AEs at least possibly related to tx, most commonly rash (53%), fatigue (42%), and elevated liver enzymes (32%). Gr 3/4 AEs were observed in 6 (32%) pts, including rash (16%), elevated liver enzymes (11%), nausea, pneumonitis, anorexia, and colitis (5% each).

Conclusions: LD Ipi/Pem was well tolerated in CPI naïve pts with MBM, with no new or unexpected AEs, and with promising efficacy. The results support a larger study to confirm benefit.

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1135P Comparison of intracranial (IC) response assessment criteria in patients (pts) with melanoma brain metastases (MBM) treated with combination nivolumab (NIVO) plus ipilimumab (IPI) in CheckMate 204

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Background: In CheckMate 204, NIVO + IPI showed high IC mRECIST objective response rates (ORRs) in pts with asymptomatic, unirradiated MBM and a lower but durable response in pts with symptomatic and/or steroid-requiring MBM. Response as a surrogate for progression-free survival (PFS)/overall survival (OS) has prompted the use of various response assessment criteria and cutoffs for target lesion size in MBM. In this exploratory analysis, ORRs and correlation of response to survival were examined by mRECIST, RANO-BM, RECIST, and volumetric response.

Methods: Pts with metastatic melanoma and $\geq$ 1 unirradiated MBM (diameter, 0.5−3 cm) received NIVO 1 mg/kg + IPI 3 mg/kg Q3W $\times$ 4, followed by NIVO 3 mg/kg Q2W for $\leq$ 24 mo. IC ORRs were assessed using mRECIST (5 mm target lesion cutoff), RECIST (10 mm), RANO-BM (5 or 10 mm), and volumetric response (5 or 10 mm), per blinded review. IC PFS and OS using a 6-wk landmark were compared for responders vs nonresponders.

Results: IC ORR was numerically higher with mRECIST or volumetric assessment compared with RANO-BM or RECIST (Table). Responder vs nonresponder PFS and OS were significantly better across the different assessment criteria; mRECIST and volumetric response showed the strongest correlations (Table). mRECIST responders who were not RANO-BM 5 mm responders (n = 14) had similar OS to RANO-BM 5 mm responders. Among 41 pts with only target lesions < 10 mm, mRECIST ORR, and OS for the responders, was similar to the overall CheckMate 204 ITT population.

Conclusions: This analysis supports mRECIST as a reliable assessment scale by showing strong differentiation of long-term benefit for responders vs nonresponders. Volumetric response also correlated with PFS/OS supporting future trial exploratory use. Responders with only MBM < 10 mm derived comparable PFS/OS benefit to ITT, supporting the inclusion of pts with smaller MBM in future trials.

Table: 1135P

	All pts (n = 119)					
	mRECIST 5 mm	RECIST 10 mm	RANO-BM 5 mm	RANO-BM 10 mm	Volumetric[b] 5 mm	Volumetric[b] 10 mm
ORR, % (95% CI)	45 (36–55)	27 (19–36)	34 (26–44)	26 (18–35)	40 (31–50)	39 (31–49)
PFS HR,[a] (95% CI)	0.06 (0.02–0.16)	0.18 (0.06–0.56)	0.13 (0.06–0.29)	0.25 (0.11–0.59)	0.04 (0.01–0.11)	0.07 (0.03–0.19)
OS HR,[a] (95% CI)	0.18 (0.07–0.45)	0.22 (0.07–0.75)	0.26 (0.10–0.71)	0.34 (0.12–1.00)	0.10 (0.03–0.35)	0.11 (0.03–0.36)

[a]Responder vs nonresponder; Cox proportional hazard model was used for hazard ratio (HR) calculation. [b]Volumetric response was defined as a 65% decrease in target lesions and progression as a 73% increase.

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1136P Regorafenib combined with BRAF-/MEK-inhibitors for the treatment of refractory melanoma brain metastases

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Background: There are no active treatment options for patients (pts) with progressive melanoma brain metastases (MBM) who have failed treatment with immune checkpoint blockade (ICB) and BRAF-/MEK-inhibitors (BRAF/MEKi). Regorafenib (REGO), an oral multi-target kinase inhibitor (incl. inhibition of RAF-dimers), has single-agent activity in pretreated melanoma (VD Mijnsbrugge et al. SMR 2022).

Methods: We report our single center retrospective review of prospectively registered pts with refractory MBM treated with REGO and BRAF/MEKi.

Results: 17 pts with stage IV-M1d melanoma were included (8F; med age 54y [33-75]; WHO PS: 0/1/2/3 resp. n=3/6/6/2 pts; 13 pts BRAFmt (12 BRAF V600mt, 1 BRAF fusion), 4 pts NRAS Q61mt). All pts previously progressed on ICB, BRAF/MEKi (all BRAFmt pts), chemotherapy (4 pts), T-VEC (2 pts), REGO mono (3 pts), and REGO + ICB (2 pts). At baseline, 15 pts had active MBM (8 pts were on steroids); 4 pts had intracranial evaluable disease only. BRAFmt pts were treated with REGO (40-80 mg QD) combined with BRAF/MEKi, NRASmt pts with REGO + MEKi (+ low-dose BRAFi to mitigate skin toxicity). There were no grade $\geq$4 TRAE. Grade 3 TRAE included arterial hypertension (n=4), and hepatotoxicity (n=2). None of the 2 pts without active MBM at baseline progressed intra-cranially. The best objective intracranial response (according to RANO-BM) in 17 response evaluable pts was: PR in 5 pts (29%; incl. 4 BRAFmt pts), and SD in 5 pts (29%; incl. 4 BRAFmt pts). In 5 pts intra- and extracranial disease control (PR, SD) were concordant. 3 pts with PR intra- had SD extra-cranially; 2 pts with SD intra- had PD extra-cranially. Assuming a potential clinical benefit of therapy beyond first PD, 10 out of 16 progressive pts continued treatment and remained clinically stable for an additional 3-48 weeks (w) (median 7w). Median time on REGO+BRAF/MEKi in BRAFmt pts was 13w [range 3-62], and 27.5w [range 3-56] on REGO + MEKi in NRASmt pts. In 3 pts treatment is ongoing (9-62w after initiation). Median PFS and OS is resp. 8.4w and 24.6w in BRAFmt pts; 8.6w and 10.1w in NRASmt pts.

Conclusions: In heavily pretreated patients with refractory MBM, REGO combined with BRAF/MEKi demonstrated promising anti-tumor activity. Further investigation in a prospective trial is warranted.

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1137P Treatment strategies and survival outcomes in a nationwide, population-based cohort of patients with melanoma brain metastases: The role of planned shift in systemic therapy and postoperative stereotactic radiotherapy

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Background: Modern therapies have significantly improved outcome for patients with melanoma brain metastases (MBM). Still, the prognosis is poor, and the optimal treatment strategy is not well defined. Here, we report on the survival outcomes of systemic and locoregional treatments in an unselected, nationwide population-based cohort of patients with MBM.

Methods: All patients diagnosed with MBM in Denmark between 2015-2022 were retrospectively included. Patients were identified using the Danish Metastatic Melanoma Database (DAMMED) and local records of surgery and radiotherapy. Data were obtained from patient records.

Results: A total of 838 patients were included. Median overall survival (mOS) of the entire cohort was 9.0 months, and 112 patients were alive >3 years after diagnosis of MBM. Treatment with immune checkpoint inhibitors (ICI), ipilimumab + nivolumab, resulted in an intracranial overall response rate (icORR) of 46%, and a 2-year OS of 49% whereas BRAF/MEK-inhibitors (BRAF/MEKi) resulted in an icORR of 56%, and 2-year OS of 20%. A subgroup of patients with symptomatic MBM, treated initially with BRAF/MEKi with planned shift to ICI, had an icORR of 70%, 2-year OS of 50% and reached the longest mOS of 26 months. Patients with meningeal carcinomatosis (n=67) had a mOS of 8.4 months. Systemic therapy significantly improved OS for these patients, but no survival benefit was observed for patients receiving ICI compared to BRAF/MEKi. In total, 230 patients underwent surgery for MBM; of these, 30 received postoperative stereotactic radiosurgery (SRS). Baseline characteristics were balanced between the two groups. No benefit in OS or intracranial progression free survival was observed for patients receiving postoperative SRS.

Conclusions: Modern systemic therapies have improved survival for real-world patients with MBM; BRAF/MEKi had the highest icORR while ICI generated more durable responses. Planned shift from BRAF/MEKi to ICI can lead to long-term survival in selected patients. Postoperative SRS for patients undergoing surgery for MBM is questioned as a standard procedure.

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1138P Intralesional administration of L19IL2/L19TNF in difficult-to-treat non-melanoma skin cancer shows a favorable safety profile and preliminary clinical activity

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Background: Non-melanoma skin cancers (NMSC), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common forms of skin cancer, with a rising incidence due to deficient sun protection and growing life expectancy. Treatment options include surgery, radiotherapy, immunotherapy, targeted therapy, or chemotherapy. Surgery typically offers high cure rates; however, surgery's suitability and/or effectiveness in certain patients (pts) may be limited by disease factors (location, functional and cosmetic impairment) or pts factors (age, comorbidities, personal preferences). Initial intralesional treatment with immunostimulatory drugs may be another therapeutic approach, potentially curing NMSC or making surgery less invasive. Here we investigate a combination of 2 immune cytokines (Bifikafusp alfa (L19IL2) and Onfekafusp alfa (L19TNF) targeting the extra domain B of fibronectin (EDB) for selective delivery of immunostimulatory payloads to the tumor site. EDB is virtually absent in healthy adult tissues but highly expressed in tumors, including NMSC.

Methods: In a single-arm, ongoing, phase II study (NCT04362722), pts with locally advanced, non-metastatic, node-negative, single or multifocal NMSC, not eligible for surgery or radiotherapy or who refuse it, are treated with 4 weekly intratumoral administrations of L19IL2/IL19TNF. 14 pts (11 BCC and 3 cSCC) have been treated and are evaluable for safety and efficacy.

Results: Administration of L19IL2/L19TNF was well tolerated with no grade 4-5 adverse events (AE). The most common treatment-related AEs were flu-like symptoms (36.4%), pyrexia (27.3%), face edema, chills, and injection site reaction (13.6%), all transient, managed with symptomatic therapy. In BCC cohort, ORR was assessed on day 36 with a 27.3% RR. In the follow-up, 5/11pts achieved pathological complete response (pCR) with an average time to pCR of 66 days from the first administration. In the 3 SCC pts, ORR was 33.3 % with 1 pCR.

Conclusions: The tolerable safety profile of L19IL2/L19TNF and the results obtained in pts with NMSC justify further exploring the potential of intralesional administration of immunostimulatory drugs in this setting.

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1139P Final results of a phase II study of pembrolizumab as first-line treatment in advanced cutaneous squamous cell carcinomas (CSCCs)

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Background: In the CARSKIN study (NCT02883556), first line pembrolizumab demonstrated promising activity and manageable safety in patients (pts) with advanced CSCC. Here we report BOR and survival endpoints.

Methods: Eligible pts with unresectable locally advanced or metastatic CSCC received pembrolizumab. The imaging assessment per RECIST v1.1 was blinded with independent central review. Objectives were BOR, PFS, DOR, OS, and safety in the ITT population; exploratory objectives were BOR and survival endpoints by PD-L1 status in the PP population excluding 2 untreated pts, 1 early non related death and 3 pts tested only with 1 assay. PD-L1 status was centrally assessed by 2 blinded independent pathologists, one using the anti−PD-L1 E1L3N clone (TPS_{E1L3N}), the other using the 22C3 antibody (TPS_{22C3} and CPS_{22C3}) with a cutoff of 1%.

Results: With a median follow-up of 26 mo, BOR was 47% with 15 PR (26%) and 12 CR (21%); 1y-PFS and OS were 49% and 72% (Table). BOR was significantly higher in PD-L1+ pts than in PD-L1 − pts using TPSE1L3N (p=0.02) or CPS22C3 (p=0.038) but not TPS22C3 (p=0.76). The optimal cutoff of CPS22C3 for BOR using a ROC curve was estimated to be ≥ 7% (Se=0.70, Sp=0.75). Pts with PD-L1+ CSCCs have a significantly better 1y-PFS using TPSE1L3N (p=0.004) but not CPS22C3 and a better 1y-OS with both antibodies (p<0.03). Severe TRAEs occurred in 10 patients (17.5%); 1 pt died of a fatal 2nd aggressive HNSCC.

Table: 1139P

Outcome [95%CI]	ITT population #57	PP population #51	TPS (EILN3)		CPS (22C3)	
			PD-L1+ pts #40	PD-L1− pts #11	PD-L1+ pts #41	PD-L1− pts #10
Best ORR	47% [34-61]	51% [34-62]	60% [43-75]	18% [2-52]	59% [42-74]	20% [3-56]
Median PFS	10.1 [4.8-NR]	13.7 [4.6 -NR]	19.6 [6.1-NR]	2.1 [1.9-NR]	13.8 [5.6-NR]	4.3 [2.0-NR]
1y-PFS	49% [37-64]	50% [38-66]	57% [43-72]	27% [10-72]	53% [39-71]	40% [19-86]
Median OS	25.3 [16.5-NR]	25.3 [16.5-NR]	NR	10.0 [4.0-NR]	NR	10.0 [2.0-NR]
1y-OS	72% [61-85]	73% [61-86]	82% [70-95]	42% [20-87]	79% [67-93]	50% [27-93]
Median DOR	NR	NR	NR	5.6 [5.6-NR]	NR	NR
1y-DOR	79% [65-97]	80% [65-97]	83 [69-100]	50 [13-100]	78 [62-97]	100

Conclusions: Our data confirm promising activity of P in first line treatment of CSCC with a manageable side effect profile. $CPS_{22C3} \geq 7\%$ appeared equivalent to $TPS_{E1L3N} \geq 1\%$ for predicting BOR and OS.

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Legal entity responsible for the study: AP-HP.

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1140P Cemiplimab versus historical systemic treatments for locally advanced (la) or metastatic (m) cutaneous squamous cell carcinomas (CSCC): Results from the French study TOSCA

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Background: The anti-PD1 antibody cemiplimab, is approved and recommended for patients with la/mCSCC based on a non-comparative pivotal study. In the absence of any prospective comparative study and to evaluate the extent of the benefit of cemiplimab versus previous therapies, the TOSCA study evaluated the effectiveness and safety of cemiplimab versus Historical Systemic Therapies (HST).

Methods: TOSCA is a large French retrospective, multicenter study in patients with laCSCC ineligible for curative surgery or radiation, or mCSCC, treated with cemiplimab via the Early Access Program (EAP) in 2018-2019, or with HST in 2013-2018 (NCT05302297). Primary endpoint was OS. Secondary endpoints were PFS, DOR, ORR, and safety. Only immunocompetent patients meeting the strict indication of the EAP were considered for effectiveness analysis using inverse probability weighting method (IPW). All patients were considered for safety analysis.

Results: A total of 280 patients were included in the study (cemiplimab, n=147 and HST, n=133) and 199 patients were considered for effectiveness analysis (cemiplimab, n=129 and HST, n=70). The median age was 81 (range 48—99) and 78 (52—93) years; males were 70% and 73% for cemiplimab and HST arms, respectively. 60% and 73% of patients had mCSCC, and 50% and 31% of patients received at least one previous systemic therapy in cemiplimab and HST arms. With a median follow-up of 20 and 10 months for cemiplimab and HST arms, and after controlling for confounding using IPW, the median OS was 21 and 10 months (hazard ratio [HR] [95%CI]: 0.57 [0.45-0.73]; *P*-value <0.0001), respectively. The median PFS was 14 and 5 months (HR [95% CI]: 0.57 [0.43-0.76]; *P*-value = 0.0001). The median DOR was 22 and 5 months (HR [95%CI]: 0.58 [0.30-1.12]; *P*-value = 0.1033). The ORR was 57% in cemiplimab group and 33% in HST group (*P*-value <0.001) including 30% and 15% of complete response, respectively. Adverse drug reactions of all grades were documented in 27% (cemiplimab) and 33% (HST) of patients.

Conclusions: TOSCA is the first comparative study in CSCC and showed significantly longer outcomes in patients treated with cemiplimab versus HST, confirming its benefits in patients with la/mCSCCs.

Clinical trial identification: NCT05302297.

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1141P Early discontinuation of cemiplimab in patients with advanced cutaneous squamous cell carcinoma

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Background: Immunotherapy has drastically changed the treatment of advanced cutaneous squamous cell carcinoma. In three clinical trials, cemiplimab and pembrolizumab have been administered up to 24 months, although most objective responses have been observed within the first 3 months. To determine if a shorter exposure time to cemiplimab was associated with the long-term maintenance of clinical activity, we assessed the outcomes of patients with advanced cutaneous squamous cell carcinoma that had an early discontinuation of cemiplimab.

Methods: This is a single centre retrospective study including patients with histologically confirmed locally advanced or metastatic CSCC treated with cemiplimab at our Institution from August 19th, 2019, to August 8th, 2022. The objective response was assessed radiologically according to the RECIST 1.1 criteria or clinically according to the WHO criteria.

Results: A total of 48 patients receiving at least one dose of cemiplimab were included. Median time of treatment with cemiplimab was 6.8 (0 − 31.6) months, with an overall response rate (ORR) of 68%. Median time to response was 2.8 (0.6 - 19.1) months. Therapy was permanently discontinued in 20 patients due to adverse events (n=3) or patients' or physician's choice after achieving a stable disease, partial or complete response (n=17). At a median follow-up of 11.6 (1.4 − 45.0) months, the median PFS after treatment discontinuation was 15.8 months. No patient relapsed. Only one patient, after being treated for a haematological pathology, developed a new primary CSCC, while pre-existing lesions maintained complete clinical response.

Conclusions: Our findings suggest that early discontinuation of cemiplimab in patients with advanced CSCC upon achieving a tumour response does not appear to negatively impact on the duration of response.

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1142P Personalized decision making in cutaneous squamous cell carcinoma: Integrating a clinico-pathological model for absolute metastatic risk into the staging systems

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Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, causing a staggering death toll comparable to that of melanoma, despite its low propensity to metastasize (2-5%). However, until recently, cSCC has been perceived as a non-life-threatening tumor, and current clinical practices are suboptimal: clinical staging systems cannot consistently and reliably identify patients at high risk of metastasis, and they do not provide absolute metastatic risk. Therefore, decisions about follow-up schedules and treatment cannot be personalized.

Methods: We sought to improve the risk stratification as defined by the American Joint Committee on Cancer (AJCC) and the Brigham and Women's Hospital (BWH), by integrating a recently developed clinico-pathological (CP) model for metastatic risk in cSCC patients. We tried to identify patients at increased risk within the low-risk group (AJCC: T1-T2, BWH: T1-T2a) and in the high-risk group (AJCC: T3-T4, BWH: T2b-T3), We performed our analysis in a Dutch nested case-control cohort (n=390); binarized the 5-year metastatic risk into CP High-Risk and CP Low-Risk, by selecting thresholds based on likelihood ratios.

Results: In the low-risk group, the metastatic risk is 1.1% (AJCC) and 1.2% (BWH). Within this group CP High-Risk patients (AJCC: 2.6%, BWH=1.9%) have an increased risk (AJCC: 10.3%, BWH: 16.2%) and would be offered follow-up; but not the CP Low-Risk patients (AJCC: 97.4%, BWH=98.1%) with a decreased risk (AJCC: 0.9%, BWH: 0.98%). In the high-risk group, the metastatic risk is 5.7% (AJCC) and 12.8% (BWH). Within this group, CP High-Risk (AJCC:7.9 %, BWH=21.8%) have an increased risk (AJCC: 40.5%, BWH: 43.4%) and could be offered more intensive follow-up and treatment (e.g., adjuvant treatment).

Conclusions: Our data show that our risk model can enhance the AJCC and BWH staging systems, by refining the risk stratification in both the low-risk and high-risk groups. This has the potential to help clinicians, dermatologists, radiotherapists, and clinical oncologists make more personalized decisions about more intense follow-up schedules and treatment of their cSCC patients.

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1143P Changes in peripheral and local tumor immunity after cemiplimab treatment early describe clinical outcomes in patients with cutaneous squamous cell carcinoma

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Background: Cutaneous squamous cell carcinoma (cSCC) − the second most common skin tumor - accounts for 20% of all deaths from skin cancer. Although the vast majority of patients can be managed with surgical excision, a small percentage of them have locally advanced or metastatic tumors for which programmed cell death 1 (PD-1) checkpoint inhibition was approved and demonstrated substantial antitumor activity. The absence of reliable markers of response and the lacking of a description of immune modulation upon treatment, highlight a clinical need to be addressed.

Methods: We collected tumor and liquid biopsies of 12 patients underwent to cemiplimab before and after 3-weeks of treatment. We profiled RNA of pre- and post-cemiplimab tumor biopsies using the PanCancer Immunoprofile Panel (Nanostring). We determined cytokines released in blood by multiplex ELISA, and lymphocytes abundance by flow cytometry.

Results: The analysis of transcriptional reprogramming in tumor biopsies showed that PD1 blockade induced the expression of PD1-regulated genes after treatment. Interestingly, cemiplimab treatment boosted immune cell activation only in responders patients (i.e. B- and T-cells), according to the host antitumor response expected upon PD-1 targeting. Focusing on peripheral markers, total regulatory T cells (Tregs) early increased in non-responders patients, but dissecting specific antigens of Treg populations, we identified the specific T-cell costimulator (ICOS) subpopulation with a different trend in responders and non-responders. ICOS-positive cells, indeed, increased their abundance in the peripheral blood only of responder patients, in line with recent data showing ICOS cells as positive markers of ICI efficacy in lung cancer. Finally, TNF-α *sera* levels decreased after treatment only in responder patients, in line with its role as a determinant of resistance to PD1 targeting.

Conclusions: Our results provided new key elements to monitor response to therapy, determining putative markers to early define responsiveness to ICI in cSCC patients and suggest how to improve their clinical management.

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1144P High-plex spatial profiling of cutaneous squamous cell carcinoma to identify biomarkers associated with clinical outcomes: The cMIC study

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Background: Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer. Early stage cSCC is often cured with simple resection +/- radiotherapy, though some can recur, most commonly in immunosuppressed (IS) individuals. In advanced cSCC, approximately 50% of patients develop primary resistance to immune checkpoint inhibitors (ICI). There is a need to identify biomarkers by characterising the tumour microenvironment (TME) within different clinical groups.

Methods: Our retrospective study profiled whole tissue sections from n=50 patients from the Princess Alexandra Hospital. Study groups (G) included immunocompetent patients with (G1) de novo, localised cSCC (n=10), (G2) regional nodal metastasis (n=10), (G3) locoregional recurrent disease (n=10), (G4) recurrent/metastatic disease treated with ICI (n=10) and (G5) IS patients (n=10). In this exploratory study, we designed a high-dimensional Nanostring GeoMx Digital Spatial Profiling (DSP) experiment which enabled simultaneous readout of >80-plex proteins in the TME to profile immune cell content, immuno-oncology drug targets, cell lineage and architecture. These features within the TME were measured against the clinical groupings to identify differentially expressed proteins between the groups for future biomarker analysis.

Results: Our preliminary analysis has identified distinct cell phenotype compositions within the TME associated with the clinical groupings. Within the tumour there was a reduction in expression of VISTA and STING immune signaling markers in localized disease (G1/2 vs G4). This was most notable within the stomal compartments. G3/4 had a lower expression of IDO1/STING/VISTA immune signaling markers compared with G5 IS individuals. Moreover, we identified an increased metabolic activity in patients with resistant disease.

Conclusions: Our study highlights the utility of spatial proteomic profiling of the TME in cSCC for the identification of biomarkers associated with biologically distinct clinical groups. This study provides the foundation work for prospective validation of putative biomarkers associated with therapy response and resistance.

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1145P Clinical characteristics and survival of patients with advanced Merkel cell carcinoma (MCC) treated with avelumab: Analysis of a prospective German MCC registry (MCC TRIM)

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Background: MCC is a rare and aggressive form of skin cancer. Avelumab was the first immunotherapy approved for adult patients with metastatic MCC in Europe. We investigated the clinical characteristics and survival outcomes of patients with MCC at the start of and after avelumab treatment.

Methods: Data from 684 patients in a prospective, noninterventional, multicenter, dynamic cohort of the MCC TRIM study who were enrolled after March 2019 were analyzed. Primary data from a study-specific electronic case report form and secondary data from the German national skin cancer registry ADOReg were combined. At data cutoff (Sept 30, 2022), patients diagnosed with unresectable stage III or IV MCC prior to avelumab treatment were included in this analysis. Survival outcomes were assessed by the Kaplan-Meier method.

Results: Of 116 patients with MCC receiving avelumab, 35.3% had stage III disease and 64.7% had stage IV. The mean (SD) age at initial diagnosis was 74.5 (10.4) y, and 62.1% of patients were male. Most patients had an Eastern Cooperative Oncology Group performance status $\leq$1 (76.7%); 21.6% had an immunosuppressive condition or took immunosuppressive medication. Diabetes was the most common comorbidity (23.3%). At a median follow-up of 28.75 mo (95% CI, 20.5-32.5 mo), median overall survival (OS) was not reached in stage III patients and was 52.0 mo (95% CI, 15.4 mo-not estimable [NE]) in stage IV patients. Median (95% CI) progression-free survival (PFS) was 11.8 mo (5.6 mo-NE) in stage III patients and 9.3 mo (3.5-13.7 mo) in stage IV patients. Most patients (86.2%) received avelumab as first-line (1L) therapy; of these, 37.0% had stage III disease and 63.0% had stage IV. Median OS with 1L avelumab was not reached in the stage III or IV group, but fewer events were observed in stage III vs stage IV patients (16.2% vs 36.5%); median PFS (95% CI) was 15.6 mo (5.6 mo-NE) and 7.3 mo (3.0-13.7 mo), respectively.

Conclusions: Demographics observed in MCC TRIM reflect those of the typical advanced MCC population. This nationwide study indicates that avelumab is effective in stage III and IV patients with advanced MCC in routine clinical practice.

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1146P Updated results from POD1UM-201: A phase II study of retifanlimab in patients with advanced or metastatic Merkel cell carcinoma (MCC)

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Background: Retifanlimab, a programmed death receptor-1 (PD-1)—blocking antibody, was recently approved in the United States for treatment of adult patients (pts) with metastatic or recurrent locally advanced MCC based on results from the open-label, single-arm POD1UM-201 study (NCT03599713). In the primary analysis including 65 chemotherapy-naive pts, responses were observed in 52% (95% CI: 40—65) of pts with 62% of responses exceeding 12 months by landmark analysis (ZYNYZ™ prescribing information). Safety was as expected for the PD-(L)1 inhibitor class. We present updated results on the full cohort of 101 pts.

Methods: Eligible pts were ≥18 years of age, had metastatic or recurrent unresectable loco-regional MCC, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and had not received prior MCC systemic treatment. Retifanlimab 500 mg was administered intravenously every 4 weeks (Q4W) for up to 2 years without premedication prophylaxis. The primary endpoint was overall response rate assessed by independent central review per RECIST v1.1. Secondary endpoints included duration of response, disease control rate, progression-free survival, overall survival, safety, and pharmacokinetics.

Results: The study enrolled 101 pts with chemotherapy-naive advanced/metastatic MCC, with the last pt initiating treatment on 24 June 2021. Pt and disease characteristics were representative of the typical MCC epidemiology. The median age was 71 (range, 38—90) years, 68 (67%) pts were male and predominantly white, 74 (73%) had an ECOG of 0, and one pt was HIV positive. A total of 91 (90%) pts had Stage IV disease, 69 (68%) had prior surgery, and 37 (37%) had prior radiotherapy. In evaluable tumour samples, Merkel cell polyomavirus was detectable in 73/96 (76%) and 83/95 (87%) had PD-L1 expression ≥1%. Efficacy and safety results for the full study population will be presented.

Conclusions: Retifanlimab has shown notable clinical activity with an acceptable safety in advanced/metastatic chemotherapy-naive MCC, and is a promising new treatment option for eligible pts.

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1147P First-line treatment (tx) patterns and overall survival (OS) of patients (pts) with advanced Merkel cell carcinoma (aMCC) in England from 2013-2022: Results of a nationwide observational cohort study

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Background: MCC is a rare, aggressive cutaneous neoplasm. In September 2017, the European Commission approved avelumab (Ave) for the tx of metastatic MCC based on demonstrated meaningful survival benefit. This study sought to investigate tx patterns and OS of pts with aMCC (stage III/IV) in the National Cancer Registration Dataset (NCRD) in England.

Methods: This cohort included pts ≥18 years and newly diagnosed with stage III/IV MCC (ICD-O: C44, 8247 morphology) between January 2013 and December 2020 in

the NCRD in England and followed up until May 2022. Summary and descriptive statistics were calculated for categorical and continuous variables. The Kaplan-Meier method was used to estimate median OS from diagnosis date (overall) and OS from initiation of 1L tx stratified by regimens received and by stage at baseline.

Results: A total of 667 pts with aMCC were included. Mean age (SD) was 77.4 years (10.3), most pts were male (61.0%), and 14.1% were immunocompromised. At diagnosis, 66.3% and 33.7% had stage III and IV disease, respectively. The mean (SD) baseline modified Deyo-Charlson Comorbidity Index was 4.0 (1.8). Overall, 478 pts (71.7%) died during follow-up; median OS from diagnosis was 18.4 months (95% CI, 15.6-20.9). In total, 199 pts (29.8%) received 1L tx (39.2% Ave, 60.8% non-Ave). When stratified by stage, 26.9% of stage III pts received systemic tx (39.5% Ave, 60.5% non-Ave); the corresponding numbers for stage IV pts were 35.6% (38.7% Ave, 61.3% non-Ave). OS from 1L initiation is presented in the table.

Table: 1147P

OS from 1L initiation	Stage III		Stage IV	
	Ave	Non-Ave	Ave	Non-Ave
n	47	72	31	49
Deaths during follow-up, n (%)	20 (42.6)	54 (75.0)	16 (51.6)	40 (81.6)
Median OS months (95% CI)	37.8 (12.9-NE)	13.0 (8.3-19.6)	19.9 (5.0-NE)	7.2 (5.9-9.1)
12-months survival rate, % (95% CI)	67 (51-79)	52 (40-63)	55 (36-70)	31 (18-44)
18-months survival rate, % (95% CI)	56 (39-69)	41 (29-52)	52 (33-67)	24 (14-37)
24-months survival rate, % (95% CI)	56 (39-69)	35 (24-46)	48 (29-64)	NE

NE, not estimable.
*Non-Ave includes 95.5% chemotherapy and 4.5% other treatment.

Conclusions: This nationwide real-world study of pts with aMCC demonstrates the effectiveness of Ave with considerably prolonged survival in pts with both stage III and stage IV disease. The study findings validate results from the JAVELIN Merkel 200 clinical trial and other observational studies.

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1148P Avelumab as second-line or later (2L+) treatment (tx) in patients (pts) with metastatic Merkel cell carcinoma (mMCC): Real-world tx patterns in France

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Background: Avelumab has been approved worldwide for the tx of mMCC based on results from the JAVELIN Merkel 200 trial. The French Health Technology Assessment Agency requested the collection of real-world data from pts with mMCC from a comprehensive registry; data for overall survival (OS), tx patterns, and time to tx failure (TTF) with 2L+ avelumab are reported here.

Methods: This retrospective noninterventional study evaluated pts with mMCC in France using 2 databases: CARADERM (French national database of rare dermatologic cancers) and Système National des Données de Santé (SNDS; national healthcare database). Pts with mMCC who initiated 2L+ avelumab outside a clinical trial between Aug 2016 and Dec 2019 were eligible. Pts were followed up for 24 months from start of avelumab. TTF was defined as time from avelumab initiation to discontinuation for any reason, including progression, toxicity, or death.

Results: 180 pts received 2L+ avelumab, including 112 pts in the CARADERM database and 68 additional pts after SNDS linkage. Median age at diagnosis was 74.0 years; 66.7% of pts were male, and 98.3% had received first-line (1L) chemotherapy alone. The most common 1L tx in evaluable pts (CARADERM database) were cisplatin or carboplatin + etoposide (59.6%) and etoposide alone (12.8%). Median follow-up was 13.1 months. Median OS from start of 2L+ avelumab was 14.6 months (95% CI, 9.9-21.3 months). Of the evaluable pts (n=175) at the last follow-up, 9.1% were receiving avelumab, 31.4% had discontinued tx, and 57.1% had died; 2.3% were lost to follow-up. Median TTF was 8.5 months (95% CI, 6.2-10.5 months) overall; in CARADERM and non-CARADERM database pts, median TTF was 9.9 months (95% CI, 6.5-14.3 months) and 6.5 months (96% CI, 4.4-9.5 months), respectively. 12- and 24-month rates of pts without tx failure were 38.9% (95% CI, 31.6%-46.1%) and 15.5% (95% CI, 10.4%-21.4%), respectively. In evaluable pts who discontinued avelumab (CARADERM only), 30.3% received no subsequent tx, 50.6% received chemotherapy alone, and 19.1% received other tx.

Conclusions: These data provide insights into tx patterns among pts with mMCC receiving 2L+ avelumab in routine clinical practice in France.

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1149P Prognosis for patients with metastatic Merkel cell carcinoma with a complete response on avelumab treatment

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Background: Immune checkpoint inhibitor (ICI) treatment of patients with metastatic Merkel cell carcinoma (mMCC) has shown high response rates, ranging from 33%-73%. The ideal duration of treatment is however currently unknown. We aimed to evaluate if avelumab treatment for mMCC can be safely stopped after 1 year of treatment and confirmed complete response (CR) by FDG-PET/CT.

Methods: Patients who received >one dose of avelumab treatment for mMCC between November 2017 and February 2022 were included in this study. Treatment was discontinued in case of a FDG-PET/CT confirmed CR after 1 year (26 cycles) of avelumab, or a CR and unacceptable toxicity earlier on. Primary endpoint was recurrence free survival (RFS).

Results: Sixty-five patients were included: 25 (38%) had a FDG-PET/CT confirmed CR at discontinuation of avelumab. In those 25 patients, reasons for discontinuation of treatment were completion of 1 year of treatment in 13 patients (52%), toxicity in 5

patients (20%) and patient preference in 7 patients (28%). Median duration of treatment in this group was 11 months (IQR 6.1-11.7). Median follow-up was 27 months (IQR 15.8-33.8). The 12 months RFS was 88% (95% CI 0.74-1) and median RFS was not reached. Two patients (9,5%) had a recurrence, at 4 and 7 months after discontinuation of treatment.

Conclusions: Avelumab treatment for patients with mMCC can be safely discontinued after one year of treatment and a PET/CT confirmed CR, as responses appear to be durable, with a 12 months RFS of 88%.

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1150P Transforming growth factor-beta-1 and soluble co-inhibitory immune checkpoints as putative drivers of immune suppression in advanced basal cell carcinoma

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Background: Basal cell carcinoma's (BCC) mortality rate is low; however, it is associated with substantial morbidity. Transforming growth factor-b1 (TGF-b1) is a key player in cell proliferation, differentiation, apoptosis, and immune regulation. TGF-b1 is associated with immunosuppression and resistance to immunotherapeutic drugs. The current study compared levels and possible associations between systemic soluble ICMs (sICMs) and a group of humoral modulators of immune suppressor cells in a cohort of patients with advanced BCC, (n=40) and a group of healthy control subjects (n=20).

Methods: We measured sICMs and immunosuppressive humoral modulators by using multiplex bead array or ELISA procedures. The sICMs comprised seven co-inhibitory (CTLA-4, BTLA, LAG-3, PD-1, PDL-1, PDL-2, and TIM-3) and eight co-stimulatory (CD27, CD28, CD40, CD80, CD86, GITR, GITRL, and ICOS) proteins, as well as the two dual-active sICPs, HVEM and TLR2. The 7 humoral modulators of immunosuppressor cells included arginase 1, fibroblast activation protein (FAP), RANTES (CCL5), interleukin-10, TGF-b1, and the M2-type macrophage biomarkers, soluble CD163 (sCD163) and sCD206.

Results: Plasma levels of six co-inhibitory sICPs, sCTLA-4, sLAG-3, sPD-1, sPD-L1, and sTIM-3 and sPD-L2 were significantly elevated in the cohort of BCC patients ($p<0.001$-$p<0.00001$), while that of sBTLA was significantly decreased ($p<0.006$). Of the co-stimulatory sICPs, sCD27 was significantly increased ($p<0.0002$) in the cohort of BCC patients, with the levels of the others essentially comparable with those of the control patients; of the dual active sICPs, sHVEM, sTLR2 was elevated ($p<0.00001$) and TLR2 comparable with the control group. Correlation heat maps revealed selective, strong associations of TGF-b1 with seven co-stimulatory (z=0.618468-0.768131) and 4 co-inhibitory (z=0.674040-0.808365) sICPs, as well as with sTLR2 (z=0.696431).

Conclusions: Notwithstanding the association of BCC with selective elevations in the levels of a large group of co-inhibitory sICPs, our novel findings also imply the probable involvement of TGF-b1 in driving immunosuppression in this malignancy, possibly via activation of regulatory T cells.

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1151P Characteristics and treatment outcomes in cutaneous adnexal carcinomas

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Background: Cutaneous adnexal tumors comprise a heterogenous group of both benign and malignant tumors evolving from the four primary adnexal structures. Malignant adnexal tumors encompass a variety of histologic subtypes with varying clinical presentation. Due to the rarity of these conditions, incidence and prevalence is not well understood. In a retrospective analysis, estimated five-year Overall Survival (OS) and Disease-Free Survival (DFS) were estimated at 73% and 98%, respectively. There is a paucity of data surrounding the preferred clinical management of cutaneous adnexal tumors due to the rarity of these entities.

Methods: Patients with malignant adnexal tumors were identified using the National Cancer Database (NCDB). We examined demographic, clinicopathologic, and treatment information. Excluded from our cohort were patients with metastatic or unknown disease stage, positive or unknown margin status, unknown radiation and/or chemotherapy status, and unknown vital status. Chi-square analyses were used to assess differences across sebaceous versus non-sebaceous histologies. Multivariable Cox proportional hazard models were used to evaluate the effects of treatment modalities on overall survival after controlling for relevant covariates (age, race, and stage).

Results: 3,694 patients were included in the final analysis. The most prevalent malignant cutaneous adnexal tumor included sebaceous carcinoma (n=1699, 46%), eccrine porocarcinoma (n = 568, 15.4%), and skin appendage carcinoma (n =415, 11.2%). In patients with fully resected cutaneous adnexal tumors with negative surgical margins, multivariable results showed that receipt of adjuvant radiation was associated with statistically significantly longer survival compared to not receiving radiation (HR .76 (95%CI 0.61 − 0.96)). Non-sebaceous histology was also associated with longer survival than sebaceous histology (HR 0.78 (95% CI 0.69 − 0.88)). After stratifying by histologic groups, adjuvant radiation was associated with longer overall survival in sebaceous carcinoma (HR 0.62 (95% CI 0.42 − 0.92)), while receipt of adjuvant radiation in non-sebaceous histology groups was not associated with overall survival (HR 0.85 (95% CI 0.65 − 1.13)). Use of adjuvant chemotherapy following R0 resection was not associated with overall survival in the sebaceous group, while in the non-sebaceous group, chemotherapy was associated with shorter overall survival (HR 3.92 (95% CI 1.94 − 7.92)).

Conclusions: Acknowledging the limitations of a retrospective evaluation of real-world data, there does not appear to be a benefit for adjuvant chemotherapy after R0 resection in cutaneous adnexal carcinomas. Alternatively, omission of adjuvant radiotherapy was associated with an increased risk of mortality.

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1152P Association of immune-related adverse events (irAE) requiring glucocorticoids (GCs) with outcome and biomarkers in advanced cutaneous malignant melanoma (CMM) treated with immune checkpoint inhibitors (ICI)

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Background: Therapy with ICIs have been successful with long-term survival benefits for some CMM patients. However, ICIs may also cause irAEs which could be serious and demand the prescription of GC. The combination of ICIs improves treatment efficacy but increases the risk for irAEs. The impact of GC treated irAE (GC-irAE) on efficacy of ICIs is not fully understood and biomarkers assessing the risk for irAE requiring GC treatment are not available. We studied a cohort of patients with metastatic CMM treated with ICI to evaluate if GC-irAE impact clinical outcome. We also investigated whether inflammation proteins in baseline plasma samples may predict the development of GC-irAE.

Methods: This is a cohort study performed at Karolinska University Hospital in Sweden including 98 subjects with advanced CMM (M1a-d), who received anti-PD1 alone (n=88), anti-PD1+ epacadostat (clinical trial, n=3) or ipilimumab + nivolumab (n=8) as 1st line therapy in most cases (85%). Clinical data regarding the use of GC to treat irAE were collected retrospectively. If GC-irAE occurred, the type of irAE was assembled. Baseline plasma samples from 58 of the 98 patients were analyzed utilizing the OLINK inflammation protein panel platform.

Results: In the whole cohort 65% were male and median age was 70 years. The median PFS and OS for the whole cohort were 12 and 38 months, respectively. Of 98 patients 44% developed GC-irAE. The most common GC-irAE were hypophysitis (11%), dematitis (7%), colitis (7%) and pneumonitis (6%). The median time to GC treatment start after ICI therapy was 146 days. The median PFS and OS for GC-irAE vs patients without GC-irAE were 24 and 73 months vs 5 and 18 months, respectively. Patients developing hypophysitis had a longer OS compared to other patients. High baseline levels of IL8 and S100A12 were associated with worse OS and high levels of DNER was associated with better OS and with risk of developing hypophysitis.

Conclusions: Patients developing a GC-irAE had significantly increased PFS and OS compared to the other patients. Further studies on potential biomarkers for risk of developing hypophysitis are warranted to timely avoid serious complications.

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1153P Incidence and characteristics of immunotherapy related adrenal insufficiency in a monocenter, pan-cancer cohort of 4314 patients

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Background: The rapidly developing field of immune checkpoint inhibitors (ICI) necessitates insights in long-term adverse events (AE), like ICI related adrenal insufficiency (irAI). In meta-analyses of clinical trials, primary AI (PAI) incidence is likely overestimated (4-7% for combination ICI), as PAI and secondary AI (SAI) are rarely distinguished.

Methods: In this monocenter, pan-cancer retrospective analysis, patients with a single malignancy who received anti-PD-(L)1 and/or anti-CTLA-4 therapy before September 10th 2021 and received (hydro/fludro)cortisone were identified. irAI was considered when AI was diagnosed in the absence of adrenal metastases, -surgery, -radiotherapy and long-term corticosteroid use. Diagnosis of PAI was based on cortisol <13 µmol/l and ACTH >60 ng/l, synacthen test and/or presence of mineral-corticoid dysfunction. SAI was diagnosed when ACTH <60 ng/l with low cortisol or in case of confirmed hypophysitis. Other irAI cases were labeled as unknown origin.

Results: Of 4314 patients with ICI, 160 (3.7%) developed irAI, consisting almost exclusively of SAI (3.1%) rather than PAI (0.05%, P<.001). irAI incidence was significantly higher for combination treatment versus anti-PD-(L)1 monotherapy (OR 4.95, 95% CI 3.55-6.97, p<.001). SAI presented as hypophysitis in 38% and as isolated adrenal deficiency in 62% of cases. Age, gender, metastatic status of the malignancy, history of endocrine or autoimmune disorder and other grade 3-4 AEs did not differ between PAI and SAI, or hypophysitis and IAD cases.

Table: 1153P Incidence of immunotherapy related adrenal insufficiency

	Anti-PD-(L)1	Anti-CTLA-4	Combination anti-PD-1 + anti-CTLA-4	Total
Melanoma	3.8% 29/768	3.1% 10/326	11.1% 59/533	6.7% 98/1466
Lung cancer	1.0% 12/1199	0	4.5% 2/44	1.1% 14/1243
Urethral and renal cancer	1.2% 3/246	0% 0/1	10.6% 15/142	4.6% 18/395
Breast cancer	2.0% 5/254	0	14.3% 2/14	2.6% 7/268
Colorectal cancer	2.4% 2/85	0	3.7% 4/108	3.1% 6/193
Bladder cancer	3.6% 4/111	0% 0/10	10.0% 5/50	5.4% 9/168
Other	0.6% 3/484	0% 0/2	5.0% 5/101	1.4% 8/581
Total	1.8% 58/3147	2.9% 10/339	9.3% 92/992	3.7% 160/4314

Conclusions: In contrast to what is suggested in trials, ICI-induced primary adrenal insufficiency was extremely rare in this real-world analysis, while secondary adrenal insufficiency was dominantly prevalent. Combination therapy leads more frequently to irAI. In conclusion, an improved understanding of irAI is needed, which may lead to improved diagnosis, and is essential for the development of predictive biomarkers.

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1154P Thromboembolic events in patients with melanoma receiving immune checkpoint inhibitors: Incidence and risk factors

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Background: Immune checkpoint inhibitors (ICI) improve survival for multiple tumor types, but are possibly associated with thromboembolism (TE). Nonetheless, for patients with melanoma specifically, the risk of TE and its association with treatment setting remain largely unknown. Therefore, we investigated the incidence of TE and associated risk factors in two groups of patients with melanoma who received either palliative or adjuvant ICI therapy between April 2016 and September 2021.

Methods: In this cohort study, baseline characteristics and TE incidences (combined incidence of venous (VTE) and arterial (ATE) thromboembolism) were retrospectively collected from patients with stage III and IV melanoma included in the MULTOMAB trial (NL55840.078.15) until 2 years after the first ICI dose or censoring (switch to alternative anticancer treatment or loss to follow-up). The association between patient characteristics and TE occurrence was analyzed by the Fine-Gray model with backward selection using all-cause death as competing risk.

Results: Out of the 458 included patients, 28 (6%) patients developed a TE during a median follow-up of 17 months, consisting of 18 (4%) VTEs and 10 (2%) ATEs. Median time to TE occurrence was 5.2 months. In the advanced disease (N=315) and adjuvant (N=143) cohort, 23 (7%) and 5 (3%) patients developed TE, respectively. The incidence rates of TE per 100 person years was 4.9 in the total cohort, and 6.4 and 2.4 in respectively the advanced disease and adjuvant cohort. In the advanced disease cohort, BMI (sHR: 1.1 per point BMI increase [95% CI, 1.02 − 1.1, P=0.007]) and nivolumab + ipilimumab combination therapy (sHR 2.5 versus monotherapy [95% CI, 1.08 − 5.6, P = 0.03]) were risk factors for TE occurrence.

Conclusions: In patients with melanoma receiving ICI therapy, TE seems to occur predominantly in patients with advanced disease. In this treatment setting, ICI combination therapy and higher BMI are risk factors for TE. Although this suggests that particularly increased tumor load is a main predisposing factor, possible prothrombotic effects of particularly ICI combination therapy cannot be ruled out. Future research should further study the etiology of TE during ICI therapy while taking disease burden into account.

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1155P Application of novel machine learning to predict immunotherapy related toxicities for metastatic melanoma patients from baseline 18F-FDG PET/CT scans

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Background: Immunotherapy (I/O) has been shown to provide durable responses in metastatic melanoma (MM) patients, however, I/O related adverse events (irAE) are frequently experienced and can be challenging. ^{18}F-FDG PET/CT medical imaging, has the potential to predict both tumor response and irAE non-invasively. Developing machine learning (ML) models to quantify features derived from medical images represents an opportunity to predict toxicity and influence clinical patient care. This study implements automated organ segmentation and ML methods using ^{18}F-FDG PET/CT images to predict irAE for patients with MM.

Methods: ^{18}F-FDG PET/CT scans from 128 patients with MM were retrospectively collected between 2009 and 2021 (IRB approved protocol). Patients received $\geq$ 1 course of I/O. Organs were segmented automatically using AIQ Solutions technology. Segmented regions were used to quantify FDG organ uptake and correlate with toxicities including adrenal insufficiency, alanine aminotransferase increase, colitis/diarrhea, pancreatitis, and thyroid dysfunction. Imaging features were extracted from organs at baseline (BL) and early follow-up. Organ uptake and changes across time were evaluated for predicting irAE. A random forest model was trained using BL organ uptake to predict occurrence of an irAE. Performance was evaluated using area under the receiver operating characteristic curve (AUC).

Results: The patients (89 male and 39 female) average age was 63 (range 23-88). Overall, there were 105 irAE grouped per organ for univariate analysis, with the high frequency of hypothyroidism, raised alanine aminotransferase and colitis/diarrhea. The overall AUC for prediction of any irAE based on the BL scan was 0.76. Change in 95th percentile between pre-I/O work up and subsequent scans of SUVs was predictive of irAE in thyroid (AUC=0.95) and bowel (AUC=0.94).

Conclusions: Our results indicate that ML using quantitative features from ^{18}F-FDG PET/CT imaging has the potential to identify irAE early. Importantly, there may be imaging features on the BL scan that indicate MM patient's likelihood of developing an irAE before starting I/O. This warrants further investigation in a prospective setting.

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1156P Immune-related adverse events in a nationwide cohort of melanoma patients treated with adjuvant anti-PD1: Seasonal variation and association with outcome

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Background: The introduction of immune checkpoint inhibitors (ICIs) has transformed the treatment of advanced melanoma. However, treatment comes with the risk of immune-related adverse events (irAEs). Especially now that immunotherapy has moved to the adjuvant setting, doctors and patients must weigh potential benefits versus risks based on as much available information as possible. Real-world data are essential for decision-making.

Methods: A nationwide study on irAEs in Danish real-world patients treated with adjuvant anti-PD1 therapy for resected stage III-IV melanoma from 2018-2022. Data were retrieved from two national databases, the IMMUNOTOX database and the Danish Metastatic Melanoma Database (DAMMED).

Results: Data from 792 patients were included. The majority of patients were male (55%) with a median age of 62 (range 16-88) at time of first treatment. In total, 697 patients (88%) experienced an irAE, the most common being fatigue (44%). Low-grade irAEs (grades 1-2) were very common, whereas different subtypes of severe irAEs (grades 3-5) were observed in 0.3-4%. In total, 121 patients (15.3%) experienced severe irAEs out of which five patients (0.6%) died due to irAE. Having at least one irAE was associated with a lower risk of melanoma relapse. Seasonal variation was observed with more frequent debut of organ-specific (gastrointestinal, ocular, musculoskeletal, and thyroid) irAEs during summer, while mild skin toxicities were more frequent in the winter period.

Conclusions: In this nationwide cohort of real-world adjuvant melanoma patients, we observe that having any grade of irAEs, as well as a severe irAE, is slightly more frequent compared to clinical phase III trials and comparable to previously published real-world studies. Further, the risk of relapse from melanoma is lower among patients experiencing an irAE. Finally, significant seasonal variation in irAE incidence was observed.

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1157P Corticosteroids and second-line immunosuppressants for immune-related adverse events and melanoma survival

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Background: Recent studies indicate an association between immunosuppressive medication for immune-related adverse events (irAEs) and impaired survival. Whether this is related to corticosteroids or second-line immunosuppressants (IS) is unknown. We assessed the association of immunosuppressive regimens with survival in patients with melanoma.

Methods: Patients with advanced melanoma who received IS for irAEs induced by first-line anti-PD-1+/-anti-CTLA-4 were included from 11 Dutch and Belgian hospitals. Associations of cumulative and peak doses of corticosteroids and use of second-line IS with progression free survival (PFS) from start of IS and overall survival (OS) since immune checkpoint inhibitor (ICI) initiation were assessed using multivariable Cox regression. Analyses were adjusted for sex, age, stage, performance status, LDH, ICI type and irAE type.

Results: Among 382 patients with irAEs, 255 had IPI+NIVO-induced irAEs and 127 had anti-PD-1-monotherapy-induced irAEs. 268 patients received only corticosteroids; 113 patients additionally received second-line IS. High peak corticosteroid dose was associated with worse PFS (HR 1.47 95%CI 1.00-2.16) and OS (HR 2.17 95%CI 1.49-3.16). Cumulative corticosteroid dose was not associated with PFS or OS (Table). Use of second-line IS was associated with worse PFS (HR 1.57 95%CI 1.04-2.38); for OS, this was the case when correction for cumulative corticosteroid dose (HR 1.57 95%CI 1.06-2.33), but not when correcting for peak corticosteroid dose (HR 1.25 95%CI 0.84-1.85). Subgroup analyses will be presented.

Table: 1157P Association of immunosuppressive irAE management with survival

	PFS HR (95%CI) since immunosuppression	OS HR (95%CI) since ICI
Univariable		
Steroid peak dose (per 100mg)	**1.90 (1.39-2.61)**	**1.89 (1.39-2.57)**
Steroid cumulative dose (per 1000mg)	1.06 (1.00-1.12)	0.95 (0.90-1.01)
2nd-line IS	**1.83 (1.32-2.52)**	**1.43 (1.04-1.97)**
Multivariable including steroid peak dose and 2nd-line IS		
Steroid peak dose (per 100mg)	1.47 (1.00-2.16)	**2.17 (1.49-3.16)**
2nd-line IS	**1.57 (1.04-2.38)**	1.25 (0.84-1.85)
Multivariable including steroid cumulative dose and 2nd-line IS		
Steroid cumulative dose (per 1000mg)	1.01 (0.94-1.08)	0.95 (0.89-1.02)
2nd-line IS	**1.64 (1.09-2.47)**	**1.57 (1.06-2.33)**

Conclusions: Our data suggest that use of second-line immunosuppressants and high peak corticosteroid dose are associated with impaired survival among patients requiring IS for irAEs, while there is no association between cumulative corticosteroid dose and survival.

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1158P Association of corticosteroid (CS) exposure with treatment failure in patients (pts) with advanced melanoma treated with immune checkpoint inhibitors (ICIs)

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Background: Around 25% of pts with advanced melanoma lose established responses to ICIs. Recent studies suggest that systemic CS, predominantly used for managing immune-related adverse events (IRAEs), could be a cause of acquired resistance to ICIs, with a detrimental effect on survival. The impact of systemic CS on pts with initial response to ICIs remains unknown.

Methods: This is a retrospective study of 113 pts with advanced melanoma treated with ipilimumab and nivolumab (I/N) at The Royal Marsden Hospital between 2013 and 2021 who achieved initial disease stability or disease response. Pts were divided into cohort A (sustained response to I/N, N = 72) and cohort B (loss of response to I/N, N = 41). The daily CS exposure was evaluated from cycle 1 of I/N (prednisolone equivalent doses). STATA was used for statistical analysis.

Results: Most pts had cutaneous melanoma (73.6% in cohort A vs 75.6% in cohort B), stage IV disease (91.7% vs 95.1%) and were treatment-naïve (86.1% vs 85.4%). More pts in cohort B had a BRAF mutation (46.3% vs 38.9% in cohort A), high LDH (29.3% vs 19.4%), brain (24.4% vs 20.8%) and liver metastases (26.8% vs 18.1%) at baseline. The median number of I/N cycles was 4 in cohort A and 3 in cohort B. Up to 27 pts in cohort A (38%) and 24 in cohort B (59%) discontinued treatment during the induction phase due to toxicity. All pts in our study were given CS for IRAEs management. Up to 97.6% of pts in cohort B received CS, compared to 69.4% in cohort A. Pts who were treated with CS had a significantly higher rate of treatment failure (44.4% vs 4.4%, $p < 0.001$). The average cumulative CS dose per patient in cohort A was 4830 mg compared to 4201 mg in cohort B ($p = 0.897$). The average daily CS dose in cohort A was 32 mg/day compared to 30 mg/day in cohort B ($p = 0.889$). Pts unexposed to CS have a trend for longer overall survival (NR vs NR, HR 0.25 [0.03-1.92]).

Conclusions: Our study suggests a correlation between systemic CS use and higher rates of treatment failure, as well as a trend for shorter survival in pts with advanced melanoma treated with I/N. The dose of CS was similar in both cohorts. However, as this is a single centre retrospective experience, these findings should be confirmed in larger studies.

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1159P Characterization of melanoma of unknown primary in the era of immunotherapy and targeted therapy in Spain: Results from the prospective real-world study GEM 1801

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Background: The clinical presentation of patients (pts) diagnosed with melanoma of unknown primary (MUP) is not clearly known, like their therapeutic assignment and their evolution in terms of responses obtained, toxicity, and relapse profile in the actuality.

Methods: GEM1801 is a prospective observational study including pts with melanoma that analyzes the clinical and pathological disease presentation patterns, the different lines of treatment choices and the health outcomes derived from treatments. Here we focus on the clinical and evolution characterization of pts diagnosed with MUP.

Results: From Aug 2018 to Dec 2022, 893 evaluable pts were enrolled, 133 (14.9%) being MUP. Median age was 63 years (range 24-93), 81 (60.9%) male. Distal metastases were present in 117 (88%) pts with most (50.4%) having $\geq$ 3 affected organs, including ganglia (53.4%), lung (41.4%) or brain (30.1%). LDH was elevated in 50 (37.6%) pts. BRAF was mutated in 79 (54.9%) pts. Adjuvant therapy was administered to 28 (21.1%) pts with MUP, being immunotherapy less frequently prescribed than in pts with known primary (17.3% vs 27.1%; p=0.017). Immunotherapy was also less frequent for the 1st line in the metastatic/locally advanced setting (53.6% vs 64%; p=0.039). Conversely, more pts with MUP were enrolled in clinical trials exploring combo of immunotherapy and targeted therapy (9.1% vs 4.8%; p=0.074).

Table: 1159P

	N, (%)	Median PFS (95% CI), months	Median OS (95% CI), months
BRAF + IT	17 (12.8)	18.9 (4.4-NR)	24.9 (24.1-NR)
BRAF + TT	40 (30.1)	13.3 (7.1-27.5)	13.9 (8.3-NR)
BRAF - IT	41 (30.8)	6.7 (3.5-NR)	17.9 (9.6-NR)

IT = Immunotherapy; TT = Targeted therapy.

Conclusions: MUP in Spain comprises a population with a multiorgan presentation and frequent brain metastasis, which was followed by worse outcomes than the general melanoma population. Having MUP diagnosis seems to influence the therapeutic assignment, specially for immunotherapy schemes.

Clinical trial identification: NCT03605771.

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1160P Methods of nivolumab administration in advanced melanoma: A comparison of patients' clinical outcomes treated with flat dose or weight-adjusted dose, FLATIMEL study

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Background: Nivolumab obtained marketing authorization in advanced melanoma (AM) with weight-adjusted (WA) dose administration (3 mg/kg/2 weeks) [1]. Based on modeling studies (no clinical data), EMA advised in 2018 that nivolumab should be administered in flat dose regimen (240 mg/2 weeks or 480 mg/4 weeks) [2 3]. The aim of the FLATIMEL study was to compare clinical outcomes of AM patients treated with both nivolumab dose calculation methods.

Methods: AM patients were prospectively included in the national multicenter MelBase database since 2013 (NCT02828202). Patients treated by nivolumab monotherapy in first line enrolled in MelBase were included in our study. We compared safety and efficacy of nivolumab in 2 groups of patients treated by flat or WA dose. The primary endpoint was the incidence of immune-related adverse events (irAEs) of grade $\geq$ 3. Secondary endpoints were incidence of irAEs of any grade, overall survival (OS) and progression free survival (PFS). Inverse probability of treatment weighting was used to balance groups on their baseline characteristics.

Results: Between June 2015 and January 2022, 546 patients followed in MelBase were included in this study: 252 in the flat dose group and 294 in the WA group. Patients with metastatic organs $\geq$ 3 ($p<0.0001$), brain metastasis ($p=0.0005$) or M1c AJCC (7th edition) tumor stage ($p=0.001$) were more frequent in the WA group. After weighting, no difference between both groups was observed for irAEs grade $\geq$ 3 (n=65, 12%), ($p= 0.51$), whereas irAEs of any grade (n=314, 57.5%) were more frequent in the flat dose group ($p=0.044$), especially muco-cutaneous and endocrine toxicities. Median OS was 32.3 and 20.6 months in flat dose and WA group respectively ($p= 0.004$), and median PFS was 3.5 and 2.8 months, respectively ($p= 0.003$).

Conclusions: There was no difference in the incidence of severe irAEs between AM patients treated by WA or flat dose of Nivolumab. Survival results were superior in the flat dose group, which may be explained by a temporal bias. Cost effectiveness studies are necessary.

Legal entity responsible for the study: MELBASE database.

Funding: INCa, Roche, BMS, Novartis, MSD, Amgen.

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1161P Therapeutic outcome of molecular profiling of melanoma patients resistant to standard treatment: Real-world data

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Background: Therapeutic options for advanced melanoma patients (pts) resistant to standard treatment (Tx): immunotherapy & anti-BRAF-based targeted therapy represent a high medical need. Objective: Our aim was to evaluate the applicability of precision medicine in melanoma pts who failed standard tx based on molecular profiling (MP) of their tumors & the resulting clinical outcome.

Methods: All pts with advanced melanoma resistant to standard tx who had a MP at Gustave Roussy between April 2021 & March 2023 were included in this retrospective study. MP was performed by using Next Generation sequencing by using Foundation one CDX/liquidCDX & it was based on 3 protocols: STING (NCT04932525), MCLA-128 (NCT03321981) & STARTRK (NCT02568267) which allowed liquid & tissue biopsies studies. Molecular actionability was based on ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) classification.

Results: We performed MP for 184 pts: 174 had melanoma, 2 pts with EWSR1-ATF1 fusion & 1 with EWSR1-CREB1, which allowed a diagnosis correction to clear cell sarcoma & the initiation of the appropriate sarcoma tx, 3 BCC, 3 cSCC & 1 Merkel cell cancer. For the 174 melanoma pts, apart from the BRAF V600 mutation (50% of the pts), a putative actionable molecular orientation was found in 51.6% of the pts. The most frequent molecular alterations were: NRAS (23.2%), PTEN (12.6%), ATM (8.4%), CDKN2A (7.4%), BRAF class II (6.3%), BRAF class III (5.3%), KIT (4.2%) PIK3CA (3.2%), MAP2K1 (3.2%), NF1 (2.1%), AKT (1.1%), HRAS (1.1%), MET (1.1%), ALK (1.1%), ARID1A (1.1%), CDK4 (1.1%), CCND1 (1.1%). Molecularly matched tx was administered to 15 pts: anti-MEK (n = 11) & imatinib (n = 2). Among the 11 pts on anti-MEK, 1 partial response was seen after 9 months of tx & the remaining 10 pts rapidly progressed after 1-3 months of anti-MEK tx as for the 2 pts on imatinib. Unfortunately, no precision medicine tx was available to target the other potentially actionable mutations at the time they were needed.

Conclusions: Potentially actionable mutations can be found in more than 50% of pts with resistant melanoma. Tumor agnostic trials based on molecular alterations should be more broadly available to evaluate the potential benefit of innovative precision medicine in this population.

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1162P Prolonged exposure to proton pump inhibitors (PPI) at the time of initiation of immune checkpoint blockade (ICB) mediates better clinical outcomes in patients with metastatic melanoma

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Background: Tumor acidity negatively regulates tumor-specific effector T cells in the tumor microenvironment. Conflicting results emerged on the impact of PPI on the efficacy of ICB.

Methods: A retrospective analysis was conducted on patients (pts) with metastatic melanoma treated with ICB between 2019 and 2020 at the Christie NHS Foundation Trust. Data on demographics, sites of disease, performance status (PS), comorbidities, types of therapy, progression-free (PFS), and overall survival (OS) were collected. Statistical analyses were performed with univariable and multivariable Cox regression models. The aim was to define the association between PPI exposure (defined as 30 days before or after the initiation of ICB and for at least 21 days concomitant with ICB) and PFS, and OS.

Results: Data was collected on 189 pts with a median age of 60 years; 57.14% were male, 88% had ECOG PS 0/1, 17% were BRAF mutant, 28% had elevated serum LDH, and 28.5% had brain metastases. 162 (86%) pts received ICB as their first line of treatment for advanced disease. The majority of pts (92%) received ipilimumab and nivolumab, and 8% received pembrolizumab. 83 (44%) of pts were identified as PPI users with a median duration of PPI use concomitantly with ICB of 365 days (range 21-1976 days). PPI use was significantly associated with longer median PFS (not reached vs. 7.3 months, Hazard ratio (HR):0.53, 95%CI:0.35-0.79, p=0.002) and longer median OS (not reached vs. 17.2 months, HR:0.47, 95%CI:0.30-0.73, p=0.001). In a multivariable regression analysis accounting for age, gender, PS, Charlson comorbidity score, BRAF status, elevated LDH, brain and liver metastases, and line of treatment, the favorable impact of PPI use on PFS (HR:0.53, 95%CI:0.35-0.81, p=0.003) and OS (HR: 0.43, 95%CI:0.27-0.69, p<0.0001) was maintained.

Conclusions: Exposure to PPI for more than 21 days at the initiation of ICB mediates better clinical outcomes. Our findings suggest that the duration and timing of PPI use should be considered when investigating the impact on ICB outcomes. Prospective studies are required to test the priming effect of PPI on tumors with acidic microenvironments.

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1163P CD39 affect the prognostic role of NLR via N2 neutrophils in metastatic melanoma patients treated with immunotherapy

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Background: The immune checkpoint inhibitors (ICIs) revolutionized cancer therapeutic landscape and substantially improved the survival of patients (pts) with advanced malignancies. Several predictive biomarkers are under evaluation, in order to identify patients who can benefit from ICI. Recently, elevated NLR, calculated from absolute neutrophil count and white cell count, were found to be independent predictors of reduced survival and increased risk of progression in melanoma patients receiving ICI. The purpose of this study is to retrospectively investigate relationship of NLR with inflammation-immune mediators.

Methods: Gene profiling analysis was performed from 78 basal PBMCs of metastatic melanoma pts treated in first line with anti-PD1 using NanoString IO360 panel. Patient's characteristics are listed in table. To identify the best genes signature the Sparse Partial Least Squares Discriminant Analysis (sPLS-DA) was applied.

Results: Overall, 78 patients were included in the analysis. Pts with high NLR at baseline (ratio >5.57) had a poorer PFS (HR=7.27, 95% CI = 3.5-14.8; p < 0.0001) and OS (HR=3.98; 95% CI = 2.0-7.9) than the pts with low NLR. Brain metastases were present in a higher proportion of pts with high NLR compared to those with low NLR (p=0.01). In the trascriptomic analysis, NLR was associated with SH2D1A, CD3, ZAP70, CD45RA genes, while a high NLR with CCNA1, LDHA, IL18R1, CD39, PTEN, MYD88 and MMP9 genes (ROC curve, AUC=0.97, p<0001). The signatures are also associated to response. In addition, CD39 expression is higher in NLR high and is associate with increase of N2 neutrophils. NLR increase on treatment is also associated to worse outcome and a specific genetic signature.

Table: 1163P

Patient characteristics	N = 78
Median age	61 (range 27-91)
Gender: female/male, n (%)	41 (53)/37 (47)
Melanoma AJCC VII Stage	
Stage IV, n (%)	74 (94)
Stage IIIC	4 (5)
Stage IIIB	1 (1)
CNS metastases at baseline, n (%)	18 (23)
BRAF Status	
Wilde type, n (%)	59 (76)
Mutation, n (%)	16 (21)
NA, n (%)	3 (3)
Response rate at 1st assessment	
Complete response, n (%)	9 (11)
Partial response, n (%)	16 (21)
Stable disease, n (%)	17 (22)
Progression disease, n (%)	36 (46)
ORR, n (%)	39 (50)
DCR, n (%)	25 (32)
LDH	
High	26 (33)
Normal	34 (44)
NA	18 (23)

Conclusions: NLR high is related with immunosuppressive, inflammatory and tumor related genes; in particular with N2 neutrophils associate to adenosine pathway activation. This could explain the prognostic role of NLR. Further investigations are needed to get additional information.

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1164P Changes of TCR repertoire in metastatic melanoma and renal cell carcinoma patients treated with nivolumab correlate with overall survival

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Background: Melanoma and renal cell carcinoma are common cancers with growing incidence rates. Nivolumab, anti-programmed-death 1 protein (PD1) antibody selectively blocks the interaction between PD-1 and its ligand PD-L1 and enables a restart of the immune response against cancer cells, significantly improving survival in patients with metastatic melanoma and metastatic renal cell carcinoma (mRCC). It was hypothesized that proliferation of specific T cell clones may be associated with response to anti-PD1 therapy. The aim of this study was to analyze T cell repertoire in metastatic melanoma and mRCC patients treated with nivolumab and to correlate in with disease progression and overall survival.

Methods: Blood samples of 35 patients with metastatic melanoma and 21 patients with mRCC were evaluated and compared to 14 healthy controls. All melanoma patients were treated in 1st or 2nd line with nivolumab, all mRCC patients were treated with nivolumab in 2nd to 5th line after prior interferon α, sunitinib, pazopanib, everolimus or axitinib. Mononuclear cells were isolated from the peripheral blood on Histopaque. Cells were stained with directly labeled anti-CD3 PerCP-Cy5.5, anti-CD4 APC, anti-CD8 APC-Cy7 and anti-TCR FITC and PE antibodies. In total, 24 Vβ TCR families were evaluated. Measurement was performed by multicolor flow cytometry.

Data were analyzed with Wilcoxon non-parametric test and principal component analysis.

Results: Significant changes in several TCR families ($p<0.001$) were confirmed: an increase of $CD4^+$ cells or an increase of $CD8^+$ cells were observed. In several patients, highly enriched individual populations of $CD4^+V\beta$ or $CD8^+V\beta$ cells were observed (>10% of $CD3^+$). In these patients, median overall survival (OS) in 5 year observation was not reached, while in patients who did not show enriched $V\beta$ cells, median OS was 3.15 years.

Conclusions: Significant changes in TCR repertoire were observed in melanoma and mRCC patients treated with nivolumab compared to healthy controls. Very high levels of CD4 and CD8 lymphocytes with defined TCR $V\beta$ families were identified in approximately 40% of patients. Clonal expansion of $CD4^+$ and $CD8^+$ cells correlates with the response to treatment and overall survival.

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1165P Single cell spatial features of in-transit melanoma associated with patient outcome to immunotherapy

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Background: Melanoma in-transit metastasis (ITM) occurs in up to 20% of patients with cutaneous melanoma. The 10-year melanoma-specific survival for patients with ITM varies from 75% to 43%. Anti-PD-1-based immunotherapy is used when patients develop unresectable stage III disease or distant metastasis (stage IV). The tumour microenvironment (TME) of ITM melanoma remains poorly understood, where distinct cellular and spatial features can influence patients' outcome to therapy. This study aims to characterise the spatial TME in ITM melanoma patients.

Methods: We performed 40-plex PhenoCycler imaging on FFPE whole-tissue sections and CITE-Seq using tumour dissociates from 20 ITM patients treated with immunotherapy, 10 biopsied at baseline and 10 biopsied at the time of progression. Using bioinformatic analysis including spatial neighbourhood characterisation and receptor-ligand analyses, we investigated the TME features in ITM melanoma.

Results: Spatial neighbourhood analysis identified tertiary lymphoid structures (TLSs) consisting of B cells, $CD8^+$ T cells and dendritic cells, and these immune cells are interfacing HLA-A^{high} melanoma at the tumour margin. An enrichment for TLSs in pre-treatment ITM was associated with good immunotherapy outcome. Distinct subtypes of macrophages were stratified by phenotypic marker expression and spatial location, and intratumoural enrichment of M1-like macrophages ($CD68^+$HLA-$DR^+CD107a^+CD163^-$) was associated with immunotherapy response. Intra-tumoural melanoma heterogeneity was demonstrated in ITMs from patients with primary resistance to treatment and at progression. The resistant TME subtypes displayed a multitude of immune evasive phenotypes, including the upregulation of immune checkpoint receptors (LAG3, VISTA, IDO1), high proliferation, collagen deposition, and low immune recruitment. Single cell sequencing analysis demonstrates cellular programs correlated with response and resistance features in ITM patients.

Conclusions: Taken together, these findings provide insights into the spatial TME interactions associated with immunotherapy response, facilitating the development of biomarkers and therapeutic targets.

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1166P Multi-modal and longitudinal characterization of the tumor and immune microenvironment from primary melanoma to in-transit and distant metastasis

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Background: In-transit metastases (ITM) in melanoma represent a clinical entity where tumor lesions are found between the primary tumor and the draining lymph node. ITM is associated with worse prognosis. However, a significant subset of patients have discordance with high burden of locoregional relapses, but durable distant progression free survival. We studied two such patients to profile the dynamics and evolution of longitudinal tumor samples and identify mechanisms underlying these heterogeneous phenotypes.

Methods: We used whole exome sequencing (WES), bulk RNAseq, snRNAseq, and high-plex Cyclic Immunofluorescence (CyCIF) imaging to profile 28 biopsies over 7 years from pt1 (acral lentiginous melanoma, with progressive disease) and 22 biopsies over 11 years from pt2 (cutaneous melanoma, with durable remission).

Results: Pt1 (progressive disease) tumors had low to absent levels of immune infiltrate, low tumor mutational burden (TMB) and 5-hmC loss. Phylogenetic analysis revealed co-evolution of seven genetic lineages with multiple independent resistance-associated alterations; the majority of distant metastases emerged from a single lineage characterized by high aneuploidy and TMB, and a likely pathogenic missense mutation in TET2. The brain metastasis diverging early in molecular evolution but emerging late in disease had the highest TMB and aneuploidy. In another lineage, we identified WNT-beta catenin transcriptional signature contributing to TIL exclusion. In contrast, phylogenetic analysis of pt2 (durable remission) revealed six co-evolved genetic lineages with acquisition of mutational signature 11 and high TMB (53 mut/MB) after dacarbazine chemotherapy. In line with this, several tumor samples contained abundant Ki67+ CD8+ TILs and regression-like stromal changes, reflective of an autonomous effective host-immune response leading to a complete remission independent of any systemic therapy.

Conclusions: This study identifies genomic and phenotypic features linked to aggressive phenotypes and distant metastasis, including high aneuploidy, TET2 mutation, and 5hmC loss. Additional spatial analysis (GeoMx) is currently ongoing.

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1167P Spatial and single cell landscaping of immune microenvironment and melanoma subpopulations of metastasizing and non-metastasizing early-stage melanomas

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Background: Patients with thin melanoma (Breslow thickness <1) at early stages are not intensively followed up due to the very low risk of developing metastatic disease. However, 3-8% of thin melanoma cases do metastasize, and recognizing them could potentially candidate them to a more intensive follow-up and even to neoadjuvant therapy. However, due to the small size of early-stage lesions and the unavailability of fresh samples for single-cell dissociation, before the development of spatial single-cell technologies a thorough landscaping of these tumours was not possible. In this study, we have applied a state-of-the-art single-cell and spatial technology to deeply characterize the immune microenvironment of metastasizing (M+) and non-metastasizing (M-) thin melanoma samples and pose the basis for biomarker discovery in this group of patients.

Methods: In collaboration with the Pathology subcommittee of the Melanoma group of the EORTC, we collected 37 M+ and 40 M- thin melanoma patient samples matched for the most prognostically relevant clinical factors, including Breslow thickness, age, gender, location of occurrence, ulceration, and mitosis. We investigate their cellular and functional landscape using 39 protein markers measured spatially at

single-cell level applying the MILAN (Multiple iterative labeling by antibody neo-deposition) method.

Results: There were no significant differences in the percentage of cell types present in M+ and M- samples. However, the analysis of recurrent cellular communities revealed that PD1+ T cells and PDL1+ macrophages were located at the tumor-stroma interface in M+ patients, whereas cellular communities with a high percentage of macrophages but no significant contact with cytotoxic T cells were present at the border of the tumor in M- patients.

Conclusions: This study gives the first spatial single cell landscape of thin melanoma and finds relevant communities in metastasizing patients that could be exploited in the future to adjust combinatorial therapies and drive better personalized medicine for thin melanoma patients.

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1168P Tumor PD-L1 predicts the outcome of PD-1-based immunotherapy in metastatic melanoma depending on the type of tissue examined

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Background: PD-1-based immune checkpoint inhibition (ICI) is the major backbone of current melanoma therapy. Tumor PD-L1 expression represents one of few biomarkers predicting ICI therapy outcome. Here, we systematically investigated whether the type of tumor tissue examined for PD-L1 expression has an impact on ICI therapy outcome prediction.

Methods: Pre-treatment tumor tissue obtained before 1st ICI therapy for non-resectable stage III/IV metastatic melanoma was prospectively collected within the DeCOG multicenter study Tissue Registry in Melanoma. Stratified by tissue type, best overall response (BOR), progression-free survival (PFS), and overall survival (OS) were correlated with tumor PD-L1 expression (cutoff $\geq$5%).

Results: Of 448 patients, tumor PD-L1 was determined on 95 primary tumors (PT; 36.8% positivity), 153 skin (34.0% positivity), 115 lymph node (LN; 50.4% positivity), and 85 organ (40.8% positivity) metastases. Skin metastases were significantly more often classified as PD-L1 negative than LN metastases (OR=0.751; 95%CI=0.599-0.956; P=0.007). PD-L1 positivity was predictive for BOR if determined on LN (CR/PR 37.5% versus 16.1%; OR=0.319; 95%CI=0.138-0.76; P=0.010), but not on skin metastases (CR/PR 36.0% versus 28.0%; OR=0.778; 95%CI=0.379-1.554; P=0.49), translating into favorable survival for PD-L1 positivity determined on LN metastases (median PFS 22.0 versus 3.5 months, HR=0.490; 95%CI=0.310-0.775; P=0.002; median OS 68.9 versus 16.6 months, HR=0.519; 95%CI=0.307-0.880P=0.014). PD-L1 positivity determined on PT (PFS= HR=0.757; 95%CI=0.467-1.226; P=0.27; OS= HR=0.528; 95%CI=0.305-0.913; P=0.032) was predictive to a lesser extent. No relevant survival differences were detected by PD-L1 determined on skin metastases. Multivariate analysis revealed tumor PD-L1 determined on LN metastases as independent predictive factor for PFS (HR=0.43; 95%CI=0.24-0.75; P=0.003) and OS (HR=0.51; 95%CI=0.27-0.96; P=0.037).

Conclusions: For outcome prediction of PD-1-based immunotherapy in melanoma, tumor PD-L1 determined on LN metastases was more reliable than that assessed on PT. PD-L1 determined on skin metastases showed no predictive value and cannot be recommended for clinical use.

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1169P Tumour transcriptional and spatial protein profiling in Mexican patients reveals that acral lentiginous melanoma is characterized by an immunosuppressive microenvironment

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Background: Acral lentiginous melanoma (ALM), although overall a rare type of melanoma, is the most common form of the disease in a number of countries in Latin America, Africa, and Asia; it is associated with a poor prognosis and recurrence. In this study, we seek to gain a better understanding of the tumor-immune components of ALM and their relationship to transcriptional programs.

Methods: Tumour samples were collected from patients undergoing treatment at the National Cancer Institute of Mexico, and have been annotated with vast clinical information. We performed transcriptome sequencing through exome-capture bulk RNA-sequencing on 65 primary tumors from 64 Mexican patients, and did spatial protein profiling using a tissue microarray on 110 tumor segments from 45 patients. Samples were collected at the National Cancer Institute of Mexico and have been annotated with vast clinical information.

Results: We identified differentially expressed genes such as *CXCL8*, *MMP1*, and T*ERT* in ulcerated lesions. RNA deconvolution showed a high abundance of cancer-associated fibroblasts (CAFs) and the absence of NK cells. Consensus clustering identified three ALM subgroups based on global gene expression. Integration of spatial protein information confirmed the high abundance of CAFs- associated markers and the absence of CD56. Fibronectin, SMA, and the cancer stem cell marker CD44 were markedly elevated. We investigated expression patterns within particular regions of interest and found that fibronectin, VISTA, SMA, IDO1, CD34, CD45, CD3, HLA-DR, and CD45RO were differentially expressed in non-tumor regions, while tumor ROIs expressed B7-H3, CD127, GAPDH, and Ki-67 significantly at higher levels. Comparisons between RNA and protein for 35 targets are being conducted.

Conclusions: So far, our analyses point to genes that could drive important prognostic characteristics. We confirmed that ALM is characterized by an immunosuppressive tumor microenvironment. The role of CAFs and the mechanisms affecting NK cells require further research. The present project will enhance our understanding of the TME components and the antitumor response in an understudied disease.

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1170P Survival outcome prediction of primary melanoma tumours from histology images using deep learning

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Background: Predictive and prognostic biomarkers represent the cornerstone of clinical oncology. Improving the prognostication of melanoma is needed to select patients for effective adjuvant therapies. Taking into account that tumor tissue contains a large amount of clinically relevant hidden information that is not fully exploited, we propose a weakly-supervised deep-learning approach on H&E-stained whole-slide image (WSI) to directly predict survival outcomes in melanoma patients.

Methods: We designed a deep neural (DL) network that extracts features from no-padding patches of WSI (tiles of size 512x512 pixels) using a self-supervised learning framework, which are then fed along with survival information into the DL network assigning a survival risk score to each WSI/patient. The model was trained and validated on 195 cases of primary melanoma diagnosed between 2015 and 2017 originating from the IHP Group and the French RicMel network. Performance was evaluated using cross-validations as well as an external set of 238 cases from the TCGA database. Concordance index (c-index) was used as a metric to assess the performance of the proposed approach.

Results: For the prediction of survival outcomes, the proposed pipeline yielded a c-index of 0.75 and 0.66 for the IHP Group cohort and TCGA dataset respectively. Furthermore, we were able to significantly discriminate the 2 groups of patients, with a good and a poor prognosis in terms of survival with $p<0.001$ for IHP and $p=0.01$ for the TCGA based on Kaplan-Meier survival analysis. Our prediction model outperforms the reported scores for the other types of tumours based on deep learning frameworks.

Conclusions: This innovative weakly-supervised deep-learning approach to HE image analysis allows the deep-network to choose its own morphological features, and thus highlights new morphological prognostic biomarkers. Based on this prognostic risk score, we aim to accelerate and improve the clinical decision-making process in the field of melanoma. Due to this exiting result, the performance of our algorithm is challenge on a third independent dataset.

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1171P Evaluation of the transcriptomic presence of tumor associated antigens (TAAs) from antibody drug conjugates (ADCs) and PD-L1 in melanoma: Options for new clinical opportunities

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Background: Identification of tumor associated antigens (TAAs) is a main goal in order to design antibodies against tumoral cells. These antibodies can be the base for the construction of antibody drug conjugates (ADCs). It is necessary to identify indications to develop combinations of ADCs with immunotherapies including check point inhibitors (CPIs). We evaluate the transcriptional co-expression of TAAs with PD-L1 (CD274) in melanoma, to identify the best ADC to be combined with anti-PD-(L)1 therapies.

Methods: Information on all ADC TAAs in clinical development was extracted from ClinicalTrials.gov and Federal Drug Administration (FDA) website. Data from TCGA was downloaded to evaluate the expression of identified TAAs in melanoma. Correlation of every pair of genes with CD274 (PD-L1) was performed with Pearson correlation coefficients. Survival outcomes were studied with Kaplan Meier curves and hazard ratios. Tumor Immune Estimation Resource (TIMER) platform was used to investigate the association between the selected TAA and immune cell populations.

Results: 32 TAAs from 123 ADCs were identified. 6 genes that coded for TAAs were upregulated in primary and metastatic melanoma compared with normal tissue, including CD22 (4.55 TMP vs 0.44 TPM), CD74 (1653.72 TPM vs 514.44 TPM), MET (13.13 TPM vs 4.44 TPM), ERBB3 (143.8 TPM vs 70.33 TPM), LIV-1 (66.01 TPM vs 32.37 TPM) and SLAMF7 (10.06 TPM vs 1.09 TPM). A positive correlation for CD74 (Rho: 0.647) and SLAMF7 (Rho: 0.65) with PD-(L)1 was observed. Expression of CD74 correlated with favorable overall survival in melanoma patients treated with any CPI (N: 397, HR: 0.52 CI 0.39-0.69, Log-rank P=3.3e-06), and for those only treated with anti-PD-1 agents (N: 325, HR: 0.52 CI 0.38-0.73, Log-rank P=7.8e-05). Similar findings were observed for SLAMF7 for any CPI (N: 397, HR: 0.5 CI 0.38-0.66, Log-rank P=3.9e-07) and anti-PD-1 (N: 325, HR: 0.53 CI 0.39-0.72, Log-rank P=4.3e-05).

Conclusions: CD74 and SLAMF7 is highly present in melanoma, correlates with PD-L1 expression and predict response to anti-PD-(L)1 therapies. This finding suggests to explore potential combinations between ADCs against these targets and anti-PD-(L)1 therapies.

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1172P Analysis of the microbiome of metastatic melanoma patients with complete response to immunotherapy

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Background: While immunotherapy has improved the prognosis of metastatic melanoma patients, a minority of patients will have prolonged remission. Recent data have emphasized the role of the gut microbiome in response to immunotherapy; however, there is a discrepancy in defining the optimal microbiome. Although recent fecal microbial transplantation (FMT) trials only included patients with sustained response to immunotherapy, a mixed response was registered, with scarce data on the antimicrobial resistance of the donors. A thorough evaluation of the gut microbiome of potential FMT donors is warranted before future trials.

Methods: A shotgun metagenomic sequencing was performed on Illumina NextSeq 2000 platform on stool samples of metastatic melanoma patients with complete and sustained response to immunotherapy (N=15).

Results: The average age of patients was 61.0 ($\pm$12.2) years. Patients usually received immunotherapy in the first line (N=14, 93.3%), with an average time to complete response of 7.6 ($\pm$ 4.6) months. Firmicutes were the most common phylum with a relative abundance of 62.1% $\pm$ 13.2, followed by the Bacteroidetes (31.7% $\pm$ 13.8). Protobacteria were present in all patients, ranging from 0.06-3.4%. On Class level, Clostridia were the most abundant (53.9% $\pm$ 10.4), followed by Bacteroidia (31.7% $\pm$ 13.8). Similar results were seen for the order level, while Lachnospiraceae were the most common family (30.2% $\pm$ 8.6) but ranged from 8.1 $-$ 43.8%, followed by Ruminococcaceae (6.7% $\pm$ 14.0), and Bacteroidaceae (6.2% $\pm$ 11.6). Only 14 bacterial families were present in all patients (25.4%). On the genus level, *Bacteroides* had the highest relative abundance (11.6% $\pm$ 6.2), followed by *Lachnospiraceae* (10.1% $\pm$ 5.9), and *Phocaeicola* (6.2% $\pm$ 4.4). 377 different species were found, with six patients (40%) reporting no traces of the *Akkermansia municiphila*. Antimicrobial resistance was most commonly found for tetracyclines (63.3% $\pm$ 6.9), macrolide-lincosamine-streptogramin B (14.5% $\pm$ 7.9), and sulfonamide trimethoprim (4.4% $\pm$ 2.4).

Conclusions: Patients with complete and sustained response to immunotherapy exhibit a heterogeneous gut microbiome with common resistance to Tetracycline antibiotics.

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1173P NRAS mutation as an independent prognostic factor for resectable Chinese acral melanoma

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Background: Acral melanoma (AM) is the most common subtype of Chinese melanoma population, taking up over 50%-60%. Compared to cutaneous melanoma, AM is lack of frequent driven mutation like BRAF alternation which only occurs around 10%. Meanwhile, 10%-15% of AM can harbor NRAS mutation. This single-center retrospective study aims to investigate the survival impact of NRAS mutant status on Chinese AM after receiving radical surgery.

Methods: We retrospectively collected AM patients who received radical surgery in Fudan University Shanghai Center with confirmative genomic information from 2017 to 2021. Information of clinicopathologic factors and recurrence and survival outcomes was retrieved from patients document database of our hospital.

Results: Totally 317 patients were recruited in our study.170 (53.6%) were males and median age was 62 years old (range 26-89). 281 (88.6%) cases had primary lesion at lower extremity. The mean Breslow thickness were 3.9mm and ulceration rate was 65.9%. According to AJCC 8th staging system, there were 12% Stage I, 32.2% Stage II and 55.8% Stage III. Genomic alternation occured included 71(22.4%) NRAS, 36 (11.4%) BRAF, 33 (10.4%) KIT and the other 177 (55.8%) widetype of these three genes. No statistical difference was observed in most of clinicopathologic factors between NRAS-mut and NRAS-wt patients. However, NRAS-mut group had higher risk of nodal metastasis beyond 1st tier basin (42.3% vs 27.2, P<0.002).With median follow-up of 22 months, NRAS-mut patients had significantly worse relapse-free survival (RFS, P<0.0001) and overall survival (OS, P=0.010). Distant metastasis-free survival (DMFS) was also numerically reduced but not reached significance (P=0.074). Multivariate analysis showed NRAS mutation was an independent prognostic factors for both RFS (P=0.008) and OS (P=0.025).Among patients receiving adjuvant anti-PD1 monotherapy, median RFS time was significantly worse for NRAS-mut patients (9 months vs 26 months, P<0.0001).

Conclusions: In conclusion, AM harboring NRAS mutation had higher risk of relapse and death as well as reduced efficacy of adjuvant anti-PD1 monotherapy compared to NRAS-wt after radical surgery. NRAS mutation was an independent prognostic factor for resectable Chinese AM population.

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1174P Sex differences in advanced melanoma in Spain: Results from the prospective real-world study GEM 1801

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Background: The incidence of melanoma is increasing in patients (pts) of both sexes, with female pts generally living longer than their male counterparts. This study assessed the sex-based difference in survival of pts with melanoma and the relationship of this difference with pathological features and response to different treatment options in Spain.

Methods: GEM1801 is a prospective observational study that analyzes the clinical and pathological disease presentation patterns, the different lines of treatment choices and the health outcomes derived from treatments. Here we focus on the sex of pts diagnosed with locally advanced unresectable or metastatic melanoma and their first line (1L) treatment assigned.

Results: From Aug 2018 to Dec 2022, 712 evaluable pts were enrolled, 430 males (60.4%) and 282 (39.6%) females. Median age was 67 years (range: 22-95). Most were superficial spreading (42.6% vs 30.5%; p<0.001), being more frequent than other types in females. Primary tumors were more frequently located in the trunk and head in males and in extremities in females (p<0.001). Chronic sun exposure was more frequent among males (12.3% vs 4.6%; p=0.002). Sex led to no statistically significant differences in therapeutic assignment. At data cutoff, the median follow-up was 14.4 m (95% CI: 13.3-16.2). Efficacy is shown in the table.

Table: 1174P

	N, (%)	Median PFS (95% CI), months	p-value Cox	Median OS (95% CI), months	p-value Cox
BRAF + IT Male	61 (58.7)	20.6 (7.9-NR)	0.381	35.8 (24.1-NR)	0.766
BRAF + IT Female	43 (41.3)	15.3 (6.5-NR)		NR (22.9-NR)	
BRAF + TT Male	109 (57.4)	9.7 (7.5-12.2)	0.001	13.9 (11.7-26.2)	0.026
BRAF + TT Female	81 (42.6)	16.8 (10.2-27.5)		26.1 (21.1-NR)	
BRAF - IT Male	158 (64.6)	9.6 (6.6-24.9)	0.827	29.6 (17.9-47.9)	0.865
BRAF - IT Female	89 (35.4)	8.8 (6.5-16.8)		23 (18.4-NR)	

IT = Immunotherapy; TT = Targeted therapy.

Conclusions: Melanoma in Spain showed sex-based differences in prevalence, histology type, primary location and risk factors exposure. Therapies are not assigned based on sex. TT in 1L showed significantly better outcomes in females, which may suggest a potential prognostic role of sex useful for therapeutic assignment.

Clinical trial identification: NCT03605771.

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1175P Return to work after neoadjuvant versus adjuvant immunotherapy in stage III melanoma patients

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Background: Neoadjuvant immunotherapy in stage III melanoma improved event-free survival compared to 1 year adjuvant therapy. Six weeks of neoadjuvant combination immunotherapy, currently tested in phase III, induces even higher response rates, allowing frequently the omission of extensive surgery and adjuvant therapy. These developments and the rising incidence of melanoma will lead to an exponential increase of melanoma long-term survivors. However, immunotherapy can cause somatic and psychological adverse effects impairing patients' daily life including their return to work (RTW), which has also a strong societal impact. Therefore, we analyzed RTW after neoadjuvant versus adjuvant immunotherapy.

Methods: 88 patients (44 neoadjuvant, 44 adjuvant), 18-66 years old, working (including voluntary work) at start therapy were included to be retrospectively telephone-interviewed concerning their RTW. Partial RTW was defined as RTW after initial discontinuation of work; full RTW was the timepoint that patients worked the same capacity, hours as prior to therapy. Database lock was date January, 3rd 2023.

Results: Patient characteristics were balanced, except for extent of surgery (index or sentinel lymph node procedure only vs therapeutic lymph node dissection) which was more frequently less extensive in the neoadjuvant cohort (64% vs 36%). Patients returned to work more quickly in the neoadjuvant group compared to the adjuvant cohort, with a 6-month partial RTW cumulative incidence of 80% vs 58% and 84% versus 73% at 12 months. At 24 months the adjuvant group catched up and partial RTW was almost the same with 91% and 92%. Incidence of full RTW was higher at all timepoints for the neoadjuvant cohort compared to the adjuvant cohort with 55% vs 38%, 70% vs 50% and 82% vs 62% at 6, 12 and 24 months, respectively. Aside neoadjuvant therapy, lower level of education, and larger extent of surgery were independent parameters associated with reduced RTW.

Conclusions: Our study suggests that treatment duration, the extent of surgery, and educational level might be factors influencing return to work in patients with stage III melanoma.

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1176P Planned drug holidays during immunotherapy in advanced and metastatic melanoma patients: A nation-wide study

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Background: The optimal duration of immunotherapy (ITH) for patients(pts) with unresectable/metastatic melanoma has not been defined and de-escalation strategies are under debate. Drug holidays are defined as intentional cessation of immunotherapy for period of time, in pts with therapy benefits, till potential progression (PD). While avails of drug holidays include reduction of toxicity and treatment cost as well as increased quality of pts' life, there are also potential risks including PD. Our study aimed to describe disease control upon drug holidays in melanoma pts treated with palliative ITH.

Methods: Pts with advanced unresectable/metastatic melanoma were treated with anti-PD1-based ITH. Patients were referred for drug holidays after $\geq$12 months of ITH. Pts who stopped the treatment due to toxicity were excluded from analysis. During study patients had imaging every 3 months. Primary endpoint was overall survival (OS), and secondary endpoints were median duration of drug holiday, 2nd progression-free survival (PFS2) after PD on drug holidays.

Results: 175 patients (80F/95M) treated for advanced unresectable/metastatic melanoma were referred for drug holidays. 116(67.4%) were *BRAF*-negative melanoma patients. 84 pts were treated with nivolumab, 6 with nivolumab+ipilimumab, 85 with pembrolizumab; and 152(86.9%) were treated in first line. Patients treated for $\geq$24 months(m) before drug holidays had significantly longer OS (p=0.003) and longer PFS till disease PD on drug holidays(p=0.00053) in multivariate analysis. PFS was dependent on best response before drug holidays with the longest in CR group (p=0.011). The median duration of drug holidays was 17 m (IQR: 8-24). At the median follow-up of 48 m (95%CI: 45-51), median OS was not reached, and 5-year OS rate was 89% (95%CI: 83-96). At ITH retreatment objective response was 64% and PFS2 rate at 1-year was 69% (95%CI: 48-99). At the time of analysis 141 pts were still on drug holidays and 11 died due to melanoma PD.

Conclusions: For melanoma pts drug holidays may be offered to ITH responders. The majority of melanoma patients on drug holidays are progression-free at 24m after ITH discontinuation. ITH rechallenge allows achieving disease control after initial progression on drug holidays.

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1177P Assessment of tumour burden reduction per photography vs magnetic resonance imaging in patients with locally advanced basal cell carcinoma receiving sonidegib 200 mg

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Background: Sonidegib is a Hedgehog pathway inhibitor approved for the treatment of locally advanced basal cell carcinoma (laBCC) in the US, EU, Switzerland, and Australia, and metastatic BCC (mBCC) in Switzerland and Australia not amenable to curative surgery or radiotherapy. This analysis compared tumour burden reduction using photography or magnetic resonance imaging (MRI) in patients with laBCC that had a time to first tumour response (TFTR) within 6 months of starting treatment.

Methods: The double-blind, multicentre, phase II BOLT study assessed the efficacy and safety of sonidegib 200 mg with laBCC. Tumour burden reduction was assessed using both colour photography and MRI by central review. Tumour response was defined as a >10 mm unidimensional decrease in tumour size. Safety assessments included adverse event (AE) monitoring.

Results: Overall, among 66 patients with laBCC receiving sonidegib 200 mg, TFTR <3 months was achieved by 31 patients per photography and 11 patients per MRI assessment; TFTR from 3 to <6 months was achieved by 8 patients per photography and 12 per MRI. For patients with a TFTR of <3 months, the median (minimum, maximum) percent change from baseline in tumour size was −18.5 (−100.0, 35.9) vs −23.8 (−100.0, −11.9) at 9 weeks, −33.4 (−100.0, 38.5) vs −54.0 (−100.0, −27.1) at 25 weeks, −30.7 (−100.0, 12.0) vs −82.1 (−100.0, −52.9) at 41 weeks, and −29.0 (−100.0, 57.8) vs −82.1 (−100.0, −58.8) at 61 weeks per photography vs MRI, respectively. For patients with a TFTR from 3 to <6 months, the median (minimum, maximum) percent change from baseline in tumour size was not available at 9 weeks, −16.0 (−100.0, 18.1) vs −37.0 (−77.3, −12.5) at 25 weeks, −32.9 (−54.7, 22.3) vs −79.2 (−100.0, −41.5) at 41 weeks, and −35.1 (−46.8, −23.4) vs −77.3 (−100.0, −31.6) at 61 weeks per photography vs MRI, respectively. Sonidegib was well tolerated, and most AEs were Grade 1/2 in severity.

Conclusions: In patients with a TFTR within 6 months of starting treatment with sonidegib, an overall greater reduction in tumour size was reported per MRI assessment vs photography, with photography underestimating the extent of tumour response.

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1178P Melanoma incidence rises for pediatrics: 15-year nationwide retrospective cohort study in Korea (2004-2019)

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Background: Melanoma is the fifth most common cancer and, although rare, is the most common skin malignancy in those under 20 years old in the United States (US), with an average annual incidence rate (IR) of 5.5-6.0 cases per million. Since the 1970s, the incidence of pediatric melanoma has increased with an average annual percent change of 2−2.9% in the US. Epidemiological knowledge and predictors of melanoma among children and adolescents (age < 20 years) in Korea are limited.

Methods: Using data from National Health Insurance (NHI) database, we identified incident melanoma cases diagnosed at 0-19 years old during 2004-2019 in Korea, respectively. Using a joinpoint regression model, associations between demographic factors and melanoma incidence rates (IR) were evaluated by calculating incidence rate ratios and 95% confidence intervals (CI).

Results: We identified a total of 1160 patients (age < 20 years) with cutaneous malignant melanoma from 2004-2019. The overall average annual melanoma incidence was 0.22 per million (95% CI, 0.21-0.23) in Korea. It increased with age (age 0-4: 0.3, age 5-9: 0.6, age 10-14: 0.6, age 15-19: 07 per 100,000 persons) but there was no difference in IR according to sex. The age-adjusted incidence of melanoma decreased 4.5% yearly from 2004 to 2012 (95% CI, -8.9%−0.1%) but increased 12.6% yearly from 2012 to 2019 (95% CI, 5.9%−19.6%). A strong correlation between melanoma IR and nevi was confirmed (OR 85.4, 95% CI 67.97 - 106.40, P < 0.001) and this was also linked to the survival rate (5-year survival rate: 97.7% vs 91.9%, P = 0.044).

Conclusions: Although the incidence of melanoma in children and adolescent is very low, it is clear that it increases in Korea. To our knowledge, this is the first report to suggest that melanoma IR trends in children and adolescent are annually increasing in Korea. Most importantly, we must increase awareness and education amongst pediatricians, internists and the general population with regard to prevention and early diagnosis of melanoma for both children and adults. In addition, the physicians should include a complete skin examination for children with congenital nevi.

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1179P The underestimated skin cancer risk after liver transplantation: A meta-analysis of 147154 patients

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Background: Recent reports have been shown an increased risk of de-novo malignancies in liver transplant recipients (LTRs) which is reported to be a leading cause of mortality in these patients. The aim of this systematic review and meta-analysis was to assess the prevalence of skin cancer in LTRs.

Methods: We systematically searched in five databases till 20th April 2023 through the search term ("liver transplantation" OR "liver transplant") AND ("skin cancer" OR "melanoma" OR "squamous cell carcinoma" OR "non-melanoma skin cancer" OR "post-transplant cancer" OR "post transplant cancer"). We used random effect model to overcome the significant heterogeneity we observed.

Results: A total of 34 studies, with 147154 LTRs were included. The pooled prevalence of skin cancer (all types) was 4.8% (95%confidence interval (CI): 3.6-6.5). Subgroup analysis based upon the follow up duration of each study, indicated that skin cancer prevalence increased with long duration of follow up: 0-4 years, 2.4% (95%CI: 0.5-9.9), 4-8 years, 4.2% (95%CI 2.9-6.2), and >8 years, 7.6% (95%CI: 4.7-12). Australia followed by South America had the highest prevalence of skin cancer, 20.6% (95%CI: 12.9-31.3), and 9.4% (95%CI: 5.8-14.8), in order; while Asia had the lowest prevalence 0.4% (95%CI: 0-3.8). The most common type of skin cancers was non-melanoma skin cancer reported as a combined type with a prevalence of 2.9% (95%CI: 1.1-6.9), followed by squamous cell carcinoma, basal cell carcinoma and Bowen's cancer, 2.5% (95%CI: 1.4-4.4), 2.5% (95%CI: 1.5-4.1) and 0.8% (95%CI: 0.2-3.2), in order.

Conclusions: Consistent with what it has been reported for other organ transplants, the results from this study showed that skin cancer following liver transplantation is not rare. LTRs in Australia should receive annual dermatologic examination due to their high prevalence of skin cancers. Moreover, non-melanoma skin cancers may be the prevalent type if skin cancer is suspected in LTRs. Substantial dermatological surveillance programs are recommended in LTRs to improve quality of life as well as the associated mortality; especially with the increased prevalence after long follow up durations.

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1180TiP Randomized phase II trial (PORTSIDE) evaluating encorafenib (enco) and binimetinib (bini) plus pembrolizumab (pembro) versus nivolumab (nivo) and ipilimumab (ipi) for the treatment of advanced BRAF-mutant melanoma

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Background: Anti—PD-1 therapy (eg, pembro, nivo) in the adjuvant setting is one of the standard-of-care regimens for patients with BRAF-mutant metastatic melanoma. However, a significant proportion of patients have a limited or no response to anti—PD-1 therapy. Therefore, there is an unmet need to determine the optimal treatment sequence in patients resistant to anti—PD-1 therapy. BRAF + MEK inhibitors (eg, enco + bini) are also treatment options for BRAF-mutant metastatic melanoma. This phase II trial will evaluate the combination of enco + bini + pembro vs nivo + ipi in participants (pts) with advanced BRAF-mutant melanoma who progressed during or after anti—PD-1 therapy.

Trial design: PORTSIDE is an international open-label trial recruiting approximately 150 pts. Pts will be randomized 1:1 to receive either enco 450 mg (QD, PO), bini 45 mg (BID, PO), and pembro 200 mg (Q3W, IV) in 21-day cycles or 4 cycles of induction with nivo 1 mg/kg (Q3W, IV) and ipi 3 mg/kg (Q3W, IV) followed by maintenance with nivo 480 mg (Q4W, IV). Pts will be stratified by type of PD-1 resistance (primary vs secondary) and baseline lactate dehydrogenase level (above vs below the upper limit of normal). Pts must be $\geq$18 years old with histologically confirmed unresectable locally advanced or metastatic cutaneous BRAF V600E/K-mutant melanoma (per AJCC 8th edition) with $\geq$1 measurable lesion per RECIST v1.1. Pts must have received only 1 prior line of systemic therapy for melanoma and have confirmed disease progression per RECIST v1.1, either during or after receipt of an anti-PD1 therapy. Pts must have an ECOG PS of 0 or 1 and adequate organ function. Pts who discontinued prior anti—PD-1 therapy due to toxicity or who may not tolerate combination therapy are not eligible. Pts must not have previously participated in the STARBOARD study (NCT04657991) or received prior treatment with BRAF and/or MEK inhibitors, ipi, combined immunotherapy with anti-PD1/L1 treatment, or any other anticancer agents. The primary endpoint is objective response rate; key secondary endpoints are progression-free and overall survival.

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1181TiP BEPCOME-MB: Treatment of BRAFV600 mutated melanoma brain metastases with encorafenib + binimetinb + pembrolizumab with or without stereotactic radiosurgery

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Background: Melanoma is an aggressive disease with a high propensity to metastasize to the central nervous system. Melanoma brain metastases (MBM) were associated with poor overall survival (OS), with a median OS of 4—5 months before the era of immune checkpoint inhibition (ICI). Nowadays, first-line treatment with BRAF/MEK inhibitors in patients (pts) with BRAFV600 mutated melanoma and MBM induces ~60% intracranial response, which are unfortunately short-lived. Combined ICI with ipilimumab + nivolumab demonstrated longer-lasting efficacy, but is associated with high rates of toxicity and very limited efficacy in patients with symptomatic MBM. Stereotactic radiosurgery (SRS) for single or multiple lesions is an effective modality to achieve MBM control. Its place upfront or later has not been established. A triplet therapy with BRAF/MEK inhibitors encorafenib (E) + binimetinib (B) and anti-PD-1 monoclonal antibody pembrolizumab (P) is an attractive strategy in BRAFV600 mutated MBM, with a rapid disease response (attributed to E+B) and durable disease control (attributed to P), even in symptomatic MBM, with potentially better tolerability than ipilimumab + nivolumab. This trial aims to test the feasibility of this regimen with or without upfront SRS.

Trial design: This phase II, randomised, controlled, open-label trial assesses the efficacy and safety of adding upfront SRS to E+B+P in the treatment of pts with BRAFV600 mutated melanoma and MBM. Patients are randomly assigned (1:1) to receive (a) E+B+P, or (b) upfront SRS of all cerebral metastases $\geq$5 mm in diameter, followed by E+B+P. Patients will be treated until disease progression. An amendment to allow previous treatment with anti-PD-1 is ongoing. Using intracranial progression-free survival (IC-PFS) assessed by central review as the primary endpoint, 150 patients will be needed to detect an increase in the median IC-PFS in the SRS + E+B+P arm (HR of 0.60 with 80% power and 2-sided 5% significance level). Secondary endpoints include response rate, disease control, OS, toxicity and quality of life. Exploratory endpoints include predictive factors of response and mechanisms of primary and acquired resistance.

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ANNALS OF ONCOLOGY driving innovation in oncology

NEUROENDOCRINE TUMOURS

1182O Temozolomide treatment induces an MMR-dependent hypermutator phenotype in well differentiated pancreatic neuroendocrine tumors

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Background: Temozolomide (TMZ), an alkylating agent, is an effective treatment. In glioblastomas, TMZ induces a hypermutator and hyperprogressor phenotype in a subset of patients through a specific MSH6-related MMR deficiency that does not seem to trigger an immune response. In contrast, in advanced colon cancer, studies suggest that TMZ priming increases the tumor mutational burden (TMB), favoring immunotherapy efficacy. TMZ treatment has been shown to be effective in patients with advanced pancreatic neuroendocrine tumors (PanNET). The aim of this study was to assess the potential of TMB-associated immunotherapy efficacy in TMZ-treated PanNET.

Methods: We examined 57 patients with low grade G1/G2 PanNET treated by TMZ +/- capecitabine in one expert center between 2009 and 2020. Sequencing of 500 cancer genes was performed on 23 pre-TMZ and 23 matched post-TMZ samples, without intercurrent DNA damaging treatment. Results were validated in an independent cohort of 1079 PanNETs profiled by Foundation Medicine. TMB >30mut/Mb was considered TMB-high and only pathogenic variant with an allele frequency ≥10% were included in this analysis.

Results: After TMZ, 29/57 (51%) PanNET became high grade G3. They showed no difference in their preTMZ clinical or molecular profile nor in the TMZ dose received. In the profiled samples, 14/23 (61%) post-TMZ samples became G3 (median Ki-67 +20%) and 6/23 (26%; 5 G3) were TMB-high. In post-TMZ samples, TMB-high samples had more pathogenic alterations in MMR genes (88% vs. 26%, p=0.003). In the validation cohort, 25/1079 PanNETs were TMB-high. 67% of these displayed the predominant alkylating signature 11 and 44% had various MMR gene alterations; of note, *MSH2* and *MSH6* alterations were significantly more prevalent in TMB-high than TMB<10 samples (16-18% vs. <1%; p<0.01). In both cohorts, none of the TMB-high samples showed the glioblastoma-specific *MSH6* mutation, suggesting a better immunogenic potential.

Conclusions: These results suggest that TMZ induces an hyperprogressor and hypermutator phenotype in a subset of PanNETs, through a potentially immunogenic mechanism, thereby opening the path to immunotherapy, a treatment not otherwise effective in patients with treatment naive PanNET.

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1183MO Molecular characterization of rectal neuroendocrine tumors (NETs) with unfavorable prognosis by multiomics analysis: A multicenter retrospective cohort study (GARNET)

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Background: Most rectal neuroendocrine tumors (NETs) are small indolent G1 tumors with good prognosis. However, a few develop distant metastasis, leading to unfavorable outcome, and its association with molecular features are unknown. This study aimed to identify genomic, transcriptomic, and epigenetic alterations that can contribute to more accurate prediction of prognosis of rectal NET.

Methods: This study was a multicenter, noninterventional cohort study, performing multiomics analysis including whole exome sequencing (WES), single nucleotide polymorphism (SNP) array-based profiling for copy number, gene expression and methylation. Patients were classified into 3 cohorts based on the prognoses (ie, cohort A [no recurrence, alive for ≥5 years from initial surgery], cohort B [alive for ≥3 years since recurrence and/or metastasis], cohort C [alive for <3 years from recurrence and/or metastasis to death]). The primary endpoint was to reveal unique molecular alterations in rectal NETs of cohorts B and C compared with cohort A.

Results: A total of 40 patients with rectal NETs were enrolled and 36 patients were analyzed (14 G1-NETs and 22 G2-NETs; 11 in cohort A, 19 in cohort B, and 6 in cohort C). WES revealed 17% (6 of 35) of recurrent somatic mutations in *CDC27*, which were only identified in cohorts B and C. Cancer genes were infrequently involved: only *SF3B1* was mutated in two cases, with the rest of genes including *TP53*, *SMAD4*, and *ATM* mutated in one case. Copy number analysis revealed 56% (19 of 34) chromosomal gain of 19p13.3 and 29% (10 of 34) loss of 16p11.2, both of which cohorts B and C predominated over cohort A. Gene set enrichment analysis between cohorts A and B showed significant enrichments of oxidative phosphorylation and *MYC* target gene sets for up-regulated genes in cohort B. Unsupervised hierarchical clustering analysis of DNA methylation revealed 3 subgroups, of which cluster 1 mainly consisted of cohort A and cluster 2 of cohorts B and C.

Conclusions: Rectal NETs with unfavorable outcomes (cohorts B and C) had unique genomic and epigenetic alterations, which might be used as a prognostic marker for risk stratification of rectal NETs.

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1184MO Safety and efficacy of everolimus (EVE) as second-line treatment in neuroendocrine neoplasms G3 (NEN G3): An AIO phase II study (EVINEC)

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Background: Well-differentiated neuroendocrine tumors G3 (NET G3) represent a separate entity from poorly differentiated neuroendocrine carcinoma (NEC). While platinum-based 1st- line chemotherapy is established in advanced NEC, there is limited efficacy of 2nd- line chemotherapies, and therapy of NET G3 is still under investigation. Since the mTOR inhibitor everolimus mediates disease stabilization in patients with NET G1/G2, and data on targeted therapy in NEN G3 were lacking, we investigated EVE as 2nd- line treatment in NEN G3.

Methods: EVINEC was a prospective, single-arm, phase 2 study planned to enroll 40 patients with histologically confirmed NET G3 or NEC G3 with progressive disease on or after platinum-based chemotherapy. Treatment was EVE at 10 mg/day. The primary endpoint was safety; efficacy measurements were secondary endpoints. Central pathology review was performed by a highly experienced pathologist.

Results: Thirty-nine patients were initially found eligible. For three of these, central review determined their tumors not to be NEN. Of the remaining 36, 13 were NET G3, 14 NEC, and 9 mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN). MiNEN patients remained on study since NEN components were NEC G3. Most frequent EVE-related adverse events were stomatitis (39%), fatigue (31%), diarrhea (28%), nausea (25%), decreased appetite (22%), epistaxis (19%), rash (19%), decreased weight (17%), back pain (14%), dry mouth (14%), aphthous ulcer (11%), dermatitis acneiform (11%), and pyrexia (11%). Two patients (6%) were affected by pneumonitis, and treatment-related infections were reported for 5 patients (14%). Median PFS and OS for the Per Protocol (PP) population were 2.2 and 12.0 mo., in NET G3 5.2 (range 0.7-18.8) and 23.9 mo., in NEC 1.8 and 5.6 mo., and in MiNEN 2.2 and 7.0 mo., respectively. Six patients were excluded from the PP set due to short treatment duration or lack of efficacy assessment.

Conclusions: No clinically relevant safety signals for EVE after prior platinum-based therapy in NEN G3 were identified. The data support efficacy in NET G3 but insufficient activity in NEC or MANEC. More data are warranted from prospective trials in NET G3 to address EVE efficacy compared to other treatments.

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1185MO Activity and safety of avelumab alone or in combination with cabozantinib in patients with advanced high grade neuroendocrine neoplasias (NEN G3) progressing after chemotherapy. The phase II, open-label, multicenter AVENEC and CABOAVENEC trials

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Background: NEN G3 are rare tumors with poor prognosis and have no established 2nd- line therapy. The role of immune checkpoint blockade in these aggressive tumors remains unclear.

Methods: We report the final analysis of the phase II AVENEC study on the effect of anti-PDL1 therapy with avelumab (AVE, 10 mg/kg iv Q2W) in 60 patients (pts) with highly proliferative neuroendocrine tumors (NET) G3 (N=22) or undifferentiated neuroendocrine carcinomas (NEC, N=38) of any origin, progressing after $\geq$ 1 chemotherapy (excluding Merkel cell and small cell lung cancer), and compare it with the interim analysis of 19 progressive NEN G3 pts treated with AVE (800 mg iv Q2W) in combination with cabozantinib (CAB, 40 mg/d po) from the ongoing phase II CABOAVENEC study.

Results: **AVENEC:** Best overall response (iRECIST) of AVE was a partial response (PR) in 3 (5%) and a stable disease (SD) in 9 (15%) pts, with a disease control rate (DCR) at 16 wks of 15 % (1 PR, 8 SD), and a median duration of response of 18.2 wks. 6 pts (10 %) achieved SD or PR for $>$ 24 wks, and 2 pts for $>$ 52 wks. Response was similar regardless of differentiation, Ki67 or primary localization. After a median follow up (mFU) of 27.9 wks, only 11 (18 %) pts were still alive with a median overall survival (mOS) of 21.3 wks (CI 15.0—nr), and a median progression free survival (mPFS) of 8.1 wks (CI 6.1-8.1). AVE was well tolerated with no drug related withdrawals and a stable quality of life (EORTC QLQ-C30). **CABOAVENEC:** preliminary data from 19 pts (12 NET G3, 7 NEC) treated with AVE + CAB show a PR in 4, SD in 5, and progress in 5 pts (5 not yet evaluable). mPFS was 48.1 wks (CI 15,9-nr) with a DCR at 16 wks of 42 % (5/12). After a mFU of 29.1 wks, 17 (85%) pts are alive, with 2 pts still on treatment for $>$ 1 yr. Adverse events of the combination therapy were as expected and manageable.

Conclusions: Only a minority of 10-15% of heavily pretreated NEN G3 pts benefit from AVE monotherapy, which is very well tolerated. However, preliminary data suggest that the combination of AVE + CAB might be more effective in a higher percentage of pts and could therefore be a promising option for 2nd -line therapy for these aggressive tumors.

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1186MO A prospective phase II single-arm trial on neoadjuvant peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE followed by surgery for pancreatic neuroendocrine tumors (NeoLuPaNET)

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Background: Surgical resection of Nonfunctioning Pancreatic Neuroendocrine Tumor (NF-PanNET) is curative in most of the cases. Neoadjuvant treatments in patients with resectable NF-PanNET at high-risk of recurrence have never been investigated. Aim of this study was to test the safety and efficacy of neoadjuvant PRRT with ^{177}Lu-DOTATATE followed by surgery in patients with resectable high-risk NF-PanNET.

Methods: This was a multi-center single-arm phase 2 trial. Treatment was PRRT with ^{177}Lu-DOTATATE (Lutathera) followed by surgery in patients with high-risk of recurrence resectable NF-PanNET. "High-risk NF-PanNET" was defined by the presence of at least one of the following: tumor size > 4 cm, nearby organ/s invasion, Ki67 >10%, vascular invasion, single liver metastasis, nodal involvement. Primary endpoints were postoperative morbidity and mortality. Secondary endpoint was the rate of objective radiological response.

Results: Thirty-one patients were enrolled in the study. Twenty-six (84%) tolerated 4 cycles of ^{177}Lu-DOTATATE whereas 4 patients did not complete 4 cycles for adverse events. One patient voluntary interrupted treatment after 2 cycles. A partial radiological response was observed in 17 patients (59%) whereas no disease progression occurred. Two patients refused to undergo surgery after ^{177}Lu-DOTATATE. Eventually, 29 patients underwent surgery after a median period of 281 days (261.5—309 days) from the enrollment. Resection of NF-PanNET was achieved in 28 patients (96.5%) whereas one patient underwent exploratory laparotomy. Pancreaticoduodenectomy (n= 11) and distal pancreatectomy (n= 11) were the most frequent operations. At final histology, the majority of patients had a NF-PanNET G2 (n= 16) and a nodal involvement (N1) was present in the 52% of cases. There was no postoperative mortality. Severe postoperative complications occurred in the 24% of patients and postoperative pancreatic fistula was the most frequent complication after surgery (34%).

Conclusions: Neoadjuvant PRRT with ^{177}Lu-DOTATATE followed by surgery for NF-PanNET is safe and effective demonstrating evidence of a high rate-of radiological response.

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1187MO Does the ENDOCAN-COMETE network improves the survival of adrenocortical carcinomas in France?

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Background: Adrenocortical carcinoma (ACC) belongs to the family of rare cancers (annual rate of 0.72-1.3 cases/million people). The French national network « ENDOCAN-COMETE », was set up in 2009 to structure care and research on ACC patients across the country. The aim of this study was to look for the survival impact of this national network organization.

Methods: ACC diagnosed between 2010 and 2017 were, first, identified from 13 cancer registries of the French network FRANCIM covering 18% of the French population. This population was described in term of characteristics, systemic managements and treatment delays. Secondly, ACC patients identified by FRANCIM were categorized as 1/ referred to one of the 11 centres of the French ENDOCAN-COMETE network at diagnosis (ACC-R) or, 2/ ACC patients lately or not referred (ACC-nR). The survival rate at 2, 3 and 5 years (2-yrs OS, 3yrs OS and 5yrs-OS) were compared, according to ENSAT stage classified as localized (stage I-II) or advanced (stage III-IV).

Results: Between 2010 and 2017, 134 ACC were diagnosed in this population (mean estimated incidence of 0.14/100000 pers-yrs): 12 (9%) were stage I, 44 (33%) stage II, 17 (13%) stage III and 48 (36%) stage IV (13 patients ENSAT stage was unknown). Among them, 124 patients were analyzed (10 patients were excluded). Eighty-seven out 124 patients (70%) were referred to an ENDOCAN-COMETE network at diagnosis (ACC-R). Mean age at diagnosis was 51.5 yrs (ACC-R) vs. 58.6 (ACC-nR). Overall Survival (OS) rates of localized ACC (ENSAT stage I-II) was significantly higher in ACC-R compared to ACC-nR : 2-yrs OS was 94% vs 65%, 3-yrs OS was 90% vs 65% and 5-yrs OS was 79% vs 51%, p=0.025 (mean OS : 6.6 vs 3.15 yrs). OS rates were similar in advanced ACC (ENSAT stage III-IV) between ACC-R vs ACC-nR. In localized ACC: 39% were ACC-R vs. 54% ACC-nR. By comparing localized ACC-R vs localized ACC-nR, we found that complete resection was found in 76% vs 68%, Weiss score median was 5 vs 5, median Ki67 was 6% vs 15%, presence of endocrine syndrome was 47% vs 35% and age was 47 vs 58 yrs, respectively. Moreover 81% of ACC-R patients received mitotane treatment vs 65% of ACC-nR.

Conclusions: Our study shows a better survival of stage I-II ACC patients treated in the French ENDOCAN COMETE network.

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1188P Landscape of Delta-like-ligand 3 (DLL3) expression across neuroendocrine neoplasms (NENs)

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Background: Delta-like-ligand-3 (DLL3) has emerged as a promising therapeutic target for neuroendocrine neoplasms (NENs), such as small cell lung cancer (SCLC). The spectrum of *DLL3* expression and correlation with genomics across NENs remains ill-defined.

Methods: We retrospectively analyzed DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing from 29 distinct NEN sites encompassing 1589 patient samples submitted to Caris Life Sciences (Phoenix, AZ). *DLL3*-high NENs were defined using a threshold TPM 10x the median expression of *DLL3* in prostate NENs. Centralized pathology review was done on NENs from prostate (n = 64), lung (n = 122), and bladder (n = 64). Immune cell fractions were inferred via quanTIseq (Finotello, 2019). Statistical significance was determined using χ^2 or Fisher's exact tests, with Benjamini-Hochberg correction for multiple comparisons.

Results: Across NENs, prostate (76%), lung (71%), and bladder (77%) displayed the highest expression of *DLL3.* High expression of *DLL3* was associated with shorter survival in all NENs compared with *DLL3*-low tumors (HR=1.9, CI=1.65-2.19, p<0.0001), with the most profound association seen in lung (HR=2.5, CI=1.26-5.09, p=0.007). In lung NENs, *DLL3* expression increased with higher pathologic grade and was more robust in lung NENs diagnosed as SCLC. *DLL3*-high NENs harbored greater rates of pathogenic alterations in *TP53* (51.2% VS 22.8%, q<0.001), *RB1* (41.6% VS 10%, q<0.001), and *KRAS* (13.6% VS 5.4%, q<0.001), and were more likely to be TMB-high (12.1% VS 4.5%) than *DLL3*-low cases. Among known neuroendocrine markers, *DLL3* expression was positively correlated with *ASCL1* and *INSM1* (rho=0.7 and 0.5, p<0.001). Lastly, *DLL3*-high NENs displayed higher fractions of immunomodulatory B cells (5.6% VS 4.5%, q<0.001), dendritic cells (4.6% VS 3.7%, q<0.001), and M1 macrophages (1.6% VS 1.1%, q<0.001).

Conclusions: High *DLL3* expression is associated with poor overall survival, advanced pathologic grade, and distinct immune landscape. Further development of DLL3-targeted therapies for high-grade NENs is warranted.

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1189P Mixed neuroendocrine-non neuroendocrine neoplasms (MiNEN): Characterization of the genomic and pathological profile

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Background: Minens is a novel defined rare entity consisting of two morphologically distinct neoplastic components: one neuroendocrine (Nen) and the other non-neuroendocrine (nNen). Because limited data are available, the epidemiology and pathogenesis of Minens remain largely unknown. This study aims to shed light on the molecular and immunological basis of such a mixed neoplasm by investigating its individual components (Nen and nNen).

Methods: A total of 18 Minen patients with available archival tissue material (under treatment at the IRCCS "G.Pascale" of Naples from 2010 to date), will be examined by clinical review, IHC analysis and sequencing via the Illumina tso500 panel. Each primary NEN and nNEN component was obtained by laser microdissection (LMC).

Results: Preliminary data showed a similiar cumulative coverage in samples. Patients had a homogeneous percentage distribution related to Snps and, excluding synonymous mutations, we found an average of 700 variants of 194 genes. Notably, 45.42% of the mutations were shared in both the parts among all the patients, while unique mutations remained unique after intersection among groups. We have also investigated Vafs of shared and unique mutations between tumoral component. Different trend was observed among exclusive mutations in each patients although the load of mutation with low Vafs stayed the same. The latter might indicate that subclone mutations arises later in the tumor's expansion, whereas the presence of high Vafs in shared mutations suggests a possible simultaneous origin in the early stages. Both phenotypes might contribute to the insurgency of the tumor. To interpret the biological role of amplified genes we performed a GO term analysis, that indicated a common involvement for of the *PI3K/AKT axis.*

Conclusions: We suggest that Minens are mainly of monoclonal origin, but they may undergo bi-phenotypic differentiation during the carcinogenesis process. New drug development should exploit the common biological vulnerabilities between the two components. From our results, a potential molecular target could see the PI3K/AKT/mTor signaling pathway involved.

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1190P Comparative gene expression and mutational profiling of neuroendocrine neoplasm in relation to clinical outcome

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Background: Neuroendocrine malignancies are heterogenous cancers with varied clinical outcomes, yet molecular landscape driving this heterogeneity has not been fully characterized. We aimed to investigate the gene expression and mutational profile of neuroendocrine neoplasms in relation to clinical outcomes to better understand the underlying biology and therapeutic targets.

Methods: Patients with neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) treated at Cleveland Clinic (2000-2022) with molecular profiling (N=66) were identified. Mutational and gene expression profiles were abstracted from EHR. Clinicopathological characteristics and overall survival (OS) were obtained from EHR. Statistical analyses were performed by R v.4.0.5 and R package Limma for differential gene expression, as well as Chi-square, Fisher Exact & Wilcoxon rank sum tests.

Results: The study cohort consisted of 38 patients with NEC, 18 NET grade 3, and 10 NET grade 1/2. Most common primary sites in NETs were small bowel (n=12, 43%) & pancreas (n=6, 21%) versus colorectal (n=10, 26%) & lung (n=7, 18%) in NECs. *EZH2* and cyclin E1 were differentially overexpressed in NEC vs. NET ($p < 0.05$), while *PTEN* and *MSLN* were differentially under-expressed in NEC vs NET ($p < 0.005$). Regarding mutational profiles, several recurrent alterations co-segregated with aggressive histology (NEC vs NET), including *TP53* ($p<0.0001$), *RB1* (p=0.0003), *KRAS* (p=0.009), & *APC* (p=0.006) mutations. *MEN1* mutation on the other hand co-segregated significantly with pancreatic primary NETs ($p<0.00001$). Among patients with NEC, higher expression of cyclin D1 & *EGFR* were associated with improved 2-year OS ($p < 0.05$). Among NECs, age less than 60 years was associated with significantly increased median OS (21 months vs 11 months, $p < 0.05$). However, there was no significant difference in OS in NET patients less than 60 vs more than 60 in our cohort. Also, there was no difference in gene expression profile in the two age groups among NETs or NECs.

Conclusions: Our analysis revealed differential expression of potentially targetable genes in NEC and NET. Higher expressions of cyclin D1 and *EGFR* were associated with statistically significant increase in 2-year OS in patients with NEC.

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1191P TTF-1 expression in lung neuroendocrine tumors (NET): A gender-related biomarker

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Background: Thyroid transcription factor-1 (TTF-1), is expressed in thyroid and lung tissue. TTF-1, assessed by immunohistochemistry (IHC), is a specific biomarker for lung adenocarcinoma, and is commonly used to confirm the pulmonary origin of neuroendocrine tumors (NET), as well. The majority of the available data suggest that TTF-1 is a favourable prognostic biomarker for lung adenocarcinomas, whereas its role in lung NET is controversial.

Methods: A multicenter retrospective study, including 155 Lung NET, all surgically removed, all with available IHC assessment for TTF-1.

Results: Median age was 59.5 years (13–86), N= 58 patients (37.4%) were males, N=40 (25.8%) were smokers, N=31 (20%) were atypical carcinoids, N=85 (54.8%) were centrally-located, N=89 (57.4%) were located in the right lung, N=4 patients (2.6%) presented a TNM stage IV at the diagnosis. Mitotic count was ≥2 per 10 high-power field (HPF) in N=35 cases (22.6%), necrosis was present in N=20 (12.9%). Grade 1 was reported in 103 cases (66.5%), whereas Ki-67 was >20% in N=5 (3.2%). TTF-1 was positive in 78 cases (50.3%), cromogranin A in 139 (89.7%) and synaptophysin in 137 (88.4%), respectively. The most common type of surgery was lobectomy in 91 patients (58.7%). Median overall survival (OS) was 46.9 months (0.6–323), median progression-free survival (PFS) was 39.1 months (0.6–323). Statistically significant associations were found between (i) TTF-1 positivity and female sex (*p=0.007*), and among (ii) TTF-1 positivity and the absence of necrosis (*p=0.018*). No other relevant associations were detected between TTF-1 and the remaining clinical or pathological variables.

Conclusions: This study highlights that TTF-1 positivity differs according to sex in lung NET patients, with a more common TTF-1 positive staining in female. Moreover, TTF-1 was associated with the absence of necrosis. These data suggest that TTF-1 could potentially represent a gender-related biomarker in this population. Further analyses

are needed to establish the value of this observation, and to determine the value of TTF-1 as prognostic biomarker for lung NET.

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1192P Smoking adversely affects survival of metastatic lung carcinoid patients: Analysis of a large international audit

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Background: Among neuroendocrine lung cancers, lung carcinoids (LC, further divided into typical [TC] and atypical [AC]) are rare, representing only the 2% of all bronchopulmonary malignancies, and lack prognostic classification and stratification.

Methods: We audited two international cohorts of patients with a confirmed diagnosis of LC for prognostic analysis. We used data from The Christie Hospital (Manchester, UK; N=282) and validated our findings using the cohort of Vall d'Hebron Hospital patients (Barcelona, Spain, N=80). We collected patient data and applied modelling strategies to identify a prognostic model for metastasis-free survival (MFS) and overall survival (OS) from metastatic disease.

Results: Blood lactic dehydrogenase (LDH) and tumour Ki67% were significant at multivariable analysis (stratified for stage) for MFS (C-index=0.69, P=0.0016), while histological subtype (TC vs AC) and other clinical variables were not. Independent prognostic factors for OS from onset of metastases included smoking history, along with known factors (patient age and performance status, proliferation index, PET maximum SUV). The model C-index was 0.84 (P=0.01678), with optimal concordance when applied to the external validation cohort from Vall d'Hebron. Previously undescribed, patients with smoking history lived shorter (median OS 34 months vs not reached, P<0.0001), and our data also suggested that the median OS could be shorter in current smokers (26.2 months) compared to ex-smokers (35.3 months).

Conclusions: We provide a novel prognostic tool to estimate patient risk, clinical trial stratification and assist clinical decisions in the rarest lung tumours. LDH blood levels have not been described as prognostic in this disease, so provide a new reliable biomarker to stratify MFS. We also describe for the first time that smoking history is an independent prognostic factor for overall survival in this cancer. Our results warrant to update the prognostic factors for LC and provide evidence to recommend that patients should stop smoking.

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1193P Evaluation of treatment appropriateness in patients submitted to surgery for non-functioning pancreatic neuroendocrine tumors (NF-PanNETs)

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Background: Currently availbale preoperative prognostic factors for non-functioning pancreatic neuroendocrine tumors (NF-PanNETs) still struggle to predict tumor aggressiveness, making an adequate management of these lesions hard to be achieved. Aims of this study were: i) to evaluate treatment appropriateness in patients submitted to surgery for NF-PanNETs, and ii) to investigate preoperative features predicting undertreatment or overtreatment in this setting.

Methods: Patients who underwent curative surgery (R0-R1) for NF-PanNETs at San Raffaele Hospital (2002-2022) were retrospectively analysed. Treatment appropriateness was categorized as appropriate treatment, overtreatment, and undertreatment. The presence of histological features of aggressiveness and the occurrence of disease relapse within one year from surgery were considered to define treatment appropriateness.

Results: Overall, 384 patients were included. Of these, 230 (60%) received an appropriate treatment, 129 (34%) an overtreatment and 25 (6%) an undertreatment. Treatment appropriateness was significantly associated with radiological tumor size ($p<0.001$), tumor site ($p=0.012$), surgical technique employed ($p<0.001$), and year of surgical resection ($p<0.001$). Surgery performed before 2015 ($p<0.001$), radiological tumor diameter <25.5mm ($p<0.001$) and pancreatic body/tail location ($p=0.018$) were identified as independent predictors of overtreatment. Radiological tumor size was the only independent determinant of undertreatment ($p=0.016$). Significantly poorer disease-free survival ($p<0.001$), overall survival ($p<0.001$) and disease-specific survival ($p<0.001$) were observed among undertreated patients.

Conclusions: Overtreatment occured in almost one-third of patients undergoing surgery for NF-PanNETs. However, over the last decade, the percentage of appropriately treated patients has been steadily increasing. Surgical management should be carefully considered in presence of lesions located in the pancreatic body-tail and/or measuring <25.5 mm, in order to further improve treatment appropriateness.

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1194P Do metastatic appendiceal NETs ever develop metachronously after appendectomy or right hemicolectomy?

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Background: Neuroendocrine tumors of the appendix are typically detected incidentally during appendectomy. A recent study reported no cases of metachronous metastases among patients with primary tumors <2cm, regardless of lymph node status or referral for completion hemicolectomy. However, questions persist regarding the possibility of metastases developing decades after surgery, particularly since appendiceal NETs are frequently diagnosed in young adults and children.We therefore sought to evaluate patients with metastatic appendiceal NETs to assess whether any had been diagnosed previously with an early stage appendiceal NET.

Methods: We analyzed a large institutional neuroendocrine tumor database to identify appendiceal NETs of all stages and ascertain whether any patients with localized tumors developed metastases, and whether any with metastatic disease had originally presented with an early-stage tumor.

Results: Out of over 5,000 patients seen in the neuroendocrine tumor clinic between 2008 and 2022, 95 were diagnosed with an appendiceal NET. Of these, only 6 patients (approximately 0.1% of total NET population) had stage 4 metastases, all diagnosed synchronously at time of initial diagnosis. All 6 patients had peritoneal disease. No patient with earlier-stage disease developed distant metastases.

Conclusions: Metastatic appendiceal NETs are exceptionally rare with a tendency to metastasize within the peritoneum. In all cases of stage 4 disease, metastases were observed at time of diagnosis. Our data provide further validation for the proposition that small local appendiceal NETs resected during appendectomy require no further surgery or surveillance.

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1195P Neuroendocrine Tumors (NETs): How Big Data (BD) techniques applied to Electronic Health Records (EHR) can improve our understanding of this patient population

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Background: Low incidence and heterogeneity of NETs complicates the study of epidemiological and clinical pathways in this population. There is an unmet need for large datasets and BD tools to fill this knowledge gap. Our study aimed to describe the demographic and clinical characteristics of patients with NETs in Spain through the application of BD techniques to EHR.

Methods: This was a retrospective, observational study in adult patients with NETs managed in 5 Spanish centers between 01/01/2014 to 31/12/2019. An unstructured search of free text from EHRs was performed by artificial intelligence (AI) techniques based on SAVANA's EHRead®, an innovative Natural Language Processing and machine learning system. Patients were included when NET was first identified (Index Date) and classified as `Incident´ or `Prevalent´ if the Index Date was within the study window or not, respectively.

Results: A total of 2,939,309 patients were screened by EHRead and 1,256 NETs cases were found: median age 60y (95% CI 59 - 62), 52% female, 41% with gastroenteropancreatic origin, and 44% were categorized as incident (Table). More than 70% of patients presented symptoms prior to diagnosis and >10% had metastases at diagnosis (>70% were non-resectable). Median time from symptom onset to first diagnosis was 0.6 years (95% CI 0.4 - 0.73). The most frequently detected comorbidities were hypertension (66%), diabetes (35%), asthma (22%), and depression (17%). A previous diagnosis of cancer different from NETs was reported in 21% of cases. Uncommon clinical events included brain metastases (1%) and familial history of NETs (1.1%).

Table: 1195P Classification of patients with NETs

	FAS (N=1,256) n (%)	Prevalent (N=700) n (%)	Incident (N=556) n (%)
Patients with symptoms before Index Date	366 (29.1)	0 (0)	366 (65.8)
Primary NET site			
Gastroenteropancreatic	412 (41.4)	235 (42.7)	177 (39.7)
Bronchopulmonary	171 (17.2)	81 (14.7)	90 (20.2)
Other*	413 (41.5)	234 (42.5)	179 (40.1)
Classified by surgery at Index Date§			
Thyroidectomy	9 (0.9)	3 (0.5)	6 (1.3)
Adrenalectomy	1 (0.1)	0 (0)	1 (0.2)
Other classifications	1 (0.1)	1 (0.2)	0 (0)
Unclassified NETs	260 (20.7)	150 (21.4)	110 (19.8)

* Paraganglioma, adrenal gland and medullary thyroid carcinomas and pheochromocytomas
§ Within +/-6 months of Index Date

Conclusions: BD Techniques should improve generation of large datasets in low incidence neoplasms and help identify uncommon events. NETs diagnosis is delayed about 6m after symptom onset and comorbidities may influence the choice of treatment.

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1196P Regional lymph node metastasis risk factors for rectal neuroendocrine tumors: A population-based study

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Background: **Regional lymph node metastasis risk factors for rectal neuroendocrine tumors: a population-based study** A short title: Regional lymph node metastasis risk factors for rectal neuroendocrine tumors **Key words:** regional lymph node metastasis, rectal neuroendocrine tumors, SEER, West China Hospital (WCH) databases, tumor size. Purpose: Risk factors for regional lymph node (r-LN) metastasis in rectal neuroendocrine tumors (R-NETs) are still undetermined. We aimed to explore risk factors for patients with r-LN metastatic R-NETs. Information on patients was obtained from the Surveillance, Epidemiology, and End Results (SEER) and West China Hospital (WCH) databases.

Methods: Patients diagnosed with R-NETs between January 2010 and December 2015 from the SEER database composed the construction cohort, while cases from the WCH database were used as the validation cohort. A novel nomogram was constructed to predict r-LN metastasis probability based on a logistic regression model. The performance of the nomogram was internally and externally validated using calibration curves and the concordance index (C-index).

Results: Multivariate logistic analysis identified four poor independent r-LN metastasis factors, including age ($\geq$ 53), differentiation grade (> G1), T stage of primary tumor (> T1) and tumor size (> 1 cm), which we selected as the four risk predictors for nomogram construction. In the internal validation and external validation, the C-index in the internal validation set and the external validation set were 0.968 and 0.877, respectively. The nomogram model was well calibrated, and the ROC curves verified the superiority of our model for clinical usefulness. In addition, the nomogram classification could more accurately differentiate risk subgroups and improve the discrimination of R-NET prognosis.

Conclusions: We developed and validated a prediction risk model of r-LN metastasis for patients with R-NETs. The novel nomogram is a reliable tool to predict the risk of r-LN metastasis, which may assist clinicians in identifying high-risk patients and devising individual treatments.

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1197P Somatostatin analogs or active surveillance in sporadic non-functioning pancreatic neuroendocrine tumors

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Background: Non-functioning, sporadic, G1-G2 pancreatic neuroendocrine tumors usually display an indolent course. Surgery is the first-choice treatment for localized tumors >2 cm. Unresectable or metastatic PanNETs expressing somatostatin receptors are treated with somatostatin analogs (SSAs). The PROMID and the CLARINET studies proved the SSA antiproliferative effect in advanced gastro-entero-pancreatic neuroendocrine tumors. The standard treatment for patients with PanNETs $\leq$2cm is active surveillance. Yet no evidence of the value of SSA treatment exist in such patient population.

Methods: We retrospectively collected data from 72 patients with sporadic non-functioning G1-G2 PanNETs$\leq$2cm, 31 treated with somatostatin analogs and 41 underwent to active surveillance at our Institution. Median progression-free survival (mPFS) and response rate (RR) were analyzed in SSA group and AS group. Survival was described by the Kaplan-Meier method with Mantel-Haenszel log-rank test. Cox-regression analysis was used to assess, both singularly and collectively, the weight of clinically relevant covariates on survival outcomes. Statistical significance was declared at two-sided $p<0.05$.

Results: At a median follow-up of 53.7 months, the median progression free survival was not reached in the treatment group versus an estimated PFS of 85 months in the control group (HR 0.11, $p = 0.01$), with a rate of progression or death up to 21.9% in

the active surveillance group. Further, in the group of patients treated with somatostatin analogs response rate was 16.1% with one complete response.

Conclusions: Our monocentric experience demonstrated a significant antiproliferative activity of somatostatin analogs in patients with sporadic, non-functionating G1-G2 PanNETs ≤2cm delaying tumor progression and distant spread in small lesions that sometimes may reveal an unpredictable aggressiveness.

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1198P Phase Ib portion of the ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after 177Lu somatostatin analogue (SSA) therapy: Safety and efficacy findings

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Background: RYZ101 (^{225}Ac-DOTATATE) is an alpha-emitting radiopharmaceutical in development for SSTR2+ solid tumors. Alpha-particles have a shorter path length/higher linear energy transfer than beta-particles, causing more frequent double-strand DNA breaks and potentially improved therapeutic index. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in advanced, well-differentiated SSTR+ GEP-NETs progressing after ^{177}Lu-SSA therapy. Herein, we report results from the phase Ib portion of the trial.

Methods: The phase Ib portion had a dose de-escalation/Bayesian optimal interval design with boundaries based on a dose-limiting toxicity (DLT) rate of 25%. Patients (pts) received RYZ101 IV q8w x4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose) 120kBq/kg; Level −1 90kBq/kg; Level −2 60kBq/kg. DLT was assessed for 56d after the first RYZ101 dose. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions/safety data were overseen by a Data Review Committee. Tumor response was assessed locally by RECIST v1.1.

Results: 17 pts have received at least one dose of RYZ101 at 120kBq/kg (4 doses: 6 pts; 3 doses: 2 pts; 2 doses: 8 pts; 1 dose: 1 pt; median 8.9MBq). Baseline characteristics: median age 63y; male (n=11); ECOG PS 0/1 (n=10/7); primary tumor site GI/pancreas (n=12/5). No DLTs, no dose de-escalation and no treatment-related serious AEs (SAEs) occurred. TEAEs requiring dose reductions occurred in 2 pts (G2 thrombocytopenia, n=2). G3/4 TEAEs occurred in 6 pts, 3 related to RYZ101 (lymphopenia, n=2; weight decreased, n=1). SAEs occurred in 4 pts (all unrelated). Confirmed objective response was seen in 5 evaluable pts. Updated efficacy data will be provided at the congress.

Conclusions: RYZ101 was well tolerated and a fixed dose of 10.2MBq was declared the recommended phase 3 dose. Initial data suggest promising efficacy. Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2MBq q8w for 4 cycles with standard of care in pts with advanced SSTR2+ GEP-NETs progressing following prior ^{177}Lu-labeled SSAs.

Clinical trial identification: ACTION-1 (NCT05477576).

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1199P MAVERIC: Phase II randomized study of everolimus as maintenance therapy for metastatic neuroendocrine neoplasms (mNEN) with pulmonary or gastroenteropancreatic (GEP) origin. Results on behalf of the GOIRC

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Background: NEN are a group of heterogeneous malignancies that most commonly arise in the GEP tract. Usually > 20% Ki-67 NEN, including both well and poorly differentiated, are treated with chemotherapy (CT) but the schedule and duration is debated and no evidence about a maintenance therapy exists.

Methods: MAVERIC is a randomized, multicentric, phase II trial. Patients (pts) with well/moderately or poorly differentiated mNEN from GEP or lung primary sites with Ki-67 between 20% and 55% in response after a first -line (1L) CT were randomized with a 2:1 ratio to maintenance therapy with everolimus 10 mg day or to observation until progression or treatment intolerance. Randomization was done using a centralized web-based system. The primary endpoint was progression free survival (PFS) and the secondary endpoints were overall survival (OS) and safety. The study design was formally non-comparative.

Results: Of 30 patients enrolled between 2015 and 2022 in 5 centers, 20 were randomized to everolimus and 10 to observation; 29 resulted eligible for the analysis. 52% had a GEP and 48% a pulmonary primary site. The median follow-up was 30.3 mo. Median PFS was longer for the experimental arm (1.8 mo vs. 11.4 mo; p=0.022). Median OS was 38.3 and 38.2 mo for the experimental and control arms, respectively (p=0.43). In the experimental arm, G3 adverse events (AEs) occurred in 55% of pts (most commonly mucositis/stomatitis (27.7%) and neutropenia (27.7%)). No G4 AEs occurred. 65% of pts required a dose reduction and 2 pts discontinued treatment due to AEs.

Conclusions: This study may suggest a role for everolimus as a maintenance therapy following 1L CT in selected pts with high-grade GEP or lung NEN with Ki67 between 20% and 55%. Homogeneous prospective studies are warranted to validate this hypothesis.

Clinical trial identification: EudraCT n. 2014-003951-72.

Legal entity responsible for the study: Lorenzo Antonuzzo.

Funding: Has not received any funding.

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1200P A phase II single-arm interventional trial evaluating the activity and safety of CABOzantinib (CBZ) plus TEMozolomide (TMZ) in lung and gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) progressed after SSA therapy, everolimus, sunitinib or PRRT: CABOTEM Trial

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Background: Both CBZ and TMZ have already shown clinical efficacy in patients (pts) with NENs when used in monotherapy. Preclinical evidence demonstrated that downregulation of c-MET increases the sensitivity of glioblastoma cell lines to TMZ, and we hypothesized that CBZ could enhance the clinical efficacy of TMZ against NENs by inhibiting c-MET. The Cabotem trial aims at evaluating the efficacy and safety of CBZ in combination with TMZ as a treatment in lung and GEP-NENs progressive to SSAs, everolimus, sunitinib or PRRT.

Methods: This is a phase II, open-label, single-arm, multicentre study. Thirty-five pts were treated with CBZ (40 mg per os daily continuously) and TMZ 100 mg/m^2/day (one week on/one week off). The primary endpoint was overall response rate (ORR) assessed by RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and 1-year OS.

Results: Of the 33 patients enrolled (M: 14, F: 19; pancreas:12; GI: 9; Lung: 8; UNK: 4), 25 are currently evaluable for response. After a median follow-up of 6 months, an ORR of 12% was recorded, with a clinical benefit rate (CR+PR+SD) of 72%. Ten patients prematurely discontinued the treatment (median: 3 months) due to severe adverse events (AEs). The most common G3/G4 treatment-related AEs were thrombocytopenia, palmar/plantar erythrodysesthesia, nausea, vomiting, appetite loss and dysgeusia.

Conclusions: The combination of CBZ and TMZ shows promising antitumor activity in patients with NENs. While tolerability appears to be an issue, the relatively high rate of toxicities observed in this study should be weighted against the characteristics of a heavily pretreated patient population.

Clinical trial identification: EudraCT 2020-001898-78.

Legal entity responsible for the study: Istituto Nazionale Tumori IRCCS G. Pascale of Naples.

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1201P Evaluation of efficacy TEMCAP regiment as first-line or further line therapy in patients with advanced, unresectable, progressive GEP-NET. Real-world data

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Background: Retrospective, single-institution study accessing the efficacy of TEMCAP regiment in pts. with advanced, unresectable progressive GEP-NET as a first or further lines after initial disease progression. Primary endpoint: progression-free survival (PFS), as initial with/without SST analogues previous therapy, PFS as second or further lines therapy using locally evaluation according to RECIST 1.1. Secondary goals: PFS in different subgroups and overall survival (OS).

Methods: 54 pts with advanced unresectable, progressive GEP-NET. Mean age 58.0 (SD+/-12.4). All histological confirmed NETs: G1 n=10, G2 n=31, G3 n=13. Standard therapy approach using TEMCAP in all subjects. Disease status and treatment efficiency were evaluated according to localization of primary, initial vs. second or further line systemic therapy, bulky (>25% of liver volume) vs. not bulky liver disease, male vs. female, BMI ≤24 or BM I>24. Standard KM method used to assess PFS and OS for all subjects and in different subgroups. Cox regression model to assess any significant covariates of PFS and OS.

Results: Pancreatic (panNET) n=32, midgut n=8; hindgut n=7 and 7 pts with CUP. PFS for all group 8.0 months (IQR 5.0-15.0), OS from initial diagnosis of GEP-NET 56.8 months (IQR 25.3-96.5); panNET n=32 -PFS=8.0 months (IQR 5.0-16.1), non-pancreas (n=22) PFS=6.2 (IQR 4.0-10.0), n.s. Initial therapy with TEMCAP n=24- PFS=9.2 (6.0-15.0) vs. second or further therapy n=30, PFS=6.0 (IQR 4.1-9.9) n.s. Bulky liver disease (n=31) PFS=7.9 (IQR 5.0-10.0) v.s. non-bulky liver disease (n=23) PFS=7.4 (IQR 4.4-17.0) n.s. Male (n=20) PFS=9.0 (IQR 5.7-15.0), vs. female (n=34) PFS=6.5 (IQR 5.0-11.5), n.s. Median BMI >24.0 PFS=7.0 (IQR 5.0-10.9), vs BMI≤24 PFS=9.0 (IQR 9.0-15.0), n.s. Cox Regression model did not find any significant predictor of improvement in PFS. In Cox regression model of OS indicated that high grade NET (G3) had HR=2.92 (CI 1.17-17.2) of death.

Conclusions: TEMCAP in real world data seems to be a good option in advanced, progressive GEP-NET with PFS=8 months, independently from the primary site, sex, BMI, liver involvement and previous therapy. Overall potential benefits in OS is seen in NETG1 or G2, but not in G3 with HR=2,92.

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1202P Final analysis of TENEC trial: A phase II trial of temozolomide (TMZ) as second-line treatment for advanced neuroendocrine carcinomas (NEC) in patients (pts) with a poor performance status (PS)

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Background: There is no consensus on the second-line regimen for pts with progressive NEC. These patients (pts) generally have poor performance status (PS) and low tolerance to combination therapy. Metronomic TMZ showed, in retrospective trials, a good safety and efficacy profile. This trial aims to assess the efficacy of TMZ given every other week in pts with advanced platinum-pretreated grade 3 (G3) poorly-differentiated neuroendocrine neoplasms (NEN) and NEC.

Methods: TENEC is an open-label, non-randomized, phase II trial that recruited pts with platinum-pre-treated metastatic neuroendocrine carcinoma. Pts received 75 mg/

m^2/day of TMZ for 7 days followed by 7 days of no treatment (regimen 1 week on/1 week off). The primary endpoint was the overall response rate (ORR) analysed by the Kaplan-Meier method. Secondary endpoints included progression-free survival (PFS), overall survival (OS), safety and tolerability.

Results: From 2017 to 2020, 38 pts were enrolled. The median age of enrolled pts was 61.5 years (25−77). Two pts (5.3%) had an Eastern Cooperative Oncology Group (ECOG) PS score of 0, 58% had an ECOG PS score of 1, 34% had an ECOG PS score of 2 and 3% had an ECOG PS score of 3. Among the pts with determined Ki67, 33.3% had a Ki67 index <55%, and 66.6% had Ki67 index ≥55%. Thirteen pts (34%) had metastases in a single site, 12 pts (31%) had two different sites of metastasis, and six pts (15%) had metastases in three or more sites. ORR was 18%, including one complete response and six partial responses. The median PFS was 6.5 months (95% CI: 5.1−14.5), and the median OS was 12 months (95% CI: 5.6−20.8). The 1-year PFS rate was 37%. No statistically significant difference in median OS (p=0.81, hazard ratio [HR] 95% CI: 0.5−1.9) and median PFS (p=0.85, HR 95% CI: 0.4−2) was observed among pts with Ki67 <55% vs ≥55%. Nausea, diarrhoea and abdominal pain were the most common adverse.

Conclusions: One-week-on/one-week-off TMZ shows promising activity in pts with NEN G3 and NEC. The excellent safety profile confirmed the possibility of using this scheme in pts with poor performance status. Randomised trials are warranted to confirm treatment benefits showed in this trial.

Clinical trial identification: EudraCT 2016-005238-31; NCT04122911.

Legal entity responsible for the study: Salvatore Tafuto.

Funding: Has not received any funding-.

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1203P Role of tumor markers before or during chemotherapy for poorly differentiated neuroendocrine carcinomas of the digestive system: An exploratory analysis of JCOG1213

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Background: Poorly differentiated neuroendocrine carcinomas (PDNECs) are high-grade neuroendocrine neoplasms with an extremely poor prognosis. Previously, we reported the results of a randomized phase 3 trial (JCOG1213), which compared between etoposide plus cisplatin and irinotecan plus cisplatin in patients with neuroendocrine carcinomas (WHO 2010) of the digestive system, showing a statistically non-significant difference in overall survival. It is unclear whether tumor markers (TM), such as NSE and ProGRP, can be predictors or monitoring indicators of the efficacy in PDNEC treatment. This exploratory analysis using the data from JCOG1213 aimed to evaluate whether 1) pre-treatment TM levels can predict treatment efficacy and 2) the change in TM levels after treatment initiation is relevant to treatment efficacy.

Methods: In 137 patients with a central pathological diagnosis of PDNECs out of 170 patients enrolled in JCOG1213, the following analyses were performed: 1) association between pre-treatment NSE/ProGRP levels (elevated or normal with the cutoff of 10 ng/mL in NSE and 46 ng/mL in ProGRP) and tumor response (RECIST v1.1), 2) association between response and the change (increased or decreased) from baseline in NSE/ProGRP at 6 weeks after treatment initiation was evaluated.

Results: 1) Pre-treatment NSE levels were elevated/normal in 127/9 patients and ProGRP levels were elevated/normal in 74/60 patients. There were no meaningful difference in terms of response rate: 58%/56% in patients with elevated/normal NSE and 61%/57% in patients with elevated/normal ProGRP. 2) The response rates were 65% (68/104) in patients with decreased NSE and 32% (8/25) in patients with increased NSE (p=0.0043). The response rates in patients with decreased/increased ProGRP were 68% (43/63)/52% (32/62).

Conclusions: In patients with PDNEC of the digestive system, pre-treatment NSE/ProGRP levels was not associated with tumor response. As treatment monitoring indicators, changes in NSE may be more relevant to tumor response than ProGRP.

Legal entity responsible for the study: Japan Clinical Oncology Group.

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Disclosure: T. Satake: Financial Interests, Institutional, Local PI: ONO, Nihon Servier. C. Morizane: Financial Interests, Personal, Advisory Board: Yakult, MSD, Servier, Boehringer Ingelheim, AstraZeneca, Taiho Pharmaceutical, Merck biopharma; Financial Interests, Personal, Invited Speaker: Novartis, Teijin Pharma; Financial Interests, Institutional, Coordinating PI: Yakult Honsha, ONO Pharmaceutical, Taiho Pharmaceutical, Eisai, MSD K.K., J-Pharma, AstraZeneca, Merck biopharma; Financial Interests, Institutional, Funding: Daiichi Sankyo RD Novare, Hitachi. N. Machida: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Ono, Taiho, MSD, Daiichi Sankyo, Yalult, Eli lilly Japan, Chugai, Astellas, Takeda, Merck biopharma, Nichi-iko, nippon-kayaku; Financial Interests, Institutional, Local PI: Bristol Myers Squibb, Ono, Daiichi Sankyo, Astellas, MSD, Amgen, ALX Oncology, Seagen. Y. 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Ltd., Toray Industries, Inc., Daiichi Sankyo Company, Limited, Chugai Foundation for Innovative Drug Discovery Science, Nippon Kayaku Co., Ltd, EA Pharma Co.,Ltd, Intuitive Surgical G.K., Takeda Pharmaceutical Company Limited, Sysmex Corporation, Tsumura & Co.; Financial Interests, Personal, Advisory Board: Bristol Myers Squibb K.K., Ono Pharmaceutical; Financial Interests, Institutional, Funding: Asahi Kasei Pharma Corporation, Chugai Pharma, EA Pharma, Eisai , Kaken Pharmaceutical, Kyouwa Kirin Co., Ltd., Nippon Covidien, Ono Pharmaceutical, Otsuka Pharmaceutical Co., Ltd., Taiho Pharmaceutical, Takeda, Teijin Pharma, Tsumura & Co., Yakult Honsha, Otsuka Pharmaceutical Factory Inc., Sumitomo Pharma Co., Ltd., Cardinal Health., Kowa Company, Ltd.. M. 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1204TiP Iadademstat in combination with paclitaxel in relapsed/refractory small cell lung carcinoma (SCLC) and extrapulmonary high grade neuroendocrine carcinoma (NEC)

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Background: Patients (pts) with extensive-stage (ES) SCLC or extra-pulmonary grade 3 (G3) NEC rapidly develop progressive disease after 1st -line cytotoxic chemotherapy, and efficacious 2nd -line treatment options are needed. Lysine Specific Demethylase 1 (LSD1, aka KDM1A) is involved in repressing transcription by removing methyl groups from mono- and di-methylated lysine 4 of histone 3, epigenetic hallmarks commonly associated with actively transcribed genes. LSD1 over-expression is associated with tumor progression and worse prognosis, and its inhibition reduces cancer cell growth, migration, and invasion. The epigenetic drug iadademstat (aka ORY-1001 or iada) is a highly potent and selective LSD1 inhibitor (LSD1i) in phase 2 clinical development for malignant indications. Iada and other LSD1is are effective in in vitro and in vivo models of SCLC by preventing INSM1 recruitment of LSD1 which results in NOTCH signaling activation, reduced NE differentiation and tumor growth inhibition. Additionally, LSD1is have been implicated in reversing chemoresistance, synergizing with paclitaxel, and enhancing immunostimulatory responses by increasing MHC-Class I expression, IFN-Type I responses and T-cell infiltration and activity.

Trial design: NCT05420636 is a multi-center, non-randomized phase II study to treat up to 42 pts with iada (150 mg oral, 5d on-2d off every week) and paclitaxel (80 mg/m2 IV weekly) in 21 day cycles. Eligibility includes adult pts with metastatic/unresectable SCLC (cohort 1) or extra pulmonary G3 NEC or metastatic/unresectable prostate or bladder cancer with G3 NE or small cell component (cohort 2), who have received 1 to 3 prior lines of therapy and progressed on or after platinum-based chemotherapy. Pts must have measurable disease, normal organ, and marrow function, stable brain mets, ECOG status $\leq$1 and not have received prior taxanes for metastatic disease. The primary endpoint is ORR per RECIST 1.1; secondary endpoints include rate of $\geq$ grade 3 toxicities, PFS, OS and DoR. Exploratory endpoints include host inflammatory cytokine and immune profile, and epigenomic and genomic analysis of tumor and peripheral blood samples.

Clinical trial identification: NCT05420636.

Legal entity responsible for the study: Fox Chase Cancer Center.

Funding: Oryzon.

Disclosure: N. Vijayvergia: Non-Financial Interests, Institutional, Local PI: BMS, ITM; Financial Interests, Personal, Advisory Board: Taiho, ITM; Non-Financial Interests, Institutional, Principal Investigator: Oryzon, Puma; Non-Financial Interests, Personal, Advisory Role: Rayze Bio. P. Ghatalia: Non-Financial Interests, Institutional, Research Funding: BMS, Oryzon, Merck. D. Faller: Financial Interests, Personal, Full or part-time Employment: Oryzon. A. Limon: Financial Interests, Personal, Full or part-time Employment: Oryzon. H.P. Soares: Financial Interests, Personal, Advisory Board: Tersera, Ipsen, AstraZeneca, Novartis, ITM. J. whetstine: Financial Interests, Institutional, Research Funding: Oryzon, Salarius Pharma; Financial Interests, Personal, Advisory Board: QSonica, Vyne Therapeutics, Daichii Sankyo, Lily Asia Ventures. H. Borghaei: Financial Interests, Personal, Advisory Board: BMS, Genentech, Eli-Lilly, Merck, EMD-serono, AstraZeneca, Novartis, Genmab, Regeneron, Amgen, Takeda, PharmaMar, Jazz Pharma, Mirati, Daiichi, Guardant, Natera, Oncocyte, BeiGene, iTeo, Boehringer Ingelheim, Puma, BerGenbio, Janssen; Financial Interests, Personal, Other, Training discussion: Pfizer; Financial Interests, Personal, Other, DSMB: Novartis; Financial Interests, Institutional, Other, Clinical trial support: BMS, Amgen; Financial Interests, Personal, Stocks/Shares, Options for scientific advisory role: Sonnetbio; Financial Interests, Personal, Stocks/Shares, Options for scientific advisory board: Nucleai, Inspira (Rgenix); Financial Interests, Institutional, Trial Chair, Investigator initiated trial support: BMS; Financial Interests, Institutional, Coordinating PI, Investigator initiated trial support: Amgen, Lilly; Financial Interests, Personal and Institutional, Trial Chair, Chair steering committee: Miratti; Financial Interests, Personal and Institutional, Steering Committee Member: Amgen, AstraZeneca; Financial Interests, Personal, Steering Committee Member, Also trial support: BMS; Other, Other, DSMB: Novartis, Takeda, Incyte, Springworks. All other authors have declared no conflicts of interest.

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1205TiP Camrelizumab combined with EP/EC chemotherapy followed by camrelizumab plus apatinib for first-line therapy of advanced extrapulmonary neuroendocrine carcinoma: A prospective, single-arm, multicenter clinical study

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Background: Extrapulmonary neuroendocrine carcinoma has a poor prognosis with a median survival of about 1 year. The current standard first-line treatment for extrapulmonary neuroendocrine carcinoma is etoposide combined with cisplatin (EP) or etoposide combined with carboplatin (EC). Camrelizumab (anti-PD-1 antibody) and apatinib (VEGFR2-TKI) have shown definite antitumor effects in a variety of solid tumors. The aim of this study is to evaluate the efficacy and safety of camrelizumab combined with EP/EC chemotherapy, followed by camrelizumab plus apatinib as first-line treatment for advanced or metastatic extrapulmonary neuroendocrine carcinoma.

Trial design: This prospective, single-arm, multicenter study plans to enroll 30 patients with advanced or metastatic extrapulmonary neuroendocrine carcinoma who have not been systematically treated. Enrolled patients will receive 4-6 cycles of EP (etoposide 100mg/m2 d1-3 iv+ cisplatin 25mg/m2 d1-3 iv, repeated every 21 days) or EC (etoposide 100mg/m2 d1-3 iv+ carboplatin AUC=5 d1 iv, repeated every 21 days) in combination with camrelizumab (200mg iv d1, repeated every 21 days). Patients with remission or stable disease will receive camrelizumab (200mg, d1, iv, repeated every 21 days) plus apatinib (250mg orally, once daily) as maintainance therapy until disease progression or unacceptable toxicity. Camrelizumab will be administered for a total of 2 years, and patients with stable or remission disease will continue apatinib treatment until disease progression. The primary endpoint of this study is objective response rate (ORR), while secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR) and safety.

Clinical trial identification: NCT05142865.

Legal entity responsible for the study: The authors.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

NEW DIAGNOSTIC TOOLS

1206O Clinical subtyping of cancer from blood based on comprehensive epigenomic profiling

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Background: Circulating tumor DNA assays that focus on somatic mutation detection in patient plasma are increasingly being incorporated into cancer detection, monitoring and therapy selection. A major limitation of these assays is the inability to assess changes in gene regulation or expression that underlie clinically relevant characteristics of cancer.

Methods: We developed a novel assay to profile tumor-derived gene regulatory programs from patients' plasma. Our approach measured histone modifications associated with active gene promoters (H3K4me3) and enhancers (H3K27ac), as well as DNA methylation, from 1cc of plasma. We measured 1,085 genome-wide profiles of gene regulation across 435 samples from 377 individuals. We demonstrated clinical validity by distinguishing cancer phenotypes based on their gene regulatory profiles.

Results: Epigenomic profiling of plasma enabled numerous advances by providing robust, clinically actionable proxies for gene expression from blood. We inferred expression of diagnostic markers and drug target genes by exploiting the correlation of plasma signal at gene promoters (Spearman rho=0.90). Plasma-based measurements of enhancer activity at binding sites of transcription factors (TFs) provided a functional activity readout for targetable TFs such as the androgen receptor (AR) in prostate cancer (Pca) and the estrogen receptor (ER) in breast cancer. We additionally detected epigenetic mechanisms of resistance, including activation of the *AR* gene enhancer in Pca, neuroendocrine trans-differentiation of Pca, and small cell transformation of *EGFR*-mutant lung adenocarcinoma.

Conclusions: We present the largest epigenomic cell-free DNA dataset reported to date. Measuring tumor gene regulatory programs from plasma enables substantial advances in precision oncology by providing clinically actionable insights that are currently only accessible from tumor tissue.

Legal entity responsible for the study: Dana-Farber Cancer Institute, Medical Oncology Department.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Employee at DFCI. Please see https://www.dana-farber.org/ for mission statement (non-profit hospital). I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Professor at HMS, Please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, No financial interest, Institutional. Filed patents related to biomarkers of immune checkpoint blockers, and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. All other authors have declared no conflicts of interest.

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1207O Beyond 100,000 genomes project: Whole genome sequencing for cancer patients within NHS Genomic Medicine Service

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Background: The 100,000 Genomes Project was a transformational UK government initiative, conducted within the National Health Service (NHS) in England. The primary goal was to undertake Whole Genome Sequencing (WGS) for patients with cancer, rare disease and infectious diseases and standardise high throughput, automated bioinformatic analysis and interpretation. The NHS Genomic Medicine Service (GMS) was launched in 2019 to enable equitable access to genomic medicine and comprehensive genomic testing using a standardised National Genomic Test Directory (NGTD). Building on the work of the 100,000 Genomes Project, WGS is now offered as routine care through the GMS for specific clinical indications.

Methods: To validate the performance of the bioinformatics pipeline for WGS analysis across different variant and tumour types, we compared WGS analysis with other genomic tests commissioned through the NGTD. Data were collected by NHS genomic laboratories for 285 tumour samples for which WGS and orthogonal testing were performed (n=1,579 tests).

Results: 87% of tests were considered by NHS laboratory scientists to be concordant with the WGS results. Critical review of 167 discordant tests revealed that discrepancies were most frequently due to limitations in somatic CNV detection by WGS

(25%), tumour in normal contamination (12%) and variants that were detected as being germline from tumour-normal WGS but could not be classified accordingly from a tumour-only panel test (11%). We reviewed clinical actionability of WGS findings for 982 tumours. Clinically relevant findings are defined as variants associated with therapeutic response, diagnostic or prognostic classification or clinical trial eligibility. Based on the outcomes reported by NHS genomic laboratories, actionable variants were found for up to 90% of patients, depending on the tumour type. The types of actionable variants varied by tumour type with sarcoma patients having the highest proportion of actionable structural variants or copy number changes and paediatric solid tumour patients having the highest proportion of germline predisposition findings.

Conclusions: WGS is a reliable and comprehensive method for identifying clinically relevant variants in cancer genomes.

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1208MO A randomized phase III trial of site-specific therapy guided by the 90-gene expression assay versus empiric chemotherapy in patients with cancer of unknown primary

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Background: Empiric chemotherapy remains the standard of care in patients with cancer of unknown primary (CUP). Evidence on site-specific therapy based on multi-gene tissue of origin assay is limited. Here we reported a randomized phase III trial to evaluate the efficacy of site-specific therapy directed by an approved 90-gene expression assay compared with the empirical chemotherapy in CUP patients (NCT03278600).

Methods: *De novo* patients with CUP not amenable to local radical treatment were randomly assigned (1:1) to receive site-specific therapy or empirical chemotherapy (taxane/gemcitabine plus platinum). The tumor origin in the site-specific therapy group were predicted by the 90-gene expression assay and treatments were administered accordingly. The primary endpoint was progression free survival (PFS) in the intention-to-treat population.

Results: From September 2017 to March 2021, 182 patients were randomly assigned to receive site-specific (N=91) or empiric chemotherapy (N=91). Site-specific therapy guided by molecular assay resulted in more treatment options than the control arm, and the standard chemotherapy regimens for CUP were administered in 26.4% vs. 92.3% ($p<0.001$) of the population, respectively. At a median follow-up of 42.9 months, the median PFS was significantly longer with site-specific therapy than with empiric chemotherapy (9.6 vs. 6.6 months; HR, 0.68; 95% CI, 0.49-0.93; p=0.017), while favorable OS was observed with site-specific therapy compared with empiric chemotherapy (28.2 vs. 19.0 months) in the intention-to-treat population. Adverse events of grade $\geq$3 were similar between the two groups (p=0.61).

Conclusions: Site-specific treatment guided by the approved 90-gene-expression assay resulted in more therapy options, significantly improved PFS and favorable OS compared with empirical chemotherapy in *de novo* CUP patients.

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1209MO Computer-aided HCC lesion detection based on deep learning and CT images

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Background: Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer and a major cause of death worldwide. It can be identified using contrast-enhanced imaging, such as CT scans however the sensitivity of radiologists in detecting HCC lesions using CT scans remains low (Se=66% [60%-72%]). The proposed computer-aided diagnostic device has been developed based on deep learning and multiphase-CT scans, with the objective of assisting radiologists in improving the accuracy of HCC lesion detection.

Methods: The deep learning (DL) model is a combination of a specifically designed convolutional 3D classifier and a state-of-the-art 3D detector (3D-RetinaUnet), taking both arterial and portal phases as input. Upstream, the portal phase is registered on the arterial phase in a non-rigid fashion. The model outputs the location of HCC tumors as 3D bounding boxes. The dataset was collected at the Assistance Publique—Hôpitaux de Paris (APHP) from multiple sites (La Pitié-Salpêtrière, Beaujon and Paul Brousse) and annotated by at least 3 liver expert radiologists with the help of the sites' case report form as a guide.

Results: The dataset contained 820 multiphase CT with 966 tumors annotated by the radiologists. These 820 patients had not received treatment for HCC prior to the CT scan. The proposed DL model was trained on 629 multiphase-CT scans and tested on the multi-phase CT of 191 patients with 223 HCC lesions confirmed by histopathology. The sensitivity of HCC lesion diagnostic reached 89% (i.e., Lesion-level sensitivity) with a median of 2.0 false positives per scan (FPs/Scan) and a mean of 3.3 FPs/Scan. 69% of the 58 small-size HCC lesions measuring between 10 mm and 30 mm were diagnosed. The patient-level sensitivity was 96.3% which means the model identified the presence of HCC in 96.3% of the patients.

Conclusions: Our HCC diagnostic rate is above the means sensitivity of radiologists and our DL model could already participate to improve the diagnostic rate of HCC. The next goal is to improve the DL model and enrich the training set with patients at risk of HCC who are also treatment-naïve, including those with small HCC. Our objective is to develop an end-to-end CADe/CADx that will enhance the performance of detecting HCC, particularly small HCC.

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1210MO Comparison of clinical and radiological features-based and radiomics features-based models for pulmonary nodule malignancy prediction on CT images

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Background: Currently, early diagnosis of pulmonary nodules still relies on radiologist reading of CT images, which needs a heavy workload, extensive experiences, and is somewhat subjective. We propose an automatic radiomics-based approach to predict the risk of lung cancer.

Methods: A total of 1,895 patients with 1,909 surgical pathology confirmed 5-30 mm pulmonary nodules (1,181 malignant, 728 benign) were enrolled in 31 centers, with clinical information (gender, age) and chest CT scans. 25 radiological features were extracted by experienced radiologists. The regions of interest (ROIs) containing target nodules on the CT images were automatically segmented by a 3D U-net model, and 2,153 radiomics features were extracted using PyRadiomics. A clinical and radiological features-based model (CRFM) and a radiomics features-based model (RFM) for pulmonary nodule malignancy prediction were constructed in a randomly sampled training set (n=950), based on the average probabilities of Randomforest, LightGBM, and Lasso algorithms, and verified independently (n1=397, n2=562). Meanwhile, a combined model integrating the scores of the above two models was established (n=397) using logistic regression, and validated independently (n=562).

Results: In two validation sets (n1=397, n2=562), the CRFM model got AUCs of 0.912 (0.882-0.942) and 0.893 (0.864-0.921), and accuracies of 0.791 (0.748-0.828) and 0.794 (0.758-0.825), while RFM model obtained AUCs of 0.881 (0.847-0.915) and 0.863 (0.832-0.894), and accuracies of 0.781 (0.738-0.819) and 0.778 (0.741-0.810), respectively. The performance of RFM model was noninferior to CRFM model as evidenced by non-significant difference in AUCs ($p>0.05$) in both validation cohorts. However, the combined model improved diagnostic accuracy with elevated AUCs of 4.6% (vs. RFM, $p<0.001$) and 1.6% (vs.CRFM, $p=0.0196$) in the independent validation set (n=562), respectively.

Conclusions: Radiomics features-based model for early diagnosis of pulmonary nodules is not inferior to clinical and radiological features-based model, with potential application when CT scan interpretation by experienced radiologists are unavailable.

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1212P Predictive value of a near-term prediction model for severe irAEs in cancer treatment with ICIs

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Background: Severe irAEs caused by ICIs affect treatment efficacy and benefit. Current research on irAEs is mainly focused on early prediction, with a lack of near-term prediction. Studies have reported that baseline neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and absolute eosinophil count (AEC) can predict irAEs. Our aim is to explore the near-term predictive value of NLR, PLR, and AEC for grade 3 or higher irAEs caused by PD-1 inhibitors.

Methods: Data were collected from cancer patients treated with PD-1 inhibitors in our department from January 2020 to May 2022. NLR, PLR, and AEC data were collected one cycle before and during the occurrence of irAEs (median cycle number was 2nd and 3rd cycles, respectively). Logistic analysis was used to analyze the correlation between NLR, PLR, AEC, and irAEs, and to construct a prediction model. The model's performance was assessed by obtaining sensitivity and specificity through the ROC.

Results: Out of the 138 cancer patients, 47 experienced grade 1-2 irAEs, and 18 had grade 3 or higher irAEs (including 2 fatal irAEs). Multivariate analysis showed that the current cycle's NLR (OR, 1.839, p=0.000) and PLR (OR, 0.994, p=0.029) were independent risk factors for irAEs. Model A predicted the occurrence of irAEs in the next cycle with an area under the curve (AUC) of 0.788, a sensitivity of 69.2%, and a specificity of 68.5%. When the Model A was ≥38.8% (cutoff value), Model B (AUC =0.900) was entered, predicting the occurrence of grade 3 or higher irAEs in the next cycle with a sensitivity of 67.7% and a specificity of 72.6%. Similarly, Model C predicted the occurrence of irAEs in the current cycle (AUC=0.865) yielded a sensitivity of 81.5% and a specificity of 86.3%. When the Model C was ≥52.8%, Model D was entered, predicting the occurrence of grade 3 or higher irAEs in the current cycle (AUC=0.888) with a sensitivity of 83.3% and a specificity of 83.0%.

Conclusions: The model consisting of NLR, PLR, and AEC in this study can predict the occurrence of grade 3 or higher irAEs within one cycle. Compared with early prediction, our near-term prediction model maximizes the number of cycles of immune therapy obtained by patients, thereby improving the effectiveness of immunotherapy, which has significant clinical value.

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1213P HRD complete: A novel NGS assay for detecting homologous recombination repair (HRR) gene alterations in prostate cancer

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Background: HRR gene alterations, which are enriched in prostate cancer (PC), are associated with sensitivity to PARP inhibitors. However, the tests available to detect HRR gene alterations are limited and usually large NGS panels with high cost and long turnaround time (TAT). A novel HANDLE (Halo-shape ANnealing and Defer-Ligation Enrichment) based NGS assay, AmoyDx HRD Complete was established to evaluate single nucleotide variant (SNV), short insertion and deletion (InDel) and homozygous deletion (HD) of 17 HRR genes in PC tissues, with 4 days TAT.

Methods: Sensitivity was validated in serially diluted cell lines with varying DNA input: with gradient mutation allele frequency (MAF) (7%, 5%, 3%) for SNV/InDel; with different tumor content (50%, 40%, 30%, 20%) for HD. Specificity was validated in wild type cell lines. Testing success rate was evaluated using 100 formalin-fixed paraffin-embedded (FFPE) PC tissues (up to 10 years old). A "three-tube" library process was developed for samples which failed DNA, library, or sequencing QC with standard process. Accuracy was assessed in >200 FFPE PC tissues, using commercially available AmoyDx HRD54 NGS kit (hybridization capture based) and AmoyDx BRCA1/2 NGS kit (CE-IVD) as reference tests.

Results: Sensitivity of HRR SNV/InDel was 99.4% (179/180, MAF 5%) with 30ng DNA. Sensitivity of HRR HD was 100% at gene level with 30% tumor content and at exon level with 40% tumor content with 100ng DNA. Specificity was 100%. 54/100 (54%) PC tissues had valid sequencing results using standard process, whereas the "three-tube" library improved the success rate to 84%. For HRR SNV/InDel accuracy, 98/100 PC tissues showed concordant results with HRD54 kit (PPA 96.8%, NPA 98.6%, OPA 98.0%). For HRR HD accuracy, 130/132 PC tissues showed concordant results with HRD54 kit (PPA 100%, NPA 98.4%, OPA 98.5%). Accuracy of BRCA1/2 SNV/InDel was further verified with 100% concordance with BRCA1/2 kit.

Conclusions: With high sensitivity and specificity, short TAT and high success rate, the CE marked (CE-IVD) HRD Complete assay provides a robust and reliable test approach to PC patients that may guide them for a better treatment option.

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1214P A novel machine learning based method to detect homozygous deletion of homologous recombination repair (HRR) genes in prostate cancer

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Background: HRR gene alterations are enriched in prostate cancer (PC) and are associated with sensitivity to PARP inhibitors. Homozygous deletion (HD), which accounts for up to 15% of HRR gene alterations in PC, is an important type of pathogenic alteration. However, the reliable detection of HD is technically challenging. Here we introduced a novel machine learning based method for HD detection in formalin-fixed paraffin-embedded (FFPE) PC tissues.

Methods: HD/non-HD simulation events (∼30000) of varying tumor cellularity and fragment size were constructed using the sequencing data of matched tumor and wild type cell lines tested by AmoyDx HRD Complete NGS panel. Seven artificial features were calculated based on genomic segment depth and minor allele frequency of single nucleotide polymorphisms, tumor cellularity and tumor ploidy. The feature data were fed into the xgboost with 10-StratifiedKFold to generate HD recognition model (training :validation datasets=7:3). Analytical performance was assessed with reference cell lines: specificity with wildtype cell lines, sensitivity with gradient HD-positive cell lines (tumor cellularity: 20%, 30%, 40%, 50%) with varying DNA input (30ng, 50ng, 100ng), reproducibility of intra- and inter-runs, and anti-interference against hemoglobin, triglycerides, xylene, paclitaxel, and ethanol. Clinical performance was evaluated using FFPE PC tissues.

Results: The trained HD model achieved 99.8% accuracy in the in silico validation dataset. Analytical validation demonstrated: 100% specificity; 100% sensitivity at gene level with 30% tumor cellularity and at exon level with 40% tumor cellularity with 100ng DNA input; 100% reproducibility; strong anti-interference capability with all HD events detected and no false positives. 132 FFPE PC tissues showed high consistency with a second validated NGS assay (PPA 100%, NPA 98.4%, OPA 98.5%).

Conclusions: A machine learning based method was successfully developed and adopted in multiple NGS assays to detect HD of HRR genes in PC tissues. It provides a reliable approach to effectively identify PC patients with HRR HD.

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1215P Comparative analysis of cfDNA liquid biopsy and tumor-based next-generation sequencing (NGS) approaches

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Background: NGS techniques can detect molecular alterations in cell-free DNA (cfDNA) isolated from plasma samples for biomarker discovery, diagnostics, and disease monitoring. We previously reported a 0.2% variant allele frequency (VAF) limit of detection (LOD) for single nucleotide variants (SNVs) and insertions and deletions (indels) with 98% and 99% accuracies and 91% and 83% sensitivities, respectively, for our cfDNA assay. To assess the clinical application of the cfDNA liquid biopsy, we compared findings with tumor-based NGS assays, including whole exome sequencing (WES) and RNA-seq.

Methods: A panel of 216 clinically actionable genes, including exonic and intronic regions, was used in the cfDNA assay. Commercial references and human cell lines were used for analytical validation. Our variant calling pipeline was used to analyze sequenced samples. WES, RNA-seq, and cfDNA analysis were performed on 65 matched patient samples. Gene fusions in cfDNA were validated with tumor RNA-seq data.

Results: Intersection was observed between traditional WES analysis and the developed liquid biopsy assay for 35.3% (23/65) patients. WES results were concordant with the cfDNA assay for a subset of mutations from the targeted gene panel for SNVs (sensitivity = 0.23) and indels (sensitivity = 0.29); for clinically actionable mutations, we observed a slightly stronger relationship (sensitivity = 0.35). The cfDNA assay identified an additional 66.2% and 31.4% SNVs and indels, respectively, within the clinically actionable gene panel compared to WES. With a LOD of 0.5% VAF, 95% sensitivity was observed for genomic fusion calling. The cfDNA assay detected clinically actionable fusion genes, such as *EWSR1—ATF1*.

Conclusions: While our WES and cfDNA analyses had low concordance, previous reports noted discordance in tumor DNA and cfDNA analyses due to tumor heterogeneity and other biological factors, such as cfDNA half-life and variations in shedding among clones. Our cfDNA panel also included genes from intronic regions and detected additional alterations not found by WES. These findings highlight the potential for this newly developed cfDNA assay to be used to guide clinical decision making.

Legal entity responsible for the study: BostonGene, Corp.

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Disclosure: A. Yudina, S. Starikov, A. Efremov, D. Sookiasian, E. Nuzhdina, M. Chasse, T. Conroy, N. English, A. Love, D. Tabakov, A. Baisangurov, C. Tazearslan: Financial Interests, Personal, Full or part-time Employment: BostonGene, Corp.; Financial Interests, Personal, Stocks/Shares: BostonGene, Corp. S. Podsvirova: Financial Interests, Personal, Full or part-time Employment: BostonGene, Corp. N. Fowler: Financial Interests, Personal, Officer: BostonGene, Corp.; Financial Interests, Personal, Stocks/Shares: BostonGene, Corp.; Financial Interests, Personal, Leadership Role: BostonGene, Corp.; Financial Interests, Personal and Institutional, Research Funding: Celgene, Gilead, Roche; Financial Interests, Personal and Institutional, Speaker, Consultant, Advisor: Celgene, Gilead, Roche; Financial Interests, Personal, Full or part-time Employment: BostonGene, Corp. A. Bagaev: Financial Interests, Personal, Leadership Role: BostonGene, Corp.; Financial Interests, Personal, Full or part-time Employment: BostonGene, Corp.; Financial Interests, Personal, Stocks/Shares: BostonGene, Corp.

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1216P A spectroscopic liquid biopsy for the earlier detection of multiple cancer types

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Background: Employing a rapid liquid biopsy platform that can support clinicians in the diagnosis of different cancers, particularly for patients who develop cancers not targeted in current screening programs, would cause a paradigm shift in cancer diagnostics. Current liquid biopsies focus on single tumor derived biomarkers, such as circulating tumor DNA (ctDNA), which limits test sensitivity, especially for early-stage cancers that do not shed enough genetic material.

Methods: The Dxcover® Cancer Liquid Biopsy has been assessed upon its ability to predict individual cancers in organ-specific classifications: brain, breast, colorectal, kidney, lung, ovarian, pancreatic, and prostate cancer. The test uses Fourier transform infrared (FTIR) spectroscopy to build spectral profiles of serum samples, and machine learning algorithms to predict disease status. We also made a further exploratory evaluation of the ability to differentiate the signature from any one of the 8 cancers from non-cancer patient samples. We assessed the test performance when the cancer samples were grouped together to mimic patients with non-specific symptoms where the cancer site was uncertain. Additionally, we have examined non-generative data augmentation methods to improve machine learning performance.

Results: Area under the receiver operating characteristic curve (AUROC) values were calculated for 8 cancer types v symptomatic non-cancer controls: most classifiers achieved AUROC values above 0.85. The cancer v asymptomatic non-cancer classification detected 64% of stage I cancers when specificity was 99% (overall sensitivity 57%). When tuned for higher sensitivity, this model identified 99% of stage I cancers (with specificity 59%). For the colorectal cancer dataset, data augmentation using a WGAN led to an increase in AUROC from 0.91 to 0.96, demonstrating the impact data augmentation can have on deep learning performance, which could be useful when the amount of real data available for model training is limited.

Conclusions: This spectroscopic blood test can effectively detect early-stage cancer, and could facilitate the requisite earlier diagnosis when treatment can be more effective.

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1217P Clinical evaluation of a CE-IVD liquid biopsy pan cancer genomic profiling test

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Background: With the accessibility of precision therapies, a robust circulating cell-free total nucleic acid (cfTNA)-based pan-cancer NGS (Next Generation Sequencing) genomic profiling liquid biopsy (LB) test is a valuable addition to identify genomic signatures for the relevant treatment options, where tissue is not available. Liquid biopsy NGS tests also offer the advantage of continual detection of evolving tumor mutations in a minimally invasive way to help inform cancer patient management.

Methods: Here we report an analysis of SNV (Single Nucleotide Variant) hotspots, gene fusion, copy number amplification (CNA) from 52 recurrently mutated oncogenes, and tumor suppressor genes in 3630 cancer patients, belonging to 44 solid organ cancers. The study used a CE-IVD approved *in vitro* diagnostic Laboratory Developed test (LDT) from Datar Cancer Genetics. The technology employs NGS tag-sequencing approach to detect pan cancer biomarkers that may guide treatment decisions and management of patients. cfTNA was extracted from peripheral whole blood to prepare tag sequencing NGS libraries and the NGS data were processed using a custom analysis pipeline that can detect up to 0.1% mutant allele frequency.

Results: The SNV analysis revealed TP53 (38%) KRAS (11%), PIK3CA (10%) as the most recurrently mutated genes across cancer types. Distinct SNV clusters were observed across major cancer types such as ESR1, PIK3CA, TP53 in breast cancers, EGFR, GNAS, TP53 in lung cancer, APC, KRAS, TP53, PIK3CA in colorectal cancer. The highest CNA prevalence was observed in MYC, FGFR1, ERBB2, CCND1, CDK4 with cancer-specific signatures. TMPRSS2-ERG emerged as the most prevalent gene fusion, followed by MET and EML4-ALK. Cancers harboring most SNV mutations are colorectal, lung, pancreas, and uterine with an average >1 SNVs detected in all patients. Breast cancer patients harbored the highest number of CNAs followed by colorectal, lung and prostate cancer.

Conclusions: This comprehensive pan cancer cfTNA LB test evaluated on Asian and Caucasian cancer patients successfully identified relevant signatures of major genomic alternations of therapeutic, diagnostic, and prognostic significance that can provide confidence to physicians in the use of the test for their patients.

Legal entity responsible for the study: Datar Cancer Genetics, Nasik, India and Datar Cancer Genetics, Guildford, UK.

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1218P Exploring cancer care pathways in seven European countries: Identifying obstacles and opportunities for the role of artificial intelligence

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Background: Cancer is considered a leading cause of mortality and morbidity worldwide. This study constitutes one part of the user requirement definition of INCISIVE EU project. The project has been designed to explore the full potential of artificial intelligence (AI)-based technologies in cancer imaging. The study aimed to map cancer care pathways (breast, prostate, colorectal and lung cancers) across INCISIVE partner countries, and identify obstacles within these pathways.

Methods: A qualitative research approach employing email interviews was used. A purposive sampling strategy was employed to recruit ten oncology specialised healthcare professionals from INCISIVE partner countries: Greece, Cyprus, Spain, Italy, Finland, United Kingdom (UK) and Serbia. Data was collected between December 2020 and April 2021. Data was entered into Microsoft Excel spreadsheet to allow content and comparative analysis. Appropriate ethical approval was obtained for this study.

Results: Delays in the diagnosis and treatment of cancer was evident from all the pathways studied. With the exception of the UK, none of the countries studied had official national data regarding delays in cancer diagnosis and treatment. There was a considerable variation in the availability of imaging and diagnostic services across the seven countries that were analysed. Several concerns were also noted for national screening for the four investigated cancer types.

Conclusions: Delays in the diagnosis and treatment of cancer remain challenging issues that need to be addressed. To effectively address these challenges, it is crucial to have a systematic reporting of diagnostic and therapeutic delays in all countries. Proper estimation of the magnitude of the problem is essential, as no problem can be effectively tackled without an accurate understanding of its magnitude. Our findings also support the orientation of the current policies towards early detection and wide scale adoption and implementation of cancer screening, through research, innovation, and technology. Technologies involving AI can have a great potential to revolutionise cancer care delivery.

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1219P Artificial intelligence-based breast cancer detection facilitates automated prognosis marker assessment using multiplex fluorescence immunohistochemistry

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Background: Prognostic markers in routine clinical practice of breast cancer are often assessed using RNA based multi-gene panels that are depending on a fluctuating tumor purity. Multiplex fluorescence immunohistochemistry (mfIHC) holds the potential for improved risk assessment.

Methods: To enable automated prognosis marker quantification, we have developed and validated a framework for automated breast cancer detection involving three different artificial intelligence analysis steps and an algorithm for cell-distance analysis using BLEACH&STAIN multiplex fluorescence immunohistochemistry. Pan-cytokeratin (panCK) antibodies were used to detect epithelial cells and antibodies directed against Myosin and p63 were used to identify basal cells.

Results: The optimal distance between Myosin$^+$ and p63$^+$ basal cells and benign panCK$^+$ cells was identified as 25 µm in breast cancer and used — combined with deep learning-based algorithms — to exclude benign glands from the analysis. Our framework discriminated normal glands from malignant glands with an accuracy of 98.4% (95% confidence interval [CI]: 97.4 — 99.3). The approach for automated breast cancer detection improved the predictive performance of several prognosis markers significantly (each $p<0.05$) and a comparison with manually assessed data using conventional brightfield immunohistochemistry showed a high concordance for a multitude of different prognosis marker such as PR, ER, GATA3, HER2, and PD-L1 (each $p<0.0001$).

Conclusions: The combined assessment of up to 5 markers in a prognosis score showed strong prognostic relevance ($p<0.001$) and was an independent risk factor in multivariate analysis ($p=0.005$). Thus, the data from this study show that automated breast cancer detection in combination with artificial intelligence-based analysis of multiplex fluorescence immunohistochemistry enables a rapid and reliable analysis of multiple prognostic parameters. The major advantage of this method is the analysis of malignant cells exclusively that cannot be achieved using RNA-based panel analysis.

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1220P Comprehensive diagnose of programmed death-ligand 1 from two-dimensional to three-dimensional in breast cancer with computer-aided artificial intelligence system

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Background: Determination of programmed death-ligand (PD-L1) status in triple-negative breast cancer (BC) by immunohistochemical (IHC) assay represents has prognostic significance in association with immune checkpoint inhibitor (ICI) therapies. However, the evaluation of PD-L1 SP142 remains challenging for pathologists since the associated tumor microenvironment complicates the immune cell (IC) scoring. Moreover, PD-L1 distribution in tumor could also lead to a risk of inaccurate patient allocation for ICI. To accurately diagnose PD-L1 status as IC score, a computer-aided artificial intelligence (AI) system is required to precisely quantify PD-L1 expression in two-dimensional and three-dimensional (3D) pathological images.

Methods: In this study, we proposed a computer-aided AI system for digital images of IHC and 3D immunofluorescence (IF) assays. This system consisted of machine learning algorithms for tumor/IC recognition, infiltration identification, and PD-L1 expression detection. Tissue clearing technology with IF and confocal microscopy were utilized to detect the spatial distribution of PD-L1 in BC specimens.

Results: The designed computer-aided AI system was based on a tumor segmentation model with a >80% accuracy and an IC recognition model with a 90% accuracy. For the IHC digital pathology, the computer-aided AI system achieved a concordance rate of 83% in comparison with PD-L1 IC interpretation by experienced pathologists. For 3D digital images, the system achieved a concordance rate of 90% with traditional pathological diagnosis. This system could serve as an integrated plugin onto existing open-source platforms. Appling the system for 3D analysis, the spatial distribution of PD-L1 showed heterogeneity across different layers. Notably, 30% cases crossed the 1% cutoff along the 3D layers, which is related to admission of immunotherapy.

Conclusions: The computer-aided AI system could improve the PD-L1 diagnosis from IHC to 3D digital images, which provides accurate prognostic significance for precision medicine.

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1221P The functional domain of BRCA1/2 pathogenic variants (PVs) as potential biomarkers of second tumor and domain-related sensitivity to PARP-inhibitors

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Background: Women carrying *BRCA1/2* germline pathogenic/likely pathogenic variants (gPVs) have elevated lifetime risk of developing both breast cancer and high grade serous ovarian/tubal or peritoneal cancer (EOC), but also pancreatic and endometrial cancer. The purpose of this study was to identify the *BRCA1/2* functional domains (FDs) associated to develop of multiple primary tumors, and the potential effect of *BRCA* PVs within the FDs on PARP-inhibitors response in EOC patients.

Methods: In this real-world, hospital-based, study we collected genetic and clinical data on EOC patients subjected to somatic and germline *BRCA1/2* genetic testing, and evaluated the presence of personal second tumor history according to mutated gene (*BRCA1* or *BRCA2*), PV type, and PV location. The *BRCA1* FDs were RING, DNA-binding domain (DBD), BRCA1 C terminus (BRCT), or other locations, and the *BRCA2* FDs were RAD51-BD, DBD, or other locations. The treatment efficacy by PV type and FD was evaluated.

Results: From May 2015 to March 2023, data from 907 patients were collected. Overall, 325 were carriers of gPVs in *BRCA1/2* genes: 228 in *BRCA1* (70.2%) and 97 in *BRCA2* gene (29.8%). In the population of *BRCA*-mutated patients, at the median age of 57 years (range 23-78), 67 showed personal second tumor history (20.6%), including 49 carriers of g*BRCA1* PVs (73.1%), and 18 of g*BRCA2* PVs (26.9%). In the group of 582 patients with genetic testing not informative, only 46 patients showed second tumor history (7.9%). The most frequent second tumors was breast cancer at the median age of 48.5 years, but also endometrial and renal carcinoma, melanoma and cholangiocarcinoma. When DFs of mutated gene were compared, the distribution was different between EOC patients with and without second tumor history. Notably, *BRCA*-mutated patients with second tumors showed an higher involvement of BRCT of *BRCA1* (24.5%) and DBD of *BRCA2* (17.8%), than *BRCA* carriers without second tumor history (27.8% and 6.3%, respectively)(p=0.02).

Conclusions: In the EOC *BRCA*-mutated patients, *BRCA1/2* PVs located in specific functional domains (FDs) might be associated to higher probability to develop multiple primary cancers, with potential effect on PARP-inhibitors benefit.

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1222P Detection of androgen-receptor splice variant 7 messenger RNA in circulating tumor cells of prostate cancer by in vitro assay

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Background: Androgen-receptor splice variant 7 (AR-V7) is constitutively activated isoform of AR and has been associated with resistance towards AR targeting therapies and development into mCRPC. Confirmation of AR-V7 expression is important step in prostate cancer diagnosis and determining the drug, but the detection of AR-V7 with tissues has limitations such as clinical challenge to poorly accessible tumor tissues before and after treatment. Here, we developed the method of AR-V7 detection in circulating tumor cells (CTC) after isolation with CytoGen's Smart Biopsy™ CTC isolator by in vitro assay of qRT-PCR with high sensitivity and specificity, overcoming the limitations of tissue biopsy.

Methods: Nested qPCR method was developed for high sensitivity and specificity of detection of AR-V7. Sensitivity and specificity were tested using AR-V7 positive cells (VCaP) and negative cells (PC-3 and Raji cells). Limit of detection of AR-V7 of nested PCR was performed with VCaP (200 cells to 20 cells, 4 points) mixed with Raji cells (1x10-5cells). Then, VCaP cells (200 cells to 20 cells, 4 points) was spiked into peripheral blood mononuclear cells of blood sample (5mL, healthy donor) to mimic CTC after isolation by CytoGen's Smart Biopsy™ CTC isolator, subsequently nested qPCR was carried out to detect of AR-V7 using each primer pairs. Non clinical sample were used.

Results: As a result of LoD test, AR-V7 expression was clearly detected even in the smallest VCaP sample and was not detected at all in the negative controls. The same clear result was also observed in the spiking test of VCaP into PBMCs isolated by CytoGen's Smart Biopsy™ CTC isolator, suggesting that clinical samples of prostate cancer could be applied with excellent sensitivity and specificity for AR-V7.

Conclusions: AR-V7 expresses only a part of cancer tissue, so it is difficult to accurately diagnose with traditional histological assays. Detection of AR-V7 in intact live CTC isolated by CytoGen's Smart Biopsy™ CTC isolator might overcome limitations of tissue biopsy. In this study, we developed a novel method of detection of AR-V7 in CTC with high sensitivity and specificity by in vitro assay and clinical test will be conducted for validation.

Legal entity responsible for the study: Cytogen. Inc.

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1223P Homologous recombination deficiency (HRD) testing on ovarian cancer ascites: A feasibility study

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Background: *BRCA1/2* and HRD tumor testing should be performed at diagnosis for patients with high-grade epithelial ovarian cancers (EOC). Peritoneal fluids drainage is carried out for those patients during and/or before surgery for staging and palliative intents. We previously demonstrated the feasibility of BRCA testing on malignant ascites. We sought to investigate the feasibility of HRD testing on the cytology specimens from EOC ascites.

Methods: At least 200 ml of ascitic fluid were prospectively collected during primary surgery from patients with EOC. The fluids were overturned, poured into four 50 ml tubes and centrifuged at 1700 rpm for 10 minutes at room temperature. Pellets were included in agarose gel and formalin-fixed paraffin-embedded (FFPE) cell blocks were obtained. DNA extracted from tumor-positive cell blocks was subjected to the SOPHiA DDM™ Dx HRD Solution. Concordances of BRCA1/2 and HRD status, *TP53* mutation and *CCNE1* copy number gain (CNG) between ascites and matched tissue tumor samples were assessed.

Results: Data were available for 8 ascites specimens with a median tumor cell content of 65% (range: 20-80%). *BRCA1/2* status was evaluable for all samples with 100% concordance between cytology and tissue samples, including 6 *BRCA1/2* wild-type cases and 2 cases harboring variants of unknown significance. HRD status was determined in 7/8 ascites specimens. HRD status was undetermined in 1 tissue sample with informative HRD testing on matched ascites. HRD status concordance among 6 evaluable paired cytology-tissue samples was 83%, including 5 HRD-negative and one HRD-positive case. Discordant and undetermined results were seen from ascites specimens with low tumor cell content. *TP53* mutations and *CCNE1* CNG were detected in 4 and 1 cytology samples, respectively, with 88% of concordance with matched tissue analysis.

Conclusions: This exploratory study showed that HRD testing on cytological specimens from EOC ascites is feasible but standardized pre-analytical procedures are required to ensure adequate samples for the analysis. Ascites might represent a valid alternative for early *BRCA1/2* and HRD status evaluation in women with EOC when tissue samples are inadequate/insufficient.

Legal entity responsible for the study: Massimo Barberis.

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1224P Detection of circulating tumor DNA (ctDNA) in untreated patients (pts) with cancer: Implications for early cancer detection (ECD)

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Background: Blood-based ECD is an emerging tool to identify cancer signals in asymptomatic individuals. ctDNA detection is impacted by several clinicopathologic factors. We report on ctDNA detection rates in pts with cancer prior to receiving treatment and in correlation with median tumor mutational burden (mTMB) rates.

Methods: Pretreatment plasma samples were analyzed using a tumor-informed ctDNA assay (SignateraTM) in 1657 pts, including breast cancer (BC, N=131), lung cancer (LC, N=57), colorectal cancer (CRC, N=1382), epithelial ovarian cancer (OV, N=36), pancreatic cancer (PC, N=17), and diffuse large B cell lymphoma (DLBCL, N=37). Stage-agnostic, exome-based mTMB was reported for BC, CRC, PC, DLBCL (internal data), LC (pmid28420421), and OV (pmid35087563).

Results: Baseline ctDNA was detected in 1621 (87%) pts; rates were lower in stage I/II (707/858, 82.4%) vs III/IV (914/998, 91.6%). In BC (mTMB 4.4 mut/MB), ctDNA detection rates were lower in hormone receptor-positive tumors (stage I/II 61.2%[74/121], III 81% [17/21]) vs triple-negative breast cancer (I/II 81.5% [75/92], III 97% [58/60]) and HER2+ tumors (I/II 73.9% [17/23], III 87.5% [7/8]); rates increased by stage in all subtypes. In LC, detection rates were lower for adenocarcinoma (mTMB 6.3 mut/MB; I/II 25% [5/20], III 73% [11/15]) vs squamous cell carcinoma (mTMB 9.0 mut/MB; I/II 85% [11/13], III 100% [9/9]). In CRC (mTMB 4.31 mut/MB with a bi-modal distribution), detection rates for stage I/II/III-IV were [(74% (71/96), 94% (421/448) and 92% (773/838)]. In OV (mTMB 1.9 mut/MB), detection rates were 60% (9/15) in stage I/II and 72% (15/21) in stage III/IV. In PC (mTMB 1.47 mut/MB), detection rates were 65% (11/17) in stage I/II and 100% (2/2) in stage III/IV. In DLBCL (mTMB 4.58 mut/MB), detection rates were 100% (13/13) in stage I/II and 92% (22/24) in III/IV.

Conclusions: Our study supports past findings that ctDNA positivity varies across cancers and histology and is higher in some later stage cancers and suggests that ctDNA detection in the presurgical setting can be detected in a majority of patients with a tumor-informed approach. Further studies are needed to understand the biological and technical factors that may impact assay's performance.

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1225P Combining ctDNA and tissue-based-genomic profiling in advanced cancer: A real-world evidence prospective study in non-Western patients treated at Gustave Roussy cancer campus

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Background: Tissue-based genomic profiling (TBGP) is the gold standard to detect targetable pathogenic variants (PV) in advanced cancer patients (ACP). Circulating tumor (ct) DNA analysis could overcome the limitation of temporal and spatial heterogeneity. Nevertheless, some targetable PV detected in TBGP could be missed by ctDNA. Also, a few studies addressed the real-world evidence (RWE) of using ctDNA in non-western ACP. We aimed to evaluate the role of comprehensive genomic profiling (CGP) combining ctDNA and TBGP in international ACP treated at Gustave Roussy cancer campus.

Methods: This is a prospective study initiated on 01/10/2021. Peripheral blood was sent to Foundation One Liquid CDx for ctDNA analysis. TBGP was performed on DNA extracted from FFPE tissue using a specific panel for each tumor type. We used the oncokb online database to assess the level of actionability of PV.

Results: 56 pts had paired analysis with 31 females, and a mean age of 59 years. The 4 most common primaries were colorectal cancer (14 pts), non-small cell lung cancer (8 pts), soft tissue sarcoma (8 pts) and breast cancer (7 pts). Success rates were 73.2% and 98.2% for TBGP and ctDNA respectively. Among the 14 pts with ctDNA success/TBGP failure, 1 had R1 (level 1 evidence for resistance), 3 L1 (level 1 evidence of actionability), 3 L4 and 45 nonactionable PV. Among the 41 pts with double success, 6 R1 and 5 L1 were detected by both techniques. Five R1 and 2 L1 were detected only in ctDNA, while 2 L1 were detected only by TBGP. Most PV detected only in ctDNA had no level of evidence (110/137).

Conclusions: Combining ctDNA and TBGP seems better than using only one technique. It should be noted that the high level of failure in FFPE-TBGP point out to the need of fresh tissue biopsies. More studies comparing the targetable PV in ACP from different countries are needed.

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1226P Multi-site validation of a deep learning solution for HER2 profiling of breast cancer from H&E-stained pathology slides

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Background: Molecular profiling of the human epidermal growth factor receptor 2 (HER2) is performed for all malignant breast cancers to inform the choice of HER2-targeted therapy. IHC and ISH are performed to establish HER2 status in standard clinical care. These tests are not only expensive and time-consuming, but also account for most of the turnaround time for diagnosis and require expert interpretation. Here, we demonstrate the effectiveness of PANProfiler Breast (HER2 Negative), a UKCA-marked deep learning (DL)-based image analysis software for HER2 profiling from whole slide images (WSIs) of routinely-used H&E-stained pathology slides.

Methods: A DL model was trained and validated on 1684 WSIs from two datasets to identify HER2-negative cases defined by IHC0, IHC1 or IHC2+/ISH-. A total of 2310 H&E images of breast cancer samples from five different sites in the UK and US were used for external validation. These images were acquired with four different scanners with each set containing a varying proportion of biopsies and resections. The model was evaluated separately for each site with 3-fold cross-validation and results were aggregated across folds. The performance was measured in comparison to HER2 status acquired via IHC and ISH in accordance with RCPath & CAP guidelines.

Results: Incidence rate for HER2-positive cases varied between 9-15% in the UK sites and was 64% for the US cohort. Overall accuracy across all sites was 93.06% (± 8.28%), reaching up to 97.99%. An average false negative rate (discordance to wet-lab assay) of 9.27% (± 0.47%) was achieved with a 100% specificity for all datasets. Performance was robust to specimen/scanner types, with accuracies of 96.46%, 95.39%, and 91.15% achieved in sites that contained only biopsies, only resections, and mixed types. Accuracy across scanners varied by a standard deviation of 9.25%.

Conclusions: We demonstrate the robustness of a DL-based HER2 profiling method in breast cancer utilising only H&E-stained WSIs. This multi-site validation study is the first-of its kind for such an approach using real-world clinical data. Our solution could facilitate fast, accurate, and systemic screening of patients for targeted treatments if integrated within the routine pathological workflows.

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1227P Novel in vivo photonics-immunoassay system, inPROBE, for the rapid detection of HER2 in breast cancer

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Background: Assessment of HER2 status is critical for diagnosis and guiding therapy in breast cancer. However, the current immunohistochemistry-based analysis of HER2 requires tissue biopsy, is time-consuming, subjective, and semi-quantitative. This is the reason for delayed or incorrect treatment decisions and worse outcomes. To address these limitations, we developed an innovative inPROBE diagnostic device, which allows for real-time quantitative and operator-independent HER2 level determination, directly in the patient's body.

Methods: The HER2 measurements were performed using the inPROBE device consisting of an optical sensor designed for the detection of the soluble HER2 or the anti-HER2 drug — Trastuzumab (TMAB). The *in vitro* inProbe testing was done on the standard HER2 protein solutions to demonstrate the device working range and the tissue accumulation of TMAB was assessed *in vivo* on the mouse xenograft model of a human HER2+ cancer. The device safety was confirmed on rats with a probe insertion into the mammary glands to monitor the clinical, biochemical and pathological changes.

Results: inProbe working range tested on HER2 solution was within the concentration of pg/ml — mg/ml with good linearity and selectivity toward HER2. In preclinical safety experiments, inPROBE insertion into the mammary glands did not cause any adverse clinical signs, changes in blood parameters, or histology. In alternative sets of experiments, the TMAB-inProbe proved its utility for direct detection of the anti-HER2 drug accumulating in the HER2+ tumor tissue.

Conclusions: HER2-inPROBE is a specific and sensitive sensor, allowing for rapid, quantitative analysis of HER2. Given its high adaptability, the inPROBE platform presents the potential to be used for the detection of various diseases biomarkers, without the need for tissue biopsy. The clinical trial to determine the diagnostic accuracy and safety of the inPROBE in 192 patients with early breast cancer is underway (NCT05415943).

Clinical trial identification: NCT05415943.

Legal entity responsible for the study: SDS Optic.

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1228P A circulating tumor cell (CTC) based assay for diagnostic immunocytochemistry profiling of lung cancer

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Background: We present a unique immunocytochemistry-based organ-specific antibody profiling assay of CTCs in suspected lung tumors (TruBlood® Lung) for non-invasive diagnosis and histological subtyping and its utility in patients unable to undergo physical biopsies.

Methods: In a prospective blinded study, blood samples from suspected lung cancer patients (n= 99) were profiled for detection of CTCs. Along with EPCAM/CK/CD45, organ-specific antibody profiling with TTF1, CK7, Napsin A, CD45, p40, Synaptophysin, and Chromogranin was performed to detect lung adenocarcinoma, squamous cell carcinoma and neuroendocrine tumors (TruBlood® Lung). After unblinding, the performance was compared with histopathology of the corresponding tissue samples.

Results: Concordance analysis could be performed in ninety-three patients. Tissue HPE was inconclusive in 4 patients and CTC assay (TruBlood® Lung) could not be performed in 4 patients. The concordance rate between cancer diagnosis by the CTC assay and histopathology was 97.8% (91/93). Among cases identified to be positive for lung cancer on CTC assay (n=91), HPE subtyping of lung cancer could be performed in 83.5% of the cases (76/91). The CTC assay was able to detect presence of cancer but unable to assign a histological subtype (subtype indeterminate) in 16.4% of the cases (15/91). Among cases that were able to be subtyped by CTC assay, the concordance rate with HPE diagnosis was 93.4% (71/76), with concordant subtyping in 76.3% of the total evaluable cohort (71/93). Discordance with histological subtyping was seen in 6.5% (5/76) cases, with CTC assay failing to identify adenosquamous (n=3), small cell (n=1) and squamous cell carcinoma (n=1) subtypes. Interestingly, in five cases of poorly differentiated carcinomas where conclusive histological subtyping was not possible on tissue HPE examination, CTC assay profiling was able to assign a subtype.

Conclusions: Our results demonstrate sensitivity of this CTC assay (TruBlood® Lung) to provide concordant HPE subtyping in 76.3% of the total evaluable cohort (71/93) and in 93.4% (71/76) of the cases subtyped by CTC assay. Thus, this assay can be useful in patients unable to undergo tissue sampling, to establish a diagnosis and conclude histopathological subtype.

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1229P Selective phenotypic and genotypic evaluation of circulating glial cells for improved diagnosis of glial malignancies

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Background: Accurate diagnosis plays a critical role in the effective management of glial malignancies. However, obtaining tissue specimens for histopathologic investigation carries inherent procedural risks. We present profiling of circulating glial cells (CGCs) by analyzing cell lineage-specific markers using immunocytochemistry (ICC) and EGFR gain by fluorescence In situ hybridization (FISH) on the Circulating glial cells.

Methods: In a prospective blinded study, blood specimens from patients suspected of Intracranial space-occupying lesions (ICSOL) (N=28) were collected before the invasive biopsy. CGCs were profiled using the TriNetra™ Glio assay that detects CGCs using ICC profiling of cell lineage markers (GFAP and OLIG2). CGCs were also used to perform FISH using EGFR gain. In a separate cohort comprising matched tissue and blood specimens from 44 cases (22 benign and malignant cases each), CGC profiling by ICC and EGFR FISH was performed to evaluate the concordance of profiled biomarkers on the circulating CGC population.

Results: TriNetra Glio assay successfully found CGCs in 23 out of 25 (92%) cases diagnosed with Glial malignancies. Among the 11 cases of Glioblastoma and 2 cases of astrocytoma Grade 3, EGFR amplification was found in 4 and 1 cases, respectively. In a matched cohort, EGFR copy gain was detected in tumor tissue in 8 (36%) among 22 cases of malignant glial tumors, and EGFR gain was also detectable in corresponding blood analysis. Among the remaining 14 samples with normal EGFR tissue status according to FISH, the CGCs also exhibited normal EGFR status. Further, among the 22 cases of benign tumors, there were no instances of EGFR copy gain detected by FISH on tumor tissue. All 22 samples were also negative for CGCs indicating high specificity.

Conclusions: We demonstrate a reliable method for detecting Circulating Glial Cells. This can offer valuable insights into diagnosis of suspected glial malignacies in cases where performing a biopsy is not possible. Moreover, molecular analysis of CGCs shows the potential in providing diagnostic insights that align with the current WHO classification system for the central nervous system.

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1230P hPG80 (circulating progastrin) is a new blood-based biomarker for diagnosis of early-stage non-small cell lung cancers

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Background: Lung cancer is the most prevalent and deadliest cancer worldwide, mainly due to its advanced stage at diagnosis. Minimally invasive method for early detection of lung cancer is an urgent need to improve patients' survival. hPG_{80} (circulating progastrin) has been previously described as a promising multi-tumors blood biomarker (You et al. *EbioMedicine,* 2020). hPG_{80} is produced and released from cancer cells and can be detected in the blood at early steps of tumorigenesis. In this study, we assess the diagnostic value and potential clinical utility of hPG_{80} in patients with non-small cell lung cancers (NSCLC), including early-stage tumors.

Methods: Plasma hPG_{80} levels were measured using the kit DxPG80.Lab (Biodena care, Montpellier, France) from two cohorts: (1) a retrospective cohort of 400 NSCLC patients comprising 100 samples per disease stage (I-IV) collected at diagnosis, before any treatment (Nice Hospital-Integrated Biobank BB-0033-00025); (2) a prospective matching age cohort of 330 healthy subjects. The diagnostic value of hPG_{80} was assessed by comparing hPG_{80} baseline concentrations in NSCLC patients with those of healthy subjects. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic accuracy of hPG_{80} using the area under the curve (AUC).

Results: Overall, hPG_{80} median concentration in all NSCLC patients was significantly higher than in healthy subjects (6.51 pM *vs* 1.95 pM, $P<0.0001$). hPG_{80} median concentrations were significantly higher in all disease stage subgroups than those in healthy subjects (6.83 pM, 7.15 pM, 6.02 pM and 6.34 pM for stage I to stage IV, respectively) ($P<0.0001$). ROC curve analysis of the entire NSCLC cohort showed that the AUC value was 0.84 (95% CI: 0.81 to 0.87). Following subgroup analysis by disease stages I-IV, the AUC values were 0.86 (95% CI: 0.83 to 0.90), 0.85 (95% CI: 0.81 to 0.88), 0.82 (95% CI: 0.78 to 0.86) and 0.84 (95% CI: 0.80 to 0.87), respectively.

Conclusions: These findings uncover the potency of hPG_{80} as a novel promising, accurate and non-invasive biomarker to diagnose NSCLC patients, notably at an early stage. Furthermore, its measurement by an ELISA assay may facilitate its routine use for cancer screening/early diagnosis.

Legal entity responsible for the study: Biodena Care.

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1231P Machine learning prediction of the case-fatality of COVID-19 and risk factors for adverse outcomes in patients with non-small cell lung cancer

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Background: Since the emergence of Coronavirus-2019 (COVID-19) across the globe, patients with cancer have been found to have an increased risk of infection with COVID-19 and are highly likely to experience a severe disease course. This study analyzed the clinical outcomes of COVID-19 in patients with non-small cell lung cancer (NSCLC) and identified the risk factors for adverse outcomes.

Methods: This study analyzed the case-fatality rate and risk factors for COVID-19 among NSCLC patients diagnosed between January 2020 and April 2022 at the Samsung Medical Center, using a machine-learning prediction method. Additionally, the study investigated the effect of COVID-19 on the systemic treatment of patients with advanced-stage NSCLC.

Results: Overall,1,127 patients were included in this study, with 10.3% of the patients being older than 75; of these patients, 51.8% were ex- or current smokers. Among the 584 cured after surgery, 91 had stable disease after concurrent chemo-radiotherapy, and 452 had recurrent or metastatic NSCLC. Of the 452 patients, 387 received palliative systemic treatment during COVID-19, including 188 receiving targeted therapy, 111 receiving cytotoxic chemotherapy, 62 receiving immunotherapy +/- chemotherapy, and 26 receiving other agents. Out of these, 94.6% continued systemic treatment after COVID-19, only one patient discontinued due to complications, and 18 changed their treatment due to disease progression. The case fatality rates were 0.86% for early-stage NSCLC, 4.4% for locally advanced NSCLC, and 9.95% for advanced NSCLC. The factors associated with fatalities included palliative chemotherapy, age ($\geq$75), diabetes, smoking history, lung radiotherapy, hypertension, sex, and COPD. The model using logistic regression and eXtreme gradient boosting performed well (AUC for both = 0.84).

Conclusions: NSCLC patients had a case fatality rate of 4.8% and most continued systemic treatment despite COVID-19. However, those with risk factors need close attention for managing COVID-19 complications.

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Disclosure: M. Ahn: Financial Interests, Personal, Advisory Board: AstraZeneca, Takeda, MSD, Yuhan, Amgen, Alpha Pharmaceutical, Janssen, BMS, Roche, Daiichi Sankyo, Merck, Boronoi. S. Lee: Financial Interests, Personal, Advisory Board: AstraZeneca/MedImmune, Roche, Merck, Pfizer, Lilly, BMS/Ono, Takeda, Janssen, IMBdx; Financial Interests, Personal, Invited Speaker: AstraZeneca/MedImmune, Roche, Merck, Lilly, Amgen; Financial Interests, Institutional, Research Grant: Merck, AstraZeneca, Lunit. All other authors have declared no conflicts of interest.

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1232P Analytic analysis of PanSeer7, a targeted bisulfite sequencing assay for blood-based multi-cancer detection for cancer early detection and tissue-of-origin identification

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Background: Many cancers are symptoms free in early clinical stages, causing nearly half of patients diagnosed in advanced-stages when therapeutic options are limited. Early cancer detection is key to improve clinical outcomes. We developed PanSeer7, a multi-cancer detection assay based on targeted bisulfite sequencing of circulating cell-free DNA (cfDNA) and evaluated its technical performances of reproducibility and sensitivity.

Methods: The PanSeer7 panel consists of 2,447 markers which are either differentially methylated between healthy and cancer samples, or distinctively methylated in a specific cancer. We assessed its reproducibility by sequencing 40 technical replicates of synthetic healthy cfDNA samples on 4 independent batches and with different inputs (2～20 ng). For its limit of detection (LOD), we prepared samples mimicking cancer plasma DNA by diluting fragmented cancer cell line DNA, from 7 common cancer types, into GM12878 control at ratios of 1/10,000 to 1/100. We tested PanSeer7's ability to identify tissue of origin (TOO) by analyzing DNA from formalin-fixed paraffin-embedded (FFPE) tissues and healthy plasma.

Results: PanSeer7 produced highly consistent methylation levels among replicates at a minimum of 10 ng input. Its technical LOD was 1/10,000 for lung cancer (LuC; H1650), liver cancer (LiC; HepG2), gastric cancer (GC; HGC27), esophageal cancer (EC; KYSE150) and colorectal cancer (CC; SW480), and slightly lower as 5/10,000 for pancreatic cancer (PC; PANC1) and breast cancer (BC; MDA-MB-231). To evaluate PanSeer7's accuracy for predicting TOO, we sequenced 38 healthy plasma and 121 FFPE tissues (17 LiC, 13 PC, 21 GC, 18 EC, 16 CC, 14 LuC and 22 BC). They were clearly clustered according to their TOO based on methylation levels. We simulated 3,500 datasets by mixing reads of cancer tissue into those of healthy plasma at ratios of 1/10,000 to 1/100, and the TOO-predicting model achieved an accuracy over 95% at a ratio of 5/10,000.

Conclusions: With excellent technical performances in both cancer detection and TOO identification, PanSeer7 is promising to be clinically applied for non-invasive multi-cancer detection.

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1233P Accurate prediction of gastrointestinal cancer tissue of origin using comprehensive plasma cell-free DNA fragmentomics features

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Background: Circulating cell-free DNA (cfDNA) is a promising biomarker for early cancer detection, and its fragmentomics features have been successfully used to detect cancer signals in blood. However, its ability to predict the tissue of origin (TOO) of cancers remains to be evaluated, which is highly desirable to differentiate the most common types of gastrointestinal (GI) cancers, including colorectal (CC), esophageal (EC), gastric (GC), liver (LC), and pancreatic cancer (PC).

Methods: Whole-genome sequencing was performed for the cfDNA of 769 cancer patients (149 CCs, 137 ECs, 149 GCs, 272 LCs, and 62 PCs), to calculate the coverage at repetitive genomic regions (RepeatsCov), the depth and the cleavage diversity around transcription start sites (TSSDepth and TSSClvDiv), and the microbiome abundance (MicrobeAb). Together with other classical fragmentomics features, including copy number variation (CNV), end motif diversity (EDM), fragment size ratio (FSR), and promoter fragmentation entropy (PFE), a stacked ensemble machine learning classifier was trained and tested with sample ratio of 1:1 to predict the TOO of the GI cancers.

Results: The performance of each single feature was evaluated first, showing that the FSR model had the highest accuracy of 67.1% while the RepeatsCov model had the lowest of 53.9%. The ensemble of all the features resulted in an accuracy of 67.6%. Interestingly, a model combining MicrobeAb, RepeatsCov and FSR achieved the highest accuracy of 69.4% for all cancers (CC: 63.8%, EC&GC: 63.3%, LC: 83.6%, and PC: 43.8%), and an elevated accuracy of 87.8% to predict the top two most likely TOOs. We also trained and tested a previously reported multi-features-based model on our data, and our classifier achieved higher accuracy (69.4% vs. 60.6%).

Conclusions: We comprehensively evaluated the classical and our newly developed cfDNA fragmentomics features in predicting the TOO of cancer signals, and showed that by combining features including MicrobeAb, RepeatsCov and FSR, we were able to maximize the accuracy in predicting GI cancers' TOO. However, results also indicate that features should be carefully selected to avoid multicollinearity or other negative effects.

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1234P HistoMate: Automated preprocessing software for digital histopathology image to enhance deep learning

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Background: Recently, the field of digital pathology has seen an increase in research utilizing deep learning techniques. This allows for predictions such as cancer diagnosis, prognosis, and treatment response, which previously required additional analysis, such as genetic analysis that was both time-consuming and costly, to be made based on pathological imaging. However, digital pathology images often contain noise, such as inconsistent staining and inconsistent annotations. To address this issue, image preprocessing is essential in deep learning analysis of digital pathology images, and various preprocessing techniques have been proposed to address issues such as bias, overfitting, and robust deep learning model development. However, automated preprocessing methods for digital pathology images have not yet been fully developed.

Methods: To address this, we have developed a user-friendly tool for image preprocessing analysis called HistoMate.

Results: HistoMate provides GUI-based image segmentation, image tiling, color normalization, and deep learning-based data augmentation to automate the preprocessing process. It also provides functionality to evaluate image quality and select appropriate patches.

Conclusions: In conclusion, HistoMate provides an automated preprocessing tool for pathological image-based research, accelerating digital pathology-based research.

Legal entity responsible for the study: The authors.

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1235P Enrichment of rare cancers in pragmatic precision cancer medicine trial: Experience from IMPRESS-Norway

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Background: IMPRESS-Norway is a DRUP-like, national clinical study for patients with advanced malignancies, where approved drugs are used outside their indication based on detailed molecular diagnostics. All hospitals in Norway treating cancer patients participate. Rare cancers comprise a group of about 200 cancers that individually occur at low to very low frequencies. For these cancers, randomized trials are difficult to conduct, and they have few approved therapeutic options. Clinical studies are therefore needed.

Methods: In IMPRESS-Norway, patients are screened with TSO500, analysing 535 genes for DNA/RNA alterations. Both tumour tissue and circulating tumour DNA are analysed. We currently have 23 drugs available through the study and can use these outside of their indications, based on identified molecular alterations in the tumour cells in an aggregated treatment algorithm and subject to discussion in a national molecular tumour board.

Results: In the first 2 years, 836 patients were included for screening in IMPRESS-Norway. Of these, 411 patients have a rare cancer diagnosis. 83 patients with a rare cancer (20.2%) were offered treatment based on the molecular diagnostics, whereas 97 of 425 screened with a common cancer (22.8%) were included in treatment cohorts. The most common drugs offered patients with rare cancers were trametinib, alpelisib and atezolizumab. The primary endpoint in the study is clinical benefit at 16 weeks of treatment, which was observed for 53% of patients with rare cancers compared to 42% for patients with common cancers.

Conclusions: In our ongoing study, 49.2% of the patients included for screening in the first 2 years had a rare cancer, and actionable molecular alterations matching one of the drugs available in the trial were found for 20.2% of the patients. We show that many of these patients benefit from advanced diagnostics and from drugs used outside of their current indication. This finding is of special importance for patient groups for whom access to clinical trials are limited due to the rareness of the disease.

Clinical trial identification: NCT04817956.

Legal entity responsible for the study: The authors.

Funding: The Regional Health Authorities, The Norwegian Cancer Society, The Radium Hospital Foundation , Pharma companies providing drug and funds for treating hospital: AstraZeneca, Roche, InCyte, Novartis, Merck, Eli Lilly.

Disclosure: A. Helland: Financial Interests, Institutional, Advisory Board, Advisory boards: Jansen, Takeda, AstraZeneca, AbbVie, Roche, BMS, Pfizer, MSD, Bayer, Lilly,; Financial Interests, Institutional, Invited Speaker, talks at meetings: AstraZeneca, Roche, AbbVie, Pfizer; Financial Interests, Institutional, Coordinating PI, BMS provides drug to patients in an investigator initiated clinical trial: BMS; Financial Interests, Institutional, Coordinating PI, Ultimovacs provides drug and funds for investigator initiated clinical trial: Ultimovacs; Financial Interests, Institutional, Coordinating PI, AstraZeneca provides drug and funds for investigator initiated clinical trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, Roche provides drug and funds for investigator initiated clinical trial: Roche; Financial Interests, Institutional, Coordinating PI, Novartis provides drug and funds for clinical trial: Novartis; Financial Interests, Institutional, Coordinating PI, Eli Lilly provides drug and funds for clinical study: Eli Lilly; Financial Interests, Institutional, Coordinating PI, Incyte provides drug and funds for clinical study: Incyte; Financial Interests, Institutional, Coordinating PI, Illumina provides assays for patients in a clinical trial: Illumina; Non-Financial Interests, Other, Board member in the

patient organisation until 2022. Provides advice and gives talks: The lung cancer patients organisation. G.O. Hjortland: Financial Interests, Institutional, Research Grant: Astra, Merck, Illumina Roche, Novartis, EliLilly, InCyte. L. Bjorge: Financial Interests, Personal, Advisory Board, Expert testimony regarding a patent application: Onsagers, Oslo; Financial Interests, Personal, Advisory Board, Expert testimony for an application to The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway: AstraZeneca; Financial Interests, Personal, Advisory Board, Part of an ad hoc advisory board for ovarian cancer: AstraZeneca; Financial Interests, Personal, Member of Board of Directors, Oslo Cancer Cluster is an oncology research and industry cluster dedicated to improving the lives of cancer patients by accelerating the development of new cancer diagnostics and treatment. Been part of the board during the period 2015-2022 (elected): Oslo Cancer Cluster; Financial Interests, Personal, Full or part-time Employment, I hold a full-time position as Medical Director and consultant in gynecologic oncology at this institution: Helse Bergen HF; Financial Interests, Personal, Full or part-time Employment, I hold a part-time position as Professor in Obstetrics and Gynecology: University of Bergen; Financial Interests, Institutional, Research Grant, Financial support for a researcher-initiated trial: AstraZeneca; Non-Financial Interests, Leadership Role, Onkologisk Forum is the interest organization for all groups of personal working with cancer patients or cancer treatment or cancer research in Norway, https://onkologiskforum.org/om-onkologisk-forum. During the period 2018-2022 I been the leader for the organization (elected position): Onkologisk Forum; Non-Financial Interests, Leadership Role, From March 2021 hold the position as president for the organization: Nordic Society for Gynecological Oncology; Non-Financial Interests, Leadership Role, Leader of the board since March 2021: Nordic Society of Gynecologic Oncology-Clinical Trial Unit; Non-Financial Interests, Advisory Role, Member of the specialist group in oncology, Sykehusinnkjøp HF, Representing Helse Vest RHF: Sykehus Innkjøp HF; Non-Financial Interests, Leadership Role, Since March 2021 I have hold the position as president for the organization. I have been a member of the organization since 2012, and a board member since 2014: Nordic Society of Gynecologic Oncology; Non-Financial Interests, Member, I have been a member since 2011: ESGO; Non-Financial Interests, Member, I have been a member since 2015: ASCO; Other, I have been evaluating grant applications from different national and international research institutions and grant providers: Different academic institutions. B. Gilje: Financial Interests, Personal, Advisory Board, June 2022 Ad Board: Gilead; Financial Interests, Personal, Advisory Board: Eli Lilly, Daiichi Sankyo, Pierre Fabre, Roche. T. Donnem, O.T.D. Nguyen, B. Mannsåker, S. Smeland, K. Tasken: Financial Interests, Institutional, Research Grant: Astra, Merck, Illumina Roche, Novartis, Eli Lilly, InCyte. A. Flobak: Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Invited Speaker: Pfizer, Pierre Fabre, Amgen, Bayer. H.E.G. Russnes: Financial Interests, Institutional, Invited Speaker, Speaker on Illumina satellite meeting (ESMO 2022): Illumina; Financial Interests, Institutional, Advisory Board, Novartis satellite meeting, Nordic Lung Cancer meeting, 2022: Novartis; Financial Interests, Institutional, Other, Debate, precision medicine, Oslo 2022 : Merck; Financial Interests, Institutional, Other, Participation, round table, Cholangiocarcinoma; Nordic meeting 2021: Incyte; Financial Interests, Institutional, Coordinating PI, Funding of 500 FMliquid test to patients in the IMPRESS-Norway trial: Roche Norway; Financial Interests, Institutional, Coordinating PI, Funding of TSO500 liquid tests for 500 patients in the IMPRESS-Norway trial: Illumina; Non-Financial Interests, Leadership Role, InPreD is an establishment in the public health care, securing disciplinary work when implementing precision diagnostics for cancer: National Infrastructure for Precision Diagnostics (InPreD); Non-Financial Interests, Leadership Role, A network structure established as part of the public health care system, to share knowledge, build competence and work with harmonisation and standardisation to implement precision medicine: National Competence Network for Precision Medicine; Non-Financial Interests, Leadership Role, Head of working group for molecular pathology and for the Norwegian association for molecular pathology: The Norwegian Association of Pathology. T.K.K. Guren: Financial Interests, Institutional, Other, Honoraria: Pierre Fabre; Financial Interests, Institutional, Local PI: Genentech/Roche, MSD, Merus, Pfizer, Ultimovacs, Eli Lilly/Loxo, Novartis, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

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1236P Feasibility of online symptom monitoring to detect lung cancer relapse in Poland

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Background: Electronic monitoring of patient-reported outcomes (ePRO) in lung cancer may allow earlier relapse detection, prolonged survival, and better utilization of healthcare resources. Wide implementation of ePRO is limited by patient digitalization level and Internet access. In 2021, more than 90% of people in Poland used Internet, and over 80% used it more than once a week. However, its use among people over 65 was below 50%. In this study, we evaluated the feasibility of ePRO in lung cancer patients in Poland.

Methods: In 2021 an ePRO tool (HORUS®) for lung cancer relapse detection was developed at the Medical University of Gdańsk. It offers weekly online questionnaires for post-treatment surveillance of lung cancer patients. The survey includes 12 questions about the most common relapse symptoms and can be approached via a website or an app. In case of health deterioration, an automatic alert is generated and sent to health caregivers, based on a real-time data analysis. Primary study outcomes are the sensitivity and specificity of the ePRO in Polish conditions. This report presents the first-year study results.

Results: Between March 2022 and March 2023, 78 eligible patients were identified, 22 of whom (28%) declined participation, mainly due to no Internet access (45%). Fifty-six patients met the inclusion criteria and entered the study. The mean age was 70 years (range 42-84), 30 (54%) patients were women and 26 (46%) were men. The median number of expected weekly questionnaires per patient during the study period was 28 (range 3-52). The total number of received surveys was 1442, from 1666 expected (86.6%). Average compliance was similar between sexes (male 87%, female 86.2%). The median percentage of weekly adherence to symptom reporting was 87.5%, with the lowest values in patients' weeks 1 and 41 (75.0%) and the highest (100%) in patients' weeks 42, 46, 50, 51, and 52.

Conclusions: To our knowledge, HORUS® is the first and only ePRO system for lung cancer surveillance in Poland. Our early results confirm the feasibility of ePRO in Polish lung cancer patients. The weekly adherence to reporting was high and did not change significantly during the study period. However, low Internet access in the elderly lung cancer population remains the limiting factor.

Legal entity responsible for the study: Ewa Pawlowska, MD.

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Disclosure: J. Jassem: Financial Interests, Advisory Board: BMS, MSD, Exact Sciences; Non-Financial Interests, Invited Speaker: Roche; Financial Interests, Invited Speaker: Pfizer, Novartis; Financial Interests, Other: Takeda. All other authors have declared no conflicts of interest.

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1237P Design and validation of a custom next-generation sequencing panel in melanoma, glioma and gastrointestinal stromal tumor

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Background: Incidence of melanoma, glioma and gastrointestinal stromal tumor (GIST) is increasing worldwide, which results in public health problems. The increasing number of markers that are tested in a correct diagnostic procedure makes gene-targeted, next-generation sequencing (NGS) a powerful tool in routine pathology practice. However, special panels for melanoma, glioma and GIST (MGG) are scarce. In this study, we designed and validated a NGS panel which included 1064 amplicons in 57 genes covering targetable alterations associated with the diagnosis and potential treatment response of MGG.

Methods: Based on extensive literature review and integrating TCGA and COSMIC databases, we developed MGG panel that is associated with diagnosis and potential treatment response of MGG. We validated this NGS panel including accuracy, reproducibility/repeatability, limit of detection (Lod), a comparative analysis between conventional methodologies and NGS using reference mutated DNA, tumor and normal tissue samples that were previously characterized.

Results: The NGS panel achieved 100% accuracy for mutation detection. Intra-experiment repeatability and inter-experiment reproducibility showed 100% concordance for one reference mutated DNA and four tumor samples, and a high correlation was observed between inter- and intra-sequencing runs. The Lod was established at a 2% variant allele frequency (VAF) for single-nucleotide variants (SNVs) and insertion-deletions (indels), and the threshold for copy number amplification and deletion was 3 and 1.4, respectively. Subsequently, we performed a comparative analysis between conventional methodologies - such as Sanger sequencing or fluorescence in situ hybridization - and NGS on 119 tumor and normal tissue samples that had been previously tested in our laboratory. The comparison between conventional methodologies and NGS showed high concordance (116/119, 97.5%).

Conclusions: This NGS panel is an accurate and sensitive method. Moreover, it is a rapid and cost-effective approach that can simultaneously detect different genetic alterations useful for the diagnosis, prognosis and treatment of patients with melanoma, glioma or GIST.

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1238P Detecting driver mutations by AmoyDx 11-gene PCR with high concordance with next-generation sequencing in Chinese non-small cell lung cancer patients

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Background: Identifying driver genes is crucial to make clinical decision for patients with non-small cell lung cancer (NSCLC). Except short turnaround time, higher success rate, it is still debating that PCR may cause false negative result due to its limited coverage. This study directly compared the performance of AmoyDx 11-gene PCR and NGS in the detection of known driver gene mutations in Chinese NSCLC patients.

Methods: FFPE samples from a total of 765 Chinese NSCLC patients were collected. The test performance of AmoyDx 11-gene PCR (*EGFR, KRAS, ALK, HER2, ROS1, MET, BRAF*, *NTRK1/ 2/3*, and *RET*) and NGS were compared.

Results: The overall percent agreement (OPA), positive percent agreement (PPA), and negative percent agreement (NPA) between AmoyDx 11-gene PCR and NGS were 98.8%, 99.3%, and 97.1%, respectively (Table). The PPA between the two assays were the same (100.0%) in common drivers (*EGFR/KRAS/ALK*) and rare drivers, the OPA and NPA were higher in rare drivers (99.5% vs. 99.9% and 98.8% vs. 99.8%) in AmoyDx 11-gene PCR. For rare drivers, concordance between PCR and NGS were shown in *HER2* (OPA: 99.7%, PPA: 95.1% and NPA: 100.0%), *ROS1* (OPA: 99.9%, PPA: 100.0% and NPA: 99.9%), *MET* (OPA:99.9%, PPA:96.4% and NPA:100.0%), *BRAF* and *RET* (OPA: 100.0%, PPA: 100.0% and NPA: 100.0%), respectively. Most of interestingly, for *EGFR* exon 20 insertion (*EGFR ex20ins*), a good concordance rate of 99.6% (PPA: 100.0% and NPA: 99.6%) was achieved.

Table: 1238P Comparison of AmoyDx 11-gene PCR and NGS for detecting known driver genes in NSCLC patients

		NGS (mutant)	NGS (wild)	OPA	PPA	NPA
Total drivers	PCR (mutant)	591	5			
	PCR (wild)	4	165	98.8%	99.3%	97.1%
Common drivers	PCR (mutant)	425	4			
	PCR (wild)	0	336	99.5%	100.0%	98.8%
Rare drivers	PCR (mutant)	156	1			
	PCR (wild)	0	608	99.9%	100.0%	99.8%
EGFR exon20ins	PCR (mutant)	24	3			
	PCR (wild)	0	738	99.6%	100.0%	99.6%
HER2	PCR (mutant)	39	0			
	PCR (wild)	2	724	99.7%	95.1%	100.0%
ROS1	PCR (mutant)	19	1			
	PCR (wild)	0	745	99.9%	100.0%	99.9%
BRAF	PCR (mutant)	19	0			
	PCR (wild)	0	746	100.0%	100.0%	100.0%
RET	PCR (mutant)	25	0			
	PCR (wild)	0	740	100.0%	100.0%	100.0%
MET	PCR (mutant)	27	0			
	PCR (wild)	1	737	99.9%	96.4%	100.0%

Conclusions: AmoyDx 11-gene PCR displayed high concordance to NGS in detecting driver mutations of NSCLC, especially rare drivers (*EGFR ex20ins*), suggesting it is an excellent choice in clinical practice.

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1239P NHS-Galleri trial enrolment approaches and participant sociodemographic diversity

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Background: Equitable access to early cancer detection is needed to reduce disparities in cancer burden, but ethnic minority and more socioeconomically deprived groups are underrepresented in clinical trials, limiting generalisability. The clinical utility of a blood-based multi-cancer early detection test for population screening is being assessed in a randomised controlled trial (NCT05611632). Here, we report enriched enrolment approaches (EEAs) used to recruit a diverse participant population aged 50—77 years.

Methods: Recruitment routes were: NHS DigiTrials, GP participant identification centres (PICs), self-referral. Enrolment took place in 11 mobile units at 151 locations in 10.5 mos. EEAs (NHS DigiTrials and PIC invitation targeting, community engagement, logistical barrier reduction) were used to boost ethnic minority enrolment, and target those in older and more deprived groups to ensure an adequate cancer event rate for assessing clinical utility. We examined (1) number of enrolled participants (all routes) vs national data and (2) number needed to invite (NNI; invited/enrolled individuals, NHS DigiTrials only), by age, sex, and proxied index of multiple deprivation and ethnicity.

Results: In all, ∼1.5 M individuals were invited and 142,940 enrolled (98% via DigiTrials) in 10.5 mos (Table). NHS DigiTrials invitation targeting increased enrolment in older and more deprived groups vs the national population. Other EEAs boosted ethnic minority enrolment. NNI was higher in most (22) vs least (4) deprived groups and in Black (33) and Asian (28) vs White (10) ethnicities.

Table: 1239P NHS-Galleri trial participant population characteristics versus those aged 50—77 years in England (age and sex), and those aged 50—79 in England and Wales combined (ethnicity and index of multiple deprivation, IMD)

		NHS-Galleri N = 142,943 (% of Total)	National (% of Total)
Age (Years)*	50—54	11	22
	55—59	16	21
	60—64	19	18
	65—69	22	15
	70—74	21	16
	75—77	12	7
Sex*	Female	50	51
Ethnicity**	White	93	92
	Asian	3	4
	Black	1	2
	Other	<1	1
	Mixed	1	<1
IMD Quintile†	1 - least deprived	16	22
	2	20	22
	3	21	21
	4	20	19
	5 - most deprived	23	16

*Office for National Statistics: Census 2021
**2019 Population Estimates by Ethnic Group
†2020 Populations by IMD decile

Conclusions: The NHS-Galleri trial used approaches that enabled rapid (10.5 mos) recruitment of a socioeconomically diverse population.

Clinical trial identification: NCT05611632; 3 November 2022.

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1240P Multi-centric validation of an AI-based sTIL% scoring model for breast cancer H&E whole-slide images

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Background: Tumor-infiltrating lymphocytes (TILs) have reached level 1A evidence as a prognostic biomarker in Breast Cancer (BC), which are scored by pathologists on Hematoxylin and Eosin (H&E)-stained tumor tissue. Despite this strong evidence, TILs are not used in daily clinical practice. Although the International TILs Working Group provides a scoring guideline for pathologists, most are not comfortable scoring TILs. Here, we develop an Artificial Intelligence (AI) model to predict the stromal TILs (sTIL %) score directly from H&E whole-slide images (WSIs) in an external validation setting from patients across multiple centers.

Methods: Patients with a digitized H&E WSI and sTIL% scored by a trained pathologist following the International TILs Working Group guidelines were included. Only patients with all relevant clinical data were collected (n=1,120). We train a gated attention-based multiple instance learning regression model (GABMIL) to predict the sTIL% score directly from the H&E WSIs. The model is trained with 5-fold cross-validation on H&E WSIs from The Cancer Genome Atlas (TCGA-BC, n=356, Aperio), and is validated on ICGC-BC (n=247, Hamamatsu), and the MATADOR study (n=517 from 34 hospitals in the Netherlands, 3dhistech). All three datasets have similar distributions for age at diagnosis, ER-, PR-, and HER2 status, and sTIL% score.

Results: We observe a linear relationship between the predicted and the pathologist's scores (Pearson's r 0.64-0.67, mean squared error 0.021-0.026) across all test datasets. If we split the ground truth into the clinically relevant sTIL-low (<30%) and sTIL-high (>=30%) groups, our model achieves an AUROC of 0.86 on TCGA test sets, 0.86 on BASIS, and 0.94 on MATADOR.

Conclusions: Our AI-based regression model achieves excellent generalization results with no visible performance drop to external cohorts from different countries and scanners. We envision that the AI-TIL scores will be used for clinical decision-making on top of well-known prognostic factors such as tumor size and lymph node status of BC patients. This will allow clinicians to estimate a patient's prognosis more accurately and tailor (neo)adjuvant systemic therapies.

Legal entity responsible for the study: Netherlands Cancer Institute.

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1241P Decoding the glycan code: Pioneering early detection of non-small cell lung cancer through glycoproteomics

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Background: Non-small cell lung cancer (NSCLC) stands as a prevailing cause of cancer-related death worldwide, largely due to the late-stage diagnosis that diminishes the prospects of cure. Abnormal protein glycosylation, a recognized hallmark of cancer, offers a promising avenue for the exploration of novel biomarkers. Recent advancements in AI-supported analytical technologies have opened possibilities for a thorough examination of cancer-specific glycoforms. The objective of this study is to identify circulating glycoproteomic biomarkers for the early detection of NSCLC, with the potential to enhance patient outcomes and revolutionize diagnostic approaches.

Methods: With a novel high resolution and high throughput glycoproteomic profiling platform combining liquid-chromatography/mass-spectrometry (LC-MS) and artificial-intelligence (AI)-powered data processing, we assessed 694 glycopeptide (GP) and non-glycosylated peptide quantification transitions in pre-treatment peripheral blood serum samples from 372 NSCLC, 148 COPD, and 494 healthy individuals. The full sample set was split into training and validation loops, with a held-out test set. Cross-validated elastic net-regularized logistic regression was performed to develop a multivariate classifier to detect NSCLC.

Results: A total of 340 statistically significantly (FDR < 0.05) differentially abundant glycopeptides (GPs)/peptides when comparing NSCLC and healthy controls, and 50 biomarkers were significantly differentially expressed between healthy controls and NSCLC samples, COPD and NSCLC samples, but not between healthy controls and COPD samples. A multivariate model achieved 85.5% specificity and 84.2% sensitivity to detect all stages of NSCLC with an AUC of 0.875 in a held-out test set. Notably, it performed well in detecting both early (stages I-II) and late stages of NSCLC (stages III-IV) with sensitivities of 81.8% and 87.2%, respectively.

Conclusions: We established a novel platform combining LC-MS and AI data processing, and identified comprehensive serum glycoproteomic profiles which allow the further clinical translations including development of effective non-invasive NSCLC screening and early detection tools.

Legal entity responsible for the study: InterVenn Biosciences.

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1242P Implementing functional precision oncology in real-world patients: Translating extensive in vitro data into personalized treatment combining genetics and functional assays

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Background: Predictive and prognostic biomarkers for personalising cancer therapy are now widely used, but their application is still far from standard of care. Focusing exclusively on DNA alterations leads to a clinically relevant outcome in 40-60 % of patients; clinical benefit is another matter. Comprehensive tumor profiling could be a tool to improve treatment efficiency, revealing more actionable characteristics for combining appropriate therapies.

Methods: 37 real world patients with progressive metastatic solid tumors were treated based on comprehensive tumor profilings (Exacta). The test method comprised genetics, expression profiling, IHC, immunocytochemistry, pharmacogenomics, and chemosensitivity using tissue or blood analyses. Therefore therapy options are found for the majority of patients (>99%),not only related to NGS. Data were collected over four years. Intrapatient analysis was applied, comparing PFS1 of the last guideline therapy with PFS2 of the matched treatment (ratio). Imaging data, side effects and quality of life were constantly recorded during the course. Individual analyses provide therapy options that are not apparent at first glance and applied drug combinations were discussed in a digital molecular tumor board.

Results: In 78% of patients, comprehensive tumour testing improved their PFS compared to the previous standard of care treatment (PFS2/PFS1>1). In 24% of patients, we observed a doubling of progression-free survival. The median PFS2/PFS1 ratio was 1.25. Worth mentioning that 54% had a PFS2 of more than 6 months (range 5-159 weeks), and eight patients still did not reach PFS2 endpoint. 46% had also a PFS1 >6months. In the univariate analyses of the ratio, significant results were found in two scenarios that had a negative impact on prognosis: a higher total number of oncogenes (p=0.04) and the presence of a p53 mutation caused a lower ratio (p=0.013). ECOG did not change significantly.

Conclusions: Combining genomic and transcriptional profiling is useful to improve personalized treatment. If possible not only targets might be considered for choice of therapy but also the context of the whole pathway network together with biomarkers.

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1243P Ocular surface squamous neoplasia early diagnosis using an AI-empowered autofluorescence multispectral imaging technique

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Background: Ocular surface squamous neoplasia (OSSN) is a common eye surface neoplastic disease ranging from non-invasive conjunctival intraepithelial neoplasia (CIN) to invasive forms of squamous cell carcinoma (SCC) that accounts for approximately 10% of ocular surface lesions. Early detection of OSSN is crucial for effective treatment. However, clinical symptoms of OSSN vary, which can result in delayed or inappropriate diagnosis without appropriate diagnostic methods. Currently, the diagnosis of OSSN relies on clinical suspicion confirmed by impression cytology or biopsy, which are invasive and may not detect small lesions. This study aims to introduce an artificial intelligence data analysis framework to empower a newly designed autofluorescence hyperspectral imaging technology developed in our group for OSSN detection.

Methods: We recruited 20 patients who had previously been diagnosed with OSSN. Biopsy specimens were collected from the patients and reprocessed without staining to obtain autofluorescence microscopy images using 25 spectral channels, each with a distinctive excitation-emission wavelength. The spectral images were pre-processed to remove unwanted random noise and then spectral features were extracted from the epithelial section of tissue images. Further, the spectral features were used to form an artificial feature image patch to train a convolutional neural network for image classification.

Results: The technique was evaluated against pathological assessment, and results showed the multispectral analysis was able to detect OSSN in all tested patients (P-value < 0.05). The trained classifier on OSSN and normal sections was found to have great performance (AUC $> 83\%$). The maps produced by the analysis were in close agreement with margins observed in H&E sections. The fully automated diagnostic method based on AI methodology produced maps of the neoplastic-non neoplastic interface that could be generated in quasi-real time and used for intraoperative assessment.

Conclusions: The study demonstrated the feasibility of using AI empowered hyperspectral autofluorescence imaging to detect OSSN and the potential for the technique to be used as a diagnostic tool in future clinical applications.

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1244P AI-based accurate PD-L1 IHC assessment in non-small cell lung cancer across multiple sites and scanners

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Background: Immunohistochemical PD-L1 expression, a tissue-based biomarker that predicts response to immune checkpoint therapy, is used to guide treatment decisions in advanced non-small cell lung cancer (NSCLC). Artificial intelligence (AI) technology may optimize PD-L1 scoring in regard to standardization, accuracy and efficiency. However, previous such approaches failed to show consistency across samples derived from different sites and scanning devices.

Methods: We developed an AI software for automated PD-L1 tumor proportion scoring (TPS) according to international guidelines. Four pathologists assessed PD-L1 expression on 146 whole-slide images (WSI) of NSCLC biopsies obtained from three institutions, four scanning hardware types and the Ventana SP263 assay. Pathologists selected one representative region of interest (ROI) per WSI and scored PD-L1 without AI assistance (path-only). After a 2-week washout period, the same pathologists were presented with the same ROIs together with AI results (AI-only). Being able to adjust the AI results, pathologists concluded the final scores (AI+path). In addition, TPS scores were determined globally on the WSIs by the AI without human intervention and were compared against clinical WSI scores.

Results: For the threshold of TPS$\geq$1%, inter-rater agreements between a) pathologist and AI+path, b) pathologist and AI-only, and c) AI-only and AI+path were 86.3%, 85.6%, and 89.7%, respectively (for TPS$\geq$50%: a) 85.6%, b) 80.8%, c) 92.5%). With AI assistance, pathologists scored faster compared to manual scoring (median time: 72 vs. 117 sec/ROI; $p<0.01$). Additionally, scoring of WSIs by the AI without human intervention showed higher agreement with clinical scores than inter-human agreement (<85%) reported in literature.

Conclusions: Using challenging validation data from three institutions and four scanners, ROI scoring with the support of our AI PD-L1 quantifier showed high agreement with pathologists, while reducing assessment time. Of note, fully automatic global AI scoring on WSIs resulted in equally high agreement rates. These results demonstrate suitability and safety of the AI system for application in clinical routine, ultimately improving accuracy and efficiency of PD-L1 scoring.

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1245P A lymph nodal staging assessment model for various histologic types of small intestinal tumors

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Background: Specific requirements of the minimum number of harvested lymph nodes for accurate nodal staging in small intestinal tumors are sparse as there is a probability that false-negative lymph nodes remain. The aim of this study is to establish a histologic-type-specific nodal staging score (NSS) model for the specific requirements of lymph nodes in small intestinal tumors by taking potential false-negative lymph nodes into consideration.

Methods: Small intestinal tumors with complete follow-up and examined/positive lymph nodes data were retrieved using the Surveillance, Epidemiology, and End Results program. Using a beta-binomial model, the probability of lymph nodes with occult disease and the NSS model were established.

Results: A total of 7649 small intestinal tumors were retrieved, including 3789 carcinoid cases, 2467 adenocarcinoma cases, 718 neuroendocrine carcinoma cases, 502 sarcoma cases, and 173 others. To reach a 0.05 false-negative probability, the minimum number of lymph nodes was 10 in carcinoid tumors, 11 in adenocarcinoma, 12 in neuroendocrine carcinoma, 7 in sarcoma, and 16 in others. Distinct NSS curves were presented among each histologic type of small intestinal tumors. The NSS of neuroendocrine carcinoma indicated that a higher number of lymph nodes was required to enable the correct staging of lymph nodes compared to other types of small intestinal tumors. The prognostic values of NSS quartiles were validated.

Conclusions: The minimum required number of examined lymph nodes varied in each histologic type of small intestinal tumors. The NSS improved the adequacy of nodal staging for patients for clinical interpretation and decision making.

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1246P Detection of alternative lengthening of telomeres (ALT) across cancer types based on tumor-normal multigene panel sequencing

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Background: Alternative Lengthening of Telomeres (ALT) is a telomerase-independent mechanism for the maintenance of telomeres, which is characterized by the absence of telomerase activity and often co-occurring loss of function somatic mutations in ATRX or DAXX. There is burgeoning evidence to suggest that ALT is associated with genetic vulnerabilities that may be exploited through synthetically lethal approaches. Here, we sought to develop a classifier to detect ALT based on multi-gene targeted sequencing data.

Methods: We developed an attention-based neural network model to detect ALT based on a clinical tumor-normal panel sequencing data (MSK-IMPACT). For training, cases with deleterious *ATRX* or *DAXX* mutations were considered ALT (n=274), whereas cases harboring *TERT* promoter hotspot mutations or gene amplification were regarded as non-ALT (n=965). The model was trained using a 10-fold cross-validation and 997 genetic and clinical features, including cancer type, telomeric content and fusion rates, copy number variation and mutational profiles, followed by

hyperparameters optimization. The model was independently validated in 619 cases across 36 cancer types with an ALT:non-ALT ratio of 1:3.

Results: In the validation cohort, the MLP classifier detected ALT cancers with an accuracy of 80% (99% CI 75.9-84.1%), a sensitivity of 69% (99% CI 64.2-74.8%), specificity of 88% (99% CI 84.6-91.4%), and a F1 score of 75% (99% CI 70.5-79.5%). In the context of samples correctly classified (n=495), ALT was significantly more frequently detected in GI neuroendocrine tumors, uterine sarcomas, as well as adrenocortical, prostate and small cell lung cancer.

Conclusions: Deep learning can detect ALT cancers from targeted sequencing data across various cancer types. This new method enables the dissection of genomic and phenotypic characteristics of ALT cancers in large retrospective cohorts with available targeted sequencing data, while providing a potentially high-throughput, accessible means to enroll patients in prospective studies targeting the ALT phenotype.

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1247P A detection model for EGFR mutations in lung adenocarcinoma patients based on volatile organic compounds

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Background: Volatile organic compounds (VOCs) are known to be associated with lung cancer, and EGFR mutations are common in lung adenocarcinoma. In this study, we aimed to investigate the potential of VOCs analysis as a non-invasive method for early detection of EGFR mutation.

Methods: We collected breath samples from 114 EGFR wild-type lung adenocarcinoma patients and 132 EGFR mutant lung adenocarcinoma patients and analyzed them using High-Pressure Photon Ionization Time-of-Flight Mass Spectrometry (HPPI-TOFMS) to detect VOCs. A detection model for EGFR mutation based on VOC analysis was established using the eXtreme Gradient Boosting (XGB) algorithm. For building the EGFR mutation detection model, all the samples were randomly split into a training set, validation set, and test set with a ratio of 5:2:3.

Results: The top ten VOC ions which were significantly different between the EGFR mutant lung adenocarcinoma patients and patients without EGFR mutation were displayed in the table ($P < 0.05$). The discrimination power of each VOC was relatively limited. Among them, 2-Ethyl-4,5-dimethylthiazole had the highest accuracy with an area under the receiver operating characteristic curve (AUC) of 0.829 (95%CI: 0.744-0.974). With the combination of these 10 VOC ions, the model performs well. The AUC for the combination model was 0.895 (95% CI: 0.810-0.980) in the validation cohort, while the AUC in the test set was 0.849 (95% CI: 0.769-0.930), indicating good diagnostic accuracy, with sensitivity and specificity of 70.7% (95% CI: 56.6%, 84.4%) and 71.4% (95% CI: 56.2%, 86.6%).

Table: 1247P The top 10 VOC ions related to EGFR mutation in lung adenocarcinoma

Chemicals	Peak area		*P*-value
	EGFR mut	RGFR wild	
Cyclohexanone oxime	242.6±103.4	139.1±234.1	<0.001
Dimethoxybenzene	522.7±1730.2	200.0±256.6	0.017
Tert-Butyl methyl ether	667.5±1655.3	278.4±302.0	0.006
2-Ethyl-4,5-dimethylthiazole	659.0±1762.2	329.7±730.8	0.039
Trimethylbenzene	375.1±617.7	202.9±185.6	<0.001
Salicylamide	310.6±332.9	203.0±187.3	<0.001
p-cymene/Cinnamyl alcohol	300.5±1002.5	123.5±130.7	0.038
L-serine/D-serine	706.2±515.0	359.9±318.0	<0.001
1-Propanethiol	2005.3±1609.7	1419.7±1673.0	0.002
4-Methylanisole/2-Methylanisole	402.1±314.4	180.1±220.1	<0.001

Conclusions: Our study suggested that VOCs analysis might be useful as non-invasive methods for early detection of EGFR mutations in lung adenocarcinoma. Further studies are needed to validate the accuracy of our model.

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1248P Development of a high performance and noninvasive diagnostic model using blood cell-free microRNAs for multi-cancer early detection

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Background: Despite recent progress, developing a low-cost and high-accuracy test for multi-cancer early detection (MCED) remains a challenge worldwide. Here, we report the development of a diagnostic model for MCED based on blood cell-free microRNAs (miRNA) using a training set composed of multiple cancer types.

Methods: We have previously assembled 3 large serum microarray datasets that assessed the expression of 2588 serum miRNAs from 6283 cancer patients (pts) across 13 cancer types and 5130 non-cancer controls, and developed a 4-miRNA model for MCED from a lung cancer training set (Cancers 2022 ,14:1450). In the current study, an expanded training set including 1408 pts from 7 cancer types and 1408 age-, gender-matched non-cancer controls was compiled with the remaining participants organized into 3 validation sets. A new diagnostic model was built from the expanded training set by Linear Model for Microarray Data (limma) and 10-fold cross-validation.

Results: A new 4-miRNA diagnostic model was developed from the training set. In validation set 1 including 1358 lung cancer pts and 1501 non-cancer controls, the model achieved 99% sensitivity and 100% specificity. In validation set 2 comprising 1438 pts across 12 cancer types and 1623 non-cancer controls, the model achieved > 90% sensitivity for 8 cancer types and at least 75% sensitivity for 3 cancer types along with 99% specificity. In validation set 3 comprising 2079 pts across 4 cancer types and 598 non-cancer controls, the model achieved >90% sensitivity for all 4 cancer types and 98% specificity. Overall, the new model showed improved performance compared to the old model ($p<0.001$).

Table: 1248P

Cancer type	N	Sensitivity of new model	Sensitivity of old model
Validation set 2			
Biliary Tract	40	100%	98%
Bladder	192	99%	98%
Breast	135	1%	0%
Colorectal	155	92%	86%
Esophageal	124	91%	85%
Gastric	150	100%	100%
Glioma	40	98%	88%
Liver	148	84%	84%
Ovarian	133	79%	62%
Pancreatic	149	91%	83%
Prostate	40	98%	92%
Sarcoma	132	75%	72%
Validation set 3			
Gastric	1067	100%	100%
Glioma	196	96%	87%
Esophageal	247	92%	85%
Prostate	569	95%	90%

Conclusions: Our study provided further evidence in demonstrating that circulating miRNA-based diagnostic models have the potential to be developed into inexpensive, highly accurate and noninvasive tests for MCED. Models trained using multiple cancer types outperformed those trained from a single cancer type.

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1249P Whole genome sequencing-based cancer diagnostics in routine clinical practice: An interim analysis of two years of real-world data

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Background: Whole genome sequencing (WGS) has matured and proven feasible and valid for routine clinical cancer care. Here, we report on the value of WGS in a real-world setting as part of standard clinical practice at the Netherlands Cancer Institute.

Methods: WGS (tumour-normal pairs at 90x-30x depth) was used for diagnostic testing in patients with metastatic cancer, rare primary tumours and cancer of unknown primary (CUP). All WGS requests initiated by medical specialists (Jan 2021-Nov 2022) were evaluated for test success rate and clinical decision consequences, as defined by detection of actionable biomarkers, relevance for CUP tissue-of-origin diagnosis, and identification of pathogenic germline alterations.

Results: A total of 888 matching tumour tissue and blood samples were received from 810 unique patients. 823/888 WGS tests were successful, leading to a clinical feasibility of 93%. The major cause of failure (47/65) was insufficient tumour cellularity (<20%). Based on preliminary analysis results (412/823 samples from 408 patients) we found clinical decision consequences of WGS-based diagnostics in 77% of patients (complete cohort data will be presented at ESMO). This is based on: (1) 73% of analysed patients (298/408) having, after assessment by a molecular tumour board, ≥1 potentially actionable biomarker for standard (24%) or experimental (63%) treatment options, (2) added value when integrated with the routine diagnostic work-up for CUP patients for identifying a primary tumour type in 66% (62/94) of patients, and (3) pathogenic germline variants in 7% (28/388) of patients (for patients that have given consent for germline analysis; ∼50% were not previously identified). For 320 patients, follow-up data (median 10 months) was available, which revealed that in 25% a WGS-informed targeted treatment was started.

Conclusions: WGS in routine clinical practice has a clinical feasibility of 93%. When successful, clinically relevant information is retrieved for 77% of patients. Short-term follow-up revealed that in 25% of patients, WGS information was used to inform treatment decision. This percentage may increase with longer follow-up and exhaustion of standard treatment lines.

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1250P Assessing lung carcinoma: A retrospective study on volume evaluation, consolidation and infiltration using chest OMX

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Background: We conducted a retrospective analysis to evaluate the volume of the lungs and determine the presence of infiltration and consolidation. To accurately interpret anisotropies and voxel spacings and to maintain resilience even when dealing with unbalanced class distributions, we used nnU-Net with quantitative and qualitative assessments to detect Lung infiltration. Utilizing TCGA-LUAD data (Lung Adenocarcinoma) and TCGA-LUSC (Lung Squamous cell carcinoma) this retrospective study on segmentation for volumetric and consolidation assessments are conducted. Chest OMX is a diagnostic tool that can assess lung volume, which in turn enables various applications such as monitoring recurrence from the changes in Lung volume; identifying infiltration and response to the treatment from Lung Volume and lobes, and detecting abnormalities in the lung from Consolidation. By providing quantitative score values, it assists in tracking changes over time and facilitating decision-making in clinical diagnosis.

Methods: We used nnU-Net, a popular deep-learning framework designed for medical image segmentation tasks. By analyzing the volume, infiltration, and consolidation characteristics of a lung carcinoma on CT scans, we can assess the tumor's behavior and response to treatment. From regional lung segmentation invasion, the burden is calculated. Additionally, measurements of discovered lung lesions and dedication to the relevant lung lobe are performed, along with fully automated lung lobe segmentation. Lobe 3D uses a deep learning system to measure the volume of the five lobes of the lung. HAA is also analyzed towards the end. Patient cases are selected irrespective of their ages from the TCGA cohort group. The primary outcome was the assessment of lung volume and the extent of the infiltration.

Results:

Table: 1250P Chest OMX: Generated diagnosis report for the case TCGA-LUSC

Left lung (LL) cm^3	1429.50
Right lung (RL) cm^3	1516.38
Left upper lobe (LUL) cm^3	807.24
Left lower lobe (LLL) cm^3	603.17
Right upper lobe (RUL) cm^3	618.34
Right middle lobe (RML) cm^3	276.84
Right lower lobe (RLL) cm^3	611.89
Left upper lobe (HAA) cm^3	170.16
Left lower lobe (HAA) cm^3	378.00
Right upper lobe (HAA) cm^3	128.18
Right middle lobe (HAA) cm^3	59.05
Right lower lobe (HAA) cm^3	394.12
Volume (LUL, LLL, RUL, RML, RLL) cm^3	(807.24, 603.17, 618.34, 276.84, 611.89)
Involvement (LUL, LLL, RUL, RML, RLL) cm^3	(378.00, 128.18, 59.05, 394.12)
Infiltration percentage (LUL, LLL, RUL, RML, RLL) %	(21.08, 62.67, 20.73, 21.33, 64.41)

Conclusions: The diagnostic tool, Chest OMX can analyze the lung tissue from CT scans to determine the volume, consolidation and extent of infiltration by cancerous cells.

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1251P Development of a deep learning algorithm for lung cancer diagnosis using methylation and fragment size profiles of cfDNA

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Background: Abnormal methylation of cell-free DNA (cfDNA) enables the diagnosis of lung cancer. In this study, we aimed to identify the best methylation marker for distinguishing lung cancer from healthy individuals, and then develop a deep learning algorithm using methylation and fragment size profiles (MFS) of cfDNA in that region.

Methods: We obtained 828 tissue samples from lung cancer patients, 74 adjacent normal tissue samples, and 656 samples of normal whole blood from the TCGA database and generated genome-wide tissue and plasma methylome data from healthy individuals and lung cancer patients using 215 Methylated DNA immunoprecipitation sequencing (MeDIP-Seq) and 24 Enzymatic Methyl-seq (EM-seq). A total of 366 DNA methylation markers were selected based on the methylation profiling of these datasets, and a targeted EM-seq panel was designed on these markers. The panel was used to produce 142 lung cancer samples (stage I: 26%, II: 11%, III: 42%, IV: 11%, unknown: 11%) and 56 healthy samples. MFS was trained on hyper- and hypo-methylated regions using convolutional neural networks. To confirm the limit of detection (LOD), sequencing was performed on diluted samples of healthy and lung cancer cfDNA with different ratios (tumor fractions of 0.1%, 0.5%, and 1%).

Results: We found that the performance was better in hypo-methylated regions than in hyper-methylated regions. The lung cancer detection performance in the test and external sets reached an accuracy of 81.5% (CI: 78.2% to 87.0%) and an AUC of 0.87 (CI: 0.83 to 0.94). At a specificity of 80%, the sensitivity for cancer detection was 77.5% (CI: 67.3% to 99.4%). The sensitivity for Lung Adenocarcinoma and Lung Squamous Cell Carcinoma at 80% specificity was 61.1% (CI: 42.7% to 94.4%) and 85.7% (CI: 71.4% to 100.0%), respectively. With serial dilution results, we detected down to 0.1% tumor fraction with a specificity of 80%.

Conclusions: This study developed and validated a methylation marker and deep learning model that can distinguish between lung cancer patients and healthy individuals using methylation and size information. This approach provides a sensitive and accurate diagnostic tool for lung cancer.

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1252P Quantitative cell signaling activity profiling of solid tumors to support personalized treatment in the FINPROVE basket trial: Presentation of skin tumor data

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Background: Although genomic profiling is commonly used to characterize tumors, clinical treatment successes are limited. For many tumors no actionable results are found. Furthermore it is often unknown if an identified genomic alteration affects cell functionality. By using the OncoSIGNal platform technology the actual tumor-driving signal transduction pathway (STP) activities can be quantified resulting in unique tumor profiling. Using healthy tissue as reference, high pathway activities can be determined in an individual patient giving guidance for personalized treatment. Recently we demonstrated for breast and ovarian tumors this approach leading to highly personalized actionable results, which can be used in the FINPROVE study. We further expanded the approach to other tumors. Here the results of STP profiling of skin tumors are presented.

Methods: Using the mRNA-based OncoSIGNal pathway activity profiling PCR test (InnoSIGN), STP activities of 7 pathways (AR, ER, PI3K, MAPK, HH, TGFβ and Notch) in 25 samples from healthy skin tissue, 35 primary melanoma, 39 metastatic melanoma and 18 basal cell carcinoma (BCC) were quantified and expressed on a scale from 0-100. Only samples with $\geq$ 50% epithelial cell content were included. High pathway activity in a tumor sample was concluded when its score was higher than the 95th percentile of reference skin STP activity.

Results: Different profiles of high pathway activity were found across skin tumor types:

Table: 1252P

	HH	MAPK	PI3K	TGFβ
BCC (n=18)	94%	44%	22%	11%
Primary melanoma (n=35)	14%	6%	51%	6%
Metastatic melanoma (n=39)	18%	15%	38%	5%

Further, within the skin tumor types, patient specific STP profiles were observed.

Conclusions: Using the OncoSIGNal test, actionable STP profiles were determined in samples from melanoma and BCC patients, creating opportunity for personalized targeted treatment. The OncoSIGNal test will be employed in the FINPROVE trial to identify patient specific actionable targets in several tumor types using tissue specific references.

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1253P Analytic validation and implementation of OncoDEEP: A pan-cancer comprehensive genomic profiling NGS assay for assessing homologous recombination deficiency (HRD)

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Background: Comprehensive genomic profiling (CGP) and reliable molecular characterization of solid tumors using NGS technology has become a key tool to facilitate biomarker-matched therapy selection. With a broad spectrum of therapies already approved or in clinical trials, rapid and scalable detection of an evolving number of therapeutically relevant genomic alterations and complex biomarkers is required. The all-in-one OncoDEEP® solution integrates both, an up-to-date comprehensive NGS panel >1MB powered by Twist Bioscience hybrid capture technology in combination with OncoDNA's bioinformatic data analysis and clinical interpretation software suite (OncoKDM and MERCURY) resulting in an integrated theranostic report. The CE-IVD approved assay covers single-nucleotide variants (SNVs), copy number variants (CNVs), deletions and insertions (indels) and loss of heterozygosity (LOH) in 638 genes and facilitates the assessment of key complex biomarkers / signatures such as homologous recombination deficiency (HRD), tumor mutational burden (TMB), or microsatellite instability (MSI). In addition, fusion gene detection (*ALK, RET, ROS1*) and *MET* exon 14 skipping events are detectable on DNA level.

Methods: Extensive validation of OncoDNA's OncoDEEP® workflow was performed on DNA from >300 FFPE tissue specimens in combination with commercial reference standards (e.g. HRD, fusion reference material) to assess analytical accuracy, sensitivity, and precision.

Results: In this initial validation study, the OncoDEEP® kit exhibited high analytic concordance, sensitivity and specificity consistent with requirements allowing the implementation of this CE-IVD assay for routine clinical application. We successfully participated in external quality assessment programs for e.g. HRD testing.

Conclusions: Our results demonstrate that OncoDNA's OncoDEEP® kit provides an efficient pan-cancer solution for accurate comprehensive genomic profiling for biomarker-matched therapy selection, including HRD, TMB and MSI. The integrated software suite allows for clinical interpretation and reporting with robust analytical performance.

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1254P Retrospective analysis of brain OMX: Diagnostic tool for structural (T1) and functional connectome (RS-FMRI) analysis of brain

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Background: The Brain OMX diagnostic tool is designed to facilitate the analysis of both structural and functional connectivity of the brain using T1-weighted structural MRI (T1) and resting-state functional magnetic resonance imaging (rs-fMRI) data. This tool utilizes a retrospective approach to gain insights into the intricate workings of the brain and its underlying connections which also assist in various stages of surgical treatment needed in neurodegenerative diseases.

Methods: The Fast Surfer pipeline is designed to be computationally efficient, allowing for the rapid processing of large-scale MRI datasets. T1-weighted structural MRI provides detailed information about the anatomical features of the brain. Functional connectivity is measured by assessing the synchronization of the Blood Oxygenation Level Dependent (BOLD) signals between different brain regions.

Results: Auditory network, cingulate network, Default Mode network, DMN and Occipital network, Dorsal Attention network, Language network, Left attention network, Right Attention network, salience network, and visual network correlations are provided. Brain complexity, neurological disorders, and personalized treatment strategies can be achieved. The correlation matrix creates a comprehensive graph from RS-FMRI.

Table: 1254P Structural analysis using BrainOMX

Subregion	Total		Left		Right	
	Volume [cm^3]	% ICV	Volume [cm^3]	% ICV	Volume [cm^3]	% ICV
Cortical white matter	462.49	33.77%	230.76	16.85	231.73	16.92
Thalamus	13.97	1.02%	7.11	0.52	6.85	0.50
Caudate	6.13	0.45%	2.96	0.22	3.17	0.23
Putamen	9.46	0.69%	4.72	0.34	4.74	0.35
Pallidum	3.67	0.27%	1.87	0.14	1.80	0.13
Hippocampus	7.18	0.52%	3.50	0.26	3.68	0.27
Amygdala	2.71	0.20%	1.36	0.10	1.35	0.10

Conclusions: By combining both structural and functional connectome analyses, the Brain OMX diagnostic tool aims to provide a comprehensive understanding of the brain's architecture for carcinomas and also its implications for neurological conditions. The tabulation shows Alzheimers neurodegenrative patient data, he connectivity can be the result of a direct anatomic connection or an indirect path via a mediating region or may have no known anatomic correlate. rs-fMRI is an imaging technique that plays a growing role in characterizing normal and abnormal functional brain connectivity in a variety of clinical conditions.

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1255P Evaluating GPT-4 as an academic support tool for clinicians: A comparative analysis of case records from the literature

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Background: Artificial Intelligence (AI) and Natural Language Processing (NLP) advancements have led to sophisticated tools like GPT-4.0, allowing clinicians to explore its utility as a healthcare management support tool. Our study aimed to assess GPT-4's ability to suggest the definitive diagnosis and the most appropriate work-up to minimize unnecessary procedures.

Methods: We conducted a retrospective comparative analysis, extracting relevant clinical data from 10 cases published at NEJM after 2022 and inputting it into GPT-4 to generate diagnostic and workup recommendations. Primary endpoint: the ability to correctly identify the final diagnosis. Secondary endpoints: its ability to list the definitive diagnosis in the five most likely differential diagnoses and determine an adequate workup.

Results: The AI could not identify the definitive diagnosis in 2 out of the 10 cases (20% inaccuracy). Among the 8 cases correctly identified by the AI, 5 (63%) had the definitive diagnosis as the top differential diagnosis list. Regarding the suggested diagnostic tests and exams, requests for exams that would not aid in the patient's final diagnosis were made in 2 cases, representing 40% of the patients whose final diagnosis was not correctly identified by the AI. Moreover, the AI could not suggest adequate treatment for 7 cases (70%). Among them, the AI suggested inappropriate management for 2 cases, and the remaining 5 received incomplete or non-specific advice, such as chemotherapy, without specifying the best regimen.

Conclusions: Our study demonstrated GPT-4's potential as an academic support tool, although it cannot correctly identify the final diagnosis in 20% of the cases. There is also a limitation regarding the management suggested by AI. In cases where the main diagnostic hypothesis was incorrectly identified or not listed as the top differential diagnosis, the AI requested unnecessary additional diagnostic tests for 40% of the patients. Future research should focus on evaluating the performance of GPT-4 using a more extensive and diverse sample, incorporating prospective assessments, and investigating its ability to optimize diagnostic and therapeutic procedures to optimize healthcare utilization.

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1256P Value of detection of peripheral blood circRNA based on digital PCR in the diagnosis of lung adenocarcinoma

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Background: Lung cancer is a cancer type with high morbidity and mortality in the word, the clinical prognosis of lung cancer patients is still poor, the main reason is the lack of effective early screening and diagnosis methods. Plasma circRNAs detected by droplet digital PCR may be ideal markers for liquid biopsy. However, droplet digital PCR detection of circRNAs in plasma for (early) diagnosis of lung adenocarcinoma has been rarely reported.

Methods: RNA sequencing analysis was performed in plasma from patients with early lung adenocarcinoma and healthy individuals. Droplet digital PCR was used to verify the differentially expressed genes. We evaluated their diagnostic efficacy and predict their biological functions of target genes.

Results: The copy numbers of circLZIC and circCEP350 in the plasma of lung adenocarcinoma patients were significantly higher than in plasma of healthy people ($P < 0.01$), they are closely related to tumor size ($P < 0.05$) and TNM stage ($P < 0.05$),and the copy numbers in postoperative plasma of the same patient were significantly lower than those in preoperative plasma ($P < 0.05$).ROC curve analysis showed that circLZIC (AUC=0.782) and circCEP350 (AUC=0.764) alone and in combination (AUC=0.863) had diagnostic value in lung adenocarcinoma, circLZIC (AUC=0.786) and circCEP350 (AUC=0.546) alone and in combination (AUC=0.803) had diagnostic value in early lung adenocarcinoma.Bioinformatics analysis revealed that circLZIC and circCEP350 had more binding sites with multiple microRNAs. Their target genes were enriched in several signaling pathways.

Conclusions: The copy numbers of circLZIC and circCEP350 were higher in plasma of lung adenocarcinoma patients than in plasma of healthy controls, significantly correlated with tumor size and TNM stage, and closely related to the occurrence and development of tumors. These circRNAs may serve as molecular markers for the diagnosis of lung adenocarcinoma.

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1257P Double heterozygous prevalence in hereditary cancer syndromes in Northern Mexico population

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Background: Double heterozygous (DH) is a rare event, in DH patients, two pathogenic variants (PV) in two genes are present in the genomic DNA. Next-generation sequencing technologies with expanded gene, and affordable and more complete tools for diagnosis in hereditary cancer field, resulted in the identification of unexpected variants, including more than one variant in a single patient. The aim of this study was to identify the prevalence of double heterozygous and determine the effect of two pathogenic variants in hereditary cancer syndromes patients from Northeast Mexico.

Methods: This multicentric study included patients from the CECIL (The CUCC Early Cancer Detection Clinic) Hereditary Cancer Registry, and from the Hereditary Cancer Program from Tec Salud. Both centers accomplish patients of the Nuevo León state and adjacent states of Northern Mexico. Patients were recruited in a period of 7 years (from March of 2016 to March of 2023), a total of 872 patients were evaluated by Medical Geneticists and tested with NGS multigene cancer panel tests.

Results: A total of 294 (33.7%) patients had at least one PV, and 9 (3%) DH (two PV). Of all the DH patients, 8 (88.8%) had the clinical diagnosis of HBOC (Hereditary Breast Hereditary Cancer Syndrome), and one (11.1%) had Lynch Syndrome diagnosis. The mean age of cancer diagnosis was 42.8 years, compared with 40.3 mean for all the analyzed patients. None of the DH patients (0%) had synchronic or metachronic neoplasias diagnosed, compared to 19 (6.46%) with one PV patients. Among the identified variants BRCA1/2 and other homologous repair genes were found in 8 (88.8%) patients. The most frequent gene identified was MUTYH in 5 (55.5%) patients, surprisingly the variant c.1187G>A, known as a founder mutation in Northern Europe, was found in 4/5 (80%). These four Mexican patients had not known European ancestry.

Conclusions: This study suggest that the concurrence of two pathogenic variants did not impact the age of diagnosis or the risk of developing multiple neoplasia. variant c.1187G>A *MUTYH* founder mutation is frequent in our mestizo population and the most frequently found in the double heterozygous state.

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1258P Does FDG PET-based radiomics have an added value for prediction of overall survival in non-small cell lung cancer?

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Background: Machine-learning and radiomics are promising approaches to improve the clinical management of NSCLC. However the additive value of FDG-PET based radiomic compared to clinical and standard imaging variables is less investigated. We

aimed to assess the prognostic role of combined use of machine-learning and radiomics in NSCLC patients.

Methods: 320 NSCLC patients underwent PET/CT with FDG at initial staging. Forty-nine predictors, including 43 textural features extracted from PET studies, SUV-max,MTV, TLG, TNM tumor stage, age and gender were analyzed. A least absolute shrinkage and selection operator (LASSO) regression was used to select features with highest predictive value. Cox's multivariate regression analysis was used to calculate individual risk scores. We divided patients into high-risk and low-risk groups using the median risk score of each prediction model. Kaplan-Meier and log-rank test were used to compare overall survival (OS) of high- and low-risk patients.

Results: Five variables including one textural feature (NGTDM_Coarseness), SUVmax and tumor stage (stage II, stage III, stage IV) showed highest predictive value at LASSO regression analysis. These variables were used to create a LASSO model (tumor stage, SUVmax and NGTDM_Coarseness) which was compared to a reference model (tumor stage, SUVmax). After a median follow-up time of 35 months, 61.6% of patients were deceased. The LASSO model classified 70% deceased and 81% alive as high- and low-risk patients respectively (Odd Ratio(OR)=[9.9, Confidence Interval(CI)=5.8,17.1]). The reference model classified 70% deceased and 82% alive as high- and low-risk patients respectively (OR=[10.7, CI=6.2,18.7]). Kaplan-Meier curves showed that both the reference model and the LASSO model significantly predicted shorter OS in the high-risk group, without any significant model difference: median OS in the high-risk group was 15 months (95%CI, 11-18) for both models while median OS was not reached in the low-risk group for both models.

Conclusions: These data indicate that radiomics does not significantly improve the prediction of outcome based on disease stage and SUVmax. Morover, the SUVmax used with the stage improves the accuracy of the stage alone based prediction.

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1259P Evolution of the diagnosis and management of CUP: A decade analysis

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Late withdrawal

1260TiP Enhancing lung nodule discrimination with a novel cfDNA test: The cancer signature ensemble (CSE) approach

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide, with over 40% of patients diagnosed at stage IV, mainly due to difficulties in early detection. Although low-dose CT (LDCT) screening assists in early diagnosis, its high false-positive rate demands more accurate and minimally invasive biomarkers. In LDCT screening, about 5% of cases exhibit lung nodules with a 5% or higher risk of malignancy (Lung-RADS category 4); however, most are benign, with actual lung cancers representing only 0.6% of the total screened population. A diagnostic test is essential to avoid unnecessary invasive examinations and identify individuals at higher lung cancer risk. Other liquid biopsy approaches using restricted range of biomarkers have diagnostic limitations for early-stage cancers.

Trial design: We are recruiting participants aged between 50 and 80 years old who have a smoking history of at least 20 pack-years and are either current smokers or former smokers who quit within the past 15 years. Eligible individuals must have lung nodules identified on chest CT scans as Lung-RADS category 4B or 4X and be scheduled for a pathological diagnosis for lung cancer with TNM stage IA. Five participating hospitals are collecting whole blood (15mL) samples and sending them to a central laboratory, IMBdx. IMBdx is extracting cfDNA, performing quality control (QC), and assessing [1] whole-genome methylation patterns, [2] fragmentomics, and [3] copy number variations. The results will be integrated into a machine learning-based algorithm to establish a cancer signature ensemble (CSE) index as a 5-tier categorical indicator for differentiating malignant and benign nodules. A training set of 150 cases will be used to develop the CSE index, and its diagnostic performance will be validated in a validation set of 150 cases. The CSE index for lung cancer discrimination is expected to exhibit a sensitivity and specificity of 75% and 95%, respectively. The study's outcomes aim to reduce unnecessary CT follow-ups or invasive tissue sampling/surgery. Future research will explore its applicability as a screening test for non-smokers or individuals at lower lung cancer risk.

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Legal entity responsible for the study: The authors.

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1261O Neoadjuvant nivolumab (N) + ipilimumab (I) vs chemotherapy (C) in the phase III CheckMate 816 trial

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Background: The phase 3 CheckMate 816 trial met both of its primary endpoints, with neoadjuvant N + C demonstrating statistically significant and clinically meaningful improvements in event-free survival (EFS) and pathological complete response (pCR) vs C in patients (pts) with resectable NSCLC; N + C continues to show long-term EFS benefit vs C. Here, we report exploratory analyses from the concurrently randomized N + I and C arms of the study.

Methods: Adults with stage IB ($\geq$ 4 cm)—IIIA (per AJCC 7th ed) resectable NSCLC, ECOG PS $\leq$ 1, and no known *EGFR/ALK* mutations were concurrently randomized to 3 cycles of N 3 mg/kg Q2W + 1 cycle of I 1 mg/kg or 3 cycles of C Q3W. Enrollment to the N + I arm closed early after the primary analysis population of the study was changed to N + C vs C on the basis of evolving external trial data. Assessments included EFS and pCR (per blinded independent review), overall survival (OS), surgical outcomes, safety, and efficacy by a 4-gene (*CD8A*, *STAT1*, *LAG3*, and *CD274* [*PD-L1*]) inflammatory signature score derived from the RNA sequencing of baseline (BL) tumor samples.

Results: In the concurrently randomized N + I (n = 113) and C (n = 108) arms, BL characteristics were generally balanced between treatment (tx) arms. At a median follow-up of 49.2 mo (database lock, 14 Oct 2022), both EFS and OS appeared to favor N + I vs C. Median EFS was 54.8 mo vs 20.9 mo with N + I vs C (HR 0.77 [95% CI 0.51—1.15]; 3-y EFS rates, 56% vs 44%). Median OS was not reached in either tx arm (HR 0.73 [95% CI 0.47—1.14]; 3-y OS rates, 73% vs 61%). pCR rate (95% CI) was higher with N + I vs C (20% [13.4—29.0] vs 5% [1.5—10.5]). Definitive surgery occurred for 74% and 76% of pts in the N + I and C arms, respectively; R0 resection rates were 80% and 71%. A high vs low BL 4-gene inflammatory score was associated with improved EFS and pCR with N + I. Grade 3—4 tx-related adverse events (AEs) and grade 3—4 surgery-related AEs were reported in 14% vs 36% and 15% vs 14% of pts in the N + I and C arms, respectively. Outcomes in key subgroups, including by PD-L1 expression, will be presented.

Conclusions: These exploratory analyses from CheckMate 816 showed potential clinical benefit and a manageable safety profile with neoadjuvant N + I vs C; N + C remains the standard neoadjuvant treatment for pts with resectable NSCLC, as previously reported.

Clinical trial identification: NCT02998528.

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1262MO Impact of a minimal versus CT-scan-based follow-up on patient-reported outcomes for completely resected non-small cell lung cancer (NSCLC) in phase III IFCT-0302 trial

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Background: The IFCT-0302 trial was a randomized multicenter trial, which found no benefit in overall survival in adding chest CT-scan and fiberoptic bronchoscopy (optional for adenocarcinomas) to a follow-up based on physical examination and chest x-ray in resected NSCLC. We present the results of patient-reported outcomes (PROs), a secondary endpoint of the IFCT-0302 trial.

Methods: PROs consisted of Health-Related Quality of Life (HRQoL), assessed using the Short Form-12 (SF-12) questionnaire, and a penibility visual analogue scale (between 0 and 10), at randomization, every 6 months during 2 years and annually until 5 years or until disease progression or second primary cancer or death if they occurred before 5 years. Time to deterioration, used to analyze longitudinal HRQoL data, was defined as the interval between randomization and the occurrence of the first clinically relevant deterioration (5 points) compared to the HRQoL score at baseline.

Results: Between January 2005 and November 2012, 1775 patients were randomized in the IFCT-0302 trial. At baseline, 756 of the 888 patients (85.1%) in the minimal follow-up group had at least one HRQoL score available, and 747 of 887 (84.2%) in the CT-based follow-up group. 80.8% and 75.6% of patients completed questionnaires up to one year, respectively. There was no difference between groups in time to deterioration for the 2 dimensions of the SF-12 questionnaire: mental dimension [HR (the minimal follow-up group vs. the CT-based follow-up group): 0.92; 95%CI (0.80; 1.15); p=0.64] and physical dimension [HR: 0.87; 95%CI (0.71 ; 1.06) ; p=0.19]. Penibility was statistically greater in the CT-based follow-up group (p<0.0001), and was related to fiberoptic bronchoscopy.

Conclusions: Analysis of PROs in the IFCT-0302 trial demonstrated that adding thoracic CT-scan in the follow-up after resection of NSCLC did not influence HRQoL but penibility was increased, due to fiberoptic bronchoscopy.

Clinical trial identification: NCT00198341.

Legal entity responsible for the study: IFCT.

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1263MO The impact of PET-CT and brain MRI for metastasis detection among patients with T1-stage lung cancer: Findings from a large cohort study

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Background: 18F-fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (PET-CT) and brain magnetic resonance imaging (MRI) are commonly used to detect metastases in lung cancer patients. However, current guidelines for the use of these methods in T1-stage lung cancer are not risk-based and need to be optimized.

Methods: T1-stage lung cancer patients who underwent pathologic examination and PET-CT plus MRI were included from January 2009 through July 2022, and their clinical-pathological and survival information was collected. The proportion of metastasis was observed in tumors with different sizes (5-30 mm) stratified by radiologic types (solid and sub-solid nodules). Additionally, a cohort of T1-stage patients who received routine CT only (or plus MRI) was set as control. The overall survival (OS) was compared between patients with and without PET-CT examination.

Results: A total of 2,298 patients receiving PET-CT were included, of which 686 (29.9%) had metastases (44.3% among the solid nodules and 23.4% among the sub-solid nodules). The proportion of metastases increased with the size, no metastasis occurred in patients with solid nodules <8mm and sub-solid nodules <10mm. Moreover, metastasis occurred in only 5% of patients with solid nodules <10mm and sub-solid nodules <13mm. Among patients without baseline metastasis, those who underwent PET-CT (n=1,691) had longer OS compared to that who received CT only (or plus MRI, n=2,581) (HR, 0.72; 95%CI, 0.52-0.99; P=0.045), while such benefits were observed among solid nodules≥10mm (HR, 0.28; 95%CI, 0.14-0.56; P<0.001) and sub-solid nodules≥13mm (HR, 0.67; 95%CI, 0.46-0.99; P=0.046).

Table: 1263MO Univariable Cox proportional hazards model analyses of overall survival in different sub-groups patients

Variable	HR (95% CIs)	P-Value
All nodules		
CT (± MRI)	Reference	0.045
PET-CT & MRI	0.72 (0.52-0.99)	
Solid nodules		
0-10 mm		
CT (± MRI)	Reference	0.560
PET-CT & MRI	NA	
≥10 mm		
CT (± MRI)	Reference	< 0.001
PET-CT & MRI	0.28 (0.14-0.56)	
Sub-solid nodules		
0-13 mm		
CT (± MRI)	Reference	0.648
PET-CT & MRI	0.78 (0.42-4.02)	
≥13 mm		
CT (± MRI)	Reference	0.046
PET-CT & MRI	0.67 (0.46-0.99)	

Conclusions: PET-CT and MRI might not benefit T1-stage lung cancer patients with solid nodules <10mm and sub-solid nodules <13mm, considering their low metastatic potency. These examinations remained recommended for T1-stage lung cancer patients with solid nodules ≥10mm and sub-solid nodules ≥13mm.

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1264MO IMpower010: Exploratory analysis of disease-free survival (DFS) by TGFβ cancer-associated fibroblast (CAF) gene signature expression in patients (pts) with resected NSCLC treated with atezolizumab (atezo) or best supportive care (BSC)

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Background: CAFs are an important component of the tumour microenvironment. TGFβ-induced CAFs have been associated with poor prognosis in several indications. In IMpower010, adjuvant atezo showed significant DFS benefit vs BSC in resected

early-stage NSCLC after chemotherapy (chemo), leading to approval of atezo after platinum-based chemo for resected (R0) PD-L1 TC ≥1% or ≥50% (SP263) stage II-IIIA NSCLC. We report results from exploratory analyses to identify predictive biomarkers for atezo outcomes using IMpower010 RNA sequencing (RNAseq) data.

Methods: The IMpower010 study design and primary data have been reported (Felip, *Lancet* 2021). The predictive effects of features including cell-type and -state gene signatures for DFS (atezo vs BSC) were evaluated from baseline (resection) tumour samples. Relevant features were identified based on variable importance scores calculated by generalised random forests method. Median DFS was estimated using Kaplan-Meier curves; HRs were estimated by Cox regressions.

Results: Of the 1005 randomised pts (ITT), 500 comprised the RNAseq biomarker-evaluable population. The TGFβ CAF gene signature had the highest variable importance. DFS HRs (95% CI) were 0.54 (0.37, 0.80) and 0.94 (0.63, 1.41) in the TGFβ CAF-high (≥ median) and -low (< median) populations (Table). Improved outcomes with atezo vs BSC in the TGFβ CAF-high population were driven by shorter DFS in the BSC arm. Baseline characteristics were generally balanced across populations.

Table: 1264MO

	Atezo median DFS, mo	BSC median DFS, mo	DFS HR (vs BSC) 95% CI
ITT	n=507 NR	n=498 37.2	0.81 0.66, 0.99
RNAseq BEP	n=248 36.1	n=252 30.4	0.71 0.54, 0.94
TGFβ CAF-low	n=123 NR	n=127 37.3	0.94 0.63, 1.41
TGFβ CAF-high	n=125 NR	n=125 29.7	0.54 0.37, 0.80
TGFβ CAF-high, squamous	n=61 NR	n=62 41.4	0.48 0.26, 0.89
TGFβ CAF-high, nonsquamous	n=64 36.1	n=63 24.7	0.60 0.36, 0.99
TGFβ CAF-high, PD-L1 TC ≥1%	n=74 NR	n=69 35.3	0.49 0.29, 0.84
TGFβ CAF-high, PD-L1 TC <1%	n=51 NR	n=56 28.6	0.64 0.36, 1.14

BEP, biomarker evaluable population; NR, not reached; TGFβ, transforming growth factor beta.

Conclusions: Exploratory analyses of IMpower010 RNAseq data showed that the TGFβ CAF-high population had improved DFS with atezo vs BSC, regardless of histology or PD-L1 expression level. These data suggest that after surgical resection, pts with enrichment of the TGFβ CAF gene signature may have improved DFS after adjuvant atezo vs BSC.

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1265P Toripalimab plus chemotherapy as neoadjuvant treatment for resectable stage IIB-IIIB NSCLC (RENAISSANCE study): A single-arm, phase II trial

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Background: Immunotherapy has changed the treatment paradigm for patients with NSCLC. Now considerable effort is focused on how to best use immunotherapy for resectable early-stage NSCLC. This study aimed to investigate the efficacy and safety of neoadjuvant toripalimab plus chemotherapy for resectable stage IIB-IIIB NSCLC.

Methods: Pts with resectable stage IIB-IIIB, wildtype EGFR/ALK NSCLC were eligible. All pts received 2-4 cycles of toripalimab (240mg, q3w) plus double platinum-based chemotherapy. Surgery was planned to occur within 4-10 weeks after the completion of neoadjuvant treatment. Primary endpoint was major pathological response (MPR). Secondary endpoints were complete pathological response (pCR), objective response rate (ORR), event-free survival (EFS), R0 resection rate and safety.

Results: From Dec 2020 to Apr 2023, a total of 100 pts (median age: 63, range: 45-76; male: 89, 89%, smoking history: 87, 87%; squamous cell carcinoma: 76, 76%) were enrolled. Disease distribution in stage IIB, IIIA and IIIB consisted of 33, 48 and 19 pts, respectively. Among the 98 pts completed the neoadjuvant treatment and received the radiological assessment, ORR was 63.3% (62/98). 1 pts (1/98, 1.0%) achieved complete response, 61 pts (61/98, 62.3%) had partial response. 83 pts underwent resection (median interval between neoadjuvant treatment and surgery: 89 days, range: 60-153). R0 resection was achieved for 81 pts (97.6%). 52 pts (52/83, 62.7%) achieved MPR, including 37 pts (37/83, 44.6%) with pCR. 40 pts underwent surgery with cN2/N1 at baseline (40/72, 55.6%) achieved nodal downstaging. 4 pts were preparing for surgery. Surgery was cancelled for 13.0% (13/100) of pts, reasons for cancellation included poor performance status (5%), adverse events (3%), unresectability (2%), disease progression (1%), patient refusal (1%), another primary tumor (1%). TRAEs of any grade occurred in 96% (96/100) of patients. The incidence of grade 3-4 TRAEs was 37% (37/100). The most common grade 3-4 TRAEs was neutropenia (32/100, 32%).

Conclusions: Neoadjuvant toripalimab plus chemotherapy resulted in promising MPR rate and manageable toxicity for patients with resectable stage IIB-IIIB NSCLC.

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1266P Prediction of lung cancer risk in ground-glass nodules using deep learning from CT images

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Background: Pulmonary nodules (PNs) are frequently detected on CT scans and may indicate early lung cancer. Among PNs, management of ground-glass nodules (GGNs) can be particularly challenging due to their long, often indolent natural course. When malignant, they are usually lepidic adenocarcinomas, for which many targeted therapies exist. Artificial Intelligence (AI)-based malignancy prediction of PNs using CT images has been demonstrated to perform well on solid and part-solid PNs. Here, we aimed to extend one such AI model to GGNs.

Methods: GGN nodules and predominantly-GGN part-solid nodules were collected from 3 sites: two UK, one US. Patients with a 5-30mm nodule on non-contrast CT were included, unless they had a history of cancer in the past 5 years, >5 nodules, or insufficient outcome data from long-term follow-up or histological diagnosis. Scans with >2.5mm slice spacing or significant imaging artifacts were excluded. The most concerning nodule on each CT study was evaluated, giving 169 cancers in 57 patients, and 347 benign nodules in 180 patients. Most patients were enrolled through a text search of radiology reports, and enriched for malignant nodules based on local data. The AI tool is based on a commercial system, further trained using GGNs from an additional UK site. Ability to predict malignancy was evaluated using the Area Under the Receiver Operating Characteristic curve (AUC) and compared to two reference models. The ability to rule benign cases out of follow-up was evaluated by calculating specificity at 100% sensitivity.

Results: The AUC of the AI model was 89.1 [95%CI, 86.3, 91.8], while the AUC of the reference models, Brock and Mayo, were 86.5 95%CI [95% CI, 83.2, 89.6; p=0.39 vs. AI] and 80.9 [95%CI76.9, 84.8; p<0.01 vs. AI] respectively. The percentage of benign GGNs ruled out for cancer at 100% sensitivity were 48.7% for the AI model, 14.1% for Brock, and 16.7% for Mayo.

Conclusions: To our knowledge, this is the first study to demonstrate the potential value of an AI model in predicting the malignancy risk of GGNs. Implementation of such models in clinical practice could lead to more appropriate use of invasive interventions among GGN patients, thereby improving patient outcomes.

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1267P Enhancing pulmonary nodule diagnosis: A combinatorial model of cfDNA methylation, plasma proteins and LDCT imaging

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Background: Low dosage computer tomography (LDCT) is widely used to detect early-stage lung cancer, but concerns regarding accuracy and overdiagnosis persist. To enhance LDCT diagnosis using non-invasive molecular features, we developed a combinatorial model to distinguish between malignant and benign pulmonary nodules.

Methods: In a prospective cohort of 608 participants with pulmonary nodules, we performed targeted methylation sequencing and protein level measurement using Proximity Extension Assay. Radiomics features were extracted from LDCT images of 448 participants. A machine learning classifier, incorporating a transformer model and deep neuron network models, was trained and tested, by integrating molecular and image features.

Results: A total of 368 samples (184 benign and 184 malignant) with matched sex and age were randomly selected as the training set. The remaining 81 benign and 159 malignant samples were used as the test set. The methylation-only model had an AUC of 0.805 [95% CI 0.755-0.852], the protein-only model had an AUC of 0.816 [0.768-0.860], and the radiomics-only model achieved an AUC of 0.865 [0.812-0.912]. A combination of methylation and radiomics features generated an enhanced model with an AUC of 0.884 [0.840-0.927] (sensitivity = 0.824 [0.744-0.883], specificity = 0.772 [0.641-0.865]), outperforming models based on other combinations of two features. Integrating protein markers further improved the model (AUC = 0.895 [0.845-0.934]), with both sensitivity (0.849 [0.774-0.905]) and specificity (0.842 [0.721-0.918]) showing significant enhancements. The combinatorial model performed well across sample groups with different nodule sizes, particularly for samples with nodules no larger than 10 mm.

Conclusions: This study integrated DNA methylation, protein, and radiomics features to construct a robust combinatorial model with optimal performance, providing potential clinical utility for the management of pulmonary nodules.

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1268P Liquid biopsy and CT-based multi-omics fusion enhances differential diagnosis of early-stage lung adenocarcinoma

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Background: Lung cancer is a leading cause of cancer-related deaths worldwide. Early detection using low-dose CT (LDCT) has shown promise in reducing mortality rates. Nevertheless, LDCT screening poses challenges, including a high false-positive rate and the risk of overdiagnosis. AI and biomarkers are crucial directions for the future of lung cancer screening. This study investigates the potential of multi-omics fusion, combining liquid biopsy biomarkers and computed tomography (CT) features, to enhance lung cancer differential diagnosis.

Methods: A total of 146 participants were enrolled, including 111 early-stage lung adenocarcinoma patients and 35 controls. High throughput extracellular vesicle long RNA (evlRNA) sequencing were performed using serum samples obtained before lung surgery. A fusion model was developed to combine image-based features and evlRNA features.

Results: Our findings suggest that evlRNA and image-based features complement each other, achieving improved performance when evlRNA features are fused with radiological features from AI, CTR, or human experts. Our methods achieve notable differential diagnosis performance; for example, combining evlRNA and radiological AI yields a 4-class AUC of 0.919 and a benign-malignant AUC of 0.948 (sensitivity: 89.1%, specificity: 94.3%). Integrating multi-omics analysis with human experts further enhances diagnostic accuracy. Additionally, we provide post-hoc explanations using Shapley values to understand feature importance in the multi-omics modeling.

Table: 1268P

Method	4-Class Analysis	(IA, MIA, AIS) vs Benign			(IA, MIA) vs (AIS, Benign)		
	AUC	AUC	Sens	Spec	AUC	Sens	Spec
evlRNA	79.2	86.4	83.9	85.7	75.8	73.3	78.9
CTR	77.6	75.7	59.5	94.3	62.9	77.3	59.2
vCTR	84.0	85.1	71.0	**97.1**	75.9	68.0	80.3
Rad	**89.0**	**92.2**	79.2	94.3	**82.9**	76.0	**85.8**
Junior expert	/	/	83.7	51.4	/	76.0	66.2
Senior expert	/	/	**91.9**	80.0	/	**85.3**	77.4
evlRNA + CTR	88.0	90.5	87.4	88.6	84.0	72.0	90.0
evlRNA + vCTR	89.1	91.0	84.6	91.4	82.7	68.0	**91.4**
evlRNA + Rad	**91.9**	94.8	**89.1**	94.3	87.2	80.0	87.1
evlRNA + Junior expert	83.4	89.9	86.4	88.6	82.8	73.3	84.5
evlRNA + Senior expert	89.3	**95.1**	86.5	**97.1**	**87.8**	**86.7**	80.2
evlRNA + Rad + Junior expert	92.4	96.0	**95.5**	91.4	87.3	78.7	**88.6**
evlRNA + Rad + Senior expert	**93.4**	**97.9**	91.8	**100.0**	**88.9**	**92.0**	80.1

Conclusions: In summary, our study demonstrated that the combination of evlRNA-based and image-based features can complement each other and that the collaborative approach between multi-omics and human analysis can further enhance the performance. These findings highlight the importance of integrating multiple modalities including effective biomarkers and CT analysis with AI algorithms, into LDCT screening through multi-omics fusion.

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1269P Machine learning model for predicting lung cancer recurrence after surgical treatment: A retrospective study using NLST and European hospital data

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Background: The rate of lung cancer recurrence following curative surgical resection is 30-55% and remains a significant challenge in patient management. Accurate prediction of recurrence risk is crucial for guiding treatment decisions, such as the use of (neo-)adjuvant chemo- or immunotherapy, the extent of lung resection, and follow-up strategies. We present a preoperative machine learning model that uses patient computed tomography (CT) images and demographic features to predict lung cancer recurrence.

Methods: We collected a dataset of 588 clinical stage I-IIIA lung cancer patients who underwent surgical treatment for lung cancer, of which 147 had lung cancer recurrence. This includes retrospectively collected CT images and associated demographic and pathological data from patients in both screening and clinical settings from the US National Lung Screening Trial (NLST) and the North Estonia Medical Centre (NEMC). The preoperative model was trained to predict the likelihood of recurrence on a diverse set of features, including radiomic features extracted from CT images and relevant clinical variables. An 8-fold cross validation strategy was used, where, in each fold, 6 (of the 8 equally sized) subsets were used for training, one for model tuning, and one for validation. As a baseline, we compare the preoperative model to ranked clinical staging. Performance was evaluated using the Area-Under-the-ROC-Curve (AUC), sensitivity, and specificity.

Results: Lung cancer recurrence prediction results are tabulated below. We find that our model performs significantly better (AUC=61.4, Sen=18.2) than preoperative staging alone (AUC=56.1, Sen=16.4, p-value=0.035).

Table: 1269P AUC, sensitivity and specificity performance of our machine learning model compared with ranked TNM staging. The specificity is set to 90.0 for a rule-in context

Predictors	AUC	Sensitivity	Specificity
TNM	56.1 (51.1, 61.2)	16.4 (10.1, 23.6)	90.0
Our model	**61.4 (56.7, 66.3)**	**18.2 (10.2, 24.5)**	90.0

Conclusions: Based on this retrospective analysis, we find that our model outperforms clinical staging prediction of lung cancer recurrence in preoperative settings. With further development, this algorithm could prove a valuable tool to aid the management of lung cancer patients.

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Disclosure: A. Gasimova, N. Waterfield Price, L. Freitag: Financial Interests, Personal, Full or part-time Employment: Optellum. All other authors have declared no conflicts of interest.

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1270P Personalized tumor-informed circulating tumor DNA (ctDNA) analysis for molecular residual disease (MRD) detection in resected non-small cell lung cancer (NSCLC) with common driver genes

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Background: This study aims to evaluate the feasibility of utilizing digital droplet polymerase chain reaction (ddPCR) for the detection of specific driver gene mutations (EGFR L858R/19del or KRAS G12C/D) in ctDNA for MRD monitoring in resected NSCLC patients with the mentioned mutations.

Methods: Plasma samples were collected every 3 or 6 months to detect EGFR L858R/19del or KRAS G12 C/D mutations from patients with resected NSCLC, using a single point assay. A binary logistic analysis was performed to assess the impact of these factors on MRD outcomes.

Results: Our study included 300 patients with resected NSCLC, with a median age of 62 years. Among them, 54% of patients had the EGFR L858R mutation, 34% had EGFR 19del, 10% had KRAS mutation, and the remaining 2% exhibited multiple mutations. The majority of participants were diagnosed with Stage IA NSCLC (71%), followed by 14% with Stage IB, 7% with Stage II, and 7% with Stage III. In terms of histological subtype, invasive adenocarcinoma accounted for 85% of cases, while 10% had Adenocarcinoma In Situ/Minimally Invasive Adenocarcinoma (AIS/MIA). The longest follow-up period was 39 months, with a median follow-up time of 33 months. A total of 607 blood samples were collected, with 10% of samples from AIS/MIA and 17% of samples from invasive adenocarcinoma showing MRD positivity. Among different gene mutations, the positive rates for MRD were 15% for EGFR L858R, 19% for EGFR 19del, and 18% for KRAS. In our binary logistic analysis, patients who received adjuvant therapy had a higher likelihood of MRD negativity (odds ratio: 0.50 [95% CI: 0.27, 0.95], $p < 0.05$). A higher TNM stage was associated with a higher likelihood of MRD positivity (OR: 2.13 [95% CI: 1.51, 2.99], $p < 0.001$).

Conclusions: Our findings indicate that ddPCR is a feasible option for detecting MRD in resected NSCLC with common driver genes, its accuracy was supported by the results of relevant subgroup analysis. Considering the elevated prevalence of EGFR mutations in the Asian population, our personalized tumor-informed approach targeting EGFR may offer a cost-effective solution. Nevertheless, additional data are necessary to substantiate its efficacy.

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1271P Identifying metabolic genes with the highest prognostic power in lung adenocarcinoma

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Late withdrawal

1272P Postoperative survival prediction in non-small cell lung cancer patients based on driver genotypes

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Background: Non-small cell lung cancer (NSCLC) is a heterogeneous disease with various driver gene mutations. Currently, it remains unknown the differences in postoperative survival among patients with different genotypes. We previously constructed a clinical nomogram that effectively predicts postoperative survival in NSCLC patients (C-index 0.71), but whether integration of gene classification improves its efficacy remains unclear.

Methods: We collected data from patients representing six distinct driver genotypes at the First Affiliated Hospital of Guangzhou Medical University. Clinical characteristics and prognosis data were collected. We compared the overall survival, disease-free survival, and recurrence-free survival among different gene types. The previous prediction model was externally validated using the above data, and its predictive performance was assessed in populations with different genotypes. Furthermore, we constructed a novel survival prediction model by integrating gene subtyping and compared its predictive performance with that of the original model.

Results: 1397 patients were enrolled in the analysis. Significant differences were observed in overall survival ($P<0.05$) and disease-free survival ($P<0.05$) and recurrence-free survival($P<0.05$) among patients with different driver genotypes. The predictive model demonstrated good generalizability within our cohort (C-index: 0.71, 95% CI 0.68 to 0.74). However, the performance of the model varied across different genotypes. The clinical factor prediction model exhibited favorable applicability in patients with EGFR L858R mutation, EGFR 19 deletion mutation, and wild-type, but were not found in patients with rare EGFR mutations, RAS/BRAF mutations and fusion mutations. The new prediction model integrating genotypes slightly improves the performance of the previous clinical model (C-index: 0.74 vs 0.71).

Conclusions: Patients with different genotypes display diverse prognostic outcomes. The predictive model maintains practice predictive performance in certain driver gene subtypes. Furthermore, the integration of genotyping with clinical risk factors yields slight improvements in prediction performance.

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1273P The prognostic value evaluation of a tissue Comprehensive Genomic Profiling (CGP)-informed personalized MRD detection assay in NSCLC

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Background: ctDNA-based molecular residual disease (MRD) detection of postoperative plasma enables refining risk stratification to guide treatment precisely. The clinical efficacy of MNavigator V1 utilizing fixed panel detection scheme has been confirmed and published. Here, we reported its V2 improved version performance.

Methods: MNavigator V2 strategy combines the advantages of two classic technologies, WES-based personalized and non-customized off-the-shelf assay. In this assay, tissue somatic mutations were identified by CGP-sequencing with a 2.3 Mb 1021-gene panel, and then the top-ranked 20 mutations were selected. Tissue-specific customized panel combined with a lung universal core panel to monitor MRD by sequencing depth $>$ 100,000x. The core panel can detect de novo mutations in ctDNA, especially targeted treatment-resistant mutations. Analytical validation was performed on a commercial MRD reference standard set, with VAF down to 0.005%. The retrospective cohort included 33 NSCLC patients (pts) treated with definitive surgery. Head-to-head compared MRD detection of this assay with MNavigator V1 that uses a 338-gene panel with a sequencing depth of 30,000x.

Results: This assay demonstrated the sample-level LOD of 0.005% by monitoring 20 variants, with a specificity of 100%. 10,625 NSCLC 1021panel sequencing data indicates 99% of pts available monitor 2 mutations, achieving 97.3% analytical sensitivity at 0.02% VAF. In the cohort, MRD was detected in 14/15 relapsed pts by both assays, apart from a brain-only metastasis pt. Recurrence-free pts with 2 years of follow-up were MRD-negative, yielding a specificity of 100% (18/18). MRD-detectable population was associated with a worse prognosis (HR=35.4). MNavigator V2 predicted relapse with a lead time of 143 days, 15 days ahead of V1. This may be related to more traced mutations (average 10 vs 5) and deeper sequencing depth, improving the capability to detect minimal tumor DNA residuals.

Conclusions: The CGP-based personalized MRD assay showed high analytical performance, and clinical assessment indicated superior sensitivity than fixed panel assays, providing greater potential for clinical benefit.

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1274P Early dynamics of circulating tumor DNA following curative hypofractionated radiotherapy related to disease control in lung cancer

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Background: We aimed to find out a dynamic pattern of ctDNA during hypofractionated RT in patients with lung cancer and its clinical relevance.

Methods: Prospectively, 24 patients with pathologically or clinically diagnosed early stage lung cancer who underwent definitive RT alone were enrolled. RT was curatively prescribed with 60 − 64 Gy in 4−20 fractions. Using the blood samples obtained before and after the start of RT including the first, second, and third day (T0−3), ctDNA was longitudinally analyzed with targeted deep sequencing by LiquidSCAN. To find a feasible index associated with progression, comprehensive variables quantifying various types of ctDNA including sum of variant allele frequency (total VAF, %), maximum of VAF (max VAF, %), sum of genomic equivalent (total GE, hGE/ml), and maximum of GE (max GE, hGE/ml) were used for the statistics.

Results: A total of 13 patients were analyzed excluding undetected cases or patients without samples within 3 days after starting RT. During median 22.2-month follow-up (range 5.2− 34.3 months), 4 patients experienced progressive disease (PD) between 7.9 and 16.6 months after RT (PD group); two local or locoregional recurrence and two lung-to-lung metastasis. The remaining 9 patients were in the state of no evidence of disease (NED group). Despite of no significance, NED group showed the highest ctDNA ratio [NJ1] (1.76−2.34) compared to the baseline level. Regarding the timing of ctDNA elevation, the Tmax, the day with the highest ctDNA level among T0−3, was significantly different between NED and PD group with total GE and max GE ($p=0.035$ and 0.021, respectively). At ROC curves, the max GE showed the best AUC (86.1%) and the cut-off value of the Tmax was 1.5 (sensitivity 55.6%, specificity 100%, positive-predictive value 100%, and negative-predictive value 50%). Tumor size $>=$3cm, squamous histology, and daily dose of 3−4 Gy were correlated to the Tmax T2 or T3. At survival analysis, only Tmax showed better disease control rate, which was marginally significant ($p=0.081$).

Conclusions: The timing of early ctDNA elevation after RT might be a potential predictive marker of good clinical response. Also, we suggested that max GE was a feasible index to check ctDNA level after RT.

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1275P Genomic analysis of lung adenocarcinoma with micropapillary component: Identification of micropapillary-related subtypes and development of a prognostic model

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Background: Micropapillary adenocarcinoma represents a highly aggressive histologic subtype of lung adenocarcinoma (LUAD), and even a minor proportion of micropapillary component (MPC) could contribute to poor prognosis. Thus, a comprehensive analysis of the genetic features of LUAD with MPC would help better understand the cancer biology and guide future treatments.

Methods: In a previous international cohort comprising over 1500 patients, we have identified 11 genes that are significantly associated with the prognosis of LUAD. In this study, we investigated the expression patterns of these 11 genes in a total of 1592 micropapillary-containing LUAD samples from The Cancer Genome Atlas (TCGA) dataset. Furthermore, LASSO Cox regression analysis was employed to predict overall survival (OS). Patients were classified into low- and high-risk groups based on the median value of the risk score. The predictive accuracy of the scoring system was

subsequently validated, and a nomogram was employed to optimize its clinical applicability range.

Results: Patients were divided into two genomic subtypes based on prognostic genes using an unsupervised clustering analysis to further investigate the special regulation mechanism. Kaplan-Meier curves demonstrated that patients in gene cluster A had significantly better overall survival (OS) times compared to those in gene cluster B. An eight-gene prognostic signature was developed using LASSO Cox regression analysis. Patients in the high-risk group exhibited a worse OS compared to those in the low-risk group (71.9 months vs. 118.5 months). Notably, patients in the high-risk group with micropapillary component had significantly worse OS compared to those in the intermediate- (HR=1.81, 95% CI 1.13-2.88, P=0.013) and low-risk groups (HR=1.03, 95% CI 0.63-1.70, P=0.910), whereas no significant difference was observed between patients without micropapillary component and the low-risk group.

Conclusions: These findings are expected to provide fresh insight into the nature of this aggressive cancer subtype, pave a new path for assessing the disease prognosis, and assist in developing personalized therapeutic strategies for patients with LUAD.

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1276P Genomic screening by multi-gene assay for perioperative targeted therapy in patients with early-stage non-small cell lung cancer: LC-SCRUM-Advantage/MRD

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Background: Several recent clinical trials on perioperative targeted therapy for oncogene-driven early-stage non-small cell lung cancer (NSCLC) are in progress. We evaluated the feasibility of multi-gene assay by preoperative biopsy tumor samples to detect actionable oncogenic drivers in patients with operable NSCLC as in part of a multicenter prospective genomic screening study in Japan (LC-SCRUM-Advantage/MRD).

Methods: Patients with operable clinical stage I to III NSCLC were eligible for this study. Preoperative biopsy tumor samples were collected before surgery, and AmoyDx Pan Lung Cancer PCR Panel (multi-PCR panel) was performed for a measurement of oncogenic drivers including EGFR, ALK, ROS1, KRAS, BRAF, HER2, RET, MET and NTRK genes. Surgical tumor samples were also collected after surgery, and used for analysis for 50 gene alterations using a next-generation sequencing system, Oncomine Precision Assay (OPA).

Results: Between August 2022 and April 2023, a total of 193 patients were enrolled in LC-SCRUM-Advantage/MRD. Of 77 evaluable patients at this analysis, 40 (52%) had stage I, 23 (30%) had stage II, 14 (18%) had stage III disease and 57 (74%) had adenocarcinoma histology. Success rate of multi-PCR panel by preoperative samples was 96%, and median turnaround time (TAT) was 4 days (range, 3-8). The frequencies of detected oncogenic drivers were 29 (39%) EGFR mutations (16, L858R; 10, ex19del; 3, uncommon), 9 (12%) KRAS (4, G12C; 5, nonG12C), 2 (3%) HER2 ex20ins and 1 (2%) RET fusion. Among patients who completed surgery and OPA by surgical samples, success rate of OPA was 98%, and median TAT was 6 days (range, 3-12). Concordance rate of detected actionable oncogenic drivers between preoperative biopsy and surgical samples was 98% (49/50), and one patient with KRAS G12D was detected only in OPA by surgical sample.

Conclusions: Multi-PCR panel showed a high success rate and a short TAT in genomic screening by preoperative biopsy tumor samples. Multi-PCR panel would help to better detect actionable oncogenic drivers in patients with early-stage NSCLC.

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Legal entity responsible for the study: LC-SCRUM.

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Goto: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical Co., Ltd., Amgen K.K., Takeda Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Amgen Inc., Amoy Diagnosties Co.,Ltd., AstraZeneca K.K., Bayer HealthCare Pharmaceuticals Inc., Boehringer Ingelheim Japan, Inc., Bristol Myers Squibb K.K., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Guardant Health Inc., Merck Biopharma Co., Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Thermo Fisher Scientific K.K., Merck Biopharma Co., Ltd., Taiho Pharmaceutical Co., Ltd.; Financial Interests, Personal, Advisory Board: Janssen Pharmaceutical K.K.; Financial Interests, Personal, Expert Testimony: Medpace Japan K.K.; Financial Interests, Personal and Institutional, Funding: Amgen Inc., Amgen K.K., AstraZeneca K.K., Boehringer Ingelheim Japan, Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Haihe Biopharma Co., Ltd., Kyowa Kirin Co., Ltd., Ignyta,Inc., Janssen Pharmaceutical K.K., Kissei Pharmaceutical Co., Ltd., Loxo Oncology, Inc., Medical & Biological Laboratories Co., Ltd., Merck Biopharma Co., Ltd., Merus N.V., MSD K.K., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sumitomo Dainippon Pharma Co., Ltd., Spectrum Pharmaceuticals, Inc., Sysmex Corporation., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Turning Point Therapeutics, Inc., Amgen Astellas BioPharma K.K., Bayer Yakuhin, Ltd., Blueprint Medicines Corporation., Life Technologies Japan Ltd., NEC Corporation., Novartis Pharma K.K.; Non-Financial Interests, Member: American Society of Clinical Oncology, The Japan Lung Cancer Society, Japanese Society of Medical Oncology, The Japanese Cancer Association. 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1277P HRD status of patients with early stage non-small cell lung cancer

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Background: There is an unmet need for post-surgical therapeutic options in early-stage NSCLC patients. PARP inhibitors (PARPi) have shown efficacy in cancer patients harboring germline or/and somatic *BRCA1/BRCA2* mutations and homologous recombination deficiency (HRD). Patient selection for targeted treatment is of crucial importance. Thus, the assessment of HRD status in patients with early-stage NSCLC may pave the way for the use of PARPi in an adjuvant setting.

Methods: Tumor specimens and peripheral blood samples were analyzed for somatic and germ-line mutations with a customized panel of 58 genes. To assess HRD status the genomic scar score (GSS) was calculated using the AmoyDx® HRD Focus Panel or AmoyDx® HRD Complete Panel. The effect of PARP inhibition on tumour growth was assessed in patient-derived xenografts, where RAD51 foci were quantified by immunofluorescence.

Results: Six of 85 patients (59 men/26 women) with operable NSCLC, carried germline mutations in *BRCA1* (n=1), *BRCA2* (n=1), *ATM* (n=3), and *PALB2* (n=1) genes. Pathogenic somatic mutations were detected in *BRCA1* (n=8), *BRCA2* (n=9), *ATM* (n=8), *PALB2* (n=3), *CHEK1* (n=3), *CHEK2* (n=6), *RAD50* (n=5) and TP53 (n=49) genes. Based on GSS, 25 (29.4%) patients were characterized as HRD and at least one somatic HRR mutated gene was observed in 15 (57.7%) of them [*BRCA1* (n=4), *BRCA2* (n=4), *ATM* (n=3), *PALB2* (n=2), CHEK2 (n=1)]. Preliminary functional experiments in HRP (HR proficient, n=5) and HRD (n=4) PDX and organoids (n=3 and n=3 for HRD and HRP respectively) indicate that HRD tumors present low RAD51 foci count (p=0.03 after damage induction) and favorable response to Olaparib and CDDP.

Conclusions: These data suggest that homologous recombination may be deficient in a substantial proportion of early-stage NSCLC patients, supporting the potential use of PARPi in HRD patients in the adjuvant or maintenance setting.

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Disclosure: All authors have declared no conflicts of interest.

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1278P ORIGEN: Multicenter study on the prevalence of EGFR gene mutations in patients with early-stage resectable non-small cell lung cancer in Spain

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Background: The presence of EGFR mutations (*EGFR*m) has therapeutic implications in patients (pts) with non-squamous non-small cell lung cancer (NSCLC). In Spain, the frequency of *EGFR*m in pts with early stage resected NSCLC was not known. The aim of the study is to determine the prevalence and characteristics of *EGFR*m in pts with early stage surgically resected non-squamous NSCLC.

Methods: Multicenter observational study of adult pt with early-stage non-squamous NSCLC (IA-IIIB) candidates for surgical treatment. The study involved 21 centers in Spain. Pts were required to sign informed consent and to have formalin-fixed, paraffin-embedded samples. Analysis of EGFR mutational status was performed in each participating site using Biocartis solution (EGFR Idylla™) which recognizes 51 mutations in exons 18-21 in a single tissue section.

Results: One hundred seventy-two pts were analyzed, median age 67.5 years, 58% male, 31% current smokers and 52% former smokers. The predominant histology was adenocarcinoma (97%) and the most frequent stage was IA (47%). Pathological diagnosis was obtained by surgery in 53% of pts and by biopsy in 47% of pts. Only 4% of pts received neoadjuvant treatment and 21.7% received adjuvant treatment. The most frequent surgery was lobectomy (79%) followed by segmentectomy (15%), pneumonectomy (3%) and wedge resection (3%). All except 1 pt had R0 resection. The prevalence of *EGFR*m was 15% (25 pt), being deletions in exon 19 (52%) the most frequent alterations, followed by mutations in exon 21 (44%; 40% L858R) and exon 20 (4%). The prevalence of *EGFR*m by stage is shown in the table.

Table: 1278P Common EGFR mutations according to tumor stage

Stage	Total	Not mutated	Mutated	Del Exon 19	Mut Exon 21 (L858R)	Mut Exon 20 (T790M)
IA	81 (71.1)	71 (87,7)	10 (12,3)	4 (4,9)	6 (7,4)	0 (0.0)
IB	31 (18.0)	24 (77.4)	7 (22.6)	4 (12.9)	3 (9.7) (1-L861Q)	0 (0.0)
IIA	7 (4,1)	7 (100,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0.0)
IIB	25 (14,5)	19 (76.0)	6 (24.0)	3 (12,0)	2 (8.0)	1 (0.6)
IIIA	19 (11.0)	17 (89.5)	2 (10.5)	2 (10.5	0 (0,0)	0 (0.0)
IIIB	4 (2,3)	4 (100,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0.0)
Unknown	5 (2,9)	5 (100,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0.0)
Total	172 (100,0)	147 (85,5)	25 (14,5)	11 (6,4)	10 (5.8)	1 (0.6)

Conclusions: In this series of pts operated on for NSCLC, frequency of *EGFR* mutation was 15%, the most frequent being exon 19 deletions and the L858R mutation, in line with data reported in Spain in advanced NSCLC. These results reinforce the importance of performing *EGFR*m testing in early-stage NSCLC to identify pt candidates to adjuvant osimertinib.

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Phase 2.: Bristol Myers Squibb; Non-Financial Interests, Other, A Multicentre, Open-label, Single-arm, Molecular Profiling Study of Patients With EGFR Mutation positive Locally Advanced or Metastatic NSCLC Treated With Osimertinib. Phase 2: AstraZeneca; Non-Financial Interests, Other, A Phase IIa, Single-arm, Multicenter Study to Investigate the Clinical Activity and Safety ofAvelumab in Combination With Cetuximab Plus Gemcitabine and Cisplatin in Participants With Advanced Squamous NSCLC: Merck Serono; Non-Financial Interests, Other, Treatment Plan CINC280A02001M to Provide Access to Capmatinib, for MET Exon 14 Skipping Non-Small Cell Lung Cancer (NSCLC): Novartis Pharmaceuticals; Non-Financial Interests, Other, An Open Label Phase II Study of Tipifarnib in Advanced Squamous Non-small Cell Lung Cancer With HRAS Mutations. 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Refractory Extensive-Stage Small-Cell Lung Cancer. [NCT02937818]: AstraZeneca; Non-Financial Interests, Other, A Randomized, Phase 3 Trial With Anti-PD-1 Monoclonal Antibody Pembrolizumab (MK-3475)Versus Placebo for Patients With Early Stage NSCLC After Resection and Completion of Standard Adjuvant Therapy (PEARLS): Merck Sharp & Dohme LLC; Non-Financial Interests, Other, A Phase 2, Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600-mutantNon-small Cell Lung Cancer: Pfizer; Non-Financial Interests, Other, A Phase III, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared With Chemotherapy in Patients With Treatment Naïve Advanced or Recurrent (Stage IIIb Not Amenable for Multimodality Treatment) or Metastatic (Stage IV) Non-Small Cell Lung Cancer Who Are Deemed Unsuitable for Platinum-Containing Therapy.: Roche; Non-Financial Interests, Principal Investigator, An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824(Bintrafusp Alfa) Versus Pembrolizumab as a First-line Treatment in Patients With PD-L1Expressing Advanced Non-small Cell Lung Cancer. [: Merck Serono; Non-Financial Interests, Other, A phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study of Osimertinib as Maintenance Therapy in Patients With Locally Advanced, Unresectable EGFR Mutation-positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-based Chemoradiation Therapy (LAURA): AstraZeneca; Non-Financial Interests, Other, A Phase 3 Study of Pembrolizumab in Combination With Carboplatin/Taxane (Paclitaxel or Nabpaclitaxel)Followed by Pembrolizumab With or Without Maintenance Olaparib in the First-lineTreatment of Metastatic Squamous Non-small Cell Lung Cancer (NSCLC): Merck Sharp & Dohme LLC. G.J. Marquez: Financial Interests, Personal, Full or part-time Employment: AstraZeneca. All other authors have declared no conflicts of interest.

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1279P Prevalence of EGFR mutations (EGFRm) in patients (pts) with resected stage I-III NSCLC: Results from EARLY-EGFR LATAM

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Background: Targeted and immune-therapies are currently recommended in early-stage NSCLC. However, biomarker prevalence data are limited in Latin America (LATAM). EARLY-EGFR (NCT04742192) determined the frequency of *EGFRm* in pts with resected stage I-III NSCLC across Asia, Middle East and Africa and LATAM.

Methods: The LATAM subset of this descriptive, observational, real-world study prospectively enrolled consecutive pts with surgically-resected stage IA-IIIB (AJCC 8th edi.) non-squamous NSCLC from Mar 2021-Oct 2022. Primary endpoint was *EGFRm* prevalence and secondary endpoints were *EGFRm* subtypes, clinico-demographics and treatment patterns. Association between *EGFRm* and clinico-demographic factors was assessed by Fisher's exact test with Monte Carlo.

Results: 80 pts were enrolled with mean±SD age of 66.5±9.7 yrs; 67.5% females and 57.5% never smokers. All pts had adenocarcinoma. Pathological stage (PS) distribution was PS I 66.3%, PS II 20.0% and PS III 13.8%. Most pts (61.3%) had right lung involvement and 85.0% were pN0. *EGFRm* prevalence was 39.5% (30/76) with similar rates in males and females (39.1% vs 39.6%; Table). *Exon-19* deletions (36.7%) and 21-*L858R* (30.0%) accounted for two-thirds of mutations. 4 of 11 (36.4%) pts with *EGFRm* were found to be PD-L1 positive. *EGFRm* rate in never smokers was significantly higher than in current and former smokers (51.2% vs 24.2%, p=0.017). 76.3% underwent only surgical resection. Of 44 PS IB-IIIB pts, 31.8% received systemic adjuvant therapy (AT), mostly platinum-based chemotherapy. Per logistic regression analysis age ≥60 years had increased odds of *EGFRm*, while smokers had decreased odds of *EGFRm* (both p<0.05).

Table: 1279P *EGFRm* in the LATAM cohort

Characteristics		N=80, n (%)	Comparison of mutation rate		
			EGFRm (N=30)	*EGFR wild type* (N=46)	Mutation Rate (%)
Age (years)	<60	21 (26.3)	05	14	26.3
	60-80	53 (66.3)	21	31	40.4
	>80	06 (7.5)	04	01	80.0
Gender	Female	54 (67.5)	21	32	39.6
	Male	26 (32.5)	09	14	39.1
Smoking history	Current	03 (3.8)	01	01	50.0
	Former	31 (38.8)	07	24	22.6
	Never	46 (57.5)	22	21	51.2[a]
Family history of lung cancer	No	72 (90.0)	28	40	41.2
	Yes	03 (3.8)	01	02	33.3
PS (AJCC 8th edi.)	I	53 (66.3)	19	31	38.0
	II	16 (20,0)	07	08	46.7
	III	11 (13.8)	04	07	36.4

Note: Four pts failed *EGFR* test [a]By smoking history (current and former vs never; p=0.017) Countries: Argentina, Chile, Colombia, Costa Rica, Dominican Republic, Mexico and Peru

Conclusions: The LATAM subset shows a *EGFRm* prevalence of 39.5%. Despite ASCO guidelines recommending AT in PS IB-IIIB, only about 32% received it. Our results are important for guiding *EGFR* testing and informing treatment strategies in LATAM with recent and upcoming approvals of targeted and immune-therapies.

Clinical trial identification: NCT04742192.

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1280P Comprehensive characterization of human lung squamous cell carcinoma identifies high TFRC expression as a mark of poorly immunogenic tumours

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Background: Lung squamous cell carcinoma (LUSC) is an aggressive tumour that accounts for 30% of all lung cancers with a 5-year survival rate of around 30%. The accumulation of CNVs and mutations on tumour suppressor genes explain the lack of directed therapies. Combination with immunotherapy in LUSC shows better efficacy than chemotherapy alone, but responses are below 50% after biomarker-based patient selection. Since tumour immunity determines the efficacy of immunotherapy, a better characterization of the immune landscape in LUSC could improve patient selection and treatment success. Altogether, this highlights the importance of identifying more precise molecular markers, as well as novel targets for LUSC treatment.

Methods: 98 early-stage patient samples Multiparametric study: Clinical annotations, targeted DNA and RNA sequencing. Immunohistochemistry (IHC): CD8, CD4, CD20,

TFRC, ferritin. Total iron staining (Turnbull Blue and Tirmann-Schmelzer methods). In vitro assays in LUSC cell lines CRISPR-KO and lentiviral-mediated overexpression of TFRC. Crystal violet. Western blot. Indirect immunofluorescence.

Results: The multiparametric analysis identified an amplification on TFRC gene in 30% of the patients associated to a transcriptional upregulation of tumour progression genes and a downregulation of immune-related genes. The reduction of immune cell infiltration according to IHC results further supported the immune-cold profile of these tumours. TFRC genomic amplification in tumour cells was translated into higher mRNA and protein levels in patient samples, which finally led to an accumulation of iron, suggesting a functional role of this copy number gain. In addition, iron positive samples showed decreased immune cell infiltration, especially CD8 T cells. While *in vitro* cell growth of LUSC cell lines was not affected by TFRC overexpression, it was significantly reduced in TFRC knockout cells.

Conclusions: Alterations in TFRC in LUSC patients have functional impact in both the tumour and the immune cells, pointing at TFRC as a potential biomarker of tumour immunity and a therapeutic target.

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1281P Effect of Fra-2 expression on tumour immunogenicity and prognosis in KRAS-mutant lung adenocarcinoma

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Background: Targeted therapies are available for lung adenocarcinoma (LUAD); however, more than 50% of patients either cannot benefit from them or become resistant, highlighting the need for alternative strategies. Our project focuses on FRA-2 (encoded by FOSL2 gene), a member of the AP-1 family that can act downstream of KRAS and EGFR pathways, two of the predominant genetic alterations observed in LUAD. Computational analyses of public databases have revealed a correlation between high FOSL2 expression and poor survival in KRAS-mutant LUAD. Consistently, tumour cell expression of Fra-2 has been found to correlate with shorter survival and higher tumour burden in a genetically engineered mouse model of LUAD driven by KRasG12V mutation and Tp53 loss.

Methods: Cell viability was assessed in primary tumour cells with Fra-2 gain- and loss-of-function, cultured from *KRasG12V/Tp53*-knockout mouse tumours. We prospectively collected fresh samples of resected LUAD tumours from patients with complete clinical and molecular annotations (N=27; 9 KRASmut), which were subjected to characterization by flow cytometry and IHC.

Results: In vitro analyses of primary tumour cells confirmed that overexpression of Fra-2 increases tumour cell viability. However, the absence of Fra-2 did not affect cell growth, suggesting that in vivo observations in Fra-2-deficient tumours could depend on anti-tumoral mechanisms that are extrinsic to tumour cells. In LUAD patients, the percentage of tumour cells expressing FRA-2 correlates with FRA-2 expression in immune cells as well as in cancer-associated fibroblasts (αSMA). FRA-2 also tends to show a positive correlation with proliferation (KI-67) and a negative correlation with T cells. A more detailed analysis by flow cytometry revealed that FRA-2 expression was related to an increased tumour density of regulatory T cells and decreased PD-1 expression, particularly in KRAS mutant tumours.

Conclusions: Our results suggest that FRA-2 could play a significant role as a mediator in the tumorigenic effects driven by KRAS mutations in LUAD, by promoting both tumour cell proliferation and immune evasion. These findings provide a new therapeutic opportunity in a clinically relevant setting.

Legal entity responsible for the study: The authors.

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Disclosure: L. Paz-Ares: Financial Interests, Personal, Advisory Board, Speaker fees: Roche, MSD, BMS, AZ, Lilly, PharmaMar, BeiGene, Daiichi, Medscape, PER; Financial Interests, Personal, Advisory Board: Merck Serono, Pfizer, Bayer, Amgen, Janssen, GSK, Novartis, Takeda, Sanofi, Mirati; Financial Interests, Personal, Other, Board member: Genomica, Altum sequencing; Financial Interests, Institutional, Coordinating PI: Daiichi Sankyo, AstraZeneca, Merck Sharp & Dohme Corp, BMS, Janssen-Cilag International NV, Novartis, Roche, Sanofi, Tesaro, Alkermes, Lilly, Takeda, Pfizer, PharmaMar; Financial Interests, Personal, Coordinating PI: Amgen; Financial Interests, Other, Member: AACR, ASCO, ESMO; Financial Interests, Other, Foundation Board Member: AECC; Financial Interests, Other, President. ASEICA (Spanish Association of Cancer Research): ASEICA; Financial Interests, Other, Foundation president: Oncosur; Financial Interests, Other, member: Small Lung Cancer Group. All other authors have declared no conflicts of interest.

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1282P Concordance of PD-L1 expression between biopsy and matched surgical specimen in early-stage non-small cell lung cancer: LC-SCRUM-Advantage/MRD

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Background: Determining the Programmed death-ligand 1 (PD-L1) expression status may help identify patients who will benefit from immune checkpoint inhibitor in perioperative treatment for early-stage non-small cell lung cancer (NSCLC). We evaluate the concordance of PD-L1 expression between biopsies and matched surgical specimens as part of a multicenter prospective genomic screening study in LC-SCRUM-Advantage/MRD.

Methods: Patients with preoperative untreated resectable clinical stage I to III NSCLC were eligible for this study. PD-L1 Tumor Proportion Score (TPS) was assessed in patients with operable NSCLC on both lung biopsies before surgery and matched surgical specimens after surgery, by using a 22C-3 Immunohistochemistry assay.

Results: Between August 2022 and April 2023, a total of 181 patients were enrolled in LC-SCRUM-Advantage/MRD. Of 62 evaluable patients at this analysis, 33(53%)/17(28%)/12(19%) had stage I/II/IIIA disease and 46 (74%) had adenocarcinoma histology, 54 (85%) were diagnosed by bronchoscopic biopsy before surgery. The success rate of PD-L1 TPS analysis in biopsy specimens was 98%, and median turnaround time was 7 days (quartile range, 3-13). In biopsy specimens, PD-L1 TPS was observed in 34 (56%), 17 (28%), and 9 (16%) cases for the cutoff values $<$1%, 1-49%, and $\geq$50%, respectively. On the other hand, all surgical specimens were successfully analyzed, PD-L1 TPS was observed in 22 (48%), 15 (32%), and 9 (20%) cases for the cutoff values $<$1%, 1-49%, and $\geq$50%, respectively. The overall concordance rate of PD-L1 TPS between biopsy specimen and matched surgical specimen was 74% (35/47). The concordance rate at a cut-off value of $<$1%/1-49%/$\geq$50% PD-L1 TPS were 91% (20/22), 53% (8/15), and 67% (6/9). The breakdown of discordant in PD-L1 TPS 1-49% between biopsy and matched surgical specimens, 86% (6/7) was TPS $<$1% in biopsy specimens.

Conclusions: PD-L1 TPS demonstrated a high concordant rate between biopsy and matched surgical specimens in patients with early-stage NSCLC. However, PD-L1 TPS 1-49% concordance rate is relatively low and may be underestimated, especially in biopsy specimens.

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Legal entity responsible for the study: National Cancer Center.

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1283P Predicting PD-L1 expression using [18F]FDG PET/CT in early stage non-small cell lung cancer (NSCLC)

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Background: Advances in the management of early stage NSCLC include the introduction of PD-1/PD-L1 checkpoint inhibitors. PD-L1 is an important biomarker but its role in early NSCLC remains unclear. PD-L1 is also closely associated to glucose transporter 1 (GLUT1) expression and the correlation of metabolic parameters measured using [18F] FDG-PET/CT has been demonstrated in advanced disease. Our aim was to investigate the association of [18F] FDG-PET/CT metabolic parameters with PD-L1 expression in a cohort of patients with resected early stage NSCLC.

Methods: We conducted a retrospective analysis of 210 patients with node-positive early stage resected NSCLC. DAKO 22C3 PD-L1 immunohistochemistry was performed on primary tumour and positive nodes and scored according to tumour proportion score (TPS) of $<$1, 1-49, or $\geq$50%. [18F]FDG PET/CT was analysed using semi-automated techniques for max, mean and peak standardised uptake values (SUV), metabolic tumour volume (MTV), total lesion glycolysis (TLG) and SUV heterogeneity index (HISUV).

Results: Patients were predominantly male (57%), median age 70 years, a majority had non-squamous NSCLC (68%), and were current smokers (89%). Stage T2(a-b) disease was common (48%) and most had negative primary PD-L1 expression (TPS $<$1%; 53%). Mean SUVmax scores of the primary tumour ($n = 210$; $p = 0.02$) and nodes ($n = 50$; $p = 0.03$) increased according to PD-L1 TPS. There were similar trends for mean SUVmean and SUVpeak values in the primary and nodes across all TPS groups. SUVmax, mean and peak scores were all significantly ($p<0.05$) associated with PD-L1 positivity using a $<$or $\geq$1% threshold. However, ROC analysis demonstrated only moderate separability with AUCs ranging 0.58 - 0.73. No statistically significant differences of mean MTV, TLG and HISUV scores were found between TPS groups.

Conclusions: This study demonstrated the association of standard [18F]FDG PET/CT metabolic parameters of SUVmax, SUVmean and SUVpeak with PD-L1 expression in early NSCLC. However, the sensitivity/specificity of these measurements for predicting PD-L1 positivity using the $<$ or $>$1% threshold was poor. Future prospective studies are warranted to determine the association, predictive role, and clinical utility of these metabolic measurements.

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1284P Lung cancer among patients with chronic obstructive pulmonary disease: A Danish 10-year observational study of the overlapping population

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Background: Lung cancer (LC) is the leading cause of cancer-related death worldwide, and up to five times more likely to occur in smokers with chronic obstructive pulmonary disease (COPD) than those with normal lung function. In this study, we investigated the overlap between patients registered with COPD and patients examined on suspicion of LC over a 10-year period in the Region of Southern Denmark.

Methods: The National Registry of COPD and the Danish LC Registry delivered data on patients with COPD and LC respectively. The cohort referred for LC diagnostics was defined by assigned classification codes provided from the Health Care Classification System.

Results: During the study period, 25,647 patients were registered with COPD during hospitalizations, or from outpatient clinics. Among these, 5.030 patients (20%) were referred to LC diagnostics, and 1,551 were diagnosed with LC. This corresponds to a LC incidence of 6% among all patients with COPD, and 31% among COPD patients referred for LC diagnostics. COPD patients referred for LC diagnostics were generally more affected by COPD compared to the group of not referred for LC diagnostics. Referred patients collected more COPD related medication (6 of 7 medicaments), performed worse in terms of lung function (FEV1% 48% vs. 50%), suffered from a higher grade of dyspnea (71% vs. 57% MRC 3-5) and experiences a higher rate of exacerbations (42% vs. 31% with 2-3 exacerbations) compared to COPD patients not referred to LC diagnostics ($p<0.05$ for all). Among all patients who underwent LC diagnostics, COPD patients displayed a higher prevalence of LC compared to the non-COPD patients (31% vs. 29%, $p<0.005$). LC patients with COPD were more likely to be stage I-II compared to the non-COPD LC population (39% vs. 24%, $p<0.05$).

Conclusions: This study reveals a substantial overlap between patients with COPD and patients undergoing LC diagnostics (20%). It suggests that patients more affected by COPD are more likely to undergo LC diagnostics, and LC patients with COPD are more likely to be diagnosed in early stages. It underlines the overrepresentation of LC patients among patients with COPD, and emphasizes the need to address these patients specifically once initiating a screening program.

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1285P Lung cancer in never smokers (LCINS): Clinicopathological characteristics and treatment outcomes from a university cancer centre in London

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Background: The patient (pt) characteristics, risk factors, and treatment outcomes of LCINS remain poorly understood. We present data from a large UK-based bespoke LCINS clinical database.

Methods: We retrospectively collected data from electronic records and analysed outcomes of LCINS pts treated at Guy's Cancer Centre, South East London, from 2010 until 2021.

Results: 483 pts were included, which accounted for 7% of all lung cancer pts. Median age was 67 years (range 25-95), 68% of pts were female (versus 43% in smokers); 50% White, 22% Black, 16% Asian, 2% mixed race, and 10% unknown (versus 72%, 5%, 2%, 2%, 18% in smokers). 8% of pts had asthma, 2% previous tuberculosis, 1% COPD, 1% interstitial lung disease, while 7% had passive smoking and 5% known asbestos exposure. 49% were overweight. 21% of pts had a history of other cancers and 5% a

first-degree family history of lung cancer. Most (64%) pts presented with stage IV disease, and 16%, 6%, and 15% with stage I, II, and III respectively. Most (80%) pts had adenocarcinoma, 9% squamous cell, and 4% small cell. 50% of pts had a driver genetic aberration, although genetic testing varied dependent on histological subtype and year of diagnosis. The commonest were *EGFR*, *ALK*, *KRAS*, and *ROS1* aberrations found in 48%, 11%, 8%, and 5% of pts tested for each gene respectively. Out of the 174 (36%) pts with stage I-III disease, 57% had curative surgery, 39% radical (chemo) radiotherapy, and 22% adjuvant chemotherapy (CT). Of all 376 metastatic pts (64% de novo and 14% relapsed), 38% had brain metastases. A total of 81%, 45%, and 23% of metastatic pts had 1, 2, and 3 lines of systemic therapy respectively. In the 1st -line setting, 47% had a tyrosine kinase inhibitor (TKI), 40% CT, and 6% CT-immunotherapy (IO). Overall, 53% of the metastatic pts had a TKI, 52% CT, and 16% IO at any treatment line. The median overall survival was 9.2, 4.0, 3.3, and 1.4 years for stage I, II, III, and IV disease respectively.

Conclusions: LCINS spans all age groups and ethnic backgrounds. Most pts are female with limited respiratory comorbidities. Pts present with advanced adenocarcinoma with a high incidence of brain metastases and driver genetic aberrations. Strategies to improve earlier stage diagnosis in LCINS are urgently needed.

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1286P Real-world outcomes in stage I-III resectable non-small cell lung cancer (NSCLC): THASSOS-INTL study

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Late withdrawal

1287P Comparing the cost-effectiveness of perioperative immunotherapy strategies in non-small cell lung cancer

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Background: Over the course of a year, the FDA approved both adjuvant atezolizumab and neoadjuvant nivolumab plus chemotherapy for resectable non-small cell lung cancer based on positive results from the IMPOWER010 and Checkmate-816 studies respectively. In this analysis, the cost-effectiveness (CE) of these two different treatment methods was evaluated in several clinical scenarios and indirectly compared.

Methods: CE was defined as the incremental cost effectiveness ratio (ICER), a measure of the cost difference per quality adjusted life years gained (QALY). Markov models were constructed to calculate the ICER of both neoadjuvant nivolumab plus chemotherapy versus neoadjuvant chemotherapy and adjuvant atezolizumab versus standard of care (SOC) (surveillance +/- chemo). For the neoadjuvant nivolumab method, CE was assessed in the intention to treat population (all stage IB-IIIA) and the PD-L1≥1% group. CE of adjuvant atezolizumab was evaluated for the stage II-IIIA PD-L1≥1% and PD-L1≥50% groups. Each of these four clinical scenarios were divided into three sub-scenarios based on the use and assumed effectiveness of immunotherapy (IO) at recurrence in the experimental arms: 1. No IO at recurrence. 2. IO at recurrence but ineffective. 3. IO at recurrence and effective.

Results: The ICERs are in the following table. Probabilistic sensitivity analyses confirmed the results of all primary analyses.

Table: 1287P

IO status at Recurrence	Neo Nivo		Adj Atezo	
	Stage IB-IIIA, any PD-L1	Stage IB-IIIA, PD-L1≥1%	Stage II-IIIA, PD-L1≥1%	Stage II-IIIA, PD-L1≥50%
No IO	−$86,599	−$95,405	−$20,112	−$39,641
Ineffective IO	−$57,250	−$87,387	$34,051	−$24,670
Effective IO	−$103,924	−$100,339	−$58,101	−$42,318

Conclusions: In eleven of twelve scenarios, the experimental arms were less costly and more effective than the SOC. Only adjuvant atezolizumab used in PD-L1≥1% patients with ineffective IO at recurrence resulted in a cost increase per QALY gained as compared to SOC. Neoadjuvant nivolumab is a more cost-effective treatment strategy than adjuvant atezolizumab even when adjuvant atezolizumab is limited to patients with a PD-L1≥50%, likely due to shorter duration of treatment with nivolumab. Further analyses can be done to confirm CE with publication of final overall survival results.

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1288P Neoadjuvant therapy with anti-PD-1/PD-L1 plus platinum-base chemotherapy for resectable stage II-III non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials

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Background: Neoadjuvant chemotherapy (CT) has limited benefit over surgery alone for resectable non-small cell lung cancer (NSCLC). Recent trials have shown promising results for combining immune checkpoint inhibitors with platinum-doublet chemotherapy (ICI plus CT).

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared neoadjuvant ICI plus CT versus CT alone in patients with resectable NSCLC. We searched PubMed, Scopus, and Cochrane Library databases, as well as the ASCO, ESMO, and AACR websites. We used a fixed effects model for analysis and assessed heterogeneity with I^2 statistics.

Results: We included six RCTs with 2,471 patients, of whom 75% were male, 47% had non-squamous, and 53% had squamous cell carcinoma (SCC). The median age was 63.3 years (ranged from 29 to 88). After neoadjuvant therapy, 84% of patients in the ICI plus CT group underwent surgery compared to 81% in the CT group (p=0.16); R0 resection was reported in 78% versus 67% of patients (p<0.01), respectively. We found a significantly higher pathologic complete response (risk ratio [RR] 5.81 [95%CI 4.26-7.92]) and major pathologic response (RR 3.57 [3.09-4.55]) in patients who received ICI plus CT than those in the CT group. Treatment with ICI plus CT provided a greater benefit of event-free survival (EFS) (HR 0.59 95%CI 0.51-0.67 p<0.00001) and overall survival (HR 0.66 95%CI 0.53-0.82 p=0.0002)compared to CT alone. ICI plus CT improved EFS regardless of PD-L1 expression, type of platinum CT, or histology. Patients with PD-L1 ≥1% achieved considerably better EFS than those with PD-L1 <1% (HR 0.40 vs 0.76, p<0.0001). Subgroup analysis showed EFS benefit for all stages (IB and II, IIIA, and IIIB). Treatment-related adverse events grades 3 or 4 were seen in 36% of patients in the intervention arm and 32% of the control arm (p=0.05).

Conclusions: Neoadjuvant therapy with anti-PD-1/PD-L1 plus CT provided significantly higher pathologic response, EFS, and OS compared to CT alone for resectable stage II-III NSCLC patients. More mature data from the trials are awaited to confirm these findings.

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1289TiP LANTERN study: A multi-omics digital human avatar for integrating precision medicine into clinical practice for lung cancer patients

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Background: Lung cancer is a highly fatal cancer with poor prognosis and management despite recent therapeutic advancements. However, Artificial Intelligence (AI) presents an opportunity to leverage multiple omics datasets to create accurate predictive models for better lung cancer care. These models can be used individually or integrated into multi-omics Digital Human Avatars (DHAs) to assist in clinical decision-making and revolutionize care and research. DHAs combine various omics-based variables with clinical factors for a comprehensive understanding of the disease, enabling personalized treatment decisions to improve patient outcomes. Introducing DHAs in clinical practice can help uncover previously unexplored links among variables and significantly enhance the understanding of lung cancer.

Trial design: Trial design: The LANTERN study is a three-year, multicenter observational clinical study funded by ERA PerMed JTC2022 that aims to develop predictive models for the diagnosis and histological characterization of lung cancer, as well as personalized treatments and feedback data loops for preventive health strategies and quality of life management. The study involves a consortium of five European institutions and will collect multi-omics data from 600 non-small cell lung cancer patients, including demographic and physiological data, medical history, clinic functional and lab data, histo-pathological, immunological and genomic data, radiomics and quantitative imaging data, and IoT-derived data. The study will develop a dedicated database for all omics domains considered and perform a comprehensive molecular characterization and genomic profiling of tumor samples. The second phase of the project will focus on building multivariate models trained through advanced ML and AI techniques. Finally, the developed models will be validated to test their robustness, transferability, and generalizability, leading to the development of Digital Human Avatars (DHAs). The LANTERN study is committed to allowing the reuse of research data according to the FAIR principles and hopes that this model will eventually be utilized in clinical routine to personalize the strategy of care in lung cancer patients.

Clinical trial identification: NCT05802771.

Legal entity responsible for the study: Prof. Filippo Lococo.

Funding: ERA PerMed JTC2022.

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1290TiP A phase II multicenter, open label, non-randomized study of neoadjuvant and adjuvant treatment with IPH5201 and durvalumab in patients with resectable, early-stage (II to IIIA) non-small cell lung cancer (MATISSE)

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Background: Adjuvant (adj) or neoadjuvant (neoadj) immunotherapy has been recently approved for the treatment of resectable early stage Non-Small Cell Lung Cancer (NSCLC), and further advances are needed. The combination of neoadj Durvalumab (D), an anti-PD-L1, combined with chemotherapy (CT) and adj D (AEGEAN) in early-stage NSCLC has recently demonstrated promising safety and efficacy. CD39 is an extracellular ectonucleotidase highly expressed in the tumor microenvironment (TME) that, sequentially with CD73, contributes to the production of adenosine (Ado), via hydrolysis of Ado triphosphate (ATP). IPH5201 is a blocking anti-CD39 monoclonal antibody that may promote antitumor immunity by accumulating immunostimulatory ATP released by CT-treated tumor cells and reducing immunosuppressive Ado levels in the TME. Moreover, IPH5201 improved the efficacy of CT+D in preclinical models. In a phase 1, IPH5201 + D was well tolerated and pharmacodynamically active.

Trial design: MATISSE is a phase II multicenter (France, Poland, Greece, Hungary, USA), single arm study (NCT05742607) sponsored by Innate Pharma, evaluating IPH5201 + D + CT in treatment-naive pts with resectable (stage II to IIIA) NSCLC. Up to 70 pts will receive neoadj IPH5201 + D in addition to platinum-doublet CT for 4 cycles followed by surgery within 40 days. Pts will thereafter receive adj IPH5201+D every 4 weeks for up to 12 cycles post-surgery or until recurrence or unacceptable toxicity. The primary objectives are to assess antitumor activity of neoadj treatment based on pathological complete response (pCR) and safety. The secondary objectives are to assess efficacy in terms of event free survival, disease free survival, feasibility of receiving the planned surgery, major pathological response, objective response rate, overall survival, pharmacokinetics and immunogenicity. Assessment of exploratory biomarkers is also planned. A Safety Review Committee will conduct evaluations on an ongoing basis and two interim analyses will be performed.

Clinical trial identification: IND:162253; NCT05742607; EudraCT: 2022-001903-42.

Legal entity responsible for the study: Innate Pharma.

Funding: Innate Pharma.

Disclosure: F. Barlesi: Financial Interests, Institutional, Advisory Board: AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly Oncology, F. Hoffmann—La Roche Ltd, Novartis, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Sanofi Aventis, Seattle Genetics, Takeda, AbbVie, Acea, Amgen, Eisai, Ignyta; Non-Financial Interests, Principal Investigator: AstraZeneca, BMS, Merck, Pierre Fabre, F. Hoffmann-La Roche Ltd., Innate Pharma, Mirati. O. Mercier: Financial Interests, Personal, Advisory Board, Board on surgical oncology (lung cancer): AstraZeneca; Financial Interests, Personal, Advisory Board, Board for CTEPH (non cancer related): MSD; Financial Interests, Institutional, Funding, Paceport Study investigator (non cancer related) Study on pulmonary hemodynamics: Edwards Lifesciences. A. Łowczak, S. Mandziuk, J. Kuzdzal, A. Dasgupta: Non-Financial Interests, Institutional, Principal Investigator: Innate. A. Koutras: Financial Interests, Personal, Advisory Board: Pierre Fabre, AstraZeneca, Gilead, Pfizer, Genesis, MSD, BMS; Financial Interests, Personal, Invited Speaker: Sanofi, Gilead; Financial Interests, Personal, Other, Travel, Accommodations: Rafarm, Lilly, Ipsen, Gilead, Pfizer; Financial Interests, Institutional, Funding: Lilly, Pfizer, Merck; Financial Interests, Institutional, Research Grant: AstraZeneca, Pierre Fabre, BMS, Demo, Faran, Amgen, Roche, Ipsen, Galenica, Win Medica. A.J. Leyco, P. Andre, C.L. Paturel, A. Boyer Chammard: Financial Interests, Institutional, Full or part-time Employment: Innate. R. Mager, P.G. Fraenkel: Financial Interests, Institutional, Full or part-time Employment: AstraZeneca.

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1291O Radiotherapy boost to 74 Gy based on FDG-PET at 42 Gy of radiochemotherapy (RCT) in patients with inoperable stage III non-small cell lung cancer (RTEP7 – IFCT 1401): A prospective multicentre, open-label, randomised, controlled trial

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Background: To assess the possibility and safety of a boost delivery up to74 Gy, based on lung tumour early response to on-treatment FDG-PET /CT (42 Gy), in inoperable patients with stage III non-small-cell lung cancer (NSCLC)treated with concomitant radio-chemotherapy (RCT).

Methods: 158 patients were prospectively included in a multicentre phase II-III study. Patients were randomized into two groups: patients from arm A (experimental) with residual metabolism on FDG-PET2 at 42 Gy received a radiation boost (74 Gy), while patients without residual uptake on FDG-PET2 at 42 Gy and patients in arm B (standard) received a standard radiotherapy (RT) dose (66 Gy). Local control rate (LCR %), median overall survival (OS, months), and progression-free survival (PFS) were analysed for three years after the end of RCT. FDG-PET parameters were measured at baseline (PET1), 42 Gy (PET2), and 6 months post-RCT (PET3). All patients were evaluated with the RECIST 1.1 criteria. The main objective was the LCR at 1 year after RCT.

Results: Patient demographic characteristics and FDG-PET parameters were similar between the two arms (A vs. B). The mean age was 62.3 years; 53.2% of lesions were stage IIIA and 45.6% were stage IIIB. The mean radiation dose was 71.65 Gy for experimental arm and 66 Gy for standard arm ($p < 0.001$). The median follow-up time was 45.1 months. The LCR at 1 year after RCT was 77.6% [95% CI: 67.6% – 87.6%] in arm A and 71.2% [95% CI : 60.8% - 81.6%] in arm B. The median OS and the PFS (months) were respectively NR [95% CI: 40.9 – NR] in arm A and 43.3 [95% CI: 33.4 - NR] in arm B, and 22.3 [95% CI: 14.8 – 33.7] in arm A and 12.3 [95% CI : 9.4 – 23.3] in arm B. Using multivariate analysis, ΔSUVmax > 66% ($p < 0.01$), Δ metabolic tumoral volume (MTV) > 100% ($p = 0.04$) between PET1 and PET3, and the boost realization ($p = 0.05$) were the only predictors of PFS. There were less acute or late toxicity in boost radiation arm.

Conclusions: Boost at 74 Gy based on interim FDG-PET is feasible and safe during thoracic RCT, without acute or late toxicity. Boost administration, ΔSUVmax, ΔMTV seem to be prognostic factors in patients with stage III inoperable NSCLC.

Clinical trial identification: N° ID RCB°: 2014-A01628-39.

Legal entity responsible for the study: Centre Henri Becquerel.

Funding: French Ministry of health (PHRC K-2014); IFCT.

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1292MO A phase II study of daily carboplatin plus irradiation followed by durvalumab for unresectable III non-small cell lung cancer patients with PS 2 or elderly (≧75 years): NEJ039A

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Background: Chemoradiotherapy followed by durvalumab consolidation therapy is standard care for patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC). However, it remains unclear about the clinical significance of durvalumab after chemoradiotherapy in patients with LA-NSCLC a performance status (PS) of 2 or aged ≥75 years.

Methods: Daily low-dose carboplatin (30 mg/m^2) was administered to patients 1 h before radiotherapy for the first 20 fractions. Radiotherapy for all patients consisted of 60 Gy administered as 30 fractions. Durvalumab at a dose of 10 mg/kg was intravenously administered every 2 weeks for up to 12 months after chemoradiotherapy. The primary endpoint was the progression free survival rate (PFS) of 12 months from the initiation of durvalumab administration. The secondary endpoints included the rate of therapeutic completion, PFS, overall survival (OS), objective response rate (ORR), and safety.

Results: Of 86 patients who underwent induction chemoradiotherapy from September 2019 to October 2021, 61 (70.9%) received durvalumab consolidation therapy. A total of 61 patients (50 males, 11 females; median age 78y; range 55-89y) was eligible for the further analysis. The PS was 0, 1, and 2 in 28 (45.9%), 27 (44.3%), and 6 (9.8%) patients. Regarding PD-L1 expression, 14 (22.9%), 17 (27.9%), 17 (27.9%), and 13 (21.3%) patient displayed levels of ≥50%, 1–49%, <1%, and unknown, respectively. The PFS rate of 12 months from durvalumab start was 51.0% (90% confidence interval [CI], 39.9 to 61.1). Therefore, the current study met the primary endpoint. The ORR after chemoradiotherapy and durvalumab consolidation was 47.0% and 57.4%, respectively. The median PFS and OS were 12.3 and 28.1 months, respectively. The rate of therapeutic completion for durvalumab was 26.2%. The most common treatment related adverse event of grade 3 or 4 was pneumonitis (6.6%). One patient died because of grade 5 interstitial pneumonitis.

Conclusions: Durvalumab consolidation after daily carboplatin with radiotherapy was effective and tolerable for LA-NSCLC vulnerable patients.

Clinical trial identification: jRCTs031190070.

Legal entity responsible for the study: North East Japan Study Group.

Funding: AstraZeneca.

Disclosure: R. Ko: Financial Interests, Personal, Invited Speaker: Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Boehringer Ingelheim, Pfizer, AstraZeneca, Ono Pharmaceutical, Daiichi Sankyo, Takeda, MSD; Financial Interests, Institutional, Research Funding: MSD, AstraZeneca. T. Nakagawa: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical , Eli Lilly Japan. N. Ishikawa: Financial Interests, Personal, Invited Speaker: AstraZeneca, Boehringer Ingelheim GmbH, GSK. T. Kondo: Financial Interests, Personal, Invited Speaker: Daiichi Sankyo, AstraZeneca, Taiho Pharmaceutical, Ono Pharmaceutical Co., Ohtsuka; Financial Interests, Institutional, Research Funding: AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, Taiho Pharmaceutical, AbbVie, Amgen, Eli Lilly, Novartis Pharma, Pfizer, AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, Abb Vie, Amgen, Eli Lilly, Novartis Pharma, Pfizer, Regeneron, Merk Bio Pharma, Blueprint Medicine, BeiGene, Daiichi Sankyo, Turning Point, HJaihe Biopharma, Janssen Pharma, Takeda Pharmaceutical, Sanofi. A. Bessho: Financial Interests, Personal, Invited Speaker: AstraZeneca; Financial Interests, Personal, Research Funding: AstraZeneca. K. Yoshimura: Financial Interests, Personal, Invited Speaker: Chugai Pharma, AstraZeneca, Sysmex. H. Kagamu: Financial Interests,

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1293MO Safety and efficacy of hypo- and conventionally fractionated thoracic radiotherapy plus durvalumab in elderly or frail NSCLC stage III patients unfit for chemotherapy: Interim results from the TRADE-hypo trial

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Background: Since patients with unresectable stage III NSCLC who are unfit for chemotherapy (CHT) due to age or frailty receive radiotherapy (RT) only, they do not have the opportunity to benefit from durvalumab consolidation after radiochemotherapy, raising the concern of undertreatment. Synergistic effects are expected when combining restored anti-tumor immune response elicited by immune checkpoint inhibition with an RT-induced increase in immunogenicity. The latter could be further boosted by hypofractionated RT, which might also be more practicable for the patient.

Methods: TRADE-hypo (NCT04351256) is an open-label, allocated phase II trial addressing safety and efficacy of durvalumab (1.500 mg Q4W, max. 12 months) combined with either hypo- (55 Gy = 20 x 2.75 Gy, "HYPO") or conventionally fractionated thoracic RT (60 Gy = 30 x 2 Gy, "CON") in previously untreated NSCLC stage III patients unfit for CHT (planned n=88). A safety stop-and-go phase (6+6 design) in the HYPO-arm addressed the potential higher pneumonitis risk. An interim futility analysis was planned with 18 response-evaluable patients in each arm (after RT start, $\geq$1 dose durvalumab, $\geq$1 response assessment (RECIST1.1), futility rule $\leq$ 8 responses).

Results: By 11/2022, a total of 38 patients were enrolled (n=13 in HYPO, n=25 in CON). In the HYPO-arm, 2 pneumonitis grade $\geq$3 events occurred, resulting in permanent recruitment stop in this arm as per protocol. In the CON-arm, benefit-risk evaluation remained favorable, and the trial continued with recruitment into this arm only. Interim futility analysis was conducted in the CON-arm only and was positive with 11/18 patients achieving tumor response (5 stable, 2 progressive disease).

Conclusions: An increased risk for pneumonitis was found in the HYPO-arm during the safety phase, leading to recruitment stop in this arm and continuation of TRADE-hypo with only the CON-arm. Interim futility analysis for the CON-arm was positive suggesting a benefit for the novel combination of durvalumab and thoracic RT for patients not suitable for CHT. Additional safety, efficacy, and biomarker data are expected for 05/25.

Clinical trial identification: NCT04351256; EudraCT: 2019-002192-33.

Legal entity responsible for the study: Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest.

Funding: AstraZeneca.

Disclosure: F. Bozorgmehr: Financial Interests, Personal, Advisory Board: Amgen, Janssen, Novartis, AstraZeneca, Novocure; Financial Interests, Personal, Invited Speaker: Novocure, AstraZeneca, MSD, Janssen; Financial Interests, Institutional, Research Grant: Roche, AstraZeneca; Non-Financial Interests, Principal Investigator: AstraZeneca, GSK, Janssen, Amgen. E.L. Buchmeier: Financial Interests, Personal, Invited Speaker, and congress sponsoring: Takeda; Financial Interests, Personal, Advisory Board: Ipsen; Financial Interests, Institutional, Local PI: BMS, AstraZeneca, Novartis, MSD, Janssen Cilag, PDC Line Pharma, Roche, GSK, Novartis; Non-Financial Interests, Member: Political Party FDP. F. Weykamp: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, Merck Sharp & Dohme. J. Alt: Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Local PI: AstraZeneca; Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca. M. Thomas: Financial Interests, Personal, Advisory Board: Sanofi, Lilly, BMS, MSD, Roche, Boehringer, Janssen, AstraZeneca, Amgen, Novartis; Financial Interests, Personal, Invited Speaker: Sanofi, Lilly, MSD, Roche, GSK, Pfizer, Janssen, AstraZeneca, Amgen, Novartis; Financial Interests, Institutional, Advisory Board: Takeda; Financial Interests, Institutional, Invited Speaker: Takeda; Financial Interests, Institutional, Funding: Roche, Takeda, BMS, AstraZeneca, Amgen. All other authors have declared no conflicts of interest.

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1294P A final analysis of a phase II study of durvalumab immediately after completion of chemoradiotherapy in unresectable stage III non−small-cell lung cancer: TORG1937 (DATE study)

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Background: The best timing of starting durvalumab after completion of concurrent chemoradiation (CCRT) for patients with unresectable stage III non-small cell lung cancer (NSCLC) has not been identified. The study was conducted to evaluate the efficacy and safety of durvalumab administered immediately after completion of CCRT in patients with unresectable stage III NSCLC.

Methods: This study was a prospective, single-arm, multicenter, phase II clinical trial. Eligible Patients with ECOG PS 0,1, and age $<$ 75 years old were enrolled and received definitive CCRT (2 cycles of platinum-based doublet chemotherapy with 60 Gy/30 Fr radiotherapy) followed by durvalumab (every 2 weeks for up to 12 months) from the next day (up to 5 days) after last radiation. The primary endpoint was 1-year progression-free survival (PFS) rate from registration as assessed by an independent review committee (IRC). Safety, objective response rate, 1-year PFS from start of durvalumab, PFS, 2-year PFS rate, 1-year and 2-year OS, and OS from registration and start of durvalumab were also evaluated. The efficacy according to the PD-L1 expression level was investigated as exploratory analysis. We present the updated final results of safety, efficacy and exploratory analysis.

Results: From January 2020 to August 2020, 50 patients were enrolled from 16 institutions and 47 patients were evaluable for efficacy and safety. Forty-two patients received durvalumab consolidation. PD-L1 expression levels were confirmed in 40 patients (tumor proportion score $\geq$ 50% in 19 patients, 1-49% in 11 patients, and $<$1% in 10 patients). The 1-year PFS rate from registration by IRC was 75.0% (60% CI: 69.0 to 80.0). Median PFS from registration was 20.8 months (95% CI: 14.9 to not reached), 2-year PFS rate was 48.6%, median OS was not reached, and 2-year OS rate was 84.5%. No unexpected adverse events and treatment-related deaths were observed. The 2-year PFS rate and 2-year OS was 40.0% and 80.0% for PD-L1-negative patients.

Conclusions: Our data support the efficacy and safety of durvalumab administered immediately after completion of CCRT for patients with unresectable stage III NSCLC.

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1295P Prospective trial of immuno-(chemo)therapy prior to resection, definitive chemo-radiotherapy, or palliative therapy in patients with borderline resectable or oligometastatic non-small cell lung cancer (KOMPASSneo)

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Background: Recent trials of immuno-(chemo)therapy (IO) prior to resection in locally advanced NSCLC report high rates of pathological response. However, primarily irresectable patients and oligometastatic patients were excluded from most studies. Moreover, there is no data on chemo-radiotherapy (CRT) after immuno-(chemo) therapy in patients who are primarily not amenable to CRT. Induction IO may enable more NSCLC patients to receive curative treatment.

Methods: We enrolled 86 patients with borderline resectable NSCLC including 22 patients with oligometastatic disease into a prospective real-world trial of induction IO followed by morphologic and metabolic reassessment and multidisciplinary board-guided curative treatment (resection [preferred] or CRT) or palliative therapy.

Results: 81 patients (94%) received curative treatment (38 resections, 43 CRT). 21 (55%) of resected patients had a major pathological response including 15 (39%) with pathological complete response. In curatively treated patients, there were 25 recurrences (31%) and 18 tumor-related deaths (22%): 6 recurrences (16%) and 1 death in resected patients, and 19 recurrences (44%) and 17 deaths (40%) in CRT-patients. There were 2 treatment-related deaths (postoperative sepsis, pneumonitis after CRT). The table shows survival of the whole population and oligometastatic patients (median follow-up 19.3 months).

Conclusions: In patients with borderline resectable NSCLC including oligometastatic disease, induction immuno-(chemo)therapy resulted in a high rate of curative treatment with promising survival. Resected patients achieved a high rate of prognostically favorable pathological response. Induction IO should be considered both for patients with stage II − III disease and for patients with oligometastatic disease.

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1296P Neoadjuvant camrelizumab and apatinib in patients with resectable non-small-cell lung cancer: One-year update from a phase II trial

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Background: Our phase 2 trial was the first to report the efficacy and safety of neoadjuvant chemo-free regimen with camrelizumab and apatinib in patients with resectable non-small-cell lung cancer (NSCLC), showing promising pathologic responses and manageable toxicity. Here, we aimed to report 1-year event-free survival (EFS) and updated safety data from the above trial.

Methods: Treatment-naïve patients with histologically confirmed resectable stage IIA-IIIB NSCLC (stage IIIB, T3N2 only) and ECOG performance status of 0 or 1 received three cycles of camrelizumab (200 mg, i.v., q2w) and apatinib (250 mg, orally, qd, for 5 days followed by 2 days off), followed by surgery after 3-4 weeks. This analysis including EFS (a prespecified secondary endpoint) and updated safety was performed after an extended follow-up from the preliminary analysis.

Results: Between November 9, 2020 and February 16, 2022, 78 patients were enrolled and treated. With a median follow-up of 19.4 months (95% CI 18.0-20.5), the median EFS was not reached (95% CI 23.2-not reached). The 6- and 12-month EFS rates were 89.4% (95% CI 79.8-94.5) and 82.3% (95% CI 71.4-89.3), respectively. The EFS rates at 6 months and 12 months in the subgroups are presented in the Table. Seventy-one (91.0%) of the 78 patients experienced at least one treatment-related adverse event (TRAE) of any grade, of which

Table: 1295P

Definitive Treatment	n	PFS				OS			
		Median (months)	HR	CI	p	Median (months)	HR	CI	p
Whole population	**86**								
Curative	81	30.4	0.0001 (vs. palliative)	0.00002 to 0.0002	<0.0001	43.3	0.13 (vs. palliative)	0.018 to 0.95	0.045
Resection	38	38.5	0.61 (vs. CRT)	0.31 to 1.20	0.15	NR	0.42 (vs. CRT)	0.20 to 0.90	0.026
CRT	43	19.1	0.0006 (vs. palliative)	0.00003 to 0.001	<0.0001	27.4	0.21 (vs. palliative)	0.033 to 1.33	0.098
Palliative	5	3.7	0.0009 (resection vs. palliative)	0.00007 to 0.01	<0.0001	10.9	0.097 (resection vs. palliative)	0.012 to 0.80	0.031
Oligometastatic patients	**22**								
Resection	8	NR	0.24 (vs. CRT)	0.069 to 0.84	0.027	NR	0.15 (vs. CRT)	0.036 to 0.62	0.0089
CRT	13	11.9	-	-	-	15.3	-	-	-
Palliative	1	NA	-	-	-	NA	-	-	-

grade 3 or above TRAEs were observed in six (7.7%) patients. No new safety signal was observed.

Table: 1296P

Subgroup	Patients (n = 78), n (%)	6-month EFS rate, % (95% CI)	12-month EFS rate, % (95% CI)
Overall	78 (100)	89.4 (79.8-94.5)	82.3 (71.4-89.3)
Disease stage			
II	38 (48.7)	94.5 (79.8-98.6)	86.2 (69.9-94.0)
III	40 (51.3)	84.5 (68.7-92.8)	78.7 (61.8-88.8)
PD-L1 expression			
<1%	35 (55.6)	85.3 (68.2-93.6)	76.2 (57.9-87.3)
≥1%	28 (44.4)	92.9 (74.3-98.2)	85.4 (65.7-94.3)
Histologic type			
Squamous cell carcinoma	59 (75.6)	91.2 (80.2-96.2)	84.1 (71.6-91.4)
Adenocarcinoma	19 (24.4)	83.9 (57.9-94.5)	76.9 (49.0-90.8)

Conclusions: The extended follow-up data shows continued benefits and a manageable safety profile with neoadjuvant camrelizumab and apatinib in patients with resectable non-small-cell lung cancer.

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1297P An open-label, prospective phase II study of tislelizumab in combination with chidamide as consolidation therapy in locally advanced, unresectable, stage III NSCLC

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Background: The PACIFIC trial established consolidation therapy with PD-L1 inhibitor as standard of care for patients with unresectable, stage III NSCLC and no disease progression after definitive chemoradiotherapy (CRT). PD-1 antibodies may synergize with HDAC inhibitors by inducing and activating NK cell and cytotoxic T cell (CTL) -mediated cellular immunity in previous studies. It is worth exploring new regimens to further improve survival for this population.

Methods: This was an open-label, prospective study. Patients with histologically or cytologically documented stageIII,locally advanced, unresectable NSCLC without progression following definitive platinum-based concurrent chemoradiation therapy (2～4 cycles) were enrolled. After cCRT, patients received Tislelizumab 200 mg Q3W intravenously and Chidamide 30 mg twice weekly orally. The primary endpoint was safety. Secondary endpoints include 6-month and 12-month PFS rates、OS and ORR. Tumor response was assessed using RECIST V1.1.

Results: At the data cut-off April 22, 2023(median follow-up time, 23.6m), 19 patients were enrolled, mean-aged was 66.3 years (range: 53-78). Patients received combination consolidation therapy for a median of 6.37 months. Adverse events of any cause and grade occurred in 68.4% (13). 3 patients (16.7%) had Grade≥3 TRAEs. The most common Grade≥ 3 TRAEs were pneumonitis (10.5%). The confirmed ORR was 84.2% (95%CI:60.4%-96.60%). The DCR was 100%. Median PFS was 20.5 months (95% CI: 4.37m-NA), and 6-month and 12-month PFS rate were 65.7% (95%CI:38.8%-83.0%) and 58.4% (95%CI:31.5%-77.8%), respectively.

Conclusions: Tislelizumab combined with Chidamide showed encouraging antitumor activity and a favorable safety profile as consolidation therapy for locally advanced, unresectable stage III NSCLC. Further sample and longer follow-up are required to obtain more accurate results.

Table: 1297P Incidence of TRAEs

TRAEs (N=19)	Any Grade, n (%)	≥Grade 3, n(%)
Pneumonitis	7 (36.8%)	2 (10.5%)
Liver injury	5 (26.3%)	0
Nausea/emesis	5 (26.3%)	0
Alopecia	4 (21.1%)	0
Hypothyroidism	2 (10.5%)	0
Myelosuppression	2 (10.5%)	0
Hepatitis	1 (5.3%)	1 (5.4%)
Myocarditis	1 (5.3%)	1 (5.4%)
Neurotoxicity	1 (5.3%)	1 (5.4%)

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1298P Chemotherapy with concurrent proton vs. photon radiotherapy in stage III NSCLC: Effects on hematological toxicity and immune therapy

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Background: Concurrent chemo-radiotherapy (CCRT) followed by adjuvant Durvalumab (D) is standard of care for fit patients (pts) with unresectable stage III NSCLC. We aimed to assess whether intensity modulated proton therapy (IMPT), compared to intensity modulated photon therapy (IMRT), can reduce hematological toxicity and whether it affects D treatment.

Methods: Retrospective data completion and analysis of a 4-center prospectively collected series of pts with stage III NSCLC receiving CCRT between 06.16-12.22, staged with FDG-PET-CT and brain imaging. Main exclusion criteria: previous cancer diagnosis and thoracic RT.

Results: 271 pts were enrolled (IMPT: n=71, IMRT: n=200). All pts received platinum-based chemotherapy (CT). Median age: 66 years, 36% had a squamous NSCLC, 41% had stage IIIA NSCLC, 89% had a WHO Performance Status (PS)=0/1, 65% had PDL-1 positive and 76% received q21 CT (no differences between IMPT and IMRT). The incidence of lymphopenia grade≥3 (G≥3) was 66.7% and 47% in the IMRT and IMPT arm respectively (p=0.032, OR 2.2, 95% CI: 1.03-4.9). In a multivariable logistic model including WHO PS, type and schedule of CT, age and gross tumor volume, IMRT remained significantly associated with higher risk of lymphopenia G≥3 (adjusted OR=2.6, 95% CI: 1.1-6.2, p=0.029). The incidence of anemia G≥3 during CCRT in the IMRT and IMPT arm was 26% and 8.5% respectively (adjusted OR=4.9, 95% CI: 1.9-12.6, p=0.001). Spearman's correlation coefficient between anemia G≥3 and body mean dose (BMD) was 0.052 (p=0.001). IMPT significantly reduced BMD compared to IMRT (p=0.04). IMPT was associated with a lower rate of PS≥2 at day 21 and 42 after CCRT (13.4% vs. 26%, p=0.039, OR 0.44 and 24% vs. 39%, p=0.024, OR 0.49, respectively). Pts treated with IMPT had higher probability of receiving adjuvant D (74% vs 52%, adjusted OR 0.35, 95% CI: 0.16-0.79, p=0.012). In the multivariable logistic model (including age and PS) IMPT was the only predictive factor for receiving D within 42 days (72% vs 51%, adjusted OR 0.4, 95% CI: 0.16-0.95, p=0.04).

Conclusions: IMPT can reduce severe lymphopenia and anemia in pts with unresectable stage III NSCLC. Pts treated with IMPT have a better PS after CCRT and they are more likely to receive adjuvant durvalumab.

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1299P The role of radiotherapy in extensive-stage small cell lung cancer after durvalumab-based immunochemotherapy: A retrospective study

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Background: The purpose of this study was to evaluate the safety and efficacy of subsequent radiotherapy after first-line durvalumab plus chemotherapy in extensive-stage small cell lung cancer (ES-SCLC).

Methods: A total of 122 patients with ES-SCLC from three hospitals during July 2019 to December 2021 were retrospectively analyzed. Inverse probability of treatment weighting (IPTW) analysis was performed to address potential confounding factors. We primarily evaluated the progression-free survival (PFS) and overall survival (OS) in association with radiotherapy.

Results: After IPTW analysis, 49 patients received durvalumab plus chemotherapy with subsequent radiotherapy (Durva+EP+RT) and 72 patients received immunochemotherapy (Durva+EP). The median OS was 17.2 *vs* 12.3 months (hazard ratio (HR): 0.38; P=0.020), respectively, and the median PFS was 8.9 *vs* 5.9 months (HR: 0.56; P=0.030), respectively. Thoracic radiation therapy (TRT) resulted in longer OS (17.2 *vs* 14.7 months) and PFS (9.1 *vs* 7.2 months) compared to radiotherapy directed to other metastatic sites. Among patients with oligo-metastasis, radiotherapy also showed significant benefits, with a median OS of 17.4 *vs* 13.7 months and median PFS of 9.8 *vs* 5.9 months compared to no radiotherapy. Continuous durvalumab treatment beyond progression (TBP) prolonged OS compared to patients without TBP, in both the Durva+EP+RT (NA *vs* 15.8 months, HR: 0.48) and Durva+EP groups (12.3 *vs* 4.3 months, HR: 0.29). Grade 3 or 4 adverse events occurred in 13 (26.5%) and 13 (18.1%) patients, respectively, in the two groups; pneumonitis was mostly low-grade.

Conclusions: Addition of radiotherapy after first-line immunochemotherapy significantly improved survival outcomes with manageable toxicity in ES-SCLC.

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1300P Treatment and clinical outcome in recurrent/refractory locally advanced NSCLC following chemoradiotherapy and consolidative durvalumab

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Background: Despite recent advances in treatment of locally advanced non-small cell lung cancer (NSCLC) most patients suffer from relapse following treatment with chemoradiotherapy and consolidative Durvalumab. To date, no treatment standards have yet been established in current guidelines. As well, there is a paucity of data regarding effectiveness of different treatment options in relapsed/refractory (r/r) NSCLC. Here, we present preliminary data on treatment and outcome of r/r NSCLC patients in a real word setting.

Methods: So far, in this analysis we assessed patients from 10 German lung cancer centers undergoing treatment for r/r NSCLC between 06/2017 and 05/2023. Primarily, overall survival (OS) and progression-free survival (PFS) was estimated in this cohort and compared to historical outcomes. In addition, both different treatment options and OS/PFS were compared between subgroups. Last follow up will be assessed by June 30, 2023.

Results: N = 122 patients were retrospectively evaluated. Median OS from initial lung cancer diagnosis was 25.8 months (20.6 − 30.9) for the entire patient cohort. Following diagnosis of r/r disease median OS and PFS was 11.7 months (9.2 − 14.2) and 6.4 months (5.2 − 7.6), respectively. In relation to all patients undergoing systemic therapy as first -line treatment (70.5%), choice of systemic agents varied, with checkpoint inhibitors (with or without chemotherapy, 34.9%) most commonly administered, followed by platinum- (30.2%) or single agent-based chemotherapy (27.9%) and targeted therapies (7.0%). Interestingly, patients treated with targeted therapy or checkpoint inhibitor-based therapy benefited in terms of overall survival compared with patients who received chemotherapy alone.

Conclusions: Patients suffering from r/r disease represent a distinct patient population showing a dismal prognosis. However, choice of first-line therapy might affect overall survival. Besides improving early detection of NSCLC recurrence prospective clinical trials are warranted to further guide treatment.

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1301P A prognostic clinical and circulating biomarker model to identify futile chemo-radiotherapy (CRT) in stage III NSCLC

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Background: CRT followed by adjuvant Durvalumab (D) is standard of care for fit patients (pts) with unresectable stage III NSCLC. However, most pts will not benefit from the CRT part of the treatment. We aimed to build a prognostic model to identify pts who may not benefit from CRT without D.

Methods: Pts with stage III NSCLC treated with curative intent CRT (platinum-doubled and chest RT to a dose of 60-66 Gy) were identified from the prospective biobank project (2003-2019; NCT01084785). No pts received immunotherapy or targeted agents, neither in the primary treatment, nor for recurrence. Clinical parameters included age, sex, performance status (PS), stage (UICC 8), BMI; circulating biomarkers were GM-CSF, IFNα2a, IFNγ, IL-10, IL-12p70, IL-1β, IL-2, IL-6, IL-8, TNF-α, IFNβ, IL-1α, IP10, MCP1, PD-L1. Cut-off points were based on maximum Log-Rank statistic (with correction for multiple testing). Overall survival (OS) was calculated from start of RT. Significance level alpha was set at 0.05.

Results: 342 pts were included: mean age 64.7 ± 9.4 yrs; 62.3 % male; PS 0: 36.3 %, 1: 50.8 %, 2 or more: 12.9 %; stage: IIIA: 42.7 %; IIIB: 45.0 %, IIIC: 12.3 %. Median follow-up was >10 years. Median OS was 1.8 years (95 % CI 1.46-2.20), the 1-, 2- and 5-year OS 65.8 %, 48.5 % and 27.5 %. In multivariate analysis, higher age (p=0.003), male gender (p=0.043), PS 2 or higher (p=0.036), stage IIIB (p=0.003) or stage IIIC (p<0.001), higher IL6 (p<0.001) and higher circulating PD-L1 (p=0.001) were significant for poorer OS. The best cut-offs for IL-6 and PD-L1 were 3.39 pg/ml and 155.52 pg/ml, respectively. The multivariate prognostic model had an AUC = 0.78 (95 % CI 0.73-0.84) for 1-year OS and 0.76 (0.71-0.81) for 2-year OS. Pts in the best prognostic group (below threshold for IL6 and PD-L1; 34.4 % of total) had a median OS of 44 months, in the intermediate group (above threshold for one biomarker; 41.8 % of total) a median OS of 20 months and in the worst group (both markers above threshold; 23.6 % of total) a median OS of 8 months.

Conclusions: This easy to apply multivariate model for OS, which includes IL6 and circulating PD-L1, may identify pts with a poor OS after standard CRT without immunotherapy. These pts may benefit from alternative treatments without platinum-based chemotherapy and RT.

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1302P Treatment outcomes and safety of durvalumab following definitive chemoradiotherapy among patients with stage III NSCLC in Thai populations: A real-world, multi-center observational study

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Background: In locally advanced non-small cell lung cancer (LA-NSCLC), durvalumab as consolidation therapy following definitive chemoradiotherapy (CRT) was established as the standard of care. Given the heterogeneity of patients with LA-NSCLC, the present study evaluated the efficacy and safety of durvalumab in a real-world, multi-center observational study.

Methods: 111 patients with LA-NSCLC, whose disease had not progressed following CRT and receiving ≥1 dose of durvalumab as part of the expanded access program (EAP) in Thailand and outside EAP were included. In addition to descriptive statistics, the survival probability was determined using the Kaplan-Meier method.

Results: A total of 78 patients from 12 centers participating in the Thailand National Lung Cancer Registry Network were enrolled. The median age was 63 years, 73% were men, 73% had non-squamous and 21.6% of patients with non-squamous histology had epidermal growth factor receptor mutation (EGFRm). Only 14% of patients had been tested for programmed death-ligand 1 (PD-L1) and 54.5% had PD-L1 expression. Most patients (89%) received concurrent CRT and carboplatin/paclitaxel was the most common chemotherapy used. 91.2% received a RT dose ≥60 Gy with a median time of durvalumab initiation from the end of RT being 42 days. Overall, 46 patients (59%) completed the 12-month treatment with a median of 24 cycles. Median follow-up time was 34.5 months (range 7—58) with 2-year PFS and OS of 64.2% and 83.3%, respectively. No significant differences in PFS were detected for EGFRm vs. wild-type *EGFR* (EGFRwt), but the median PFS was 39 months for EGFRm vs. 27 months for EGFRwt. Immune-related AEs (irAEs) of any grades and grade ≥3 were reported in 41% and 10.3%, respectively. Pneumonitis was the most frequent irAEs (18%), and 6.4% were grade ≥3, leading to discontinuation in 6/78 patients (7.7%).

Conclusions: Durvalumab after definitive CRT showed a promising outcome and was well-tolerated in this real-world study. Although a high prevalence of EGFRm is noted in this region, favorable PFS outcomes were observed regardless of *EGFR* mutation status.

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1303P Immune-modulating effects on tumor draining lymph nodes following neoadjuvant chemoradiotherapy combined with immunotherapy in patients with T3-4N0-1 NSCLC

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Background: The addition of neoadjuvant immunotherapy to chemoradiotherapy (CRT) prior to surgical resection was investigated in locally advanced non-small cell lung cancer (NSCLC) patients (INCREASE trial, NTR-NL8435). Tumor-draining lymph nodes (TDLN) play a key role in the immune response against tumors and are often part of the healthy surrounding tissue exposed to radiotherapy. This study investigated the immune-modulating effects of neoadjuvant immunotherapy and CRT on TDLN in T3-4N0-1 NSCLC patients.

Methods: Resected TDLN were collected from: (i) participants in the INCREASE trial who received neoadjuvant ipilimumab/nivolumab combined with CRT (n=25), and (ii) a control cohort of matched NSCLC patients treated with standard CRT induction therapy (n=25). TDLN were selected based on radiation dose received [low (<5 Gy), intermediate (20-30 Gy) or high dose (50-60 Gy)] and stained with duplex immunohistochemistry for CD8/Ki67, PD1/FOXP3 and CD8/cleaved caspase-3. Hotspot areas were then manually analyzed.

Results: Higher counts of proliferating CD8 T-cells were observed within TDLN in all three categories of radiation exposure in the INCREASE cohort compared to control patients (p=<0.0001, p=0.02, p=<0.0001 for low, intermediate and high dose), as well as higher counts of activated PD-1+ Tregs (p=<0.0001 for all nodes). Furthermore, higher numbers of Ki67+ CD8 T-cells and PD-1+ Tregs were observed with increasing radiation dose (INCREASE high-dose vs low-dose, p=0.0095 for CD8 T-cells and p=0.0298 for Tregs). No relationship was observed between radiation dose exposure and the induction of apoptosis by cleaved caspase-3 in CD8 T-cells.

Conclusions: Higher rates of proliferating CD8 T cells and activated PD-1+ Tregs in TDLN were seen when immunotherapy was added to induction CRT in T3-4N0-1 NSCLC patients, suggesting the enhanced priming of effector CD8 T-cells, accompanied by a simultaneous increase in Tregs. High radiation dose led to an increase of CD8 T-cells and Tregs in the INCREASE cohort. Further analyses with spatial transcriptomics and quantitative pathology imaging is needed to reveal spatial positioning of PD-1+ Tregs in relation to proliferating CD8 T-cells.

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1304P A structured multidisciplinary approach for diagnosing immune-related pneumonitis in patients undergoing adjuvant durvalumab for stage III non-small cell lung cancer

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Background: In inoperable stage III NSCLC, the standard of care is chemoradiotherapy and adjuvant durvalumab (IO) for 12 months. Pneumonitis is the commonest toxicity leading to IO discontinuation. Failure to distinguish between radiation-induced changes, IO pneumonitis and infection can lead to unnecessary IO discontinuation. We investigated use of a structured multidisciplinary review of CT-scans, radiation dose distributions and clinical symptoms for the diagnosis of IO pneumonitis.

Methods: An ethics-approved retrospective study was conducted at an academic medical center for stage III NSCLC patients treated with chemoradiotherapy and adjuvant IO between 2018-2021. A thoracic radiologist reviewed baseline and follow-up chest CT-scans, systematically scored radiological features suspected for pneumonitis using a published classification system (Veiga C, Radioth Onc 2018), and had access to the radiation dose distributions. Next, two thoracic oncologists reviewed each patients' case record, CT-scans and radiation fields. A final consensus diagnosis incorporating views of expert clinicians and the radiologist was made. IO pneumonitis was diagnosed only when both the radiologist and pulmonologists were in agreement.

Results: Among the 45 included patients, 14/45 (31.1%) had a pneumonitis scored in patient records. IO was discontinued in 11/45 cases (24.4%). Review by the radiologist led to a diagnosis of IO pneumonitis only in 6/45 patients (13.3%). Review by thoracic oncologists led to a diagnosis of IO pneumonitis in only 4/45 patients (8.9%). In addition, a suspicion of an immune-related pneumonitis was rejected in 3 separate patients (6.7%), after the thoracic oncologists had reviewed the patient's radiation fields.

Conclusions: In patients treated using the PACIFIC regimen, multidisciplinary assessment of CT-scans, radiation doses and patient symptoms, resulted in fewer diagnoses of immune-related pneumonitis (8.9%). In contrast, routine clinical assessment by treating pulmonary oncologists led to discontinuation of IO in 24.4% of patients. This highlights the need for multidisciplinary review in order to avoid inappropriate cessation of adjuvant IO.

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1305P Importance of the resected lung tumor specimen in patients with locally advanced and metastatic non-small cell lung cancer undergoing prior targeted therapy

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Background: For patients who show downstaging of lung cancer following targeted therapy, salvage surgery can be considered. Resection of regrowing pulmonary masses can also be performed to acquire a tumor specimen. The aim of this study is to evaluate the prognosis of patients who have undergone prior tyrosine kinase inhibitor (TKI) treatment and later lung surgery.

Methods: The deidentified data of NSCLC patients admitted to eight university hospitals affiliated with the Catholic University of Korea were obtained from the Clinical Data Warehouse (CDW) database. Forty patients who had prior targeted therapies and later received surgical resection were evaluated for the study. The primary endpoint was overall survival, defined as the time between surgical resection and death or censoring. The secondary endpoint was postoperative progression-free survival.

Results: Of 40 patients diagnosed with adenocarcinoma. 36 (87.8%) received prior EGFR TKI treatment, while 4 (9.8%) received ALK TKI treatment. At the time of TKI initiation, 31 (77.5%) were staged as IV, and 9 (22.5%) were staged as III. Salvage surgery was performed in 18 patients (45.0%), and 22 (55.0%) underwent resection for biopsy purposes. At the time of resection, tumor burden was unchanged in 7 patients (17.5%), significantly regressing in 12 patients (30.0%), and increasing in 21 patients (52.5%). Among the 28 patients with EGFR mutations from resected tumor specimens, 9 (32.1%) exhibited the T790M mutation. Next-generation sequencing of the resected samples identified mutations such as MET amplification and TP53. Only one postoperative complication, atrial fibrillation, was observed. Patients with poor preoperative ECOG (Eastern Cooperative Oncology Group) scores had significantly worse 1-year and 2-year survival rates (P=0.014 and P=0.011, respectively). There was a significant difference in 6-month PFS rates between groups stratified by pleural invasion levels (PL0-3) (P=0.029). Furthermore, patients with T790M mutation showed a trend towards improved PFS (P=0.052).

Conclusions: Lung surgery following targeted therapies is safe and can be used to predict the prognosis of patients with initially unresectable NSCLC.

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1307P The Biocartis Idylla GeneFusion Assay (RUO) for lung cancer testing: The experience of testing over 5000 tumours in routine practice

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Background: Lung non-small cell carcinoma molecular profiling is challenging due to the number of alterations to assess, the small size of the samples and the quick turnaround required in order to offer patients the optimal treatment. We implemented the Biocartis Idylla™ GeneFusion Assay (RUO) two years ago for ALK, ROS1, RET and MET exon 14 testing. The assay is designed to specifically target 17 fusions variants in ALK, 13 in ROS1 and 7 in RET gene. This provides specific detection of 93% of ALK, 98% of ROS1 and 85% of RET fusion events as reported on COSMIC. We report on our experience on over 5000 cases tested over 2 years.

Methods: We prospectively tested lung cancer samples on the Idylla™ Platform as part of routine lung profiling locally and from over 60 UK hospitals. Tissue requirements were 1 - 3 x 5 µm sections; tumour burden was assessed on an HE stain prior to running the assay to ensure minimum 10% tumour content. Sections are loaded into the Idylla™ Cartridge; run time 180 mins; interpretation is via automated analysis using pre-defined cut offs within the Idylla™ software. Fusions (ALK, ROS1, RET) and MET ex 14 rearrangement are called with corresponding Cq values alongside internal DNA and RNA controls. Manual interrogation of the amplification curves is possible through the Idylla™ Explore software, if required.

Results: We have tested over 5000 tumours so far.

Table: 1307P Rate of positivity (ROP) and rate of failure (ROF) for GeneFusion assay

TEST	DETECTED	NOT DETECTED	INVALID	TOTALS	ROP (%)	ROF (%)
ALK Specific	66	4803	410	5394	1.3	7.6
ROS Specific	18	4845		5394	0.4	
RET Specific	24	4843		5394	0.5	
GEN - MET exon 14	106	4759		5394	2.1	

Conclusions: Our data shows a level of detection of ALK, ROS1, RET, MET exon14 as expected from published data. We had almost 100% of concordance with ALK and

ROS1 immunostaining. Test failure was due to either poor quality of RNA or insufficient material to pass QC metrics. More importantly, the assay allows testing to be successfully completed in samples unsuitable for NGS due to low tumour burden. In conclusion, the Idylla™ GeneFusion Assay offers a rapid, sensitive and specific method for lung sample profiling in routine practice.

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1308P Diameter threshold for lung nodules at low-dose CT screening: Chinese population screening experience

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Background: High false positive rates in LDCT screening are an important concern. The study aims to explore the diagnostic performance of different diameter thresholds for various lung nodules to reduce unnecessary follow-up LDCT scans and the waste of medical resources.

Methods: Participants were recruited from the "Guangzhou Lung-Care Project" at the First Affiliated Hospital of Guangzhou Medical University in China between 2017 and 2021. The average transverse diameter of lung nodules was measured by semi-automatic segmentation. Positive outcomes were divided into two groups: outcome 1-lung cancer diagnosis with AAH/AIS, and outcome 2-lung cancer diagnosis without AAH/AIS. We calculated the area under the receiver-operating characteristic curves (AUCs), sensitivity, specificity, positive prediction rate(ppv) and negative prediction rate (NPV) to evaluate the diagnostic performance of lung cancer under each threshold between 5mm to 10mm.

Results: In the first year after LDCT screening, 126 cases of lung cancer (including 13 cases of AAH/AIS) were diagnosed among the participants of 11,705 (5,425 men and 6,280 women; median age 59). Increase the average transverse diameter threshold from 5 to 7mm in all lung nodules (solid, part-solid, non-solid), and gradually increase the AUC in outcome 1 (0.766 to 0.825) and outcome 2 (0.78 to 0.839). From 7 to 10mm, the AUC in outcome 1 (0.825 to 0.764) and outcome 2 (0.839 to 0.778) is gradually reduced. In the outcome 2, when the diameter threshold was increased from 5mm to 8mm, the specificity (60.06% to 90.82%) and ppv (6.57% to 19.02%) increased significantly, the sensitivity was reduced (94.02% to 76.07%). When the diameter threshold was increased from 8mm to 10mm, the sensitivity was significantly reduced (76.07% to 60.68%) and specificity (90.82% to 94.88%) and ppv (19.02% to 25.13%) increased slightly. There is no obvious difference between outcome 1 and outcome 2 in the above indicators.

Conclusions: Our study demonstrates that setting a diameter threshold of 8mm for LDCT screening of lung nodules achieves better overall diagnostic performance, reducing false positives and unnecessary follow-up scans while minimizing medical resource waste.

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1309P Immune exhaustion in tumor-free lymph nodes of non-small cell lung cancer (NSCLC) patients is associated with performance status and survival

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Background: Tumor-draining lymph nodes are crucial in initiation and maintenance of antitumoral immune activity. Immune cell exhaustion in these lymph nodes is associated with low therapeutic efficacy and poor prognosis. The effect of different markers of immune exhaustion on patients' performance status and survival is not yet fully understood.

Methods: Expression profiling of 770 immune-related genes in N1 and N2 tumor-free lymph nodes was performed using the PanCancer IO 360 panel by NanoString Technologies. We analysed the association between immune exhaustion data and performance status and survival using Student's t-test and Cox regression.

Results: We performed immune transcriptomics on tumor-free lymph nodes of 16 stage II/III NSCLC patients. Patients with worse performance status (ECOG 1/2 vs. 0) showed increased levels of immune dysfunction as measure by increased Tumor Immune Dysfunction and Exclusion (TIDE) scores ($p=0.05$). In particular, ECOG score was associated with increased levels of immune exhaustion marker IDO1 ($p=0.02$). IDO1 ($HR= 1.003$, $p=0.02$) and LGALS9 ($HR= 1.011$, $p=0.001$) expression in N1 and expression of CD276 ($HR= 1.005$, $p=0.01$) in N2 lymph nodes were associated with worse survival.

Conclusions: Our data confirm the relevance of immunological exhaustion in lymphatic tissues of NSCLC patients. Increased IDO1 expression is associated with higher ECOG score and worse survival and needs to be further investigated.

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1310P Loratadine: A potential game-changer in lung cancer treatment with improved survival outcomes

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Background: Tumor-associated inflammation suggests that anti-inflammatory medication could be beneficial in cancer therapy. Loratadine, an antihistamine, has demonstrated improved survival in certain cancers. This study investigates loratadine's anticancer mechanisms in lung cancer. Tumor-associated inflammation suggests that anti-inflammatory medication could be beneficial in cancer therapy. Loratadine, an antihistamine, has demonstrated improved survival in certain cancers. This study investigates loratadine's anticancer mechanisms in lung cancer.

Methods: A retrospective cohort of 4,522 lung cancer patients from 2006 to 2018 was analyzed to identify non-cancer drug exposures associated with prognosis. Cellular experiments, animal models, and RNAseq data analysis were employed to validate findings and explore the antitumor effects of loratadine.

Results: The retrospective study revealed a positive association between loratadine use and improved lung cancer survival. Cellular assays showed that moderate loratadine doses induced apoptosis, cellular senescence, and reduced epithelial-mesenchymal transition (EMT). Interestingly, high loratadine doses triggered pyroptosis and interacted with apoptosis through caspase-8. Animal models indicated that loratadine impeded tumor growth in C57BL/6 mice but not in nude mice xenografts, suggesting potential immune response involvement in apoptosis and pyroptosis.

Conclusions: Loratadine use is linked to enhanced survival in lung cancer patients, potentially due to its role in modulating cell death, inflammatory, and immune responses by regulating the interplay between apoptosis and pyroptosis via caspase-8. Further research on other antihistamines and their immune response to tumors is warranted.

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1311P Understanding the basis for intrinsic resistance to KRASG12C inhibitors

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. KRAS is the most frequent mutated oncogen in lung adenocarcinoma (LUAD), but it has been recognized as undruggable for many years. KRASG12C inhibitors (KRASG12Ci), are being tested in clinical trials and have revealed promising results in LUAD patients. With these results, two KRASG12Ci have been approved for the treatment of LUAD patients by the FDA, which marks the first approved targeted therapy for KRAS-mutated tumors. While these therapies hold great promise, they face the same limitation as other targeted therapies, the therapeutic potential of these inhibitors can be impaired by resistance. Deciphering intrinsic resistance mechanisms to KRASG12Ci is of prime relevance to predict which patients may benefit from these therapies and to propose therapeutic alternatives.

Methods: The efficacy of two different KRASG12Ci was tested in different KRASG12C-mutated models, *in vitro* in a panel of 8 LUAD cell lines and 7 PDX-derived organoids (PDXDO) models and *in vivo* in a panel of 7 patient-derived xenografts (PDX) models. Thus, we define the intrinsic and resistance models, and compare the genomic (WES) and transcriptomic (WTS) data to find a signature that defines the intrinsic resistance to each drug.

Results: Among the 8 LUAD cell lines, we found 3 very sensitive cell lines and 2 intrinsic resistant ones. Among the 7 PDXDO models, we found 4 sensitive models and 3 intrinsic resistant ones. And among the PDX models we found two very sensitive models and two intrinsic resistant ones. These ratios are representative of what was found among patients in clinical trials. Comparative transcriptomic analysis from sensitive and intrinsic resistant models showed different basal levels of expression and/or activation of downstream signaling pathways of KRAS, ARF or PLC and of various receptors such as ERBB, FGFR or IGF-1R.

Conclusions: 1) We found a transcriptomic signature that define the intrinsic resistance, characterized by a greater basal expression and/or activation of some RTKs and signaling pathways. 2) We identificate some molecular alterations which could be responsible of the intrinsic resistance and could acts as predictive biomarkers and/or serve as therapeutic targets in combination with KRASG12Ci.

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1312MO Combining the antigen-presenting cell activator eftilagimod alpha (soluble LAG-3) and pembrolizumab: Overall survival data from the first line non-small cell lung carcinoma (NSCLC) cohort of TACTI-002 (phase II)

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Background: Eftilagimod alpha (E), a soluble LAG-3 protein, acts as an MHC class II agonist triggering activation of antigen-presenting cells (APC). Subsequently downstream T-cells (e.g. CD4/CD8) are recruited, possibly leading to stronger anti-tumor responses than with pembrolizumab (P) alone, especially in tumors non-overexpressing PD-L1. We hereby report initial overall survival (OS) results of the 1st line non-small cell lung carcinoma (NSCLC) cohort in TACTI-002.

Methods: Patients (pts) with measurable 1st line metastatic NSCLC unselected for PD-L1 were recruited. Primary endpoint (EP) was objective response rate (ORR) by iRECIST. Secondary EPs included OS, ORR by RECIST 1.1, duration of response (DoR), progression free survival (PFS), safety & biomarkers. Pts received 30 mg E SC q2w for 8 cycles (1 cycle= 3 weeks) & then q3w up to 1 yr with P 200 mg IV q3w up to 2 yrs. Imaging was done q9w & assessed by investigator. PD-L1 was centrally assessed (22C3). The study was powered (80%) with a 1-sided alpha of 2.5% to detect an ORR increase from 23% (historical results for P) to 35%.

Results: From Mar 2019-Nov 2021, 114 pts enrolled using modified Simon's two-stage design. Median follow up of 20.4 mo (cut-off Mar 31, 2023). Median age was 67 (44—85) & 74% were male. ECOG PS was 0 & 1 in 37% & 63% of pts. Pts had squamous (35%) or non-squamous (63%) carcinoma. All PD-L1 subgroups were represented; 77.8% had TPS <50%. Pts received median 9 (1—35) P & 13 (1—22) E doses. Median (m) OS unselected for PD-L1 was 22.6 mo (52.6% events) & mDoR was 21.6 mo. Onset of responses was quick (median: 2.1 mo). Comparable results by RECIST 1.1. Efficacy by PD-L1 shown in the table. Safety was presented prior at SITC 2022.

Table: 1312MO

Efficacy parameter	ORR, % [95% CI] by iRECIST	mPFS, mo [95% CI] by iRECIST	mOS, mo [95% CI]
ITT (N=114); PD-L1 unselected	40.4 [31.3—50.0]	6.6 [4.6—9.8]	22.6 [14.9—35.0]
By PD-L1 TPS (N=90)			
≥1% (N=58)	48.3 [35.0—61.8]	11.2 [6.3—16.6]	25.0 [12.1—38.8]
<1% (N=32)	31.3 [16.1—50.0]	4.2 [2.1—6.2]	15.5 [7.4—19.8]
1—49% (N=38)	44.7 [28.6—61.7]	9.3 [4.4—15.7]	23.4 [9.3—35.5]
≥50% (N=20)	55.0 [31.5—76.9]	16.3 [4.0—43.9]	38.8 [8.1—38.8]

Conclusions: E + P shows encouraging OS results in line with excellent ORR, PFS and DOR in 1st line NSCLC overall and in all PD-L1 subgroups. This combination warrants further late-stage clinical investigation.

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1313MO Safety and preliminary efficacy of AZD7789, a bispecific antibody targeting PD-1 and TIM-3, in patients (pts) with stage IIIB–IV non-small-cell lung cancer (NSCLC) with previous anti-PD-(L)1 therapy

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Background: AZD7789 is a monovalent, bispecific, humanised IgG1 that blocks PD-1 and T cell immunoglobulin and mucin domain 3 (TIM-3), receptors that regulate antitumour T cell activity and myeloid activation. Dual blockade of PD-1 and TIM-3 may overcome or delay anti-PD-(L)1 resistance. Here we report dose escalation results from a phase 1/2a, first-in-human, multicentre, open-label trial of AZD7789 monotherapy in pts with stage IIIB–IV NSCLC with ≥1 prior line of systemic therapy including ≥1 anti-PD-(L)1 agent.

Methods: Eligible pts were ≥18 yr old with ECOG PS 0–1. Dose cohorts ranged from 2–2000 mg IV Q3W: 2–225 mg in an accelerated titration design, and 750–2000 mg using mTPI-2. The primary objective was safety, including dose-limiting toxicities (DLTs). Secondary/exploratory objectives included efficacy, pharmacokinetics (PK), PD-1 receptor occupancy (RO), and immunogenicity. Data cutoffs were 13 Feb 2023 for safety and 11 Jan 2023 for efficacy.

Results: In total, 39 pts received AZD7789 2–2000 mg; median age 66 yr, 56% male, 36% PD-L1 status <1%, 33% PD-L1 1–49%, and 28% PD-L1 ≥50%, and 80% had acquired resistance to prior anti-PD-(L)1 therapy (≥6 mo of treatment exposure). Treatment emergent AEs (TEAEs) occurred in 82% of pts and were Grade (Gr) ≥3 in 23%. The most common TEAE was increased blood creatinine (18%); no TEAE led to discontinuation. Treatment related AEs (TRAEs) occurred in 41% of pts; the most common was asthenia (8%). There were no DLTs or Gr ≥3 TRAEs. On-treatment scans were available for 19 pts: 7 had stable disease, including 2 with unconfirmed partial responses, 11 had progression, and 1 was not evaluable. Target lesion shrinkage was observed in 8 pts. PK was generally dose proportional, with $t_{½}$ ~7 days; antidrug antibodies had limited impact on PK. Doses ≥225 mg led to durable PD-1 RO >90% on peripheral T cells. As of 13 Feb 2023, 24 pts remained on AZD7789; updated data will be presented.

Conclusions: AZD7789 has manageable safety and shows preliminary efficacy at tolerable doses. Evaluation is ongoing in immunotherapy-naive pts with NSCLC and pts with acquired resistance to immunotherapy.

Clinical trial identification: NCT04931654; June 18, 2021.

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1314MO TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer (NSCLC) with actionable genomic alterations (AGAs)

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Background: Once targeted therapies and platinum-based chemotherapy (PBC) become ineffective in patients (pts) with advanced/metastatic (a/m) NSCLC with AGAs, few treatments with limited benefit are available. Dato-DXd is an antibody-drug conjugate composed of a TROP2 directed monoclonal antibody covalently linked to a highly potent cytotoxic payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. We report primary results from the global, open-label, phase 2 TROPION-Lung05 trial (NCT04484142) evaluating Dato-DXd in pts with a/m NSCLC with AGAs progressing on or after ≥1 AGA-specific therapy and PBC.

Methods: Dato-DXd 6 mg/kg was given every 21 days to pts with a/m NSCLC, ECOG status 0 or 1, and ≥1 documented AGA in *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*. The primary endpoint was confirmed objective response rate (cORR)

by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR) and disease control rate (DCR) by BICR, and safety.

Results: A total of 137 pts received ≥1 dose and had a median age of 61.0 y; 71.5% had ≥3 prior lines of therapy for a/m NSCLC; 56.9% had *EGFR* mutations. As of 14 Dec 2022, 85.4% discontinued therapy, 63.5% had disease progression, and 49.6% died. Median pt duration on study was 15.2 months (mo); cORR was 35.8%, DCR, 78.8%, and median DOR, 7.0 mo; similar response was seen in pts with *EGFR* mutations (Table). The most common grade ≥3 TEAEs were stomatitis (9.5%), anemia (5.8%), and increased amylase (5.8%).

Table: 1314MO Primary results (N = 137)

Efficacy[a]	
cORR, n (%) (95% CI)	49 (35.8) (27.8-44.4)
Complete response	4 (2.9)
Partial response	45 (32.8)
cORR in pts with *EGFR* mutation	34 (43.6)
DCR, n (%)	108 (78.8)
Median DOR in confirmed responders, months	7.0
Safety, n (%)	
Grade ≥3 TEAEs	65 (47.4)
Serious TEAEs	34 (24.8)
TEAEs associated with:	
Dose reduction	30 (21.9)
Drug discontinuation	13 (9.5)
Death	2 (1.5)[b]
Adjudicated drug-related ILD	
Grade 1/2	4 (2.9)
Grade ≥3	1 (0.7)[c]

[a]By BICR. [b]Two cases associated with disease progression, unrelated to study drug by investigator. [c]One grade 3 reported event, with death due to disease progression by investigator and adjudicated grade 5 ILD.

Conclusions: Dato-DXd showed encouraging antitumor activity, with a clinically meaningful and durable response, in heavily pretreated pts with NSCLC with AGAs. The safety profile was manageable and consistent with prior safety observed with Dato-DXd. These data support inclusion of pts with AGAs in the TROPION-Lung01 study (NCT04656652).

Clinical trial identification: NCT04484142.

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Hoffmann-La Roche Ltd., Genentech Inc., GSK Research and Development Limited, Janssen Cilag International NV, Merck Sharp & Dohme Corp, Merck KGAA, Mirati Therapeutics Inc, Novartis Pharmaceutica SA, Pfizer, Takeda Pharmaceuticals International; Non-Financial Interests, Leadership Role, President (2021-2023): SEOM (Sociedad Espanola de Oncologia Medica); Non-Financial Interests, Member, Member of Scientific Committee: ETOP (European Thoracic Oncology Platform); Non-Financial Interests, Member, Member of the Scientific Advisory Committee: CAC Hospital Universitari Parc Taulí. W. Su: Financial Interests, Personal, Other, Consulting or advisory role: Merck, MSD, Bayer, Roche; Financial Interests, Personal, Other, Honoraria; Consulting or advisory role: Lilly. H. 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1315MO Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non-small cell lung cancer (NSCLC)

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Background: *NRG1* fusions are rare oncogenic drivers of NSCLC and other solid tumors. These chimeric proteins bind HER3, leading to HER2/HER3 heterodimerization and oncogenic transformation. Zenocutuzumab (MCLA-128; Zeno) is a bispecific antibody that overcomes HER3-mediated NRG1 signaling in NRG1+ cancer. Zeno is

being evaluated in the ongoing pivotal phase 2 eNRGy study and early access program (EAP). Updated NRG1+ NSCLC data are presented.

Methods: Patients (pts) with advanced NRG1+ NSCLC determined by NGS, previously treated with or not candidate for standard therapy, age $\geq$ 18 y, ECOG PS $\leq$ 2, and measurable (RECIST v1.1) or evaluable disease were enrolled. Zeno (750 mg IV Q2W) was administered until disease progression or unacceptable toxicity. Tumor imaging was conducted Q8W. The primary endpoint is investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints include duration of response (DOR) and safety.

Results: As of 01 Feb 2023, 85 pts with NRG1+ NSCLC (78 eNRGy/7 EAP) were enrolled. Efficacy was assessed in 65 pts who received $\geq$ 1 dose of Zeno and were enrolled by 01 Aug 2022 to allow for the opportunity for $\geq$ 6 months (mo) follow-up and met the criteria for the primary efficacy population. The median age was 64 y (range 32-86), 65% were female, 29%/63%/5% pts had ECOG PS 0/1/2 (missing 2 pts). Most were Asian (52%) or White (37%), 77% had visceral metastases, 98% had adenocarcinoma histology, and 1 pt had non-measurable disease. Common fusion partners were *CD74* (52%) and *SLC3A2* (23%). Pts received a median of 2 prior systemic therapies (range 0-6), 78% with platinum-based chemotherapy; 12% were treatment naïve. In the 64 pts with measurable disease, the confirmed ORR was 34% (22/64; 95% CI 23-47). 50/64 (78%) pts had target lesion reduction. Median DOR was 12.9 mo with responses ongoing in 11/22 (50%) pts. Kaplan-Meier estimate of 6-mo DOR rate was 79%. Among 85 pts treated with Zeno, Grade $\geq$ 3 individual AEs irrespective of causality occurred in $<$ 4% pts. No pt discontinued Zeno for a treatment related AE.

Conclusions: In this updated analysis, Zeno provides robust and durable efficacy in advanced NRG1+ NSCLC, with a well-tolerated safety profile.

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1316MO BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with non-small cell lung cancer: Updated results from first-in-human phase I study

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Background: BL-B01D1 is a first-in-class novel antibody drug conjugate (ADC) consisting of an EGFRxHER3 bispecific antibody bounded to a novel TOP-I inhibitor payload via a cleavable linker. We now report updated safety/efficacy results from the NSCLC patients (pts) of the BL-B01D1 phase I study.

Methods: This study enrolled pts with locally advanced or metastatic NSCLC and tested doses of 2.5, 3.0, and 3.5 mg/kg administered on D1D8Q3W, as well as doses of 5.0 and 6.0 mg/kg administered on D1Q3W.

Results: As of Mar 31st, 2023, 114 NSCLC pts who failed standard treatment were enrolled and received at least one dose of BL-B01D1. The most common TRAEs (>10%, all grade/≥ G3) were anemia (59%/25%), leukopenia (59%/28%), neutropenia (51%/32%), thrombocytopenia (48%/23%), nausea (36%/<1%), vomiting (34%/2%), alopecia (27%/0%), decreased appetite (24%/<1%), asthenia (23%/0%), mouth ulceration (21%/0%), diarrhea (20%/<1%), hypophagia (19%/0%), hypokalemia (15%/0%), hypoalbuminemia (12%/0%), rash (11%/0%). No ILD was observed. 88 pts were evaluable for efficacy (at least 1 post-baseline tumor assessment), mPFS for EGFRmut and EGFRwt NSCLC was 6.9 (4.3, ∼) and 5.2 (3.9, ∼) months, respectively, although these results are still considered immature. The study is currently ongoing and further updates regarding DoR, mPFS, and other results will be provided during the meeting.

Table: 1316MO

	NSCLC (EGFRmut) (n=38)[1]	NSCLC (EGFRwt) (n=50)[2]
Median prior treatment line (range)	3 (1-7)	2 (1-8)
Best overall response, n		
PR	24	22
SD	10	25
PD	4	3
ORR[3], % (95% CI)	63.2% (46.0-78.2)	44.0%(30.0-58.7)
DCR, % (95% CI)	89.5% (75.2-97.1)	94.0% (83.5-98.8)

[1]All had prior EGFR TKI, 89% (34/38) had prior 3rd-generation EGFR TKI and 74% (28/38) had prior platinum-based chemotherapy (PBC). [2]All had prior PBC, 90% (45/50) had prior anti-PD-1/L1 and PBC. [3]During 12/2022∼01/2023, 9 pts (4 EGFRmut, 5 EGFRwt) had skipped at least 25% of the planned doses due to COVID-19 during 1st and 2nd tumor assessments.

Conclusions: BL-B01D1 demonstrated encouraging efficacy in heavily pretreated metastatic/locally advanced NSCLC, especially in pts with EGFRmut. The observed toxicity is deemed acceptable.

Clinical trial identification: NCT05194982.

Legal entity responsible for the study: Sichuan Baili Pharmaceutical Co., Ltd.

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1317MO Updated study results of pelcitoclax (APG-1252) combined with osimertinib in patients (pts) with EGFR-mutant non-small cell lung cancer (NSCLC)

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Background: Investigational agent pelcitoclax is a dual BCL-2/BCL-xL inhibitor that enhances antitumor effects of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) osimertinib in preclinical models. In pts with TKI-naïve *EGFR*-mutant NSCLC, pelcitoclax plus osimertinib was well tolerated and showed preliminary efficacy (Zhang L et al. *J Clin Oncol* 2022). Here, we provide updated safety and efficacy results of this combination therapy.

Methods: The recommended phase 2 dose of pelcitoclax was established at 160 mg weekly plus osimertinib 80 mg daily. After completion of dose escalation and 2 dose expansions, pts were divided into 3 cohorts by treatment line: Cohorts 1 and 2 (EC-1 and EC-2) included pts with disease resistant to first- and third-generation EGFR-TKIs, respectively; Cohort 3 (EC-3) included pts whose disease was previously untreated with EGFR-TKIs.

Results: As of February 16, 2023, 64 pts (median age, 56 years; 54% female) were treated with pelcitoclax plus osimertinib. Among them, 8 were in EC-1, 29 in EC-2, and 27 in EC-3. Among 26 efficacy-evaluable pts in EC-3, 20 partial responses (PRs [76.9%]) were observed. For pts with *TP53* and *EGFR*-positive mutations in EC-3, 13/16 (81.3%) PRs were observed, and the median progression-free survival (range) was 16.39 (8.11-NR) months. Preliminary biomarker data from pts in EC-2 suggested that high BCL-xL expression was associated with antitumor efficacy. A total of 64 (100%) pts in all cohorts experienced treatment-related adverse events (TRAEs), which were grade ≥ 3 in 12 (18.8%). Common TRAEs included increased aspartate aminotransferase (70.4%) and alanine aminotransferase (59.3%), reduced platelet counts (33.3%), increased serum amylase (25.9%), and increased blood creatinine (22.2%).

Conclusions: Based on these findings, pelcitoclax plus osimertinib is of potential clinical interest to improve outcomes of pts with *TP53*- and *EGFR*-mutant NSCLC. Further studies are needed to elucidate the role of pelcitoclax when combined with osimertinib in treating this pt population. Internal study: APG1252NC101; CT.gov: NCT04001777.

Clinical trial identification: NCT04001777.

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Funding: Ascentage Pharma Group Corp Ltd (Hong Kong).

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1318MO First-in-human study of ABBV-637, an EGFR-targeting BCL-XL–inhibiting antibody-drug conjugate combined with osimertinib (OSI) in relapsed/refractory, EGFR-mutated non-small cell lung cancer (NSCLC)

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Background: ABBV-637 is an antibody-drug conjugate consisting of an epidermal growth factor receptor (EGFR)—targeting antibody and BCL-X_L inhibitor. Preclinical data demonstrate potent antitumor activity of ABBV-637 plus OSI in mutant EGFR NSCLC through reactivation of the apoptotic pathway.

Methods: This phase 1 dose escalation and expansion study (NCT04721015) explored the safety and preliminary efficacy of ABBV-637 as second- (2L) and third-line (3L) combination therapy with OSI. Enrolled adults had relapsed/refractory (RR) NSCLC with EGFR mutation, ECOG 0—1, and prior response and subsequent disease progression on OSI. Enrolled patients being treated at 2L and 3L had no inclusion/exclusion criteria for specific targetable mutations. ABBV-637 (12 or 20 mg/kg) was dosed IV Q4W; OSI (80 mg) was given daily in 28-day cycles. Endpoints included the rates of treatment-emergent adverse events (TEAEs), objective response (ORR), disease control (DCR), and best overall response. Disease- and drug-related biomarkers were evaluated.

Results: Forty-two patients were treated; median age was 65 (range: 44—79), and 64% had ≥2 prior lines of therapy. Median duration of ABBV-637 treatment was 113 days (range: 28—288). Most common TEAEs were increases in aspartate (38%) and alanine aminotransferase (33%), nausea (33%), and fatigue (21%). The ORR was 14% in 3L cohorts and 10% in 2L (Table). DCR was 73% and 65% in 3L and 2L, respectively. In 2L, confirmed responders did not have targetable bypass alterations.

Table: 1318MO

Characteristic	Total (N=42)	
Safety, n (%)		
TEAEs	41 (98)	
Grade ≥3	17 (40)	
ABBV-637-related deaths	0 (0)	
Preliminary efficacy, n (%)	**Cohort A†+ Bi‡ (3L) (n=22)**	**Cohort Bii§ (2L) (n=20)**
Best overall response*		
Complete response (CR)	0 (0)	0 (0)
Partial response — all (PR)	5 (23)	3 (15)
Partial response — confirmed (cPR)	3 (14)	2 (10)
Stable disease (SD)	11 (50)	10 (50)
Progressive disease	6 (27)	7 (35)
Objective response rate (CR+cPR)	3 (14)	2 (10)
Disease control rate (PR+SD)	16 (73)	13 (65)

*Based on RECIST 1.1; †dose escalation (3L; n=5); ‡dose expansion (3L; n=17); §dose expansion (2L). 2L, 2nd-line therapy (post osimertinib alone); 3L, 3rd-line therapy (post osimertinib and platinum chemotherapy).

Conclusions: ABBV-637 plus OSI showed clinical activity and a manageable safety profile in patients with RR NSCLC. Biomarker data suggest that response to ABBV-637 plus OSI may be enriched by excluding patients with targetable bypass mechanisms; ongoing research is needed to confirm association of mutation and patient selection.

Clinical trial identification: NCT04721015.

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1319MO Intracranial efficacy of HER3-DXd in patients with previously treated advanced EGFR-mutated NSCLC: Results from HERTHENA-Lung01

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Background: For patients (pts) with *EGFR*-mutated NSCLC after failure of EGFR TKI and platinum-based chemotherapy (PBC), available therapies provide limited benefit. CNS metastases occur in the majority of these pts and portend a poor prognosis. HER3-DXd (patritumab deruxtecan) is an antibody-drug conjugate consisting of a fully human monoclonal antibody to HER3 attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker. In the phase 2 HERTHENA-Lung01 trial (NCT04619004), HER3-DXd showed promising efficacy and a manageable safety profile in pts with advanced *EGFR*-mutated NSCLC following an EGFR TKI and PBC. Pts with stable brain metastases (treated or untreated) were included. We report an exploratory analysis of intracranial efficacy.

Methods: In pts (N=225) treated with HER3-DXd 5.6 mg/kg IV Q3W, intracranial responses were assessed by blinded independent central review of cranial CT/MRI (CNS BICR; per CNS RECIST) at baseline, every 6 wk to wk 24, every 12 wk thereafter.

Results: 95 pts had brain metastases at baseline; 23 had measurable target lesions and 72 only had nontarget lesions. Pts had a median of 3 (range, 1-11) prior systemic therapies in the advanced setting. As of 21 Nov 2022, median study duration was 13.1 (range, 9.0-20.5) mo, median treatment duration was 4.2 (range, 0.7-14.7) mo. CNS BICR confirmed objective response rate (cORR) was 20% (Table; in pts with no prior radiotherapy to the brain, cORR was 37%). Median duration of response was 8.5 mo. 60% of pts had a CNS best objective response of SD and 14% had PD. In pts with target lesions, 15/23 had a reduction in the sum of diameters (cORR, 22%).

Table: 1319MO

CNS BICR	All pts (N=95)	Prior local CNS-directed radiotherapy		
		<6 mo from start (n=36)	≥6 mo from start (n=29)	None (n=30)
cORR, n (%) [95% CI][a]	19 (20.0) [12.5-29.5]	5 (13.9) [4.7-29.5]	3 (10.3) [2.2-27.4]	11 (36.7) [19.9-56.1]
CR, n (%)[b]	15 (15.8)	3 (8.3)	2 (6.9)	10 (33.3)
PR, n (%)	4 (4.2)	2 (5.6)	1 (3.4)	1 (3.3)
SD/non-CR/non-PD, n (%)	57 (60.0)	25 (69.4)	20 (69.0)	12 (40.0)
PD, n (%)	13 (13.7)	5 (13.9)	4 (13.8)	4 (13.3)
NE, n (%)	6 (6.3)	1 (2.8)	2 (6.9)	3 (10.0)
DOR, median (95% CI), mo	8.5 (8.1-NE)	NE (NE-NE)	8.1 (2.8-NE)	8.4 (5.8-NE)

CR, complete response; DOR, duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease. [a] CR + PR. [b] 11 pts with CR only had nontarget lesions

Conclusions: HER3-DXd demonstrated efficacy in *EGFR*-mutated NSCLC CNS metastases, with durable responses. These data add to the growing body of evidence that systemic treatment is feasible in pts with brain metastases and support further investigation of HER3-DXd in this context.

Clinical trial identification: NCT04619004.

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1320MO Early evidence of efficacy in patients (pts) with non-small cell lung cancer (NSCLC) with HER2 exon20 insertion (ex20ins) mutations treated in a phase I study with BAY 2927088

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Background: BAY 2927088, an oral, reversible, potent tyrosine kinase inhibitor, has anti-tumour activity against *EGFR* and *HER2* mutations, including ex20ins, in preclinical models. Here we report preliminary safety and efficacy of BAY 2927088 in pts with *EGFR*- or *HER2*-mutant NSCLC.

Methods: This is an ongoing, open-label, multicentre, first-in-human, phase I trial. Eligible pts must have advanced NSCLC with an *EGFR* and/or *HER2* mutation and disease progression after ≥1 systemic treatment. BAY 2927088 is orally administered daily in 21-day cycles and follows a Bayesian adaptive dose-selection model. Backfill is concurrent and includes escalation doses found to be safe and potentially efficacious. The primary objectives of the study are safety, tolerability, pharmacokinetics and maximum tolerated dose. Secondary objectives include the overall response rate (ORR) and the recommended phase II dose. Data cut-off was 18 August 2023.

Results: A total of 76 pts from the dose-escalation/backfill phases were evaluable for safety. 59% were female, median age 60 (range 35-81) years, and 72% never smokers. 97% of pts had received ≥1 systemic anti-cancer treatment. *EGFR* and *HER2* ex20ins mutations were present in 18% and 26% of pts, respectively. Five dose-limiting toxicities were reported in 5 pts. Overall, 87%/25% of pts had drug-related any-grade/grade 3-4 treatment-emergent adverse events (TEAEs). No pts had drug-related TEAEs leading to treatment discontinuation. The most common drug-related TEAEs were diarrhoea (75%, mainly grade 1-2), paronychia (25%) and dry skin (22%). The ORR was 26% overall (18/69, including 4 unconfirmed partial responses [uPR]). Of note, the ORR was 60%, including 1 complete response, 8 PR and 3 uPR, in 20 evaluable pts with *HER2* ex20ins mutant disease.

Conclusions: In an early phase I analysis of pts with *EGFR*- or *HER2*-mutant NSCLC, BAY 2927088 demonstrated a manageable safety profile up to 60 mg daily. In pts with *HER2* ex20ins mutant disease, BAY 2927088 showed encouraging preliminary antitumour activity. These results warrant further investigation of BAY 2927088 in pts with NSCLC.

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1321MO Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2 (ERBB2)-mutant (HER2m) metastatic non–small cell lung cancer (NSCLC) with and without brain metastases (BMs): Pooled analyses from DESTINY-Lung01 and DESTINY-Lung02

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Background: ~20% of pts with HER2m NSCLC have BM at metastatic diagnosis. T-DXd is the first HER2-directed therapy for pts with pretreated, advanced HER2m NSCLC. We report post hoc pooled analyses of T-DXd efficacy/safety in this population with vs without baseline (BL) BMs from DESTINY-Lung01 (DL-01) and DESTINY-Lung02 (DL-02).

Methods: Pts with and without BMs were evaluated from the DL-01 (data cutoff [DCO], Dec 3, 2021) HER2m cohort (6.4 mg/kg; 35 and 56 pts) and the DL-02 (DCO, Dec 23, 2022) cohorts treated with T-DXd 5.4 mg/kg (32 and 70 pts) or 6.4 mg/kg (19 and 31 pts); 6.4 mg/kg arms were pooled. Pts with stable BL BMs (asymptomatic; not requiring treatment) were eligible. Tumor assessments were performed every 6 weeks (MRI/CT). Systemic objective response rates (ORRs), duration of response (DoR), sites of progression, and treatment-emergent adverse events (TEAEs) were determined in pts with and without BL BMs. Intracranial (IC)-ORR, IC-DCR, and IC-DoR were analyzed in pts with measurable and nonmeasurable BL BMs.

Results: 31% and 38% of pts given T-DXd 5.4 mg/kg and 6.4 mg/kg, respectively, had detectable BL BMs, among whom 46.9% and 55.6% had untreated BMs. Systemic ORRs were similar (Table). IC-ORRs were 25.0% (5.4 mg/kg) and 18.5% (6.4 mg/kg) with complete IC responses in 4 and 1 pts. In pts with BL BMs, IC progression occurred in 13/32 and 20/54 pts on T-DXd 5.4 mg/kg and 6.4 mg/kg, respectively; in pts without BL BMs, 1/70 and 8/87 had IC progression. Generally similar safety outcomes were seen in pts with vs without BMs, with a trend of higher rates of grade ≥3 TEAEs in pts with BMs (64.5% vs 47.1% [5.4 mg/kg]; 75.9% vs 63.2% [6.4 mg/kg]).

Conclusions: T-DXd showed IC activity in pts with metastatic HER2m NSCLC, some with complete IC responses. The presence of BL BMs did not impact systemic response among pts treated with T-DXd.

Table: 1321MO Efficacy summary

	T-DXd 5.4 mg/kg (DL-02)		T-DXd 6.4 mg/kg (DL-01/DL-02 pooled)	
	BM n = 32	Non-BM n = 70	BM n = 54	Non-BM n = 87
Confirmed systemic ORR, n (%)	15 (46.9)	35 (50.0)	27 (50.0)	51 (58.6)
DCR, n (%)	29 (90.6)	66 (94.3)	50 (92.6)	80 (92.0)
DoR, median, months	4.6	16.8	7.2	14.1
IC-ORR,[a] n (%)	8 (25.0)	–	10 (18.5)	–
CR	4 (12.5)	–	1 (1.9)	–
PR	4 (12.5)	–	9 (16.7)	–
SD	18 (56.3)	–	31 (57.4)	–
PD	3 (9.4)	–	4 (7.4)	–
IC-DCR,[a] n (%)	26 (81.3)	–	4 (7.4)	–
IC-DoR, median, months	9.2	–	4.4	–

[a]IC response per modified RECIST v1.1; all measurable brain lesions were considered target lesions. Nonmeasurable BL BMs only: 18/32 (5.4 mg/kg); 24/54 (6.4 mg/kg).

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Employment: Nippon Boehringer Ingelheim Co. Ltd.. K. Nakagawa: Financial Interests, Personal, Invited Speaker: Ono Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., MSD K.K., Pfizer Japan Inc., Nippon Boehringer Ingelheim Co., Ltd., Taiho Pharmaceutical Co.,Ltd., Bayer Yakuhin, Ltd., Incyte biosciences Japan, Merck Biopharma Co., Ltd., Janssen Pharmaceutical K.K., Bristol Myers Squibb Company, Medical Mobile Communications Co., Ltd, Novartis Pharma K.K., Daiichi Sankyo Co., Ltd.; Financial Interests, Personal, Advisory Board: Ono Pharmaceutical Co.,Ltd., Eli Lilly Japan K.K.; Financial Interests, Personal, Writing Engagement: Yodosha Co., Ltd.; Financial Interests, Institutional, Research Grant: Amgen Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co.,Ltd., EP-CRSU Co., Ltd., EPS Corporation., Eisai Co., Ltd., GSK K.K., MSD K.K., IQVIA Services Japan K.K., Janssen Pharmaceutical K.K., Kobayashi Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co.,Ltd., Nippon Kayaku Co.,Ltd., Sanofi K.K., PRA Healthsciences, SRL Medisearch Inc., Syneos Health Clinical K.K., Taiho Pharmaceutical Co.,Ltd., Takeda Pharmaceutical Co.,Ltd., CMIC Co., Ltd., Pfizer R&D Japan G.K., Labcorp Development Japan K.K., Pfizer Japan Inc., Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., Ascent Development Services, Eisai Inc., Bayer Yakuhin, Ltd. M. Nagasaka: Financial Interests, Personal, Advisory Board: AstraZeneca, Daiichi Sankyo, Novartis, EMD Serona, Pfizer, Eli Lilly, Genentech; Financial Interests, Personal, Other, Consultant for tumor board: Caris Life Sciences; Financial Interests, Personal, Speaker's Bureau: Takeda, Janssen, Mirati, Blueprint Medicine; Non-Financial Interests, Personal, Other, Travel Support: AnHeart Therapeutics. K.M.C. Pereira: Financial Interests, Personal, Full or part-time Employment: Daiichi Sankyo. A. Taguchi: Financial Interests, Personal, Stocks/Shares: Daiichi Sankyo Co., Ltd.; Financial Interests, Personal, Full or part-time Employment: Daiichi Sankyo Co., Ltd. A. Ali: Financial Interests, Personal, Full or part-time Employment: Daiichi Sankyo. M. Karnoub: Financial Interests, Personal, Full or part-time Employment: Daiichi Sankyo. R. Yonemochi: Financial Interests, Personal, Full or part-time Employment: Daiichi Sankyo. P.A. Jänne: Financial Interests, Personal, Advisory Role: AstraZeneca, Pfizer, Roche/Genentech, Chugai Pharmaceuticals, Eli Lilly, SFJ Pharmaceuticals, Voronoi, Biocartis, Novartis, Sanofi, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Bayer, Eisai, Allorion Therapeutics, Accutar Biotech, AbbVie, Monte Rosa, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotechnology, Duality; Financial Interests, Personal, Funding: Boehringer Ingelheim; Financial Interests, Personal and Institutional, Funding: Daiichi Sankyo, Takeda Oncology; Financial Interests, Personal, Advisory Board: Mirati Therapeutics; Financial Interests, Personal, Stocks/Shares: Gatekeeper Pharmaceuticals; Financial Interests, Institutional, Funding: Puma; Financial Interests, Personal, Invited Speaker: Revolution Medicines; Financial Interests, Personal, Royalties: LabCorp. All other authors have declared no conflicts of interest.

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1322MO Insights into tumour dissemination and progression using longitudinal Imaging and ctDNA in the TRACERx lung cancer study

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Background: Longitudinal imaging and circulating tumour DNA (ctDNA) can map tumour growth and patterns of metastatic spread on a lesion-by-lesion level. In this study, we investigated the role of ctDNA as a biomarker in monitoring tumour growth in 102 metastatic lung cancer patients enrolled in the TRACERx study, tracking volumetric dynamics of 341 metastases.

Methods: Patients were categorised based on total volume growth rate: Slow >100mm3/day, Stable <100mm3/day and Rapid >600mm3/day. Individual metastases within patients were categorised into 'High' and 'Low' growth rate based on the median growth rate for all lesions across the cohort. In addition, RNAseq data from 122 regions belonging to 44 metastases mapped to imaging at autopsy were analysed in 13 patients enrolled in the PEACE study. For 28 patients, ctDNA was used to track 200 clonal or subclonal mutations in 214 plasma samples to assess total disease burden and metastatic subclones.

Results: Growth rate correlated with number of lesions at relapse and overall survival (OS). Median OS was 55.0, 25.4 and 8.5 months for Slow, Stable and Rapid classes respectively ($p<0.001$). Gene set enrichment analysis demonstrated enrichment in signalling pathways associated with cell proliferation when comparing the gene expression patterns between 'high' and 'low' growth rate lesions. Early postsurgical ctDNA detection was associated with higher ctDNA shedding at disease relapse. Total ctDNA tracked with tumour volume in the post-relapse setting, and patients with extrathoracic relapse showed higher ctDNA shedding. For eight patients in the PEACE cohort, we assessed the subclonal composition of ctDNA, tracking lesions with specific subclones detected at autopsy. These subclones were mapped to metastatic lesions measured on imaging. ctDNA subclonal fraction tracked with changes in tumour volume upon treatment response and subsequent progression. For all eight patients' lesion-specific subclones could be detected from day 1 post-surgery prior to detection by radiological imaging.

Conclusions: Our results demonstrate that ctDNA can accurately reproduce observed patterns of metastatic growth on imaging, suggesting it can be used in the detection and monitoring of metastatic disease.

Clinical trial identification: The TRACERx study (NCT01888601) is a prospective observational cohort study and PEACE (NCT03004755) is a national research autopsy programme, both approved by independent research ethics committees (13/LO/1546 and 13/LO/0972/AM05, respectively).

Legal entity responsible for the study: Cancer Research UK.

Funding: Cancer Research UK.

Disclosure: A. Hackshaw: Financial Interests, Institutional, Advisory Role: Roche. C.Z. Abbosh: Financial Interests, Institutional, Full or part-time Employment: AstraZeneca; Financial Interests, Institutional, Invited Speaker: AstraZeneca, Bristol Myers Squibb; Financial Interests, Personal, Other, PCT/GB2017/053289: Patent Application; Financial Interests, Personal, Other, PCT/US2017/028013: Patent Application; Financial Interests, Personal, Other, PCT/EP2022/077987: Patent Application. A.M. Frankell: Financial Interests, Personal, Other, PCT/EP2022/077987: Patent application. C. Swanton: Financial Interests, Personal, Invited Speaker, Activity took place in 2016.: Pfizer, Celgene; Financial Interests, Personal, Invited Speaker, October 26th 2020: Novartis; Financial Interests, Personal, Invited Speaker: Roche/Ventana, BMS, AstraZeneca, MSD, Illumina, GSK; Financial Interests, Personal, Advisory Board, AdBoard - November 12th, 2020: Amgen; Financial Interests, Personal, Advisory Board, Current - since 2018: Genentech; Financial Interests, Personal, Advisory Board: Sarah Canon Research Institute; Financial Interests, Personal, Advisory Board, Joined October 2020 . Also have stock options: Bicycle Therapeutics; Financial Interests, Personal, Other, Consultancy: Medicxi; Financial Interests, Personal, Advisory Board, Member of the Science Advisory Board. Also had stock options until June 2021: GRAIL; Financial Interests, Personal, Other, Consultancy agreement: Roche Innovation Centre Shanghai; Financial Interests, Personal, Advisory Board, 29 November - 1 December 2022: Novartis; Financial Interests, Personal, Invited Speaker, Oncology Collective - 2nd Nov - 4 Nov 2022 - Atlanta, USA: Roche; Financial Interests, Personal, Advisory Board, ctDNA Advisory Board - 24th March 2023: AstraZeneca; Financial Interests, Personal, Invited Speaker, Pfizer Oncology 'Leading the revolution for the future: Pfizer; Financial Interests, Personal, Full or part-time Employment, Chief Clinician since October 2017: Cancer Research UK; Financial Interests, Personal, Ownership Interest, Co-Founder of Achilles Therapeutics. Also, have stock options in this company: Achilles Therapeutics; Financial Interests, Personal, Stocks/Shares, Stocks owned until June 2021: GRAIL, Apogen Biotechnologies; Financial Interests, Personal, Stocks/Shares: Epic Biosciences, Bicycle Therapeutics; Financial Interests, Institutional, Research Grant, Funded Rubicon grant - October 2018 - April 2021.: Bristol Myers Squibb; Financial Interests, Institutional, Research Grant, Collaboration in minimal residual disease sequencing technologies.: Archer Dx Inc; Financial Interests, Institutional, Research Grant: Pfizer, Boehringer Ingelheim; Financial Interests, Institutional, Invited Speaker, Chief Investigator for the MeRmaiD 1and 2 clinical trials and chair of the steering committee.: AstraZeneca; Financial Interests, Institutional, Research Grant, Research grant from Oct 2019 - July 2023 - Genetics of CIN and SCNAs for Targeted Discovery (SCEPTRE): Ono Pharmaceutical; Financial Interests, Institutional, Research Grant, Research Grants from 2015: Roche; Financial Interests, Personal, Other, Co-chief investigator: NHS-Galleri Clinical Trial; Financial Interests, Institutional, Research Grant, from October 2022: Personalis; Non-Financial Interests, Principal Investigator, Chief Investigator for MeRmaiD 1and 2 clinical trials: AstraZeneca; Non-Financial Interests, Member of Board of Directors, From 2019-2022: AACR; Non-Financial Interests, Other, Board of Directors: AACR; Non-Financial Interests, Advisory Role, EACR Advisory Council member: EACR. M. Jamal-Hanjani: Financial Interests, Personal, Invited Speaker, Invited speaker honorarium: Oslo Cancer Cluster, Astex Pharmaceutical; Financial Interests, Personal, Invited Speaker, Speaker honorarium: Pfizer, Bristol Myers Squibb; Non-Financial Interests, Advisory Role, Scientific Advisory Board and Steering Committee member: Achilles Therapeutics; Other, I am named as co-inventor on patent PCT/US2017/028013 relating to methods for lung cancer detection: Patent. All other authors have declared no conflicts of interest.

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1323MO Immune evasion across space and time in patients with lung cancer enrolled in the PEACE autopsy study

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Background: Checkpoint inhibitors (CPIs) improve survival of patients with metastatic non-small cell lung cancer (NSCLC). However, in many patients the duration of response is limited, and some patients derive no benefit at all. Among key determinants of CPI response are genomic alterations that impair the anti-tumour immune response. In primary NSCLC these alterations are common. However, due to challenges collecting metastasis samples, the prevalence and distribution of these alterations across metastases within patients, and how this impacts response to CPI is not known.

Methods: The PEACE autopsy study in tandem with the TRACERx study enables multiregion tumour sampling from diagnosis of NSCLC to death, allowing immune evasive capacity to be tracked across space and time. We performed exome sequencing on 84 primary tumour regions and 320 metastases from 21 patients recruited to these studies. Mutations and copy number alterations were called with our bioinformatic pipeline and used to infer tumour clones in each sample, their phylogenetic relationship and metastatic migration history. The neoantigen landscape and genomic alterations in genes involved in immune evasion ('IE alterations') were then characterised in each clone.

Results: We find IE alterations are frequent in metastases and emerge via distinct evolutionary paths. In a subset of patients, immune evasive primary tumour clones seed metastases, giving rise to metastases with poor T cell infiltrate that share IE alterations with the primary. In others, primary tumour seeding clones do not harbour IE alterations. Compared to patients with shared IE alterations, these patients' metastases have higher T cell infiltrate and acquire more metastasis unique IE alterations after seeding. Measuring the radiological growth of individual metastases in 7 of these patients treated with CPIs in the DARWIN II trial, we observe homogenous

progression of metastases in patients with shared IE alterations, while patients with metastasis unique IE alterations exhibit heterogeneous metastasis growth rates.

Conclusions: When IE alterations occur in relation to metastatic seeding dictates the distribution of immune evasive capacity across metastases, which impacts metastasis growth during CPI therapy.

Clinical trial identification: PEACE - NCT03004755, TRACERx - NCT01888601, DARWIN II - NCT02314481.

Legal entity responsible for the study: UCL Clinical Trials Centre.

Funding: The PEACE study and TRACERx study are funded by Cancer Research UK (grants C416/A21999 and C11496/A17786, respectively). The PEACE study is additionally supported by funding from the Rosetrees Trust (grant A2204). A subset of patients in this work were treated with immunotherapy on the DARWIN II study, which is an academic study sponsored by UCL funded by funded by Hoffman La Roche.

Disclosure: D. Moore: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, Takeda; Financial Interests, Personal, Advisory Role: Thermo Fisher, Eli Lilly, Amgen, Janssen, MIM Software, Bristol Myers Squibb. N. McGranahan: Financial Interests, Institutional, Stocks/Shares: Achilles Therapeutics. C. Hiley: Financial Interests, Personal, Invited Speaker: AstraZeneca. C. Swanton: Financial Interests, Personal, Invited Speaker, Activity took place in 2016: Pfizer, Celgene; Financial Interests, Personal, Invited Speaker, October 26th 2020: Novartis; Financial Interests, Personal, Invited Speaker: Roche/Ventana, BMS, AstraZeneca, MSD, Illumina, GSK; Financial Interests, Personal, Advisory Board, AdBoard - November 12th, 2020: Amgen; Financial Interests, Personal, Advisory Board, Current - since 2018: Genentech; Financial Interests, Personal, Advisory Board: Sarah Canon Research Institute; Financial Interests, Personal, Advisory Board, Joined October 2020 . Also have stock options: Bicycle Therapeutics; Financial Interests, Personal, Other, Consultancy: Medicxi; Financial Interests, Personal, Advisory Board, Member of the Science Advisory Board. Also had stock options until June 2021: GRAIL; Financial Interests, Personal, Other, Consultancy agreement: Roche Innovation Centre Shanghai; Financial Interests, Personal, Advisory Board, 29 November - 1 December 2022: Novartis; Financial Interests, Personal, Invited Speaker, Oncology Collective - 2nd Nov - 4 Nov 2022 - Atlanta, USA: Roche; Financial Interests, Personal, Advisory Board, ctDNA advisory Board - 24th March 2023: AstraZeneca; Financial Interests, Personal, Invited Speaker, Pfizer Oncology 'Leading the revolution for the future: Pfizer; Financial Interests, Personal, Full or part-time Employment, Chief Clinician since October 2017: Cancer Research UK; Financial Interests, Personal, Ownership Interest, Co-Founder of Achilles Therapeutics. Also, have stock options in this company.: Achilles Therapeutics; Financial Interests, Personal, Stocks/Shares, Stocks owned until June 2021: GRAIL, Apogen Biotechnologies; Financial Interests, Personal, Stocks/Shares: Epic Biosciences, Bicycle Therapeutics; Financial Interests, Institutional, Research Grant, Funded RUBICON grant - October 2018 - April 2021: Bristol Myers Squibb; Financial Interests, Institutional, Research Grant, Collaboration in minimal residual disease sequencing technologies.: Archer Dx Inc; Financial Interests, Institutional, Research Grant: Pfizer, Boehringer Ingelheim; Financial Interests, Institutional, Trial Chair, Chief Investigator for the MeRmaiD 1and 2 clinical trials and chair of the steering committee.: AstraZeneca; Financial Interests, Institutional, Research Grant, Research grant from Oct 2019 - July 2023 - Genetics of CIN and SCNAs for Targeted Discovery (SCEPTRE): Ono Pharmaceutical; Financial Interests, Institutional, Research Grant, Research Grants from 2015: Roche; Financial Interests, Personal, Other, Co-chief investigator: NHS-Galleri Clinical Trial; Financial Interests, Institutional, Research Grant, from October 2022: Personalis; Non-Financial Interests, Principal Investigator, Chief Investigator for MeRmaiD 1and 2 clinical trials: AstraZeneca; Non-Financial Interests, Member of Board of Directors, From 2019-2022: AACR; Non-Financial Interests, Other, Board of Directors: AACR; Non-Financial Interests, Advisory Role, EACR Advisory Council member: EACR. M. Jamal-Hanjani: Financial Interests, Personal, Invited Speaker, Invited speaker honorarium: Oslo Cancer Cluster, Astex Pharmaceutical; Financial Interests, Personal, Invited Speaker, Speaker honorarium: Pfizer, Bristol Myers Squibb; Non-Financial Interests, Advisory Role, Scientific Advisory Board and Steering Committee member: Achilles Therapeutics; Other, I am named as co-inventor on patent PCT/US2017/028013 relating to methods for lung cancer detection: Patent. All other authors have declared no conflicts of interest.

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1324MO CNS outcomes of lazertinib vs gefitinib in EGFR-mutated advanced NSCLC: A LASER301 subset analysis

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Background: Up to 50% of patients (pts) with non-small cell lung cancer (NSCLC) develop central nervous system (CNS) metastases (mets), which are a major source of mortality in NSCLC. Lazertinib (laz), a CNS-active 3rd-generation (gen) tyrosine kinase inhibitor (TKI) targeting mutant epidermal growth factor receptor (EGFR), improved progression-free survival (PFS) vs the 1st-gen TKI gefitinib (gef) in the LASER301 study. Here, we compared laz vs gef among LASER301 pts with CNS mets.

Methods: In the phase 3 LASER301 study (NCT04248829), treatment (tx)-naïve pts with EGFR-mutated advanced or metastatic NSCLC were randomized 1:1 to laz (240 mg/day) or gef (250 mg/day). Pts with symptomatic/unstable CNS mets were excluded. If tx was required for pts with asymptomatic/stable CNS mets, radiation and/or surgery, and steroids were completed >2 weeks before randomization. Magnetic resonance imaging was performed at screening, every 6 weeks for 18 months (mo), then every 12 weeks relative to randomization, using the same modality at each follow-up. Endpoints assessed by blinded independent central review and RECIST v1.1 included intracranial PFS (iPFS), intracranial objective response rate (iORR), intracranial duration of response (iDoR), and depth of intracranial response.

Results: Of 393 pts in LASER301, 45 (23%) receiving laz and 41 (21%) receiving gef had measurable and/or non-measurable baseline (BL) CNS mets. BL characteristics were balanced between groups, with most pts having 1−3 CNS lesions (laz: 91%, gef: 83%). Median BL target lesion size was 20.0 mm (laz) and 16.0 mm (gef). Median iPFS in the laz group was 28.2 mo (95% confidence interval [CI]: 14.8, 28.2) vs 8.4 mo (6.7, not reached [NR]) in the gef group (hazard ratio: 0.42; 95% CI: 0.20, 0.89; P=0.02). iORR was higher for the laz (n=17, 94%) vs gef (n=11, 73%) group. At data cutoff, median iDoR in the laz group was NR (8.3, NR) vs 6.3 mo (2.8, NR) in the gef group. The median best change from BL in CNS target lesion size was -57% and -47% for laz (n=17) and gef (n=14), respectively. No new safety signals were identified from LASER301.

Conclusions: In pts with BL CNS mets, laz significantly improved iPFS vs gef with more durable responses. Laz has the potential to improve CNS outcomes in NSCLC.

Clinical trial identification: NCT04248829.

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Legal entity responsible for the study: Yuhan Corporation.

Funding: Yuhan Corporation.

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Pfizer, AstraZeneca, MSD, Yuhan; Financial Interests, Personal, Research Funding: MSD. A. Zimina: Non-Financial Interests, Principal Investigator, Participation as PI in Yuhan LASER-301 trial: Yuhan. Y. Lee: Financial Interests, Personal, Speaker's Bureau: Pfizer, Boryung, Eli Lilly, Takeda; Financial Interests, Personal, Other, Consultant: Ono, Takeda, Yuhan, Guardant Health. L. Yueh Ni: Financial Interests, Personal, Other, Panel of Discussion for Hepatocellular Carcinoma: AstraZeneca; Financial Interests, Personal, Advisory Board, Advisory Board Meeting for early breast cancer management in our current practice.: Roche; Financial Interests, Personal and Institutional, Local PI, Research Title: A multicentre, open-label, single-arm, molecular profiling study of patient with EGFR mutation-positive locally advanced or metastatic NSCLC treated with Osimertinib: AstraZeneca; Financial Interests, Personal and Institutional, Local PI, Research Title: A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937): MSD; Financial Interests, Personal and Institutional, Local PI, Research Title: A Phase III, Randomized, Double-blind Study to Assess the Efficacy and Safety of Lazertinib versus Gefitinib as the First-line Treatment in Patients with Epidermal Growth Factor Receptor Sensitizing Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer: Yuhan; Financial Interests, Personal and Institutional, Local PI, Research Title: A phase II randomized study of the combination of Ribociclib plus goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer - RIGHT Choice Study: Novartis; Financial Interests, Personal and Institutional, Local PI, Research Title: A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1+ Non-Small Cell Lung Cancer: Regeneron; Financial Interests, Personal and Institutional, Local PI, Research Title: A Phase 3 study to Evaluate Zimberelimab (AB122) Monotherapy Compared to Standard Chemotherapy or Zimberelimab Combined with AB 154 in Front-Line, PD-L1 Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer: Arcus; Financial Interests, Personal and Institutional, Local PI, Research Title: A Prospective, Multicenter, Non-Interventional Genomic Profiling Study in Subjects with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) using Foundation Medicine: Roche; Financial Interests, Personal and Institutional, Local PI, Research Title: A Phase 3, randomize, double-blind trial of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) in participants with treatment naive, metastatic non-small cell lung cancer (NSCLC) whose tumors have a tumor proportion score (TPS) greater than or equal to 1% (LEAP-007): MSD. Y.K. Pang: Financial Interests, Personal, Research Funding: MSD, AstraZeneca, Sanofi.; Financial Interests, Personal, Speaker's Bureau: Pfizer; Financial Interests, Personal, Advisory Board: Novartis, Specialised Therapeutics, MSD, Boehringer Ingelheim, Sanofi-Aventis, Orient Europharma, Eurodrug Laboratories.. C.H. Fong: Financial Interests, Personal, Local PI, Investigator fees: Yuhan Corporation, Janssen Research & Development, LLC, Arcus Biosciences, Inc., Novartis Pharmaceuticals, Hoffmann-La Roche. J.H. Kang: Financial Interests, Personal, Advisory Board: Amgen, AstraZeneca, Merck, Daiichi Sankyo; Financial Interests, Personal, Invited Speaker: Boeringer Ingelheim, Roche, MSD, Ono, Yuhan, Takeda; Financial Interests, Personal, Research Grant: ONO, Daiichi Sankyo, Boeringer Ingelheim; Financial Interests, Personal, Steering Committee Member: Yuhan. P. Danchaivijitr: Financial Interests, Personal, Speaker's Bureau: MSD, Roche, AstraZeneca, BMS; Financial Interests, Personal, Advisory Board: MSD, Roche, AstraZeneca, BMS. H. Lee: Financial Interests, Personal, Full or part-time Employment: Yuhan. S. Park: Financial Interests, Personal, Full or part-time Employment: Yuhan Co. I. Cicin: Other, Principal investigator: Jounce Therapeutic. All other authors have declared no conflicts of interest.

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1325P Sunvozertinib as first-line treatment in NSCLC patients with EGFR Exon20 insertion mutations

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Background: Sunvozertinib (DZD9008) is a rationally designed, irreversible EGFR inhibitor targeting *EGFR* mutations with wild-type EGFR selectivity. Primary analysis of two ongoing pivotal studies (WU-KONG1 [NCT03974022] and WU-KONG6 [NCT05712902 & CTR20211009]) have demonstrated promising efficacy and safety of sunvozertinib in advanced NSCLC patients with *EGFR* Exon20 insertion mutations (exon20ins) in $\geq 2^{nd}$ line settings. Herein, we reported preliminary results of sunvozertinib in treatment naïve *EGFR* exon20ins NSCLC.

Methods: NSCLC patients with *EGFR* exon20ins who did not receive prior systemic anti-cancer therapy were enrolled into two ongoing studies: WU-KONG1, a multinational phase I/II study; and WU-KONG15 (NCT05559645), a phase II investigator-initiated study. Sunvozertinib was administered orally at 200 mg or 300 mg QD until discontinuation criteria were met. Efficacy analysis included patients with at least one post-treatment tumor assessment according to RECIST 1.1 by independent review committee (IRC).

Results: As of February 21, 2023, a total of 28 patients were included in the efficacy analysis (200 mg, n = 19; 300 mg, n = 9). Median age was 67 years, and 75.0% (21/28) were female. Baseline ECOG PS was 0 or 1. Majority of patients (96.4%, 27/28) had metastatic diseases at study entry, with 21.4% (6/28) having > 3 metastatic sites and 32.1% (9/28) having baseline brain metastasis (BM). The most frequent mutation subtypes included 769_ASV (39.3%, 11/28), 770_SVD (10.7%, 3/28) and others. By IRC, 20 patients achieved tumor response, with a best objective response rate (ORR) of 71.4% (200 mg, 68.4%; 300 mg, 77.8%). Median duration of response has not been reached. Safety findings were consistent with results of previous sunvozertinib studies. The most common TEAEs included diarrhea, CPK increase, and skin rash. Majority of the AEs were of CTCAE grade 1 or 2, and clinically manageable.

Conclusions: In the 1st line setting, sunvozertinib as monotherapy demonstrated promising anti-tumor efficacy and acceptable safety profile in NSCLC patients with *EGFR* exon20ins. A phase III, multinational, randomized study (WU-KONG28, NCT05668988) is ongoing to compare sunvozertinib to chemotherapy as 1st line treatment for *EGFR* exon20ins NSCLC.

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Legal entity responsible for the study: Dizal Pharmaceutical.

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1326P Osimertinib in patients with EGFR-mutated NSCLC and leptomeningeal or brain metastases: Results of the IFCT-1804 ORBITAL trial

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Background: Advanced Non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations are at an increased risk of developing central nervous system (CNS) metastases, which can lead to significant morbidity and mortality. Although osimertinib is the recommended first-line treatment in this population, its efficacy in treating CNS metastases has been poorly studied.

Methods: ORBITAL is a multicenter phase II trial investigating the efficacy and safety of osimertinib 80 mg/d in EGFR-mutated NSCLC patients with leptomeningeal metastases (cohort 1) or patients with brain metastases who have not received prior EGFR-Tyrosine kinase inhibitor or radiation therapy (cohort 2). The primary endpoint was objective response rate (ORR) at 6 months, secondary endpoints included progressionfree survival (PFS), overall survival (OS), CNS ORR and CNS PFS. Brain magnetic resonance imaging (MRI) was performed every 6 weeks during first year and then every 8 weeks.

Results: 53 patients were included (8 patients in cohort 1 and 45 patients in cohort 2, 70% were female and 62% never smokers). Median age was 68 years. EGFR mutations were mostly del19 (60.4%) and L858R (30.2%). The number of previous lines of therapy was ≥1 in 75% of patients in cohort 1 and 11.1% in cohort 2. The median follow-up time was 11.2 months in cohort 1 and 19.8 months in cohort 2. ORR at 6 months was 37.5% (n=3/8, CI95%: 4.0%-71.0%) in cohort 1 and 60% (n=27/45, CI95%: 45.7%-74.3%) in cohort 2. Median PFS was 7.4 months [CI95%: 2.7-NR] (12-month PFS: 21.4%) and 12.6 months [CI95%: 6.9-26.2] (12-month PFS: 52.2%), in cohort 1 and 2 respectively. Median OS was 7.4 months [CI95%: 2.7-NR] (12-month OS: 46.9%) and 30.3 months [CI95%: 15.6-NR] (12-month OS: 74.7%), in cohort 1 and

2 respectively. In cohort 2, CNS ORR at 6 months was 57.8% (n=26/45, CI95%: 43.3%-72.2%) and CNS PFS was NR [CI95%: 9.7-NR]. Safety /tolerability were as expected with no new safety signal.

Conclusions: Osimertinib demonstrated clinically meaningful responses in patients with EGFR-mutated NSCLC against both leptomeningeal and brain metastases. Safety profile was acceptable and manageable. Tumour and blood samples will be analysed for exploratory biomarkers.

Clinical trial identification: EudraCT: 2019-002805-23.

Legal entity responsible for the study: IFCT (French Thoracic Intergroup).

Funding: AstraZeneca, IFCT.

Disclosure: D. Planchard: Financial Interests, Personal, Advisory Board: AstraZeneca, BMS, Merck, Novartis, Pfizer, Roche, Samsung, Celgene, AbbVie, Daiichi Sankyo, Janssen, Seagen, Gilead, Pierre Fabre; Financial Interests, Personal, Invited Speaker: AstraZeneca, Novartis, Pfizer, priME Oncology, Peer CME, Samsung, AbbVie, Janssen; Non-Financial Interests, Principal Investigator, Institutional financial interests: AstraZeneca, BMS, Merck, Novartis, Pfizer, Roche, Daiichi Sankyo, Sanofi-Aventis, Pierre Fabre; Non-Financial Interests, Principal Investigator: AbbVie, Sanofi, Janssen. A.C. Toffart: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, BMS, MSD, Sanofi; Financial Interests, Personal, Expert Testimony: AgirADom, Amgen, AstraZeneca, BMS, Ipsen, Janssen, Pfizer, Roche, Sanofi, Takeda; Financial Interests, Personal, Other, Support for attending meetings and/or travel: AstraZeneca, Roche, Takeda. A. Madroszyk Flandin: Financial Interests, Personal, Research Grant: AstraZeneca, Roche; Financial Interests, Personal, Expert Testimony: AstraZeneca, Roche; Financial Interests, Personal, Other, Support for attending meetings and/or travel: AstraZeneca, Pfizer. M. Wislez: Financial Interests, Personal, Speaker, Consultant, Advisor: Amgen, BMS, MSD, AstraZeneca, Roche, Lilly; Financial Interests, Personal, Financially compensated role: Sanofi, Amgen, BMS, MSD, AstraZeneca, Sanofi, Lilly. S. Hiret: Financial Interests, Institutional, Advisory Board: BMS, Takeda, AstraZeneca, Sanofi, Roche; Financial Interests, Institutional, Other, support for attending meeting: Novartis. V. Gounant: Financial Interests, Personal, Other, Personal fees: MSD, Chugai, Novartis, Boehringer, AstraZeneca, BMS, Takeda, Pfizer; Non-Financial Interests, Personal, Non-financial benefits: AstraZeneca, BMS, Takeda, Pfizer. E. Giroux-Leprieur: Financial Interests, Personal, Speaker, Consultant, Advisor: Amgen, AstraZeneca, Ipsen, Lilly, MSD, Novartis, Pfizer, Sanofi, Takeda; Financial Interests, Personal, Other, Support for attending meetings and/or travel: Takeda, MSD, AstraZeneca, Roche. P. Tomasini: Financial Interests, Speaker, Consultant, Advisor: AstraZeneca, Roche, Amgen, JNJ; Financial Interests, Other, Support for attending meetings and/or travel: AstraZeneca, BMS. C. Mascaux: Financial Interests, Personal, Other, Honoraria: Roche, AstraZeneca, BMS, Pfizer, Sanofi, MSD, Takeda, Janssen; Financial Interests, Personal, Speaker, Consultant, Advisor: Roche, Sanofi, Takeda, Pfizer, BMS, MSD, AstraZeneca, Kephren, Amgen, Janssen, GSK; Financial Interests, Personal, Other, Travel: MSD; Non-Financial Interests, Personal, Non remunerated activity: Boehringer Ingelheim. V. Westeel: Financial Interests, Personal, Speaker, Consultant, Advisor: Amgen, Amgen, AstraZeneca, BMS, MSD, Roche, Sanofi; Financial Interests, Personal, Other, Support for attending meetings and/or travel: AstraZeneca, BMS, Janssen, MSD, Roche, Sanofi; Financial Interests, Personal, Other, Participation on a Data Safety Monitoring Board or Advisory Board: Amgen, AstraZeneca, Ipsen. A. Cortot: Financial Interests, Personal, Advisory Board: Novartis, Pfizer, Takeda, Janssen; Financial Interests, Personal, Other, IDMC: Roche, Novartis; Financial Interests, Personal, Speaker, Consultant, Advisor: Pfizer, Takeda, Amgen, AstraZeneca, Roche; Financial Interests, Personal, Other, Training: Novartis. All other authors have declared no conflicts of interest.

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1327P First-line osimertinib in patients with EGFR mutated lung cancer with uncommon mutations (OCELOT study – interim analysis)

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Background: The results of the FLAURA study established osimertinib as the new first-line (1L) standard of care for patients with the two 'common' types of epidermal growth factor receptor mutation-positive (EGFR+) advanced non-small-cell lung cancer (aNSCLC). Uncommon EGFR mutations (non-exon 19 del and L858R) occur in up to 20% of patients; however, the efficacy of osimertinib in this population is not well understood. To date, small prospective studies, retrospective case series, and case reports have signaled that osimertinib has a role in the treatment of patients with uncommon EGFR mutations.

Methods: This is a multicentered Canadian phase II investigator-initiated study of (cohort A) osimertinib in the third-line (3L) rechallenge of patients with EGFR+ aNSCLC, following 1L treatment with osimertinib and 2L therapy with platinum pemetrexed chemotherapy; and (cohort B) 1L osimertinib in patients with uncommon EGFR mutations (exon 20 insertions are not permitted). Cohort B has a planned accrual of 85 patients. The primary endpoint is objective response rate (ORR) in 3L osimertinib rechallenge; 1L ORR in patients with uncommon mutations is a key secondary endpoint. The OCELOT study, NCT04335292, is continuing to enroll participants.

Results: 74 patients have been accrued to date, including 35 in Cohort B. At the time of preparation, 22 had evaluable disease. The most frequent 'uncommon' EGFR mutation was G719X (n=11), followed by L861X (n=8) and S768I (n=5). The confirmed ORR was 45% and disease control rate (DCR) was 77%. Confirmed ORR/DCR for evaluable patients with G719X (n=11), L861X (n=3) and S768I (n=5) mutations were 45%/73%, 100%/100%, and 60%/100%, respectively. Updated data including ORR, progression free survival, time to treatment failure and 1-year over survival rate will be presented. Safety and toxicity profile is consistent with published data on osimertinib.

Conclusions: Osimertinib appears to be highly active and well tolerated in patients with the more frequent 'uncommon' EGFR mutations (G719X, L861X, and S768I). The OCELOT study will be the largest study to date of 1L osimertinib in patients with EGFR+ aNSCLC harboring uncommon mutations.

Clinical trial identification: NCT04335292.

Legal entity responsible for the study: Dr. Mark Vincent.

Funding: AstraZeneca.

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1328P Analysis of data from the AENEAS study assessing the third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), aumolertinib, and virtual comparison with osimertinib

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Background: TKIs targeting the EGFR revolutionized care of patients (pts) with non-small cell lung cancer (NSCLC) harboring EGFR mutations. Resistance to 1st/2nd-generation EGFR TKIs inevitably develops, with clone(s) harboring T790M EGFR mutations emerging in 50–70% of cases. 3rd-generation EGFR TKIs active against T790M and common EGFR-activating mutations are in development; only osimertinib and aumolertinib have regulatory approvals.

Methods: We have described a novel approach for assessing treatment efficacy using measurements of tumor burden to estimate rates of growth and regression of tumors designated ***g*** and ***d***, respectively. Data from thousands of pts with diverse tumors have shown ***g*** is inversely correlated with OS. We analyzed data from the randomized phase III AENEAS study comparing aumolertinib with gefitinib.

Results: 94% of the data could be analyzed; notably more pts than included for the primary PFS endpoint. Tumor growth reflected in a detectable ***g*** was found in 89% of both arms, including many not scored as progression. Superiority of aumolertinib was evident in statistically slower ***g*** values [and longer tumor doubling times, TDT] for aumolertinib [***g*** = 0.0006/day (0.0005-0.0011); TDT 1155 days] than gefitinib, [***g*** = 0.0012/day (0.0007-0.0020); TDT, 578 days], p<0.0001. Aumolertinib was superior in slowing ***g*** in tumors with Ex19del alterations compared to L858R mutations [p=0.0018], and superior to gefitinib in slowing ***g*** in tumors with Ex19del alterations [p<0.0001] just missing significance for L858R mutations [p=0.0687] – possibly due to smaller number of pts. Aumolertinib slowed ***g*** in non-smokers compared to smokers [p=0.0066] and superior to gefitinib in slowing ***g*** in non-smokers [p<0.0001]. Finally, ***g*** values with aumolertinib were comparable to published osimertinib values.

Table: 1328P Median *rate of tumor growth (g)* by line and type of therapy

Line of therapy	Type of therapy	N	Median *g*/day	Tumor Doubling Time
Data from USFDA Analysis [Gong, ASCO 2020]				
Front	Mono 1stGen EGFRi*	237	0.0012/day	578 days
Front	Osimertinib	243	0.0007/day	990 days
Data from analysis of AENEAS study				
Front	Gefitinib	215	0.0012/day	578 days
Front	Aumolertinib	214	0.0006/day	1155 days

*1st generation EGFR inhibitors, gefitinib or erlotinib

Conclusions: Like osimertinib, aumolertinib is a highly effective third-generation EGFR-TKI.

Clinical trial identification: NCT03849768.

Legal entity responsible for the study: Hansoh Pharmaceutical Group Co, Ltd.

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1329P FIND: A phase II study to evaluate the efficacy of erdafitinib in FGFR-altered NSCLC

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Background: Alterations in FGFR1-4 genes have oncogenic capability with sensitivity to kinase inhibition in several solid tumours and hematological malignancies. FGFR alterations occur in approximately 2% of non-small cell lung cancer (NSCLC) patients (pts), predominantly with squamous cell histology (sqNSCLC). We present results of a study evaluating the efficacy of the selective FGFR1-4 inhibitor erdafitinib in pts with FGFR-altered NSCLC.

Methods: NSCLC pts were screened within the national Network of Genomic Medicine for FGFR mutations/translocations. Molecular eligibility was based on available preclinical and clinical data to FGFR alterations and assessed by a study specific molecular board. Pts were treated with erdafitinib in 3 cohorts: High confidence activating FGFR translocations (1), high confidence activating FGFR mutations (2) and low confidence activating FGFR alterations (3). The primary objective was the best confirmed overall response (OR) on erdafitinib in the cohorts 1 and 2 assessed by RECIST 1.1 every 8 weeks. Pts were treated until disease progression or unacceptable toxicity. Tumor samples and blood were collected before treatment and at disease progression. Sample size calculation was based on Simon's two-stage minimax design. Evidence of efficacy was defined as 1/8 OR in the first and 4/15 ORs in the second stage for cohort 1 and 2 separately.

Results: Between 7/2019 and 9/2022, 26 pts were enrolled, 4 pts failed screening. The majority of pts were male (77%) and had sqNSCLC (73%). All pts were current or previous smokers. Of 22 pts on erdafitinib, 7 were in the cohort 1, 8 in the cohort 2 and 7 pts in the cohort 3. FGFR3-TACC3 fusions were the most frequent genetic alterations. In the cohort 1, two pts achieved partial response (PR). However, one PR remained unconfirmed (uPR). The best response in the cohort 2 was stable disease. The most observed adverse events of any grade were hyperphosphatemia in 50% and diarrhea in 45% of pts.

Conclusions: According to the first stage results of the two-stage Simon's design, erdafitinib showed preliminary efficacy in NSCLC with FGFR translocations. Further molecular, pharmacological and clinical data are needed to evaluate the efficacy of FGFR inhibition in NSCLC, especially in pts with FGFR mutations.

Clinical trial identification: EudraCT: 2018-000399-13.

Legal entity responsible for the study: University of Cologne.

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1330P Updated results of the efficacy and safety of KN046 (a bispecific anti-PD-L1/CTLA-4) in patients with metastatic non-small cell lung cancer (NSCLC) who failed prior EGFR-TKI(s)

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Background: KN046 is a novel bispecific antibody that inhibits both PD-L1/PD1 and CTLA-4/CD80/CD86 pathways. We previously showed the efficacy and safety of KN046 plus chemotherapy in advanced NSCLC with EGFR sensitivity mutation who progressed after tyrosine kinase inhibitor(s) (TKIs) from Cohort D of the phase II trial. Here, we report the updated survival and safety data.

Methods: This is an open-label, multi-center, multiple cohorts, single arm study to evaluate the efficacy, safety and tolerability of KN046 in NSCLC. Subjects with EGFR sensitizing mutation (Ex19del or L858R), who had failed from prior EGFR-TKI(s) without platinum-based chemotherapy were enrolled. All subjects enrolled received KN046 5 mg/kg Q3W combined with chemotherapy (Pemetrexed, 500 mg/m^2, Q3W

and carboplatin AUC5, Q3W), until disease progression, intolerable toxicity and other discontinuation criteria. Primary endpoint was objective confirmed response rate (ORR) per RECIST version 1.1.

Results: From Jan 7, 2020 to Dec 17, 2021, 26 patients with metastatic NSCLC were enrolled. The median follow-up was 17.8 months (95% CI, 13.0, 19.5) at the data cutoff of Jul 30, 2022. The ORR was 26.9% (7/26, 95% CI, 11.6 , 47.8%), DCR was 84.6% (22/26, 95% CI, 65.1, 95.6%) with 7 PR and 15 SD. The CBR was 38.5% (10/26, 95% CI, 20.2, 59.4%). The mPFS was 5.5 months (95% CI, 4.2, 6.8) and the mOS was 20.2 months (95% CI, 11.5, -). Grade 3 or higher TRAEs occurred in 15 (57.7%) of the 26 patients due to chemotherapy or KN046. The most common grade 3 or higher TRAEs were infusion reaction (5/26 [19.2%]), decreased platelet count (4/26 [15.4%]) and anemia (3/26 [11.5%]).

Conclusions: KN046 demonstrated encouraging OS benefit and a favorable safety profile in advanced NSCLC with EGFR sensitivity mutation who progressed after EGFR-TKI(s). Further study is warranted to confirm the clinical results.

Clinical trial identification: NCT03838848.

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1331P Resistance mechanisms in EGFR-mutated advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with first-line osimertinib (osi) and monitoring plasma mutational load: Preliminary results of REM study

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Background: The ongoing REM trial is a translational prospective multicenter Italian study aiming to monitor *EGFR*-mutated pts through liquid biopsy and explore potential mechanisms of primary and acquired resistance.

Methods: *EGFR*-mutated aNSCLC pts receiving first-line osi are prospectively enrolled. Plasma samples are collected before starting treatment (T0), after 10 (T1) and 28 days (T2) and at the time of radiological/clinical progression (T3). *EGFR* mutations (mut) in plasma are analyzed by real-time polymerase chain reaction (RT-PCR) and by next-generation sequencing (NGS). A semiquantitative index (SQI) is given by the RT-PCR, related to the amount of EGFR mut cell-free DNA (cfDNA) present in plasma sample. Change from baseline in EGFR SQI is considered as a difference from baseline to different time-points (T0—T1 and T0—T2).

Results: Since August 2022, 34 pts were included (data cut-off March 2023): mainly females (N=24, 70.6%) and never smokers (N=23, 67.6%); median age at diagnosis was 70.5 years (IQR 67-77). The majority of pts had a common*EGFR* mut (exon 19 deletion: N=18, 52.9%; L858R mut N=12, 35.3%). The objective response rate was 70.6% (95% CI, 52.5-84.9), while survival data were immature at time of analysis. The concordance between tissue and plasma was 76.5% (95% CI, 58.9-89.3). A higher tumour burden (defined as 3 or more metastatic sites at diagnosis) was related to higher SQI at T0 (OR 3.12, 95% CI: 2.70-12.81, p=0.004). Clearance of plasma *EGFR* mut at T2 was detected in 20 out of 26 pts (76.9%). A correlation between change in EGFR SQI and response rate was found: a decrease of baseline EGFR SQI (T0-T2) >=50% was associated with increased probability of reaching an objective response (OR: 13.5, 95% CI: 1.1- 165.9, *p*=0.042). Two pts experienced radiological progression at first assessment and both had no clearance at T2.

Conclusions: *EGFR* mut monitoring 10 days after the start of first-line osi has the potential to be used as predictive marker in order to personalize treatment of *EGFR*-mutated aNSCLC pts. Updated results including NGS analyses at T0 and correlation of co-mutations in cfDNA with outcome will be presented at the Conference.

Clinical trial identification: CESC IOV 2021-107-PU.

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1332P Efficacy and safety of gefitinib plus bevacizumab versus gefitinib monotherapy in patients with EGFR L858R mutant non-small cell lung cancer (NSCLC): A randomized, open-controlled, single-center trial

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Background: Dual inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor pathways may be a potential therapeutic strategy for EGFR mutant NSCLC. This study was conducted to assess the efficacy and safety of gefitinib (Gef) plus bevacizumab (Bev) for EGFR L858R mutation-positive NSCLC.

Methods: 80 patients were randomly assigned to receive either Gef at 250 mg/day alone (group G, n = 39) or with Bev at 7.5 mg/kg every 3 weeks (group GB, n = 41). The primary endpoints were safety and progression-free survival (PFS), and the secondary endpoint was objective response rate (ORR). Genomic biomarkers and resistance mechanism were investigated.

Results: There was a significant reduction in the risk for progression in the group GB compared with the group G (HR = 0.49) with the median PFS (mPFS) of 15.1 vs. 8.2 mon (P =0.0031). The ORR was significantly higher in group GB than in group G (90.2% vs. 59.0%, P = 0.005). Adverse events were similar between two groups (85.4% vs. 70.7%, P=0.27). ctDNA status at 43 days after treatment initiation (D43) was associated with PFS, which was longer in patients with ctDNA negative (-) at D43 than those with ctDNA positive (+) at D43 in both groups (17.0 vs. 12.2 mon, P=0.008 in group GB; 10.2 vs. 4.3 mon, P<0.001 in group G). In 67 patients with matched baseline (BS) and D43 plasma samples, patients were divided into three groups: BS ctDNA- and D43 ctDNA- for type A, BS ctDNA+ and D43 ctDNA- for type B, and BS ctDNA+ and D43 ctDNA+ for type C. In type B, ORR was significantly higher in the group GB than in group G (100% vs. 64.7%, P=0.008). Type B had a comparable PFS with type A, both significantly longer than type C in both groups (mPFS 19.1, 18.8 and 11.2 mon for type A, B and C, P=0.016 in group GB; 15.9, 10.2 and 4.7 mon for type A, B and C, P<0.001 in group G). Post-progression samples from the group G showed a trend toward to higher frequency of T790M mutations compared with the group GB (70.6% vs. 38.5%, P=0.13).

Conclusions: Combined therapy of gefitinib with bevacizumab exhibited a significant improvement in PFS in patients with EGFR L858R mutant NSCLC. The post-treatment ctDNA and dynamic change were potential biomarkers of efficacy.

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1333P A global phase 1b study of ORIC-114, a highly selective, brain penetrant EGFR and HER2 inhibitor, in patients with advanced solid tumors harboring EGFR Exon 20 or HER2 alterations

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Background: Insertion mutations within exon 20 of both EGFR and HER2 are oncogenic drivers and are most commonly found in NSCLC. EGFR exon 20 insertion mutations occur in 4-10% of all EGFR-mutated NSCLC. Brain metastases are present in approximately one-third or more of these cases but are not addressed by available therapies directed against these mutations. ORIC-114 is a highly selective, brain penetrant, orally bioavailable, irreversible inhibitor designed to selectively target EGFR and HER2 with high potency against exon 20 insertion mutations, making it a promising therapeutic candidate to address the unmet medical need of having both meaningful systemic as well as CNS antitumor activity.

Methods: ORIC-114-01 (NCT05315700) is an ongoing i3+3 dose escalation (Part I), followed by dose optimization (Part II), and dose expansion (Part III) study in patients with advanced solid tumors harboring an EGFR or HER2 alteration who have exhausted available treatment options, including patients with active brain metastases. Primary objectives are safety/tolerability and pharmacokinetics of ORIC-114. Part I will determine the provisional RP2Ds and/or MTD for optimization in Part II and, subsequently, the optimal RP2D for Part III. Secondary endpoints will evaluate antitumor activity by RECIST v1.1, including intracranial responses in patients presenting with brain metastases at baseline.

Results: As of 03 April 2023, 32 patients received ORIC-114 across 8 dose levels administered QD or BID. The most common TRAEs reported in $\geq$10% of pts were rash (34%), stomatitis (28%), paronychia (25%), diarrhea (19%), dermatitis acneiform (16%), mucosal inflammation (13%), and pruritis (13%). The vast majority of these events were mild (G1) to moderate (G2) in severity with no MTD reached. Grade 3 TRAEs occurred in 6 patients, all of which resolved with dose modifications; there were no Grade $\geq$4 TRAEs. Early evidence of both systemic and intracranial antitumor activity was observed.

Conclusions: ORIC-114 has demonstrated an acceptable safety profile and preliminary antitumor activity, including in the CNS, at doses predicted to be active. Enrollment is ongoing and updated data will be presented.

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1334P Activity of first line immunotherapy or chemo-immunotherapy in advanced NSCLC with SMARCA4 deficiency

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Background: SMARCA4 deficient (SMARCA4d) non-small cell lung cancer (NSCLC) has a poor prognosis. The activity of first line immune-checkpoint blockers (ICB) or chemo-ICB and the potential impact of co-mutations is scarcely explored in patients with SMARCA4d NSCLC.

Methods: This is a monocentric, retrospective study evaluating patients with advanced NSCLC, screened for SMARCA4 alterations and treated with first line chemo-ICB or ICB alone. SMARCA4d was defined as loss of BRG1 in immunohistochemistry or the presence of deleterious *SMARCA4* in liquid or tissue biopsies assessed by next-generation sequencing. Progression-free survival (PFS), overall survival (OS) and the impact of co-mutations (*STK11, KEAP1*) were compared between patients with or without SMARCA4d.

Results: A total of 128 patients were included: 36 with SMARCA4d (12 in IHC, 31 in NGS, 7 both) and 92 without SMARCA4d (control group). Patients with SMARCA4d had a median age of 57 years, were male in 64% cases and smokers in 94% cases, similar to the control group. Histology type was adenocarcinoma in 53% versus 82% ($p<0.001$) in control, with more cases of undifferentiated or large cell neuroendocrine carcinoma in the SMARCA4d group. TMB value was 13 vs 5 mut/Mb ($p<0.001$), median PD-L1 expression was 0 vs 5% ($p=0.3$) in SMARCA4d versus control, with no differences in immune blood counts. *STK11* and *KEAP1* mutations were frequently co-mutated with SMARCA4d (53% vs 26%, $p=$ 0,01; 37% vs 13%, $p=$ 0,01, respectively. The median PFS under ICB+/- chemotherapy was 4.0 months (CI 95% 2.87- 7.7) vs 7.37 months (CI 95% 6.53-11.3) ($p=$ 0.005) in SMARCA4d versus control, and the median OS was 9.3 months (CI 95% 7.0 — NR) vs 27.6 months (CI 95% 27.3 - NA) ($p<$ 0.0001), respectively. In patients with *STK11/KEAP1* mutations, median OS was 7 months (95% CI 5-NR) versus 13.3 months (95% CI 10.5-35.8) ($p=0.19$) in SMARCA4 and control, respectively.

Conclusions: SMARCA4d seems to negatively impact survival outcomes and the efficacy of ICB, despite high TMB. Novel treatments are rapidly needed.

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1335P Phase Ib study to evaluate the safety and tolerability of osimertinib with ipilimumab in EGFRm NSCLC

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Background: Osimertinib (Osi) is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) indicated in the 1st line treatment of EGFR mutated(m) metastatic NSCLC (mNSCLC). Although the combination of Osi with PD-1/PD-L1 inhibitors is prohibitive due to excessive toxicity, combinations with other immune checkpoint inhibitors, such as CTLA4 inhibitor Ipilimumab (Ipi), remain largely unexplored. In a phase 1 trial, we evaluated the combination of EGFR TKI erlotinib and Ipi in EGFRm mNSCLC. The study was closed due to gastrointestinal dose-limiting toxicities (DLTs), but we observed unprecedented improvement in survival (median OS 42.3m). Based on this observation, we designed a phase 1 trial of Osi with Ipi in EGFRm mNSCLC. Here we present results from the dose escalation phase.

Methods: This is a single-center, phase 1B trial. Eligible pts required a stable dose of 1st line Osi (40 or 80mg/day) for >/= 28 days w/o disease progression. The trial was initiated with cohort1(C1), Osi daily + Ipi 3mg/kg/3 wk with a safety run of 6 pts and planned expansion at this dose if <=1/6 pts experience DLTs, but de-escalation to cohort 2 (C2), Osi daily + Ipi1mg/kg/3wk if >/= 2/6 pts experience DLTs. C2 would be expanded if <= 1/6 pts experienced DLTs, and trial would be closed if >/= 2/6 pts experience DLTs. The study's primary objective was to determine the tolerability (NCI CTCAEv5) of Osi + Ipi. Key secondary endpoints are ORR, PFS, and OS.

Results: 10 pts (4 C1;6 C2) were enrolled between 9/2020-3/2022. The majority of pts were never smoker, female 80%, white 100% with an ECOG of 1. 3 DLTs (1 G3 thromboembolic event, 2 G2 diarrhea) were observed in the 2/4 pts in C1, hence de-escalation C2 enrolled 6 additional pts. Most common all-grade TRAEs were diarrhea in 60% (6/10), fatigue, nail changes and rash (40%, 4/10 pts) each. G3-4 TRAEs were infrequently observed with G3 hepatitis, diarrhea, anorexia, and weight loss in 10% (1/10) pts each. Most G3 TRAEs were observed in C1. 1/6 pts (17%) experienced G3 weight loss in C2. C2 dose was selected for dose expansion (8 additional pts accrued to date).

Conclusions: In EGFRm NSCLC pts the combination of Osi with Ipi (1mg/kg/3wk) was safe and tolerable. This dose is currently undergoing additional evaluation in the dose expansion cohort.

Clinical trial identification: NCT04141644.

Legal entity responsible for the study: The Huntsman Cancer Institute at the University of Utah.

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1336P Small cell transformation in EGFR-mutated non-small cell lung cancer (EGFR+ NSCLC): Efficacy of immune checkpoint inhibitors or tyrosine kinase inhibitors combined with platinum-based chemotherapy

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Background: Given the broad application of 3rd generation tyrosine kinase inhibitors (TKI) as standard 1st line treatment for EGFR+ NSCLC, small cell transformation (SCT) as a mechanism of adaptive resistance is seen more frequently. Little is known about optimal treatment strategies and prognosis is generally poor in this subset of patients.

Methods: We conducted a retrospective study on the efficacy of different treatment strategies: platinum-based chemotherapy alone (C) vs. immune checkpoint inhibitors in combination with C (ICI+C) vs. tyrosine kinase inhibitors in combiation with C (TKI+C) in patients with EGFR+ NSCLC and SCT treated at 19 centers in Europe and the United States.

Results: Of a total of 40 patients, 16 received ICI+C, 9 TKI+C, and 15 C alone as first treatment after SCT. Median time from TKI initiation to SCT was 22 months. Half of the patients (48%) presented with brain metastases at the time of SCT. Overall response rate was 54% for ICI+C, 60% for TKI+C, and 46% for C alone. Median progression-free survival (PFS) was 5 months (95% confidence interval [CI] 3.2-6.8) for ICI+C, 6 months (CI 3.6-8.4) for TKI+C, and 4 months (CI 3.4-4.6) for C alone. Median overall survival (OS) from first SCT treatment was 18 months (CI 8.9-27.1) for ICI+C, 11 months (CI 9.8-12.1) for TKI+C, and 8 months (CI 5.3-10.6) for C alone. EGFR L858R subtype was associated with improved OS (Hazard ratio 0.31 [CI 0.11-0.85]). The impact of follow-up therapies will be presented at the conference.

Table: 1336P

	C	ICI + C	TKI +C
ORR (CI)	46%	54%	60%
PFS (months, CI)	4 (3.4-4.6)	5 (3.2-6.8)	6 (3.6-8.4)
OS (months, CI)	8 (5.3-10.6)	18 (8.9-27.1)	11 (9.8-12.1)
	Hazard ratio 0.44 (CI: 0.18-1.08)		

Conclusions: Although limited by its retrospective nature, our data suggest that combination therapies, ICI+C in particular, might be superior to C alone in EGFR+ NSCLC with SCT.

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1337P Real-world utilization and outcomes of dacomitinib as first-line therapy in Asian patients with advanced EGFR mutation−positive NSCLC: An interim analysis of the ARIA study

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Background: Dacomitinib, a second-generation, irreversible tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), provided statistically significant progression-free survival improvement over gefitinib in treatment-naive patients with advanced *EGFR* mutation−positive non-small cell lung cancer (NSCLC) in a global phase 3 study (ARCHER 1050; NCT01774721). Here, we report interim analysis of ARIA, a non-interventional study of dacomitinib's real-world (RW) utilization and associated clinical outcomes in Asian patients with advanced *EGFR* mutation−positive NSCLC.

Methods: This longitudinal, multicenter cohort study collected prospective and retrospective data from patients with advanced *EGFR* mutation−positive NSCLC who were treated with first-line (1L) dacomitinib based on routine practices and their best interest. Study objectives were to describe patient demographics and clinical characteristics, treatment patterns of dacomitinib use, and RW outcomes of 1L dacomitinib.

Results: 300 patients from China (n=262), India (n=24), and Malaysia (n=14) were enrolled and included in the analysis. Starting dose was 30 mg once daily (QD) in 159 patients (53%), 45 mg QD in 138 (46%), and other doses in 3 (1%). As of Jan 31, 2023, 81 patients (27.0%) had dose decreases, 13 (4.3%) dose increases, 35 (11.7%) interruptions, and 107 (35.7%) permanently discontinued dacomitinib. Six (2.0%) permanent treatment discontinuations were due to treatment-related toxicities. 1L dacomitinib safety and treatment outcomes are shown in the table.

Table: 1337P Safety and treatment outcomes of 1L dacomitinib

ITT population	Total (N=300)
Duration of 1L dacomitinib treatment, median (IQR), months	13.1 (11.8)
Patients with any TRAEs, n (%)	121 (40.3)
Most common TRAEs, n (%)	
Rash	74 (24.7)
Diarrhea	65 (21.7)
Paronychia	43 (14.3)
TTF, median (95% CI),[a] months	21.4 (17.3-35.9)
rwPFS, median (95% CI),[a] months	25.3 (20.1-NR)

1L, first line; IQR, interquartile range; ITT, intention to treat; NR, not reached; rwPFS, real-world progression-free survival; TRAE, treatment-related adverse event; TTF, time to treatment failure. [a] Calculated using the Kaplan-Meier method to obtain 95% confidence interval.

Conclusions: To our knowledge, this is the largest RW study conducted for dacomitinib. Interim analysis shows efficacy of 1L dacomitinib; safety data in the RW setting were generally consistent with dacomitinib's known safety profile. These results support 1L dacomitinib use in patients with advanced *EGFR* mutation−positive NSCLC.

Clinical trial identification: NCT04609319.

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1338P Cerebrospinal fluid pharmacokinetic study of lazertinib and pemetrexed in patients with EGFR-mutant non-small cell lung cancer with leptomeningeal metastases: KCSG21-01 LAZARUS trial

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Background: Lazertinib, an irreversible third-generation EGFR tyrosine kinase inhibitor (TKI), has shown high blood-brain barrier (BBB) penetration in preclinical studies. In this study, we present cerebrospinal fluid (CSF) pharmacokinetic (PK) study from a phase II trial investigating lazertinib and pemetrexed in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) patients with leptomeningeal metastases (LMs).

Methods: This is a single-arm, phase II study that enrolled patients with cytologically confirmed LM and EGFR-mutation. Patients were administered lazertinib at a daily dose of 240mg along with pemetrexed at a dose of 500mg/m^2 every 3weeks. The primary endpoint was post-LM overall survival (OS). Secondary endpoint included PK studies. To evaluate the through concentration of lazertinib, plasma and CSF samples were collected serially before the start of the 2nd and 3rd cycles. The concentration ratio of CSF to free plasma (FP) was analyzed.

Results: CSF and plasma PK samples were available from 32 patients. All the patients had previously failed treatment with 1st or 2nd generation EGFR TKIs. At the second cycle, the median CSF concentration was 1.05 ng/ml (range, 0.13-17.8 ng/ml), and the median plasma concentration was 213.2 ng/ml (range, 59.0-934.1 ng/ml). There was a correlation between the concentration of lazertinib in CSF and FP (r=0.38; P=0.032), with a mean CSF/FP concentration of 0.77 and a median CSF/FP concentration ratio of 0.5 (range: 0.09-6.0). At the third cycle, the median CSF concentration was 1.04 ng/ml (range, 0.07-139.0ng/ml), and the median plasma concentration was 212.3 ng/ml (range, 48.3-803.7 ng/ml). The mean CSF/FP concentration was 0.71, and the median CSF/FP concentration ratio was 0.45 (range: 0.09-4.28) at the third cycle.

Due to short follow-up time, there was no significant difference in CSF/FP concentration ratio and survival.

Conclusions: These results suggest that lazertinib had a promising CSF/FP concentration ratio in patients with EGFR-mutant NSCLC with LMs. Given its high potency for penetrating the BBB, lazertinib may be a therapeutic option for LMs from a pharmacokinetic perspective.

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1339P Real-world experience of dacomitinib in mEGFR Advanced NSCLC: A single centre experience

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Background: Dacomitinib, an irreversible tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), is approved in advanced non-small cell lung cancer (NSCLC) with mutated EGFR. Literature on real world experience of dacomitinib is lacking, especially in patients (pts) with brain metastasis and uncommon EGFR mutation.

Methods: This is single centre retrospective study of EGFR mutated advanced NSCLC pts treated with dacomitinib between July'19 and Feb'23. Clinicopathologic features, treatment details, toxicity and treatment outcome were recorded.

Results: Total 111 pts were treated with median age of 62 years (range: 39-82). ECOG performance status (PS) was 1 in 65 pts, 2 in 37 pts and 3 in 9 pts. 42 (38%, n=96) pts had brain metastasis and 21 pts received WBRT. Type of mutations was Del 19 in 66 pts, L858R in 35 pts, G719X in 4 pts, G719X and S768I in 2 pts, L861Q in 2 pts, and Del 19 + L858R, Exon 20ins + L858R in one patient each. Starting dose of dacomitinib was 45 mg in 43 pts and 30 mg in 68 pts (61%). Intracranial response (n=27) was − CR in 2 pts, PR in 18 pts, SD in 5 pts, and PD in 2 pts. 41 out of 52 pts underwent re-biopsy on progression, 17 pts had EGFR T790M mutation and 3 had small cell transformation. After a median follow-up of 19 months (95 CI: 14.4-23.2), the median PFS was 21.5 months (95% confidence interval [CI]: 18.7 − 26.2) and median overall survival (OS) was 31.2 months (95 CI: 23.4 − not reached). PFS was inferior in pts with brain metastases (p=0.003) and 30 mg starting dose (p=0.004), but not OS and neither with type of mutation or dose modification. 81(73%) pts had any grade of toxicity and 53 pts (47%) had any grade 2 & 3 toxicity. Total 25 pts (23%) required dose modification (Table).

Table: 1339P

Variables	Groups	HR	P
Progression-free survival			
Brain metastases	Absent (n=54)	1	
	Present (n=42)	2.9	0.003
	Not known (n=15)	1.4	0.53
Type of mutation	Del 19 (n=69)	1	
	L858R (n=34)	1.6	0.12
	Uncommon mutation (n=8)	1.5	0.47
Starting dose of dacomitinib	30 mg (n=68)	1	
	45 mg (n=43)	0.9	0.004
Dose modification	Not required (n=88)	1	
	Required (n=23)	0.6	0.14
Overall survival			
Brain metastases	Absent (n=54)	1	
	Present (n=42)	1.6	0.22
	Not known (n=15)	0.8	0.7
Type of mutation	Del 19 (n=69)	1	
	L858R (n=34)	1.5	0.32
	Uncommon mutation (n=8)	1.6	0.48
Starting dose of dacomitinib	30 mg (n=68)	1	
	45 mg (n=43)	1	0.8
Dose modification	Not required (n=88)	1	
	Required (n=23)	0.9	0.9

Conclusions: To best of our knowledge, this is largest real-world study of dacomitinib in mEGFR advanced NSCLC. Dacomitinib is active in pts with brain metastasis, uncommon EGFR mutation, in patients with poor PS, and at 30 mg starting dose. Dacomitinib showed very good PFS with manageable safety profile.

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1340P Propensity score matching analysis for osimertinib versus comparator first-generation EGFR tyrosine kinase inhibitors as first-line treatment in patients with advanced EGFR-mutated non−small cell lung cancer: A Chinese, multicenter, real-world cohort study

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Background: The phase 3 FLAURA trial compared osimertinib with either erlotinib or gefitinib in the first-line treatment of EGFR-mutant lung adenocarcinoma and showed longer PFS, OS and a similar safety profile. However, the efficacy and safety of osimertinib as a first-line treatment still need to be investigated in a real-world setting.

Methods: 1556 patients with EGFR-mutated non−small cell lung cancer (NSCLC) who received osimertinib or a first-generation EGFR tyrosine kinase inhibitor (TKI) as first-line treatment were identified from the CAPTRA-Lung database. 1:2 propensity score matching (PSM) was used to adjust for clinical bias. Progression-free survival (PFS) and overall survival (OS) were compared using Kaplan-Meier analysis. Cox proportional hazards regression was used to identify factors associated with progression and survival.

Results: 202 patients receiving osimertinib and 404 patients receiving first-line EGFR TKIs were enrolled. The objective response rate (ORR) was 63.4% vs. 48.0% (P<0.001) and the disease control rate (DCR) was 95.5% vs. 96.8% (P=0.443) in the osimertinib arm and the comparator arm separately. Median progression-free survival was 19.4 months (95% confidence interval [CI], 14.3 to 24.4) in the osimertinib arm and 10.9 months (95% CI, 9.3 to 12.5) in the comparator arm (hazard ratio for progression, 0.47; 95% CI, 0.38 to 0.59; P < 0.001). Median overall survival was 40.5 months (95% CI, 27.1 to 54.0) versus 34.3 months (95% CI, 30.6 to 38.0) in the osimertinib and comparator groups, respectively (hazard ratio for death, 0.76; 95% CI, 0.58 to 1.00; P = 0.045). Most adverse events were mild and there were no treatment-related deaths. Patients treated with osimertinib showed a similar safety profile to the comparator EGFR TKIs.

Conclusions: In the real-world setting, osimertinib also demonstrated longer PFS, OS and a similar safety profile to comparator EGFR TKIs when given as first-line treatment to NSCLC patients.

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1341P Real-world molecular testing, treatment patterns and clinical outcomes in Chinese advanced NSCLC patients, who have progressed on first-line EGFR-TKI therapy (PISCES)

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Background: The aim of PISCES study is to assess the molecular testing, treatment patterns and clinical outcomes among Chinese patients progressed on first-line (1L) EGFR-TKI monotherapy in real-world setting.

Methods: This prospective study enrolled *EGFR* mutant, locally advanced or metastatic NSCLC patients progressed on 1L EGFR-TKI monotherapy from May 2020 to May 2021 in 16 Chinese hospitals. The treatment patterns and clinical outcomes were recorded.

Results: 292 patients received 1L EGFR-TKI monotherapy were enrolled. 93.8% (274/292) of patients received first/second generation (1/2G) EGFR-TKI and 6.2% (18/292) received third generation (3G) EGFR-TKI. 74.8% (205/274) of patients who progressed on 1L 1/2G EGFR-TKI underwent genetic testing, and 47.8% (98/205) of them were T790M positive (T790M+). 91.8% (90/98) of T790M+ patients received 3G EGFR-TKI as 2L therapy. Among the 107 patients with T790M negative (T790M-), 47.8% (51/107) received 3G EGFR-TKI, 25.2% (27/107) received chemotherapy and 8.4% (9/107) received prior 1/2G EGFR-TKI plus local therapy as 2L therapy. Among 18 patients progressed on 1L 3G EGFR-TKI, half (9/18) of them received chemotherapy, 27.8% (5/18) switched to another 3G EGFR-TKI. The overall median PFS (mPFS) of patients who had received 2L treatment was 9.1 months (95%CI, 7.6-11.2). The mPFS of patients receiving 2L 3G EGFR-TKI, prior 1/2G EGFR-TKI plus local therapy, and chemotherapy was 10.5 months (95%CI, 8.7-13.7), 10.2 months (95%CI, 5.3-19.2) and 5.5 months (95%CI, 3.3-8.6), respectively. Among those receiving 2L 3G EGFR-TKI treatment, T790M+ patients achieved significantly longer mPFS compared to T790M- patients (13.7 vs 7.6 months, P=0.012). For patients with T790M-, the mPFS was comparable (7.6 vs 5.5 months, P=0.07) when received 3G EGFR-TKI and chemotherapy as 2L therapy.

Conclusions: Most patients progressed on 1L EGFR-TKI monotherapy underwent genetic testing in Chinese real-world setting. The vast majority of T790M+ patients received 3G EGFR-TKIs treatment. Although almost half of T790M- patients received 3G EGFR-TKI as 2L therapy, these patients achieved suboptimal clinical outcome.

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1342P Effect of the timing of intervention in craniocerebral radiotherapy on prognosis of patients with EGFR-mutant lung adenocarcinoma with brain metastasis

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Background: The probability of brain metastasis (BMs) in lung cancer patients with epidermal growth factor receptor (EGFR) mutation is always high. Craniocerebral radiotherapy is the cornerstone for the treatment of BM, which plays an indispensable role together with EGFR-TKI. However, the timing of intervention in craniocerebral radiotherapy has always been a controversial issue. The purpose of this study was to evaluate the efficacy of craniocerebral radiotherapy in patients with EGFR mutant lung adenocarcinoma BM before and after EGFR-TKI resistance.

Methods: A total of 217 patients with advanced non-small cell lung cancer (NSCLC) and EGFR mutations were enrolled in this retrospective cohort study. Propensity score matching (PSM) was conducted using a nearest-neighbor algorithm (1:1) to adjust for demographic and clinical covariates. The patients were divided into two groups according to the timing of craniocerebral radiotherapy intervention.: before EGFR-TKI resistance and after EGFR-TKI resistance. Intracranial progression-free survival (iPFS) and overall survival (OS) were calculated. Kaplan—Meier analysis was used to compare iPFS and OS between the two groups. Brain radiotherapy included WBRT, local radiotherapy, and WBRT+Boost.

Results: The median age at diagnosis was 54 years (range: 32—81 years). Most patients were female (65.9%) and non-smokers (77.4%). Eighty-nine pairs of patients were matched using PSM. The median iPFS for before EGFR-TKI resistance (n=46) and after EGFR-TKI resistance (n=46) was 17.9 and 9.5 months, respectively(P=0.0376). The median OS for before EGFR-TKI resistance (n=89) and after EGFR-TKI resistance (n=89) was 36.9 and 42.1 months, respectively(P=0.6626).

Conclusions: In *EGFR*-mutant lung adenocarcinoma patients with BM, craniocerebral radiotherapy before EGFR resistance is beneficial to the prolongation of iPFS in patients, but this prolongation does not translate into the benefit of OS.

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1343P Amivantimab as a salvage strategy post TKI (osimertinib/mobocertinib) in EGFRm NSCLC

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Background: Amivantamab is a dual EGFR and MET inhibitor that has been approved for EGFR exon 20 mutations. Osimertinib-treated EGFRm patients may progress through cMET amplification. In such circumstances, amivantamab may be a salvage therapy. Here, we present 13 patients who received amivantamab on top of their previous EGFR TKI for disease progression (Group A - common EGFRm+ & Group B - EGFR Exon20+).

Methods: A retrospective case series study at Shaare Zedek Medical Center between October 2021 and March 2023 of patients who received amivantamab on top of previous EGFR TKI on progression outside of clinical trial after local IRB approval. The study aim to present safety as well as preliminary efficacy. Patient records served as the basis for data collection, PET-CT or CT scans were used to assess systemic response, and for followup. ORR was defined by RECIST 1.1.

Results: 13 pts, 4 male 9 female, median age 65 years (range 45-73). 9 had common mutation (Group A) and 4 uncommon (Group B). 8 group A pts had osimertinib as last line, one afatinib while in Group B 3 pts had mobocertinib, and 1 had poziotinib. Amivantamab was administered on top of previous line in all pts (Table). The objective response rate (ORR) was 37.5% in group A and 25% in group B. Median duration of therapy (mDOT) was 2.3 months in group A and 5.5 months in group B (long — rank p value 0.38), The median progression-free survival was 4.7 months in both groups. Safety profile was driven mainly by amivantamab where grade $\geq$3 toxicity was nausea, diarrhoea, and skin rash (mainly scalp). 16% patients had a grade 3 infusion reaction.

Conclusions: Incorporating amivantamab to prior EGFR TKI treatment appears to be a feasible option, although osimertinib stands out as the most well-tolerated TKI with clinical efficacy. Further studies should aim to identify patient subgroups and confirm these findings through prospective analysis.

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1344P A real-world (rw) observational study of long-term survival (LTS) and treatment patterns after first-line (1L) osimertinib in patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive (m) advanced non-small cell lung cancer (NSCLC)

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Background: Osimertinib, a third-generation, irreversible, central nervous system-active, EGFR tyrosine kinase inhibitor (TKI) that selectively inhibits EGFR-TKI sensitising and EGFR T790M resistance mutations, is the preferred 1L treatment for EGFRm advanced NSCLC. We present results from the US cohort of a global rw observational study of LTS and treatment patterns after 1L osimertinib in advanced EGFRm NSCLC.

Methods: Adults with stage IIIB—IV EGFRm NSCLC who initiated 1L osimertinib monotherapy between Apr 2018—Mar 2020 were identified from the Flatiron Health database. Primary endpoints: overall survival (OS), time to next treatment or death (TTNTD) and treatment patterns; secondary endpoints: baseline characteristics and time to treatment discontinuation (TTD; a rw progression-free survival [PFS] surrogate). OS, TTNTD and TTD were also assessed in a subset of pts aligned with the FLAURA trial (NCT02296125) inclusion criteria (FLAURA-like cohort). Endpoints were reported descriptively.

Results: Among 773 pts, median age was 70 yrs (interquartile range [IQR] 61—78), 68% were female, 59% were White, 54% had no/unknown smoking history, 64% had ECOG PS 0 or 1 and 89% had Exon 19 deletion or L858R EGFR mutations. With a median follow-up of 24 mos (IQR 10—36), median OS, TTNTD and TTD (95% confidence interval [CI]) for all pts were 29.8 mos (27.2—32.1), 18.5 mos (17.0—21.3) and 16.3 mos (15.0—18.1), and for the FLAURA-like cohort (n=453) were 33.3 mos (30.0—37.2), 22.3 mos (18.5—25.2) and 19.4 mos (16.4—23.0), respectively. Overall, 39% of pts received subsequent therapy (Table).

Table: 1344P

Subsequent therapy received, n (%)	All pts (N=773)
Yes	299 (39)
No	
Remained on 1L osimertinib	173 (22)
Discontinued 1L osimertinib	50 (6)
Died	251 (32)
Therapy received	
2L therapy	**(n=299)**
IO + CT	74 (25)
Osimertinib + CT	47 (16)
CT	39 (13)
1G or 2G EGFR-TKI	33 (11)
IO	28 (9)
Other	78 (26)
3L therapy	**(n=138)**
IO + CT	24 (17)
Osimertinib + CT	15 (11)
CT	28 (20)
1G or 2G EGFR-TKI	14 (10)
IO	11 (8)
Other	46 (33)

Percentages have been rounded to the nearest whole number and may not sum to 100%. 1G, first-generation; 1L, first-line; 2G, second-generation; 2L, second-line; 3L, third-line; CT, chemotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; IO, immunotherapy; pts, patients.

Conclusions: In a large rw cohort of pts with EGFRm advanced NSCLC treated with 1L osimertinib, median OS and TTD were consistent with median OS and PFS in FLAURA (Ramalingam NEJM 2020 ; Soria NEJM 2018), reinforcing the effectiveness of osimertinib in the real world.

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1345P Preclinical activity of ORIC-114, a highly selective, brain penetrant, irreversible kinase inhibitor, against atypical mutations in EGFR

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Background: EGFR mutations are oncogenic drivers commonly found in non-small cell lung cancer (NSCLC). Patients with atypical mutations in EGFR have a worse prognosis than those with classical mutations and need effective therapies. In addition to exon 20 insertion mutations in EGFR, another related category of atypical mutations are P-loop and alpha C-helix compressing (PACC) mutations, the majority of which lack approved therapies. ORIC-114 is a brain penetrant, orally bioavailable, irreversible small molecule inhibitor designed to selectively target EGFR and HER2 with strong potency against exon 20 insertion mutations, making it a promising therapeutic to potentially address this unmet medical need, including in NSCLC patients with active central nervous system (CNS) metastases. We further explored the potential of ORIC-114 in other atypical mutations in EGFR and herein report the preclinical results.

Methods: To comprehensively characterize the potential of ORIC-114, biochemical and isogenic cell assays were developed for a variety of atypical mutations in EGFR, including primary and acquired PACC mutations, and assessed for potency. Additional in vivo analysis was performed to further assess free unbound exposures in brain.

Results: ORIC-114 is a potent inhibitor of PACC mutants with low to sub nanomolar activity across most atypical mutations assessed in both biochemical and cell-based assays. The potency on PACC mutants is similar to the potency on exon 20 insertion mutations in EGFR. In addition, ORIC-114 was found to be highly brain penetrant in the setting of an intact blood-brain-barrier in dogs, with high unbound brain-to-plasma partition coefficient Kp,uu,brain of 1.5.

Conclusions: ORIC-114 demonstrated best-in-class properties including high free unbound exposure in brain, exquisite selectivity across the kinome, and potent activity across atypical mutations in EGFR, including PACC mutations and exon 20 insertion mutations. ORIC-114 is a promising therapy for NSCLC patients with atypical mutations in EGFR, including those with active CNS metastases, and is currently being evaluated in a global clinical trial (NCT05315700).

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1346P Efficacy and safety of high dose furmonertinib combined with intrathecal injection in EGFR-mutated advanced NSCLC patients with LM progressed on osimertinib

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Background: We observed that leptomeningeal metastases (LM) occurred more in patients with site-specific resistant to osimertinib than first-generation EGFR-TKI, while these patients lacked of effective therapy. Furmonertinib 160 mg has been demonstrated encouraging efficacy in EGFR-mutated advanced NSCLC with central nervous system (CNS) metastases. This retrospective study aimed to evaluate the efficacy and safety of high dose furmonertinib combined with intrathecal injection methotrexate (MTX) or pemetrexed (PEM) in EGFR-mutated NSCLC patients with LM site-specific resistance to osimertinib.

Methods: Patients confirmed EGFR-mutated advanced NSCLC with LM progressed on osimertinib or other third-generation TKIreceived furmonertinib 160 mg or 240 mg combined with intrathecal injection MTX or PEM until disease progression. The primary endpoint was central nervous system progression-free survival (CNS PFS), and secondary endpoints were LM response rate according to RANO criteria, PFS, overall survival (OS) and safety.

Results: This retrospective study analysed the efficacy and safety of 23 EGFR-mutated advanced NSCLC patients with LM at Beijing Tiantan Hospital between June 2021 and April 2023. The median age was 63 years (range: 41-78) , ECOG PS$\geq$2 65.2%, 82.6% patients had received other third-generation EGFR-TKI previously, all patients were adenocarcinoma. The median follow-up time was 8.2 months (range: 0.9-14.1), the median CNS PFS was 10.8 months, LM response was observed in 6 (31.6%) of 19 patients with available data. The median PFS was 10.8 months, the median OS was NR. The CSF tumors cells decreased from baseline was observed in 14 (73.7%) of 19 patients with available data, and the CSF tumor cells clearance was observed in 6 (31.6%) patients. Neurologic function was improved in 18 (90.0%) of 20 patients. The most common treatment-related adverse events (TRAEs) were dry skin (17.4%) and elevated AST/ALT (17.4%). Nograde 3 or higher TRAEs observed.

Conclusions: High dose furmonertinib combined with intrathecal injection showed encouraging efficacy in EGFR-mutated advanced NSCLC patients progressed on osimertinib or other third-generation TKI.

Legal entity responsible for the study: The authors.

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1347P Peripheral osimertinib (osi) plasma trough concentration (Cmin,SS) as surrogate parameter for development and progression of brain metastasis (BM) in patients (pts) with EGFR+ advanced non-small cell lung cancer (aNSCLC)

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Background: Osi is designed to have better central nervous system (CNS) efficacy than other epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). However, 21% and 24% of pts treated in 1st or 2nd line develop CNS progression, mainly consisting of BM. A possible reason may be pharmacological failure of osi, due to low $C_{min,SS}$ and intracranial levels. However, data on osi $C_{min,SS}$ and BM related outcomes in Caucasians is lacking.

Methods: Retrospective study in three Dutch hospitals, collecting osi $C_{min,SS}$ from pts treated with osi 80 mg once daily for *EGFR*+ aNSCLC. Pts with parenchymal BM at start of osi were allocated to the BM-cohort and those without known BM to the no-known-BM-cohort. Pts were further allocated into subgroups based on osi $C_{min,SS}$ (low, middle or high). The primary outcome in both cohorts was cumulative incidence of BM development and progression.

Results: 173 pts were included, 28% had BM at osimertinib initiation (BM-cohort). In both cohorts, most pts were female (71% BM-cohort and 69% no known BM-cohort) and approximately half of the pts received osi in 2nd line (49% BM-cohort and 51% no known BM-cohort). Median follow-up was 22.8 months and at data cut-off 39% of pts still used osi without progression of BM. In the BM-cohort, 18 out of 49 pts (37%) experienced BM progression. Competing risk analysis showed a cumulative incidence of BM progression of 20% (95% CI 2.6 − 49.0), 31% (95% CI 10.6 − 53.9) and 31% (95% CI 10.8 − 54.5) after 12 months for the $C_{min,SS}$ low, middle and high subgroups respectively and 20% (95% CI 2.6 − 49.0), 52% (95% CI 23.8 − 74.2) and 57% (95% CI 24.9 − 79.7) after 20 months for the corresponding subgroups. In the no-known-BM-cohort, 4% developed BM during osi and no differences were found between the $C_{min,SS}$-subgroups.

Conclusions: This study suggests no relationship between plasma blood osi trough levels ($C_{min,SS}$) and cumulative incidence of BM development and progression in pts with *EGFR*+ aNSCLC.

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1348P Management of paresthesia in patients treated with lazertinib: Integrated analysis of LASER201 and LASER301 studies

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Background: Lazertinib, a third generation, highly mutant-selective, irreversible EGFR TKI, has demonstrated efficacy in locally advanced or metastatic *EGFR*-mutated NSCLC as front line and later line treatment with a manageable safety profile at the dose of 240 mg/day. Paresthesia, an uncommon adverse event (AE) for EGFR TKIs, was reported in 33% and 39% of patients receiving lazertinib in the LASER201 (NCT03046992) and LASER301 (NCT04248829) studies. We performed an integrated analysis of these studies to characterize the clinical features of paresthesia and related AEs, and examined the effect of lazertinib dose reduction (DR) on drug exposure, safety and clinical efficacy.

Methods: Patients treated with lazertinib 240 mg/day in the LASER201 and LASER301 studies were included in the analysis (332 patients). Lazertinib plasma trough concentrations at steady state (C_{trough}) were measured at doses of 240 mg/day and 160 mg/day (post-DR). Efficacy outcomes including PFS were compared in patients with and without DR for any reason in LASER301.

Results: Paresthesia and related AEs including hypoesthesia and neuropathy were reported in 160 (48%) of 332 patients. Most AEs were of CTCAE grade 1 or 2 without serious AEs. Paresthesia leading to DR was infrequent (22 patients; 7%). Median time to paresthesia onset was 105 days (range: 2—799); time to DR due to paresthesia was 252.5 days (range: 64—1135). Median post-DR C_{trough} levels in DR patients were similar to those in non-DR patients (post-DR: 168.5 ng/mL; non-DR: 177.9 ng/mL). In the LASER301 study, DR occurred in 42 of 196 patients assigned to 240mg/day lazertinib. Median PFS was similar in patients with and without DR: 18.0 months (95% CI: 14.8—not reached) for DR patients vs 23.3 months (95% CI: 16.7—26.1) for non-DR patients. In the LASER201 study, 12 of 76 T790M-positive patients experienced DR due to any cause. Of 13 patients in the LASER301 study with paresthesia leading to DR, AE severity decreased in 9 patients (63%) after DR to 160mg/day, including complete AE resolution in 1 patient.

Conclusions: Most paresthesia and related AEs were grade 1 or 2 and DR due to paresthesia was infrequent. Lazertinib DR to 160 mg/day may alleviate paresthesia severity without compromising clinical outcomes.

Clinical trial identification: LASER 201 study, phase 1/2 NCT03046992; LASER 301 study, phase 3 NCT04248829.

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1349P Continuing osimertinib in combination with chemotherapy after osimertinib failure reduces CNS progression in patients with EGFR-mutated NSCLC and CNS metastases

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Background: Central nervous system (CNS) metastases are common among patients with epidermal growth factor receptor mutation positive (EGFRm) non-small cell lung cancer (NSCLC). Chemotherapy (ChT) is the standard treatment for patients with metastatic EGFRm NSCLC patients failing osimertinib but has limited CNS activity. The role of continuing osimertinib concurrently with ChT after osimertinib failure for CNS control is uncertain.

Methods: This retrospective study included patients with metastatic EGFRm NSCLC who progressed on osimertinib and received ChT from 01/11/2017 to 17/03/2023. Primary endpoint is comparison of time to CNS progression between patients treated with osimertinib plus ChT versus ChT alone after progression on osimertinib. Time to CNS progression was defined from the starting date of ChT to radiological progression of CNS metastases. Hazard ratios and 95% confidence interval were estimated by Cox regression.

Table: 1349P

Total population	OSIM+ (n=33)	OSIM- (n=147)	Hazard Ratio (95% CI)	P value
Median PFS — months (95% CI)*	6.2 (5.5-6.8)	4.8 (4.2-5.4)	0.72 (0.48-1.09)	0.12
CNS progression — no. (%)	**7 (21)**	**33 (22)**	**0.74 (0.33-1.68)**	**0.88**
Patients with known CNS metastases	**(n=30)**	**(n=52)**		
Median PFS — months (95% CI)*	6.2 (5.6-6.7)	4.8 (4.1-5.5)	0.62 (0.38-1.00)	0.05
CNS progression — no. (%)	**6 (20)**	**24 (46)**	**0.32 (0.13-0.81)**	**0.02**
Salvage WBRT — no. (%)	2 (7)	11 (21)	0.24 (0.05-1.08)	0.06

*CNS/systemic progression or death PFS, progression free survival

Results: A total of 180 patients were analyzed. Median age was 62 (34-80). 28 (16%) received osimertinib as first-line treatment. 33 patients continued osimertinib with ChT (OSIM+) and 147 patients received ChT alone (OSIM-). Prior to starting ChT, 30/33 (91%) and 52/147 (35%) patients had known CNS involvement, among which 8 and 27 had received prior whole brain radiotherapy (WBRT), in the OSIM+ versus OSIM- arms respectively. In the total population, osimertinib plus ChT did not reduce risk of CNS progression. In patients with known CNS metastases, osimertinib plus ChT significantly reduced CNS progression. Numerically fewer patients in the OSIM+ arm received salvage WBRT.

Conclusions: Continuing osimertinib concurrently with ChT after osimertinib failure may reduce CNS progression in patients with known CNS metastasis, and the risk of being subjected to WBRT. Future prospective study is warranted to address this issue.

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1350P Survival benefits of local treatment (LT) for brain metastases (BMs) in patients (pts) with EGFR-mutant non-small cell lung cancer (EGFR-mt NSCLC) treated with osimertinib

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Background: Osimertinib is a standard treatment for pts with EGFR-mt NSCLC and is highly effective for BMs. It is unclear whether upfront LT for BMs prolong survival of pts with EGFR-mt NSCLC. The aim of this study was to reveal the survival benefit of upfront LT for BMs in pts with EGFR-mt NSCLC treated with osimertinib.

Methods: We conducted a multicenter (9 centers in Japan), retrospective cohort study of consecutive pts with EGFR-mt NSCLC who had BMs before the initiation of osimertinib between August 2018 and October 2021. Pts with meningitis were excluded. We divided all pts into two groups: pts who received upfront LT for BMs followed by osimertinib (Upfront LT group) and pts who received osimertinib without upfront LT (Osimertinib alone group). Overall survival (OS) and central nervous system progression free survival (CNS-PFS) between the two groups were compared. Inverse probability treatment weighting (IPTW) analysis with propensity scores was performed to adjust for potential confounding factors.

Results: A total of 121 pts was enrolled: median (range) age 72 (40—89) years; 83 (69%) female; 92 (76%) ECOG PS 0—1, 29 (24%) PS 2—4; 116 (96%) adenocarcinoma; EGFR status 57 (47%) 19del, 64 (53%) L858R; number of BMs 37 (31%) single, 84 (69%) multiple; median (range) maximum size of BMs 10 (1—51) mm; Symptoms of BMs 26 (21%) yes, 95 (79%) no; 45 (37%) upfront LT, 76 (63%) osimertinib alone. IPTW-adjusted Kaplan-Meier curves showed that OS of pts in the upfront LT group was significantly longer than that of pts in osimertinib alone group (median, Not reached (NR); 95% CI, NR—NR versus median, 31.2 months; 95%CI, 21.7—33.2; p=0.021). IPTW-adjusted HR for OS was 0.37 (95%CI, 0.16—0.87). IPTW-adjusted HR for CNS-PFS was 0.36 (95%CI, 0.15—0.87).

Conclusions: These results suggest that upfront LT for BMs followed by osimertinib may improve survival for pts with EGFR-mt NSCLC despite the high CNS activity of osimertinib.

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1351P Efficacy of early stereotactic body radiotherapy to the primary lung lesion in patients with NSCLC harboring sensitive EGFR mutations treated with first-line EGFR-TKIs

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Background: The addition of consolidative stereotactic body radiotherapy (SBRT) improved the survival for EGFR-mutated NSCLC treated with EGFR-TKIs. However, the optimal timing of SBRT remains unclear. The current study aimed to investigate the clinical outcome of the early and delayed SBRT to primary lung lesions in patients with EGFR-mutated NSCLC treated with first-line EGFR-TKIs.

Methods: The patients with EGFR-mutated advanced (stage IIIB-IV) NSCLC who were suitable to receive SBRT for the primary lung tumors after first-line EGFR-TKIs treatment were enrolled. The early SBRT group was defined as patients who received SBRT for their primary lung lesions at the maximal response of TKIs treatment. The delayed SBRT group was defined as patients who received SBRT after the occurrence of oligoprogression in the primary lung tumor. The primary endpoints were progression-free survival 1 (PFS1, time from the start of first-line EGFR-TKIs treatment to disease progression) and PFS2 (time from the start of first-line EGFR-TKIs treatment to disease progression after SBRT). Overall survival (OS) and adverse effects (AEs) were secondary endpoints. A two-sided P value of 0.05 was considered statistically significant.

Results: One hundred and eighty-four patients were screened, and 34 patients were eligible for enrollment in this study. The median age of the entire cohort was 61 years (range, 37—67 years), and 22 (64.7%) patients were male. Eighteen patients (52.9%) were non-smokers. Of the 34 eligible patients, 19(55.9%) received early SBRT to lung primary tumor and 15(44.1%) received delayed SBRT to lung primary tumor. The early

SBRT group had a significantly longer median PFS1 than the delayed SBRT group (30.0 months vs. 9.0 months, $P < 0.001$). The median PFS2 in the early SBRT and delayed SBRT groups were 42.0 and 33.0 months, respectively ($P = 0.521$). The median OS of both groups has not been reached. No severe toxicities (≥grade 3) were recorded.

Conclusions: Early SBRT to the primary lung lesion significantly improved PFS and is a new potentially effective and tolerable treatment option for patients with advanced NSCLC who had stable disease during first-line EGFR-TKIs treatment.

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1352P Plasma metabolic signatures uncover therapeutic response and prognosis of third-generation EGFR-TKI treatment in patients with NSCLC

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Background: Advanced *EGFR* T790M-mutant non-small cell lung cancer (NSCLC) inevitably develops resistance to third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) therapy. Metabolic reprogramming supports EGFR-TKI resistance, while thorough metabolomics clinical studies are limited.

Methods: Here, we enrolled 202 NSCLC patients from phase I and IIa clinical studies and characterized responsive metabolic features of third-generation EGFR-TKI by metabolomics, genomics and proteomics.

Results: The most frequent concurrent driver gene mutations were *TP53*, *RB1,* and *PIK3CA and* non-driver gene *PIK3CG*. Shorter progression-free survival (PFS) was related to *PIK3CG* (HR=3.55, P=0.06) or *RB1* (HR=2.56, P=0.05) mutations and *RB1* mutation was also correlated with shorter overall survival (OS) (HR=3.08, P=0.012). Baseline plasma metabolites revealed responder (R) featured by elevated glycerophospholipid and non-responder (NR) characterized by increased unsaturated fatty acids. *RB1* and *PIK3CG* mutations were positively correlated with unsaturated fatty acids and negatively associated with glycerophospholipids. Moreover, the circulating metabolic landscape implicated two distinct metabolic subtypes (C1 and C2), suggesting that subtype C2 with worse OS was characterized by *PIK3CG* mutation and higher unsaturated fatty acids. Proteomics revealed C1 harbored increased levels of biosynthesis of fatty acid, fatty acid degradation, and fatty acid metabolism pathways compared to the C1 subtype. In vitro experiments, Orlistat combined with BPI-7711 had reduced IC50 (508.08nM) in comparison with BPI-7711 alone (1328nM). Furthermore, we confirmed that exogenous fatty acids promoted cell viability upon BPI-7711 treatment (IC50=1704nM versus 1328nM) through decreasing EGFR expression. Meanwhile, fatty acids downregulated FASN and upregulated CPT1A expression, which may reduce the de nove synthesis of fatty acids and influence fatty acid oxidation.

Conclusions: This study revealed the metabolic landscape of advanced T790M-mutant NSCLC patients, providing the potential guide of personalized third-generation EGFR-TKI treatment and therapeutic target for overcoming resistance.

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1353P Effect of TP53 co-mutation in non-small cell lung cancer (NSCLC) with driver mutations

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Background: *TP53* variants are common in NSCLC and have been reported as predictive of response and prognostic of poor outcome in *EGFR*-mutant NSCLC. The impact of *TP53* co-mutation in NSCLCs carrying rarer driver mutations with approved targeted treatments is unclear.

Methods: Records of 236 patients with rare driver mutation positive NSCLC at Princess Margaret Cancer Centre were reviewed. Associations between *TP53* status, baseline demographics and outcomes (response [ORR], survival [OS], progression-free survival [PFS]), were investigated. ORR (to first-line targeted therapy only) was compared via Fisher's exact test. OS and PFS were compared by Kaplan-Meier estimates, and Cox regression adjusted for stage at diagnosis with wildtype (WT) as reference.

Results: *TP53* variants were found in 88/236 (37%; table) with two+ driver mutations in 22 (9%). There were no significant demographic differences between *TP53*-mutated (MUT) and WT except for smoking status (never smokers 58% *TP53-MUT v* 70% *TP53*-WT, p=0.002). ORR to first-line targeted treatment was 54% vs 71% in the *TP53*-MUT and WT cohorts, respectively (p=0.09). More patients with *TP53*-MUT cancer had progressive disease (PD) as best response (27% *v* 8%, p=0.005). Median PFS was 19.6 mos for *TP53*-MUT (95% CI 14.4-24.3) *v* 42.7 mos for WT (CI 31-72.9) (stage-adjusted hazard ratio (aHR) 2.35, CI 1.62-3.39; p<0.001). Median OS was significantly shorter in the *TP53*-MUT cohort at 20.9 mos (CI 17.3-30.7) compared to 66.4 mos (CI 54.8-not reached) (aHR 3.30, CI 2.20-4.95; p<0.001). In a subset with fusion mutations (*ALK*, *ROS1*, *RET, NRG1*), we saw similar trends in ORR (67% *TP53*-MUT *v* 88% WT, p=0.11), PFS (aHR 2.83, CI 1.52-5.27; p=0.001), and OS (aHR 5.00, CI 2.42-10.33; p<0.001).

Table: 1353P

	***TP53* wildtype (n=148) N (%)**	***TP53* mutated (n=88) N (%)**	**p value**
Median age (range)	62.1 (31.8, 91.0)	64.8 (22.0, 90.0)	0.40
Female sex	91 (61%)	49 (56%)	0.46
Never smoker	99 (70%)	49 (58%)	0.06
Adenocarcinoma	141 (95%)	83 (94%)	0.99
Stage at diagnosis I/II III IV	32 (22%) 31 (21%) 85 (57%)	16 (18%) 15 (17%) 57 (65%)	0.54
Brain metastases at any time	49 (36%)	31 (37%)	0.90
Driver mutations ALK BRAF V600E EGFR exon 20 ins Uncommon EGFR HER2 exon 20 ins HER2 oncogenic SNV KIT MET exon 14 skip NRG1 RET ROS1 Multiple	44 6 3 3 27 4 0 18 2 10 15 16	9 1 5 3 21 6 1 17 0 6 8 11	
Response to first line targeted treatment CR PR SD PD Non-evaluable	n=100 1 (1%) 64 (65%) 19 (19%) 8 (8%) 8 (7%)	n=49 0 22 (45%) 6 (12%) 13 (27%) 8 (14%)	0.005

Conclusions: *TP53* co-mutation with multiple rare driver mutations is predictive of poor response to targeted treatments and prognostic of shorter OS and PFS in NSCLC.

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1354P Beyond the common mutation: Examining chemotherapy success in uncommon EGFR mutations

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Background: Some prospective studies have shown that second-generation tyrosine kinase inhibitors (TKIs) provide better control in patients with non-small-cell lung cancer (NSCLC) with uncommon epidermal growth factor receptor (EGFR) mutations. However, studies comparing second-line chemotherapy efficacy between NSCLC patients with common and uncommon EGFR mutations remain rare. This retrospective study compared treatment outcomes in these patients.

Methods: Patients with EGFR-mutated advanced-stage NSCLC who received first-line EGFR-TKIs in a tertiary referral center were retrospectively reviewed between January 2010 and August 2022. Patients with a negative T790M test at disease progression who received second-line chemotherapy were enrolled. Progression-free (PFS)and

overall (OS) survival were compared between advanced NSCLC patients with common and uncommon EGFR mutations using Kaplan−Meier and log-rank tests.

Results: Total 209 (54.8%) patients had a negative T790M mutation test and received second-line chemotherapy, of which 192 (92.3%) had a common EGFR mutation (exon 19 deletion or exon 21 L858R substitution), and 17 (8.2%) had an uncommon EGFR mutation. Patients in the common EGFR mutation group had significantly longer PFS than those in the uncommon EGFR mutation group (4.57 vs. 2.57 months, $p = 0.031$). While patients in the common EGFR mutation group had longer OS than those in the uncommon EGFR mutation group, the difference was nonsignificant (12.53 vs. 9.70 months, $p = 0.501$). A Cox proportional hazard regression analysis controlling for potential confounding factors indicated that an uncommon EGFR mutation was an independent prognostic factor for PFS(hazard ratio [HR] = 2.15, 95% confidence interval [CI]: 1.27−3.64).Being male was only the independent poor prognostic factor for OS (HR = 1.64, 95% CI: 1.22−2.21).

Conclusions: To our knowledge, this is the first study investigating the impact of EGFR mutation subtypes on second-line chemotherapy efficacy. This study suggests that patients with uncommon EGFR mutations have poorer chemotherapy responses and shorter survival than those with common EGFR mutations. The development of new treatment strategies for these patients remains an unmet need.

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1355P Evaluation of the role of variant allele frequency in EGFR mutated non-small cell lung cancer treated with first line osimertinib

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Background: The efficacy of Osimertinib (Osi) in advanced EGFR mutated non-small cell lung cancer (aNSCLC) is associated to type of EGFR mutations (EGFRm) and line of treatment, while the impact of cell clonality is still controversial. We aimed to evaluate the effect of variant allele frequency (VAF), as a surrogate of clonality, in the first line treatment with Osimertinib in EGFR mutated aNSCLC.

Methods: We retrospectively collected data of 60 aNSCLC harbouring a common EGFRm (Ex19dels or Ex21 L858R) treated with at least one cycle of first-line Osi from January 2019 to September 2022 at Fondazione IRCCS Istituto Nazionale Tumori of Milan. Next Generation Sequencing analyses were performed at baseline. According to median VAF (mVAF), patients were divided into two subgroups (VAFhigh > mVAF and VAFlow < mVAF). Differences in median progression free survival (mPFS), objective response rate (ORR) and disease control rate (DCR) between subgroups were analysed. Fisher's exact test was used to compare proportions. Survival was estimated through Kaplan-Meier method and compared by Cox-proportional Hazard model.

Results: In our cohort, mVAF was 0,39. Baseline characteristics were equally distributed between subgroups. With a median follow up of 14,2 months (mo), mPFS in the overall population was 17 mo (0.95 CI 12,2-30,1). No statistically differences in mPFS were found according to mVAF (HR 1,34, 15 mo 0.95CI [11,8-NA] vs 20,9 mo 0.95CI [11,9-NA], p=0.45, in VAFlow and VAFhigh, respectively). Similarly, mVAF did not impact on DCR and ORR (92,3% vs 96,6%, p=0,922 and 65,5% vs 65,4%, p=1 in VAFhigh vs VAFlow, respectively). Finally, no differences were observed between the two subgroups in terms of clinical characteristics associated with worse prognosis (presence of brain metastasis, number of metastatic sites and TP53 comutation).

Conclusions: Our study suggests that EGFR mVAF has a low impact in predicting the benefit of first-line Osi. Further investigations in a larger cohort and with a longer follow up, including a more comprehensive analysis of the genomic landscape, may help in clarifying the role of VAF in predicting the clinical outcomes to Osi.

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1356P 10-year survivors treated with tyrosine kinase inhibitor for advanced non-small cell lung cancer

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Background: The development of tyrosine kinase inhibitors (TKI) has led to the emergence of long-term survivors in advanced non-small cell lung cancer (NSCLC), with a part of them surviving more than 5 years. However, no studies have examined the 10-year survivor in patients (pts) with advanced NSCLC receiving TKI. This study aims to clarify characteristics of the 10-year survivors.

Methods: We have retrospectively reviewed the clinico-genomic findings of advanced or recurrent NSCLC pts with driver oncogene who received TKIs at the National Cancer Center Hospital East between 2002 and 2012. We defined pts who survived more than 10 years as the long survivor group and others as the non-long survivor group.

Results: The analysis included 387 pts. The survival rate at the 5- and 10-year were 21% and 7%. 27 pts (7%) were in the long survivor group and 360 pts (93%) were in the non-long survivor group. The types of driver alterations were as follows: 358 EGFR mutations, 24 ALK fusions, 4 ROS1 fusions and 1 RET fusion. A comparison analysis between long survivor and non-long survivor showed that the median age was 60 (range 23-89) vs. 64 (range 25-84) (P = 0.005); female was 22 (81%) vs. 213 (59%) (P = 0.02); ECOG-PS 0-1 was 27 (100%) vs. 334 (93%) (P = 0.24) ; never smoker was 18 (67%) vs. 195 (54%) (P = 0.23); fusion genes were 5 (19%) vs. 24 (7%) (P = 0.04). Among EGFR-mutated pts, there were no differences in the fraction of EGFR mutation subtypes between the two groups. The proportion of deaths from non-lung cancer including cardiovascular disease and other site of cancer after 5 and 10 years was 7% and 33%, and pts survived longer than 10 years had a higher proportion of deaths from non-lung cancer compared to the others (P = 0.01).

Conclusions: 10-year survivors had characteristics of younger age, female, and with fusion alterations, while there are no difference EGFR subtype. Despite achieving 5-year survival, two-thirds did not achieve 10-year survival. The increase of deaths from non-lung cancer in the long-term survivor, emphasizing the importance of monitoring and managing cardiovascular and other cancer complications.

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1357P Bevacizumab improved prognosis for advanced EGFR mutant lung adenocarcinoma with brain metastasis receiving cerebral radiotherapy

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Background: Cerebral radiotherapy can reduce recurrence and improve overall survival (OS) in patients with brain metastasis (BM) from Epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma. Bevacizumab (Avastin), an anti-Vascular endothelial growth factor (VEGF) monoclonal antibody, angiogenesis inhibition and alleviates blood-brain barrier (BBB) damage and brain edema through its blocking VEGF. However, whether bevacizumab combined with cerebral radiotherapy can further increase the efficacy and improve the prognosis of patients is unclear. This study aimed to evaluate the effect of bevacizumab on OS in BM patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) undergoing cerebral radiotherapy.

Methods: A total of 178 patients with EGFR-mutant lung adenocarcinoma and BM who received cerebral radiotherapy met the inclusion criteria for this retrospective study, including 70 patients in the bevacizumab treatment group and 108 in the non-bevacizumab group. The Kaplan-Meier method was used for survival analysis. Univariate and multivariate analyses were performed to identify EGFR-mutated BM prognostic factors for these patients. Cerebral radiotherapy included whole-brain radiotherapy (WBRT), local radiotherapy, and WBRT + Boost.

Results: At the end of the last follow-up period, 176 patients (74.3 %) had died, and the median OS was 33.25 months. We observed a significant difference in the median OS between the bevacizumab and non-bevacizumab groups (45.8 months vs 32.0 months, P =0.007). Patients treated with bevacizumab after cerebral radiotherapy had a longer median OS than patients treated with bevacizumab before cerebral radiotherapy (59.4 months vs 33.7months, P=0.0198).

Conclusions: Bevacizumab could improve OS in BM patients with EGFR mutation-positive NSCLC receiving cerebral radiotherapy. This improvement was more obvious after cerebral radiotherapy, possibly as a result of bevacizumab alleviating radiation brain necrosis caused by brain radiotherapy.

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1358P Safety of tepotinib + EGFR TKI (osimertinib or gefitinib) in patients with EGFRm NSCLC

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Background: Promising clinical activity has been reported in the INSIGHT 2 study of tepotinib (TEP) + osimertinib (OSI) in patients (pts) with *EGFR*m NSCLC with *MET* amplification (*MET*amp) progressing on OSI, with an ORR of 43.9% (95% CI: 33.9, 54.3) and a mDOR of 9.7 months (5.6, ne). TEP monotherapy has been extensively studied in *MET*ex14 skipping NSCLC (N=313) and is generally well tolerated, with low discontinuation rates due to treatment-related AEs (TRAEs; 14.7%). The most common TRAE is peripheral edema (67.1%, Grade 3 11.2%). Our aim is to further characterize the safety profile of TEP in combination with EGFR TKIs.

Methods: TEP 500 mg (450 mg active moiety) was administered in combination with OSI 80 mg (INSIGHT 2; NCT03940703) or gefitinib (GEF) 250 mg (INSIGHT; NCT01982955) QD until disease progression, intolerable toxicity, or withdrawal. To manage AEs, each drug could be dose reduced but if discontinuation was needed, both drugs were stopped. AEs were graded by NCI-CTCAE v5.0.

Results: As of Sep 26, 2022, 187 pts with *EGFR*m NSCLC (65% <65 yrs, 62% female, 72% Asian, 70% nonsmokers, 75% ECOG PS 1) had received TEP + EGFR TKI: 129 +OSI and 58 +GEF. TRAEs were mostly Grade 1—2 and included diarrhea, peripheral edema, and paronychia (Table). TRAEs leading to dose reduction of TEP (≥3 pts) were decreased appetite, peripheral edema, and nausea. There were few discontinuations due to TRAEs (≥2 pts: peripheral edema and pneumonitis). Two deaths considered to be treatment related (due to pneumonitis and dyspnea) occurred in pts receiving TEP+OSI.

Conclusions: TEP in combination with an EGFR TKI was well tolerated in these pts with progressive disease post-first-line therapy, and reflects the safety profile of the individual compounds. Lower incidence of peripheral edema in pts with *EGFR*m NSCLC versus *MET*ex14 skipping NSCLC may be due to younger age and/or the EGFR TKI combination. TEP+OSI provides a potential chemotherapy-sparing oral targeted therapy option for patients with *EGFR*m *MET*amp NSCLC that has developed resistance.

Table: 1358P

TRAEs*	INSIGHT 2 N=129		INSIGHT N=58	
Grade; ≥15% of pts	Any	≥3	Any	≥3
Any, n (%)	**106 (82.2)**	**35 (27.1)**	**52 (89.7)**	**21 (36.2)**
Diarrhea	60 (46.5)	0	33 (56.9)	3 (5.2)
Peripheral edema	45 (34.9)	5 (3.9)	12 (20.7)	2 (3.4)
Paronychia	26 (20.2)	1 (0.8)	9 (15.5)	1 (1.7)
Decreased appetite	23 (17.8)	4 (3.1)	11 (19.0)	1 (1.7)
Nausea	20 (15.5)	2 (1.6)	6 (10.3)	0
ALT increase	13 (10.1)	2 (1.6)	10 (17.2)	1 (1.7)
Lipase increase	12 (9.3)	3 (2.3)	10 (17.2)	7 (12.1)
Rash	11 (8.5)	0	13 (22.4)	2 (3.4)
Amylase increase	9 (7.0)	0	11 (19.0)	7 (12.1)
Pruritus	4 (3.1)	0	9 (15.5)	0
Leading to dose reduction	**22 (17.1)**		**5 (8.6)**	
TEP	20 (15.5)		4 (6.9)	
OSI/GEF	5 (3.9)		2 (3.4)	
Leading to discontinuation	**7 (5.4)**		**2 (3.4)**	

*Related to TEP and/or EGFR TKI (OSI/GEF).

Clinical trial identification: NCT03940703 and NCT01982955.

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1359P Relationship between tumor TP53 gene mutation, circulating anti-p53 antibodies and response to first-line osimertinib in EGFR-mutated NSCLC patients

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Background: Osimertinib is the standard of care in Epidermal Growth Factor Receptor (EGFR)-mutated advanced Non-Small-Cell Lung Cancer (NSCLC). The MELROSE study, a multicentric phase II trial (NCT03865511) was designed to identify resistance mechanisms in treatment-naive EGFR-mutated NSCLC patients receiving osimertinib. We have evaluated the impact of *TP53* mutations on the response to osimertinib.

Methods: The MELROSE trial enrolled 150 patients with EGFR-mutated (exon 19 deletion, n=88; L858R mutation, n=62) NSCLC. All patients received osimertinib. Tumor assessment was performed every 3 months, with brain and thoracoabdominal CT-scan. Tumor tissues collected at diagnosis were analyzed by next generation sequencing (QIAseq targeted DNA custom panel, QIAGEN). Anti-p53 antibodies were quantified in plasma using the automated Elecsys anti-p53 immunoassay (Cobas, Roche).

Results: Primary analysis of the whole cohort (data cutoff on April 4, 2023) showed a median PFS of 17.4 months (95% CI: 14.9-21.8). Tumor *TP53* genotyping was successfully performed for 116 patients. *TP53* mutations were detected in tumors of 74 patients (63.8%). Most mutations were present on exons 5 (n=14), 6 (n=13), 7 (n=12) and 8 (n=18). The presence of a *TP53* mutation was associated with a reduced median PFS (16.4 months) as compared to wild type tumors (27.5 months; p=0.0034; HR 2.15; 95% CI: 1.29-3.60). Anti-p53 antibodies were detected at baseline in the plasma of 17.8% of the patients tested (26/146). The presence of antibodies was strongly associated with the existence of a *TP53* mutation (p=0.001). Patients presenting detectable anti-p53 antibodies at baseline had a significantly lower median PFS (16.4 months) as compared to patients not presenting antibodies (20.0 months; p=0.034; HR 1.72; 95% CI: 1.04-2.83).

Conclusions: The existence of a *TP53* gene mutation in patients' tumor significantly impacted their PFS, suggesting that future clinical trials should include *TP53* genotyping at randomization. Baseline quantification of anti-p53 antibodies could also be used to early identify a fraction of patients presenting a *TP53* alteration, and identify patients who may benefit less from osimertinib treatment.

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1360P Updated patient-reported outcomes from the CROWN study: Analyses in first-line ALK+ patients with (w) and without (w/o) baseline brain metastases (BMs) and w or w/o central nervous system adverse events (CNS AEs)

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Background: Lorlatinib (LOR) demonstrated superior systemic and intracranial efficacy and favorable patient-reported outcomes (PROs) compared with crizotinib in the phase 3 CROWN study. Here we report PROs from the 36-month follow-up analysis in LOR-treated patients (pts) w and w/o baseline BMs and w or w/o CNS AEs.

Methods: Post hoc descriptive quality of life (QoL) analyses using the EORTC QLQ-C30 and QLQ-LC13 were presented for data up to cycle 38 (data cutoff: Sep 20, 2021). Longitudinal mixed-effect models evaluated score changes from baseline; clinically meaningful improvements (CMIs) were defined as a ≥10-point change.

Results: Of 148 LOR pts, 37 had baseline BMs while 111 did not (PRO completion rate, ≥95.6%). Pts w baseline BMs had lower scores than those w/o BMs on all functioning domains. Global QoL generally improved regardless of baseline BM status, although there was a trend for greater QoL improvement in pts w baseline BMs vs those w/o: pts w baseline BMs had CMIs starting from cycle 2, whereas pts w/o BMs did not have CMIs until cycle 38. Cognitive and emotional functioning scores remained stable over time regardless of baseline BM status. For cognitive functioning, pts w BMs had small numerical improvements over time (0.6 to 4.2) while pts w/o BMs had small numerical deteriorations (−2.7 to −6.6). For emotional functioning, CMIs were more frequently observed longitudinally in pts w baseline BMs. CNS AEs in LOR pts were evaluated by the EORTC QLQ-C30 cognitive and emotional functioning PRO domains. Emotional functioning scores generally improved over time, independent of presence or absence of CNS AEs. Slight declines in cognitive functioning scores over time in pts w or w/o CNS AEs were not clinically meaningful.

Conclusions: These updated PRO results from the CROWN study continue to show the benefit of LOR in the first-line setting in *ALK*+ pts. Both pts w or w/o baseline BM continue to maintain/improve global QoL, emotional functioning, with generally no significant deterioration in cognitive functioning. Pts w or w/o CNS AEs had similar longitudinal patterns in PRO domains.

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1361P Alectinib for treatment-naïve advanced ALK+ NSCLC selected via blood-based NGS: Updated analyses of outcomes, circulating tumour (ct)DNA and biomarker subgroups from BFAST Cohort A

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Background: BFAST (NCT03178552) is an ongoing global, open-label, multicohort study assessing the activity of therapies in patients (pts) with advanced/metastatic NSCLC harbouring actionable genetic alterations identified in ctDNA via NGS. In a previous analysis of the BFAST *ALK*+ NSCLC cohort, a high overall response rate (ORR) was reported in pts treated with alectinib. We present updated data with longer follow-up, and exploratory correlative ctDNA and biomarker analyses.

Methods: Pts aged ≥18 years with treatment-naïve stage III/IV NSCLC had comprehensive genomic profiling via NGS on ctDNA at screening. Pts with *ALK* fusions (*ALK*+) received alectinib 600 mg twice daily. Primary endpoint: investigator (INV)-assessed ORR; key secondary endpoints: INV-assessed progression-free survival (PFS), duration of response (DOR), overall survival (OS), safety. Blood samples for exploratory analyses were collected every 2 cycles during treatment, and at disease progression if feasible.

Results: The cohort included 87 *ALK*+ pts; median survival follow-up was 52.0 months (range 2.6—62.6). At data cutoff (24 Feb 2023), 34 (39.1%) pts remain on alectinib. Median PFS data for the overall population and per subgroup are presented in the table. In the overall population, ORR was 89.7% (95% CI 81.3—95.2); median DOR was 35.1 months (95% CI 24.8—49.7); 48-month OS rate was 58.3% (95% CI 47.8—68.7). Most pts (93%) had complete clearance of ctDNA (no *ALK* fusion reads) by Cycle 3 Day 1. Pts without *ALK* clearance had poor PFS (7.1 months; 95% CI 5.6—NE). No new safety signals were identified.

Conclusions: BFAST is the first trial with mature clinical data using prospective blood-based NGS screening of *ALK* to select pts for treatment with alectinib. PFS data were consistent with the ALEX study. Concurrent *TP53* mutation and high baseline ctDNA levels were associated with poorer prognosis; ctDNA clearance was associated with better outcomes.

Table: 1361P

Patient subgroup (*ALK*+)	N (% of total population)	Median PFS, months (95% CI)
Overall population	87 (100)	33.0 (20.5—44.2)
TP53 co-mutation vs *TP53* wild type	38 (44) vs 49 (56)	18.7 (12.6—36.9) vs 39.5 (29.4—NE)
Baseline cTF ≥1% vs <1%	47 (54) vs 40 (46)	18.4 (14.5—40.5) vs 41.5 (31.5—NE)
Baseline cTF ≥10% vs <10%	13 (15) vs 74 (85)	12.7 (7.4—NE) vs 36.9 (29.4—51.6)
EML4 fusion partner vs other fusion partners	73 (84) vs 14 (16)	33.0 (22.2—42.0) vs 33.3 (5.4—NE)
ctDNA: no clearance vs clearance*	5 (6) vs 66 (93)	7.1 (5.6—NE) vs 36.8 (29.4—51.5)

*N=71 patients with Cycle 3 Day 1 data. cTF, composite tumour fraction; NE, not estimable

Clinical trial identification: NCT03178552.

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1362P Association of baseline (BL) anaplastic lymphoma kinase (ALK) fusion detected by circulating tumor DNA (ctDNA) with clinical features and outcomes in the phase III ALTA-3 trial

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Background: In ALTA-3 (NCT03596866), treatment with brigatinib and alectinib showed similar efficacy in patients (pts) with *ALK*+ NSCLC. We report the results of an exploratory correlative pooled analysis of the association of BL *ALK* fusion status, as detected by ctDNA, with clinical features and outcomes in ALTA-3.

Methods: ALTA-3 was a randomized, open-label study of brigatinib 180 mg once daily (7-day lead-in at 90 mg) vs alectinib 600 mg twice daily in pts with advanced *ALK+* NSCLC after progression on crizotinib. For this analysis, *ALK* fusion detection in plasma at BL by ctDNA sequencing was correlated with clinical features (tumor size, target lesion number, organ site involvement, smoking status) and outcomes (median progression-free survival [mPFS; estimated by Kaplan-Meier methods]). ctDNA sequencing was conducted retrospectively with AmoyDx (Chinese pts) and Resolution Bio ctDx™ next-generation sequencing panels. Tumor size was represented as sum of the longest diameter (SLD) of target lesions (RECIST v1.1 criteria). Association between *ALK* status and clinical features was estimated by odds ratios (OR).

Results: Of 248 pts in ALTA-3, ctDNA from plasma collected at BL from 232 pts was sequenced. *ALK* fusions were detected in 78 (*ALK* ctDNA+) and not detected in 154 (*ALK* ctDNA−). *ALK* ctDNA− pts had longer mPFS compared with *ALK* ctDNA+ pts (mPFS 22.5 vs 11.1 months, respectively; hazard ratio 0.48; 95% confidence interval [CI] 0.32−0.71; P=0.0002). *ALK* ctDNA− pts were more likely to have SLD less than or equal to the median (39 mm) compared with *ALK* ctDNA+ pts (OR 0.32, 95% CI 0.17−0.59). *ALK* ctDNA+ status was associated with >1 (median) BL target lesion (OR 0.27, 95% CI 0.14−0.50) and >3 (median) involved organ sites (OR 0.40, 95% CI 0.21−0.73). Smoking status did not impact ctDNA detection of *ALK* fusion status or outcomes.

Conclusions: Detectable BL *ALK* fusion by plasma ctDNA is an indicator of poor prognosis and is associated with increased tumor size, number of metastases, and organ site involvement. *ALK* fusion detection using BL ctDNA could be a surrogate for disease burden and may identify pt populations for escalation strategies in the future.

Clinical trial identification: NCT03596866.

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1363P Genomic heterogeneity of ALK rearrangements and acquired resistance pathways in ALK+ Advanced non-small cell lung cancer (NSCLC) treated with upfront alectinib: Preliminary results of GALILEO project

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Background: Longitudinal genomic evaluation of ALK+ ANSCLC patients treated with 1L alectinib is poorly explored in clinical practice.

Methods: GALILEO (Genomic ALteratIons and cLonal EvOlution in ALK+ NSCLC) is national observational prospective cohort study on ALK+ ANSCLC pts treated with new generation ALK-TKIs. Comprehensive genomic profiling was performed on pre-treatment FFPE tissue of ALK+ ANSCLC identified by using FISH and/or IHC. At the time of progression, DNA-based NGS was repeated on newly obtained tissue (if feasible) or blood ctDNA (FM1 CDx/Liquid®).

Results: In this preliminary analysis, 30 ALK+ ANSCLC pts who started 1L alectinib by Dec 2020 were evaluable. In pre-treatment samples, NGS identified 26 (86.6%) EML4-ALK fusion (V1: 9, V2: 2; V3: 11; NOS: 4), 6 (20%) non canonical fusions (1 alone, 5 conc. with EML4-ALK), 8 (30%) ALK Internal/Intrachromosomal rearrangements (4 intron 19, 2 exon 19, 1 intron 18, 1 C2orf44; 2 alone, 6 conc. with ALK-fusions); in one case, any ALK-alteration was detected. As the data cut-off (median FU: 37 mo.), 14 pts had radiological progression (PD). Among 11 alectinib-responder pts (CR/PR or SD > 6 mo.), 4 patients presented de-novo ALK-SNV [G1202R (50%); E1210K (25%); I1171N/T (25%)], 4 pts had no ALK-SNV (DNMT3A M+: 3 pts; SEDTD2 M+: 2 pts, TP53 M+: 2 pts), 1 pt had oncogene-switch (EGFR); 2 pts failed ctDNA-NGS (low purity). Among 8 pts who received 2L lorlatinib, we observed 3 PR in ALK SNV+ pts, 2 SD ≥6 mo. and 3 PD in pts without ALK-SNV. In post-lorlatinib NGS-assay, 2 pts had ALK-compound mutations, while 4 pts had newly off-target alterations (CDKN2A/B CDKN2B loss, NF1 deletion, DNMT3A/ARID1A/CHECK2 M+).

Conclusions: Implementation of longitudinal genomic assessment is required in order to provide an extensive overview of resistance mechanisms and clinical outcomes according to current ALK-inhibitors treatment sequences.

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1364P ctDNA analysis of SAF-189s efficacy in ALK+ advanced non-small cell lung cancer (NSCLC)

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Background: SAF-189s is a next-generation inhibitor of *ALK/ROS1* tyrosine kinase, which has been shown to have anti-tumor activity against *ALK/ROS1* fusion-positive non-small-cell lung cancer (NSCLC), including CNS activity due to its ability to penetrate the blood-brain barrier. Here we present a circulating tumor DNA (ctDNA) biomarker analysis of patients (pts) with advanced, *ALK*-rearranged NSCLC treated in phase 2a study.

Methods: Tumor tissue samples were collected from all enrolled pts for *ALK*-fusion detection by VENTANA ALK (D5F3) IHC assay. Plasma samples were collected at baseline and disease progression. Next-generation sequencing for ctDNA was done using Lung cancer 180-gene panel (Genetron). PFS was evaluated according to *ALK* alteration status.

Results: By the cut-off date of Dec 13th, 2021 (median PFS follow-up 11 mo), a total of 143 NSCLC *ALK*-fusion positive pts had been enrolled and treated with SAF-189s (80 mg, n=19; 120 mg, n=47, 160 mg, n=64; 210 mg, n=13), including 100 ALKi-naïve pts and 43 ALKi-refractory pts (received crizonitib and/or next-generation ALKi). ctDNA at baseline was tested in 143 pts with a *ALK*-fusion positivity rate of 53.8% (77/143). The main fusion partner of *ALK* was *EML4*, accounting for 93.6% (73/78). The most common fusion variants were v3 (34.5%, 27/78), v1 (28.2%, 22/78), and v2 (10.3%, 8/78). Pts with v1 variants showed a longer mPFS than v3 variants (16.5 mo vs. 13.8 mo, p=0.188). There was no significant difference in the distribution of *ALK* fusion variants between ALKi-naïve and ALKi-refractory groups. Of 25 pts who progressed with SAF-189s, two *ALK* mutations, G1202R and I1179T, were newly identified in 3 pts. I1179T has not been previously reported and is speculated to be a novel *ALK*-resistant mutation. *TP53* co-mutations were detected in 47% pts, but it was not shown to have a significant effect on outcomes. Gene co-occurrence survival analysis showed that mPFS of pts harboring *FAT3/FAT4* mutations were significantly shorter than those without *FAT3/FAT4* mutations (8.9 mo vs 16.5 mo, p=0.012).

Conclusions: Clinical utility of ctDNA was demonstrated, not only at baseline by identifying fusion types and subgroups of *ALK+* NSCLC pts that may benefit more from SAF-189s, but also at progression by tracking *ALK*-resistant mutations.

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1365P Neurocognitive adverse events related to lorlatinib in non-small cell lung cancer: A systematic review and meta-analysis

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Background: Lorlatinib (LOR), a 3rd generation tyrosine kinase inhibitor (TKI), has shown promising activity in NSCLC. However, the treatment has been associated with an increasing number of neurocognitive adverse events (NAEs). This systematic review and meta-analysis evaluated the NAEs associated with LOR therapy in NSCLC patients.

Methods: PubMed, Scopus, and the Cochrane Library were searched for clinical trials and observational cohort studies investigating LOR for NSCLC patients. NAEs were defined as the cluster terms of cognitive effects, mood effects, speech effects, and psychotic effects. Heterogeneity was examined with the I^2 statistics and random-effect model was used to pool studies.

Results: Sixteen studies were included with 1,147 patients, of whom 56% were female, 8% were Asians, 8% had a history of smoking, 62% had brain metastasis, and 1% ECOG 2 or higher. Most patients had previously received an early-generation TKI before the LOR. A pooled analysis of NAEs showed a prevalence of cognitive effects in 15.57% of overall population (95% CI 8.40 − 22.73, I2 90%), mood effects in 11.93% (95% CI 5.80 − 18.06, I2 89%), speech effects in 6.56% (95% CI 1.79 − 11.34, I2 91%), and psychotic effects in 4.15% (95% CI 1.46 − 6.83, I2 74%). In a subgroup analysis, we found higher rates of cognitive effects in clinical trials than in real-world data (23.57% vs. 9.36%, $p = 0.05$), and a significant difference was also seen in mood effects (18.64% vs. 3.70%, $p < 0.01$). NAEs were manageable with dose modification, temporary interruption, and/or concomitant medication.

Conclusions: Our study revealed that LOR is associated with cognitive, mood, speech and psychotic effects in approximately 16%, 12%, 7%, and 4% of patients, respectively. We found significant differences in the prevalence of cognitive and mood effects between clinical trials and real-world data. Additionally, all analyses had a high heterogeneity among studies. Collectively, these findings underscore the importance of educating patients and healthcare professionals regarding LOR-associated NAEs to facilitate early detection and management of NAEs, aiming to improve NSCLC patients' quality of life.

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1366P Association between the adverse events and serum concentrations of lorlatinib in patients with advanced ALK-positive lung cancer

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Background: Lorlatinib is a third-generation anaplastic lymphoma kinase (ALK) inhibitor, has been the standard of care for untreated and previously treated patients with advanced ALK-positive non-small cell lung cancer (NSCLC). The common adverse events (AEs) of lorlatinib leading to drug discontinuation or dose reduction were hyperlipidemia, edema, and central nervous system (CNS)/ psychiatric disorders. The association between AEs and serum concentrations of lorlatinib remains unclear.

Methods: We retrospectively reviewed advanced ALK-positive NSCLC patients treated with lorlatinib between December 2018 and July 2022. The association between AEs and serum concentrations of lorlatinib was assessed at 28 days (± 14 days) after the initiation of lorlatinib using a high-performance liquid chromatography tandem mass spectrometry.

Results: Among 55 eligible patients, the median age was 54 years (range: 23−79) and the median number of treatment lines was 2 (range: 2-10). Most patients were female (29 [53%]) and performance status 0-1 (48 [87%]). Grade 3 or higher AEs occurred in 23 patients (42%) including hyperlipidemia in 18 (33%), edema in 5 (9%), and CNS/ psychiatric disorders in 4 (7%). Discontinuation or dose reduction was required in 21 patients (38%). Serum concentrations were measured in 36 patients (65%) and were significantly higher in the patients experiencing grade 3 or higher AEs than those without (462 ng/mL vs 177 ng/mL, $p<0.01$). On the other hand, there was no significant difference in progression-free survival (PFS) between the patients who had experienced the discontinuation or dose reduction within the first 6 months and those who had not (12.8M vs 5.2M, p=0.14).

Conclusions: The incidence of grade 3 or higher AEs with lorlatinib was associated with high serum concentrations at the first month of treatment. Drug discontinuation or dose reduction had no impact on PFS.

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1367P Predictive clinical characteristics for body weight gain in patients treated with alectinib: Analyses of J-ALEX, ALUR, and ML29453

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Background: Alectinib has emerged as one of the anaplastic lymphoma kinase (ALK) directed therapy of choice in patients with advanced *ALK+* non-small cell lung cancer (NSCLC). Body weight gain is a side effect reported in 12% of patients, caused by an increased amount of body fat. Baseline waist circumference has been found to be a positive predictor of the increase in visceral adipose tissue. We hypothesize that baseline body mass index (BMI) is positively associated with body weight gain.

Methods: Individual data from patients treated with alectinib were obtained via Vivli data-sharing platform. Studies with body weight data were selected. All body weight measurements during the first year of treatment were included. A mixed-effects model with random intercept was conducted to assess the trend of % change in body weight over time and to explore the effect of baseline characteristics on % change in body weight from baseline.

Results: Three prospective trials with body weight data were eligible (J-ALEX, ALUR, ML29453). All 309 patients were included in the analysis. During the first year of treatment, 2632 measurements of body weight were documented. Data from J-ALEX (n=103) was analyzed separately, as reference values for BMI differ between Japanese and Western populations. Percent change in body weight increased significantly over time in the mixed-model analyses in both J-ALEX ($\hat{\beta} = 0.48$, $p < 0.001$) and ALUR/ML29453 ($\hat{\beta} = 0.31$, $p = 0.001$). In the ALUR/ML29453 dataset there was an association between baseline albumin level and % change in body weight ($\hat{\beta} = 0.08$, $p = 0.003$). A maximum body weight gain of $\geq$ 10% during the first year was observed in 23 patients (22.3%) in J-ALEX and 31 patients (15.0%) in ALUR/ML29453.

Table: 1367P Baseline characteristics

	J-ALEX	ML29453	MO28928
	n = 103	*n = 129*	*n = 77*
Population	Japan	USA	Europe and Asia
Baseline characteristics			
Age (in years)	59 ± 14	55 ± 13	54 ± 12
Sex (M) (%)	39.8	43.4	58.4
Weight (kg)	55.9 [12.8]	70.5 [19.6]	70.0 [23.3]
Baseline BMI (kg/m^2)	21.9 [3.8]	24.1 [6.8]	25.8 [5.7]
Albumin baseline (g/L)	39 [7]	38 [6]	37 [9]

Conclusions: A significant and clinically relevant increase in body weight was observed in the first year of treatment with alectinib. Baseline BMI was not predictive for body weight gain. Informing patients before start of alectinib is strongly recommended.

Clinical trial identification: Trials included in analysis: J-ALEX trial, JO28928, JapicCTI-132316 ML29453, NCT02271139 ALUR trial, MO29759, CT02604342.

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1368P LUMINATE 102: A real-world study on biomarker testing rates among patients with non-small cell lung cancer (NSCLC) across lines of therapy

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Background: Molecular testing for biomarkers in patients (pts) with advanced/metastatic NSCLC (a/mNSCLC) is essential for diagnostic testing and use of targeted therapy. Testing patterns across lines of therapy (LOT) for pts with a/mNSCLC remain unclear.

Methods: This retrospective real-world study used ConcertAI Patient360™ database to assess biomarker testing patterns among adults with nonsquamous a/mNSCLC (2017—2022). Eligible pts received $\geq$1 LOT with $\geq$90-day follow-up. Biopsy and biomarker testing assessed actionable genetic alterations (*ALK, BRAF, EGFR, KRAS, NTRK, RET, ROS1*) and PD-L1 by LOT (first-, second-, third-line [1L, 2L, 3L]), test modality (IHC, FISH, CISH, NGS, PCR), and sample type (tissue/liquid).

Results: 4528 pts were included; median age 67 years and from a community setting (76%). NGS rate at 1L was 57% overall (2017—2022) and increased to 80% during 2020—2022. Testing for $\geq$1 biomarker was 85% (1L), 31% (2L), 26% (3L) (overall, 2017—2022); and 89% (1L), 37% (2L), 28% (3L) (2020—2022). *EGFR, BRAF, KRAS, RET,* and *ROS1* (Table) were mostly tested using NGS (56% at 1L vs 51% IHC, 21% FISH, and 10% PCR). Testing was most often conducted with tissue at 1L (64%) and liquid in 2L+ (41% each of tested 2L pts and 3L pts). At 2L, only 6% of pts had tissue re-biopsy, which dropped to 4% in 3L. Pts with 1L targeted therapy had higher re-testing (41% vs 25%, P<0.001) rates regardless of sample type in 2L than those who did not.

Conclusions: Tissue was most frequently used in 1L for biomarker testing by NGS for genetic alterations or IHC for PD-L1; however, tissue was not regularly re-biopsied in 2L+ settings. Biomarker testing rates drop as pts navigate through LOT. Re-testing rate is higher among pts with an actionable mutation in 1L. Standardization of biomarker testing post-1L is needed to facilitate optimal later-line treatment decisions and individualized care for pts with a/mNSCLC.

Table: 1368P

	N	Any biomarker (%)	PD-L1 (%)	*ALK* (%)	*BRAF* (%)	*EGFR* (%)	*KRAS* (%)	*METexon 14 (%)*	*NTRK* (%)	*RET* (%)	*ROS1* (%)
1L	4528	85	71	73	65	78	64	46	40	55	71
2L	1394	31	19	24	23	26	22	19	15	21	24
3L	473	26	14	20	20	22	19	16	11	18	21

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1369P BrigAlec study: Focus on alectinib efficacy after brigatinib exposure in BrigALK2 study (GFPC 02-2019)

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Background: Brigatinib and alectinib are both next-generation ALK inhibitors (ALKi) showing efficacy in naïve and post-crizotinib ALK+ advanced non-small-cell lung cancer (aNSCLC). Real-life data on alectinib efficacy after brigatinib failure are missing.

Methods: BrigALK2 study retrospectively assessed the efficacy of brigatinib in 183 *ALK*$^+$ aNSCLC pretreated with at least one ALKi during the brigatinib French Early-Access Program (1 August 2016—21 January 2019). BrigAlec study made a focus on alectinib activity after brigatinib treatment, according to post-brigatinib treatment line in BrigALK2.

Results: 92 (50.3%) patients received $\geq$ 1 agent(s) post-brigatinib. 30 (16.4%) received alectinib: 19 (10.3%) patients were treated with alectinib immediately after brigatinib, 11 (4.9%) following at least one line of treatment. At data cut-off, median follow up was 25.5 (95% CI: 10.6-30.5) months. Median duration of brigatinib treatment (mDOT) and median progression free survival according to investigator (InvmPFS) were 13.6 (95% CI: 6.3-17.7) and 10.9 (95% CI: 6.2-20.2) months, respectively. For patients who received alectinib immediately after brigatinib, mDOT was 7.1 (95% CI: 2.1-18.2) months, mInvPFS, 4.8 (95% CI: 2.0-12.5) months and mOS, 27 (95% CI: 12.5-NR) months from the start of alectinib treatment. Response (RR) and disease control rates (DCR) were 25% and 60%, respectively. Among this subgroup, reasons for brigatinib discontinuation were toxicity and progressive disease for 5 and 14 patients, respectively. mDOT and mPFS were 18.2 (95% CI: 3.4-21.6) and 12.5 (95% CI: 3.3-17.9) months for the former and 5.7 (95% CI: 0.9-10.6) and 3.4 (95% CI: 0.9-9.2) months for the latter, respectively. For patients receiving at least one treatment between brigatinib and alectinib, with a median follow up of 13.3 (95% CI: 2.3-31.5) months, mDOT, mInvPFS and mOS were 11.7 (95% CI: 0.7-21.5), 5.0 (95% CI: 0.5-18.8) and 16 (95% CI: 2.3-NR) months, respectively. RR and DCR were 10 and 30.

Conclusions: According to our retrospective real-life study, alectinib after brigatinib treatment remains an option in metastatic *ALK*+ NSCLC, especially if brigatinib is discontinued due to toxicity.

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1370P Efficacy and safety of ensartinib in ALK-positive non-small cell lung cancer patients with brain metastases: A multicenter, open-label, single-arm, phase II study

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Background: Brain metastases (BM) are a major cause of mortality in patients (pts) with ALK-positive (ALK+) non—small cell lung cancer (NSCLC). Here, we evaluated efficacy and safety of ensartinib, an ALK-TKI, in ALK+ NSCLC pts with BM.

Methods: This ongoing, multicenter, open-label phase 2 study enrolled locally advanced/recurrent/metastatic ALK+ NSCLC pts with BM, having $\leq$1 prior chemotherapy. Eligible pts were brain-enhanced MRI/CT-confirmed BM without CNS metastasis (except clinically stable)/risk of cerebral hemorrhage, and with $\geq$1 measurable intracranial lesion having no radiotherapy based on Response Assessment in Neuro-oncology BM (RANO-BM). Pts received 225 mg ensartinib orally once daily. Primary endpoint was intracranial objective response rate (iORR) by RANO-BM.

Results: As of Mar 24, 2023, 17 pts were enrolled. 14 pts who had $\geq$1 efficacy assessment were included in efficacy/safety analysis. Pts received ensartinib as 1st (1/14, 7%) or 2nd (13/14, 93%) -line therapy (with prior crizotinib). The iORR was 71.4% (10/14; 95% CI, 41.9%-91.6%), with median intracranial duration of response of 13.01 months (Table). The intracranial disease control rate and median intracranial progression-free survival (iPFS) were 100.0% and 13.63 months. Median PFS was 13.63 months. Overall survival was immature. Median cerebrospinal fluid/plasma concentration ratio was 1.52% in 10 pts, consistent with reported in phase I study of ensartinib. No mini mental status examination decline (>3 from baseline) events observed. Grade $\geq$3 treatment-related adverse events (TRAEs) occurred in 28.6% pts, with no grade 5 TRAEs/deaths. Most common TRAE was rash (85.7%).

Table: 1370P

	Intracranial per RANO-BM (n=14)
Best objective response, n (%)	
Complete response	2 (14.3)
Partial response	8 (57.1)
Stable disease	4 (28.6)
Progression disease	0
Not evaluable	0
Objective response rate, % (95% CI)	71.4 (41.9, 91.6)
Disease control rate, % (95% CI)	100 (76.8, 100.0)
Time to progression, months (95% CI)	13.63 (4.44, not evaluable)
Duration of response, months (95% CI)	13.01 (5.42, not evaluable)
Progression-free survival, months (95% CI)	13.63 (4.44, not evaluable)

Conclusions: Ensartinib showed promising intracranial efficacy with high blood-brain barrier penetration and a tolerable safety profile in ALK+ NSCLC pts with BM. Study is ongoing and final results will be presented in future.

Clinical trial identification: NCT03753685.

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1371P First-line alectinib vs. brigatinib in advanced metastatic NSCLC with ALK rearrangement: Real-world data

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Background: Alectinib and brigatinib are second-generation anaplastic lymphoma receptor tyrosine kinases (ALKs) that are widely used as first-line therapy for treating ALK-positive advanced non-small cell lung cancer (NSCLC). Given the lack of a head-to-head comparison of these drugs as first-line therapies, this retrospective observational study aimed to compare the real-world efficacy and safety of alectinib and brigatinib.

Methods: Patients who received alectinib or brigatinib as the first-line treatment for ALK-positive advanced NSCLC were evaluated for clinical outcomes of objective response rate (ORR), intracranial ORR, time to next treatment (TTNT), progression-free survival (PFS), overall survival (OS), and safety profiles.

Results: Of 208 patients who received either alectinib or brigatinib as a first-line treatment, 176 received alectinib and 32 received brigatinib. At the data cutoff point, the median follow-up duration was 10.6 months (95% CI: 9.7—11.5) in the brigatinib group and 24.6 months (95% CI: 19.4—29.9) in the alectinib group. The ORR was 91.9% with alectinib and 92.2% for brigatinib (p-value: 0.54, 95% CI: 0.35—7.30); the intracranial ORR rates were 94.6% and 100%, respectively. The rate of progression-free survival at 12 months was comparable between the alectinib group and the brigatinib group (84.8% vs. 84.1%, p-value: 0.93), and the median TTNT, PFS, and OS were not reached in either group. Treatment-related adverse events were usually mild, and treatment discontinuation due to adverse events was rare in both groups.

Conclusions: Alectinib and brigatinib had similar clinical benefits when used as the first-line treatment of NSCLC patients with ALK rearrangement in the real world.

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1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial

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Background: Repotrectinib, a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI), has shown clinical activity and manageable safety in pts with *ROS1+* NSCLC or *NTRK+* locally advanced/metastatic solid tumors in the pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). This is the first report of repotrectinib efficacy by Blinded Independent Central Review (BICR), with 8.7 mo minimum follow-up in pts with TKI-naïve and -pretreated *NTRK+* solid tumors, including NSCLC, and safety in all pts treated at the recommended phase 2 dose (RP2D).

Methods: Pts with *NTRK+* solid tumors were enrolled in TKI-naïve and -pretreated cohorts. RP2D was 160 mg QD for 14 d, then 160 mg BID. Phase 2 primary endpoint: confirmed objective response rate (cORR) by BICR.

Results: At data cutoff (19 Dec 2022), median follow-up was 17.8 mo (range, 8.7—64.6) in the TKI-naïve cohort (n = 40), and 20.1 mo (8.7—69.4) in the TKI-pretreated cohort (n = 48). The table shows efficacy in pts with *NTRK+* solid tumors and subgroups of interest. NSCLC was the most common tumor (TKI-naïve, 52%; TKI-pretreated, 29%). In TKI-naïve *NTRK+* NSCLC, cORR was 62% (95% CI, 38—82) and estimated 12-mo duration of response (DOR) and progression-free survival (PFS) was 92% (95% CI, 76—100) and 64% (43—86), respectively. In TKI-pretreated *NTRK+* NSCLC, cORR was 42% (18—71) and estimated 12-mo DOR and PFS was 44% (1—88) and 23% (0—49), respectively. In all pts treated at RP2D in TRIDENT-1 (n = 426), dizziness (62%; grade ≥3, 3%) was the most common treatment-emergent adverse event (TEAE). Grade ≥3 TEAEs occurred in 51% of pts (29% treatment-related AEs). Treatment discontinuation rate due to TEAEs was 7% (3% due to treatment-related AEs).

Conclusions: In TRIDENT-1, with 8.7 mo minimum follow-up, repotrectinib showed robust responses and durable clinical activity in both TKI-naïve and -pretreated pts with *NTRK+* solid tumors, including NSCLC. Repotrectinib safety at RP2D was manageable, consistent with prior reports.

Table: 1372P Repotrectinib in *NTRK+* solid tumors

***NTRK+* solid tumors**[a]	**TKI-naïve (n = 40)**	**TKI-pretreated (n = 48)**
Efficacy, % (95% CI)		
cORR[b]	58 (41—73)	50 (35—65)
12-mo DOR	86 (71—100)	39 (16—62)
12-mo PFS	56 (40—72)	22 (8—36)
***NTRK+* solid tumors by prior TKI**[c]		
cORR,[b] % (95% CI)		
Prior larotrectinib (n = 23)	—	43 (23—66)
Prior entrectinib (n = 24)	—	54 (33—74)
***NTRK+* solid tumors with solvent front mutations**		**(n = 25)**
Efficacy, % (95% CI)		
cORR[b]	—	60 (39—79)
12-mo DOR	—	33 (7—58)
12-mo PFS	—	21 (4—39)

[a]Tumors included NSCLC (52% TKI-naïve; 29% TKI-pretreated), salivary gland cancer (8%; 17%), thyroid cancer (12%; 8%), soft tissue sarcoma (8%; 12%); others <10% each.
[b]Per RECIST v1.1.
[c]May have received 1-2 prior TKI.

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1373P Efficacy and safety of taletrectinib in patients (Pts) with ROS1+ non-small cell lung cancer (NSCLC): Interim analysis of global TRUST-II study

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Background: Taletrectinib, a next-generation, CNS-active, ROS1 TKI with selectivity over TRKB, demonstrated high overall and intracranial response rates, prolonged PFS, activity against G2032R, and was well tolerated in TRUST-I (NCT04395677). We report interim results of taletrectinib from the pivotal phase 2 trial, TRUST-II (NCT04919811), in advanced ROS1$^+$ NSCLC pts from North America, Europe, and Asia.

Methods: TRUST-II, a multicenter, open-label, single-arm study in pts with ROS1$^+$ tumors, has 4 cohorts: 1) NSCLC: ROS1 TKI-naive, $\leq$1 line of chemotherapy (CT); 2) NSCLC: 1 prior ROS1 TKI, $\leq$1 line of CT; 3) NSCLC: $\geq$2 ROS1 TKIs, $\leq$1 line of CT; and 4) solid tumors including NSCLC if ineligible for cohorts 1-3: $\leq$3 ROS1 TKIs, $\leq$2 lines of CT. Eligible pts had ECOG PS 0—1 and could have asymptomatic or treated/controlled CNS involvement. All pts started taletrectinib at 600 mg QD. The primary endpoint is independent review committee (IRC)-assessed confirmed objective response rate ($cORR_{IRC}$); other key endpoints include investigator-assessed cORR ($cORR_{INV}$), disease control rate (DCR), time to treatment response (TTR), DoR, PFS, and safety.

Results: Interim efficacy results are from 18 pts in cohort 1 and 22 pts in cohort 2 with $\geq$2 disease assessments (39% and 59% of pts had brain metastases, respectively). $cORR_{INV}$ was 94% (17/18; 95% CI: 73, 100) in cohort 1 and 55% (12/22; 95% CI: 32, 76) in cohort 2; DCR was 100% and 91%, respectively. $cORR_{IRC}$ will be presented. In both cohorts, median TTR was 1.4 mo; median DoR was not reached. As of March 31, 2023, 72 pts were included in the safety population that received $\geq$1 dose of taletrectinib. Median duration of exposure was 3.7 mo. Overall, 90% had a treatment-emergent adverse event (TEAE), mostly grade 1—2. The most common TEAEs were increased ALT (61%) or AST (61%), and nausea (38%). No treatment-related AE (TRAE) led to discontinuation or death; 24% of pts had a TRAE leading to dose reduction.

Conclusions: In this ongoing global pivotal phase 2 study, taletrectinib demonstrated robust and consistent clinical activity with TRUST-I, including high response rates and a tolerable safety profile in both TKI-naive and TKI-pretreated pts with ROS1$^+$ NSCLC.

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1374P Survival and therapy analysis of small-scale ROS1-mutant non-small cell lung cancer (NSCLC) patients

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Background: *ROS1* fusions are well treatable aberrations in NSCLC. Besides solvent-front mutations (SFM) in resistance to targeted therapy, small-scale *ROS1* mutations are largely unknown. We exploratively analyzed the clinicopathological characteristics, survival and therapy of small-scale *ROS1* mutations in NSCLC patients without activating *ROS1* fusions or SFMs.

Methods: Next-generation sequencing was performed on tissue samples from NSCLC patients within the Network Genomic Medicine. Patients with *ROS1* fusions and SFMs were excluded. We analyzed the characteristics of the patients, their survival and their response to systemic therapy.

Results: Of 10,396 patients analyzed, 101 (1.0%) patients harbored small-scale *ROS1* mutations. Most patients were male (73.3%) and smokers (96.6%). Nearly half of the patients presented with squamous-cell carcinoma (SqCC, 40.4%). Most mutations were transversions (50.5%), and 66% were in the kinase domain. Besides *TP53* mutations (65.3%), *KRAS* (22.8%), *EGFR* (5.9%), *PIK3CA* (9.9%) and *FGFR1-4* mutations (8.9%) co-occurred. In 10 (9.9%) patients, *ROS1* mutation was the only aberration detected. The median overall survival (mOS) of all stage IV patients was 10.5 months and the survival differed significantly in patients with or without *KRAS* co-mutations (9.7 vs 21.5 months, p=0.02, HR 2.6, 95% CI: 1.1-5.9). Altough not significant, the most common *KRAS* mutation in this cohort G12V (n=7/17) worsened survival (4.4 versus 9.7 months). Patients significantly benefited from treatment with immune-checkpoint blockade (21.5 vs 4.4 months, p=0.003, HR 0.14, 95% CI: 0.03-0.6). *KRAS* co-mutant patients treated with ICB only had an mOS of 8 months. In three patients with co-occurring mutations, qualifying for and having received targeted therapy (2x *EGFRmut*, 1x *MET* fusion), mOS was 23.5 months (95% CI: NA).

Conclusions: The cohort's clinical characteristics contrasted *ROS1*-fused cohorts. Co-occurrence of *KRAS* mutations led to shortened survival and patients benefited from ICB. Our data does not support the idea of *ROS1* small-scale mutations as strong oncogenic drivers in NSCLC, but rather as relevant bystanders altering the efficacy of treatment approaches.

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1375P Beamion Lung 1, an ongoing phase Ia/Ib trial of the HER2 TKI, BI 1810631 in patients (pts) with advanced solid tumors with HER2 aberrations: Latest data

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Background: The ongoing phase Ia/Ib trial determines the safety, MTD, PK, PD and preliminary efficacy of BI 1810631 in pts with HER2 aberration-positive solid tumors (NCT04886804).

Methods: Phase Ia: pts with HER2 aberration-positive advanced/unresectable/metastatic solid tumors refractory/unsuitable for standard therapy were enrolled. Pts received escalating doses of BI 1810631 BID (starting dose 15 mg) or BI 1810631 QD (starting dose 60 mg). Phase Ib will initially include pts with advanced/metastatic *HER2* TK domain mutation-positive, pre-treated NSCLC. Additional cohorts may be included. Primary endpoints: MTD based on number of pts with DLTs (phase Ia); ORR (phase Ib). Secondary endpoints: number of pts with DLTs throughout entire treatment (Tx) period and PK parameters (phase Ia/Ib); DoR, DCR, duration of disease control and PFS (phase Ib).

Results: As of 9 Mar 2023, 43 pts had been treated. Pts had NSCLC (n = 27), lung cancer (unspecified; n = 5), colorectal cancer (n = 3), or other tumors (n = 8). Most pts had a pathological HER2 mutation. Pts received BI 1810631 at 15, 30, 60, 100, 150 mg BID (n = 3/3/4/4/3) or 60, 120, 180, 240, 300 mg QD (n = 5/4/6/6/5). Median number of cycles was 4 (range 1—15). Tx is ongoing in 26 pts. To date, 4 DLTs have been observed (grade [G] 2 edema [60 mg BID], G2 diarrhea [150 mg BID], G3 anemia [60 mg QD], G3 increased ALT [180 mg QD]). The MTD has not been reached with either schedule. Tx-related adverse events (TRAEs) were reported in 28 pts (65%; BID/QD 76/58%). The most common TRAEs were diarrhea (33%; BID/QD 47/23%), increased ALT (9%; BID/QD 6/12%) and increased AST (9%; BID/QD 6/12%). Four pts (BID/QD 1/3) had grade 3 TRAEs (increased ALT [n = 3]; increased AST [n = 1]). Of 24 evaluable lung cancer patients (17 are still on Tx), 11 responded (all PRs) and 12 had SD. Two patients with other tumors (esophagus; cholangiocarcinoma) also achieved PR.

Conclusions: These preliminary data indicate that BI 1810631 is well tolerated and shows strong efficacy signals across all dose levels in pts with pretreated HER2 aberration-positive solid tumors. Recruitment into phase Ib is ongoing with the QD regimen. Updated phase 1a data, and emerging Phase1b data, will be presented.

Clinical trial identification: NCT04886804.

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1377P Differential impact of EGFR exon 20 insertion location on tyrosine kinase inhibitor sensitivity

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Background: *EGFR* exon 20 insertion mutations (*EGFR*ex20ins) can be classified as near-loop and far-loop based on their location. The underlying structural difference between near- vs. far-loop *EGFR*ex20ins and its impact on various other novel EGFR TKIs response are not well understood.

Methods: We assessed *in vitro* activity of multiple EGFR TKIs against a panel of BaF3 cells expressing *EGFR*ex20ins mutations. Molecular Dynamics (MD) modeling of near- vs. far-loop *EGFR*ex20ins, with and without binding of EGFR TKIs was performed. Clinical responses (tumor size reduction and progression free survival) were analyzed by near- vs. far-loop insertion location in ZENITH20 and EXCLAIM trials.

Results: *In vitro* testing with different *EGFR*ex20ins indicated a favorable IC_{50} for afatinib, CLN-081, and poziotinib in near-loop (A767-P772) versus far-loop (H773-R776) insertions, whereas mobocertinib had similar IC_{50} values in near- and far-loop insertions. MD modeling using free-energy calculations indicated that wildtype EGFR displayed distinct inactive and active states with a relatively high transitional energy barrier. In comparison, the near-loop (S768insSVD) exhibited multiple states separated by shallow barriers whereas the far-loop (H773insNPH) was conformationally more rigid. The differential p-loop orientation change in near- vs. far-loop insertions played an active role in TKI binding, stabilization, and selectivity. Clinical data supported the in vitro differential impact of insertion location. In the ZENITH20 trial (n=82), in pre-treated *EGFR*ex20ins lung cancer patients, poziotinib had superior activity in near-loop than far-loop tumors both on tumor size reduction (-25.9% vs. -9.8%, p=0.0014) and PFS (11.1 vs. 3.5 months, Log Rank p=0.016). In the EXCLAIM trial platinum-pretreated patients (n=76), mobocertinib demonstrated robust activity in both groups as assessed by tumor size reduction (near -38.5% vs. far -34.1%, p=0.59) and PFS (12.0 vs. 13.0, Log Rank p=0.99).

Conclusions: Preclinical and clinical data indicated that near- vs far-loop *EGFR*ex20 insertions differentially impact sensitivity to individual TKIs. Thus, knowledge of insertion location may allow for more effectively tailored TKI therapy.

Clinical trial identification: ZENITH20: NCT03318939; EXCLAIM: NCT02716116.

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1378P Efficacy and safety of tunlametinib (HL-085) combined with vemurafenib in patients with advanced BRAF V600-mutated solid tumors: A multicenter, phase I study

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Background: Addition of a MEK inhibitor to a BRAF inhibitor enhances tumour growth inhibition, delays acquired resistance of the MAPK pathway in *BRAF* V600-mutated cancers. We assessed the safety and efficacy of tunlametinib (HL-085), a novel highly selective MEK1/2 inhibitor, in combination with vemurafenib in patients(pts) with advanced *BRAF*-mutated solid tumors.

Methods: In this phase I study, pts with advanced solid tumors who had progressed on or shown intolerance to standard treatment were enrolled and received escalating doses of tunlametinib combined with vemurafenib in dose-escalation phase (followed a 3 + 3 design). Patients received tunlametinib at dose levels of 0.5, 6, 9, 12, and 15 mg BID, together with vemurafenib 960 mg BID, in 21-day cycles. In dose-expansion phase, tunlametinib 12mg + vemurafenib 960mg, tunlametinib 12mg + vemurafenib 720mg and tunlametinib 9mg + vemurafenib 720mg dose groups were evaluated. The tunlametinib 9mg + vemurafenib 720mg was determined as the recommended phase 2 dose (RP2D).

Results: As of the data cut-off date on 04, Nov, 2022, a total of 72 pts with solid tumors were enrolled. The most common AE were CK elevation, anemia and rash which were predominantly grade 1/2. 33 pts with non-small cell lung cancer (NSCLC) have been evaluated for response. The objective response rate (ORR) was 60.6% (95% CI: 42.1%, 77.1%), a median duration of response (DoR) was 11.3 months (95% CI: 3.9, NE), and a median progression free survival (PFS) was 11.7 months (95% CI: 5.6, NE) . At the RP2D, ORR was 60.0% (95%CI: 32.3%, 83.7%) and mPFS was 10.4 months (95% CI: 5.6, NE). 24 pts with metastatic colorectal cancer (mCRC) at all doses, ORR was 25.0% (95%CI: 9.8%, 46.7%), mDoR was 5.5 months (95% CI: 2.9, NE), and mPFS was 6.2 months (95% CI: 4.8, 7.6). Antitumor activity was also seen in papillary thyroid carcinoma and pancreatic ductal adenocarcinoma.

Conclusions: Tunlametinib in combination with vemurafenib showed promising antitumor activity and manageable safety profile in pts with *BRAF* V600-mutated solid tumors. Further studies are ongoing.

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1379P Preliminary results of phase II KUNPENG study of vebreltinib in patients (Pts) with advanced NSCLC harboring c-MET alterations

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Background: C-MET alterations implicated as a negative prognostic factor. It can occur as exon 14 (METex14) skipping mutations, gene amplification, and protein overexpression. Vebreltinib (PLB-1001) is a potent highly selective c-MET inhibitor, which has shown promising results in pts with NGS-identified advanced METex14 skipping NSCLC in our previous phase I study. Here we present data from pts with METex14 mutation (Cohort 1) from a phase II, open-label, multicenter and multi-cohort KUNPENG study of PLB1001 conducted in locally advanced or metastatic NSCLC pts with c-MET alterations.

Methods: Eligible pts were ≥18 years of age, ECOG PS 0∼1 with stage IIIB/IV NSCLC. Pts in Cohort 1 received 200 mg of Vebreltinib twice daily (28 days as a cycle) until disease progression, death, AE leading to discontinuation or withdrawal of consent. The primary endpoint was objective response rate (ORR) assessed by blinded independent review committee (BIRC) per RECIST v1.1. Secondary endpoints included investigator-assessed (INV) ORR, disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS) and overall survival (OS).

Results: As of 09-Aug-2022, 113 pts were enrolled, among whom 52 pts were in Cohort 1. 32.7% (17/52) pts previously received systematic therapy for advanced or metastatic NSCLC. The primary endpoint ORR was 75% (95% CI: 61.1%∼86.0%) per BIRC, while the ORR was 77.1% (95% CI: 59.9%∼89.6%) in treatment-naïve pts and 70.6% (95% CI: 44.0%∼89.7%) in previously-treated pts. ORR per INV was 69.2% (95% CI: 54.9%∼81.3%), while the ORR was 74.3% (95% CI: 56.7%∼87.5%) in treatment-naïve pts and 58.8% (95% CI: 32.9%∼81.6%) in previously-treated pts. Per BIRC, DCR was 96.2%, median DoR was 15.9 months, median TTR was 1.0 month, median PFS was 14.1 months and median OS was 20.7 months. Among pts with baseline brain metastases (N=5), ORR was 100.0%. The most common (≥20%) TRAEs in all the 113 pts were peripheral edema (56.6%), hypoalbuminemia (22.1%) and hypoproteinemia (19.5%). Most of the TRAEs were grade 1/2.

Conclusions: Vebreltinib showed promising efficacy and favorable safety in patients with *METex*14 mutant NSCLC.

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1380P Treatment (Tx) sequencing with tepotinib in previously treated patients (pts) with MET exon 14 (METex14) skipping NSCLC in the VISION trial

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Background: Tepotinib, a MET TKI, is approved for Tx of advanced/metastatic *MET*ex14 skipping NSCLC, after immunotherapy (IO) and/or platinum (plat)-based chemotherapy (CT) in the EU, and regardless of prior Tx in other countries including the UK and Switzerland. In the VISION trial, tepotinib showed durable activity regardless of prior Tx, including in first line (1L) (1L outcomes: ORR, 56.1%; mDOR, 46.4 mo; and mPFS, 12.6 mo). We report long-term efficacy in previously treated pts (i.e. in second [2L], second or later [2L+], and third or later [3L+] lines) and prior/post-tepotinib Tx (data cut-off: Nov 20, 2022).

Methods: Pts received tepotinib 500 mg (450 mg active moiety) QD. Primary endpoint was objective response (RECIST v1.1) by IRC. Prior/post-tepotinib Tx was investigator's choice; outcomes were reported per investigator.

Results: Of 313 pts, 149 received tepotinib as 2L+ Tx (median age, 70.8 years), including 92 in 2L (median age, 70.4) and 57 in 3L+ (median age, 71.9). Across all prior Tx lines, ORR was 28.9%, mDOR was 6.0 mo, and mPFS was 5.0 mo. Outcomes were similar across prior regimens, including plat-based CT without IO (n=99), IO monotherapy (n=59), and IO+CT (n=22; **Table**). Compared with prior Tx, tepotinib outcomes in 2L+ were greatly improved (ORR, 45.0%; mDOR, 12.6 mo; mPFS, 11.0 mo) and were consistent regardless of Tx line (2L, 3L+) or smoking history. At the data cut-off, 139 (93.3%) 2L+ pts had discontinued tepotinib, and 70/139 (50.4%) had started subsequent Tx, including plat-based CT without IO (n=16), IO monotherapy (n=22), IO+CT (n=4), and MET TKIs (n=34). Across all subsequent MET TKIs after 2L+ tepotinib, best response was PR in 2 and SD in 10 pts.

Table: 1380P

Outcomes with:	Pts receiving Tx, n	ORR, %	mDOR, mo	mPFS, mo
All Tx lines prior to tepotinib by investigator assessment*	149	28.9	6.0	5.0
Plat-based CT without IO	99	29.3	5.0	4.0
IO monotherapy	59	22.0	6.0	4.0
IO+CT	22	22.7	5.0	5.0
Tepotinib by IRC				
2L+	149	45.0	12.6	11.0
2L	92	45.7	12.6	10.9
3L+	57	43.9	10.8	11.0

*mDOR and mPFS were based on a descriptive analysis. CT, chemotherapy; DOR, duration of response; IO, immunotherapy; IRC, independent review committee; m, median; mo, months; ORR, objective response rate; PFS, progression-free survival; pts, patients; Tx, treatment.

Conclusions: Tepotinib showed clinically meaningful efficacy in 2L+, 2L and 3L+, which was far greater than with standard of care Tx in prior lines. Despite pre-tepotinib Tx, a high proportion of 2L+ pts went on to receive post-tepotinib Tx, often including MET TKIs.

Clinical trial identification: NCT02864992.

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1381P TOGETHER: Pooled real-world datasets of METex14 skipping NSCLC and adjusted comparison of upfront (chemo-) immunotherapy with tepotinib from VISION

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Background: The TOGETHER study was designed for flexible pooling of *MET*ex14 skipping non-small cell lung cancer (NSCLC) patient (pt) datasets to characterize real-world (rw) outcomes before approval of MET inhibitors.

Methods: Seven datasets were used to analyze rw progression-free (rwPFS) and overall (rwOS) survival in advanced NSCLC with *MET*ex14 skipping according to Kaplan-Meier. Indirect treatment comparisons (ITC) were performed with propensity score reweighting of pts who received first-line (1L) immunotherapy (IO) alone or with chemotherapy (chemo) to match the characteristics of 111 pts with positive tissue biopsies (T+) who received 1L tepotinib in the VISION study (NCT02864992; data cut: Nov 2022).

Results: As of Jan 2023, TOGETHER included 309 pts (mean [SD] age 71.1 [9.7] years, 48% male, 52% with smoking history [SM]), with 615 lines of therapy administered between 2004 and 2022. For 1L IO+chemo (n=26; mean age 66.8 [SD 12.4], 65% SM) median rwPFS in TOGETHER was 5.7 months (95% CI: 3.1, 17.5) before and 6.9 mo (95% CI: 5.7, 29.4) after weighting, compared with 15.9 mo (95% CI: 11.3 , ne) for 1L tepotinib (HR 0.52 [0.29, 0.93]; p=0.03). For 1L IO monotherapy (n=48; mean age 73.2 [SD 9.1], 67% SM), median rwPFS in TOGETHER was 3.9 mo (95% CI: 2.7, 7.1) before and 3.4 mo (95% CI: 2.0, 9.7) after weighting compared with 15.9 mo for 1L tepotinib (HR 0.37 [0.24, 0.58]; p<0.01). Although confounded by subsequent treatments, median OS was also longer for tepotinib with 29.7 mo (95% CI: 19.1, ne) compared with 22.1 mo (95% CI: 12.6, ne) for IO+chemo (HR 0.77; p=0.38) and 18.9 mo (HR 0.64; p=0.05) for IO monotherapy. Other rw 1L treatments were chemo (n=128; mean age 69.3 [SD 9.5], 55% SM) with a median rwPFS of 4.8 mo (95% CI: 4.1, 6.2), and crizotinib (n=62; mean age 74.6 [SD 11.0], 56% SM) with a median rwPFS of 7.4 mo (95% CI: 4.4, 10.9). Median rwPFS was shorter for 2L+ chemo (4.3 mo, n=95) or 2L+ IO monotherapy (3.3 mo, n=83), and longer for 2L+ crizotinib (8.1 mo, n=68).

Conclusions: This large retrospective analysis shows poor rw outcomes for *MET*ex14 skipping NSCLC pts under standard treatments prior to the uptake of novel MET inhibitors. Matched ITC suggests longer PFS and OS with 1L tepotinib compared with 1L IO+chemo or IO monotherapy.

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1382P Liquid biopsies (LBx) and tissue biopsies (TBx) for identifying MET exon 14 (METex14) skipping in advanced NSCLC: Analyses from the phase II VISION study of tepotinib

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Background: LBx and TBx have complementary roles in detection of NSCLC driver alterations, such as METex14, which predicts efficacy of MET inhibitors. The only MET inhibitor trial to enroll based on prospective detection of METex14 in LBx and/or TBx is the VISION trial of tepotinib. We evaluated patient (pt) characteristics and outcomes according to METex14 positivity in LBx and/or TBx (data cut-off: Nov 20, 2022).

Methods: *MET*ex14 was centrally assessed in prescreening by NGS analysis of fresh LBx (Guardant360® or Archer®MET) and/or archival or fresh TBx (Oncomine Focus or Archer®MET). Pts in Japan could enroll based on local TBx RT-PCR via the LC-SCRUM program. Parallel LBx/TBx testing was recommended but not mandatory. Eligibility required LBx-positive (L+) and/or TBx-positive (T+) status.

Results: Of 313 pts, 208 (66.5%) were T+ and 178 (56.9%) were L+. L+ pts had worse baseline prognostic features than T+ pts, including more pts with ≥3 target lesions (27.5% vs 18.8%) or ECOG PS 1 (76.4% vs 72.1%), higher median sum of target lesion diameters (67.1 vs 55.2 mm) and worse health-related quality of life (mean EORTC QLQ-C30 GHS, 53.9 vs 60.1). In 180 T+ pts with matching LBx results, *MET*ex14 was detected in ctDNA (L+) in 74 (41.1%) (i.e. T+/L+) and was undetectable (L−) in 106 (58.9%) (i.e. T+/L−). ORRs were slightly higher in T+/L+ pts, but T+/L− pts had longer DOR, PFS and OS. Overall meaningful durable efficacy was seen in treatment-naive and previously treated pts (Table).

Table: 1382P

	Treatment-naive		Previously treated	
	T+/L− (n=52)	T+/L+ (n=42)	T+/L− (n=54)	T+/L+ (n=32)
ORR, % (95% CI)	57.7 (43.2, 71.3)	64.3 (48.0, 78.4)	44.4 (30.9, 58.6)	53.1 (34.7, 70.9)
mDOR, months (95% CI)	ne (10.4, ne)	19.4 (7.6, ne)	12.6 (5.1, 20.8)	9.9 (4.4, 15.4)
mPFS, months (95% CI)	22.1 (14.8, ne)	12.1 (7.8, 49.7)	13.8 (8.2, 24.9)	8.2 (5.5, 13.7)
mOS, months (95% CI)	32.7 (15.3, ne)	28.5 (14.2, ne)	20.8 (15.6, 32.5)	19.8 (10.0, 26.5)

CI, confidence interval; DOR, duration of response; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Conclusions: Tepotinib had robust and durable activity in T+ pts with L− or L+ status. While both LBx and TBx are suitable and complementary for detecting *MET*ex14, LBx may preferentially select pts with a poorer prognosis and higher tumor load. Undetectable *MET*ex14 in baseline ctDNA may define a more favorable treatment outcome. Differences in populations identified by TBx and LBx should be considered when interpreting trial data.

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1383P Efficacy of capmatinib compared to standard of care for German patients with locally advanced or metastatic NSCLC harboring METex14 mutations: Results from the RECAP study

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Background: Capmatinib, a selective MET inhibitor, is approved by EMA and other health authorities worldwide for the treatment of adult patients (pts) with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping (*MET*ex14) mutations. The RECAP study provided comparative evidence of capmatinib vs standard of care (SoC) in first (1L) and second line (2L) NSCLC pts with *MET*ex14 mutations (NCT05796726).

Methods: The RECAP study is a historical comparison of capmatinib pts from the GEOMETRY mono-1 study with an external control arm of SoC pts from German routine care collected via a retrospective chart review. Analyses were performed both naive and propensity score adjusted. Evaluated outcomes included efficacy endpoints such as overall survival (OS), progression-free survival (PFS), overall response rate (ORR), time to CNS progression (CNSprog) and exploratory safety endpoints.

Results: A total of 119 1L and 46 2L pts were included in the chart review and compared to 60 1L and 81 2L pts treated with capmatinib. For 1L pts, the naive comparison showed a significant benefit of capmatinib for OS (median 25.49 vs 14.59 months; HR 0.58; 95% CI 0.39-0.87; p=0.011), PFS (median 12.45 vs 5.03 months; HR 0.44; 95% CI 0.31-0.63; p<0.001) and ORR (event rate 68.3 vs 26.9%; RR 2.54; 95% CI 1.80-3.58; p<0.001). In 2L, OS, PFS and ORR showed trends favoring capmatinib with no significant results. Notably, CNSprog resulted in a significant benefit with

capmatinib in 1L and 2L. No patient developed new, symptomatic brain metastases during capmatinib treatment. Propensity score adjusted analyses showed consistent results to naive analysis. Exploratory safety endpoints indicate a manageable safety profile for capmatinib.

Conclusions: For 1L pts, clinically relevant effects of capmatinib are seen in all efficacy and safety endpoints before and after adjustment. 2L results are consistently in favor of capmatinib but are limited by low patient numbers. Overall, RECAP demonstrates the important role of capmatinib for NSCLC pts harboring *MET*ex14 mutations with significant efficacy in preventing the development of brain metastases.

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1384P Phase II study of cabozantinib in patients with MET-altered lung cancers

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Background: MET alterations occur in about 5% of lung cancers and define a subgroup associated with sensitivity to MET tyrosine kinase inhibitors (TKIs). Only type I MET TKIs have been approved for these patients. In contrast, cabozantinib is a type II multikinase inhibitor with activity against MET.

Methods: In this single-arm phase 2 trial, patients (pts) with stage IV *MET*-altered lung cancers received cabozantinib 60 mg daily until progressive disease or intolerable toxicity. A Simon two-stage minimax design was used. If at least 2 responses were observed among 16 evaluable pts, the trial would proceed to the 25-patient second stage. The primary endpoint was objective response rate (ORR).

Results: The target of 25 pts was met. Among pts evaluable to date, 19 pts (79%; 19/24) had a *MET* exon 14 alteration only (skipping mutation, n=17; *MET* fusion with exon 14 exclusion, n=2), 2 pts (8%) had *MET* amplification only, and 3 pts (12%) had a concurrent *MET* exon 14 alteration and *MET* amplification. In cases with available tissue, FACETS confirmed *MET* amplification (≥6 copies), and MET immunohistochemistry was diffusely positive (>50%) in all cases. Most pts (84%, 20/24) received a prior MET TKI (crizotinib, n=15; capmatinib, n=4; tepotinib, n=1); 16 pts (67%) and 13 pts (54%) received one or more prior lines of chemotherapy and immunotherapy, respectively. The ORR was 17% (4/24; 95% CI 6.8-35.8%; *MET* skipping mutation, n=3; concurrent *MET* skipping mutation and *MET* amplification, n=1) and the disease control rate was 71% (95% CI 50.8-85.1%; partial response, n=4; stable disease, n=13, one with *MET* D1228N). Of the 4 pts with a partial response, 2 had received crizotinib and 1 capmatinib. The median progression-free survival was 6 months (95% CI 3.9-8.8 months), and the median overall survival was 9 months (95% CI 4.0-13.5 months). The most frequent treatment-related adverse events were grade 1 and 2 palmar-plantar erythrodysesthesia (42%), fatigue (38%), and diarrhea (38%).

Conclusions: Cabozantinib was active in MET-dependent cancers. Due to its alternative type II binding mode, cabozantinib can be useful in the treatment of type I TKI resistance. As proof of concept, 3 of 4 responses were observed in patients with type I MET TKI progression.

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1385P Genomics of early progression on selpercatinib in patients with RET fusion-positive lung cancers

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Background: Selective RET inhibitors transformed the treatment (tx) paradigm of *RET* fusion-positive (*RET*+) lung cancers. For selpercatinib, the median progression free survival (PFS) is 22.0 months (mos) for tx naive patients and 24.9 mos for platinum doublet pretreated patients. Genomic factors associated with early versus late progression are unknown.

Methods: We analyzed data from 80 patients with *RET*+ LC identified between January 2014 and March 2023 utilizing a DNA-based hybrid capture tumor next generation tumor sequencing assay (MSK-IMPACT) and plasma ctDNA assay (MSK-ACCESS). Patients with radiologic progression (PD) on selpercatinib ≤ 3 mos from initiation were classified as "rapid progressors", >3- 24 mos as "intermediate progressors", and ≥24 months as"late progressors." Baseline and post-PD MSK-IMPACT and MSK-ACCESS specimens were evaluated. Patients with post-PD biopsies were evaluated for acquired resistance (AR) (classified as on-target (secondary *RET* mutations), off-target (non-*RET* OncoKB level 1-4), and unknown).

Results: Among 80 patients with *RET*+ LC, 63 had pre-tx tumor sequencing and 35 patients had post-tx tumor/ctDNA sequencing. 58% (n=46/80) progressed on selpercatinib. PD was classified as rapid, intermediate, and late in 9% (n=7), 35% (n=28), 14% (n=11), respectively. Acquired resistance (AR) was identified in 48% of cases. Six patients had on-target AR and 17 patients had off-target AR. Most common off-target AR included *MET* amp (9%), *KRAS* mutation (6%), *PIK3CA* mutation (6%), *CDKN2A* mutation (6%), and *FGFR1* amp (6%). There were no differences in age, gender, ethnicity, prior tx, or PDL1 status between these groups. Pre-tx *TP53*, *KEAP1*, and *ARID1A* mutations were more common in rapid and intermediate versus late PD (p=0.03, p=0.02, p=0.06). Off-target mechanisms of resistance appeared to be enriched in rapid and early progressors vs late progressors (75% vs 51% vs 25%, p=0.3).

Conclusions: *RET* fusion+ NSCLCs that progressed on selpercatinib prior to two years, an approximation of the drug's median PFS, were enriched for select co-occurring alterations (e.g., *TP53, KEAP1*, and *ARID1A* mutations) in pre-tx samples and off-target resistance in post-PD samples.

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1386P Validation of MET amplification using next-generation sequencing in lung adenocarcinoma

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Background: *MET* gene amplification is a potential therapeutic target in lung adenocarcinoma (LUAD) currently identified by fluorescence in situ hybridization (FISH). Next-generation sequencing (NGS) has become an essential diagnostic tool for routine biomarker profiling of cancer patients, including the detection of copy number alterations (CNAs). The aim of this study was to evaluate the concordance between these two methods and identify potential limitations of NGS implementation.

Methods: Thirty cases with *MET* amplification detected by FISH were retrospectively selected from a cohort of 567 LUAD diagnosed between 2018 and 2022 (prevalence: 5.3%). Cases were classified according to the current Camidge-2021 FISH criteria as 5 low-amplified (*MET*/CEP7 ratio $\geq$1.8 to $\leq$2.2), 11 medium-amplified (*MET*/CEP7 ratio $>$2.2 to $<$4) and 14 high-amplified (*MET*/CEP7 ratio $\geq$4). Tumor area and tumor cell percentage were annotated to later evaluate complete molecular alterations by NGS using the Oncomine Precision Assay.

Results: Detection of *MET* amplification was concordant in only 16 out of 30 cases (5 cases were excluded due to insufficient DNA), and no correlation was found between *MET* copy number determined by FISH and NGS (R^2=0.346). Distribution of amplification categories was random: 2 cases showed low-amplification, 7 medium-amplification, and 7 high-amplification. Slight differences were observed between concordant and discordant cases in: *MET* enumeration (12.4 vs. 9.3 gene copies), *MET*/CEP7 ratio (4.8 vs. 3.2), tumor area (15 vs. 11mm2), and DNA concentration (12 vs. 7 ng/µl), but none of them were statistically significant. FISH results of the 9 discordant cases were reviewed and high copy number heterogeneity was observed in 7 of them and focal amplifications were observed in 2. In 7 out of 9 discordant cases, co-alterations were detected: 2 *KRAS* (p.G12C and p.Q61H), 2 *BRAF* non-V600, 2 *MET* exon 14 skipping and one *EGFR* p.L858R.

Conclusions: The detection of *MET* amplification by NGS did not show satisfactory concordance with the results obtained by FISH, likely due to the high heterogeneity in *MET* gene copy number enumeration. As a result, complementary determination by FISH is necessary, given the lack of standardized criteria for establishing CNAs positivity by NGS.

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1387P Efficacy of first-line treatment options in advanced HER2-altered non-small cell lung cancer: A multi-center retrospective study

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Background: HER2 alterations are identified in 2-4% of non-small cell lung cancer (NSCLC), indicating poor clinical outcomes. Due to the deficiency of effective targeted therapies in the first-line setting, chemotherapy alone or combined with Bevacizumab, immune checkpoint inhibitors (ICIs) or both are recommended as standard options. However, the optimal therapy is still undetermined.

Methods: Stage IV NSCLC patients with HER2 alteration were retrospectively analyzed from 6 cancer centers in China between May 2017 and February 2023. All the patients received chemotherapy alone (C), chemotherapy combined with Bevacizumab (BC), chemotherapy combined with ICIs (IC), or chemotherapy combined with Bevacizumab and ICIs (IBC) as first-line strategies. The clinical outcomes were evaluated.

Results: Eighty patients with HER2 mutation (75/80) or amplification (5/80) were included, in which 10 patients received chemotherapy alone, 37 received BC, 24 received IC, and 9 received IBC treatment. Compared with chemotherapy, combination therapy significantly improved mPFS (8.47 months VS 4.97 months, p$<$0.0001). Further analysis based on different combination mode showed that, each of the combination therapeutics, including BC (mPFS 7.27 m, HR=0.31, 95% CI: 0.14-0.68, p$<$0.001), IC (mPFS 8.47m, HR=0.20, 95% CI:0.08-0.48, p=0.004) and IBC (mPFS 16.3m, HR=0.08, 95% CI: 0.02-0.25, p$<$0.001), gave beneficial PFS compared with chemotherapy. In our effort to determine the optimal combination strategy, we found IBC treatment gave longer mPFS compared with BC (HR=0.15, 95% CI: 0.04-0.50, p$<$0.001) and IC (HR=0.43, 95% CI: 0.16-1.18, p=0.092). However, the efficacy of IC and BC schemes are comparable.

Table: 1387P

Groups	Patient number	ORR, % (95% CI)	DCR, % (95% CI)	mPFS, months (95% CI)
Chemotherapy	n=10	30.0(1.60,58.4)	100(100,100)	4.97 (4.09, 5.84)
Combination	n=70	25.7(15.5,36.0)	91.4(84.9,98.0)	8.47 (7.28, 9.35)
IC	n=24	29.2(11.0,47.4)	87.5(74.3,101)	8.47 (7.15, 9.78)
BC	n=37	18.9(6.30,31.5)	91.9(83.1,101)	7.27 (6.27, 8.26)
IBC	n=9	44.4(12.0,76.9)	100(100,100)	16.3 (8.83, 23.8)
ALL	n=80	26.3(16.6,35.9)	92.5(86.7,98.3)	7.63 (6.35, 8.92)

Conclusions: Chemotherapy-based combination strategies improve patient survival compared with chemotherapy in the first-line therapy of HER2-altered NSCLC, while the IBC mode lead to the optimal PFS.

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1388P Real-world prognostic value of RET fusions in advanced non-small cell lung cancer (aNSCLC)

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Background: *RET* fusions are found in 1−2% of patients (pts) with NSCLC. RET inhibitors (RETi) have recently been approved for *RET* fusion-positive (*RET*+) aNSCLC, but the prognostic value of *RET* fusions is unclear. This study aimed to describe the overall survival (OS) of pts with *RET*+ or *RET* wild-type (*RET*-WT: no *RET* alterations) NSCLC using real-world data from two large databases.

Methods: This was a retrospective, observational study using US-based data from 1) a nationwide Flatiron Health−Foundation Medicine NSCLC clinico-genomic de-identified database (FH-FMI CGDB) and 2) a nationwide longitudinal electronic health record-derived FH de-identified database (FH). Pts with aNSCLC diagnosed between 1 Jan 2011 and 31 Dec 2021 (CGDB) or 30 Sep 2022 (FH) with known *RET* fusion status were included. Pts with other actionable gene alterations or previous treatment with RETi or a clinical study drug in any line were excluded. The primary objective was to compare the OS of pts with *RET*-WT vs *RET*+ aNSCLC in 1) all pts (index date: date of advanced diagnosis) and 2) pts who received first-line (1L) chemotherapy plus cancer immunotherapy (index date: start of 1L therapy). Hazard ratios (HRs) for left-truncated OS (to account for immortal time from index to *RET* testing) were adjusted for confounding variables using a multivariate Cox proportional regression model.

Results: Overall, 45 (CGDB) and 60 (FH) pts with *RET*+ aNSCLC, and 5,890 (CGDB) and 16,566 (FH) pts with *RET*-WT aNSCLC were included in the analysis. Pts with *RET*+ NSCLC tended to be younger ($<$65 yrs old: 51% vs 33%), less frequently smokers (8% vs 47%), and less commonly had *KRAS* (7% vs 34%) and *TP53* (42% vs 72%) mutations than *RET*-WT pts. In CGDB and FH, there was no significant difference in OS between *RET*-WT and *RET*+ pts (Table).

Conclusions: Data from this real-world study using two large databases show that pts with *RET*+ aNSCLC do not have a different prognosis than pts with *RET*-WT aNSCLC. These data suggest that *RET* fusions have no prognostic value in aNSCLC.

Table: 1388P

Cohort	*RET* fusion status	Pts with *RET*+ or *RET*-WT NSCLC from the CGDB			Pts with *RET*+ or *RET*-WT NSCLC from the FH database		
		Events/N	Median OS (95% CI)	Adjusted[‡] HR (95% CI)	Events (n/N)	Median OS (95% CI)	Adjusted HR[‡] (95% CI)
All pts*	*RET*+	25/45	12.0 (5.2—25.1)	1.08 (0.72—1.63)	33/60	12.9 (7.1—27.2)	1.28 (0.83—1.97)
	RET-WT	4,101/5,890	7.9 (7.4—8.3)		10,958/16,566	8.7 (8.5—9.0)	
1L chemotherapy + cancer immunotherapy[†]	*RET*+	9/16	14.9 (10.6—NR)	0.93 (0.47—1.85)	6/14	7.0 (4.5—NR)	1.10 (0.49—2.45)
	RET-WT	946/1,603	10.5 (9.5—11.1)		2,647/4,572	10.3 (9.8—10.9)	

*Index: advanced diagnosis date; [†]index: start of 1L therapy; [‡]adjusted by multivariate Cox proportional regression model for multiple covariates.

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1389P Efficacy of poziotinib in HER2 exon 20 insertion NSCLC patients who received prior platinum-based and HER2 targeted therapies

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Background: Poziotinib (Pozio) is an oral pan-ErbB tyrosine kinase inhibitor (TKI) of EGFR and HER2 exon 20 mutations with demonstrated clinical activity and an expected safety profile. There is an unmet medical need for patients who progressed on platinum-based (PLT) or/and HER2 targeted therapy. Pozio is being studied in a multi-cohort, global, phase 2 study (ZENITH20). Here, we present the efficacy and safety results of pozio in patients with NSCLC HER2 exon 20 mutations who previously received 2+ lines of therapies including HER2-targeted therapies.

Methods: Patients with HER2 exon 20 NSCLC who previously received 2+ lines of systemic therapy were enrolled in 2 cohorts of ZENITH20. Poziotinib was administered orally either as 16 mg QD or 8 mg BID until disease progression or toxicity. The endpoints were ORR, PFS, and DOR, evaluated by a central, independent review committee (IRC) using RECIST 1.1 and safety.

Results: 91 patients were treated with pozio (69 16 mg QD and 22 8 mg BID) as 3rd line. Of these, 35 patients (25 16 mg QD; 10 8 mg BID) had prior HER2 therapy such as trastuzumab, TDM1, and T-DXd. The median age was 63 yrs; 71% females, 60% non-smokers, and 14% had stable brain metastases at study entry. 46% had 2 lines and 54% had 3+ lines of prior therapy (median of 3). In patients who received pozio in 3rd line, the ORR was 31% (28/91) with 95% confidence interval of [22, 41] by IRC. The median DOR was 6.4 m and median PFS was 5.8 m. The efficacy was consistent independent of types and sequence of prior therapies. ORRs were 30% with PLT+any systemic therapy; 30% with PLT+docetaxel and 43% with PLT+TKI. In 35 patients that had a prior HER2 therapy, the ORR was 29%; DCR was 71%; median DOR was 5.5 m and median PFS was 5.6 m. Responses by local review were seen in 4 of 8 prior T-DXd treated patients. The most common Grade $\geq$3 AEs were rash (42%), diarrhea (31%), and mucositis (23%). 82% had dose interruptions, 74% had dose reductions, and 15% discontinued drug due to related AEs.

Conclusions: Poziotinib demonstrated clinically meaningful efficacy in patients who received prior 2+ lines of therapy including HER2 therapy. ZENITH20 study provides a large dataset in the 3rd or later line setting of HER2 exon 20 mutations in NSCLC who have very limited treatment options.

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1390P Real-world characteristics, treatment patterns and outcomes of patients with advanced HER2/ERBB2-mutant non-small cell lung cancer (NSCLC) in France and Germany

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Background: HER2 mutations (HER2m) are a potential therapeutic target in 2—3% of patients with non-squamous NSCLC; however, real-world evidence on demographics and outcomes is limited. We assessed patient characteristics and treatment patterns for advanced HER2m NSCLC at a French and a German academic centre.

Methods: Adults with advanced HER2m non-squamous NSCLC were identified at Institut Curie, France (study: 1 Jan 2011—22 Apr 2022) and Thoraxklinik Heidelberg, Germany (1 Jan 2014—5 May 2022). Lines of therapy (L) and treatment pathways were characterised. Demographic/clinical characteristics were analysed by descriptive statistics; survival was assessed by Kaplan—Meier analysis. Real-world progression-free survival (rwPFS) was time between L start and earliest progression event (Germany), discontinuation due to progression (France), next L start or death.

Results: Of 55 patients with advanced HER2m NSCLC (n=17, France; n=38, Germany), the median age at diagnosis was 66 years, 63.6% were female and 74.6% had ECOG scores of 0 or 1. 48 patients (87.3%) received at least 1L, 29 (52.7%) received at least 2L and 19 (34.5%) received at least 3L. The most common regimens were carboplatin + pemetrexed (13/48, 27.1%) and carboplatin + pemetrexed + pembrolizumab (9/48, 18.8%) in 1L and pembrolizumab (6/29, 21.0%), carboplatin + pembrolizumab + pemetrexed (3/29, 10.3%) and pemetrexed (3/29, 10.3%) in 2L. The most common treatment pathway began with non-platinum-based chemotherapy or platinum-based chemotherapy in 1L (26/48, 54.2%) and immunotherapy in 2L (7/26, 26.9%) (Table). Median real-world overall survival from the start of 1L was 16.5 months (95% CI: 12.3—29.8). Median rwPFS in the 1L was 5.1 months (95% CI: 3.5—8.5).

Conclusions: Chemotherapy was the mainstay in 1L; diverse regimens were used in 2L. Poor survival suggests a need for novel therapeutic options for advanced HER2m NSCLC.

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Table: 1390P

Regimen	1L (n = 48)		2L (n = 29)		3L (n = 19)	
	n	%	n	%	n	%
HER2 targeted[a]	1	2.1	1	3.4	4	21.1
HER2 targeted[a] + IMT	0	0	0	0	1	5.3
HER2 targeted[a] + non-plat	0	0	4	13.8	0	0
IMT	3	6.3	8	27.6	1	5.3
IMT + non-HER2 targeted[b] + non-plat + plat	1	2.1	0	0	0	0
IMT + non-plat + plat	11	22.9	3	10.3	1	5.3
Non-HER2 targeted[b]	1	2.1	1	3.4	0	0
Non-HER2 targeted[b] + non-plat	0	0	2	6.9	2	10.5
Non-HER2 targeted[b] + non-plat + plat	4	8.3	0	0	0	0
Non-plat	1	2.1	6	20.7	7	36.8
Non-plat + plat	26	54.2	4	13.8	3	15.8

[a]Neratinib, afatinib, poziotinib, trastuzumab, or trastuzumab emtansine. [b]Alectinib, bevacizumab, ceritinib, or ramucirumab. IMT, immunotherapy; non-plat, non-platinum-based chemotherapy; plat, platinum-based chemotherapy.

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1391P Capmatinib vs docetaxel as second- or third-line (2/3L) therapy in patients (pts) with METex14-mutated advanced NSCLC (aNSCLC): The GeoMETry-III trial

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Background: Capmatinib (cap), a selective MET inhibitor, is approved by multiple health authorities worldwide, including US, Japan, and EU, in *MET*ex14-mutated aNSCLC population, based on the phase 2 GeoMETry mono-1 study (NCT02414139). Here, we report the available efficacy and safety of cap vs docetaxel (doc) from GeoMETry-III trial.

Methods: GeoMETry-III is a multicenter, open-label, randomized, phase 3 trial (NCT04427072). Eligible pts included *EGFR* wild type, *ALK* rearrangement−negative, stage IIIB/IIIC or IV *MET*ex14−mutated NSCLC who have progressed on 1/2L of systemic therapy. Primary and key secondary endpoints were progression-free survival (PFS) and overall response rate (ORR) by blinded independent review committee (BIRC) assessment per RECIST v1.1, respectively. Although 90 pts were planned to be included in this study, due to slow enrollment, the study was terminated early with 22 patients enrolled.

Results: As of Feb 15, 2023, data cutoff, 22 pts were randomized 2:1 to cap (n = 15) or doc (n = 7) arms. Baseline characteristics were generally comparable between arms. The observed benefit with cap vs doc in median PFS was not statistically significant: 6.1 months vs 4.1 months; HR, 0.46; 95% CI 0.16-1.3; $P = 0.066$. Of 15 pts in cap arm, 8 had partial response (53.3%, 95% CI 26.6-78.7) vs none in doc arm (95% CI 0-41.0). Disease control rate was 73.3%; 95% CI 44.9-92.2 vs 57.1%; 95% CI 18.4-90.1, respectively. Median duration of response in cap was 9.9 months; 95% CI 2.9-NE. Five of 6 doc-treated pts crossed over to cap (at 1.4, 1.9, 6.0, 6.3, and 13.7 months from doc start due to progression), which confounded the overall survival results. No new safety signals were observed for cap. Most frequent treatment-related AEs (≥25%, any grade) in cap were peripheral edema (46.7%) and nausea (33.3%); and in doc were, alopecia (66.7%), anemia (50.0%), asthenia, conjunctivitis, lacrimation increased, onycholysis (33.3% each).

Conclusions: Overall, the numerical differences in PFS and ORR showed trends favoring cap, and together with safety, are consistent with previous results of the pivotal GeoMETry mono-1 study. The GeoMETry-III trial was terminated early due to enrollment constraints.

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1392P Safety and efficacy of crizotinib in MET mutated (METmut) advanced non-small cell lung Cancer (aNSCLC): Results from the Drug Rediscovery Protocol (DRUP)

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Background: *MET*muts occur in 3% of NSCLC and are associated with poor survival. Despite known sensitivity of *MET*mut NSCLC to MET inhibition, no EMA approved

therapies existed for this indication before 2022. In this study, safety and efficacy of oral tyrosine kinase (TK) inhibitor crizotinib, approved for *ALK*+ and *ROS1*+ NSCLC, were evaluated in *MET*mut aNSCLC.

Methods: In DRUP (NCT0295234), cancer patients (pts) are treated with drugs outside their labeled indication, based on their molecular profile. Previously treated and treatment naïve pts with *MET*mut aNSCLC were included and treated with crizotinib 250 mg BID until disease progression or intolerable toxicity. Pts with known symptomatic, untreated brain metastases were excluded. Primary endpoints were clinical benefit (CB: RECIST v1.1 confirmed objective response (OR) or stable disease (SD) $\geq$ 16 weeks) and safety. Pts were enrolled using a Simon like 2-stage model, with 8 pts in stage 1 and if $\geq$ 1/8 pts had CB, 24 pts in stage 2.

Results: Between 09/2018 and 10/2022, 44 pts were screened, 30 started treatment and 24 were evaluable for response. Median age was 75 [IQR, 69 − 78]. ECOG performance status was 0, 1 and 2 in 6 (25%), 12 (50%) and 6 (25%) pts, respectively. 19 pts (79%) were treatment naïve, 5 (21%) had received checkpoint blockade and/or platinum based chemotherapy. 1 (4%) complete response (CR), 14 (58%) partial responses and 2 (8%) SDs $\geq$ 16 weeks were observed, with resulting OR-rate of 62% (95% CI, 41 − 81) and CB-rate of 71% (95% CI, 49 − 87). After 20.2 months median follow-up, median progression-free and overall survival were 8.3 (95% CI, 6.0 − NA) and 13.0 months (95% CI, 8.0 − NA), respectively. 23 treatment-related grade $\geq$ 3 adverse events occurred in 12/30 pts (40%) and led to treatment discontinuation in 2 (6%). The pt who achieved CR had a TK domain mutation (p.H1094Y), all others exon 14 skipping *MET*muts. Post hoc whole genome sequencing of pre-treatment biopsies of 11 pts (46%) did not reveal any biomarkers for (non-)response.

Conclusions: Crizotinib proved highly effective in pts with *MET*mut aNSCLC, with a manageable toxicity profile. Additional research is warranted to identify biomarkers for response.

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1393P Characteristics of MET gene and its relationship with TMB/MMR genes in Chinese NSCLC population

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Background: Patients with driver-gene mutations in NSCLC can benefit significantly from corresponding targeted therapy, but respond poorly to immunotherapy (such as EGFR, ALK). As a driver-gene of NSCLC, the relationship between the characteristics of MET and many immune indicators in the Chinese population is still unclear. This study aims to elucidate the characteristics of the MET gene and its relationship with immune indicators in the Chinese NSCLC population.

Methods: 732 Formalin-Fixed Paraffin-Embedded (FFPE) lung adenocarcinoma samples were collected and detected by Next Generation Sequencing 603-gene panel from July, 2021 to March, 2023 were selected from the study. The biomarkers of immunotherapy (TMB-High [$\geq$10/Mb], and MMR-related genes (MLH1, MSH2, MSH6, PMS2) were also calculated.

Results: Among the 732 subjects included in the previous detection, a total of 32 cases were detected to carry MET-related mutations. The detection rate of MET gene was 4.37%. The median age was 65 (13-97). 15% of patients belonged to exon 14 skipping type (5/32); MET amplification accounted for the least, accounting for only 6% (2/32). The top 3 of mutation frequency were Met_L221W (4/32), MET_Q1067K (2/32), and MET_F206S (2/32). The gene partners of Met co-mutation were analyzed, and the top five genes were PPP2R1A, HIST1H3G, CDKN1B, SYK, and ERBB4. In the analysis of the immune indicators of the MET mutant population and wild-type population, the Mann-Whitney U test found that among the TMB indicators, the mean value of the MET group was 8.09 with SD of 7.91, and the mean value of the un-MET group was 5.94 with SD of 4.98. MET was correlated with TMB with statistical difference (P value 0.02).We also paid attention to MET and MMR-related genes. The analysis showed that there was a significant relationship between MET group and wild-type MET group and MMR gene (p-value: 0.026).

Conclusions: In the Chinese NSCLC population, there is a correlation between MET expression and TMB, and the MET mutation will increase the TMB value. MET expression was significantly correlated with MMR-related gene mutations.

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1394P Real-world experience in treatment of patients with non-small cell lung cancer with BRAF and cMET Exon 14 skipping mutations

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Background: BRAF and cMET Exon 14 skipping are rare mutations of NSCLC. Opposite to other alterations, the preferred treatment sequencing in 1st and 2nd line is not clear.

Methods: We created an international registry for patients (pts) with advanced NSCLC harboring BRAF and cMET exon 14 skipping mutations, diagnosed from Jan 2017 until June 2022, excluding pts enrolled in clinical trials. Clinicopathologic and molecular data were collected, and treatment patterns were recorded. Clinical endpoints according to treatment assignment were assessed using Kaplan-Meier curves and Cox regression models.

Results: Data on 58 pts from 7 centers across 5 countries were included in the final analysis. Forty patients had cMET exon 14 skipping mutation and 18 had BRAF V600E mutation. Main characteristics: median age 66.7 (range: 36.0-91.0) years, female sex (48.0%), never or past smokers (71.0%), performance status 0-1 in (84.0%), adenocarcinoma (86.2%), stage IIIC - IV at diagnosis (82.2%), bone and brain metastasis (45.0%, and 21.0%, respectively). Mutations were uniformly diagnosed by NGS in all centers. Programmed death-ligand 1 TPS was $<$1% in 18%, 1-49% in 34% and $>$50% in 48% of cases. Fifty-three and 28 pts received 1st and 2nd line treatments, respectively, among which 52.8% received targeted therapy (TT) in 1st line and 53.5% in 2nd line. Overall response rate (ORR) and disease control rate (DCR) for 1st line treatment with TT vs. other (IO +/- CT) was 55.6% vs. 21.7% (p = 0.0084) and 66.7% vs 39.1% (p =

0.04), respectively. Type of treatment in 1st line (TT vs. IO +/- CT) affected Time to Treatment Discontinuation (TTD), 11.6 m vs. 4.6 m, p = 0.006. Overall survival for the whole group was 15.4 m and was not statistically influenced by the type of treatment (19.2 m vs. 13.5 m; p = 0.83).

Conclusions: This real-world retrospective study suggests that TT in the 1st line is the preferred option for the treatment of pts with advanced NSCLC with BRAF and cMET exon 14 skipping mutations, as opposed to IO +/- CT, due to higher ORR and DCR, longer TTD and the fact that almost half of the patients did not receive 2nd line treatment. U Janzic and W. Shalata contributed equally to this study.

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1396P HER2 testing pattern, characteristics of locally advanced or metastatic NSCLC patients by HER2 testing in France

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Background: HER2 targeted treatment impacted the management of NSCLC patients (pts) with HER2 mutations; however, real-world data on HER2 testing in NSCLC pts is limited. This abstract aims to describe HER2 testing and characteristics of locally advanced or metastatic (LAM) NSCLC pts in France.

Methods: This is a retrospective analysis of observational data from the EpidemioStrategy and Medical Economics (ESME) Lung Cancer Database from France (NCT03848052). Patients >18 years diagnosed with LAM NSCLC from 2015 without any other previous malignancy were included in the analysis.

Results: ESME includes 22561 LAM NSCLC pts who met the eligibility criteria. Of those, 33.4% received at least 1 HER2 test and 10.3% of tested pts received >1 test. HER2 testing decreased over time (2015 27.7%, 2016 21.0%, 2017 17.1%, 2018 12.6%, 2019 9.7%, 2020 3.7%). 2.5% of tested pts had HER2 alteration. 81.4% of LAM NSCLC pts received HER2 testing after LAM NSCLC diagnosis, with a median time of 28 days from LAM NSCLC diagnosis to test result. 58.2% received first HER2 test result before 1st line treatment, and the median time to treatment start from the test result was 20 days. Primary tumor tissue was the most common sample material for HER2 testing (71.5% of pts), followed by metastasis tissue (27.4%) and blood (3.9%). Age at initial and LAM-NSCLC diagnosis were similar between HER2 tested and not tested pts. However, the HER2 tested group had a higher proportion of female pts and those ≤60 years old. Pts with ECOG PS record showed that HER2-tested pts had better performance status. HER2 tested group had higher proportion of non-squamous NSCLC (95.3% vs 69.7%) and more pts were diagnosed with de novo LAM NSCLC (80.2% vs 74.0%) and at stage 4 (84.2% vs 76.8%).

Table: 1396P Characteristics of LAM NSCLC patients by HER2 test status

	HER2 not tested (n=15301)	HER2 tested (n=7530)
Gender, female	4689 (31.2%)	3016 (40.1%)
Age at LAM diagnosis		
Year, median (min-max)	65 (24-98)	64 (21-97)
≤ 60 years, n (%)	4762 (31.7%)	2756 (36.6%)
ECOG PS at LAM diagnosis		
Score 0-1*, n (%)	1726/2858 (60.4%)	953/1391 (68.5%)
Histology		
Non-squamous, n (%)	10480 (69.7%)	7174 (95.3%)
adenocarcinoma	*8747 (58.2%)*	*6439 (85.5%)*
Squamous, n (%)	4551 (30.3%)	356 (4.7%)
Setting at LAM diagnosis		
Stage IV, n (%)	11540 (76.8%)	6339 (84.2%)
Relapse, n (%)	3908 (26.0%)	1491 (19.8%)

* based on number of pts with ECOG PS records

Conclusions: These results revealed that HER2 testing rates for LAM NSCLC pts were low and have decreased over time, with a remarkable drop in 2020 in France; and NSCLC pts with specific characteristics had higher HER2 testing rate.

Legal entity responsible for the study: Unicancer.

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1397P Prevalence, molecular characterization, and prognosis of MET−overexpressing non-small cell lung cancer (NSCLC) in a real-world patient cohort

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Background: Antibody-drug conjugates (ADCs) may extend targeted therapy to patients (pts) whose tumors express an antigen regardless of the presence of a driver mutation. Telisotuzumab vedotin (ABBV-399), a first-in-class MET (or c-Met)-directed ADC, had promising monotherapy anticancer activity in previously treated pts with MET-overexpressing (OE), non-squamous *EGFR* wild type NSCLC (Camidge et al. JCO. 2022;40:16 suppl, 9016). Characterization of MET OE NSCLC, a novel biomarker-defined therapeutically relevant subgroup, is thus warranted. MET OE was evaluated in a real-world cohort and co-associated with mRNA expression, *MET* gene amplification (*MET*amp) and mutations, and outcomes to understand prognosis of MET OE NSCLC.

Methods: The cohort comprised treated pts with stage IV NSCLC seeking care at City of Hope National Medical Center in ≥2016 and had tissue adequate for MET immunohistochemistry (IHC). MET OE was determined using anti-MET clone SP44 IHC assay (Roche Tissue Diagnostics; positive if ≥25% cells at 3+ intensity). MET FISH, RNAseq, and whole exome sequencing were conducted. Clinical data were extracted from electronic health records, and unadjusted hazard ratios from 1L treatment initiation until death or censoring were calculated. Pts receiving targeted therapy in 1L were excluded.

Results: 84 pts were included; 77% had samples taken prior to metastatic spread. 21 (25%) were MET OE positive. MET OE was not associated with history of smoking. *MET*amp was found in 5/69 tumors evaluated (9%); of these, 2 were MET OE. Only 2 pts had *MET* mutations; neither were exon 14 skipping and one was MET OE. MET mRNA, evaluated in 58 cases, was 4-fold higher in MET OE NSCLC vs not OE. 1L regimens used were chemotherapy (52.4%), chemotherapy + immune checkpoint

inhibitor (ICI; 26.2%), or ICI (21.4%). The unadjusted hazard ratio for death in pts with MET OE NSCLC vs not OE was 2.04 (95% CI: 1.02, 4.10).

Conclusions: Pts with MET OE NSCLC had worse prognosis compared with those without MET OE, when treated with standard of care including ICI. Given the development of MET-directed ADCs, MET OE (distinct from *MET*amp) may be a future target for characterization and treatment of NSCLC.

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1398P Hepatotoxicity in patients (pts) with KRASG12C-mutated non-small cell lung cancer (NSCLC) treated with sotorasib after prior immunotherapy (IO)

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Background: Sotorasib after prior IO may increase the risk of immune-related toxicities. We aimed to investigate the potential association between the time interval between prior IO and sotorasib and the incidence of severe hepatotoxicity. IO levels at baseline and on-treatment sotorasib levels were also evaluated.

Methods: Pts with *KRAS*^{G12C}-mutated NSCLC treated with sotorasib were prospectively enrolled in our biomarker study (NCT05221372). On-treatment ALT/AST was collected. Severe hepatotoxicity was defined as grade $\geq$3 ALT or AST increase (CTCAE v5.0). Plasma samples were collected for IO and sotorasib concentrations. Sotorasib concentrations were measured by validated liquid chromatography-mass spectrometry to calculate trough concentrations (C_{trough}). IO concentrations will be analysed shortly.

Results: At data cut off (April 28th 2023), 90 pts were included, of which 79 (88%) received prior IO. Median time on sotorasib was 107 days (range 28 − 799). The incidence of severe hepatotoxicity was significantly higher in pts with prior IO than those without (29% vs 0%, p=0.04). Pts receiving sotorasib <6 weeks after IO (n=18) had a significantly higher incidence of severe hepatotoxicity than those with intervals of 6-12 weeks (n=24) and $\geq$12 weeks (n=37) (78% vs 25% vs 8%, respectively, p<0.001) (Table). Sotorasib concentrations of 108 samples from 46 pts were evaluable. Median C_{trough} did not differ between those with or without severe hepatotoxicity (90 versus 126 ng/mL, p=0.10).

Conclusions: IO followed by sotorasib was associated with severe hepatotoxicity, especially in pts with a short interval between treatments. No association with systemic sotorasib levels was found, further suggesting the influence of prior IO. Relation with baseline IO levels will be presented at the conference. Our results strongly suggest a minimum interval of 6 weeks between last IO course and sotorasib initiation to reduce the risk of hepatotoxicity.

Table: 1398P

	No IO (n=11)	Prior IO per interval between last IO and sotorasib (n=79)			
		$\leq$6 weeks (n=18)	6 to 12 weeks (n=24)	$\geq$12 weeks (n=37)	p-value
Any-grade hepatotoxicity	7 (64%)	14 (78%)	16 (67%)	8 (22%)	<0.001
Grade ≥3 hepatotoxicity	0 (0%)	14 (78%)	6 (25%)	3 (8%)	<0.001
Worst grade					<0.001
Grade 1	6 (55%)	0 (0%)	7 (29%)	4 (11%)	
Grade 2	1 (9%)	0 (0%)	3 (13%)	1 (3%)	
Grade 3	0 (0%)	12 (67%)	5 (21%)	2 (5%)	
Grade 4	0 (0%)	2 (11%)	1 (4%)	1 (3%)	
Treatment modification	0 (0%)	14 (78%)	7 (29%)	3 (8%)	0.003
Interruption and reduction	0 (0%)	7 (39%)	5 (21%)	2 (5%)	
Treatment discontinuation	0 (0%)	7 (39%)	2 (8%)	1 (3%)	
Days to grade ≥3 hepatotoxicity, median (range)	N/A	56 (24 − 85)	49 (25 − 91)	57 (35 − 65)	0.975

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1399P Tumor-immune microenvironment analysis of de novo and acquired KRAS-mutated non-small cell lung cancer

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Background: With the emergence of novel *KRAS*-targeted drugs, molecular analysis of unique *KRAS* mutations in non-small cell lung cancer (NSCLC) has become increasingly relevant. Acquired *KRAS* mutations are a known resistance mechanism in driver mutation-positive (DM+) NSCLC. The impact of acquired vs. *de novo KRAS* mutations on the tumor-immune microenvironment (TIME) is unknown.

Methods: Mutation status was assessed using next-generation sequencing (Caris Life Sciences) with paired whole-exome and whole-transcriptome sequencing (Illumina NovaSeq). *KRAS*-mutated (*KRAS*mt) subgroups were defined as *de novo KRAS*mt NSCLC (*KRAS* only identified driver − DN) and DM+ NSCLC with acquired *KRAS* mutations (concurrent *KRAS*mt with other known drivers − ACQ). Immune pathway enrichment was assessed with single sample gene set enrichment analyses (SSGSEA). Hierarchical agglomerative clustering (HAC) was performed on expression of a panel of immune checkpoints to define immune low/medium/high clusters. Fisher's exact, Chi-square, and Mann-Whitney U tests were used, as appropriate, to assess statistical significance and corrected for multiple hypothesis testing (q<0.05/FDR <0.25).

Results: 6240 *KRAS*mt NSCLC cases were identified - 6186 DN, 54 ACQ. A trend ($p<0.05, q>0.05$) toward increased expression of immune checkpoints PD-L1, TIM-3, and CD86, as well as a significant enrichment of TNFα, IFNα, IFNλ, JAK-STAT, and inflammatory response signaling pathways were observed in ACQ compared to DN. HAC analysis to delineate the immune profile associated with specific *KRAS* mutations revealed that the distribution of *KRAS* mutations was significantly different among immune clusters in the DN but not the ACQ subgroup (see table).

Table: 1399P

KRAS subgroup	DN			ACQ		
Immune checkpoint expression cluster	Low (n=2708)	Medium (n=2738)	High (n=760)	Low (n=17)	Medium (n=31)	High (n=6)
G12C (%)	38.6	41.6	41.8	41.2	25.8	50.0
G12V (%)	19.4	18.7	20.8	11.8	22.6	0.0
G12D (%)	15.7	14.1	10.3	17.7	19.4	16.7
G12A (%)	6.5	6.3	7.9	11.8	6.5	0.0
G13C (%)	3.8	3.3	4.3	5.9	3.2	16.7
Q61H (%)	4.5	4.3	4.9	5.9	9.7	16.7
Other (%)	11.4	11.7	10.0	5.9	12.9	0.0

Conclusions: Differences in the TIME were observed between DN and ACQ *KRAS*mt NSCLC. *KRAS* mutation subtype frequency appeared to differ according to TIME phenotype in DN *KRAS*mt NSCLC. The clinical and therapeutic implications of these findings warrant further investigation.

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1400P Real-world effectiveness and safety of sotorasib in patients with KRAS G12C mutated metastatic non-small cell lung cancer (NSCLC): Results of the IFCT-2102 Lung KG12Ci study

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Background: Sotorasib has demonstrated robust activity in phase 3 trial in pretreated NSCLC patients (pts) with KRAS G12C mutation. However, its effectiveness and safety in a real-world (RW) setting, particularly when administered after treatment with immune checkpoint inhibitors (ICI), remains to be confirmed.

Methods: Multicenter retrospective study including NSCLC pts who received at least one dose of sotorasib as part of the French expanded access program between February 2021 and April 2022. The primary objective was to evaluate real-world progression-free survival (rwPFS), and the secondary objectives included overall survival (OS) and reporting of sotorasib-related hepatic toxicity.

Results: At time of intermediate database lock a total of 313 pts with data collection completed (out of 446 included) were considered in this analysis. At time of sotorasib initiation: median age 66 years (range [39-85]), males (56%), PS2+ (30%) and smokers (95%). Brain metastases (BM) were present in 116 (37%) pts, with 53% in progression. PD-L1 expression was $<1\%$ in 33%, $\geq$ 1-49% in 35% and $\geq$ 50% in 23% of the pts. The median number of lines of treatment before sotorasib was 2.0, and the last treatment before sotorasib included ICI in 164 pts. The median follow-up time was 13.7 months (ms). Median rwPFS was 4.2 ms [95%CI 3.3;4.9], and median OS was 9.3 ms [95%CI 7.9 ;12.3]. Objective response rate (ORR) was 34.3% [95%CI 28.4; 40.1] and disease control rate (DCR) was 64.2%. Median duration of response was 3.9 ms [95%CI 2.9;5.6]. In BM, DCR was 65.9% with 18.7% of ORR. Hepatic grade 3 or 4 treatment-related adverse events (TRAEs) were reported in 7% pts, with ALAT elevation observed in 3.5% and ASAT elevation observed in 2.2% of pts. Among 263 pts who stopped treatment, 42 (16%) discontinued sotorasib due to toxicity, including hepatic toxicity (26 pts), diarrhea (14 pts) and other reasons (8 pts).

Conclusions: Our IFCT-2102 study confirms the effectiveness of sotorasib in pretreated KRAS G12C-NSCLC pts, and its safety profile is manageable with hepatic grade 3 or 4 TRAEs occurring in 7% of pts. Our findings support the use of sotorasib as a treatment option in this population.

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1401P Impact of KRAS mutation on non-small cell lung cancer survival outcomes

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Background: The Kristen Rat Sarcoma (*KRAS*) activating mutation represents the most frequent oncogenic alteration in non-squamous non-small cell lung cancer (nsq-NSCLC). We aimed to describe the characteristics, treatment patterns and survival outcomes of a real-world population of advanced NSCLC according to the *KRAS* status.

Methods: From January 2011 to December 2021, we identified from the ESME database (NCT03848052) patients with a metastatic nsq-NSCLC. Patients with other druggable oncogenic alterations were excluded. Patients were grouped according to KRAS status: mutated (*KRAS*m) versus wild-type (*KRASwt*). We analyzed *KRASm* subtype prevalence, patient and tumor characteristics, treatment history, and overall survival (OS). We analyzed patients' survival outcomes according to the period of care to assess the impact of the implementation of immunotherapy as standard of care in France (available from 2017 in monotherapy and 2019 in combination with chemotherapy). Given that the proportional-hazards assumption is not verified, we used the restricted mean survival time (RMST). RMST is the average survival time until a milestone time point.

Results: We identified 6 818 patients of whom 2 916 (42.8%) were *KRAS*m. Among the *KRASm* tumors, 1272 (43.6%) were *KRAS*-G12C. According to KRAS-status (mutant vs. wild-type): 41.4% vs. 33.8% were women ($p<0.01$); 3.9% vs. 10.9% were non-smokers ($p<0.01$); 45.0% vs. 37.0% had a high PD-L1 expression (>50%; $p<0.01$), 33.5% vs. 30.8% had brain metastasis ($p=0.06$). After a median follow-up of 52.9 months (95% CI 51.2 - 55.5), median OS was 13.2 months (95% CI 12.3 - 14.1) for *KRAS*m and 15.1 months (95% CI 14.4 - 15.5) for KRASwt patients ($p<0.01$).

Table: 1401P RSMT for OS at one year according to KRAS status and period of care

	KRASwt			KRASm		
	n	RSMT 1year-OS	95% CI	n	RSMT 1year-OS	95% CI
2014-2016	1735	9.38 months	9.22 — 9.52	1029	8.90 months	8.68 — 9.09
2017-2018	1277	9.35 months	9.17 — 9.53	1012	8.93 months	8.71 — 9.13
2019-2021	767	9.33 months	9.09 — 9.55	811	9.39 months	9.15 — 9.58

Conclusions: *KRAS*m appears to be a poor prognostic factor for metastatic nsq-NSCLC. The advent of chemotherapy-immunotherapy seems to have mitigated this pejorative impact. The prevalence of high PD-L1 in the *KRAS*m tumors may explain this improvement of survival outcomes.

Legal entity responsible for the study: Unicancer.

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1402P Real-world routine KRAS testing practices in France for patients (pts) with advanced or metastatic (AM) non-small cell lung cancer (NSCLC): Data from the ESME cohort

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Background: Sotorasib is available in France since 2019 in clinical trials and now early access program for *KRAS G12C* AM NSCLC pts who progressed after ≥1 treatment line. *KRAS* testing is recommended at metastatic stage for all non-squamous (nsq) and non-smokers squamous (sq) NSCLC. Our aim is to understand routine *KRAS* testing practices for AM NSCLC pts.

Methods: We performed a retrospective observational cohort study of AM NSCLC patients included in the Epidemio-Strategy and Medical Economics (ESME) Lung

Table: 1402P

	KRAS tested at any time (N=9714)	*KRAS* not tested (N=10467)
Male %	60.5	71.3
ECOG at AM diagnosis [1] % 0-1 ≥2	69.4 30.6	57.1 42.9
Histology at initial diagnosis % Nsq Sq	95.4 4.6	61.6 38.4
Stage at initial diagnosis [2] % Early Locally advanced Metastatic	19 9 70.1	25.8 13.1 58.4
L1 received %	86.1	75.7
EGFR testing %	93.9	20
PDL1 testing %	46.5	37.5
For nsq pts Smoking status[3] % Non-smoker Former smoker Smoker Median number of pack-years Smoker [4] Former smoker [5]	N=9271 13.9 50.7 35.5 40 35	N=6452 12.2 52.7 35.1 40 40

Pts without data in KRAS tested and KRAS not tested cohorts respectively (1) 7 835 ; 8 485 (2) 186;286 (3) 368;445 (4) 405;387 (5) 609;500

Cancer Database from 07/2015 to 10/2021. Pts were split in 4 subgroups: *KRAS* not tested; *KRAS* tested at any time of the disease; *KRAS* tested before first-line treatment (L1); *KRAS* tested after L1 and before L2. We analyzed 2 periods: 2015-2018 and 2019-2021, according to the date of AM diagnosis.

Results: 20 181 AM NSCLC pts were included. 48.1% were tested for *KRAS* at any time of the disease, without evolution between 2015-2018 and 2019-2021 (48.7% and 43.5%, respectively). Among *KRAS* tested pts (n=9714), 74.1% were tested before L1 and 23% after L1 / before L2. *KRAS* and *KRAS G12C* were positive for 37.8% and 14.7% of pts respectively. *KRAS* positive pts (n=3668) were tested on tumor (72.1%), metastasis (26.6%) and blood (3%). We described the main differences in pts characteristics overall as no difference was observed between pts tested for *KRAS* before L1 and after L1 / before L2.

Conclusions: Approximately half of AM NSCLC pts were not tested for *KRAS*, without evolution between 2015-2018 and 2019-2021.The emergence of *KRAS G12C* inhibitors should lead to an increase in AM NSCLC pts testing according to guidelines.

Legal entity responsible for the study: Unicancer.

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1403P Sotorasib in KRAS p.G12C mutated advanced NSCLC: Real-word data from the Italian Expanded Access Program

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Background: Sotorasib showed a significant improvement of progression free survival (PFS), safety and quality of life over docetaxel in patients with KRAS p.G12C—mutated advanced non—small-cell lung cancer (NSCLC) in the CodeBreak-200 study. Here we report real-world efficacy and tolerability data from NSCLC patients who received sotorasib within the Italian expanded access program (EAP).

Methods: Sotorasib (960 mg, orally, once daily) was available on physician request for KRAS p.G12C mutant advanced NSCLC patients who were pretreated with standard regimens or unfit for approved therapies. Clinical-pathological and molecular data were collected from the Italian ATLAS real-word registry. Patients underwent CT-scan and responses were evaluated by RECIST criteria. Efficacy and tolerability outcomes have been assessed.

Results: A total of 190 advanced NSCLC patients were treated across 30 Italian centres. The overall patients' median age was 68 years old (range 32-85). Most patients were male (62%), former (49%) or current smokers (42%), with ECOG performance status 0/1 (84%) and adenocarcinoma subtype (89%). Tumor PD-L1 expression was $\geq$ 50%, 1-49% and <1% in 25%, 37% and 31% of patients, respectively. Patients had received a median of 2 (0—4) previous lines of systemic therapy, with 44% and 33% of them receiving sotorasib in 2nd and 3rd line, respectively. Overall, response rate was 26% and disease control rate 66%. Median PFS was 6.1 months (95% CI: 5.6 — 9.1). Median overall survival (OS) was 8.2 months (95% CI: 6.7-13.6) without significant differences across the main clinical subgroups [age (< 70 *vs* $\geq$ 70 years, p= 0.83), treatment line ($1^{st}/2^{nd}$*vs* $>2^{nd}$, p=0.3), brain metastases (p=0.53)]. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 32 patients (17%), with no significant differences between who received or not previous immunotherapy (16% *vs* 14%, respectively). The most common TRAEs were hepatotoxicity (12%), diarrhea (3%) and asthenia (1%).

Conclusions: Real-world data from the Italian EAP confirm the activity and tolerability of sotorasib in pre-treated patients with KRAS p.G12C-mutated advanced NSCLC.

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1404P Clinical characteristics and therapeutics sequences of KRAS G12C metastatic non-small cell lung cancer (mNCSLC) patients treated by sotorasib in the French pre-marketing authorization (MA) early access program (cohort temporary authorization of use, cATU)

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Background: Sotorasib is the first specific and irreversible KRAS G12C inhibitor that showed superiority vs docetaxel in CodeBreaK 200 phase 3 study, with a median PFS of 5.6 mos (HR: 0,66) and an acceptable safety profile for sotorasib. In France, sotorasib has been authorized before MA for patients with KRAS G12C mNSCLC who progressed after at least one treatment line. Here, we present the clinical characteristics of patients included in the cATU.

Methods: From 08/2021 to 06/2022, data from 1011 pts, of which 958 received sotorasib, were collected in 249 centers.

Table: 1404P

Variable	Results
Median age, years [Q1-Q3] *n=1011*	65.9 [58.8-72]
Male, % *n=1011*	58.7
Smoking status Non / former / current, % *n=1009*	3.6 / 79.4 / 17
Adenocarcinoma, % *n=1004*	94.8
ECOG PS, % *n=1011* 0 1 ≥2	20 58.9 21.2
PD-L1, % *n=1010* <1 [1-49] ≥50 Undetermined	40.9 30.2 21.8 7.1
KRAS testing by NGS, % *n=1010*	84.1
Brain metastases (active), % *n=1011*	29.4 (10.1)
Sotorasib therapy line 2 / 3 / ≥4, % *n=997**	53.3 / 27.1 / 19.6
Median of prior lines *n=1004*	1
First-line therapy, % *n=997* CT IO CT+IO	33.9 12.7 48.6

*39 pts didn't receive sotorasib at all 80% of patients were exposed to chemotherapy (CT) and immunotherapy (IO) before sotorasib: ∼50% simultaneously, ∼30% sequentially. 51% of patients received sotorasib directly after IO. With a median follow-up of 8.9 [0.2-17.5] mos, the median duration of treatment was 8.1 [0.1-17.5] mos. These data must be interpreted with caution because of the short follow-up period.

Results: Main characteristics of this population are presented below:.

Conclusions: Nearly 1000 pts, ineligible to clinical trials, were treated by sotorasib through French cATU, highlighting the unmet therapeutic need. The main technique to retrieve KRASG12C was NGS. Clinical characteristics are consistent with those of CodeBreaK 200 trial pts, with a relatively lower proportion of patients with PD-L1≥50%. More than half of the patients received sotorasib in 2L, reflecting conditional marketing authorization granted in Europe. Real-life data on sotorasib efficacy, safety and QoL are currently studied by academic institutions.

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1405P Sotorasib in KRAS G12C-mutated NSCLC: A multicenter real-world experience from the expanded access program in Germany

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Background: Sotorasib is a first-in-class KRAS p.G12C-inhibitor that has entered clinical trials in pretreated patients with non-small cell lung cancer (NSCLC) in 2018. It remains unclear whether response to sotorasib and outcomes differ in a real-world setting when including patients of higher risk.

Methods: Patients with KRAS p.G12C-mutated advanced or metastatic NSCLC received sotorasib within the German multicenter sotorasib expanded access program between April 2021 to February 2022. Data on effectiveness, tolerability, and survival were analyzed in the full cohort and in subgroups of special interest such as patients with co-occurring mutations and across PD-L1 expression levels.

Results: We analyzed 173 patients who received sotorasib after a median of 2 previous treatment lines (range, 0 to 7). Every fourth patient had a poor performance status and 38% had brain metastases (BM) at the time of sotorasib initiation. The objective response rate was 38.7%. The median overall survival was 9.8 months (95% CI, 6.5 to not reached), with a 1-year mortality rate of 48.5%. Response to sotorasib was lower among patients with a positive PD-L1 expression (TPS ≥1%) and a co-occurring *KEAP1* mutation, respectively. Patients with *KEAP1* had a higher risk of 1-year real-world disease progression (HR 2.0, 0.9 to 4.2, p=0.01). Patients with poor performance status had significantly inferior 1-year overall survival (HR 2.2 ,95% CI 1.12 to 4.54, p=0.003). Other patient factors such as BM, *STK11*, and *TP53* mutations had no impact on response and survival. Subgroup analysis indicated an intracranial non-progression rate of 74.5%, with an intracranial real-world progression-free survival of 7.5 months (95% CI 3.7 to 11.4). Dose reductions and permanent discontinuation were necessary in 35 (21.5%) and 7 (4.3%) patients, respectively, mostly due to gastrointestinal toxicity including liver enzyme elevation, irrespective of whether the immediate previous treatment line contained a checkpoint inhibitor or not.

Conclusions: These first results from a real-world population in Germany confirm promising effectiveness of sotorasib for the treatment of advanced KRAS p.G12C-mutated NSCLC. Patients with co-occurring *KEAP1* mutation seem to derive less benefit.

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1406P Outcomes of patients with metastatic EGFR mutant lung cancer requiring dose modifications of first line osimertinib

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Background: Osimertinib is a standard first line treatment for advanced EGFR mutant lung cancer. While EGFR tyrosine kinase inhibitors are generally well tolerated, side effects, including diarrhea and rash, are common and often require dose modifications. The impact of osimertinib dose modification on survival outcomes is not known.

Methods: Patients with metastatic EGFR mutant lung cancer who received first line osimertinib between 2020 and 2022 were retrospectively identified using pharmacy records in British Columbia, Canada. Patient charts were reviewed to determine the incidence of dose reductions or treatment cessation of osimertinib due to toxicity. The type of toxicity leading to the treatment modification was also recorded. The median time to treatment discontinuation (mTTD) and the median overall survival (mOS) of patients requiring dose modification was compared to those who did not require modification using Kaplan Meier analysis and log rank testing.

Results: The analysis identified 311 patients and with a median follow up time of 26 months. 72 (23%) patients required a dose modification due to toxicity. At time of analysis, 52/72 (72%) of the dose modification group had stopped osimertinib vs 142/239 (60%) in the no modification group. The most frequent toxicities leading to dose reduction or cessation included diarrhea (17), skin toxicity (13), respiratory symptoms (10), anorexia (9), and cardiotoxicity (6). Pneumonitis occurred in 9 patients (3% of the study population). Twenty patients ultimately discontinued osimertinib due to toxicity. The mTTD was shorter in the dose reduction group, 14.3 months (95%CI 11.0-21.3) vs 21.9 months (95%CI 16.9-24.5) in the no reduction group (p=0.042). Second line treatment was received by 19/52 (35%) in the dose modification group and 59/145 (42%) in the no modification group. The mOS of patients requiring dose modifications was 27.6 months (95% CI 21.1-34.1), which was similar to patients not requiring dose modifications, mOS 26.8 months (95% CI 21.9-33.1), p=0.868.

Conclusions: Nearly one quarter of patients treated with osimertinib required a dose reduction or treatment cessation. Despite this, dose modifications did not lead to worse mOS.

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1407P Characteristics and treatment sequences of patients (pts) with KRAS G12C, other KRAS and non-KRAS advanced or metastatic (AM) non-small cell lung cancer (NSCLC) in the French ESME cohort

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Background: *KRAS* G12C mutation is found in 14% of NSCLC. Pts with *KRAS* G12C AM NSCLC have not been well characterized in routine clinical setting. Our objective was to describe pts with *KRAS* G12C AM NSCLC and compare them to pts with other *KRAS* and non-*KRAS* AM NSCLC.

Methods: We performed a retrospective observational cohort study of AM NSCLC pts included in the Epidemio-Strategy and Medical Economics (ESME) Lung Cancer Database and diagnosed between 2015 and 2021. Pts tested for *KRAS* mutation before first-line treatment (L1 or during the disease for pts who didn't receive any L1) were divided in 3 subgroups: *KRAS* G12C (positive *KRAS* G12C mutation), other *KRAS* (positive for *KRAS* mutation other than G12C) and non-*KRAS* (negative for all *KRAS* mutations).

Results: A total of 1073 pts carried *KRAS* G12C (15%), 1642 *other KRAS* (23%) and 4295 *non-KRAS* (61%). Among *KRAS* G12C pts, 58% were male, and the median age was 63 years. The majority (98%) had a smoking history. 68% had an ECOG PS of 0-1. 69% had *de novo* stage IV. The most frequent metastatic sites involved were bone (42%), brain (35%) and contralateral lung (27%). *STK11* appears to be the most common co-mutation (54%) when tested. When PD-L1 status was screened (43%), one third had PD-L1≥50%, and one third had PD-L1<1%. In 2015, most pts received platinum-based chemotherapy (CT) alone (89%) in 1L; this proportion decreased to 55% in 2019 given the benefit of immunotherapy (IO) combined to CT or as monotherapy. In L2, treatments were evenly used in 2015 but IO monotherapy peaked in 2018 to 65%. In L3, IO and other treatments were quite stable over time. The patient and disease characteristics were similar in other *KRAS* and non-*KRAS* pts, except a higher proportion of non-smokers (20%) and a less frequent *STK11* mutation (28%) in non-*KRAS* pts than in the 2 other groups. Treatments were similar in the 3 subgroups except the peak of IO observed in L2 in 2017 and in L3 in 2018 for other *KRAS* pts.

Conclusions: In real-world clinical practice, clinical characteristics and treatment sequences of pts with *KRAS* G12C AM NSCLC are similar to those of other *KRAS* mutations or wild-type *KRAS* pts except for the prevalence of *STK11* co-mutation and the proportion of non-smokers.

Legal entity responsible for the study: Unicancer.

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1408P Differences on immune biomarkers between KRAS G12C and KRAS non-G12C mutated non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) can harbor different *KRAS* mutations. Although targeted therapy is available for *KRAS* G12C-mutant NSCLC, immune checkpoint inhibitors (ICIs) are still the first line treatment (tx) for these patients (pts). Here we aimed to assess the outcomes on ICIs for *KRAS* G12C compared to *KRAS* non-G12C-mutant pts.

Methods: This is an observational, retrospective, multicenter study in pts with *KRAS*-mutant NSCLC treated with ICIs (monotherapy or combination) between January 2017 and January 2023. Targeted sequencing was performed in most cases. Clinicopathological and molecular data were collected. We evaluated pts characteristics, tx response and survival outcomes from the beginning of ICIs in *KRAS* G12C vs non-G12C tumors.

Results: A total of 169 pts were included. NGS was performed in 105 pts, *STK11* and *TP53* were the most frequent co-mutated genes present in 4.4%/15% G12C/non-G12C (p=0.110) and 20%/35% G12C/non-G12C (p=0.143), respectively. There were no differences in median progression free survival (PFS) between G12C/non-G12C (8.8 vs 7.1 months(m) respectively p=0.727). In the multivariate analysis, PD-L1 negative tumors and ECOG ≥1 remained independently associated with worse PFS (p=0.010 and p= 0.002 respectively). Regarding overall survival (OS), harboring a G12C mutation was associated with a better OS compared with non-G12C tumors (mOS 16.2m vs 10.4m p=0.033), conversely PD-L1 negative tumors and basal ECOG of ≥1 was associated with worse OS (p= 0.002 and p<0.001 respectively).

Table: 1408P Patient's characteristics

N (%)	G12C (n=75)	Non-G12c (n=94)	p-value
Median age	62.9	63.8	0.471
Sex			0.220
Male	45 (60)	66 (70.2)	
Female	30 (40)	28 (29.7)	
Tobacco			0.203
Former	34 (45.4)	53 (56,4)	
Current	41 (54.6)	41 (43.6)	
Stage			0.630
I-III	17 (21.7)	22 (23,4)	
IV	58 (78.3)	72 (76.6)	
M1 CNS	14 (18.6)	24 (25.5)	0.381
M1 liver	14 (18.6)	20 (21.3)	0.820
ICIs treatment line			0.604
1	57 (76)	75 (80)	
≥2	18 (24)	19 (20)	
PD-L1			0.397
Negative (0%)	17 (22.7)	30 (32)	
Positive (≥0%)	58 (77.3)	64 (68)	
ECOG			0.887
0	31 (41.4)	41 (43.6)	
≥1	44 (58.6)	53 (56.4)	

Conclusions: Our work shows that patients with *KRAS* non-G12C tumors are more frequently PD-L1 negative and harbor a higher proportion of *STK11* co-mutations conditioning a worse OS on immunotherapy treatment. Innovative therapeutic strategies need to be investigated for these patients.

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1409P DEnosumab in combination with PD-1 checkpoint blockade for MAINtenance therapy of KRAS-mutant advanced NSCLC after first-line immunotherapy: A prospective, single-arm, phase II trial (DEMAIN)

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Background: Currently, there is still an unmet therapeutic need for patients (pts) with *KRAS*-mutated (mut) non-small cell lung cancer (NSCLC). Preclinical models have demonstrated the potential efficacy of the receptor activator for NF-κB ligand (RANKL) inhibitor in *KRAS*-mutant NSCLC. However, no clinical trials have been conducted to confirm the efficacy and safety of RANKL inhibitor combined with PD-1 inhibitors in this subset of pts.

Methods: Eligible pts had advanced *KRAS*-mutated NSCLC and were receiving first-line PD-1 inhibitor-based therapy. Pts were treated with PD-1 inhibitor (q3w) and denosumab (120 mg, q4w) for subsequent maintenance therapy regardless of bone metastases. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were objective response rate (ORR), overall survival (OS) and safety. Biological samples were retained for exploratory analysis.

Results: As of 30 March 2023, 20 pts were recruited for maintenance therapy, of which 13 (65.0%) pts had bone metastases. The median age was 65.5 (range: 40-74) years and the majority of patients were male (75.0%). Median PFS (mPFS) for the entire treatment course (mPFS1) and maintenance therapy (mPFS2) was 329 (95% CI: 277-380) days and 196 (95% CI: 145-247) days, respectively. Median OS was not reached. The most common adverse events (AEs) were dental symptoms (20%) and hypothyroidism (10%), and one (5%) pt discontinued the treatment due to grade 2 immuno-hepatitis. No grade 3-4 AEs occurred. Subgroup analysis suggested a greater survival benefit in patients with $KRAS^{G12C}$ mutation than in patients with $KRAS^{non\text{-}G12C}$ mutation (mPFS1, p=0.026; mPFS2, p=0.049). Interestingly, patients with bone metastases (mPFS1, p=0.138; mPFS2, p=0.100) appeared to benefit more than those without. Exploratory analysis (n=14) suggested that neither baseline tissue RANKL levels nor baseline blood soluble RANKL levels were associated with the survival benefit.

Conclusions: The combination of denosumab and PD-1 inhibitors demonstrated antitumor activity in the advanced *KRAS*-mutated NSCLC with a good safety profile, which warrants further investigation.

Clinical trial identification: Chinese Clinical Trial Registry (ChiCTR2100047759).

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1410P Characterization of patients with advanced non-small-cell lung cancer (NSCLC) harboring KRASG12C mutation and their associated direct healthcare costs in Spanish routine clinical practice (SILK study)

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Background: Around 15% of patients (pts) with NSCLC harbor the $KRAS^{G12C}$ mutation. In a changing landscape of $KRAS^{G12C}$ treatment (tx), there is a need for updated real-world evidence on characteristics and outcomes of routine clinical practice. Here we present characteristics, tx patterns, outcomes, and direct healthcare costs in pts with NSCLC and $KRAS^{G12C}$ in the Spanish clinical practice.

Methods: Observational, retrospective, multicenter study in pts with newly diagnosed locally advanced (not candidate for radical tx) or metastatic NSCLC and $KRAS^{G12C}$. Pts participating in clinical trials with *RAS* inhibitors were excluded. The study collected clinical and economic data from medical records and administrative databases from 1st Jan 2016 to 9th Mar 2022 (diagnosis period: Jan 2016-Oct 2021).

Results: A total of 127 pts were included (median age 65 years, 71% male, 43%/54% current/former smokers, 82% ECOG≤2, 57% ≥2 metastatic site). PD-L1 expression was analysed in 104 pts at baseline: 19/104 (18%) pts had a PD-L1 expression <1%, 45/104 (43%) pts 1-50%, and 40/104 (39%) pts ≥50%. 94 pts (74%) received systemic tx. The most common first line tx was platinum-based chemotherapy alone (71%). Table shows progression free survival and overall survival. 124 and 103 pts had available global and disease-related (d-r) economic data, respectively. Total global cost over study period was €5,780,686 (total global mean cost per pt: €46,618) with a total pharmacological cost of €2,373,384 (mean cost per pt: €19,140). Total d-r cost was €4,245,504 (total d-r mean cost per pt: €41,218) with a d-r pharmacological cost of €2,177,712 (mean cost per pt: €21,142).

Conclusions: The real-world data confirm limited outcomes for most $KRAS^{G12C}$ pts and emphasize the high clinical and economic burden of these pts' care in an evolving tx landscape. Evaluating the impact of new and effective targeted therapies is warranted.

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AstraZeneca, Janssen; Financial Interests, Personal, Invited Speaker: Roche/Genentech; Financial Interests, Institutional, Funding: AstraZeneca. E. Arriola: Financial Interests, Personal, Advisory Board: Roche, Boehringer Ingelheim, Lilly; Financial Interests, Personal, Invited Speaker: Takeda, MSD, AstraZeneca, BMS, Thermo Fisher Scientific, Guardant Health, Pfizer; Financial Interests, Personal, Other, Co-founder: Trialing Health; Financial Interests, Institutional, Research Grant: AstraZeneca. S. Palanca: Financial Interests, Personal, Speaker, Consultant, Advisor: Roche Pharma, AstraZeneca, Lilly; Financial Interests, Personal, Advisory Role: Janssen; Financial Interests, Personal, Research Funding: Roche Pharma, AstraZeneca; Financial Interests, Personal, Invited Speaker: Pfizer, Amgen, Takeda; Financial Interests, Personal, Research Grant: Roche Pharma, Amgen. L. Planellas, A. Lloansi Vila: Financial Interests, Personal, Full or part-time Employment: Amgen. All other authors have declared no conflicts of interest.

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1411P Tusamitamab ravtansine plus ramucirumab as 2L therapy or beyond in patients with metastatic NSq NSCLC and high CEACAM5 expression (CARMEN-LC04)

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Background: Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) expression is often higher in malignant versus normal lung tissue. Tusamitamab ravtansine (tusa rav), an antibody-drug conjugate of humanized CEACAM5 antibody linked to cytotoxic DM4, showed promising antitumor activity and safety in heavily pretreated metastatic nonsquamous non-small cell lung cancer (mNSQ NSCLC) with high CEACAM5 expression. Docetaxel ± ramucirumab (ram) every 3 weeks is standard second-line therapy for mNSQ NSCLC without targetable mutations after progression on immunotherapy ± chemotherapy.

Methods: CARMEN-LC04 is an open-label phase 2 study (NCT04394624) assessing combination tusa rav 100 mg/m^2 every 2 weeks (Q2W) + ram 8 mg/kg Q2W in patients with mNSQ NSCLC and high CEACAM5 expression (≥2+ intensity in ≥50% of tumor cells by immunohistochemistry). Patients had progression after an immune checkpoint inhibitor + platinum-based chemotherapy; patients with *EGFR* or *BRAF* mutations or *ALK/ROS* alterations had progression on targeted therapy. Primary endpoints were dose-limiting toxicity (DLT) in the first 4 weeks for Part 1 and objective response rate (ORR: confirmed complete response [CR] or partial response [PR]) per RECIST v1.1 for Part 2. Safety, disease control rate (DCR: CR + PR + stable disease), and progression-free survival (PFS) were assessed.

Results: As of April 2023, 31 total patients were treated in Parts 1 and 2. The median duration of exposure was 24.1 weeks (range, 3.9–106.0), with 6 (19.4%) patients still on treatment. No DLTs were observed (DLT-evaluable patients, n = 6). ORR was 19.4% (6/31) with 1 CR; DCR was 83.9% (26/31). Target lesion shrinkage occurred in 23/31 (74.2%) patients. Median PFS was 5.7 months (95% confidence interval, 5.4–9.1). Treatment-emergent adverse events (TEAEs) occurred in all patients; 12 (38.7%) patients had a Grade ≥3 TEAE. Seven (22.6%) patients had ≥1 corneal TEAEs: 5 (16.1%) Grade 2 and 2 (6.5%) Grade 3 as worst Grade. No treatment-emergent interstitial lung disease or toxic death was reported.

Conclusions: Tusa rav + ram showed encouraging efficacy. The safety of this combination was consistent with the safety profile of each drug, with no unexpected safety signals.

Table: 1410P

	PFS, median (95%CI), m	OS, median (95%CI), m
TL 1		
CTx (n=60)	2.8 (2.4-4.0)	5.0 (3.3-7.4)
IO (n=23)	17.8 (3.7-NR)	31.9 (7.4-NR)
CTx + IO (n=10)	13.2 (0.2-NR)	NR (0.5-NR)
TL 2		
CTx (n=9)	1.6 (1.0-9.0)	9.2 (1.5-14.3)
IO (n=20)	4.2 (1.4-12.5)	10.4 (2.8-17.9)
TL 3		
CTx (n=7)	2.1 (0.1-9.9)	6.6 (0.1-25.8)
Date of diagnosis *		
Jan 2016-Sep 2017 (n=24)[‡]	NA	6.8 (4.4-18.5)
Oct 2017-Oct 2021 (n=66)[§]	NA	7.7 (4.0-20.5)

CI, confidence interval; CTx, chemotherapy; FU, follow up; IO, immunotherapy; m, months; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression free survival; TL, treatment line *Periods due to a major change in Spain: IO can be used as TL 1 from Oct 2017 [‡]Median FU6.8 m [§]Median FU6.6 m

Clinical trial identification: NCT04394624.

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1412P SAKK 17/18-ORIGIN trial: Efficacy and safety from a multicenter phase II trial of gemcitabine and atezolizumab in patients with advanced NSCLC progressing on immune checkpoint inhibitors

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Background: A significant number of patients (pts) with advanced non-small cell lung cancer (NSCLC) do not respond to therapy with immune checkpoint inhibitors (ICI). After relapse, treatment options are limited. We have previously demonstrated in a preclinical *in vivo* model that the combination of ICI and gemcitabine (GEM) can overcome resistance to ICI or GEM alone. ORIGIN (NCT04480372) is a multicenter phase II trial of GEM and atezolizumab (ATEZO) in patients with advanced non-small cell lung cancer (NSCLC) and mesothelioma (MPM) progressing on ICI. Here we report the data of the NSCLC cohort.

Methods: Eligible pts had ECOG PS 0-2, with confirmed NSCLC stage IIIB-IV with disease recurrence or progression during or after ≥ prior line of ICI or chemo-ICI and available tissue for translational research. Pts received GEM (1000mg /m2 IV d1, 8 q3w) and ATEZO (1200 mg IV q3w). The primary endpoint (EP) was overall response rate (ORR) of the full analysis set (FAS) evaluated by independent radiological

assessment. 35 pts were needed based on a one-sided type I error of 10% and a power of 80% for H_1 ORR ≥25% compared to H_0 ORR ≤11%. Key secondary EPs were progression free survival (PFS), disease control rat (DCR) at 18 weeks, duration of response (DoR), overall survival (OS) and safety.

Results: Between 03/2021 and 10/2021 37 pts were accrued and received GEM+A-TEZO after a median of 2 prior lines of treatment (range 1-8). 36 patients were included in the FAS. Pts with ECOG PS 0, 1 and 2 were 25%, 56% and 19% resp; females represented 44% of pts and median age was 67y (48-80). At data cutoff, median follow-up was 17.6 mo. ORR was 31% (one-sided 90%CI: 20%, 95%CI: 16%-48%) and 22% of pts had stable disease. Median PFS was 4.0 mo (95% CI: 2.5-5.3), DCR at 18 weeks was 42% (95%CI: 26%-59%); median DoR was 5.2 mo (95% CI: 1.1-not reached) and median OS 8.2 mo (95% CI: 6.1-10.1). Treatment-related AEs occurred in 89% (G3-4, 59%) and led to discontinuation in 19% of pts. Extensive translational research on longitudinal blood samples is ongoing.

Conclusions: ORIGIN met its primary endpoint with an ORR of 31% in heavily pre-treated NSCLC patients with no unexpected toxicity profile of GEM or ATEZO.

Clinical trial identification: NCT04480372.

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1413P Patient-reported outcomes (PROs) from a phase 2 trial of telisotuzumab vedotin (Teliso-V) in c-Met−overexpressing, EGFR wild type, non-squamous non-small cell lung cancer (c-Met OE, EGFR WT, NSq NSCLC)

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Background: The phase 2 LUMINOSITY trial (NCT03539536) of Teliso-V monotherapy has shown acceptable safety & promising efficacy in previously treated patients (pts) with c-Met OE, *EGFR* WT, NSq NSCLC. Interim PRO data are reported.

Methods: Pts received Teliso-V (1.9 mg/kg) Q2W. PROs were assessed using the European Organisation for Research and Treatment of Cancer quality of life (QOL) questionnaires in lung cancer (LC13) & palliative cancer care (C15-PAL). Time to deterioration (TTD) beyond meaningful change threshold (MCT; ≥10 points from baseline) & mean change from baseline (mCFB) were analyzed.

Results: 59 pts were evaluated. Median no. of prior therapies was 1 (range 1−3); median follow-up was 81 d. The table shows median TTD. For cough, pain in chest, pain in other parts, & QOL domains where median TTD was not reached, mCFB analyses revealed initial trends toward improvement. Cough, pain in chest, & overall QOL improved beyond MCT in wk 41, 49, & 41, respectively; pain in other parts trended toward deterioration. mCFB analyses revealed trends toward improvement for the LC13 symptom of hemoptysis, and for alopecia, sore mouth. Peripheral neuropathy deteriorated beyond MCT; dysphagia showed no consistent time trend. For C15-PAL, mCFB trend improved for nausea and vomiting, dyspnea (improved beyond MCT in wk 41), pain, fatigue, emotional function, and insomnia over a sustained duration for ≥29 wk, then deteriorated. Appetite loss worsened initially but improved in wk 41. Constipation improved initially then trended toward deterioration in wk 41 & 45.

Conclusions: This interim analysis suggests extended TTD and trends toward improvement from baseline in key lung cancer symptoms, physical functioning, & QOL; and deterioration in peripheral neuropathy. Impact of Teliso-V monotherapy on PROs will also be assessed at LUMINOSITY trial conclusion and in the phase 3, TeliMET NSCLC-01 trial (NCT04928846).

Table: 1413P Time to deterioration in symptoms, functional domains, and QOL

Instrument	Domains	Event/N	Median TTD, wk (95% CI)
LC13	Cough	7/59	NR
	Dyspnea	22/59	33 (12, NE)
	Pain in chest	9/59	NR
	Pain in arm/shoulder	22/59	20 (12, 34)
	Pain in other parts	17/59	NR
C15-PAL	QOL	18/59	NR
	Physical function	20/59	43 (8, NE)

NE, not estimable; NR, Kaplan-Meier curve did not reach 50%.

Clinical trial identification: NCT03539536.

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1414P Impact of co-mutations on the prognosis of targeted therapy in EGFR-mutant advanced NSCLC: A result of real-world study

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Background: The aim of this study was to observe the concurrent genetic profiles of EGFR-mutated advanced Chinese non-small cell lung cancer (NSCLC), as well as to analyze the effects of diverse concurrent genetic alterations on the prognosis in EGFR-mutated NSCLC treated in first-line with EGFR-TKI.

Methods: The CAPTRA-Lung (NCT03334864) database was used to retrieve 307 patients with advanced EGFR-mutated NSCLC between January 1, 2018 and January 1, 2022 in our institution. Of those, 103 patients were detected by next-generation sequencing (NGS) and the results showed other concurrent genetic alterations. We divided them into two cohorts: those who were sequenced with NGS at baseline were included in cohort 1, and those who received NGS after progression to first-line therapy were contained in cohort 2. The follow-up deadline was October 1, 2022.

Results: The following genes are found to be most frequent in the entire cohort: TP53 mutation (n = 64, 62.14%), EGFR amplification (n = 14, 13.59%), KRAS mutation (n = 13, 12.62%), PIK3CA mutation (n = 13, 12.62%), and DNMT3A mutation (n = 13, 12.62%). Most of the TP53 mutations have been identified in exons 5 (16/64), 6 (9/64), 7 (10/64), 8(9/64), etc. For KRAS mutations, G12V (4/13) and G12S (3/13) were the most common mutation types, and E545K (5/13) and H1047R (2/13) were the most frequently alterations observed in PIK3CA. Cohort 1 constituted 68 patients (mean [SD] age, 60.93 [9.051] years; 55.9% female). Multivariate analysis demonstrated that alterations in TP53 (HR 1.946, 95% CI 1.112-3.403; P = 0.020) and MET (HR 3.581, 95% CI 1.070-11.992; P = 0.039) were independently correlated to poor progression-free survival (PFS). Cohort 2 encompassed 35 patients (mean [SD] age, 56.80 [8.741] years; 71.4% female). Multifactorial analysis showed that TP53 mutation (HR 2.198, 95% CI 1.006-4.803; P = 0.048) and RB1 mutation (HR 8.798, 95% CI 1.604-48.269; P = 0.012) were independent risk factors for PFS with first-line targeted therapy.

Conclusions: This research added to the evidence that co-alterations such as TP53, MET, and RB1 are prospective prognostic biomarkers in NSCLC patients treated with EGFR-TKI.

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1416P Recurrence of infusion-related reaction (IRRs) associated to avimantamab

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Background: Infusion-related reaction (IRR) are a common toxicty of amivantamab, with a high incidence during the first infusion (97%). However, subsequent injections are usually not affected, unless there is a delay in treatment for several weeks. We evaluate the risk of IRR after the resumption of amivantamab, based on the duration of the free treatment interval.

Methods: This was a retrospective observational study to evaluate the recurrence of IRR in advanced non-small cell lung cancer patients treated with amivantamab and lazertinib in Gustave Roussy (2019-2023).

Results: Baseline characteristics of patients are summarized in the table. 24 patients were included, 12 (50%) presented IRR during the first infusion, and only one of them presented previous history of allergy. 9 patients had a temporary discontinuation of treatment, but only 2 had an IRR recurrence (these 2 had experienced an IRR during first cycle). Median time of treatment discontinuation was of 25.57 days for those patients without IRR recurrence and 44 days for those who presented it. Both patients with IRR recurrence had a temporary withdrawal due to another toxicity (at day 29 and 59 respectively) being of CTCAE grade 3 and 2 respectively. 5 patients (41.6%) needed corticoesteroids and 6 (50%) received antihistamines as treatment for the IRR. Only one patient required magnesium sulfate. A third IRR recurrence was experienced in both patients (grade 2 and 1 respectively), leading to permanent treatment discontinuation for one patient. None of the patients progressed to amivantamab and both are still alive.

Table: 1416P

Gender (N) Female Male	**15 9**
Median age, Years (IQR)	66 (39-81)
Molecular profile (N) EGFR exon 19 EGFR exon 20 EGFR L858R MET overexpression MET exon 14 skipping mutation	11 1 9 1 2
Median number of previous lines (IQR)	2

Conclusions: Recurrence of IRR after the first episode is frequent and must be taken into account when reintroducing amivantamab after a temporary withdrawal of $\geq$1 month. IRR recurrence does not seem to have a detrimental impact on treatment efficacy.

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1417P Change in healthcare resource use and associated costs of patients with metastatic lung cancer between 2013 and 2019: An observational study from the French national claims database

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Background: Treatment landscape in metastatic lung cancer is quickly evolving, including targeted therapies and immunotherapies. Both treatments have shown improved survival but are also associated with increased costs. This study aimed to describe the evolution of costs associated with metastatic lung cancer in France.

Methods: From the French national claims database (SNDS), a dynamic cohort of patients identified between 2013 and 2019 with metastatic lung cancer and a marker for the presence of metastases (ICD-10 code or at least one reimbursement for Bevacizumab or Pemetrexed) was constituted. Healthcare resource use was described each calendar year through the percentage of patients with at least one record for each expenditure item. The associated costs were reported monthly and estimated from the health insurance perspective. The trend over the study period for the total mean monthly cost was studied using Joinpoint software.

Results: Between 2013 and 2019, 116 686 patients with a metastatic lung cancer were identified (67.1% of men, median age of 65 years). The percentage of patients with at least one overnight hospitalization decreased from 85.2% in 2013 to 67.6% in 2019 while the use of day hospitalizations remained stable (about 40%). The percentage of patients with outpatient care increased over the study period: medical visits (from 82.6% to 88.0%), lab tests (from 74.1% to 83.5%), medical procedures (from 72.0% to 83.2%). The total mean monthly cost per patient decreased between 2013 and 2019 (from 5,683€ to 4,653€), by 2.85% per year (95%CI: -4.13 to -1.56, $p<0.0001$). An increase in drugs acquisition costs (from 1,015€ to 1,365€) and a decrease in the cost of overnight hospitalizations (from 3,110€ to 1,990€) were observed.

Conclusions: This study highlights that the increase in drugs acquisition costs has been offset by a decrease in hospitalization costs, resulting in a decrease in global management costs of patients with metastatic lung cancer in France between 2013 and 2019. These findings may be the result of French health policy and may also be related to improved disease management.

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1418P Impact of TTFields therapy on global and functional health-related quality of life (HRQoL) in metastatic non-small cell lung cancer (mNSCLC) from the pivotal LUNAR study

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Background: Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell survival. The randomized, pivotal LUNAR study met its primary endpoint, demonstrating significantly improved OS with TTFields/standard of care (SOC; investigator's choice immune checkpoint inhibitor or docetaxel) vs SOC in mNSCLC following platinum failure without added systemic toxicity. A prior study in glioblastoma showed that adding TTFields therapy to standard chemotherapy did not adversely affect HRQoL. Herein we report global and functional HRQoL from LUNAR.

Methods: Adults with mNSCLC progressing on/after platinum therapy were randomized 1:1 to TTFields/SOC or SOC. HRQoL was assessed at baseline (BL) and every 6 weeks (to 54 weeks) by the EORTC QLQ-C30 questionnaire. HRQoL outcomes from global health and functional scales are reported here. Scores were calculated as mean change from BL (change of $\geq$10 points considered clinically relevant). Time to deterioration (TTD) was defined as time from BL to a deterioration of $\geq$10 points without a subsequent $\geq$10-point improvement (and no death before the confirmatory assessment). TTD was estimated by Kaplan−Meier plots with medians by Greenwood's formula and comparisons by 2-sided log-rank tests.

Results: BL scores were comparable for patients receiving TTFields/SOC (n=134) vs SOC (n=136) in global health status and functioning. Overall, there were no notable differences in change from BL in these scales over time between groups. There were no significant differences between TTFields/SOC vs SOC for median TTD in global health status (4.4 vs 4.0 months, P=0.91), physical functioning (3.2 vs 4.2 months, P=0.58), role functioning (3.0 vs 2.8 months, P=0.59), emotional functioning (6.6 vs 5.7 months, P=0.96), cognitive functioning (3.7 vs 4.4 months, P=0.23), or social functioning (4.0 vs 3.9 months, P=0.66).

Conclusions: The HRQoL analysis conducted as part of LUNAR demonstrated that the TTFields device did not adversely affect the quality of life of patients receiving standard second-line therapies, supporting its incorporation into management guidelines for recurrent or progressive, platinum-refractory mNSCLC.

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1419P TACSTD2 (Trop-2) constitutes a promising antibody-drug conjugate target for patients with non-small cell lung cancer brain metastases

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Background: Brain metastases (BM) are a frequent complication in patients with non-small lung cancer (NSCLC). Treating BM is challenging as the blood-brain barrier can limit intracranial drug delivery. Data from different trials suggest that antibody-drug conjugates (ADC) can have clinically relevant intracranial activity. This study aims to characterize the gene expression of ADC targets in NSCLC-BM to guide treatment decisions.

Methods: Gene expression data from 125 BM resected from patients with NSCLC were obtained from 3 public datasets. Gene expression of 14 ADC targets (*ERBB2, ERBB3, TACSTD2, MET, GPNMB, PTK7, MSLN, CD276, TF, AXL, EGFR, SLC34A2, CEACAM5* and *ROR2)* was evaluated to identify those consistently expressed across the cohorts. Additionally, hierarchical clustering was used to stratify NSCLC-BM, in each dataset separately, based on the combined relative gene expression of the common 25% most variable genes: *MSLN, CEACAM5* and *SLC34A2*. Furthermore, association between clusters and clinical covariates was assessed for one of the datasets with available data (N=63).

Results: Gene expression evaluation showed that *TACSTD2* (Trop-2) was ubiquitously highly expressed across datasets, suggesting that *TACSTD2* could be a promising ADC target for NSCLC-BM. Contrarily, *ROR2* showed consistently lower expression and would probably not be a good candidate in NSCLC-BM. Transcriptional patterns from the 3 most variable ADC targets (*MSLN*, *CEACAM5*, and *SLC34A2*) yielded common subgroups in all datasets defined by the following expression levels (respectively): High/High/High, Low/High/High, High/Low/Low. These groups did not correlate with clinical covariates.

Conclusions: Gene expression evaluation of ADC targets in NSCLC-BM resulted in the identification of *TACSTD2* expression across all datasets. *TACSTD2* might be a promising ADC target for patients with NSCLC with BM. Further validation is warranted in terms of protein expression. Our results underscore the potential value of gene expression profiling to identify new targets and improve patient selection in the context of NSCLC-BM ADC therapy.

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1420P Real-life management of octogenarians with NSCLC in a French nationwide cohort

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Background: Due to scarce publications, no specific recommendations have been published for the management of octogenarians with NSCLC. In a real-life prospective observational, multicenter study we analyze their clinical and biological characteristics, modalities of treatments by stage, overall survival (OS) and its evolution in ten years.

Methods: Between 01/01 and 12/31/2020, all patients diagnosed with a Lung Cancer (LC) in 82 participating centers, were included in a nationwide cohort (KBP-2020). Here, we report data on octogenarians with NSCLC compared to those under 80 y.o (<80). OS was calculated using the Kaplan-Meier method. Management and OS were compared to the previous cohort (KBP-2010).

Results: 8,999 LC were included in KBP-2020, 1026 (11.4%) were NSCLC over 80 y-o. Median age was 83.7, 33.7% were female, 40.0% had a PS≥2 (*vs* 21.9% in <80), 61.2% had lost weight (mean 6.8kg) at diagnosis (vs 53.2% in <80), 32.2% were non-smokers (vs 10.8 % in <80), 62.7% had an adenocarcinoma. By stage, there were 19% localized (N=188), 18.8% locally advanced (N=186) and 62.2% metastatic (N=615) disease. Biomolecular analysis was performed in 65% of cases.

Compared to KBP-2010, in octogenarians, surgery was performed in 46.3% of localized disease (*vs* 26%), thoracic radiotherapy or chemotherapy in 33.3% (vs 25.5%) and 38.9% (vs 41.5%), respectively of locally advanced disease and systemic therapy was given in 55.7% of metastatic disease (vs 52.1%). Chemotherapy, targeted therapy or immunotherapy were performed in 25.4%, 18.2% and 14.9% of metastatic patients, respectively. In 2020, median OS for all NSCLC octogenarians was 8.7 months [7.0 - 9.9] *vs* 5.0 months [4.6 - 5.8] in 2010.

Conclusions: Compared to youngest patients, octogenarians more often had a PS≥2, lost weight, were non-smokers, had an EGFR or a MET exon 14 mutation. Compared to 2010, in 2020 surgery was performed more frequently as targeted therapy and immunotherapy while chemotherapy was less often offered resulting in better OS.

Clinical trial identification: NCT04402099.

Legal entity responsible for the study: CPHG (Collège des Pneumologues des Hôpitaux Généraux).

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1421P AI-powered intracranial tumor response predicts systemic progression with high concordance in endpoint evaluation in the phase III CROWN study

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Background: Imaging reading for endpoint evaluation in clinical trials presents challenges in reproducibility and accuracy, limiting the use of novel endpoints beyond human capabilities. This analysis explored the feasibility of AI-powered intracranial response assessment and uncovered novel imaging prognosticators in the phase III CROWN study.

Methods: 72 patients (40 patients in the crizotinib arm, 32 patients in the lorlatinib arm) with CNS metastases at baseline in the CROWN study (NCT03052608) underwent intracranial response assessment using MRI at screening and then every 8 weeks until disease progression. VBrain, an FDA-approved brain tumor AI, was used to generate response assessments that were compared with those performed by 2 neuro-radiologists from the blinded independent central review group for the study using modified RECIST (mRECIST). The sum of tumor diameter changes at first on-treatment tumor scan from baseline, denoted as early tumor shrinkage (ETS), was assessed with Cox's proportional hazard model to estimate drug efficacy.

Results: For target lesion measurements, AI showed a high correlation with the independent readers (Pearson correlation coefficient $\rho=0.94$). The intracranial objective response rate assessed by AI was 27.5% and 71.9% in the crizotinib and lorlatinib arms, respectively. Among 666 time-point assessments, discordance rates were 35.1% between AI and reader 1, 33.5% between AI and reader 2, and 35.7% between the 2 readers. The time to intracranial progression (iTTP) derived from AI and human readers showed no significant difference by log-rank test. AI tracked 394 tumors beyond mRECIST, with a median ETS of -41.8% for all these lesions vs -24.4% for target lesions by mRECIST. Brain-wide ETS better predicted systemic TTP (HR 0.40, [95% CI 0.21−0.76], $p<0.01$), while target-lesion ETS showed no significant difference (HR 0.59, [95% CI 0.32−1.09], $p=0.09$) by ETS categories > or <= to median ETS.

Conclusions: There was high agreement between AI and readers in lesion measurement, response assessment, and endpoint evaluations in the CROWN study. ETS leveraging all brain lesions may uncover a potential prognostic indicator of response in ALK-positive advanced NSCLC patients.

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Table: 1420P

Gene	EGFR		KRAS G12C		MET ex14		BRAF V600E		HER2		RET		ALK		ROS1	
	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%	N+/ N tested	%
NSCLC ≥80 y	141/553	25.5	52/381	13.6	25/219	11.4	14/364	3.8	9/293	3.1	2/69	2.9	11/559	1.9	7/488	1.4
NSCLC <80 y	379/3426	11.1	520/2741	19.0	39/1616	2.4	81/2553	3.2	35/2013	1.7	10/561	1.8	94/3923	2.4	61/3365	1.8

1422P Comprehensive genomic profiling (CGP) changes management and improves survival in patients with advanced non-small cell lung cancer (aNSCLC)

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Background: Advances in therapies for patients with NSCLC require personalizing treatment based on patients' tumor genetic profiles to improve outcomes. Approaches to evaluate tumor biomarkers include a range of testing from single gene/small panel to CGP which includes hundreds of genes and signatures like TMB and MSI. This study compared actionable biomarker detection, targeted therapy receipt, and clinical outcomes in patients with aNSCLC tested with CGP vs small panels (SP).

Methods: This is a retrospective study of adult patients in the US community setting diagnosed with aNSCLC between 1/1/2015 and 12/31/2020. Patients were followed from aNSCLC diagnosis (index) until the earliest of death or study-end and (9/30/2021) categorized based on the most comprehensive testing during follow-up as SP ($\leq$52 genes) or CGP (>52 genes). Biomarker actionability was defined by OncoKB[1]: FDA recognized (Level 1), standard of care (Level 2), standard of care predictive of resistance (Level R1). Likelihood of receipt of matched therapy was assessed using logistic regression; Kaplan-Meier and Cox proportional hazards models were used to assess real- world overall survival (rwOS).

Results: Among 3,884 patients (median age 68y, 50% female, 73% Non-Hispanic White), 20% received CGP and 80% SP as the most comprehensive test. The proportion of patients with $\geq$1 actionable biomarker was significantly higher in CGP than SP (32% vs 14%; p<0.001). Of patients with actionable biomarkers, 43%(CGP) and 38% (SP) received matched therapies (p=0.20). Among treated patients: (1) CGP prior to 1st line treatment was associated with higher likelihood of receiving matched therapy (OR=3.21[95%CI: 1.98, 5.19]); (2) patients receiving CGP testing during follow-up had greater median rwOS (22 months[95%CI:18-25] vs. 15 months[95% CI:14-16]) and reduced risk of mortality (HR: 0.80[95% CI: 0.72, 0.89]) compared to SP.

Conclusions: Patients who received CGP had improved use of matched therapies and greater rwOS compared to SP. . Broader adoption of CGP may improve detection of actionable biomarkers, facilitating appropriate timely delivery of precision therapies resulting in better outcomes.

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1423P Clinical impact of radiological diagnosis of lymphangitic carcinomatosis in patients with extensive non-small cell lung cancer treated with immunotherapy

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Background: Lymphangitic carcinomatosis (LC) is a pathological feature secondary to lymphatic or haematological spread, without an immune cell infiltrate but with radiological appearances of inflammation. Immunotherapy (IO) is now standard of care in early and late-stage non-small cell lung cancer (NSCLC). LC correlates with poor prognosis, but its effects on immunotherapy response are unknown. Here we aim to explore the predictive relevance of the radiological diagnosis of LC in patients with advanced NSCLC treated with single agent immunotherapy (SAIO) or with chemo-immunotherapy (CIO).

Methods: Demographic and clinical data of patients treated with first-line IO between January 2016 and December 2020 was retrospectively collected, and patients with LC identified using pre-treatment CT reports. A paired control arm matched for gender, age ($\leq$70 or >70), smoking status, PS, PDL1 (<1%, 1-49% and $\geq$50%), stage and treatment was used to compare clinical outcomes. Chi-square Log-Rank (Mantel-Cox) test was used to compare Progression-Free Survival (PFS) and Overall Survival (OS).

Results: A total of 484 patients had been treated with first-line SAIO or CIO, 46 (10.6%) with LC. 41 of them (89%) had non-squamous histology. 29 (63%) were treated with SIAO and 17 (37%) with CIO. Comparing tumours with LC versus the rest, PDL1 expression was <1%; 24 vs 11%, 1-49%; 9 vs 11% and $\geq$50%; 65 vs 71%. Grade 3/4 IO toxicity rates were similar (48% vs 45%). Comparing patients with LC versus a paired control population (n=73), overall response rates were 28% vs 56%, with disease progression rates of 37 vs 25%. Median PFS was 5 vs 9 months (HR 1.57, 95% C.I. 1.054 − 2.35, p=0.019) and median OS was 9 vs 17 months (HR 1.49, 95% C.I. 0.995 − 2.224, p=0.046). Brain metastases on progression were more common in patients with LC (20% vs 8%). Using univariate Cox regression analysis, PFS and OS were not influenced by the treatment received (SAIO or CIO).

Conclusions: Lymphangitis Carcinomatosis (LC) in patients with NSCLC treated with immunotherapy correlated with lower response rates, poorer PFS and OS. Addition of chemotherapy did not improve outcomes. LC may represent a pre-treatment marker of primary resistance to immunotherapy.

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1424P Outcome of thromboembolic events and its influence on survival time of advanced NSCLC patients receiving antiangiogenic therapy

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Background: Antiangiogenetic therapy and lung cancer, *per se*, are associated with an increased risk of thromboembolic (TE) events. We aim to evaluate the influence of TE on the outcome of advanced non-small cell lung cancer (NSCLC) patients receiving antiangiogenic therapy.

Methods: This retrospective cohort study included advanced NSCLC patients receiving antiangiogenic therapy, including bevacizumab and ramucirumab, from March 2013 to May 2021 at Taichung Veterans General Hospital. All TE were confirmed by objective image studies. We evaluated the prevalence, pattern, treatment, and outcome of TE and its influence on survival time.

Results: A total of 427 patients were included. Of them, 345 (80.8%) received bevacizumab, 24 (5.6%) received ramucizumab, and 58 (13.6%) received both. The overall prevalence of TE was 10.1% (n = 43). Deep vein thrombosis (DVT) was the most common TE (n = 20), followed by pulmonary embolism (PE) (n = 14), combined PE and DVT (n = 6), and cerebral vascular accidents (n = 3). Among them, 46.2% of DVT did not occur in the typical lower extremities. Two patients died of TE, which presented with massive middle cerebral artery territory infarction. Among patients with continuous use or reuse of antiangiogenetic therapy, 18.2% had recurrent TE events. At TE, 28 patients experienced progressive disease (TE with PD), while tumor status remained stable in another 15 patients (TE without PD). The post-TE survival of patients without and with PD was 8.9 months (95% CI 3.9-13.9) vs. 2.2 months (95% CI 0.1-4.3), P = 0.012. As compared with patients without TE (31.4 months [95% CI 27.1-35.7]), TE with PD patients experienced a significantly shorter overall survival (20.1 months [95% CI 15.5-24.6]), but TE without PD patients had comparable survival time (32.7 months [95% CI 7.4-28.1]) (P = 0006). Multivariate analysis suggested that the use of hormone analog and proteinuria independently predicted a higher TE prevalence among TE with PD patients (aOR 2.79 [95% CI 1.13=6.92]; P = 0.027) and TE without PD patients (aOR 4.30 [95% CI 1.13-16.42]; P = 0.033), respectively.

Conclusions: Owing to the different influences on the survival time and risk factors, TE with PD and TE without PD may be two different disease entities.

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1425P Clinical utility of liquid biopsy for the early diagnosis of EGFR mutant advanced lung cancer in real-life setting (CLEAR)

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Background: Timely diagnosis with complete molecular profiling is essential in advanced lung cancer. Although tissue sampling remains the gold standard, liquid biopsies provide an alternative option for timely molecular characterization, especially for epidermal growth factor receptor (EGFR) testing in lung cancer.

Methods: All patients referred at the Centre Hospitalier de l'Université de Montréal (CHUM) with a radiological suspicion of advanced lung cancer and no known prior tumour molecular testing were prospectively screened and consented. Plasma and tissue samples were retrieved for EGFR testing and mutations were analyzed using Cobas® cell-free DNA (cfDNA). The CLEAR study evaluated plasma and tissue EGFR testing and the clinical impact on the management of suspected lung cancer patients.

Results: Between November 2019 and January 2023, a total of 312 patients were initially screened for eligibility for inclusion in the study and 7 patients were excluded for history of treated lung cancer. Median age was 68 years, 55% were female, 17% were non-smokers, and 30% were active smokers. 83% had non-small cell lung cancer and 70% of patients had stage IV disease. 8% and 10% EGFR mutations were detected by cfDNA and tissue biopsy, respectively. EGFR exon 19 deletion was the most frequent mutation, detected in 59% of patients. Median time to EGFR result was 28 days and 3 days for tissue and plasma sampling, respectively. cfDNA was 100% specific and 72% sensitive for EGFR status. Positive predictive value was 100% and the negative predictive value was 95%. Osimertinib was initiated within a median of 12 days of cfDNA results and up to 21 days before tissue results. Cranial radiotherapy was avoided in 6 EGFR-positive patients with brain metastases.

Conclusions: Early detection of EGFR mutations by cfDNA reduces time to diagnosis and accelerates therapy initiation. Cobas® assay is specific, with high positive and negative predictive values. Decreased delays to access targeted therapy can decrease improper treatment choices and alleviate complications of untreated disease while awaiting molecular results from tissue biopsies.

Legal entity responsible for the study: The authors.

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1426P Real-world data on next-generation sequencing using comprehensive genomic profiling assays for detecting driver oncogenes in advanced non-small cell lung cancer: Analysis with the National Database of Japan

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Background: Comprehensive genomic profiling (CGP) assays have been utilized with advanced solid tumor patients who have completed standard chemotherapy in Japan. These assays are expected to investigate the driver oncogenes comprehensively, especially for patients with advanced non-small cell lung cancer (NSCLC) whose driver oncogenes have not been detected at initial diagnosis. However, there are few reports on the proportion of advanced NSCLC patients with undetected driver oncogenes at initial diagnosis who have newly identified driver oncogenes using CGP assays.

Methods: We retrospectively analyzed patients with advanced NSCLC who received CGP assays between August 2019 and March 2022. Patients under the age of 20 years were excluded. We used the Center for Cancer Genomics and Advanced Therapeutics database. The driver oncogenes were defined as EGFR, ALK, ROS1, BRAF V600E, KRAS, HER2, MET exon 14 skipping, RET and NTRK. We investigated the proportion of driver oncogenes in patients with NSCLC and which were newly identified using CGP assays.

Results: A total of 986 NSCLC patients who received CGP assays were enrolled. The adenocarcinoma, squamous cell carcinoma, not other specified, other types of patients were 764 (77.5%), 128 (13.0%), 86 (8.7%), and 8 (0.8%) cases, respectively. Among all patients, 451 (45.7%) patients were detected driver oncogenes. Among 330 NSCLC patients with undetected EGFR, ALK, ROS1, and BRAF V600E at initial diagnosis, 121 (36.7%) patients had newly identified driver oncogenes. EGFR mutation was 4 (1.2%) patients of exon 19 deletion, 1 (0.3%) patient of exon 21 L858R, 12 (3.6%) patients of exon 20 insertion, and 1 (0.3%) patient of G719A. ALK and BRAF V600E were 1 (0.3%) patient, respectively. The other driver oncogenes detected using CGP assays were 23 (7.0%) patients of KRAS G12C, 40 (12.1%) patients of KRAS non-G12C, 20 (6.1%) patients of HER2 mutation, 14 (4.2%) patients of MET exon 14 skipping, and 4 (1.2%) patients of RET.

Conclusions: CGP assays are useful for identifying driver oncogenes in patients with advanced NSCLC, especially for patients whose driver oncogenes were not identified at initial diagnosis.

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1427P Exploration of the value of leptomeningeal biopsy in diagnosing and treating non-small cell lung cancer with leptomeningeal metastasis

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Background: To explore the value of ventriculoperitoneal (VP) shunting combined with leptomeningeal metastasis (LM) biopsy in diagnosing and treating driver mutation-positive non-small cell lung cancer patients with LM (NSCLC-LM).

Methods: We retrospectively analyzed 32 driver mutation-positive NSCLC-LM patients who underwent VP shunting or Ommaya reservoir implantation from June 2019 to June 2021. Pathological result of the LM biopsy, post-operative adverse events (AE), and clinical outcomes were analyzed.

Results: Of the 32 recruited NSCLC-LM patients, tumor was detected from LM biopsy from 21 patients, leading to a detection rate of 65.6% (21/32). LM sample from one patient underwent genomic profiling and was found to harbor *EGFR* rare mutations p.G719S and p.L816Q and mutated *TP53*. Median overall survival was 16.8 months (95% confidence interval [CI] 8.7-24.8) since LM diagnosis and 10.6 months (95% CI 7.2-13.9) since VP shunting or Ommaya reservoir implantation. postoperative complications included intracranial infection (1/32, 3.1%), incisional surgical site infection (1/32), perioperative mental disorders (1/32). All AEs were Grade 1 or 2 and improved upon treatment.

Conclusions: LM biopsy is safe and feasible for driver mutation-positive NSCLC-LM patients. Importantly, LM biopsy can be used to diagnose otherwise difficult cases and identify actionable genomic alterations for targeted therapy.

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1428P Clinical benefit of combination chemo-immunotherapy in first-line treatment for patients over the age of 65 or 75 with metastatic NSCLC

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Background: Anti-PD-1/PD-L1 plus chemotherapy (CT) is considered the standard of care in first line treatment of metastatic NSCLC. However, the clinical benefit of this combination in older patients is controversial.

Methods: We performed a meta-analysis (MA) of randomized trials that compared PD-1/PD-L1 inhibitor plus CT with CT alone in first line of treatment for older patients with advanced NSCLC. Subgroups of patients over 65 and over 75 were analyzed. The outcomes included overall survival (OS) and progression-free survival (PFS). A fixed-effect model was used.

Results: We analyzed 9 trials with an anti-PD-1 (camrelizumab, cemiplimab, nivolumab, pembrolizumab, tislelizumab or toripalimab) and 6 trials with an anti-PD-L1 (atezolizumab, durvalumab or sugemalimab), including 3371 patients (41%) over the age of 65 and 212 patients (<10%) over the age of 75. Most of the patients were men (65%), PS 0/1 (98%), PD-L1+ (66%) and smokers (82%). In patients >65 years, anti PD-(L)1 +/- CT was significantly associated (hazard ratio [95% confidence interval]) with prolonged OS (0.82 [0.74-0.91]; $p = 0.0003$) and PFS (0.65 [0.60-0.72]; $p < 0.00001$) compared to CT alone. Survival benefits occurred in both anti-PD-1 and anti-PD-L1 trials. For patients over 75 years of age, OS benefit was not statistically significant (0.80 [0.58-1.09]; $p = 0.16$).

Conclusions: For patients over the age of 65 with untreated NSCLC, the anti-PD-1/PD-L1 combination with CT, compared with CT alone, is associated with significantly improved OS and PFS. Due to the low number of patients it is difficult to conclude for those over 75.

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1429P Homologous recombination repair (HRR) gene mutation: A novel biomarker for precision genomics testing in advanced lung cancer

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Background: With the rapidly evolving targeted therapy in lung cancer, a study was done to identify a new biomarker HRR gene mutation by precision genomics-based testing and to determine its relationship with immunotherapy biomarkers.

Methods: 228 cancer patients underwent the FoundationOne CDx genetic testing for the presence of HRR gene mutation over 3 years. The HRR gene includes ATM, ARID1A, BARD1, BRCA 1/2, BRIP1, CDK12, CHEK1/2, FANCA/E/G, PALB2, PPP2R2A, RAD51B/C/D, RAD54L. PD-L1 (IHC) testing and Next-Generation Sequencing (NGS) testing were done to detect alterations in 324 genes including HRR gene mutation, microsatellite instability (MSI) and tumor mutational burden (TMB). 30 patients with advanced lung cancer who underwent the genetic testing were divided into two groups of HRR gene mutated vs HRR gene wild-type (WT) and tested for statistical significance.

Results: Among 228 cancer patients analyzed, the overall HRR gene mutation prevalence was 26.31% (N=228). In the study population of 30 patients with advanced lung cancer, the age (mean 68.9, SD 8.86 years), 43.33% males (n=13), 56.67% females (n=17), at least one HRR gene mutation was detected in 26.66% (n=8) and 73.33% (n=22) of patients were HRR gene WT. Histopathology was NSCLC in 80% (n=24) and SCLC in 20% (n=6) of patients. The difference in means of TMB (mut/Mb) between HRR gene mutated (Median=7.50, IQR 3.75-21.25) and HRR gene WT (Median=8.00, IQR 5.25-12.25) groups using the Mann-Whitney U test was not statistically significant ($P>.99$). The comparison of PD-L1 status ($P=.23$), MSI status ($P>.99$) between HRR gene mutated and HRR gene WT groups using fisher's exact test was not statistically significant.

Conclusions: The HRR gene mutation in advanced lung cancer was independent of the predictors for immunotherapy response (TMB, MSI and PD-L1 biomarkers). Further clinical trials are needed to assess the efficacy of combining poly ADP ribose polymerase (PARP) inhibitors with immunotherapy in the future.

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1430P Excellent performance of a fast and fully-automated RNA based genefusion assay conducted on a large fusion positive non-small cell lung cancer cohort within a multicenter study

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Background: In patients with advanced non-small cell lung cancer (aNSCLC) timely therapeutic decision making is critical. In the past decade the treatment options for aNSCLC have expanded, along increased numbers of biomarkers that need to be tested, often on small and sparse material with multiple testing technologies. This may result in an undesired prolonged time to treatment and in the worst case even to non-feasible analysis. To elucidate the performance of the Idylla™ GeneFusion Assay, which simultaneously covers the biomarkers ALK, ROS1, RET and MET exon 14 skipping, a multicenter study was conducted in a routine clinical setting involving 12 clinical centers across Europe.

Methods: A total of 326 archival aNSCLC formalin fixed paraffin embedded (FFPE) samples were included. The results of the Idylla™ GeneFusion Assay were compared with the biomarker status determined earlier with routine reference methods (including FISH, IHC, RT-PCR, and NGS). A total of 179 biomarker positive cases (85 ALK, 33 ROS1, 20 RET and 41 MET exon 14 skipping) were included, making this one of the largest fusion positive datasets tested. The Idylla™ detects ALK, ROS1 and RET fusions using both fusion specific and expression imbalance detection, allowing for the detection of less common fusions not covered by the fusion specific PCR's.

Results: FFPE sample types used were 44% resected specimen, 46% tissue biopsies, 9% cytological specimen and 1% unknown. 67% of the centers used only 1 or 2 FFPE sections (5 or 10µm). The Idylla™ GeneFusion Assay demonstrated a low failure rate (0.9%). It showed also a high sensitivity/specificity, respectively for the following actionable biomarkers in NSCLC: 96.1%/99.6% for ALK, 96.5%/98.9% for ROS1, 100%/99.6% for RET and 92.5%/100% for MET exon 14 skipping.

Conclusions: Since results are available within 3 hours, the Idylla™ GeneFusion Assay technology has emerged as a highly relevant time efficient upfront screening tool in FFPE samples. Moreover, detection of potentially novel fusions based on the principle

Table: 1429P

HRR genes	(n)	Immunotherapy biomarkers	HRR gene mutated,(n)	HRR gene wild-type,(n)
ATM	2	TMB ≥10 High	50% (4)	31.82% (7)
ARID1A	1	TMB <10 Low	50% (4)	68.18% (15)
BARD1	1	MSI-High	0	0
BRCA 1/2	1	MS-Stable	100% (8)	100% (22)
CDK12	1	PD-L1 TPS%		
FANCA/E/G	2	Negative <1%	75% (6)	45.45% (10)
RAD51B/C/D	1	Low 1-49%	25% (2)	22.72% (5)
BRIP1, CHEK1/2, PALB2, PPP2R2A, RAD54L	0	High ≥50%	0	31.82% (7)
Precision genomics-based testing		**% patients** (n=30)		
YES (EGFR, ALK, KRAS G12C)		16.66% (5)		
NO (Non-targetable biomarkers)		83.33% (25)		
HRR gene mutated		32% (8)		
HRR gene WT		68% (17)		
First-line systemic therapy Chemotherapy(CT)/ Immunotherapy (IO)/ Targeted therapy(TT)		**% patients** (n=30)		
CT		30% (9)		
CT + IO		50% (15)		
IO		10% (3)		
TT		10% (3)		

of expression imbalance may be easily verified with either IHC, FISH or NGS without delaying the treatment initiation.

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1431P The nNGM Preclinical Platform: Preclinical research to generate evidence for patients with non-small cell lung cancer harboring variants of unknown significance

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Background: The national network genomic medicine lung cancer (nNGM) improves patient care of non-small cell lung cancer (NSCLC) patients by applying harmonized state-of-the-art molecular testing. Patients with actionable alterations can benefit from targeted molecular therapy options. However, systematic molecular testing frequently also leads to the discovery of mutations with no clear clinical actionability, commonly classified as variants of unknown significance (VUS). Since individual VUS are often rare, generation of evidence from clinical trials is difficult. The preclinical platform of the nNGM aims to provide functional data on VUS by combining preclinical research efforts with clinical data available from the nNGM network, thereby generating evidence for patients with VUS.

Methods: Clinicians can contact the preclinical platform with characterization requests for VUS. An expert team compiles literature data, clones the mutations into in vitro model systems, and conducts functional testing for oncogenicity and resistance mechanisms. Results are recorded in the MURIPEDIA knowledge data base, and correlation of predicted treatment sensitivity and clinical response informs a self-learning, evidence-generating system. The service is integrated with individual and collaborative research activities of the contributing groups for the systematic generation of preclinical evidence and includes computational methods for driver detection, and the setup of organoid biobanks as the groundwork for future patient-derived in vitro models.

Results: A total of 32 on-demand requests have been processed by scientists from the preclinical platform. Specialized in vitro testing with a turnaround time of 6 − 12 weeks is available for VUS occurring in EGFR, FGFR1, FGFR2, FGFR3, FGFR4, ROS1, or BRAF. From 19 requests concerning VUS of EGFR with no prior available data, 6 novel EGFR in vitro drivers were identified and profiled.

Conclusions: The nNGM preclinical platform offers a comprehensive on-demand characterization service for VUS in NSCLC patients supporting the concept of knowledge-generating patient care in the nNGM.

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1432P Tumor stage shift in lung cancer during the COVID-19 pandemic: A real-world data study of the Network Oncology Registry

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Background: Lung cancer patients are vulnerable towards severe COVID-19 outcomes due to multiple risk factors such as smoking, older age or certain cancer treatments. During the COVID-19 pandemic the lung cancer care was significantly altered. As increasing data point towards a shift towards the diagnosis of more advanced tumors during the pandemic in lung cancer patients we evaluated cancer stages I-IV in lung cancer, especially NSCLC patients, newly diagnosed between 2018 and 2022 in a certified German lung cancer center.

Methods: Demographic data as well as tumor-related data were retrieved from the network oncology registry and evaluated retrospectively at the time of diagnosis. The study has been approved by the ethics committee of the Medical Association Berlin (Eth-27/10).

Results: In total 1118 lung cancer patients were included in the registry study. Comparing lung cancer patients from single pandemic years to the pre-pandemic year 2018, a significant 6.9% (p=0.02) drop of stage II lung cancer diagnoses was seen in 2022. Furthermore, when looking at NSCLC patients, significant tumor stage shifts were observed during 2021 and 2022: while the proportion of stage IV diagnosed NSCLC patients increased by 10.7% (p=0.03) during 2021, the proportion of stage II NSCLC decreased by 8.2% (p=0.01) in the following year compared to the pre-pandemic year 2018. No significant shifts were observed for SCLC patients. Finally yet importantly, a 12% decline of lung cancer diagnoses in 2021 and a 17.2% decline in 2022 was documented when comparing with diagnoses in 2018.

Conclusions: COVID-19-related delays and patient's reluctance have led to clinically meaningful decreases of lung cancer diagnoses in a certified German lung cancer center. Additionally, a significant increase of stage IV NSCLC diagnosis (2021) and a significantly decreased diagnosis of stage II lung cancer, particularly NSCLC tumors (2022), during the COVID-19 pandemic were observed. The implication of these results on the cancer care, patient's health-related quality of life and the lung cancer mortality will need to be urgently evaluated in the near future.

Legal entity responsible for the study: Research Institute Havelhöhe at the hospital Gemeinschaftskrankenhaus Havelhöhe.

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1433P CNS efficacy of atezolizumab, bevacizumab, carboplatin and paclitaxel in patients with non-small cell lung cancer and actionable mutations

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Background: Prospective and retrospective data support the use of Atezolizumab in combination with Bevacizumab, Carboplatin and Paclitaxel (ABCP) in patients with extensive non-small cell lung cancer with EGFR mutations after exhausting oral targeted therapy. The atezo-brain study showed CNS efficacy of upfront atezolizumab and platinum doublet in patients without EGFR or ALK alterations and untreated brain

metastases (CNS mPFS 6.9 months). The clinical impact of ABCP in patients with brain metastases and EGFR or ALK alterations remains unknown. Here we aimed to quantify the clinical impact of ABCP in our patient population with actionable mutations and brain metastases.

Methods: Patients with actionable mutations and CNS disease treated at the Clatterbridge Cancer Centre with ABCP between 2019 and 2022 were identified. All patients had been consistently selected, monitored, and documented by the same team. Data was collected retrospectively. Progression-free survival (PFS) and Overall Survival (OS) were quantified from day 1 of cycle 1.

Results: 19 patients had brain metastases at baseline, with an average age of 59 (range 32-77). 4 had ALK translocations, 2 had rare EGFR mutations and 13 had common EGFR mutations. 4 patients had received brain radiotherapy. 13 patients had asymptomatic brain metastases and 7 patients had well-controlled CNS symptoms. They all had an average of 11 cycles of treatment (median 7). Disease control was achieved in 14 patients (74%) with partial response in 9 of them (47%). There was a 94% concordance in intracranial vs extracranial response. All patients with CNS symptoms experienced a subjective improvement after an average of 13 days, although one patient was then noted to have CNS progression on brain MRI at week 9. The median PFS was 5.71 months (CNS mPFS 6.79 months) and the median OS was 11.21 months. Grade 3-4 toxicity leading to treatment modification occurred in 10 patients (53%), but none leading to treatment discontinuation.

Conclusions: Our data indicates CNS efficacy of ABCP regardless of the actionable mutation or previous CNS treatment, with frequent and quick responses. This supports the use of ABCP in patients with actionable mutations and untreated brain metastasis.

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1434P Machine learning features derived from spatial interaction of immune cell families are associated with survival in NSCLC patients post-immunotherapy

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Background: The spatial architecture of B and T cells in the tumor microenvironment (TME) is known to be associated with treatment response in cancer patients. However, more complex spatial statistics to characterize the interaction of more than two immune cell types could further inform our understanding of tumor response to immunotherapy (IO). In this work we sought to evaluate quantitative metrics of higher order spatial relationships between multiple (>2) cell types to better characterize and predict overall survival (OS) in NSCLC patients.

Methods: The study included quantitative immunofluorescence images of pre-IO tumor biopsy specimen of 135 NSCLC patients from five centers with OS information. To predict OS, a set of 223 image features that characterize the spatial interplay of different cell types (CD4+, CD20+, CD8+, tumor, and stroma) in the TME were extracted. First, every nucleus belonging to each immune cell family was detected using an image analysis program (MATLAB) to identify the cell's expression, subsequently the cell coordinates were recorded. The algorithm then identifies each triplet of distinct cells in proximity of each other to form spatial triangles. Features relating to the density, neighborhood, and proximity of nuclei were subsequently extracted. A risk score (RS) was then computed for each patient using the least absolute shrinkage and selection operator. To predict OS, the Cox regression model was trained on 100 patients (St) and validated on 35 patients (Sv). The discriminative ability of the features was assessed using Kaplan-Meier and log-rank tests.

Results: The RS was significantly associated with OS in both St (HR: 1.76; 95% CI = 1.09 - 2.85; P = .02), and Sv (HR: 2.8; 95% CI= 1.18−6.68; P=.01). RS based risk stratification showed greater accumulation of tumor, CD4 T cells, and CD20 B cells in very close proximity of each other in low-risk patients, compared to high-risk patients.

Conclusions: Machine learning derived features describing the higher order spatial relationships between tumor, CD20 B cells, and CD4 T cells were found to be associated with OS in NSCLC patients treated with IO. Additional, independent multi-site validation of these findings is warranted.

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1435P Clinical and molecular study with digital support of advanced non-small cell lung cancer patients: SNF-CLIMEDIN, a prospective randomized Hellenic Cooperative Oncology Group (HeCOG) study: Interim analysis

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Background: SNF-CLIMEDIN aims to provide comprehensive care to advanced NSCLC patients through 3 pillars: clinical, molecular and digital. Molecular profiling is not yet reimbursed. In the era of new therapies remote support tools are needed.

Methods: In this prospective randomized non-interventional study in 200 NSCLC patients receiving standard 1st line therapy, 161 genes are analyzed via NGS. Clinicians report Adverse Events (AEs) in a study database; patients record AEs in a digital platform and are randomized to receive (investigational) or not (control) educational and supportive content. The impact of digital support on QoL is evaluated.

Results: This unplanned interim analysis studied 100 patients from 15 HeCOG centres. The Table shows clinical and molecular characteristics. The most common 1st line therapy was IO-chemo (80%). PR was 32%, SD 31%, 1-yr OS 64%, med PFS 5 months and med OS 8 months. Clinicians reported fatigue, haematological, liver and skin toxicities as the commonest gr3-4 AEs, while patients in the platform most often reported fatigue, cough, nausea, diarrhoea and anorexia. More AEs were reported in the platform than in the study database (89% vs 68% of patients, $p<0.05$). Platform use was higher in the investigational arm and rural areas. Patient-reported AE improvement was 78.4% (80.8% investigational vs 75.8% control). Most pts reporting AEs at least twice had ≥50% improvement. QoL and socio-demographic correlations with digital platform use will be presented.

Table: 1435P

Clinical			Molecular
Age median	68 yrs		
Characteristic	%	Aberration	%
Male	80	TP53	59
Smoker	85	KRAS	27
Residence Urban	85	STK11	12
Live with Family	82	SMARCA4	10
Pensioners	59	EGFR	6
>High school education	73	BRAF	6
ECOG PS 0-1	97	PIK3CA	5
De Novo mets	88	PTEN	5
Adenocarcinoma	66	BRCA1/2, ATM	9
PDL-1 (+)	56	NOTCH	9
		MYC	5

Conclusions: The study provides prospective evidence on NSCLC patients' clinical and molecular profiles, treatment patterns and outcomes. Digital education and support led to increased AE reports and improvements, especially in the investigational arm.

Socio-demographic factors influenced platform engagement, highlighting the significance of digital initiatives for patient-centered NSCLC care.

Clinical trial identification: NCT05372081.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

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1436P Prospective study utilizing ctDNA genome-wide copy number variations for longitudinal monitoring of patients with advanced non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. While the development of targeted therapies has led to significant improvements in NSCLC patient outcomes, resistance can develop over time. Hence, there is need for reliable methods to monitor treatment response and identify tumor relapse. Circulating tumor DNA (ctDNA) in plasma has emerged as a promising biomarker for NSCLC, which can be used for longitudinal tumor monitoring.

Methods: The study recruited 69 patients with advanced NSCLC and collected their blood samples at the baseline. Patients were treated with targeted therapies tailored to their biomarker profiles. Blood samples were collected approximately every three months until disease progression, and were delivered to a central laboratory for ctDNA analysis. The study applied PredicineSCORE, a low-pass whole-genome sequencing (LP-WGS) assay, to monitor disease progression during treatment.

Results: In this ongoing study, baseline blood samples from 69 enrolled patients were tested, of whom 12 patients had longitudinal blood samples tested at multiple follow-up time points. Using the ctDNA assay, gene copy variants related to NSCLC were detected at baseline, including copy gain of EGFR (n=11), PIK3CA (n=10), KRAS (n=9), AKT3 (n=8), AKT2 (n=7), ERBB2 (n=7), and copy loss of TP53 (n=8), FAT1 (n=7), BAP1 (n=7), BRCA2 (n=7), and RB1 (n=6). The assay also measured the genome-wide copy number burden (CNB) levels in plasma samples as an approach for treatment monitoring. Among the 12 patients whose longitudinal samples were tested, 7 were observed to have a CNB decrease during treatment, which was correlated with their clinical response. Notably, the study also found that 2 patients had an increase in CNB, preceding the clinical detection of disease progression.

Conclusions: Next-generation sequencing (NGS)-based ctDNA tests using plasma have demonstrated remarkable molecular profiling capabilities in advanced NSCLC patients. PredicineSCORE-based LP-WGS assays performed in the study have revealed the copy number burden profiles of NSCLC, which provides potential biomarkers for longitudinal monitoring of treatment response and disease progression.

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1437P Clinical and economic burden of tissue re-biopsy (TRB) vs. tissue followed by liquid biopsy (TFLB) in metastatic non-small cell lung cancer (mNSCLC) patients

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Background: Tissue biopsy (TIB) is the gold standard for biomarker testing in mNSCLC patients. Although TIB is common, it is associated with potential invasive procedure-related complications. Liquid biopsies are used when tissue is unavailable or insufficient for testing. Studies suggest that TFLB has comparable diagnostic accuracy to TIB for detecting genetic alterations in mNSCLC patients. Liquid biopsies are increasingly used to genotype a tumor in a less invasive manner. This study compared TIB-related complications and healthcare costs with TRB vs. TFLB in mNSCLC patients.

Methods: US administrative claims were assessed retrospectively for patients diagnosed with mNSCLC between July 2016 to June 2021 to identify adult Medicare Advantage or commercially insured patients with ≥2 biopsy claims, and whose first biopsy was tissue-based. The second biopsy defined the cohorts: TRB or TFLB. To control for possible confounding factors, study cohorts were matched 1:1 using propensity-scores (PSM).

Results: The study comprised 470 patients post-PSM, each group had 235 patients. TFLB had a lower TIB-related complication rate and associated healthcare costs compared with TRB (Table). Furthermore, mean number of complication-related healthcare visits were lower for TFLB than TRB group; outpatient visits (0.51 v 1.12, p=0.002), inpatient stays (0.45 v 0.67, p<0.001) and inpatient days (3.49 v 6.60, p=0.002).

Table: 1437P Comparison of outcomes between study cohorts

	TFLB (N = 235)	TRB (N = 235)
TIB-related complications (%)*	65.1	84.7
Pneumothorax*	17.5	46.0
Prolonged air leak >5 days*	1.3	11.9
Hemorrhage	14.0	18.3
Infection*	23.0	31.9
Thrombotic complications	13.2	8.5
Cardiovascular complications	38.7	42.1
Death	0.4	2.6
Mean [SD] TB complication-related healthcare costs - US$		
Medical costs*	8,494 [15,706]	19,741 [30,641]
Office visits*	20 [71]	51 [219]
Outpatient visits	251 [1,672]	336 [1,562]
Emergency room visits	119 [590]	85 [358]
Inpatient stays*	8,076 [15,338]	18,918 [30,012]
Other medical costs	29 [148]	352 [3622]

*P-value <0.05

Conclusions: The analysis suggests that TFLB, compared with traditional TRB, is a method that carries less economic burden and fewer TIB-related complications to detect actionable genetic mutations during mNSCLC diagnostic work-up.

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1438P Cemiplimab for advanced non-small cell lung cancer: Squamous subgroup analysis for EMPOWER-Lung 1 and 3

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Background: Outcomes for patients (pts) with squamous non-small cell lung cancer (NSCLC) treated with immunotherapy are generally poorer than pts with non-squamous NSCLC and have fewer treatment options. We report an exploratory subgroup analysis of pts with squamous NSCLC who were treated with cemiplimab from two phase 3 clinical trials.

Methods: EMPOWER-Lung 1 (NCT03088540) and EMPOWER-Lung 3 (NCT03409614; part 2) included pts with squamous or non-squamous advanced NSCLC without EGFR, ALK or ROS1 aberrations. In EMPOWER-Lung 1, pts with ≥50% programmed cell death-ligand 1 (PD-L1) were randomized 1:1 to first-line (1L) cemiplimab monotherapy or platinum-doublet chemotherapy (chemo). In EMPOWER-Lung 3, pts irrespective of PD-L1 level were randomized 2:1 to 1L cemiplimab + chemo or placebo + chemo.

Results: In both trials, ∼43% of pts had squamous histology. In EMPOWER-Lung 1, at median follow-up of 37.1 mo, for squamous pts treated with cemiplimab vs chemo, median overall survival (OS) was 22.7 vs 13.5 mo (HR: 0.51; 95% CI: 0.37, 0.69), and median progression-free survival (PFS) was 8.3 vs 5.9 mo (HR: 0.44; 95% CI: 0.32, 0.59). The objective response rate (ORR) was 43.9% vs 22.1%, and the median duration of response (DOR) was 16.0 mo (95% CI: 10.4, 33.0) vs 4.3 mo (95% CI: 4.2, 6.1), respectively. In EMPOWER-Lung 3 part 2, at a median follow-up of 28.4 mo, for squamous pts treated with cemiplimab + chemo vs placebo + chemo, median OS was 22.3 vs 13.8 mo (HR: 0.61; 95% CI: 0.42, 0.87), and median PFS was 8.2 vs 4.9 mo (HR: 0.56; 95% CI: 0.41, 0.78). ORR was 46.6% vs 26.9%, and the median DOR was 13.8 mo (95% CI: 11.0,18.2) vs 11.3 mo (95% CI: 4.2, 21.4), respectively. Patient reported outcomes and safety results will be described for both studies in the presentation.

Table: 1438P

	EMPOWER-Lung 1† Squamous	EMPOWER-Lung 3 Part 2 Squamous
	Cemiplimab (n=123) vs chemo (n=122)	Cemiplimab + chemo (n=133) vs placebo + chemo (n=67)
OS, median, mo	22.7 vs 13.5	22.3 vs 13.8
OS HR (95% CI)	0.51 (0.37, 0.69)	0.61 (0.42, 0.87)
PFS, median, mo	8.3 vs 5.9	8.2 vs 4.9
PFS HR (95% CI)	0.44 (0.32, 0.59)	0.56 (0.41, 0.78)
ORR, %	43.9 vs 22.1	46.6 vs 26.9
DOR, median (95% CI), mo	16.0 (10.4, 33.0) vs 4.3 (4.2, 6.1)	13.8 (11.0,18.2) vs 11.3 (4.2, 21.4)

†PD-L1 ≥50% population. Data cutoff dates: EMPOWER-Lung 1: 4 Mar 2022; EMPOWER-Lung 3 Part 2: 14 June 2022.

Conclusions: Subgroup analysis with long-term follow up data from two large phase 3 studies demonstrate improved clinical benefit of cemiplimab as 1L monotherapy or in combination with platinum-doublet chemo over chemo alone in pts with squamous NSCLC.

Clinical trial identification: NCT03088540; NCT03409614.

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1439P Brain radiotherapy combined with camrelizumab and platinum-based chemotherapy as first-line treatment for advanced NSCLC with brain metastases: A multicenter, open-label, single-arm, phase II study

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Background: Preclinical data have shown a synergistic effect of radiotherapy (RT) combined with immunotherapy. However, the effect of combining RT with immunotherapy remains unknown for advanced NSCLC with brain metastases (BMs). This study aimed to assess the preliminary efficacy and safety of brain RT combined with camrelizumab plus platinum-based chemotherapy as first-line treatment in NSCLC patients (pts) with BMs.

Methods: Treatment-naïve pts with NSCLC and BMs were adults who had no known EGFR/ALK/ROS1 alterations and had at least one measurable intracranial and extracranial lesions per RECIST 1.1. Eligible pts received camrelizumab (200 mg) and platinum-based chemotherapy intravenously every 3 weeks for 4-6 cycles after stereotactic radiosurgery or whole-brain RT. Subsequently, pts without disease progression received maintenance treatment with camrelizumab ± pemetrexed every 3 weeks up to 24 months, or until disease progression or intolerance. The primary endpoint was 6-month progression-free survival (PFS) rate.

Results: Between May 6, 2020 and April 25, 2023 (data cutoff), 65 pts were enrolled and treated. The primary endpoint 6-month PFS rate was 70.2% (95% CI 56.3-80.4). With a median follow-up of 11.2 months (95% CI 9.0-17.0), the median PFS was 8.7 months (95% CI 7.5-15.7), and median overall survival was 21 months (95% CI 15.1-NE). Of the 65 pts, 49 (75.4%) pts had a confirmed partial response and 14 (21.5%) had stable disease, with the overall objective response rate (ORR) and disease control rate of 75.4% (95% CI 63.1%-85.2%) and 96.9% (95% CI 89.3%-99.6%). The intracranial ORR was 81.5% (95% CI 70%-90.1%). Adverse events (AEs) of any grade occurred in 64 (98.5%) of the 65 pts, and grade 3 or 4 AEs were observed in 32 (49.2%) pts, with the most common being neutrophil count decreased (14 [21.5%]) and white blood cell count decreased (11 [16.9%]). No treatment-related deaths occurred.

Conclusions: The combination of brain radiotherapy, camrelizumab and platinum-based chemotherapy showed promising efficacy and manageable toxicity for treatment-naïve advanced NSCLC with BMs.

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1440P Final top-line results of the BGBC008 phase II, multicenter study of bemcentinib and pembrolizumab (bem+pembro) in second-line (2L) advanced non-squamous (NS) non-small cell lung cancer (NSCLC) (NCT03184571)

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Background: Treatment options in 2L metastatic NS NSCLC remain limited with modest outcomes to date. AXL, a receptor tyrosine kinase, mediates resistance to immune- and chemotherapy (CT) and is a poor prognostic biomarker in NSCLC. Bemcentinib (bem), a highly selective oral AXL inhibitor, potentiates the immune-checkpoint inhibitor (ICI) effect in pre-clinical models, providing a strong scientific rationale for the bem+pembro combination in this patient population (PP).

Methods: BGBC008 is a ph2 open-label, single-arm study of bem+pembro in 2L NS NSCLC: ICI-naïve patients (pts) (cohort A), CT-naïve pts (cohort B) and pts with prior CT+ICI (cohort C). Primary endpoint was objective response rate (ORR); secondary endpoints included safety, progression-free survival (PFS) and overall survival (OS). Exploratory analyses assessed PD-L1 (by TPS) and AXL (by H-score) status impact on outcomes.

Results: The study enrolled 99 safety-evaluable pts; median age 65 years (range 39-86); 90 pts were efficacy-evaluable (EE). Most common adverse events were gastrointestinal disorders (G $\leq$2) in >20% of pts and transient liver enzyme increase (G $\leq$3) in 10% pts. Median (m) OS and mPFS were 13 and 6.2 months (mths), respectively. AXL status impacted mOS: 14.8 vs 9.9 mths (p=0.029) for AXL >5 vs AXL $\leq$5, respectively. No difference in mOS (10.6 vs 12.4 mths) or mPFS (6 vs 7 mths) in PD-L1+ (TPS$\geq$1) vs PD-L1- (TPS<1) pts, respectively. The ORR of 11.1% in all EE pts and 21.9% in pts with AXL >5 favourably aligns with therapies in 2L NSCLC. Median OS and mPFS in KRAS mutated ($KRAS^{MT}$) (n=20) and KRAS wild-type ($KRAS^{WT}$)(n=36) were 14.1 vs 10.0 mths (p=0.49) and 9.8 vs 3.8 mths (p=0.009), respectively. The mOS and mPFS for the PD-L1- (n=6) and PD-L1+ (n=11) $KRAS^{MT}$ pts were 18 vs 11.4 mths (p=0.017) and 17.3 vs 6.1 mths (p=0.09), respectively.

Conclusions: Bem+pembro was well tolerated and efficacious compared to historical controls. Survival benefit was observed in pts with AXL >5, regardless of prior therapy or PD-L1 status. The promising efficacy signal observed in $KRAS^{MT}$ pts warrants further validation.

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Legal entity responsible for the study: BerGenBio Ltd.

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1441P Atezolizumab and bevacizumab (atezo + bev) ± radiotherapy (RT) vs docetaxel (doc) in checkpoint inhibitor (CPI)−experienced metastatic NSCLC (mNSCLC): Results from the phase Ib/II MORPHEUS-lung study

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Background: The MORPHEUS platform was designed to accelerate development of novel cancer immunotherapy combinations across tumour types. The adaptive design of these global, open-label, randomised, phase Ib/II studies allows a single control arm to be compared with multiple experimental arms and provides the flexibility to open new arms or close existing arms. We report interim analysis results from the MORPHEUS-Lung study in CPI-experienced patients (pts) with mNSCLC.

Methods: Cohort 2 (C2) of MORPHEUS-Lung is enrolling pts with *EGFR/ALK* WT mNSCLC that has progressed on prior platinum and a CPI (anti−PD-L1/PD-1) given concurrently or sequentially. The primary endpoints are investigator-assessed ORR (RECIST v1.1) and safety. Secondary endpoints include PFS and OS. Biomarkers are also being explored. C2 pts with non-squamous mNSCLC randomised to the atezo +

Table: 1441P

	Atezo + bev n=40	Doc (control) n=32
Response, n (%)		
Confirmed ORR	7 (18)	5 (16)
DCR	26 (65)	18 (56)
Median survival (95% CI), mo[a, b]		
PFS	6.9 (4.3, 8.3) HR 0.77 (95% CI:	4.5 (3.4, 5.9) 0.44, 1.34)
OS	13.7 (8.5, NE) HR 0.99 (95% CI:	18.6 (7.0, 21.0) 0.50, 1.94)
Pts with ≥1 AE, n (%)		
Grade 3-5	16 (40)	19 (59)
Worst Grade: 4	0	4 (13)
Worst Grade: 5	0	1 (3)[c]
Tx related	31 (78)	31 (97)
Serious	12 (30)	8 (25)
Leading to withdrawal from any treatment	2 (5)	5 (16)

NE, not estimable. [a]Per RECIST 1.1. [b]Median survival follow-up: atezo + bev, 8.5 mo; doc, 7.2 mo. [c]Grade 5 pneumonia considered by the investigator to be tx related.

bev, atezo + bev + RT or doc (control) arms were included in the analysis. Data from the atezo + bev + RT arm will be presented at the meeting along with updated data for the atezo + bev and doc arms.

Results: At data cutoff (24 Aug 2022), the efficacy and safety populations included 72 pts (atezo + bev, n=40; doc, n=32). The median age was 63 y, 72% of pts (n=52) were male and 81% (n=58) had PD-L1+ NSCLC per local testing. Confirmed ORR was 18% (n=7) and 16% (n=5) in the atezo + bev and doc arms, respectively (Table); 1 pt (3%) had a complete response (atezo + bev). Gr 3-5 AEs occurred in 40% (n=16) and 59% (n=19) of pts in the respective arms (Table). Tx-related Gr 4/5 AEs only occurred in the doc arm.

Conclusions: MORPHEUS-Lung interim analysis results suggest that atezo + bev is a potential tx option for CPI-experienced pts with mNSCLC. No new safety signals were identified, and AEs were consistent with the known safety profiles of the individual agents. Atezo + bev was tolerable, with fewer Gr 3-5 AEs and tx withdrawals than with doc.

Clinical trial identification: NCT03337698.

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1442P DURATION: A multicenter randomized phase II trial investigating sequential mono- (mCTX) or doublet-chemotherapy (dCTX) followed by durvalumab (D) in older or frail patients with advanced non-small cell lung cancer (NSCLC)

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Background: NSCLC is a disease of the elderly, but frail and older patients (pts) are underrepresented in clinical trials with scarce data to guide treatment.

Methods: DURATION (NCT03345810) was a phase 2 trial conducted in 31 German centers between 12/17-01/22. 201 older or frail stage IV NSCLC pts (age $\geq$70 years and/or Charlson Comorbidity Index $>$ 1 and/or performance status (PS) ECOG $\geq$ 2) were stratified to receive mCTX or dCTX according to the modified Cancer Aging Research Group score (mCARG $>$3 or $<$3, respectively), and subsequently randomized between 4 cycles of CTX and 2 cycles of CTX followed by D. Primary endpoint was the rate of treatment-related grade III/IV adverse events (AEs).

Results: The median follow-up was 36.8 months (mo) with 17% of pts censored. Median age was 76 years (range 56-90), 59 pts (30%) had an ECOG PS $\geq$2 and 112 pts (56%) a CCI $>$1. The PD-L1 tumor proportion score was 0%, 1-49% and $>$50% in 42%, 50% and 8% of pts, respectively. The rate of grade III/IV AEs was 34%, 34%, 24% and 29% for dCTX , dCTX-D, mCTX-D and mCTX respectively (p=0.68). Treatment-related deaths were reported in 1% (n=2, dCTX-D and mCTX). 2nd-line treatment (proportion anti-PD-1/PD-L1) was administered in 57% (43%), 42% (12%), 31% (16%), 38% (22%) cases after dCTX, dCTX-D, mCTX-D and mCTX, respectively. In the modified per-protocol (PP) population (including pts treated until cycle 3, excluding pts with major protocol deviations), the median overall survival (OS) was 14.3 vs 11.1 mo for dCTX and dCTX-D (HR 1.2, p=0.46) and 10.2 vs 8.3 mo for mCTX-D and mCTX (HR 0.7, p=0.25). Pts with mCARG $\leq$3 had significantly longer OS compared to patients with mCARG $>$3 in the PP population (11.0 mo vs. 5.3 mo in median, HR 2.10, p$<$0.001).

Conclusions: The mCARG score stratified older or frail pts with advanced NSCLC for safe treatment conductance on dCTX, resulting in longer OS without increased toxicity compared to mCTX. The rate of grade III/IV-AEs did not exceed 34% and treatment-related mortality was $\leq$ 1% in both strata. Immature data show a numerical OS advantage for mCTX-D compared to mCTX, which may be related to the low rate of 2nd-line treatment $<$ 40% in these most frail cases.

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1443P Patient-reported outcomes (PROs) with cemiplimab plus chemotherapy (CEMI + CHEMO) for first-line treatment of advanced non-small cell lung cancer (aNSCLC): PD-L1 level subgroups in EMPOWER-Lung 3

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Background: In EMPOWER-Lung 3 (NCT03409614), a Ph 3 double-blind randomised 2:1 trial, CEMI + CHEMO (n=312) vs placebo (PBO) + CHEMO (n=154) was evaluated as 1st-line treatment for aNSCLC with any PD-L1 expression level. OS and PFS across PD-L1 level subgroups <1%, 1–49% and ≥50% were previously reported. Exploratory analyses were conducted to evaluate PROs across these subgroups.

Methods: PROs were assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. A longitudinal mixed-effect model for repeated measures analysis was used to compare treatment groups for global health status (GHS)/quality of life (QoL) and all functional and symptom scales. Time to definitive clinically meaningful deterioration (TTD) was compared between treatment groups; comparisons were made using a stratified log-rank test and proportional hazards model.

Results: Significant delays in TTD favouring CEMI + CHEMO vs PBO + CHEMO was observed in pain and alopecia across PD-L1 subgroups. Significant delays in TTD favouring CEMI + CHEMO was observed in cognitive functioning and haemoptysis in PD-L1 <1%; in physical, role and emotional functioning and symptoms of fatigue, nausea/vomiting, dyspnoea and dysphagia in PD-L1 1–49%; and in role functioning and symptoms of dyspnoea, coughing, haemoptysis and sore mouth in PD-L1 ≥50%. CEMI + CHEMO resulted in significant favourable differences vs PBO + CHEMO in overall change from baseline in pain symptoms in both PD-L1 <1% and 1–49%. Statistically significant overall change from baseline favouring CEMI + CHEMO was also observed in cognitive functioning in PD-L1 <1%; in emotional functioning in PD-L1 1–49%; and in symptoms of coughing and alopecia in PD-L1 ≥50%. The differences in overall change from baseline and delay in TTD for GHS/QoL numerically favoured CEMI + CHEMO vs PBO + CHEMO across all PD-L1. No analyses yielded statistically significant PRO results favouring PBO + CHEMO on any QLQ-C30 or QLQ-LC13 scale.

Conclusions: Across PD-L1 subgroups in patients with aNSCLC, CEMI + CHEMO resulted in significant overall improvement and delayed TTD in multiple patient-reported functioning and cancer-related and lung cancer–specific symptoms.

Clinical trial identification: NCT03409614.

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1444P Sintilimab with two cycles nab-paclitaxel / platinum as first line therapy for advanced squamous non-small-cell lung cancer: The final analysis and biomarker results

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Background: PD-1 antibody combined with 4-6 cycles platinum-based chemotherapy has been the standard 1st line treatment for recurrent or advanced squamous (sq)-NSCLC. This study evaluated the effect and safety of sintilimab plus 2 cycles nab-paclitaxel/carboplatin for treatment-naïve stage IIIB-IV sq-NSCLC.

Methods: This is a single arm, multi-center, phase II study, advanced sq-NSCLC patients received sintilimab (200mg, IV) with nab-paclitaxel / carboplatin every 3 weeks for 2 cycles, followed by sintilimab (200mg, Q3W) until disease progression, or unacceptable toxic effects, or up to 2 years. The primary endpoint was progression-free survival (PFS). The secondary endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS) and safety. Peripheral blood circulating tumor DNA (ctDNA) were measured at baseline as well after 1 cycle (C1) and 2 cycles (C2) treatment. Here we report the final analysis and biomarker results.

Results: 48 patients were enrolled, 47 received at least once treatment, 44 had at least once tumor assessment. The median PFS and OS were 10.68 months (95%CI: 6.4-17.8) and 21.9 months (95% CI: 17.0-NE). PFS rates at 12m and 24m were 38.2% and 20.4%. OS rates at 12m and 24m were 78.9% and 47.8%. The ORR and DCR were 70.5% (95%CI: 54.8-83.2) and 93.2% (95%CI: 81.3-98.6), with a median DOR of 16.5m (95%CI: 7.0-20.6). 42 patients (91.3%) experienced treatment related adverse events (TRAEs), 5 were grade3/4, the most common TRAE were anemia, α-hydroxybutyrate dehydrogenase elevated and alanine aminotransferase elevated. Patients with abnormalities in BRAC2, BRINP2, FBXW7, KIT or RB1 exhibited a poorer PFS. The clearance of ctDNA after C2 treatment was found to be an independent predictor of superior response and longer PFS. Median PFS for patients with cleared ctDNA versus those with uncleared ctDNA were 18.1m compared to 4.3m, respectively.

Conclusions: Sintilimab combined with two cycles nab-paclitaxel/carboplatin showed encouraging PFS/OS and manageable safety as first line treatment for advanced squamous NSCLC. The ctDNA clearance might be a potential predictor for the efficacy.

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1445P A randomized phase III trial on Pembrolizumab Alone versUs pembrolizumab-chemotherapy in first LInE NSCLC (PAULIEN), results of the interim analysis

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Background: To date, first-line pembrolizumab monotherapy (PEM) has not been compared to pembrolizumab + chemotherapy (PEM/CT) in metastatic non-small cell lung cancer (NSCLC) with PD-L1 TPS ≥50%. However, the regimen that provides the highest response rate, crucial for when a tumor response is urgently needed, is unknown. Here, we report the interim results of the PAULIEN study (NTR 8896), aiming to identify the regimen (PEM or PEM/CT) with the highest response rate.

Methods: This open label, phase 3, multicenter trial aimed to randomize (1:1) 84 patients with untreated metastatic NSCLC with PD-L1 TPS ≥50% and a high tumor burden to receive PEM (200mg fixed, 3 or 6 weekly) or PEM (200mg fixed, 3 weekly) + platinum-based chemo-doublets with either pemetrexed or paclitaxel. Pemetrexed and PEM were continued as maintenance therapy. Patients in the PEM arm received CT after progressive disease. Stratification factors included age, performance status, T-stage and histology. Co-primary endpoints were objective response rate (ORR) and disease control rate (DCR) at week 6 and 12 per RECIST v1.1. Secondary endpoints included progression-free survival, overall survival and safety. A planned interim analysis was performed (data cut-off March 1st, 2023).

Results: 50 patients were randomized to PEM (n=19) and PEM/CT (n=31). Baseline characteristics were well balanced between arms. 42 patients were radiologically evaluable of whom 17 patients received PEM and 25 patients PEM/CT. The PEM arm demonstrated an ORR at week 6 of 38% vs. 44% in the PEM/CT arm (p=0.68) and a DCR of 88% vs. 88% (p=1.0). At week 12, the PEM arm demonstrated an ORR of 74% vs. 68% in the PEM/CT arm (p=1.0) and a DCR of 93% vs. 91% (p=1.0), respectively. The incidence of grade 3-4 treatment-related adverse events was 28% (PEM) vs. 52% (PEM/CT). No treatment-related deaths occurred.

Conclusions: In this interim analysis, the tumor response rate with first-line PEM alone was comparable to that of PEM/CT in metastatic NSCLC patients with PD-L1 TPS ≥50%,. No new safety signals were observed. More data is needed to explore subgroups that may still benefit from adding chemo to PEM in this population.

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1446P Preliminary efficacy and safety of rilvegostomig (AZD2936), a bispecific antibody targeting PD-1 and TIGIT, in checkpoint inhibitor (CPI)-pretreated advanced/metastatic non-small-cell lung cancer (NSCLC): ARTEMIDE-01

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Background: Rilvegostomig is a bispecific, humanised IgG1 targeting PD-1 and TIGIT, receptors that suppress antitumour T cell activity. Initial data from the first-in-human study showed favourable tolerability and early antitumour activity in patients (pts) with CPI-pretreated advanced/metastatic NSCLC. Here we report updated data from dose escalation and expansion (Parts A + B).

Methods: Pts in the initial phase of this open-label, multicentre study had stage III unresectable or stage IV NSCLC, PD-L1 tumour proportion score ≥1%, and primary or secondary CPI resistance. Part A evaluated 70−1500 mg IV Q3W; Part B evaluated the recommended phase 2 dose (RP2D). Primary and secondary endpoints included safety, tolerability, preliminary efficacy, and PK.

Results: As of 13 Apr 2023, 83 pts were enrolled (Part A, n=51; Part B, n=32). Pts were 63.9% male, median age was 63.0 yr, and 22.9% had squamous histology. Overall, 22.9% had 1 prior line of therapy, 34.9% had 2, 24.1% had 3, and 18.1% had >3. Median duration of therapy was 12.4 wk. Rilvegostomig was well tolerated (Table); RP2D was 750 mg. Four pts had confirmed partial responses (PRs) and 33 had stable disease (SD); 6-month disease control rate (DCR) was 31.3%. Median progression-free survival was 2.1 mo (95% CI, 2.0, 4.1). Updated clinical and translational data (e.g. molecular response based on ctDNA) will be presented.

Conclusions: Rilvegostomig was well tolerated and had antitumour activity in heavily pretreated pts who had progressed on CPI therapy. Further investigation is ongoing in CPI-naïve cancer patients.

Table: 1446P Safety and efficacy of rilvegostomig

Safety, n (%)	N=83
Treatment-emergent AEs (TEAEs), any grade / grade ≥3	75 (90.4) / 25 (30.1)
Treatment-related AEs (TRAEs), any grade / grade 3*	45 (54.2) / 7 (8.4)
Serious TEAEs	25 (30.1)
Serious TRAEs	6 (7.2)
AEs leading to discontinuation	3 (3.6)
Efficacy	**Evaluable pts (n=83)**
Objective response, % (95% CI)	4.8 (1.3, 11.9)
Confirmed PR	4 (4.8)
SD, n (%)	33 (39.8)
Duration of response, mo, median (range)	Not calculable (2.1, 10.3)
DCR at 9 wk, n (%)	37 (44.6)
DCR at 27 wk, n (%)	26 (31.3)
Progression-free survival, mo, median (95% CI)	2.1 (2.0, 4.1)

*No Grade 4 or 5 treatment-related AEs were reported.

Clinical trial identification: NCT04995523; 9 August, 2021.

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1447P IMscin001 part 2 updated results: Efficacy, safety, immunogenicity and patient-reported outcomes (PROs) from the randomised phase III study of atezolizumab (atezo) subcutaneous (SC) vs intravenous (IV) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

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Background: IMscin001 Part 2 met its co-primary endpoints of non-inferior drug exposure for Cycle 1 C_{trough} and $AUC_{0\text{-}21d}$ for atezo SC vs IV (Burotto ESMO-IO 2022). Efficacy, safety and immunogenicity were similar between arms at primary analysis. Here, we report updated data.

Methods: Cancer immunotherapy-naïve patients with locally advanced or metastatic NSCLC for whom platinum therapy had failed were randomised 2:1 to receive 1875 mg atezo SC or 1200 mg atezo IV q3w. Secondary endpoints were efficacy (OS, PFS, ORR, DOR), safety, immunogenicity and PROs. PROs were collected on Day 1 of Cycles 1-6 and then every second cycle until treatment discontinuation. Healthcare providers (HCPs) completed SC and SC vs IV perspective questionnaires after giving ≥3 doses of atezo SC or ≥3 doses of atezo SC and IV each, respectively.

Results: At data cut-off (16 Jan 2023; median follow-up: 9.5 mo), ≈60% of OS events had occurred. Median OS was 10.7 mo for SC vs 10.1 mo for IV; immunogenicity and safety were also similar between arms (Table). Mean PRO scores were within 10% between arms for global health status, role and physical functioning, and satisfaction with therapy. 90% (70/78) of HCPs reported that giving atezo SC was fairly easy/very easy, 85% (66/78) were satisfied/very satisfied with atezo SC and 75% (33/44) agreed that administering atezo SC could save time compared with IV.

Table: 1447P

	SC (n=247)	IV (n=124)
Median administration time (95% CI), min	7.1 (6.6, 7.4)	40.0 (37.5, 45.0)
Efficacy		
OS events, %	58	64
OS, median (95% CI), mo	10.7 (8.5, 13.8)	10.1 (7.5, 12.1)
Confirmed ORR, (95% CI), %	11.0 (7.4, 15.6)	10.5 (5.7, 17.3)
Confirmed DOR, median (95% CI), mo	15.1 (5.6, NE)	11.2 (4.2, NE)
Safety, %		
Any Grade AE	88	84
Anaemia	19	17
Dyspnoea	11	15
Fatigue	12	13
Grade 3/4 AE	21	31
Grade 5 AE	6	6
Serious AE	19	27
AE of special interest	31	28
Hepatitis	12	14
Hypothyroidism	11	7
Rash	9	11
AE leading to atezo discontinuation	4	7
Infusion-related reaction	0	3
Injection site reaction	4	0
Grade 1/2	4	0
Immunogenicity		
ADA incidence, %	21	14

NCT03735121. ADA, anti-drug antibody; NE, not estimable.

Conclusions: At this updated analysis, OS data were mature and similar between arms. Safety was also similar and consistent with the atezo IV profile for approved indications. ADA incidence for both arms was in the historic range for atezo IV. PROs were similar for both arms, and HCPs reported easy/very easy administration and potential time savings for atezo SC. These results support atezo SC as an alternative to IV.

Clinical trial identification: NCT03735121.

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1448P First-line nivolumab (NIVO) plus ipilimumab (IPI) with two cycles of chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC): Results from an interim analysis of the non-interventional FINN study

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Background: The CheckMate 9LA study showed that NIVO + IPI with 2 cycles of chemotherapy (chemo) vs chemo alone significantly improved overall survival (OS) for patients (pts) with metastatic NSCLC. The FINN real-world study (NCT04794010) aims to evaluate this regimen in clinical practice in Germany.

Methods: Enrollment for the prospective, observational study is ongoing, with 90 sites and 650 pts planned in Germany. Pts ≥18 years old with metastatic NSCLC are eligible if they began first-line NIVO + IPI with 2 cycles of chemo according to the approved EMA label. During the planned ≤5-year follow-up period (from treatment [tx] initiation until death, withdrawal of consent, loss of follow-up, or end of study), assessments will be conducted per routine local clinical practice. The primary

endpoint is OS. Secondary endpoints include progression-free survival, tx duration, patient characteristics, and safety.

Results: At the interim analysis (Jan 31, 2023), 256 pts were enrolled (median follow-up duration: 5.6 months). Median (range) age was 67 (43–86) years and 60.9% were male. Other patient characteristics are presented (Table). Tx-related adverse events (AEs) of all grades occurred in 53.9% of pts, and tx-related severe AEs occurred in 17.6% of pts. There was 1 tx-related death from immune-mediated hepatitis. We will present an update of the data with longer follow-up (data cutoff July 2023).

Table: 1448P Patient characteristics* (N = 256), n (%) unless noted

Age group, years <66 66–75 >75	120 (46.9) 102 (39.8) 33 (12.9)
Smoking status Current Former Never	98 (38.3) 111 (43.4) 28 (10.9)
Eastern Cooperative Oncology Group performance status 0 1 2 3	74 (28.9) 142 (55.5) 26 (10.2) 5 (2.0)
Number of metastases, median (range)	2 (0–12)
Histology Squamous Non-squamous	89 (34.8) 163 (63.7)
Metastasis stage M1a (contralateral lung) M1b/M1c (extrathoracic metastasis)	39 (15.2) 173 (67.6)
Metastasis site Brain Liver	51 (19.9) 49 (19.1)
Radiotherapy No/yes	204 (79.7)/48 (18.8)
Surgery No/yes	208 (81.2)/44 (17.2)
Systemic therapy/chemo No/yes/unknown	217 (84.8)/33 (12.9)/2 (0.8)

*Excludes missing data.

Conclusions: The FINN study will describe patient characteristics, efficacy, safety profile, and tx patterns of first-line NIVO + IPI with 2 cycles of chemo in clinical practice in Germany. At interim analysis, pts had a manageable safety profile.

Clinical trial identification: NCT04794010.

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1449P The preliminary data from a single-arm, open-label, multicenter phase II clinical trial: KN046 combined with axitinib as first-line (1L) treatment for NSCLC

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Background: KN046 is a novel bispecific domain antibody, which blocks both PD-L1 and CTLA-4. KN046 combined with platinum-based chemotherapy as 1L treatment for NSCLC had shown promising efficacy and tolerability in the previous clinical trial. (2022 ESMO 1029P). Herein, we present the promising preliminary data of KN046 combination with axitinib as 1L treatment for NSCLC.

Methods: Eligible subjects with recurrent/metastatic NSCLC, treatment-naive and PD-L1 expression ≥1% will be enrolled and receive KN046 5mg/kg IV Q3W and axitinib 5mg orally bid. This study adopts a Simon's optimal two-stage design. In the 1st stage, 17 subjects will be enrolled, and the 2nd stage enrollment will be discontinued if objective response (CR or PR) observed in less than 5 subjects. Otherwise, 37 subjects will be enrolled in the 2nd stage. The primary endpoint is ORR. The secondary endpoints include DoR, safety, PFS and OS.

Results: As of data cut-off date (Mar 17, 2023), 22 subjects were enrolled, the median age was 64.5y (min:37, max:73), 90.9% were male. ECOG score was 0 (4.5%) and 1 (95.5%). PD-L1 expression was ≥50% in 22.7% of the subjects. 15 subjects completed at least one tumor assessment. In the efficacy analysis set, the ORR was 66.7% (10/15). The median follow-up for DoR was 4.21 m (95% CI,1.22, NE). The 3-m DoR rate was 100% (95% CI, 100.00, 100.00). The median study follow-up was 2.83 m (95% CI,0.72, 5.12). The 6-m PFS rate was 76.6 % (95% CI, 41.16, 92.28), The mPFS and mOS was not reached. The incidence of TEAE was 81.8% (18/22), of which KN046-related TRAE was 63.6% (14/22). Majority was grade 1-2. The incidence of KN046-related CTCAE Grade ≥3 TRAE was 9.1% (2/22). The most frequent TRAE was AST increased 9.1% (2/22) and ALT increased 4.5% (1/22). The incidence of irAE was 13.6% (3/22), No CTCAE Grade ≥3 irAE was found. There was no KN046-related death.

Conclusions: KN046 combined with axitinib is well tolerated and has shown very promising efficacy and safety signal in 1L treatment for advanced NSCLC. The 2nd stage of enrollment is ongoing and a phase 3 RCT is planned to further confirm the clinical benefit of KN046 and axitinb combo as a viable chemo free option for the 1st line NSCLC patient.

Clinical trial identification: NCT05420220.

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1450P Addition of bevacizumab to first-line chemoimmunotherapy in NSCLC with liver metastases

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Background: Liver metastases create a unique immunosuppressive microenvironment in patients with advanced non-small cell lung cancer (aNSCLC) and are associated with poorer outcomes when treated with chemoimmunotherapy, especially in non-squamous (ns-) aNSCLC.

Methods: We retrospectively analyzed data from IMpower150 and IMpower130, which included patients with ns-aNSCLC without EGFR/ALK/KRAS alterations, treated with first-line chemotherapy (CT) with/out atezolizumab (CT+IT) and/or bevacizumab (CT+IT+AA, CT+AA). Data was available on the VIVLI platform.

Results: Out of the 1,523 evaluable patients, 20.4% (n=311), 46.4% (n=707), 19.7% (n=300), and 13.4% (n=205) received CT+IT+AA, CT+IT, CT+AA, and CT, respectively. 13.9% (n=212) of the patients had liver metastases (LM). LM were associated with lower serum albumin and higher lactate dehydrogenase levels, a greater number of metastatic sites (all $p<0.001$) and poor outcomes across all treatment regimens except for patients treated with upfront CT+IT+AA (Table). In the overall population, CT+IT+AA achieved longer progression-free survival (HR for PFS: 0.74, $p<0.001$) but not overall survival (HR for OS: 0.91, $p=0.38$) compared to CT+IT. Of all included variables (age, smoking status, Lung Immune Prognostic Index (LIPI), albumin levels, ECOG performance status, and number of metastatic sites), only LM+ patients yielded substantial OS benefit of CT+IT+AA vs. CT+IT (HR for PFS: 0.44, $p<0.001$; HR for OS: 0.43, $p=0.002$, Table). No benefit of CT+AA over CT in patients with/out LM was observed.

Table: 1450P Impact of liver metastases on PFS and OS across all regimens and on response to CT+IT +/- AA

Impact of LM across regimens					
Regimen		**HR for OS (LM+ vs. LM-)**		**p-value**	
CT		1.8 (1.1-2.9)		0.02	
CT+AA		2.2 (1.5-3.3)		<0.001	
CT+IT		2.5 (1.9-3.2)		<0.001	
CT+IT+AA		1.0 (0.6-1.7)		0.94	
Addition of bevacizumab to CT+IT					
		Overall		**LM+ patients**	
		CT+IT	**CT+IT+AA**	**CT+IT**	**CT+IT+AA**
PFS	**n**	707	311	103	39
	Events	548	210	90	27
	mPFS	6.8 (6.0-7.1)	8.3 (7.7-9.9)	4.4 (3.9-5.4)	8.0 (5.7-13.4)
	6M-PFS	53.4%	67.0%	28.4%	58.3%
	p	<0.001		<0.001	
OS	**n**	707	311	103	39
	Events	336	128	74	16
	mOS	18.6 (16.3-20.5)	19.2 (16.8-NR)	8.7 (6.5-11.2)	16.8 (12.9-NA)
	12M-OS	63.6%	67.5%	36.7%	65.5%
	p	0.35		0.002	

Conclusions: LM are associated with poor outcomes in patients with aNSCLC treated with CT, CT+AA and CT+IT but not CT+IT+AA. The addition of bevacizumab to CT+IT improves outcomes (PFS and OS) in patients with liver metastases and helps correct its negative prognostic impact. The presence of liver metastasis may help in guiding treatment selection in first-line aNSCLC.

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1451P Identifying long-term responders to immune checkpoint blockade: Potential utility of serum proteomic profiling in metastatic non-small cell lung cancer

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Background: Immune checkpoint blockade (ICB) has significantly impacted the treatment landscape in non-small cell lung cancer (NSCLC). However, this benefit is restricted to a subset of patients. While these results are encouraging, it is crucial to identify those patients who benefit the most from ICB and those who are refractory. Here we investigate the potential utility of longitudinal serum proteomic profiling to identify predictive biomarkers.

Methods: We included 40 metastatic NSCLC patients who received ICB treatment at Hospital del Mar, Barcelona between 2017-2021. Patients were categorized as long-term responders (LTR, n=20) if they had maintained radiologic response for more than 2 years or non-responders (NR, n=20) if they had disease progression at first radiological evaluation. Serum protein levels were assessed longitudinally (before treatment, previous cycle 2) using the Olink® Explore 384 Oncology panel.

Results: LTR had a greater proportion of high PD-L1 expression (p=0.01). Analysis of baseline serum samples showed an increase in LTR of proteins levels related to apoptosis and autophagy (CASP8, ATG4A), TCR signaling pathway (STAT5B, CRACR2A) and myeloid differentiation (ZBTB16, ARG1) ($p<0.05$ for all proteins). Higher levels of proteins related to immunosuppression and tumorigenesis (PDCD1, TGFBR2, KLK4, KLK6) prior to the second cycle of ICB were associated with poorer response to ICB, with non-responders exhibiting significantly higher levels ($p<0.05$ for all). Gene set enrichment analysis showed that LTR had an increase in myeloid cell differentiation process, while higher levels of immunoregulatory interactions between lymphoid and non-lymphoid cells were observed in NR ($p<0.001$ for all).

Conclusions: Our findings suggest that patients with high levels of proteins related to apoptosis, autophagy, TCR signaling, and myeloid differentiation at baseline may identify LTR to ICB. Our study underscores the potential use of baseline and longitudinal assessment of serum proteomics as valuable tools for patient selection who are suitable candidates for ICB. Further studies are needed to validate these findings and establish their potential clinical utility.

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1452P Factors associated with real-world (rw) outcomes among pts with metastatic NSCLC (mNSCLC) receiving select immuno-oncology (IO) regimens: CORRELATE

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Background: PD-(L)1 inhibitors ± chemotherapy (CTx) have demonstrated significant survival benefit vs CTx in randomised controlled trials (RCTs) in mNSCLC. However, subgroups that may benefit less from current standard of care regimens have emerged, such as those with mutations (m) in *STK11*, *KEAP1* and *KRAS*. One aim of CORRELATE was to determine factors associated with OS and rwPFS in pts receiving 1L IO treatment (tx).

Methods: This analysis included pts from the US Flatiron Clinico-Genomic Database who had mNSCLC (progressed or *de novo*), started 1L IO tx between 1 Nov 2016 and 31 May 2021, and met eligibility criteria based on 4 RCTs for tx with a US approval in mNSCLC (KEYNOTE [KN]-024 [n=95], KN-189 [n=462], KN-407 [n=122] and

IMpower150 [n=4]). Association of pt characteristics and select 2-way interactions with OS and rwPFS were explored. Those variables that were statistically significant ($p<0.05$) were included in multivariate Cox regression models along with *STK11*, *KEAP1*, *KRAS* and PD-L1 status.

Results: Of 683 pts, 65% were aged ≥65 y, 88% white and 54% male. 21% had PD-L1 ≥50% and 34% had PD-L1 ≥1% (53% unknown PD-L1); 80% had ECOG performance status (PS) 0/1 and 90% were former/current smokers. 15%, 13% and 31% had *STK11*m, *KEAP1*m and *KRAS*m tumours, respectively. Median OS was 15.2 mo (95% CI 13.5−17.6); median rwPFS was 6.0 mo (5.6−6.8). Multivariate Cox regression showed male sex (p=0.021), lower PD-L1 expression (p=0.030), higher PS ($p<0.0001$) and multiple baseline mets ($p<0.0001$) were associated with higher risk of death; and lower PD-L1 expression (p=0.049), higher PS ($p<0.0001$) and multiple baseline mets ($p<0.0001$), with higher risk of progression/death. Pts with *STK11*m had a higher risk of death (HR 1.52 [95% CI 1.17−1.97]; p=0.002) and progression/death (1.54 [1.22−1.94]; $p<0.0001$). Pts with *KRAS*m had an increased risk of death vs *KRAS* wild-type; this effect was greater among non-smokers (HR 2.66 [1.33−5.35]); p=0.006).

Conclusions: In pts with mNSCLC receiving 1L IO tx at primarily community US practices, *STK11*m was associated with worse OS and rwPFS. Smoking history modified the effect of *KRAS*m on OS. These hard-to-treat populations may require novel combination tx approaches to overcome resistance.

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1453P Trends in treatment regimens and survival in the use of immune checkpoint inhibitors for lung cancer treatment in the Netherlands from 2016-2020

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized lung cancer (LC) treatment. This study aims to describe the trends of ICI in LC treatment.

Methods: We evaluated treatment regimens and clinical outcomes in the use of ICIs for LC in the Netherlands from 2016-2020 using data from the Netherlands Cancer Registry (NCR) on first-line treatments, and performed a secondary analysis using a local cohort within the University Medical Center Groningen (UMCG) containing all-line treatments. Between 2016-2018, the NCR contained mostly data from patients treated in randomized controlled trials (RCTs) as clinical guidelines advised ICIs only in later treatment lines, whilst NCR data from 2018-2020 and from the UMCG from 2016-2020 were mainly collected outside RCTs. Descriptive statistics and annual percentage change (APC) were used to evaluate changes over time. Also, a survival analysis was performed.

Results: The proportion of first-line ICIs in LC treatment increased from 1.1% in 2016 to 54.9% in 2020 in the Netherlands (6816 patients in total, APC=14.5%, p=0.002). In the UMCG, increases were observed in the proportion of any-line ICI-chemotherapy combination (APC=12.4%, p=0.049), patients surviving ≥1 year (APC=5.8%, $p<0.001$), and partial response as best overall treatment response (APC=9%, p=0.049), whilst NCR data showed no significant changes over the years. NCR median overall survival (OS) was higher in the period 2016-2018 compared to 2019-2020 (83.4 vs 72.7 weeks, $p=<0.001$), whilst in the UMCG, 2016-2018 showed a lower median OS compared to 2019-2020 (39.3 [95%CI 32.9-48.6] vs 72.4 weeks [95%CI 52.7-87.4]).

Conclusions: The use of ICIs for LC treatment in the Netherlands increased over the years. Survival data showed better response in the use of ICI as any-line treatment in the UMCG from 2019-2020, contrary to data from patients in the NCR. An explanation for this is the inclusion of mainly RCT patients in the NCR data during the early years of ICI use and the recent shift from second to first-line treatment. As new ICI based drugs emerge, updated analyses will be needed using real-world data to evaluate the real benefits of these newly developed treatments.

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1454P Radiomic analysis predicts response to immunotherapy in metastastic non-small cell lung cancer (mNSCLC): Preliminary results

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Background: Immunotherapy (IT) with single-agent immune-checkpoint inhibitors (ICI) is standard treatment in all comers mNSCLC patients (pts) with PD-L1 expression >50%. However, inter- and intratumoral heterogeneity of PD-L1 expression limits its predictive value. Radiomics has the potential to integrate imaging and biological data thus recapitulating tumor tissue heterogeneity. We used a machine learning approach to test computed tomography (CT) tumor radiomic features in terms of predictive value of immunotherapy response.

Methods: We retrospectively analyzed radiological and clinical data of 190 pts who received first-line immunotherapy with Pembrolizumab (P) for non-oncogene addicted mNSCLC with PDL1>50% treated at our Institution from 2017 to 2022. Baseline contrast-enhanced CT (CECT) imaging of the primary tumor was contoured to isolate a polygonal region of interest (ROI) enclosing the whole tumor volume and the peripheral tumor area (3mm thickness). After thresholding and filtration of images, radiomic analysis was conducted to isolate 107 radiomic features of mean grey level (GL) values within the ROIs. Median progression-free survival (PFS) was calculated from start of IT to first evidence of progression or death. A machine learning approach with cross-validation (Orange Data Mining Software) was applied to select the best radiomic features in terms of PFS predictive value.

Results: After pre-processing of CECT imaging, 78 eligible pts were finally included in the radiomic analysis. Median PFS was 5 months. In the whole series, 33% and 22% of pts were classified as hyper-responders (PFS>24 months) and hyper-progressive (PFS<1 month), respectively. PDL1 expression level (50-75% vs >75%) was not predictive of PFS at univariate analysis (3 vs 5 months, p 0.147). After machine learning selection with 10-fold cross validation, 30 out of total 107 radiomic features were extracted to best predict PFS (9 vs 2 months, $p<0.005$).

Conclusions: Preliminary results of this exploratory analysis indicate that as predictive PFS factors, radiomic features outperform common clinico-pathological factors including PD-L1 expression even at thresholds >75% and >90%. Validation of these results is warranted.

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1455P Nivolumab (nivo) resumption in patients with advanced or metastatic non-small cell lung cancer (aNSCLC): Survival outcomes based on France and Germany real-world data (RWD)

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Background: Nivo as monotherapy for the treatment of aNSCLC after prior chemotherapy (chemo) was approved by EMA in 2015 and has been used in clinical practice since. In this study, we describe RW survival outcomes of patients with aNSCLC who resumed nivo after interrupting an initial nivo treatment received as 2+ line-of-therapy (LOT).

Methods: This study leverages RWD collected in 2 prospective, non-interventional studies: EVIDENS (NCT03382496; France) and ENLARGE (NCT02910999; Germany) on patients with aNSCLC treated with nivo. Data were pooled and two cohorts were defined: 1) nivo resumption cohort (patients who re-started nivo after an interruption of $\geq$6 weeks) and 2) chemo cohort (patients who received chemo or other systemic anti-cancer therapy after nivo). Demographics and clinical characteristics were described, and overall survival (OS) was estimated using Kaplan-Meier methods from the start of the "index treatment" (LOT following the initial nivo treatment).

Results: Among 2,266 patients (1,397 from France and 869 from Germany), 210 (9.3%) resumed nivo after an initial interruption of $\geq$6 weeks. 697 (30.8%) started a chemo treatment after nivo, among which 171 - from the ENLARGE study - had data required for this analysis and constituted the chemo cohort. Median age was 67 (range: 41-89) in the nivo resumption cohort and 64 (21-83) in the chemo cohort. In both cohorts, majority of patients were male and received their index treatment as third LOT. Median OS was 19.6 months (mo) [95% CI: 16.2-25.2] for the nivo resumption cohort and 9.1 mo [7.1-10.0] for the chemo cohort. Nivo-resuming patients who had received an initial nivo treatment of $\geq$3 mo had a median OS of 22.8 mo, compared to 10.7 mo in patients with $<$3 mo initial nivo treatment. In the chemo cohort, patients with a duration of initial nivo therapy of $\geq$3 mo had a median OS of 9.9 mo in subsequent treatment, compared with 7.1 mo in patients with $<$3 mo of initial nivo treatment.

Conclusions: OS data show that patients with aNSCLC who interrupted their initial nivo treatment may benefit from resuming nivo, primarily when initial exposure to nivo lasted for more than three months.

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1456P Exploring biological and molecular factors as outcome predictors for pembrolizumab (Pem) or pembrolizumab-chemotherapy (Pem-CT) in advanced non-small cell lung cancer (NSCLC)

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Background: Pem and Pem-CT are first-line treatments for non-oncogene addicted NSCLC, but no validated predictors of benefit beyond PD-L1 are available. We explored the impact of biological or molecular factors on outcomes with Pem or Pem-CT.

Methods: We retrospectively collected data from patients (pts) treated with Pem or Pem-CT in three European centers. We categorized NLR and LDH into good, intermediate, and poor groups based on none, one, or both NLR$\geq$3 and LDH$>$upper limit of normal. Molecular profiles at baseline were obtained from tissue or blood samples, with varying techniques and panels among and within centers. We used multivariable Cox regression models to explore prognostic impact of NLR-LDH categories, differential efficacy of the treatments in the categories and in *KRAS*-mutant (mut) tumors. We adjusted for center and known prognostic factors (age, gender, PS ECOG, number of metastatic sites, brain and liver metastases), included if associated with progression free survival (PFS) and/or overall survival (OS) with a $p<0.05$ in univariate Cox models.

Results: We included 440 pts, 224 treated with Pem and 216 with Pem-CT. Pem population was older ($p<0.0001$), but the groups were balanced for other prognostic factors. At a median (m) follow up of 16.3 and 12.9 months for Pem and Pem-CT group, mPFS and mOS were 7.6 and 15.9 months; 7.2 and 22.8 months, respectively. The combination of baseline NLR-LDH was prognostic for both Pem and Pem-CT (Table). No statistically significant difference between the treatments was seen in the subgroups. 159 (36%) tumors were *KRAS*-mut. In *KRAS*-mut tumors no difference was seen between the two treatments neither in PFS ($p=0.55$) nor OS ($p=0.79$).

Table: 1456P

	OS			PFS		
	HR	95%CI	*p*	HR	95%CI	*p*
NLR-LDH			<0.001			<0.001
Good	1,00	Ref		1,00	Ref	
Intermediate	1,63	1.04-2.57		1,93	1.33-2.80	
Poor	2,79	1.75-4.44		2,42	1.63-3.60	

Conclusions: Combining baseline NLR and LDH provides a prognostic stratification, regardless of the addition of CT to Pem as first-line treatment. No difference between the two strategies was seen in the *KRAS*-mut tumors.

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1457P Oligometastatic non-small cell lung cancer: Impact of local and systemic treatment approaches on clinical outcome

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Background: Oligometastatic (OMD) non-small cell lung cancer (NSCLC) is a distinct but heterogeneous entity. Current guidelines recommend locally ablative therapy if technically feasible. Still, evidence is lacking to guide the choice of optimal multimodal treatment approaches and their impact on clinical endpoints.

Methods: Electronic medical records and clinical databases (years 2004 – 2022) from two major German comprehensive cancer centers were searched for cases with OMD NSCLC and treatment patterns. Prespecified OMD criteria included presence of $\leq$5 metastases in $\leq$2 organ systems, excluding primary tumor and mediastinal lymph nodes. Endpoints of this retrospective analysis were overall survival (OS), disease-free survival (DFS, first-line therapy until recurrence) and time-to-treatment failure (TTF).

Results: A total of 207 patients with OMD NSCLC were identified (46.9% female; median age 60.8; median follow-up 32 months; T1-2 vs. T3-4 51%/49%, N0-1 vs. N2-3 48%/52%, M1a 10.7%, metastases in one organ system 89.7% vs. multiple 10.3%). A dedicated OMD treatment strategy was explicitly specified in 164 patients (79.2%). Locally ablative therapy was applied to all tumor sites in 140 patients (67.6%), including radiotherapy (85%) and/or surgery (73.6%). Median OS of the full analysis cohort was 27.7 months, with 27.2% OS at 5 years. Median OS in patients receiving locally ablative therapy to all NSCLC sites amounted to 33.4 months (5y rate 35.7%) with a median DFS of 10.6 months (11.2% at 5y). First-line therapy included systemic therapy in 167 patients (80.7%), which was associated with doubling of DFS (median 12.2 vs. 6.0 months, $p<0.001$), and a trend towards improved OS. First-line chemoimmunotherapy was only approved in 2018/2019, thus limiting follow-up in this subgroup. Nevertheless, DFS (HR 0.5, $p=0.025$, 2y rate 46% vs. 15%) and TTF (HR 0.45, $p<0.001$) were greatly improved with first-line chemoimmunotherapy vs. chemotherapy.

Conclusions: Patients with OMD NSCLC benefit from multimodality approaches integrating systemic therapy and local ablation of all cancer sites. Although true freedom from recurrence is rare, extended OS can be achieved in a substantial fraction of patients.

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1458P Pucotenlimab (HX008) - humanized anti-PD-1 monoclonal antibody plus pemetrexed and platinum as first-line treatment for advanced non-squamous non-small-cell lung cancer (nsqNSCLC): A single-arm multicenter phase II study

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Background: Pucotenlimab is a novel anti-PD-1 IgG4 monoclonal antibody. Several clinical trials conducted in China have demonstrated its efficacy and safety in various solid tumors including gastric cancer and breast cancer. Here we report a phase II study result of pucotenlimab for nsq-NSCLC without EGFR/ALK mutations.

Methods: In this open-label phase II study, patients naive to systemic treatment were enrolled with histologically diagnosed stage IIIB or IV nsq-NSCLC. Patients were received intravenous Pucotenlimab 200mg Q3w for up to 35 cycles, combined with platinum + pemetrexed Q3W for 4 cycles and followed by maintenance pemetrexed Q3W (all intravenous). The primary endpoint was overall response rate (ORR) and safety, and the secondary endpoints were progression-free survival (PFS), duration of response (DOR) and overall survival (OS).

Results: From September 25th, 2020 to April 15th, 2021, a total of 43 patients were enrolled and followed up with a median of 13.1 months by the cut-off date (August 3th, 2022). 22 patients achieved partial response and 20 remained stable disease, respectively, contributing an ORR of 48.8% (95%CI: 38.9%, 59.2%) and a DCR of 95.3% (95%CI: 88.7%, 98.4%). The median PFS, DOR were 11.1 months (95%CI: 6.8, 14.4) and 13.9 (95%CI: 6.6, NE) months, respectively. The median OS was not reached. The common treatment-related adverse events (TRAEs) of any grade included anemia (79.1%), neutrophil count decreased (72.1%), white blood cell count decreased (67.4%) and platelet count decrease (53.5%). Neutrophil count decreased (32.6%) was the most reported grade 3/4 TRAE.

Conclusions: Pucotenlimab combined with pemetrexed plus platinum demonstrated promising efficacy and safety for the 1st line nsq-NSCLC patients without EGFR/ALK mutations.

Clinical trial identification: NCT04750083.

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1459P Preliminary efficacy and safety of KN046 (a bispecific anti-PD-L1/CTLA-4) in patients with metastatic non-small cell lung cancer who previously treated with immune checkpoint inhibitor(s)

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Background: KN046 is a novel bispecific antibody that inhibits both PD-L1/PD1 and CTLA-4/CD80/CD86 pathways. Previous phase I (KN046-CHN-001, NCT03733951) and phase II (KN046-201, NCT03838848) trials showed promising anti-tumor effects of KN046 in non-small cell lung cancer (NSCLC) patients who had failed prior immune checkpoint inhibitor(s) (ICIs) therapy. We present the efficacy and safety outcomes of KN046 in this population from KN046-CHN-001 and Cohort C of KN046-201.

Methods: KN046-CHN-001 and KN046-201 assessed the efficacy, safety and tolerability of KN046 in NSCLC. Eligible patients had NSCLC that progressed after ICI(s) and platinum-based chemotherapy. Patients with EGFR mutation and/or ALK translocation were excluded. All patients received KN046 (26 at 5 mg/kg Q2W, 2 at 5 mg/kg Q3W, 2 at 300mg Q3W and 1 at 3 mg/kg Q2W) by IV infusion. The primary endpoints were confirmed ORR by RECIST version 1.1 (KN046-201) and safety (KN046-CHN-001).

Results: Between April 19, 2019 and July 13, 2020, 31 pts with metastatic NSCLC who failed ICI(s) and platinum-based chemotherapy were enrolled. At the data cutoff of July 30, 2022 for KN046-201 and August 31, 2021 for KN046-CHN-001, the median follow-up was 25.0months (95% CI, 24.4, NE). Among all 31 pts, the ORR was 3.2% (1/31, 95% CI, 0.1, 16.7%), disease control rate (DCR) was 38.7% (12/31, 95% CI, 21.8, 57.8%), clinical benefit rate (CBR) was16.1% (5/31, 95% CI, 5.5, 33.7%). Median progression-free survival (mPFS) was 2.8 months (95% CI, 1.8, 3.7) and median overall survival (mOS) was 13.3 months (95% CI, 6.5, 17.5). 7(22.6%) out of the 31 subjects had experienced treatment-related adverse event (TRAE) at grade 3 or higher levels. Commonly reported TRAEs of grade 3 or higher were anemia (9.7%), febrile neutropenia (3.2%), fatigue (3.2%).

Conclusions: KN046 was well tolerated and demonstrated encouraging OS benefit in NSCLC patients who had failed prior ICI(s) therapy. Further study is warranted to confirm the clinical results.

Clinical trial identification: KN046-201, NCT 03838848; KN046-CHN-001, NCT03733951.

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1460P GALLANT-1: GB1211 galectin-3 (Gal-3) inhibitor plus atezolizumab (atz) for first line treatment in patients (pts) with advanced/metastatic non-small cell lung cancer (NSCLC)

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Background: Gal-3 expression in tumours is associated with resistance to checkpoint inhibitors (CPIs). In a preclinical study, Gal-3 inhibitor GB1211 restored CPI-binding to their targets in the presence of Gal-3 (Mabbitt et al. J Clin Oncol 2022), and enhanced CPI effects in NSCLC mouse models (Vuong et al. Cancer Res. 2019). The GALLANT-1 study (NCT05240131) will assess whether GB1211 + atz (a CPI) increases anti-tumour effects in pts with NSCLC.

Methods: GALLANT-1 is a phase IB/IIA study of first line GB1211 + atz in pts with advanced/metastatic NSCLC. Part A is an open-label dose confirmation study of GB1211 200 mg or 100 mg twice daily (BID) + atz 1200 mg every 3 weeks; Part B is a 12-week, randomized double-blind study of the safety and efficacy of the GB1211 dose from Part A + atz vs placebo + atz. Following Part B, pts will continue into an open-label extension study until disease progression or unacceptable toxicity occur. Here we report data from the ongoing Part A.

Results: In the 200 mg cohort (n = 7), all pts had an adverse event (AE); most were mild (Grade [Gr] 1−2) and no serious AEs were deemed related to GB1211 alone. After 2 weeks of therapy, 2 severe (Gr 3−4) autoimmune skin rashes were observed: pemphigus deemed related to atz, and perivascular lymphocytic infiltration deemed related to GB1211 + atz; both responded to steroids. As per protocol, it was recommended that the study continue but with a reduced dose (100 mg BID) in new pts (n = 2); 9 AEs (all Gr 1−2) were reported in these 2 pts. Two partial responses, as assessed by investigators, have been seen: 1 confirmed (100 mg cohort; Week 6; time on therapy: 14 weeks) and 1 awaiting confirmation (200 mg cohort; Week 18; time on therapy: 23 weeks). Steady-state plasma exposure at 200 mg was consistent with pharmacokinetic (PK) simulations, predicting a 2-fold increase compared with healthy volunteers at 100 mg. GB1211 PK did not seem altered in pts with NSCLC vs healthy volunteers.

Conclusions: This is the first clinical study to show that combining GB1211 with atz may enhance the CPI effect. As the AEs have been manageable, Part A will continue with the 100 mg GB1211 dose to confirm the selected dose for Part B.

Clinical trial identification: NCT05240131.

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1461P Predictive value of residual FDG-PET metabolic activity in metastatic non-small cell lung cancer (mNSCLC) patients (pts) with long-lasting response to immune checkpoint inhibitors (ICIs)

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Background: The optimal duration of ICIs treatment in mNSCLC is debated, arbitrarily fixed to 2 years in the 1st line setting. Unfortunately, pts will mostly relapse months or years after the end of the treatment (EOT). Physicians tend to confirm the partial or complete obtained response before stopping it, by performing ^{18}F-FDG -PET (PET). However, the interpretation of residual fixative areas remains unclear.

Methods: This is a bi-center retrospective study of mNCSLC pts who completed 2 years of ICI, or stopped it due to adverse event without progression and underwent a PET at the EOT. Collected data were: age, smoking status, PDL1 and KRAS status, type and line of treatment, ICI duration.

Results: We enrolled 80 pts who began ICIs between Sept. 2016 and Nov. 2021. Median follow up was 35.9 months. Median age was 61 years (range: 56-69), sex ratio was 1:1, 93.5% were current/former smokers, 87.5% had adenocarcinoma, 54% had PDL1>50%. ICI was given as monotherapy and as first line in 41% and 67.5% of pts respectively. Molecular analysis revealed KRAS G12C mutation in 29% pts. Median ICIs duration was 23.4 months (range: 3-48), 55 pts completed 2 years of ICI, 22 discontinued due to toxicity, 3 for others reasons. The 2-year progression-free survival (PFS) probability was 96% (range:92-100). Median SUVmax was 1.9 (range: 0-17). 55% pts had PET residual fixation (RF): 36% on initial lung tumor, 15% on mediastinal lymph nodes and 5% on extrathoracic sites. 6 pts underwent an excision surgery or a biopsy of a RF: 4 were immune-mediated inflammatory reactions, 2 found the initial histology. 6 pts were locally treated for RF by radiotherapy or surgery. Of the 17 pts who relapsed: 12 had a RF on the PET after ICIs. Conversely, 5/36 pts (14%) without RF relapsed. The presence of a RF was not associated with the PFS in univariable analysis (HR=2.4, 95%CI: 0.8-6.9, P=.121) and after adjusting for duration and type of ICI treatment (HR=1.4, 95%CI: 0.5-4.3, P=.539).

Conclusions: Positive 18F-FDG-PET/CT is not associated with relapse after completion of ICI treatment but has good negative predictive value. Treatment of oligopersistence after partial response to ICI based on PET-scan remains controversial.

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1462P Phase Ia study of MIDRIX4-LUNG, a quadrivalent autologous dendritic cell immunotherapy, in patients with metastatic non-small cell lung cancer

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Late withdrawal

1463P IL-6 triggers chemoimmunotherapy resistance by creating immunosuppressive tumor microenvironment in non-small cell lung cancer

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Background: Chemotherapy in combination with anti-PD-1/PD-L1 antibodies (chemoimmunotherapy) has become the standard treatment for advanced non-small cell lung cancer (NSCLC). Our previous studies highlighted that low baseline concentrations of IL-6 in plasma specimens or tumor tissues responded better to anti-PD-1/PD-L1 immunotherapy alone. However, the role of baseline IL-6 levels in predicting responses to chemoimmunotherapy and the development of resistance to chemoimmunotherapy has not been fully understood yet.

Methods: To confirm the predictive value of IL-6 in the baseline plasma, we conducted an enzyme-linked immunosorbent assay (ELISA) in a group of 123 advanced NSCLC patients who received chemoimmunotherapy. Next, we evaluated the role of IL-6 in chemoimmunotherapy resistance and the underlying mechanisms in mouse models of both lung adenocarcinoma and lung squamous cell carcinoma.

Results: Based on our cohort of 123 NSCLC patients, we found that patients with progressive disease had a higher baseline level of IL-6 in their plasma. Additionally, the potential predictive value of the baseline level of IL-6 in plasma samples for responses was confirmed with area under curve (AUC) up to 0.677. Patients with a low baseline concentration of IL-6 also had a longer progression-free survival and overall survival, with a cut-off value of 7.002 obtained from receiver operating characteristic curve (ROC). Meanwhile, univariate and multivariate Cox regression analyses revealed that baseline IL-6 level in plasma samples was an independent prognostic predictor. Further experiments in mouse models showed that overexpression of IL-6 weakened the anti-tumor effects of immunotherapy in combination with chemotherapy. Immunohistochemical studies also revealed that $CD8^+$ T cells decreased while M2 macrophages, regulating T cells, and myeloid-derived suppressor cells infiltration increased in the IL-6 overexpressing group.

Conclusions: Our study highlights the potential of baseline IL-6 levels as a useful predictive biomarker for chemoimmunotherapy in NSCLC. IL-6 promotes an immunosuppressive tumor microenvironment, suggesting that targeting IL-6 could be a promising approach for cancer treatment.

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1464P Impact of age on the benefit of immunotherapy for metastatic squamous cell lung cancer: An NCDB database analysis

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Background: Immunotherapy represents an alternative to chemotherapy and clinical trial for squamous cell lung cancer. Due to the underrepresentation of elderly patients in clinical trials, it is not clear whether they derive similar benefit from immunotherapy as their younger patients.

Methods: A retrospective analysis using National Cancer Database (NCDB) was conducted in patients diagnosed with metastatic squamous cell lung carcinoma between 2016 and 2019. Kaplan Meier survival plots were used to examine survival outcome of different age groups: 19-49, 50-79 and 80 and older. Each age group was examined for benefit from chemotherapy (CR), chemotherapy + immunotherapy (CI), immunotherapy (IO), and no treatment (NR). Cox regression analysis was used to identify factors associated with overall survival.

Results: Of the 24,111 patients analyzed, 3,072 were 80 years or older. Patient who received immunotherapy had much better overall survival than those without. The one-year and two- years overall survival in these groups are CI: 52.98%, 18.10%; IO: 46.85%, 16.34%; CR: 40.11%, 10.73% and NR: 11.13%, 3.81% respectively. Although overall survival declined with age, age itself was not responsible for the poor outcome coming with it. No significant interaction effect was found between age and treatment. In multivariate analysis, HR was 1.01; 0.91-1.11; P=0.862 in age 19-49 and HR 1.02; 0.98-1.06, P=0.397 in age 50-79 compared to age 80 year or older (HR 1.0). Different age groups benefited similarly to all treatments. Compared to CR only (HR 1.0), treatment with CI conferred the best survival outcome HR 0.73; 95% CI 0.71-0.76; $P<0.001$; IO comes in next with HR 0.84 95% CI 0.80-0.88; $P<0.001$ and NR performed the worst (HR 2.90; 95% CI 2.80-3.0; $P<0.001$), suggesting that differences in survival is related to factors other than age.

Conclusions: Although immune senescence is of concern in senior patients receiving immunotherapy, older patients with squamous cell lung cancer benefit from treatment with immune therapy and chemotherapy combination, immunotherapy, chemotherapy as much as younger patients. Age itself is not associated with immunotherapy inefficacy.

Legal entity responsible for the study: Zhonglin Hao, MD.

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1465P Clinical impact of proton pump inhibitor on the therapeutic outcome of non-small cell lung cancer patients with PD-L1 TPS ≥50% receiving pembrolizumab monotherapy versus immune checkpoint inhibitor plus chemotherapy: A retrospective multicenter cohort study

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Background: Pembrolizumab monotherapy and immune checkpoint inhibitor plus chemotherapy (ICI/Chemo) have been approved as first-line treatment for non-small cell lung cancer (NSCLC) with programmed death ligand 1 tumor proportion score (PD-L1 TPS) ≥50%. However, the clear distinction between the two therapeutic options remains unclear. It was reported that using proton pump inhibitors (PPI) and antibiotics correlated with poorer treatment outcomes of ICI monotherapy for NSCLC.

Methods: We retrospectively enrolled consecutive PD-L1 TPS ≥50% advanced NSCLC patients who received pembrolizumab monotherapy or ICI/Chemo as first-line treatment. We analyzed the association between treatment outcome and patient characteristics, including concomitant drug history in each group. Comparing the treatment outcome, propensity score matching was used to reduce bias.

Results: The study included 425 patients, with 271 receiving pembrolizumab monotherapy and 154 receiving ICI/Chemo. According to the multivariate analysis, a history of PPI usage was independently associated with shorter progression-free survival (PFS) in pembrolizumab monotherapy group(hazard ratio (HR): 1.38, 95.0% CI: 1.00—1.91; P = 0.048), but not in ICI/Chemo group (HR: 0.83, 95.0% CI: 0.48—1.45; P = 0.515). In patients with a history of PPI, both the median PFS (19.3 months vs. 5.7 months, P=0.002) and the median overall survival (OS) (not reached vs. 18.4 months, P=0.025) were significantly longer in ICI/Chemo group than in pembrolizumab monotherapy group. In patients without a history of PPI, the median PFS (18.8 months vs. 10.6 months, P=0.259) and the median OS (not reached vs. 29.9 months, P=0.211) was not significantly different between each group.

Conclusions: History of PPI usage was negatively associated with treatment outcome of pembrolizumab monotherapy, but not ICI/Chemo in NSCLC patients with PD-L1 expression ≥50%. Our observations in real-world settings suggest that the history of PPI usage may be a predictive clinical factor to be considered in treatment decision-making in this population.

Legal entity responsible for the study: Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine.

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1466P Gut microbiota mediates the protective effects of postbiotics attenuating the immune-related adverse events in non-small-cell lung cancer patients: A randomized, controlled trial in Chongqing, China

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Background: To evaluate the effects of JK5G postbiotics on regulating the imbalanced gut microbiota and its impacts on the efficacy and incidence rate of immune-related adverse events (irAEs) in non-small-cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs).

Methods: We conducted a randomized, controlled trial in China and included non-squamous or squamous NSCLC patients without EGFR, ROS1, and ALK alteration, stage IIIb-IV. Patients were randomly (1:1) divided into two groups to receive four cycles of programmed cell death-1 (PD-1) plus chemotherapy plus placebo (control group) or to receive PD-1 plus chemotherapy plus JK5G postbiotics (JK5G group). The primary endpoint were adverse effects, quality of life (QoL), 16S DNA sequencing of gut microbiota, blood inflammatory cytokines, and lymphocyte subsets. This study was registered at www.chictr.org.cn (ChiCTR2200064690).

Results: 60 patients were enrolled. The JK5G group had better QoL and nutritional levels, as well as lower depression symptoms than the control group (all $p < 0.05$). The JK5G group had a lower incidence of anemia (55.56% vs. 11.11%, $p = 0.012$), decreased lymphocyte count (33.33% vs. 0%, $p = 0.019$), decreased appetite (55.56% vs. 16.67%, $p = 0.035$), nausea (55.56% vs. 11.11%, $p = 0.012$), and asthenia (50.00% vs. 11.11%, $p = 0.034$) than the control group. Moreover, JK5G attenuated intestinal flora imbalance, accompanied by increased Faecalibacterium, Ruminococcaceae, and fecal butyrate concentration. Furthermore, JK5G administration significantly decreased the pro-inflammatory markers, including TNF-α, IL-2, and C-reactive protein (CRP) ($p < 0.05$). Significant increases in CD3+CD4+ T cells and CD4/CD8 ratio were observed in the peripheral blood of JK5G group patients ($p < 0.05$).

Conclusions: Our current findings indicated that JK5G postbiotics may attenuated irAEs, enhanced the QoL and nutrition levels in advanced NSCLC patients who received ICIs. JK5G postbiotics could improve the gut microbiota structures and accompanied with the ameliorate of tumor microenvironment and inflammation.

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1467P Combination therapy of envafolimab and suvemcitug with chemotherapy in patients with non-small cell lung cancer (NSCLC): Results from a phase II clinical trial

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Background: The combination of anti—PD-1/PD-L1 antibody and chemotherapy with or without anti-angiogenic agent has shown antitumor activity in NSCLC. This study aims to assess the efficacy and safety of envafolimab (anti- PD-L1 antibody) in combination with suvemcitug (anti-VEGF antibody) and chemotherapy as second-line or later therapy in patients(pts) with advanced NSCLC.

Methods: This was an open-label, multi-cohort, multicenter, phase II trial conducted in China. In Cohort C, NSCLC pts with at least one prior line of treatment were enrolled, stratified by the history of prior immunotherapy (IO). Envafolimab plus suvemcitug and docetaxel were administrated until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) assessed by investigator review using RECIST v1.1. Secondary endpoints included progression-free survival (PFS), duration of overall response (DoR), disease control rate (DCR) and safety.

Results: As of March 31, 2023, there were 40 pts were enrolled in NSCLC cohort, including 20 IO treated NSCLC and 20 IO naïve NSCLC. 72.5% (29/40) pts were treated with one prior therapy and 27.5% (11/40) pts with EGFR/ALK / ROS1 alterations. For IO treated NSCLC, with a median follow-up time of 6.5 (4.6, 7.9) months, 18 pts have at least one assessment, the ORR and DCR were 27.8% (5/18) and 83.3% (15/18) respectively. The PFS was not reached (NR) (3.02-NR). Grade 3/4 TRAEs occurred in 13 pts (65.0%), most commonly occurred were neutrophil count decreased ($n = 8$; 40.0%) and leucopenia ($n = 6$; 30.0%). For IO naïve NSCLC, the median follow-up time was 6.3 (4.8, 7.1) months,17 pts have at least one assessment, 3 patients achieved partial response and the DCR was 82.4% (14/17). The PFS was NR (2.99-NR). Grade 3/4 TRAEs occurred in 15 pts (75%), most commonly occurred were neutrophil count decreased ($n = 12$; 60%) and leucopenia ($n = 11$; 55%). There was no grade 5 TRAE in either cohort.

Conclusions: This phase II clinical trial demonstrated antitumor activity and manageable safety profile of immunotherapy plus anti-angiogenic agent and chemotherapy in pts with NSCLC, who had failed at least one line of therapy.

Clinical trial identification: NCT05148195.

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1468P Patients' perspective on tolerability of dostarlimab in NSCLC: Patient-reported outcomes from the phase II PERLA trial

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Background: In the phase II double-blind PERLA trial (NCT04581824), dostarlimab + chemotherapy (DCT) showed similar efficacy to pembrolizumab + CT (PCT) as first-line treatment (tx) for patients (pts) with metastatic non-oncogene-driven, non-squamous, non-small cell lung cancer (NSCLC); the proportion of pts experiencing tx-related adverse events (TRAEs) or AEs leading to tx discontinuation was similar between groups [1]. Exploratory analyses of pt-reported measures of tolerability were conducted.

Methods: Eligible pts with ECOG 0—1 were randomized 1:1 to receive ≤35 cycles (C) of DCT or PCT every 3 weeks (Q3W) (CT: ≤35 C of 500 mg/m^2 pemetrexed + ≤4 C of cisplatin or carboplatin). Patient-reported outcome version of CTCAE (PRO-CTCAE) and the tolerability item of FACT-G (FACT-GP5) were collected at Day 1 C1, then Q3W to Week 12, Q9W to Week 48, Q12W to end of tx, at end of tx, and 30-day safety follow-up.

Results: Completion rates for PRO-CTCAE (DCT N=96/PCT N=88) and FACT-GP5 (DCT N=95/PCT N=87) were >80% up to C4, then decreased in both tx arms. At baseline (BL), only the urinate frequently item had >10% of pts reporting occurrence as "frequently" or greater per PRO-CTCAE (DCT: 11.5% [n=11/96]; PCT: 10.2% [n=9/88]); "severe" or greater severity and "quite a bit" or greater interference responses were reported in <10% of pts. At C13 (∼1 yr of tx) urinate frequently was similar between arms ("frequently" or greater in DCT: 12.5% [n=4/32]; PCT: 10% [n=2/20]). Relative to BL, at C13 muscle and joint ache frequency, severity and interference responses of "quite a bit" or greater were increased in both arms, but occurred in <16% of pts. Per FACT-GP5, at BL (i.e., before trial tx) 85.3/94.3% of DCT/PCT pts were "not at all" or "a little bit" bothered by tx side effects; at C13 this was 77.4/84.2% and no pts in either arm were "very much" bothered.

Conclusions: Most pts reported little or no bother from tx side effects and responses were similar across tx arms, suggesting interventions are tolerable from pt perspective. These results supplement previously reported PERLA data and support further investigation of dostarlimab combined with existing and novel therapies in metastatic NSCLC. 1. Peters S, et al. 2022; Oral; ESMO-IO (7—9 Dec, Geneva). Funding: GSK (213403).

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1469P The role of the CXCL12/CXCR4 pathway in the immunotherapy of non-small cell lung cancer

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Background: Peripheral blood mononuclear cells (PBMCs) trafficking is regulated by chemokines, which may interfere with their migration towards tumors and even collaborate in the efficacy of immunotherapy. In our study, we investigated whether the CXCL12/CXCR4 pathway plays a role in the efficacy of immunotherapy in non-small cell lung cancer (NSCLC) by analyzing the immunophenotypic profile of PBMCs expressing CXCR4 in peripheral blood (PB) and the expression of its ligand CXCL12 in tumor.

Methods: We identified T, B and NK lymphocytes, monocytes, and dendritic cells expressing CXCR4 in PB using flow cytometry in a prospective cohort of NSCLC patients (experimental group) before starting monotherapy with anti-PD-1 immunotherapy. As a control, we studied patients with advanced cancer before starting any non-immunotherapy treatment. The relative frequency of immune subpopulations in PB was correlated with treatment outcomes. Patients were classified according to high ($\geq$ 55th percentile) or low ($\leq$ 45th percentile) expression in PB for each cellular subpopulation. Uni- and multivariate survival analyses were performed using Cox regression and logistic regression. The expression of CXCL12 in tumor tissue was studied and correlated with the expression of its receptor (CXCR4) in PBMCs.

Results: Experimental group included 39 patients and control group 40. Low expression in PB of CXCR4-expressing CD8+ T lymphocytes was correlated with a greater benefit from immunotherapy: median OS NR vs 22.0 months, HR 0.6, $p<0.01$, with significance in multivariate models; and median PFS 14.2 vs 5.0 months, HR 0.38, $p=0.05$, with significance in multivariate models. ORR: trend towards significance. These differences were specific to the experimental group and were not observed in the controls. Low expression in PB of these lymphocytes was correlated with a higher expression of CXCL12 in tumors (trend towards significance: $p=0.14$). No significant results were obtained in any of the other subpopulations studied.

Conclusions: Patients diagnosed with advanced NSCLC with low expression of cytotoxic T lymphocytes in PB expressing CXCR4 show greater benefit from immunotherapy, due to greater tumor infiltration of lymphocytes receiving homing signals from the expression of CXCL12 in the tumor.

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1470P Statin use and overall mortality in patients with advanced non-small cell lung cancer receiving anti-PD(L)1 immunotherapy: A SEER Medicare database analysis

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Background: Statins, commonly used to lower cholesterol, are inhibitors of Yes-associated protein (YAP), a transcription co-activator mediating cell survival and anti-tumor immunity. Concurrent statin with anti-PD1 immune checkpoint blockade (ICB) has shown preclinical synergy, and studies suggest improved survival among ICB-treated patients (pts) with non-small cell lung cancer (NSCLC) who take statins. We used the United States Surveillance Epidemiology and End Results (SEER) Medicare-linked database to assess overall mortality in a real-world population of pts with NSCLC receiving anti-PD(L)1 ICB and concurrent statin.

Methods: Pts in SEER ($\geq$65 years old) diagnosed with NSCLC in 2007—2017 and treated with anti-PD(L)1 ICB were included. ICB and statin therapy status were ascertained from Medicare claims. Pts were followed from date of first ICB claim until date of death, 4 weeks from last ICB claim, or 12/31/2018 (database cutoff), whichever came first. Hazard ratios (HR) were estimated using Cox regression models adjusted for propensity score, NCI comorbidity Index, and demographics to determine the association between time-updated statin use and overall mortality.

Results: 1401 pts were included, with 142 total deaths attained over 8710 person-months. 662 pts were statin-users and 739 were non-users. Statin users were more likely to be men compared to non-users (55% vs 43%). Median duration of anti-PD(L)1 ICB claim was similar for statin users and non-users (4.1 vs 4.2 months, respectively). Concurrent statin was associated with a 38% lower overall mortality (HR 0.62, 95% CI 0.41-0.94) compared to no statin. When extending follow-up beyond cessation of ICB claim, benefit was attenuated (HR 0.9, 95% CI 0.78-1.05). Subgroup data showed similar trends in overall mortality benefit when restricting to anti-PD-1 ICB (HR 0.63, 95% CI 0.42-0.93), as well as to simvastatin (HR 0.59, 95% CI 0.32-1.07) and atorvastatin (HR 0.67, 95% CI 0.42-1.07).

Conclusions: Concurrent statin use was associated with decreased overall mortality in a real-world population of pts with advanced NSCLC treated with anti-PD(L)1 ICB. Analyses from this dataset focused on lung-cancer specific mortality are ongoing.

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1471P Immunotherapy prolongs long-term real-world survival compared to chemotherapy for metastatic non-small cell lung cancer: A propensity score-matched analysis

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Background: Survival benefit of immunotherapy (IO) has been demonstrated in clinical trials for patients with metastatic non-small cell lung cancer (mNSCLC) but no real-world study was found in literature to measure the long-term treatment effect compared to chemotherapy (CT). This retrospective and observational study aimed to evaluate whether IO has improved the long-term real-world overall survival (rwOS) and real-world time to receive next line of therapy (rwTTNT) in mNSCLC based on Flatiron Health oncology database.

Methods: Electronic health records of patients who received either IO (IO mono or IO+CT) or CT in first line (1L) and second line (2L) treatment from January 1, 2015 and onwards were extracted. Eligible patients were selected to match based on a developed propensity score to balance covariates that may confound the treatment effect. The effect of IO rwOS and rwTTNT was estimated using Cox regression. Subgroup analysis was performed to assess effect modification of known prognostic factors in mNSCLC.

Results: A total of 16,856 1L patients and 6,570 2L patients were included in the analysis. Patient characteristics between IO and CT arms were balanced after 1:1 propensity score matching with replacement. The maximum follow-up was 7.1 years for 1L and 7.3 years for 2L. Among 1L IO patients, median rwOS was 10.8 months (95% CI: 10.5 — 11.2) (vs. 1L CT: 9.0 [95% CI: 8.7 — 9.3]) with hazard ratio (HR) 0.84 (95% CI: 0.80 — 0.89). The HR for rwTTNT was 0.54 (95% CI: 0.51 — 0.57). Among 2L IO patients, median rwOS was 8.9 months (95% CI: 8.6 — 9.4) (vs. 2L CT: 8.3 [95% CI: 7.8 — 9.0]) with HR 0.91 (95% CI: 0.84 — 0.98). The HR for rwTTNT was 0.74 (95% CI: 0.69 — 0.79). Subgroup analyses among IO patients showed better survival outcomes for patients with younger age, low ECOG score, low comorbidity index, no history of smoking, PD-L1 positivity, and high PD-L1 expression level. The treatment effects increased over time and persisted until the end of the follow-up period.

Conclusions: IO was associated to prolong overall survival and delay receiving next line of therapies in mNSCLC patients. The significant survival benefits were found even after several years of follow-up.

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1472P Radiotherapy affects immunotherapy efficacy based on tumor mutation status in patients with metastatic NSCLC

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Background: Radiotherapy (RT) may enhance the antitumoral response of immunotherapy (IO) in metastatic non-small-cell lung cancer (mNSCLC). However, whether tumor mutation status can affect RT's effect on IO efficacy in mNSCLC is unknown.

Methods: We retrospectively studied all patients with mNSCLC who had tumor mutation profiles and were treated with IO at our institution from 2011 to 2022. Patients were excluded if they received targeted therapy, prior concurrent chemo-RT followed by durvalumab, or RT after IO discontinuation. We analyzed their demographic data, tumor mutation profiles, and compared progression-free survival (PFS) and overall survival (OS) between different subgroups. Kaplan-Meier method and log-rank test were used for survival analysis.

Results: A total of 171 patients were included. 66% received RT either prior to or during IO. Pembrolizumab was the most used IO agent (77%). IO was given mostly in the frontline setting (59%). Among 113 patients who received RT, ALK mutation (n=5) was associated with significantly shorter PFS of IO than those without ALK mutation (n= 108) (2m vs. 5.7m, p<0.0001). Similarly, MYC mutation (n=8) was associated with significantly shorter PFS than those without MYC mutation (n= 105) (3.3m vs. 6.2m, p=0.016). PFS of IO was not affected by the following genes: EGFR, KRAS, TP53, BRAF, ERBB2, BRAF, PIK3CA, TERT, and FGFR. For patients with tumors carrying STK11 mutation, those who received RT (n=21) had longer PFS of IO than those (n=8) without RT (6.5m vs. 2.8m, p=0.05). For patients with tumor carrying ARID1A mutation, those who received RT (n=11) had shorter PFS and OS of IO than those (n=7) without RT (PFS: 5m vs. 22.9m, p=0.08; OS: 16m vs. 28.1m, p=0.037, HR 0.28, 95% CI 0.08 − 0.9). No difference in the outcomes of IO between RT and no RT in the following mutations: EGFR, ERBB2, PIK3CA, KRAS, MET, and TP53.

Conclusions: In our real-world cohort, ALK and MYC mutations affect outcomes of IO in mNSCLC patients who received RT. RT is associated with better outcomes of IO in mNSCLC patients with STK11+, but poorer outcomes in those with ARID1A+. Our findings suggest certain gene mutations can affect radiotherapy's effect on immunotherapy efficacy in mNSCLC. Further prospective studies are needed to verify these results.

Legal entity responsible for the study: The authors.

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1473P Efficacy of anti-PD1/PDL1 antibody monotherapy in patients with advanced non-small cell lung cancer with increased hepcidin expression

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Background: T cell-promoted tumor ferroptosis, a form of iron-induced regulated cell death, is involved in the anti-tumor activities of immune checkpoint inhibitors (ICIs). The Efficacy of ICIs on advanced non-small cell lung cancer (aNSCLC) with iron metabolism disorders is unknown. Iron is an essential factor in metabolic pathways. However, iron facilitates the production of oxygen radicals, which may result in ferroptosis. This study explored the efficacy of anti-PD1/PDL1 monotherapy on survival in patients with aNSCLC with increased hepcidin expression.

Methods: A retrospective observational study was conducted in histologically confirmed aNSCLC patients with samples for hepcidin immunohistochemical staining. Eligible patients initiated nivolumab, pembrolizumab, or atezolizumab monotherapy as any line of treatment; the data cutoff was May 6, 2023. The hazard ratio for death was estimated with the use of the Kaplan−Meier method. Between-group comparisons were performed with the use of the log-rank test. Effects of hepcidin on ferroptosis induced by IFNg were examined using a lung cancer cell line.

Results: The 45 eligible patients included 39 (86.7%) men; the median age was 72 years (range, 36-83 years); 3 (6.7%) of 45 patients with driver gene mutations. The median patient follow-up was 15.3 months (26 days to 87.8 months). The median time to death was 69.6 (95% CI, not reached) and 15.3 months (95% CI, 0.94 − 29.7) for hepcidin High (TPS $\geq$ 50%) and None or Moderate (TPS $<$ 50 %), respectively. The hazard ratio and p-value for OS with hepcidin High versus None or Moderate were 0.55 (95% CI, 0.23 to 1.34) and p $=$ 0.19. The cytotoxicity of IFNg on A549 cells was enhanced by hepcidin with increasing levels of endogenous reactive oxygen species, a feature of ferroptosis.

Conclusions: In our cohort, aNSCLC patients with increased hepcidin expression and anti-PD1/PDL1 antibody monotherapy showed a longer survival time, but statistically insignificant probably due to a small sample size. Further study with a larger sample size is required to validate the effect of hepcidin on anti-PD1/PDL1 monotherapy. The potency of anti-PD1/PDL1 monotherapy enhancement by modulation of iron metabolism-related factors needs to be explored.

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1474P Outcome of nivolumab and ipilimumab-based therapy for advanced non-small cell lung cancer with low or negative PD-L1 expression

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Background: Immunotherapy is currently the standard care for advanced non-small cell lung cancer (NSCLC) in the first line. The combination therapy of nivolumab and ipilimumab addresses an unmet clinical need, as single immune checkpoint inhibitor (ICI) therapy has limited efficacy in PD-L1-negative NSCLC. This combination therapy may also benefit patients with NSCLC who have low PD-L1 expression.

Methods: A retrospective, multicenter observational study was conducted to evaluate the efficacy of nivolumab and ipilimumab-based therapy (dual group) and single ICI-based therapy (single group) for patients with low or negative PD-L1 expression.

Results: Between December 2018 and October 2022, a total of 240 patients with advanced/recurrent NSCLC and low/negative PD-L1 expression who received combination immunotherapy were enrolled. The median age of the patients was 72 years. PD-L1 Tumor Proportion Score (TPS) was negative in 109 patients (45.4%), 1-10% in 69 patients (28.7%), 11-20% in 19 (7.9%), 21-30% in 21 (8.8%), and 31-49% in 17 (7.1%). The median observation period was 11.5 months. The single group consisted of 201 patients (83.8%) and the dual group consisted of 39 patients (16.2%). In the overall population, there was no significant difference in overall survival (OS) and progression-free survival (PFS) between both groups after propensity score matching. However, in the patients with PD-L1 TPS negative and 1-20%, the dual group had a tendency for longer PFS and OS than the single group. In the dual group, patients with PD-L1 TPS 0-20% had significantly longer PFS (10.5 months (5.0-NA) vs. 4.1 months (0.23-NA), p=0.017) and OS (NA months (18.6-NA) vs. 9.0 months (0.23-NA), p=0.0014) than those with PD-L1 TPS 21-49%. In the single group, there was no association between PD-L1 expression and PFS/OS.

Conclusions: The results suggest that nivolumab and ipilimumab-based therapy may be a better treatment option, especially for patients with negative and lower PD-L1 TPS (<20%). Updated results with a larger patient population and an extended observation period will be presented at upcoming congresses.

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1475P Torque teno virus DNA load as biomarker for tumor response to mono immune checkpoint inhibition in non-small cell lung cancer

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Background: The ubiquitous Torque Teno Virus (TTV) in serum may reflect immune status and is used clinically as a biomarker of immunosuppression in solid organ recipients. Its ability to reflect functional T-cell activity as a measure of immune suppression may be applicable in lung cancer patients as well, considering the role of tumor induced immunosuppression in these patients. We hypothesize that TTV DNA load, or its change early in treatment, may reflect response to mono immune checkpoint inhibition (ICI) with a PD-1 inhibitor.

Methods: This retrospective, exploratory study included patients with non-small cell lung cancer (NSCLC) who started treatment with pembrolizumab or nivolumab between 2014 and 2022. Patients were selected on durable response (≥6 months response or stable disease) and non-response (progressive disease as best response), and were divided into two equal groups. Subsequently, TTV DNA load was measured quantitively on prospectively collected plasma samples via the OncoLifeS biobank. TTV DNA load at baseline was compared, as well as change in TTV DNA load after 4-6 weeks to baseline.

Results: A total of 63 patients were included, 31 responders and 32 non-responders. Median progression free survival (mPFS) was 193 weeks [IQR 50 weeks — not reached] vs 6 weeks [IQR 5 —6 weeks]. Responders were slightly younger (median 64 vs 70 years, p=0.05) and had a better performance status (PS 0 in 58% vs 25%, p=0.03), all other baseline characteristics were comparable. TTV DNA load at baseline was above the threshold in 44 patients (70%). Median TTV DNA load was 2.77 log copy numbers/mL (cp/mL) [IQR 2.13 — 3.27] in responders and 3.25 cp/mL [IQR 2.26 — 2.80] in non-responders, p=0.173. Change in TTV DNA load after 4-6 weeks compared to baseline was -0.13 cp/mL [IQR-1.73 — 0.10] in responders vs -0.33 [IQR -1.61 — 0.20] in non-responders (p=0.833). Cox-regression analysis, adjusted for sex, age and PS, showed no correlation between change in TTV DNA load, and mPFS and overall survival.

Conclusions: Level of immune suppression in this cohort of NSCLC patients measured by TTV DNA load, either at baseline or change after 4-6 weeks after mono ICI, was not associated with tumor response or survival.

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1476P Outcomes to first-line pembrolizumab in patients with advanced NSCLC and high PD-L1 expression: A Spanish multicentric study

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Background: Pembrolizumab stands as a first-line option for patients (p) with advanced NSCLC and high PD-L1 expression (≥50%). Several factors influenced outcomes such as antibiotic (AB) exposure, low body mass index (BMI), certain metastasic location (e.g. bone), or ECOG-PS of 2.

Methods: We performed a multicenter retrospective study in 8 Spanish hospitals to evaluate clinical outcomes according to several factors in patients with stage IV high PD-L1 expression NSCLC treated with first-line pembrolizumab in clinical practice. We included data from patients treated between May 2017 and July 2022.

Results: Among the 494 patients, median age was 67.2 years (29.4-89.43), 379p (76.7%) were male, 138p (27.9%) had an ECOG PS of 0, 269p (54.5%) had an ECOG PS of 1, 87p (17.6%) had an ECOG of ≥2 and 230p (46.6%) had a BMI of <24.9. 158p (32.0%) had bone metastases. 175p (35.5%) had antibiotic (AB) exposure during treatment with pembrolizumab or 4 weeks before initiation, and 210p (42.5%) underwent treatment with corticosteroids during treatment with pembrolizumab or 4 weeks before initiation [>10mg prednisone equivalent (>10mg PDNe)]. 308p (62.3%) had proton pump inhibitors (PPi) exposure. With a median follow-up of 12.6 months (m), the median overall survival (OS) and the progression-free-survival (PFS) were 16.9m (95% CI 12.9-19.2) and 9.9m (95% CI 7.7-12.1), respectively, and the overall response rate (ORR) was 43.3%. Multiple variables were associated with survival after univariate analysis (Table). After multivariate analysis, corticosteroid treatment (HR 1.41) and ECOG (HR 2.40) maintained a prognostic impact: poor PS (ECOG ≥2) and having been exposed to corticosteroids were predictive of poor outcome.

Table: 1476P

	Median OS - months (95% CI)	p-value (univariate analysis)
ECOG PS		
0 (N=138)	36.7 (20.3-53.2)	
1 (N=269)	14.8 (11.7-17.9)	
2 (N=81)	2.7 (1.8-3.7)	
3 (N=6)	0.3 (0.03-0.2)	< 0.001
Corticosteroid exposure		
No (N=284)	22.3 (17.9-26.7)	
Yes (N=210)	11.4 (8.0-14.7)	< 0.001
Reason for treatment with corticosteroids		
irAEs (N=57)	NR	
Baseline conditions/symptom management (N=153)	4.8 (1.4-8.3)	< 0.001
PPi exposure		
No (N=186)	23.0 (18.1-28.0)	
Yes (N=308)	12.6 (9.5-15.7)	0.002
Bone metastases		
No (N=336)	20.2 (16.6-23.8)	
Yes (N=158)	9.3m (4.9-13.7)	0.001
Best response to IO		
CR (N=30)	NR	
PR (N=184)	NR	
SD (N=113)	15.7 (13.8-17.8)	
PD (N=117)	4.0 (3.1-5.0)	
Not evaluated (N=50)	0.8 (0.6-1.0)	<0.001

Conclusions: First-line pembrolizumab in advanced NSCLC patients with high PD-L1 expression should only be used in patients with good PS. Patients with PS 2 are in urgent need of new treatment approaches.

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1477P STK11 mutations predict poor prognosis for advanced NSCLC treated with first-line immunotherapy or chemo-immunotherapy according to KRAS, TP53, KEAP1, and SMARCA4 status

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Background: The upfront treatment of non-oncogene addicted NSCLC relies on immunotherapy single-agent (IO) or in combination with chemotherapy (CT-IO). Genomic aberrations such as *KRAS*, *TP53*, *KEAP1*, *SMARCA4*, or *STK11* may impact the survival outcomes. The prognostic role of *STK11* mutations under upfront IO or CT-IO is still unclear.

Methods: We performed an observational study of 145 patients (pts) treated with first-line IO or CT-IO for advanced non-squamous (nsq) NSCLC at our institution tested with an extensive lab-developed NGS panel. The primary objective was to assess the clinical outcomes of *STK11* mutated (mut) pts. Then, we performed an external validation through the public OAK/POPLAR dataset, including nsq NSCLC pts treated with single-agent IO or CT.

Results: Most pts were male (59.7%), former smokers (61.1%), with ECOG PS 0-1 (84%), and received first-line CT-IO (58.6%). 44.8% had a mutation in *KRAS*, 21.4% in *KEAP1*, 50.3% in *TP53*, 13.1% in *SMARCA4*, and 14.4% in the *STK11* gene. In 14/21 pts *STK11* and *KRAS* mutations co-occur (p=0.053). The median overall survival (OS) was 13.2 months (mo.) (95% CI, 8.6-19.6), while the median progression-free survival (PFS) was 6.5 mo. (95% CI, 4.8-8.9). The mOS was 8 mo. (95% CI, 5-16.7) for *STK11* mut pts and 17.3 mo. for *STK11* WT pts (95% CI, 8.9-24.4) (p=0.038). *TP53* (8.3 vs 17.3), *KRAS* (9.2 vs 15.9), and *KEAP1* (8.9 vs 15.9) mut pts evidenced a trend for dismal mOS. *SMARCA4* status had no impact on mOS. *STK11* mutations were detrimental to OS in the univariate (HR 1.74, p=0.041) and multivariate model (HR 1.97, p=0.025) after adjusting for sex, age, ECOG PS, treatment (IO vs CT-IO), *KRAS*, *KEAP1*, *TP53*, *SMARCA4* status. Genomic alterations did not impact the mPFS in our cohort. Within the OAK/POPLAR dataset, STK11 mutations (60/818 pts) were significantly associated with increased death risk in the univariate (HR 2.01, p<0.001) and multivariate model (HR 1.66, p=0.001) after adjusting for age, sex, treatment (IO vs CT), *KRAS*, *KEAP1*, *TP53*, *SMARCA4* status.

Conclusions: *STK11* aberrations hampered the mOS of nsq NSCLC pts treated with first-line IO or CT-IO. The negative prognostic impact seems to be unrelated to IO administration.

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1478P Circulating pre-treatment T-Cell receptor repertoire as a predictive biomarker in non-small cell lung cancer patients treated with pembrolizumab

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Background: The circulating T-cell receptor (TCR) repertoire is a dynamic representation of overall immune responses in an individual.

Methods: We prospectively collected baseline blood from patients treated with first-line pembrolizumab monotherapy (N=48) or in combination with chemotherapy (N=65), and sequenced the Complementarity Determining Region 3 (CDR3) of the TCR beta chain from whole blood-derived DNA. TCR repertoire metrics were correlated with clinical benefit (objective response or stable disease $\geq$ 6 months), progression-free survival (PFS), overall survival (OS) and immune-related adverse events (irAEs). We built a logistic regression model combining all four TCR-β repertoire metrics to predict clinical benefit. Receiver operating characteristic (ROC) analysis of the resulting logistic regression model probabilities was used to identify the best cut-off values to maximise sensitivity and predict clinical benefit.

Results: We observed an association between a reduced number of unique TCR clones and clinical benefit among patients treated with pembrolizumab monotherapy (RR=2.86, 95%CI 1.04-8.73, P=0.039). For patients treated with pembrolizumab plus chemotherapy, increased number of unique clones (HR=2.96, 95%CI 1.28-6.88, P=0.012) and Shannon Diversity (HR=2.73, 95%CI 1.08-6.87, P=0.033), and reduced evenness (HR=0.43, 95%CI 0.21-0.90, P= 0.025) and convergence (HR= 0.41, 95%CI 0.19-0.90, P=0.027) were associated with improved PFS, while only increased number of unique clones (HR= 4.62, 95%CI 1.52-14.02, P=0.007) was associated with improved OS. Logistic regression models combining the TCR repertoire metrics improved the prediction of clinical benefit and was strongly associated with OS (HR=0.20, 95%CI 0.05-0.76, P<0.0001). Reduced TCR conversion was associated with increased irAEs needing systemic steroid treatment (P=0.04).

Conclusions: Pre-treatment circulating TCR repertoire might serve as a predictive biomarker for clinical outcomes among patients with advanced NSCLC treated with pembrolizumab alone or combined with chemotherapy.

Legal entity responsible for the study: Edith Cowan University.

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1479P Association between high baseline low density neutrophils and resistance to immunotherapy in untreated non-small cell lung cancer: Molecular characterization of low-density neutrophils

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Background: Circulating LDNs have been previously associated with resistance to ICI in NSCLC. We have compared the efficacy of ICI and CT + ICI in untreated patients with high LDNs. We studied the association of LDNs with clinical variables. We have compared LDNs and high-density neutrophils (HDNs) regarding activity and maturity. We have compared HDNs of NSCLC patients and healthy donors.

Methods: PBMCs from 35 patients treated with ICI and 41 treated with CT + IT were purified from fresh peripheral blood by Ficoll gradient. HDNs were purified using Mono-Poly™ buffer. Baseline LDNs were quantified by flow cytometry. Efficacy of ICI and CT + ICI was compared among those with high LDNs. Activity and maturity of LDNs and HDN were studied with PD-L1, HLA-DR, LOX1, CD119, CXCR2, CXCR4, CD10, CD95, CD62L, CD101.

Results: High levels of LDNs were found in 55.3%. Non-sq NSCLC presented higher mean levels, 22.4% vs 11.3% ($p = 0.047$). ORR was higher with CT + IT compared with ICI, 59.1% vs 0% ($p = 0.001$). mPFS and mOS were longer with CT + IT, 8.9 mo vs 1.3 mo ($p < 0.001$) and 24.6 mo vs 1.41 mo ($p = 0.008$). No differences were detected in > 70 years old. A depletion of LDNs was observed in responders to CT + IT. In patients with high LDNs, fast progressive disease (PD) was more frequent with ICI (75% vs 36.4%, $p = 0.031$). In patients treated with ICI, fast-PD was more frequent when LDNs were high (75% vs 16.7%, $p = 0.002$). LDN were more aged (CXCR4+ CXCR2-, 29.9% vs 1.95%), less immature (CXCR4+ CXCR2+, 49.2% vs 82.6%) and expressed higher LOX1 and PD-L1 (57.5% vs 41.8% and PD-L1, 2.7% vs 0.97%) than HDNs. HDNs from patients and healthy donors were equivalent.

Conclusions: LDNs are a distinct circulating myeloid subpopulation, with lower prevalence of immature neutrophils, that can be enriched in patients with NSCLC. High baseline LDNs are associated with resistance to ICI monotherapy. CT + IT can overcome this resistance.

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1480P Integrating the on-treatment mGPS improves prognostic accuracy of imaging-based staging in patients with non-small-cell lung cancer (NSCLC) treated with immune-checkpoint inhibitors

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Background: The clinical standard for response evaluation and treatment monitoring in advanced non-small cell lung cancer (NSCLC) is repeated, imaging-based staging. However, on immune checkpoint inhibition (ICI), many patients achieve stable disease (SD) as the best overall response. Clinical outcomes in this group vary widely, and whether measuring tumor size adequately captures the complex, dynamic processes following immune checkpoint inhibition is controversial. Hence, complementary biomarkers that improve outcome prediction are needed. A promising candidate is the modified Glasgow prognostic score (mGPS), a well-established prognostic score based on the serum markers C-reactive protein (CRP) and albumin that has demonstrated to predict clinical outcomes in a variety of oncological settings.

Methods: We re-evaluated the mGPS at the time of first staging (6 weeks after the start of therapy) in patients with NSCLC treated with atezolizumab (anti-PD-L1 antibody) in the phase 3 OAK trial.

Results: In patients treated with anti PD-L1 ($n = 412$), the on-treatment mGPS yields prognostic information similar to radiological staging (c-index 0.65 (95 % confidence interval 0.61 − 0.68) vs 0.61 (0.57 - 0.64). Notably, the mGPS low-risk subgroup is larger (54.4 %) compared to the partial response (PR) subgroup (7,5%). In the clinically heterogenous SD subgroup, on-treatment mGPS strongly correlated with survival (intermediate risk HR 2.4, $p < 0.001$, high-risk HR 3.5, $p < 0.001$, compared to low risk). On-treatment mGPS was also prognostic in patients with progressive disease (PD, intermediate risk HR 1.7, $p = 0.033$, high-risk HR 2.9, $p < 0.001$, compared to low risk). Remarkably, patients with PD and low-risk mGPS at first staging had a higher 12-month survival probability compared to patients with SD with intermediate or high-risk mGPS (67.0% vs 64.0%/47.7%).

Conclusions: Integrating on-treatment biomarkers into imaging-based staging can improve outcome prediction. A multi-modal approach to response assessment more akin to current practice in many hematologic malignancies should be further investigated in solid oncology, particularly in the context of immunotherapy.

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1481P Singular immune-related adverse events and efficacy outcomes of immune checkpoint inhibitors in advanced non-small cell lung cancer

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Background: ICIs have transformed the treatment of advanced NSCLC patients, no real-world data are available about the immune-related adverse events (irAEs). This retrospective study aimed to assess the safety and effectiveness of PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer (NSCLC) and to analyze the association between singular irAEs and effectiveness.

Methods: This was a retrospective study of the clinical data of patients with NSCLC treated with PD-1/PD-L1 inhibitors as 1ª or 2ª lines from Marzo 2015 to Marzo 2022 at Hospital Universitario Regional de Málaga. We evaluated association of irAE with efficacy, response and overall survival. Kaplan-Meier and Cox proportional hazard analyses were performed.

Results: A total of 510 patients were included in this analysis. Any grade IrAEs were seen in 307 (60%) patients. Of these (Table), 135 (43,9%) patients had grade 1 toxicities, most commonly cutaneous (96), colitis (54), rheumatologic (46) and hepatitis (42). 112 (36,4%) patients had grade 2 toxicities pneumonitis (47), cutaneous (29), colitis (28). 53 (17,2%) patients had grade 3 toxicities: hepatitis (15), pneumonitis (13), cutaneous (10). 8 (2,6 %) patients had grade 4 toxicities hepatitis (5), pneumonitis (2), DRESS syndrome (1). For patients assessed for efficacy, objective response rate (ORR) to ICI was higher in patients with irAEs [46% vs 14%] p=0,001. In fact, the presence of any irAEs had a significantly improved median OS compared to those without irAEs (19,3 months vs 6,5 $p = 0.0001$) (Median OS in G1-2 20 months and G 3-4 16,2 months had significally higher OS vs non irAEs 6,1 months; p=0,0001). Singular toxicities that predict greater OS >30 months were (Hepatitis G4, endocrine G1 and cutaneous G2); point out toxicities with deleterious effects (colitis G3 and pneumonitis G4). Multivariable analysis demonstrated that the development of any irAEs was related to a significantly improved OS (HR 0.47, 95% 0.26-0.68, $p = 0.0001$).

Table: 1481P Summary of singular toxicities and OS (overall survival) in months

IrAEs N 307	Cutaneous 135 OS	Pneumo 92 OS	Colitis 89 OS	Hepatitis 79 OS	Rheuma 76 OS	Endocrine 61 OS	Renal 40 OS
G1 135	96 28.2	29 18.3	54 21.4	42 18.7	46 28.8	40 37.8	19 21.4
G2 112	29 31.1	47 13.8	28 21.4	17 19	28 20.1	18 28.8	14 28.2
G3 53	10 13.4	13 15.3	7 7.2	15 20.6	2 3.8	3 -	7 7.2
G4 8	-	3 1.9	-	5 40.6	-	-	-
Non N Ir 203	375 9.0 p=0.0001	418 11.4 p=0.54	421 11.2 p=0.018	431 11.6 p=0.146	434 11.1 p=0.001	449 11.1 p=0.001	470 12.6 p=0.05

Conclusions: This study confirms the feasibility and the safety of ICIs in a large, real-world cohort of patients with NSCLC. The development of irAEs in NSCLC patients treated with immunotherapy may predict better treatment efficacy and overall survival.

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1482P Multicenter pharmacokinetic study of pembrolizumab for non-small cell lung cancer in elderly adults aged over 75 years

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Background: Pembrolizumab (Pemb) is a key drug for the treatment of advanced or recurrent non-small cell lung cancer (NSCLC). However, there are limited data on Pemb use in older adults aged >75 years with NSCLC, especially in terms of pharmacokinetics (PK).

Methods: This open-label multicenter observational study aimed to evaluate real-world data on the safety, efficacy, and blood concentrations of Pemb (both monotherapy and combination therapies) in older adults with NSCLC. Blood samples for PK analysis were collected immediately before Pemb administration. Quantitative Pemb concentrations were measured by liquid chromatography-mass spectrometry.

Results: We enrolled 100 patients from July 2019 to September 2020; one patient was excluded due to stage migration. Patient characteristics were as follows: median age, 78 (75—87) years; male/female ratio, 70/29; performance status (PS) 0—1/2—3, 85/14; adenocarcinoma/squamous cell carcinoma/others, 62/25/12; stage I—III/IV/postoperative recurrence (TNM 7th edition), 9/60/30; PD-L1 TPS <1%/1%—49%/≥50%, 12/31/48; and monotherapy/combination therapy, 65/34. The best overall efficacy was CR/PR/SD/PD (7/40/32/20), and the response rate was 47.5%. The median progression-free survival (PFS) and overall survival (OS) were 8.0 and 19.0 months, respectively. The adverse event profile was generally similar to that reported in previous studies. In total, 77 blood samples were collected immediately before the second cycle (C1 trough). Although no clear association between Pemb concentrations and patient background was found, PFS and OS were significantly shortened in the population with low C1 trough, a population characterized by lower PS, high number of metastatic organs at the beginning of treatment, and low blood albumin level.

Conclusions: In older adults aged >75 years with NSCLC and low albumin levels and PS and a high number of metastatic organs, C1 trough of Pemb is reduced and not expected to prolong PFS and OS.

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1483P Challenge of systemic first-line treatment of elderly lung cancer patients

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Background: At the time of diagnosis the majority of the lung cancer (LC) patients (pts) are old and have comorbidities. These elderly pts are underrepresented in clinical trials and their therapy options are limited. For pts whose tumor expresses PD-L1 at a lower level (TPS <50% or ICS <10%) combined platinum-based chemo-/immunotherapy is the recommended first line therapy, but elderly pts are usually unfit to receive these therapies at the regular dosage. A single-agent immunotherapy might be effective in some cases, but is only approved for pts with high PD-L1 expressing tumors (TPS ≥50% or ICS ≥10%). Data about the efficacy and safety of therapy for elderly LC pts are very limited.

Methods: In our retrospective data analysis all pts older than 75 years with LC regardless of stage treated at a German certified LC center and primary LC diagnosis from 2017 until 2022 were included. Progression-free and overall survival, objective response rate, and adverse events (AEs) resulting in therapy discontinuation were assessed for pts with systemic therapy. Data of geriatric assessment and its influence on therapy were analysed.

Results: 365 out of all 1.837 newly diagnosed LC pts from 2017 to 2022 were older than 75 years. Of these pts, 115 pts (31.5%) underwent primary surgery and 15 pts (4.1%) primary radiotherapy; 143 pts (39.2%) received only systemic treatment and 92 pts (25.2%) had best supportive care. 43 pts (11.8%) sufferered from small cell LC and 322 pts (88.2%) non-small cell LC. 99 pts with systemic therapy (69.2%) received combined chemo-/immunotherapy, 31 pts (21.7%) immunomonotherapy and 13 pts (9.1%) a small molecule inhibitor. 22 pts with systemic therapy (15.4%) had an ECOG performance status (PS) of 0, 80 pts (56 %) a PS of 1, 36 pts (25.1%) PS of 2 and 5 pts (3.5%) a PS of 3. All elderly pts with high PD-L1 expressing tumors received immunomonotherapy. 89 pts (90%) of 99 pts with chemo-/immunotherapy received platinum-based chemotherapy. Of these, 30 pts (30%) had to stop therapy prematurely due to AEs.

Conclusions: Many elderly pts received combined platinum-based chemo-/immunotherapy, but therapy was often prematurely stopped due to AEs. A quarter of the pts with systemic therapy had a PS of 2. Only few pts with a poor PS (2/3) were treated with monochemotherapy.

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1484P Impact of concomitant KRAS/STK11 or KRAS/KEAP1 mutations on response to immune checkpoint inhibition in NSCLC: A real-world data analysis

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Background: *STK11* and *KEAP1* mutations are among the most common gene alterations in lung adenocarcinoma and are associated with poor response to immunotherapy in patients with *KRAS* mutations. There is limited data on the clinical relevance of these alterations in a real-world setting.

Methods: Clinicopathologic and genomic data from patients with advanced lung cancer who underwent tissue-based panel next-generation sequencing (NGS) analysis, using the FoundationOne CDX assay, between January 2021 and February 2023 were retrospectively analyzed. Clinical outcomes were evaluated based on the molecular alterations and co-alterations that occurred.

Results: Of 100 patients (median age = 68 y [range: 40-92]), 51 women (51%), 39 smokers (39%), *KRAS* mutations were detected in 25 cases (25%), *STK11* in 12 (12%) and *KEAP1* mutations were found in 7 (7%) patients (pts.), respectively. Further alterations were *EGFR* exon 18-21 in 12 patients (12%), *BRAF p.V600E* in 3 pts. (3%), *ERBB2* ampl. 3 pts. (3%), *ALK* fusion in 2 pts. (2%), *ROS* fusion 1 (1%), *MET* exon 14 skipping mutation in 2 pts. (2%), *ERBB2* mutation in 1 pts. (1%), *EGFR* exon 20 insertion in 1 pts. (1%). In 5 patients (5%) concomitant *KRAS/STK11* mutations were detected. One patient showed KRASwt with concominant *STK11* mutation. Concomitant *KRAS/KEAP1* mutations were detected in 2 patients (2%). None of the patients with *STK11* or *KEAP1* mutations had concurrent *EGFR* mutations in exon 18-21, *ALK* fusions, or *ROS* fusions.

Conclusions: Therapeutically relevant gene variants were detected in the analyzed real world population. The data indicate that *STK11* or *KEAP1* mutations should be interpreted in the context of *KRAS* mutations and could serve as a clinical biomarker for poor response to immunotherapy in patients with lung adenocarcinomas. In addition, the data highlight the benefit of panel sequencing that includes the *STK11* and *KEAP1*.

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1485P Systemic inflammatory index dynamics at 6 weeks as an early surrogate for clinical benefit in patients with NSCLC and PD-L1≥50% expression treated with pembrolizumab: Data from the real-life practice

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Background: Pembrolizumab is the standard first-line treatment for patients with metastatic Non-Small Cell Lung Cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression of ≥50%. However, early loss of clinical benefit is observed in many cases. There is a need to identify predictors of this phenomenon in the real-world population.

Methods: This study is a retrospective analysis of patients (pts) with stage IV NSCLC treated with pembrolizumab in routine practice, who received treatment for at least 6 weeks. Inclusion criteria included good performance status (ECOG 0-1), no active brain metastases, and no *EGFR* or *ALK* alterations. The median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. The log-rank test and Cox regression model were used for uni- and multivariate analysis.

Results: A group of 216 pts were included. The objective response rate was 35.6%, 25.5% of pts had PD, while 11.2% of pts died before the first CT-scan. Median PFS and OS were 9.88 months (95% CI 4.85-14.92; 127 events) and 14.88 months (95% CI 9.84-19.91; 122 events), respectively. The median Systemic Inflammatory Index (SII) was 1260 in the overall population. In univariate analysis, SII >1260 had a negative impact on PFS ($p=0.047$) and OS ($p<0.022$). Tumour burden ≥111.5 mm ($p<0.045$) was a negative prognostic factor for OS. Other factors assessed were not relevant. An increase in the SII of more than 25% after 6 weeks of treatment correlated with a higher likelihood of early progression ($p<0.001$) and shorter OS ($p<0.001$). The differences were more pronounced in the subgroup of patients with an initial SII >1260. On multivariate analysis, higher tumour burden (HR 1.52, $p=0.028$, 95%CI 1.043-2.018) and an increase in SII at 6 weeks of more than 25% (HR 2.62, $p<0.001$;95%CI 1.625-4.234) were found to be negative prognostic factors for OS.

Conclusions: Pembrolizumab is effective in pts treated in daily practice. Taking into account additional factors, such as inflammatory index, may help to identify the optimal patient population. The dynamics of SII after 6 weeks of treatment may be a surrogate for clinical benefit.

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1486P Treatment patterns and real-world clinical outcomes of metastatic non-small cell lung cancer patients in the immunotherapy era

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Background: We describe PDL1 testing, treatment utilization and clinical outcomes in a real-world cohort of metastatic non-small cell lung cancer (mNSCLC) patients in a 2.5-million-member state-mandated health services database in Israel.

Methods: Newly diagnosed mNSCLC patients initiating systemic anti-cancer treatment between 01-Jan-2017-31-Dec-2020 were identified from the National Cancer Registry and Maccabi Healthcare Services database. Overall survival (OS) was estimated using Kaplan Meier analysis. The data cut-off date was 30-June-2021.

Results: Among 843 patients, 85% and 15% had adenocarcinoma (NSQ) and squamous cell carcinoma (SQ) histologies: of these 43% and 26% were female, median age was 67 and 69 years, 73% and 92% ever-smokers, 55% and 48% with 0-1 performance status (PS) respectively. Most patients with NSQ and SQ were tested for PD-L1(83.4% and 89.9% respectively), mostly within 30 days of diagnosis and prior to first-line (1L) treatment initiation. PD-1/PD-L1 inhibitor monotherapy (PDM) or combination (PDC) was the most common 1L therapy for NSQ and SQ histology (49% and 69%). For NSQ patients with no known EGFR/ALK/ROS1 and receiving PDM, PDC and platinum doublet therapy (PDT), the median OS from initiation of 1L was 12.5 (9.9-17.9), 14.8 (10.5-19.4) and 7.5 (6.4-12.2) months respectively, and for a subgroup of patients with PS 0-1, the median OS was 25.1 [4.9-NR], 17.6 [14.3-NR] and 12.7 [9.6-15.1] months respectively.

Conclusions: Our real-world data supports the benefit of PD-1/PD-L1 inhibitors in patients with mNSCLC.

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Table: 1486P 1L systemic anti-cancer treatment patterns in mNSCLC by PD-L1 status, N=843

	Adenocarcinoma				Squamous cell carcinoma		
1L Class of anti-cancer systemic therapy n (%)	PD-L1<50 n=344	PD-L1≥50 n=252	Missing n=118	Total n=714	PD-L1<50 n=68	PD-L1≥50 n=48	Total n=129
Platinum doublets	100 (29.0)	2 (0.8)	33 (28)	135 (19.0)	26 (38.2)	4 (8.3)	34 (26.4)
TKI inhibitors	93 (27.0)	53 (21.0)	69 (58.5)	215 (30.1)	1 (1.5)	1 (2.1)	3 (2.3)
PD-1/PD-L1 monotherapy	6 (1.7)	142 (56.3)	2 (1.7)	150 (21.0)	2 (2.9)	33 (68.8)	40 (31.0)
PD-1/PD-L1combinations	137 (39.8)	54 (21.4)	9 (7.6)	200 (28.0)	37 (54.4)	10 (20.8)	49 (38.0)

Drug class "other" for NSQ and SQ and SQ patients with "missing" PDL1 status — not presented here due to n<20. Missing includes patients who were never tested or had an inconclusive test result

1487P Real-world efficacy and safety of anlotinib in combination with PD-1/PD-L1 inhibitors as first-line or second-line treatment in advanced non-small cell lung cancer: Updated results

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Background: Immune checkpoint inhibitors (ICIs) regimens are the cornerstone of first-line treatment of advanced non-small cell lung cancer (NSCLC).Anlotinib is a multi-targeted tyrosine kinase inhibitor selective for VEGFR, FGFR, PDGFR, and c-kit. The ALTER 0303 trial showed that anlotinib improved both PFS and OS in later-line treatment for advanced NSCLC. Anti-angiogenesis agents has synergistic effect with ICIs. Anlotinib combined with PD-1/PD-L1 inhibitors as first-line or second-line treatment in advanced NSCLC showed encouraging efficacy and good tolerability. This is an update of the real-world study.

Methods: This is a prospective, multicenter real-world study. The NSCLC cancer patients who received anlotinib in combination with PD-1/PD-L1 inhibitors in first-line or second-line were enrolled. The primary endpoint was PFS, and secondary endpoints were ORR, DCR and OS. The response to treatment was evaluated according to RECIST version 1.1. In addition, adverse events were evaluated by CTCAE v5.0.

Results: From Aug 2021 to May 2023, 147 patients were enrolled in fifteen centers and 104 of them have received at least one tumor assessment. Median age was 66.3 (range:40-84); 82.7% male, 6.7% brain metastasis, 67.3% ECOG PS 1. 60 (57.7%) and 44 (42.3%) patients received anlotinib combined with PD-1 inhibitors as first-line and second-line therapy, respectively. Among all patients, 29 patients were partial response (PR), 72 patients were stable disease (SD), illustrating ORR of 27.9% and DCR of 97.1%. In the first-line, ORR was 30.0%, DCR was 96.6%. In the second-line, ORR was 25.0%, DCR was 97.7%.The median follow-up time was 9.4 months (95%CI:8.1-10.7). Median PFS and median OS were not reached. The most common Grade 3-4 AEs were decreased lymphocyte count (3.8%), decreased platelet count (2.8%), decreased white blood cells (1.9%), neutropenia (1.9%), hand-foot syndrome (1.0%) and there were no Grade 5 toxicities.

Conclusions: The combination of anlotinib and PD-1/PD-L1 inhibitors may represent a new treatment option as first-line or second-line treatment in advanced NSCLC. The further exploration is ongoing.

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1488P Exploring efficacy and safety of immune checkpoint inhibitors (ICI) in extensive stage (ES)- small-cell lung cancer (SCLC) in specific populations: Real-world data from the Durvalumab Expanded Access program Regional European cohort (DEAR)

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Background: Platinum-based chemotherapy (CT) with PDL-1 blockade is the standard of care in ES-SCLC. Relevant randomized controlled trials were restricted to patients(pts) with ECOG PS 0-1 at initiation of therapy. These trials also prohibited use of consolidation radiotherapy (RT) or salvage RT to treat of oligo-progression. We aimed to evaluate outcomes in pts with poor ECOG PS and those receiving non-palliative RT, as well as the prevalence and outcomes of durvalumab (DRV) beyond progression.

Methods: A retrospective data collection including pts from 11 centers in four countries. Primary endpoints were overall survival (OS) and duration of treatment (DOT) in the overall population and in the subgroup of pts with ECOG ≥2. Secondary endpoints included safety, OS and DOT in pts treated with non-palliative RT as well as the use of ICI beyond progression.

Results: A total of 100 pts received durvalumab with CT for ES-SCLC. 68% were male, median age was 65 years (range 39-83) and 23% had an ECOG ≥2. Overall, 29% of patients received RT during durvalumab treatment, 22% as salvage/consolidation. Fifteen pts (15%) were treated with DRV beyond progression for a median of 4 cycles (range 1-14). Median OS in the entire cohort was 11.5mo, 13.3mo in pts with ECOG 0-1 and 10.3mo in pts with ECOG ≥2 (p=0.028). Median DOT in the entire cohort was 4.5mo and 4.2 in pts with ECOG ≥2 (p=0.006). Pts receiving non-palliative RT showed a trend toward improved OS and DOT (Table). Eight pts (8%) discontinued DRV due to immune-related adverse events.

Table: 1488P mDOT and mOS in pts receiving non-palliative RT

	All patients	Pts with consolidation/salvage RT	P-VALUE
mDOT with durvalumab (months)	4.5	5.9	0.056
mOS (months)	11.5	14.7	0.190

Conclusions: Treatment with CT and DRV is safe and effective in pts with ES-SCLC with ECOG PS ≥2 as well as in pts receiving concomitant radiotherapy. Treatment discontinuation rate due to toxicity was comparable to that reported in the CASPIAN study.

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1489P To investigate the differences in efficacy between immunotherapy and combined immunotherapy in elderly patients with non-small cell lung cancer

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Background: Lung cancer is the leading cause of cancer death worldwide. In recent years, the therapeutic landscape for advanced non-small cell lung cancer (NSCLC) has changed with the rise of targeted therapies and immunotherapy. Elderly patients represent approximately half of the patient population, but studies on the treatment of elderly patients are limited.

Methods: A retrospective collection of 244 patients with pathologically confirmed NSCLC at APL General Hospital's First Medical Center and Fifth Medical Center, including 69 patients treated with immune monotherapy and 175 patients treated with combined immunotherapy. Cox regression analyses were used to assess whether there were differences in efficacy between immune monotherapy and combined immunotherapy.

Results: A total of 244 elderly patients were included in the study, and the analysis found that combined immunotherapy has a longer median OS. Patients with distant lung cancer metastases (HR 1.633, 95% CI 1.133-2.354), using immunotherapy as a second-line treatment (HR 1.717, 95% CI 1.238-2.380), and with pleural effusion (HR 1.772, 95% CI 1.246-2.522) had a shorter OS, whereas the patients treated with the combined immune therapy had a longer OS (HR 0.538, 95% CI 0.387-0.748). For patients aged 60-65 years with pleural effusion and second-line use of immunotherapy shortened OS. OS was shorter in patients aged 65-75 years with brain metastases and longer in patients receiving the combined immunotherapy. Multivariate analysis showed that BMI >24.8 and the use of combined immunotherapy were protective factors for OS and that the presence of pleural effusion was a risk factor. For patients aged 60 to 65 and 65 to 75, the presence of pleural effusion was a risk factor. Among patients >75 years, we only found a longer OS in patients with BMI >24.8(P=0.023).

Conclusions: For older patients with advanced NSCLC, the survival benefit of using combined immunotherapy is higher than that of immune monotherapy. However, that there was no difference in the efficacy of immune monotherapy or combined immunotherapy in this group (P =0.762), but patients with a BMI >24.8 had a longer OS.

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1490P Removal of TNF-Rs frees TNF-α's anticancer activity alone or in combination chemo- or immunotherapy in advanced NSCLC

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Background: Tumor necrosis factor (TNF-α) has anticancer activity. Tumors neutralize TNF-α by shedding excess soluble TNF receptors (sTNF-Rs) in the tumor microenvironment preventing TNF-α from binding to tumor membrane bound sTNF-Rs, triggering cell death pathways. Removal of sTNF-Rs via apheresis liberates the anticancer effects of TNF-α alone or with anticancer agents.

Methods: Protocol CP7-008 [NCT04690686] evaluated LW-02 Column Immunopheresis® ('LW-02 CI') in advanced (Stages IIIB/IV) squamous or adenocarcinoma NSCLC patients (pts), who progressed 1or 2 line(s) of treatment (1st-line with a platinum salt). Sixteen (16) pts were assigned to 1 of 3 arms to receive LW-02 CI 3x/week: with atezolizumab (Arm 1, n=7), with paclitaxel (Arm 2, n=3) or as monotherapy (Arm 3, n=6; pts progressed 2 lines, or 1 but not suitable for Arm 1) for 16 weeks. Clinically stable and/or objectively improved pts could receive extended therapy.

Results: Safety and tumor burden changes were evaluated in two groups—pts that had at least 1 LW-02 CI treatment ('ITT') and pts treated ≥4 weeks (≥4 wks). Pts' tumor burden was assessed via RECIST 1.1 (or iRECIST if appropriate). After 644 LW-02 CI procedures, 373 AEs (including 22 SAEs) were reported; 18 AEs (14.8%), including 3 SAEs (13.6%), had a causal relationship to treatment with the LW-02 Column. All were Grades 1 or 2, except for 2 Grade 3 SAEs. All resolved, and none required treatment discontinuation. For tumor burden, the best overall response was stable disease (11 pts), durable for ≥8 wks. Other endpoints were duration of treatment (DoT), overall survival (OS), disease control rate (DCR) and progression free survival (PFS). The results are summarized for both groups below.

Table: 1490P Median DoT, OS, DCR and PFS

Endpoint *(mos)*	Overall		Arm 1		Arm 2		Arm 3	
	ITT	≥4 wks	ITT	≥4 wks	ITT	≥4 wks	ITT	≥4 wks
DoT	**4.1**	**4.7**	**4.3**	**4.7**	**5.4**	**5.4**	**3.0**	**3.5**
OS	**9.9**	**11.1**	**16.5**	**17.0**	**9.5**	**9.5**	**7.7**	**10.2**
PFS	**4.1**	**5.2**	**4.0**	**4.0**	**7.7**	**7.7**	**5.5**	**5.8**
DCR *%*	**68.8**	**84.6**	**57.1**	**80.0**	**100.0**	**100.0**	**66.7**	**80.0**

Conclusions: LW-02 CI alone or combined with chemo- or immunotherapy appears safe with clear anticancer efficacy signals in treating advanced NSCLC. These results, when compared with data from existing therapies, warrant further investigation.

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1491P PD-L1 TPS ≥50% predicts durable response after discontinuing immune checkpoint inhibitors in metastatic non-small cell lung cancer patients

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Background: The optimal duration of immune checkpoint inhibitors (ICI) in metastatic non-small cell lung cancer (NSCLC) remains uncertain. Some physicians administer ICI for 2 years then discontinue it according to the designs of clinical trials, while other physicians continue ICI until progression. This study aims to explore the clinical course after discontinuation of ICI and identify factors related with durable responses after ICI cessation.

Methods: We retrospectively analyzed 45 patients with metastatic NSCLC who received ICI for ≥1.5 years and then discontinued treatment. All patients showed complete response or partial response or stable disease. Patients who initiated ICI between Jan 2014 and Dec 2020 were enrolled. Clinical factors including PD-L1 status were analyzed.

Results: The median duration of ICI treatment was 23.4 months, and the median follow-up duration from ICI discontinuation was 14.1 months. Thirty-five patients (77.7%) showed durable response after ICI cessation which lasted for median 17.0 months without any treatment, while 10 patients showed disease progression. Durable response was significantly associated with PD-L1 TPS ≥50% (28/31, OR 0.12, 95% CI 0.01-0.80, p=0.013). PD-L1 TPS ≥50% was significantly associated with longer PFS (median not reached *vs*. 41.9 months, HR 0.16, 95% CI 0.04-0.68, p=0.005). In multivariate analysis, only PD-L1 TPS ≥50% was an independent predictor of longer PFS after ICI discontinuation (HR 0.17, 95% CI 0.04-0.71, p=0.015).

Table: 1491P Baseline characteristics

	Durable response (n=35)	Disease progression (n=10)	P value
Male	32 (91.4%)	9 (90.0%)	1.000
Age	67 (37-79)	65 (59-78)	0.714
PD-L1 TPS	90% (0-100)	15% (0-100)	0.005*
≥1%	30 (90.9%)	6 (75.0%)	0.528
≥50%	28 (84.8%)	3 (37.5%)	0.019*
ICI agent			1.000
Pembrolizumab	21 (60.0%)	3 (30.0%)	
Nivolumab	10 (28.6%)	6 (60.0%)	
Others	4 (11.4%)	1 (10.0%)	
ICI line			0.124
1	15 (42.9%)	1 (10.0%)	
≥2	20 (57.1%)	9 (90.0%)	

Conclusions: PD-L1 TPS ≥50% predicts durable response without any treatment after ICI discontinuation in metastatic NSCLC patients treated with ≥1.5 years of ICI. Further biomarker research is required to identify which patients should continue receiving ICI and which can be tried with ICI cessation.

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1492P Retrospective study of the real-world safety profile of extended dosing 6-weekly pembrolizumab in comparison to traditional 3-weekly dosing schedule for treatment of lung cancer and melanoma in a Queensland hospital

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Background: Due to the widespread uptake of 6-weekly Pembrolizumab (6wklyP) in the COVID-19 era, this audit attempts to clarify differences in clinically relevant immune therapy related adverse events (irAEs) between 6wklyP and traditional 3-weekly Pembrolizumab (3wklyP).

Methods: Oncology patients at the Gold Coast University Hospital with Advanced Melanoma or Metastatic Non-small cell lung cancer (NSCLC) who received single agent 3wklyP 200mg, 6wklyP 400mg or those who sequentially received 3wklyP followed by 6wklyP between 2017-2022 were analysed for frequency of clinically significant (Grade3-4) irAEs. Total time of immunosuppression for treatment of irAEs was recorded. Data was extracted from the electronic medical record and analysed using Cox-proportion hazard analysis.

Results: In total, 69 and 112 patients received 6wklyP and 3wklyP respectively. There were 52 patients with Melanoma and 129 patients with NSCLC. 30 patients received sequential treatment. Average observation time for toxicity was 327 days for 6wklyP and 352 days for 3wklyP. 17/69 (24.6%) patients who received 6wklyP developed Grade 3-4 irAEs compared with 9/112 (8%) 3wklyP patients (HR of 3.03; CI 1.34-6.83, p= 0.007). Grade 1-4 irAEs were 32/69 (46.4%) with 6wklyP and 31/112 (27.7%) with 3wklyP. 6/30 (20%) patients who received 6wklyP after initially receiving 3wklyP had Grade 3-4 irAEs (HR 0.56, CI 0.24-1.37; p= 0.187). Mean immunosuppression time for treatment of Grade 3-4 irAEs for 6wklyP and 3wklyP was 91 days and 55 days respectively (p =0.76). 6/17 (35.3%) 6wklyP patients required Steroid sparing agents to treat their Grade3-4 irAEs compared to 1/9 (11.1%) 3wklyP patients.

Conclusions: 6wklyP was associated with significantly higher immune therapy related adverse events than 3wklyP. Sequential delivery of 6wklyP after 3wklyP did not significantly alter clinically significant adverse effects. Immunosuppressive management of irAEs were not statistically different between arms however there was a higher rate of steroid sparing immunomodulation requirement with 6wklyP.

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1493P A phase II, multi-center, open-label, dose-optimization study evaluating telomere targeting agent THIO sequenced with cemiplimab in patients with advanced NSCLC: Preliminary results

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Background: THIO (6-thio-2'-deoxyguanosine) is a small molecule, first-in class direct cancer telomere targeting agent which selectively targets telomerase positive (TERT+) cancer cells. It is incorporated de novo in synthesized telomeres leading to chromatin uncapping, DNA damage signals generation and rapid apoptosis. Preclinical data in NSCLC indicates that low doses of THIO induce sensitivity to immune check point inhibitors (ICIs) when administered prior to an ICI.

Methods: This is a phase 2, dose-optimization clinical study in adults with advanced NSCLC who either progressed or relapsed after 1L treatment with ICI alone or in combination with chemotherapy. Using a modified 3+3 design, the safety lead-in (Part A) enrolled 10 patients who received THIO, 360 mg IV [120 mg QD, D1—3], followed by 350 mg cemiplimab on D5, Q3W. The primary endpoints are safety, ORR, DCR. Once the safety of the 360 mg is characterized, additional patients are randomized in the dose-finding portion of the study (Part B). Using a Simon 2-stage design, a total of 123 patients (41 patients/arm) will be assigned to one of the THIO doses: 360, 180, or 60 mg followed by cemiplimab Q3W for up to 1 year. Disease status is assessed at 6-week intervals through cycle 5 and every 9 -12 weeks thereafter.

Results: As of April 2023, 13 patients received at least one dose of THIO followed by cemiplimab (10 in Part A and 3 in Part B). All patients had 1-3 prior treatments and had documented disease progression. In Part A, no DLTs were reported (n = 10 subjects, 9 evaluable and 1 replaced due to delayed toxicities from a previous treatment). Most AEs were G1; G3 anemia in 1 patient (8%); G3 nausea, G3 AST/ALT elevations reported in 2 patients (15%) and one death not treatment related; 29 cycles were administered, and 4 patients had at least one radiographic evaluation after 2 cycles. The first 2 patients enrolled were discontinued after 5 and 4 cycles respectively due to withdrawal of consent and delayed recovery of toxicities; they are alive and progression-free with no new treatment at 10- and 9-months follow-up.

Conclusions: The study continues patient enrollment at all 3 dose-levels.

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1494P Fruquintinib combined with sintilimab and chemotherapy as the first-line treatment in advanced naive EGFR- and ALK-negative non-squamous non-small cell lung cancer(nsq-NSCLC): Updated results of a phase II trial

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Background: Furoquitinib(F) is an orally highly selective tyrosine kinase inhibitor targeting VEGFR1,2,3. We previously reported some results of NCT04956146, which demonstrated that F plus PD-1 inhibitor sintilimab(S) and platinum-based chemotherapy(chemo) had encouraging efficacy and manageable toxicity as the first-line treatment for advanced naive EGFR- and ALK-negative nsq-NSCLC. Herein, we present updated results.

Methods: This single-arm, open-label, phase II study consists of a safety lead-in phase (Part 1) and dose expansion phase (Part 2). In Part 1 the F taken orally at 5 mg (2 weeks on/ 1 weeks off, Q3W) plus S (200mg, iv, d1,Q3W) and chemo(Q3W). After 4～6 cycles followed by maintenance therapy with F(RP2D) plus S and pemetrexed or not. DLT was observed for 1 cycle. The primary objective of Part 1 is to assess the safety and confirm the RP2D of F. The primary objective of Part 2 is to estimate the PFS and the secondary endpoints including ORR, DCR, OS, and safety.

Results: From February 2022 to May 2023, 26 pts were enrolled. The median age was 62 years, with males 92.3%, ECOG PS 0 73.1%, and the median sum of longest diameters (SLD) is 100.805mm. Pts with PD-L1 TPS ≥1%, < 1%, and unknown were 14,

8, and 4 respectively. Of 20 evaluable pts, ORR and DCR were 80% and 100%. According to PD-L1 level, ORR was 91.7% and 57.1% for pts with PD-L1 TPS ≥1% and < 1%. ORR was 60% for baseline SLD < median SLD and 100% for median SLD > median SLD. Median PFS was not reached yet. All pts experienced≥1 treatment-emergent adverse events (TEAEs). The most common Gr≥3 TEAEs (≥10% pts) were Neutrophil count decreased (42.3%), Anaemia(15.4%), Gamma-glutamyltransferase increased(11.5%) and hypertriglyceridaemia (11.5%).

Conclusions: This finding showed promising efficacy for fruquintinib combined with sintilimab and chemo in pts with advanced NSCLC as a first-line treatment with a manageable safety profile. This study might represent a potential treatment option for pts with unresectable or metastatic advanced naive EGFR- and ALK-negative nsq-NSCLC.

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1495P Cemiplimab plus chemotherapy versus chemotherapy in non-small cell lung cancer with PD-L1 ≥1%: EMPOWER-Lung 3 results

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Background: In EMPOWER-Lung 3 (NCT03409614; Part 2), a randomised, double-blind, placebo-controlled phase 3 trial, cemiplimab + chemotherapy (chemo) versus chemo alone showed improved overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and patient-reported outcomes (PRO) and an acceptable safety profile in patients with advanced squamous and non-squamous non-small cell lung cancer (NSCLC) with all levels of programmed cell death-ligand 1 (PD-L1) expression and without *EGFR*, *ALK* or *ROS1* aberrations. Cemiplimab + chemo received FDA approval in 2022 as first-line treatment for advanced NSCLC irrespective of PD-L1 levels. In 2023, it received European Commission approval for PD-L1—positive patients. Here we describe outcomes for patients with PD-L1 expression ≥1% from EMPOWER-Lung 3 Part 2. PRO and subgroup results will be further described in the presentation.

Methods: A total of 466 patients were randomised 2:1 to receive 4 cycles of platinum-doublet chemo in combination with cemiplimab 350 mg (n=312) or with placebo (n=154) every 3 weeks up to 108 weeks. The primary endpoint was OS. Secondary endpoints included PFS and ORR. This post hoc analysis included patients with PD-L1 ≥1% with ∼2-year follow-up data (cutoff 14 June 2022).

Table: 1495P

EMPOWER-Lung 3 Part 2	Patients with PD-L1 ≥1% (N=327)	
	Cemiplimab + chemo (n=217)	Chemo alone (n=110)
OS, median, months	23.5	12.1
HR (95% CI)	0.52 (0.39, 0.70); *P*<0.0001	
PFS, median, months	8.3	5.5
HR (95% CI)	0.47 (0.36, 0.61); *P*<0.0001	
ORR, %	47.9	22.7
Odds ratio (95% CI)	3.09 (1.83-5.21); *P*<0.0001	
Complete response, n (%)	11 (5.1)	0
Partial response, n (%)	93 (42.9)	25 (22.7)
Duration of response, median (95% CI), months	17.5 (13.1, 21.5)	6.5 (4.2, 10.3)
Grade ≥3 TEAEs, n/N (%)	105/217 (48.4%)	30/109 (27.5%)

Results: In 327 patients with PD-L1 ≥1%, median OS was longer with cemiplimab + chemo than chemo alone (23.5 vs 12.1 months; HR: 0.52, *P*<0.0001). Median PFS was 8.3 months with cemiplimab + chemo versus 5.5 months with chemo alone (HR: 0.47, *P*<0.0001). ORRs were 47.9% vs 22.7%, with a response duration of 17.5 and 6.5 months. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 48.4% of patients with cemiplimab + chemo versus 27.5% with chemo alone. The safety profile for cemiplimab + chemo in patients with PD-L1 ≥1% was generally consistent with that in overall patients.

Conclusions: Cemiplimab + chemo showed improved efficacy compared with chemo alone in PD-L1—positive patients with advanced NSCLC.

Clinical trial identification: NCT03409614; Part 2.

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1496P Higher levels of CSF-1 support resistance to immune checkpoint inhibitors in advanced non-small cell lung cancer

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Background: Since the recruitment and polarization of TAMs are regulated by CSF-1R/CSF-1, the expression levels of these factors may be indicative of TAM physiology and correlated with antitumoral immunity and response to therapy. This study aimed to investigate the influence of CSF-1R/CSF-1 activation levels on tumor response in patients with advanced non-small cell lung cancer (NSCLC) receiving first-line immune checkpoint inhibitor (ICI) therapy.

Methods: This bicentric study included a prospective cohort of 88 patients with advanced NSCLC treated with ICIs as first-line therapy. Plasma levels of CSF-1 were assessed by ELISA. Peripheral blood mononuclear cells were used both for immunomodulatory assays and to produce macrophages through CSF-1 treatment. To assess the mechanism of CSF-1-mediated suppression of immunotherapy, Isolated PBMC, activated with phytohemagglutinin (PHA) with or without pembrolizumab (20 nM), were cultured alone, or in the presence of macrophages or on an established NSCLC monolayer. INFγ levels and CD8+ proliferation/activation were assessed through ELISA assay and flow cytometry respectively.

Results: Plasma levels of CSF-1 were found to be higher in patients resistant to ICI therapy (8898 vs. 14031 pg/mL, $p < 0.001$). Higher levels of CSF-1 were associated with poor therapy response (RR = 7,944; $p = 0.013$), disease progression (RR = 8.556; $p < 0.001$), and shorter survivals (PFS, 50 days vs. 305 days; $p < 0.001$; OS, 248 days vs. 1369 days, $p < 0.01$). In vitro, recombinant CSF-1 inhibited CD8+ activation and interferon gamma (INFγ) production that was induced by PHA and Pembrolizumab. The use of Pexidartinib (PLX-3397), a CSF-1R inhibitor, reversed the effects of CSF-1 by restoring lymphocyte activation. However, these effects were dependent on the presence of monocytes/macrophages, suggesting that the immune suppression mediated by CSF-1 was an indirect effect resulting from the stimulation of monocytes that promote their differentiation into macrophages.

Conclusions: Our study suggests that plasma levels of CSF-1 could serve as a useful predictive biomarker for resistance to ICIs, while targeting the CSF-1/CSF-1R signaling pathway could potentially overcome resistance to ICIs in patients with NSCLC.

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1497P Gut microbiome is associated with the clinical response to anti-PD-1 based immunotherapy in untreated advanced non-small-cell lung cancer

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Background: Lung cancer is a malignancy with extremely high morbidity and mortality, of which non-small cell lung cancer (NSCLC) accounts for about 85%. With the advent of immunotherapy has brought survival benefit to NSCLC patients, some patients still be hard to achieving satisfactory outcomes. The link between gut microbes and immunotherapy is strong, but the role they play in NSCLC immunotherapy is unclear. The aim of this study was to investigate the relationship between gut microbial composition and the efficacy of immunotherapy in NSCLC.

Methods: Patients with advanced NSCLC receiving first-line immunotherapy were enrolled, and fresh stool samples were collected before and after 2 cycles of anti-PD-1 monoclonal antibody treatment for metagenomics sequencing and annotation using the KEGG and MetaCyc databases for subsequent differential flora analysis and functional analysis, and correlated the results with outcomes at 41 months.

Results: A total of 51 patients with advanced NSCLC treated with first-line immunotherapy were included in this study, and the relative abundance of *Streptomyces*, *Corynebacterium*, *Kineosphaera*, and *Schaalia* genus under the *Actinomyces* phylum was increased in the R group, and the PFS (progression-free survival time) of patients with high relative abundance of *Schaalia* and *Corynebacterium* genus was significantly longer than in those with low relative abundance. Functional analysis revealed reduced levels of glycolysis in the R group and may be due to the enrichment of *Schaalia* genus. The BMI and fasting glucose values of the patients may be influential factors in the relative abundance of *Schaalia* genus. In addition, the type of irAE occurrence was also correlated with the composition of gut microbes.

Conclusions: We have newly discovered that *Schaalia* genus under the *Actinobacteria* phylum may influence the efficacy of immunotherapy in NSCLC patients by inhibiting the level of glycolysis through affecting the level of PFP. Therefore, *Schaalia* flora may be a potential marker for predicting the efficacy of immunotherapy in NSCLC patients, and interfering with the levels of *Schaalia* or PFP is expected to be a new target to enhance the efficacy of immunotherapy in NSCLC patients.

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1498P HGF/MET pathway is associated with poor efficacy of Immune checkpoint inhibitors (ICIs) in advanced-stage NSCLC

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Background: A pilot study has revealed a significant correlation between high levels of circulating HGF and poor response to ICIs therapy in late-stage NSCLC patients treated with ICIs. This study aimed to evaluate the prognostic value and role of the HGF/MET pathway in first-line immunotherapy treatment in advanced NSCLC patients.

Methods: We included 82 consecutive patients, 49 treated with immunotherapy and 33 treated with chemotherapy alone as a group control. We analysed the plasma levels of HGF by ELISA. Immunohistochemistry was used to assess the expression levels of PD-L1, MET, and CD8+ T-Cell infiltration. The contribution of HGF/MET to NSCLC response to ICIs was further investigated by culturing peripheral blood mononuclear cells (PBMC)stimulated with 10 μg/mL phytohemagglutinin (PHA) and/or pembrolizumab (20 nM). The cells were cultured with recombinant HGF or co-cultured with NSCLC patients-derived explants.in the presence of cMET inhibitors Crizotinib or SGX. The immune response was quantified through CD8+ activation and INFγ production.

Results: Correlation tests demonstrated that lower HGF levels were associated with a good response to ICIs (RR=2.143; p=0.004) and low progression (RR=0; p=0.01). Patients with low HGF levels (< Q1) at treatment initiation had longer progression-free survival (PFS) (841 vs 136.5 days; HR = 0.26 95% CI 0.1292-0.5411; p=0.0003) and longer overall survival (OS) (median not reached vs. 489 days; HR 0.36; 95% CI 0.1505-0.8408; p=0.02). Furthermore, when activated PBMCs were cultured in the presence of recombinant HGF or on NSCLC monolayer, the activation/proliferation of CD3+CD8+ lymphocytes, was inhibited, even in the presence of pembrolizumab. The addition of HGF/MET inhibitors (Crizotinib and SGX) suppressed the immunosuppressive properties of recombinant HGF or NSCLC, stimulating INFγ production.

Conclusions: Our study found that high levels of HGF in the peripheral blood are associated with poor response to ICIs, disease progression, and shorter survival in patients with advanced NSCLC. Furthermore, we showed through in vitro experiments that inhibiting the HGF/MET signaling pathway could be a promising therapeutic approach to enhance the efficacy of ICIs in this patient population.

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1499P Wnt5-ROR2 signalling mediated resistance to immune checkpoint inhibitors in advanced non-small cell lung cancer

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Background: Emerging evidence suggests that Beta-catenin-independent Wnt signaling is upregulated in lung carcinogenesis, but few studies have investigated its prognostic value or its impact on the immune response in NSCLC patients undergoing checkpoint inhibitors (ICIs therapy. **The goal** of this study is to examine the prognostic significance of non-canonical Wnt signaling molecules, and their potential value as drug targets to enhance the efficacy of ICIs in NSCLC patients.

Methods: This study enrolled a prospective cohort of 52 patients with advanced NSCLC receiving immune checkpoint inhibitors (ICIs) therapy. Samples (plasma and lung biopsies) were collected at various stages of treatment and analysed for Wnt expression using RT-qPCR, flow cytometry, ELISA assays, and immunohistochemistry. To investigate the mechanism of Wnt-mediated drug response, including response to ICIs and/or chemotherapy, stimulated PBMCs (anti-CD3/CD28 + rh-IL2) were treated with or without pembrolizumab and cultured/co-cultured with recombinant Wnt5a,Wnt inhibitors and NSCLC explants.

Results: We found higher levels of Wnt5a and Wnt5b in patient's samples. Wnt5a was upregulated in patients' plasma compared to healthy donors (1262 vs 372.0 ± pg/mL, $p < 0.001$). Samples collected at first evaluation had low levels of Wnt5a compared to the baseline (1262 vs 771.9 pg/mL, $p < 0.01$). Wnt5a expression was related with poor therapy response (RR =2.4; p = 0,05) and shorter survivals (PFS non reached vs 259 days, HR =0.141, $p < 0.01$). ELISA analysis of supernatants from NSCLC cell culture showed that supporting the fact that Wnt5a and Wnt5b are produced by tumor cells. In vito experiments demonstrated that recombinant Wnt5a as well as NSCLC monolayer, suppressed lymphocytes activation and the production of INF γ. These effects were reverted by Wnt inhibitors, including porcupine inhibitors.

Conclusions: The preclinical results of our study provide comprehensive validation for the modulation of Wnt as a drug candidate to improve the effectiveness of immunotherapy in treating NSCLC. Our findings offer compelling evidence that Wnt5 signalling can serve as predictive biomarkers and drug targets to prevent disease relapse in advanced NSCLC patients receiving ICIs.

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1500TiP REFINE-Lung is a multicentre phase III study to determine the optimal frequency of pembrolizumab in non-small cell lung cancer utilising a novel multi-arm design

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Background: Standard regimens for anti-PD1 agents nivo and pembro may result in overtreatment. These agents have high target affinity, saturate PD1 at low concentrations, occupy PD1 long after discontinuation and have a flat dose-response relationship across a wide range tested. Lower doses or longer administration frequency may retain efficacy. New approaches to optimise treatment regimens are required to enhance cost-effectiveness, pt quality of life and toxicity. However, conventional 2-arm non-inferiority designs are inefficient for this. We present a new multi-arm trial design to tackle the problem, implemented in the UK multicentre phase III REFINE-Lung study that aims to determine the optimal treatment frequency of pembro in NSCLC. Pts progression free after 6 months of standard therapy are randomised to 5 pembro frequency reduced arms (q6w, q9w, q12w, q15w and q18w). By evaluating the frequency-response relationship, the longest frequency that is equivalent to standard of care within a pre-defined margin will be determined.

Trial design: The REFINE-Lung trial (NCT05085028) is a multicentre, randomised open-label, phase III trial in advanced NSCLC, utilising a novel Multi-Arm Multi-Stage Response Over Continuous Interventions (MAMS-ROCI) design. 1750 pts aged $\geq$18 and progression free at six months of 1st line pembro and planning to continue, will be enrolled from up to UK 35 hospital groups. Pts will be randomised equally to 5 dose frequency arms, starting with q6w (control) vs. q12w arms for an interim analysis of safety. If q12w PFS is not significantly reduced, remaining q9w, q15w and q18w arms will be opened. Pts who progress may re-escalate to q6w therapy. Primary objective is to determine the optimal dose frequency of pembro, defined as the longest dose interval non-inferior to standard therapy using 2-year survival as the primary outcome. Secondary endpoints include OS, PFS, toxicity, quality of life and cost effectiveness. An exploratory sub-study will explore fundamental aspects of cancer immunotherapy and develop novel biomarkers of response, resistance and toxicity. The trial is currently open at 26 centres.

Clinical trial identification: Sponsor Protocol No.: C/41/2021; EudraCT: 2021-004908-18; NCT05085028.

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1501TiP A phase III global study of telisotuzumab vedotin versus docetaxel in previously treated patients with c-Met overexpressing, EGFR wildtype, locally advanced/metastatic nonsquamous NSCLC (TeliMET NSCLC-01)

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Background: Non-small cell lung cancer (NSCLC) encompasses over two-thirds of lung cancer diagnoses, most presenting as advanced disease. c-Met (MET protein) is overexpressed in NSCLC. In this study, we investigate telisotuzumab vedotin (Teliso-V), a first-in-class antibody-drug conjugate composed of a c-Met—targeting antibody (telisotuzumab) and a microtubule polymerization inhibitor (cytotoxin monomethyl auristatin E). Interim efficacy analysis of the phase 2 LUMINOSITY study (NCT03539536) of Teliso-V monotherapy showed an objective response rate (ORR) of 37% (95% CI: 24—51) in previously treated patients (pts) with c-Met overexpressing epidermal growth factor receptor (*EGFR*) wildtype (WT) nonsquamous NSCLC and 52% (95% CI: 31—73) in the high c-Met overexpressing group.

Trial design: This randomized, open-label, global phase 3 study (NCT04928846) evaluates the efficacy, safety, pharmacokinetics, and pharmacodynamics of Teliso-V monotherapy compared with docetaxel in pts with locally advanced/metastatic c-Met overexpressing *EGFR* WT nonsquamous NSCLC who have progressed on prior therapy. Enrollment began in May 2022. To be eligible across global sites, pts must be $\geq$18 years old with c-Met overexpressing (ie, $\geq$25% tumor cells at 3+ intensity by IHC assay [anti-MET clone SP44; Roche Tissue Diagnostics]) locally advanced/metastatic *EGFR* WT NSCLC, with ECOG score $\leq$1. Pts must have progressed on at least one prior line of therapy, which can include no more than one line of prior chemotherapy, and must be naïve to c-Met—targeted antibodies and docetaxel. Target enrollment is 698 pts. Pts will be randomized 1:1 to Teliso-V (1.9 mg/kg every 2 weeks) and docetaxel (control, 75 mg/m^2 every 3 weeks). Treatment continues until disease progression or discontinuation criteria are met. Co-primary endpoints are progression-free survival by independent central review and overall survival. Secondary endpoints include ORR, duration of response, and patient-reported outcomes. Safety, adverse events (AEs), drug discontinuation or dosing modification due to AEs, and tolerability will be assessed.

Clinical trial identification: NCT04928846.

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Legal entity responsible for the study: AbbVie.

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1502TiP A phase I/IIa trial of ChAdOx1 and MVA vaccines against MAGE-A3 and NY-ESO-1

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Background: While immunotherapy is a critical modality for the treatment of many cancers, many patients (pts) do not respond to checkpoint blockade. Vaccination against tumour antigens has potential to enhance this, and despite the historically limited success of vaccines in monotherapy, effective immune induction is observed. Prime-boost viral vaccination is a highly potent platform, priming immunity with the CHAdOx1 adenoviral vector, followed by MVA vaccinia vector boosting, against MAGE-A3 and NYESO-1. Nonclinical data to support the rationale for enhanced CHAdOx1-MVA efficacy, in combination with chemo- and immunotherapy, has been generated in an *in vivo* surrogate model (McAuliffe J et al, 2021). The MAGE-A3 antigen is expressed on tumours of a high percentage of cancer patients including non-small cell lung cancer (NSCLC). NYESO-1, expressed on a subset of MAGE-A3$^+$ tumours, has the additional advantage of being highly immunogenic in cancer patients, either spontaneously or in response to peptide vaccination. The safety, tolerability, efficacy and immunogenicity of ChAdOx delivery of MAGE-A3/NYESO-1 antigens, boosted by MVA-MAGE-A3 (MAGE-A3$^+$ pts) or MVA-MAGE-A3 and MVA-NYESO-1 (MAGE-A3$^+$NYESO-1$^+$ pts) are explored in this trial.

Trial design: This is a multi-centre, first-in-human, phase I/IIa, randomised, open label trial, run in the UK, for patients scheduled to receive first-line chemo-immunotherapy containing pembrolizumab as standard of care (SoC) treatment, for Stage III/IV NSCLC (and potentially additional indications) expressing MAGE-A3 +/- NYESO-1 (NCT04908111). Patients receive trial vaccination from Cycle 3 of their SoC treatment. In the initial Safety Run-In Stage, opened in October 2021, all patients receive ChAdOx1-MAGE-A3-NYESO prime vaccination and either MVA-MAGE-A3 single boost (3 evaluable pts) or MVA-MAGE-A3 and MVA-NYESO double boost (3 evaluable pts) vaccinations with SoC. The currently expanding Rolling Recruitment Stage includes a NSCLC Randomised Cohort of approximately 80 pts, randomised 1:1 to addition of vaccination. The primary objective is safety and tolerability, with key secondary objectives of immunogenicity and clinical efficacy. Tertiary objectives include correlative translational analyses.

Clinical trial identification: CRUKD/20/001, Release date: 07 Dec 2020.

Legal entity responsible for the study: Cancer Research UK Centre for Drug Development.

Funding: Has not received any funding.

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1503TiP A phase II study of cemiplimab plus BNT116 versus cemiplimab alone in first-line treatment of patients with advanced non-small cell lung cancer with PD-L1 expression ≥50%

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Background: Cemiplimab is an anti—programmed cell death-1 (PD-1) antibody approved as first-line monotherapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with ≥50% PD-ligand 1 (PD-L1) tumour cell expression. A high unmet medical need remains for patients with no or limited response to anti—PD-1/PD-L1 therapy. As prognosis is poor for these patients, there is growing interest in combining anti—PD-1 compounds with therapeutic cancer vaccines. BNT116 is an investigational mRNA-based therapeutic cancer vaccine consisting of a fixed set of 6 liposomally formulated RNAs, each encoding a different tumour-associated antigen frequently expressed in NSCLC.

Trial design: This is a randomised, multicentre, open-label phase 2 study of cemiplimab plus BNT116 versus cemiplimab alone in treatment-naive patients with stage IIIB, IIIC, or IV squamous or non-squamous NSCLC, who are ineligible for surgical resection or definitive chemoradiation. Patients must have PD-L1 expression on ≥50% of tumour cells (determined by analysis of resected tumour samples) and no actionable *EGFR, ALK*, or *ROS1* aberrations. Patients in arm A will receive cemiplimab beginning Cycle 1 Day 1 (C1D1). Patients in arm B will receive cemiplimab beginning C1D1 and BNT116. The primary endpoint is objective response rate per blinded independent review committee of cemiplimab plus BNT116 versus cemiplimab alone. Secondary endpoints will assess other antitumour activities of cemiplimab plus BNT116 versus cemiplimab alone, as measured by objective response rate per investigator assessment, duration of response, progression-free survival, and overall survival, as well as safety and tolerability. Enrollment of up to 100 patients is planned. Enrolment is ongoing.

Clinical trial identification: NCT05557591.

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1504TiP HARMONi: Randomized, double-blind, multi-center, phase III clinical study of ivonescimab or placebo combined with pemetrexed and carboplatin in patients with EGFR-mutant locally advanced or metastatic non-squamous NSCLC who have progression following EGFR-TKI treatment

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Background: For patients (pts) with *EGFR*-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard. Drug resistance remains a challenge and an effective therapy after progression is needed. Ivonescimab (SMT112/AK112) is a novel bispecific antibody that provides dual blockade of PD-1 and VEGF activity. And coengagement of these 2 targets increases affinity to PD-1 by more than 10 fold. Given the correlation between VEGF-A and PD-1 expression in the tumor microenvironment, simultaneous blockade of these 2 targets by ivonescimab may produce enhanced antitumor activity, with an improved safety profile, compared to co-administration of individual anti-PD-(L)1 and an anti-VEGF agents. Phase 2 trial data reported that in 19 pts with *EGFR* mutated NSCLC who progressed following TKI therapy, the response rate to ivonescimab plus pemetrexed and carboplatin was of 68.4% (13/19) and a tolerable safety profile in the total population (N=83) treated with ivonescimab plus chemotherapy.

Trial design: HARMONi is a randomized, double-blind, multiregional phase 3 trial of ivonescimab or placebo in combination with pemetrexed and carboplatin in pts with locally advanced or metastatic *EGFR*-mutant NSCLC. 470 pts will be randomized 1:1 and to receive ivonescimab/placebo plus pemetrexed and carboplatin (Q3W, 4 cycles, 21 days per cycle) followed by ivonescimab/placebo plus pemetrexed for maintenance therapy for up to 2 yrs until progression or unacceptable toxicity. The co-primary endpoints are overall survival and progression-free survival assessed by IRC per RECIST v1.1. Secondary endpoints include overall response rate, incidence/severity of adverse events and immunogenicity of ivonescimab. Key eligibility criteria include advanced or metastatic NSq- NSCLC with an activating EGFR mutation, Eastern Cooperative Oncology Group Performance Status 0 or 1 and progression on/following third generation EGFR-TKI. The study will be a multi-national study including United States, Cana, Euroadpe and China.

Clinical trial identification: NCT05184712.

Legal entity responsible for the study: Summit Therapeutics and Akeso Biopharma.

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1505TiP TROPION-Lung07: A phase III trial of datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) as first-line (1L) therapy in advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC) with PD-L1 expression

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Background: Immunotherapy has improved survival in patients (pts) with adv/met NSCLC. However, outcomes remain poor in pts with PD-L1 expression <50%, and more efficacious treatments are needed. Dato-DXd is an antibody-drug conjugate composed of a TROP2 directed monoclonal antibody covalently linked to a highly potent cytotoxic payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. In the phase 1b TROPION-Lung02 trial, Dato-DXd + pembro ± Pt-CT had tolerable safety and promising antitumor activity in pts with adv/met NSCLC, notably as 1L therapy and irrespective of PD-L1 levels. Here, we describe the TROPION-Lung07 trial of Dato-DXd + pembro ± Pt-CT in pts with adv/met NSCLC without actionable genomic alterations (AGA) and PD-L1 expression <50%.

Trial design: TROPION-Lung07 (NCT05555732) is a global, randomized, open-label, phase 3 trial of 1L Dato-DXd + pembro ± Pt-CT in pts with nonsquamous adv/met NSCLC without AGA with PD-L1 expression <50%. Dato-DXd + pembro ± Pt-CT will be compared with pemetrexed + pembro + Pt-CT. Approximately 975 pts will be randomized 1:1:1 to Dato-DXd 6 mg/kg + pembro 200 mg (max, 35 cycles) ± Pt-CT (cisplatin 75 mg/m^2 or carboplatin area under the curve 5; max, 4 cycles) every 3 weeks (Q3W) or pemetrexed 500 mg/m^2 + pembro 200 mg + Pt-CT Q3W. Pts will be stratified by PD-L1 levels, Eastern Cooperative Oncology Group performance status, geographic region, and investigator choice of Pt-CT. Pts must have stage IIIB/C NSCLC ineligible for resection or definitive chemoradiation or stage IV disease and must not have received prior systemic therapy for adv/met NSCLC. The primary endpoints are progression-free survival by blinded independent central review and overall survival. Secondary endpoints include objective response rate (ORR), duration of response, time to response, disease control rate, and safety. Pt-reported outcomes, pharmacokinetics, and biomarkers will be explored. Enrollment is currently ongoing in the United States, Australia, China, Japan, Republic of Korea, Taiwan, and Thailand.

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1506TiP A single-arm, phase II study of amivantamab (AMI), lazertinib (L) and pemetrexed (P) for first-line treatment of recurrent/metastatic non-small cell lung cancers (NSCLCS) with epidermal growth factor receptor mutations in Exons 19 or 21 (EGFR 19/21): AMIGO 1 (LACOG0821)

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Background: Osimertinib (osi) is the current first-line standard treatment for patients with NSCLCs with EGFR 19/21. Data suggest that combining EGFR tyrosine kinase inhibitor (TKI) with chemotherapy may be superior to a sequential approach of first-line TKI followed by salvage therapy. AMI is an EGFR/MET bi-specific antibody currently approved for NSCLCs with EGFR exon 20 insertions, but which is also being evaluated for NSCLCs with EGFR 19/21 in combination with chemotherapy (MARIPOSA-2 study) after osi progression. We designed AMIGO-1 to test the primary hypothesis that, in the first-line setting, the triplet regimen of AMI, combined with the 3rd generation irreversible TKI L, and P will improve progression-free survival (PFS) compared to historical controls, with an acceptable safety profile.

Trial design: AMIGO 1 is a single-arm, phase 2, multicenter trial, conducted through LACOG. Eligibility criteria include treatment-naïve, PS 0−1 patients with advanced NSCLCs with EGFR 19/21. Patients receive L 240mg PO daily, plus 21-day cycles of P 500mg/m^2 IV on Day 1, plus A: 1400mg IV (1750mg if body weight >=80Kg) once weekly in cycle 1; 1400mg IV (1750mg if body weight >=80Kg) on Day 1 in cycle 2; 1750mg IV (2100mg if body weight >=80Kg) at Day 1 from cycle 3 onwards. The primary endpoint is 18-month PFS (18m-PFS), estimated by the Kaplan-Meier method. A one group chi-square test with a type I error of 0.1 (one-sided) will have 80% power to detect the difference between the null hypothesis (18m-PFS of 50%, achieved with osi alone) and the alternative hypothesis (18m-PFS of 65%) with a sample size of 49. AMIGO-1 trial was opened to recruitment in May 2023 in research centers in Brazil. Clinical trial information: NCT05299125. This trial in progress is the first to assess the triplet regimen of lazertinib, amivantamab, and pemetrexed as first-line treatment for (NSCLCs) with EGFR mutations and will provide benchmark results to be contrasted with the present standard of care and future treatment combinations that are currently undergoing evaluation in phase 3 trials (eg. FLAURA2, MARIPOSA).

Clinical trial identification: NCT05299125.

Legal entity responsible for the study: Latin American Cooperative Oncology Group (LACOG).

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1507TiP Phase Ib multicenter study of trastuzumab deruxtecan (T-DXd) and immunotherapy with or without chemotherapy in first-line treatment of patients (pts) with advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) and HER2 overexpression (OE): DESTINY-Lung03

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Background: T-DXd is a HER2-directed antibody-drug conjugate available for the treatment of pts with metastatic NSCLC with activating *HER2* mutations, HER2+ breast or gastric cancer, or HER2-low breast cancer. DESTINY-Lung01 showed efficacy of T-DXd monotherapy in heavily pretreated pts with unresectable/metastatic, HER2-OE, nonsquamous NSCLC. In preclinical studies, the combination of T-DXd and immunotherapy was more effective than either therapy alone, and the addition of chemotherapy may improve efficacy. This trial is evaluating T-DXd alone or in combination with durvalumab (durva) or MEDI5752 (a PD-1/CTLA-4 bispecific antibody) with or without chemotherapy in pts with unresectable/metastatic, HER2-OE, nonsquamous NSCLC.

Trial design: DESTINY-Lung03 (NCT04686305) is a phase 1b, open-label, multicenter, dose-escalation and -expansion study in pts with HER2-OE unresectable, locally advanced or metastatic, nonsquamous NSCLC. In part 1 (enrollment completed), pts with disease progression after 1 or 2 lines of systemic therapy in the recurrent/metastatic setting receive T-DXd monotherapy or T-DXd + durva in combination with cisplatin, carboplatin, or pemetrexed. Part 2 of the trial was not initiated. In part 3, pts who have not received prior treatment for advanced or metastatic disease will receive T-DXd in combination with MEDI5752, with or without carboplatin; pts in this phase must not have a history of prior immunotherapy for early disease and must lack activating *EGFR* mutations, an *EML4-ALK* fusion, or other targetable alterations. The primary endpoint is the frequency of adverse events (AEs) and serious AEs (SAEs) with T-DXd + durva + chemotherapy (part 1) or T-DXd + MEDI5752 ± chemotherapy (part 3). Secondary endpoints include confirmed objective response rate, duration of response, disease control rate, progression-free and overall survival, pharmacokinetics, and immunogenicity in all arms as well as the frequency of AEs and SAEs with T-DXd monotherapy (part 1).

Clinical trial identification: NCT04686305.

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1508TiP The 1920-EORTC-BIORADON study: Molecular characterization of non-small cell lung cancer (NSCLC) and indoor radon exposure in Europe

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Background: Lung cancer is the leading cause of cancer death worldwide. Radon is a radioactive gas tending to accumulate inside homes and it is considered one of the leading causes of lung cancer in non-smokers. The 2013/59 EURATOM directive regulates indoor radon in Europe, however regulating measures vary between countries. Radon emits alpha-ionizing radiation linked to a wide variety of cytotoxic/genotoxic effects; but the radon-associated molecular profile has never been described. Driver oncogenic alterations have been identified in non-small lung cancer (NSCLC), such as mutations (EGFR, ERBB2, BRAF, MET, etc.) or chromosomal fusions (ALK, ROS1, etc.), mainly in non-smokers, with no clear risk factor identified. Preliminary data suggest an association between radon and driver alterations in NSCLC. BIORADON's primary objective is to study the correlation of molecular profiles of NSCLC in patients with indoor radon concentration with special focus on drivers.

Trial design: This is a prospective observational study of 975 patients with all-stages NSCLC. Patients with current/previous history of NSCLC (survivors up to 5 years) will be enrolled in 30 centers from 5 European countries (Spain, France, Portugal, Belgium, Italy). Participants must have been living in the current home for $\geq$2 years before the diagnosis and molecular profile must have been previously performed in routine care to classify patients in 3 cohorts (each cohort n=325): A: driver-mutation group; B: driver-fusion group and C: control group. Patients will receive two alpha-track detectors to measure radon at their home for $\geq$ 3 months and complete a questionnaire, including demographics, home characteristics, smoking/environmental/occupational exposure. After measurement, the detectors will be sent to a central laboratory for analysis. A blood sample is collected and archived FFPE specimen is optional for additional research. All clinical data are electronically collected. Secondary objectives are the correlation of clinical/pathological profiles with radon +/- other risk factors. The duration of the study is 3 years (since 04/22) and enrolment period is estimated to be 18 months. This study is part of the RADONORM Consortium.

Legal entity responsible for the study: European Organisation for Research and Treatment of Cancer Research and Treatment of Cancer (EORTC).

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1509TiP The 1825-EORTC, ALKALINE: Activity of lorlatinib based on ALK resistance mutations on blood in ALK positive NSCLC patients previously treated with second generation ALK inhibitor

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Background: Optimal therapeutic sequence has not yet been established in patients with *ALK* positive advanced non-small cell lung cancer (aNSCLC) developing *ALK* resistant mutations after treatment with 1st/2nd generation(gen.) ALK inhibitors (ALKi). Treatment selection based on *ALK* resistance mutations may be a strategic approach for the decision-making process as each ALKi has a different spectrum of coverage of *ALK* mutations. Liquid biopsy (ctDNA) can provide a non-invasive option to identify resistant mechanisms. Lorlatinib is a 3rd gen. ALKi that overcome *ALK* dependent resistance and being active against multiple *ALK* mutations that confer resistance to other inhibitors. ALKALINE aims to assess the activity of lorlatinib based on the presence of ALK mutations identified on ctDNA in patients progressing on 2nd gen. ALKi. A preselection sub-study will assess the time of emergence of resistance mutations in blood in patients under treatment with 2nd gen. ALKis.

Trial design: ALKALINE is a phase II, open-label, multicenter, single-arm study in 84 pts with *ALK+* aNSCLC progressing on 2nd gen. ALK TKI. ctDNA is performed before lorlatinib to stratify pts in 3 cohorts: A: if $\geq$ 1 ctDNA *ALK* mutations, B: non-*ALK* mutations and C: no ctDNA detected. Eligible patients receive lorlatinib until disease progression (PD), unacceptable toxicity or occurrence of any withdrawal criterion. Lorlatinib beyond PD is allowed if clinical benefit. Imaging, including brain MRI and ctDNA are performed every 2 months until week 40 and then 3 monthly. A prospective sub-study will assess the time to emergence of resistance mutations and its impact on outcomes in patient on treatment with 2nd gen. ALKi. ctDNA is collected 3 monthly until PD to 2nd gen. ALK inh. (RECIST v.1.1). Pts in the sub-study will enter the main study during PD based on RECIST v1.1. Primary endpoint is progression-free survival rate at 12 months in cohort A as assessed by Blinded Independent Central Review based on RECIST v1.1. Secondary objectives will evaluate activity in cohorts B and C, toxicity and patient reported outcomes. The estimated duration of the ALKALINE is 72 months, with an enrolment period of 42 months.

Clinical trial identification: EudraCT: 2019-003862-41; EU: 2022-502449-82-00; NCT04127110.

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1510TiP Efficacy study of osimertinib in treatment-naïve patients with EGFR mutant non-small cell lung cancer (NSCLC) according to TP53 mutational status (TEMPLE-2/ NCT05785208)

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Background: Osimertinib (Osi) is the standard first-line therapy for patients (pts) with advanced NSCLC harbouring common Epidermal Growth Factor Receptor (EGFR) mutations. Not all pts achieve durable benefit during treatment developing early resistance. Increasing evidence suggest a potential implication of Tumor Protein 53 (TP53) in the biological mechanisms underlying resistance to Tyrosine Kinase Inhibitors (TKIs). Our previous study on EGFR+ advanced NSCLC pts receiving first-line gefitinib showed that additional coexisting mutations (ACM) significantly decrease the efficacy of TKIs and, among them, TP53 mutations were exclusively documented in poor/intermediate responders than in good, supporting the potential role of this gene in influencing the response to anti-EGFR agents. These data highlight the need of applying more informative and comprehensive techniques for molecular analysis and treatment monitoring to implement the prediction of the awaited TKIs efficacy, identify pts who will not benefit from TKIs and ideally build for them a rational polytherapy strategy.

Trial design: TEMPLE-2 (NCT05785208) is a prospective, biomarker-driven, multicenter, open-label, clinical trial to evaluate the efficacy of Osi in treatment-naïve patients affected by EGFR+ NSCLC according to TP53 mutational status. Inclusion criteria are: age >18 years, histologically confirmed diagnosis of EGFR+ NSCLC, available tumor tissue sample. The study consists of a screening phase to assess eligibility; a treatment phase in which pts will receive Osi at standard dose of 80 mg daily and a follow-up phase to monitor survival status and subsequent therapies. A population of 122 enrolled pts is expected, 61 TP51-wilde type and 61 TP-53 mutant. Primary endpoint is Progression Free Survival (PFS) according to TP53 mutational status; key secondary endpoints are Overall Survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR), Time to Central Nervous System (CNS) Progression, CNS ORR and Safety. Concomitant genomic alterations will be evaluated in tissue and blood at baseline and progression; ctDNA will be monitored during treatment. Enrollment is ongoing.

Clinical trial identification: NCT05785208.

Legal entity responsible for the study: Fondazione Policlinico Universitario Agostino Gemelli IRCCS.

Funding: AstraZeneca.

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OESOPHAGOGASTRIC CANCER

1511O Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Survival results from the phase III, randomized, double-blind, placebo-controlled KEYNOTE-811 study

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Background: In a previous analysis of the phase III KEYNOTE-811 study, pembrolizumab (pembro)/trastuzumab and chemotherapy (chemo) vs placebo (pbo)/trastuzumab and chemo provided an ORR of 74% vs 52% in the first 264 pts. These data led to FDA approval of first-line pembro/trastuzumab and chemo for HER2+ mG/GEJ adenocarcinoma. We present results of a prespecified interim analysis of PFS.

Methods: Eligible patients (pts) aged ≥18 years with treatment-naive unresectable, HER2+ mG/GEJ adenocarcinoma irrespective of PD-L1 status were randomized 1:1 to pembro 200 mg IV Q3W or pbo IV Q3W plus chemo (5-FU and cisplatin [FP] or capecitabine and oxaliplatin [CAPOX] and trastuzumab [SOC]). Randomization was stratified by region, PD-L1 status, and chemo choice. Treatment continued for ≤2 years or until disease progression or intolerable toxicity. Dual primary end points were PFS (RECIST v1.1, BICR) or OS. Data cut-off for this interim analysis was May 25, 2022. Per the DSMC, OS assessment is ongoing.

Results: At data cut-off, 698 pts were randomized (350 to pembro + SOC; 348 to pbo + SOC). Median follow-up was 28.4 mo. In all pts, pembro + SOC vs pbo + SOC significantly improved PFS (median 10.0 vs 8.1 mo; HR 0.72; 95% CI 0.60-0.87; p=0.0002). In pts with PD-L1 CPS ≥1, median PFS was 10.8 vs 7.2 mo (HR 0.70; 95% CI, 0.58-0.85). 24-mo PFS rates were 27% vs 13%. At data cut-off, 75% of required OS events had occurred. OS follow-up is ongoing. ORR was 72.6% vs 59.8% with pembro + SOC vs pbo + SOC (73.2% vs 58.4% [PD-L1 CPS ≥1]); median (range) DOR was 11.2 mo (1.1+ to 40.1+) vs 9.0 mo (1.4+ to 38.3+). Approximately 31% vs 19% of responders had a response duration ≥24 mo. Grade ≥3 drug-related AE rates were 58% vs 51%. Grade 5 drug-related AEs occurred in 4 (1.1%) vs 3 (0.9%) pts, respectively.

Conclusions: First-line pembro plus trastuzumab and chemo provided superior PFS, and improved ORR with durable responses vs pbo plus trastuzumab and chemo in pts with unresectable, HER2+ mG/GEJ adenocarcinoma, notably in pts with PD-L1 CPS ≥1. These efficacy and safety data continue to support use of this regimen in the first-line setting.

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1512MO Perioperative camrelizumab (C) combined with rivoceranib (R) and chemotherapy (chemo) versus chemo for locally advanced resectable gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The first interim analysis of a randomized, phase III trial (DRAGON IV)

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Background: The efficacy of standard perioperative chemotherapy for patients (pts) with localized resectable G/GEJ cancer still needs to be further improved. This ongoing multicentred, randomized, open-label, phase III study compared efficacy and safety of perioperative C plus R and chemo (SOXRC) versus chemo alone (SOX) in localized resectable G/GEJ adenocarcinoma.

Methods: Pts with T3-4aN$^+$M0 were randomized 1:1 to SOXRC (C 200 mg IV D1 + R 250 mg PO QD D1-21 + oxaliplatin 130 mg/m^2 IV D1 + S-1 PO BID D1-14, Q3W) or SOX for 3 cycles pre/post D2 surgery, then R plus C (SOXRC) or S-1 (SOX) up to 17 cycles per investigator's choice. Stratification was by tumour location (GEJ vs G) and bulky N (yes vs no). Blinded independent review committee (BIRC) assessed pathological complete response (pCR, ypT0) and investigators assessed EFS were primary endpoints. The secondary endpoints were major pathological response (MPR), total pCR (ypT0N0), R0 resection, DFS and OS. The planned sample size was 512 pts. The main analysis of pCR would be conducted after the first 360 randomized pts had the opportunity for D2 surgery.

Results: Of the first 360 randomized pts (SOXRC n=180; SOX n=180), 71.4% had gastric cancer and 28.6% had GEJ cancer; 66.7% had T4 and 100% had N$^+$ with balanced baseline between arms. 179 pts received neoadjuvant therapy, 164 completed all neoadjuvant therapy and 155 underwent surgery (SOXRC); 177, 169 and 156 did the same (SOX). In the ITT population, BIRC-assessed pCR was 18.3% (95% CI 13.0-24.8) for SOXRC and 5.0% (95% CI 2.3-9.3) for SOX, with a statistically significant improvement of 13.7% (95% CI 7.2-20.1, $p<0.0001$); MPR was 51.1% vs 37.8%; tpCR was 16.7% vs 4.4%. In the surgery set, R0 resection was 98.7% (SOXRC) vs 94.2% (SOX). Surgical complications occurred at rates of 27.7% (SOXRC) and 30.1% (SOX). Preoperative grade $\geq$3 treatment-emergent adverse events occurred at rates of 36.3% (SOXRC) and 16.3% (SOX).

Conclusions: The trial showed perioperative C combined with R and chemo significantly improved pCR compared to chemo alone with a tolerable safety profile for localized resectable G/GEJ adenocarcinoma.

Clinical trial identification: NCT04208347.

Legal entity responsible for the study: Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

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1513MO A phase II study of nivolumab plus low dose ipilimumab as first -line therapy in patients with advanced gastric or esophago-gastric junction MSI-H tumor: First results of the NO LIMIT study (WJOG13320G/CA209-7W7)

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Background: Microsatellite instability-high (MSI-H) is an established biomarker for response to immune checkpoint inhibitors. Herein, we report the efficacy and safety of nivolumab plus low-dose ipilimumab as first-line therapy in MSI-H advanced gastric or esophagogastric junction cancer (GC) patients from the phase II study.

Methods: Eligible patients were unresectable advanced, recurrent, or metastatic GC with a histologically confirmed diagnosis of adenocarcinoma; confirmed MSI-H status with the MSI-IVD Kit (FALCO); no prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease. Nivolumab (240 mg) biweekly and ipilimumab (1 mg/kg) every six weeks were given until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) assessed by a blinded independent central review (BICR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety.

Results: Between November 2020 and Aug 2022, 29 patients were enrolled from 935 screened cases. The median age was 75 (range 54-84), and 44.8% of patients were male. At the data cut-off (December 12, 2022), 3 and 15 patients achieved confirmed complete and partial responses with ORR of 62.1% (95% CI: 42.3-79.3). The DCR was 79.3% (95% CI, 60.3-92.0). With the median follow-up of 9.0 months (range, 4.0-18.0), the median PFS was 13.8 (95% CI, 13.7-NR) months, and median DOR and OS were not reached yet. 12-month PFS and OS rates yielded 73% (95% CI, 52-86) and 80% (95% CI, 57-91), respectively. The most common reason for treatment discontinuation was adverse events. The safety profile was consistent with the known profiles of nivolumab plus low dose ipilimumab, and there were no unexpected safety signals. Treatment-related death was not observed.

Conclusions: The chemo-free strategy with a combination of nivolumab and low-dose ipilimumab demonstrated high and robust efficacy with good tolerability in MSI-H GC patients.

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1514P Randomized, global, phase III study of tislelizumab (TIS) + chemotherapy (chemo) vs placebo (PBO) + chemo as first-line (1L) treatment for advanced/metastatic esophageal squamous cell carcinoma (ESCC): RATIONALE-306 update

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Background: At interim analysis (IA) of RATIONALE-306 (NCT03783442), 1L TIS + chemo demonstrated a statistically significant, clinically meaningful improvement in overall survival (OS) vs PBO + chemo, with a manageable safety profile, in patients (pts) with advanced/metastatic ESCC. Here, we report updated efficacy and safety data with minimum (min) 2 years' follow-up.

Methods: Adults with unresectable locally advanced recurrent/metastatic ESCC and no prior systemic treatment for advanced disease were enrolled and randomized (1:1; stratified by region, prior definitive therapy, and investigator [INV]-chosen chemo) to receive TIS 200 mg (Arm A) or PBO (Arm B) IV Q3W + chemo (platinum + fluoropyrimidine or platinum + paclitaxel), until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS in the intent-to-treat population. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DoR) per INV, and safety.

Results: 649 pts were randomized (Arm A n=326, Arm B n=323). At data cutoff (Dec 31, 2022), min study follow-up was 25.2 months; improvements in OS, PFS, ORR, and DoR in Arm A vs B (Table) were maintained relative to the IA. Similar to the IA, incidences of any-grade (96.6% vs 96.3%) or ≥grade 3 (66.7% vs 64.5%) treatment-related adverse events (TRAEs) were comparable between Arms A and B, respectively; treatment-emergent adverse events leading to treatment discontinuation were higher in Arm A (31.8%) vs B (22.1%). In Arm A vs B, respectively, serious TRAEs occurred in 29.3% vs 19.6% of pts; TRAEs leading to death occurred in 1.9% and 1.2%.

Table: 1514P

	Arm A: TIS + chemo (n=326)	Arm B: PBO + chemo (n=323)
mOS, mo (95% CI) HR (95% CI)	17.2 (15.8, 20.1) 0.67 (0.56, 0.80)	10.6 (9.3, 12.1)

Continued

Table: 1514P Continued

	Arm A: TIS + chemo (n=326)	Arm B: PBO + chemo (n=323)
24-mo OS, % (95% CI)	37.9 (32.5, 43.2)	25.0 (20.2, 30.0)
mPFS, mo (95% CI)[a] HR (95% CI)	7.3 (6.9, 8.3) 0.61 (0.51, 0.73)	5.6 (4.9, 6.0)
24-mo PFS, % (95% CI)	18.1 (13.6, 23.1)	7.2 (4.4, 11.0)
ORR, % (95% CI)[a]	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
mDoR, mo (95% CI)[a]	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
24-mo DoR, % (95% CI)	19.6 (13.9, 25.9)	10.1 (5.0, 17.1)

[a]Per INV. CI, confidence interval; HR, hazard ratio; m, median; mo, months.

Conclusions: After min 2 years' follow-up, 1L TIS + chemo continued to demonstrate clinically meaningful improvements in OS and PFS and durable tumour response benefit vs PBO + chemo in pts with advanced/metastatic ESCC, with no new safety signals.

Clinical trial identification: NCT03783442.

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1515P Maintenance rucaparib after first-line platinum-based chemotherapy in advanced esophagogastric (OG) adenocarcinoma: Interim results from the PLATFORM trial

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Background: PLATFORM is a prospective, open-label, multi-centre, adaptive phase II trial assessing maintenance therapy in patients (pts) with OG adenocarcinoma after platinum-based first-line induction chemotherapy. HER2 -negative pts were randomised 1:1 to surveillance or rucaparib.

Methods: After 18 weeks of platinum-based chemotherapy, pts with response or stable disease were randomised, stratified by performance status, region, and disease extent. Pts in the control arm had 4- weekly surveillance visits vs. receiving rucaparib 600mg twice daily every 28 days to progression, death, or toxicity. Interim analysis target accrual of 61 pts was met, the futility endpoint was 12-week progression free rate (PFR). We also report progression-free survival (PFS) from randomisation to progression or death (pre-specified p-value of 0.025) and toxicity.

Results: 125 pts were randomised to the control arm and rucaparib. At data cut-off (28 April 2023) median follow up was 41 months (mo). 59 control and 62 rucaparib pts were evaluable for 12-week PFR; 36% in the control arm and 55% in the rucaparib arm had stable disease (Odds Ratio 2.2, 97.5% CI 1.0-5.1, p = 0.035). 39% of all pts had measurable disease at baseline and no responses were seen in either arm.

Median PFS was 2.8 mo in the control arm vs. 4.2 mo in the rucaparib arm (HR 0.70, 97.5% CI 0.46 − 1.08, p = 0.063). The 6 mo PFS rate was 20.4% (97.5% CI 9.9 - 33.5) in the control arm vs. 29.5% (97.5% CI 17.4 − 42.8) in the rucaparib arm but there was no difference in median survival (HR 1.15, 97.5% CI 0.73 − 1.82, p = 0.495). Grade ≥3 treatment related adverse events was 19% in the rucaparib arm and no new safety signals identified.

Conclusions: Interim results showed prolonged disease control in pts receiving maintenance rucaparib after first-line platinum-based chemotherapy. Translational biomarker analysis including homologous recombination deficiency testing may identify a subgroup of pts that could derive additional benefit from maintenance rucaparib.

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1516P Health-related quality of life (hrqol) analysis from KEYNOTE-859: First-line (1L) pembrolizumab (pembro) + chemotherapy (chemo) for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

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Background: In the phase III KEYNOTE-859 study (NCT03675737), 1L pembro + chemo significantly improved OS, PFS, and ORR vs placebo (pbo) + chemo regardless of PD-L1 expression and had a manageable AE profile in patients (pts) with locally advanced/metastatic HER2-negative G/GEJ adenocarcinoma. Prespecified exploratory HRQoL outcomes are reported.

Methods: HRQoL was assessed in treated pts who completed ≥1 HRQoL assessment using the EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L questionnaires. Least squares mean (LSM) changes from baseline (BL) to wk 18 in QLQ-C30 GHS/QoL; physical functioning (PF) and role functioning (RF) subscales; nausea/vomiting and appetite loss symptoms scales; QLQ-STO22 pain symptom scale; and EQ-5D-5L VAS were compared using a constrained longitudinal data analysis model (covariates: Tx by study visit interaction and stratification factors). Time to deterioration (TTD; ≥10-point decline from BL in a given scale/subscale) was estimated using the Kaplan-Meier method; between-arm difference (HR) was determined using a stratified Cox proportional hazards model.

Results: The latest timepoint at which the predefined rates of completion (≥60%) and compliance (≥80%) were met was wk 18. From BL to wk 18, LSM changes in QLQ-C30 GHS/QoL, PF, RF, nausea/vomiting, and appetite loss and EQ-5D-5L VAS were similar between arms; the QLQ-STO22 pain scale favored pembro + chemo (Table). TTD (HR; 95% CI) in QLQ-C30 GHS/QoL (0.87; 0.72-1.04), PF (0.91; 0.76-1.08), RF (0.90; 0.76-1.06), appetite loss (1.00; 0.82-1.22), and nausea/vomiting (0.95; 0.79-1.14) were similar between arms; the QLQ-STO22 pain scale favored pembro + chemo (0.76; 0.58-0.98).

Table: 1516P

	Change from BL to wk 18, LSM (95% CI)		Difference in LSM change from BL to wk 18 (95% CI)
	Pembro + chemo	Pbo + chemo	
EORTC QLQ-C30	**n = 771**	**n = 771**	N/A
GHS/QoL	0.40 (-1.37 to 2.18)	-0.85 (-2.62 to 0.93)	1.25 (-1.07 to 3.58)
PF	-5.87 (-7.53 to -4.22)	-7.53 (-9.18 to -5.88)	1.65 (-0.64 to 3.94)
RF	-5.41 (-7.59 to -3.22)	-7.97 (-10.15 to -5.79)	2.57 (-0.38 to 5.52)
Nausea/ vomiting	1.06 (-0.75 to 2.87)	1.36 (-0.45 to 3.16)	-0.30 (-2.67 to 2.07)
Appetite loss	-3.43 (-6.10 to -0.76)	-4.85 (-7.51 to -2.19)	1.42 (-1.93 to 4.77)
EORTC QLQ-STO22 pain	**n = 754** -8.21 (-9.91 to -6.51)	**n = 752** -5.64 (-7.34 to -3.94)	-2.57 (-4.72 to -0.41)
EQ-5D-5L VAS	**n = 771** -0.69 (-2.12 to 0.73)	**n = 771** -1.91 (-3.33 to -0.49)	1.22 (-0.65 to 3.08)

Conclusions: HRQoL data from KEYNOTE-859, combined with efficacy and safety results, support a favorable benefit-to-risk profile for pembro + chemo as a new 1L Tx option for advanced HER2-negative G/GEJ adenocarcinoma.

Clinical trial identification: NCT03675737.

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1517P Patient-related outcomes (PROs) after early palliative care (PC) (EPC) compared with standard oncologic care (SOC) for patients (pts) with metastatic upper gastrointestinal cancers (mUGIC): Results of the randomised EPIC trial

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Background: Beyond the report of an improvement in quality of life with EPC in pts with lung cancers, Temel et al. (NEJM 2010) also claimed for a survival benefit observed as a secondary endpoint. This prompted us to address the overall survival (OS) benefit of EPC within the EPIC trial dedicated to mUGIC pts.

Methods: EPIC is a randomised (1:1), open-label, phase III trial aimed to estimate OS of EPC compared to SOC for ECOG-PS $\leq$ 2 pts with mUGIC. Other objectives were PROs (quality of life [QoL, EORTC QLQ-C30], time until definitive deterioration [TUDD] of QoL, depression and anxiety scores [HADS], number of pts receiving chemotherapy in their last 30 days of life, and the presence or absence of advanced directives in pt files. With the following hypotheses: 1- year OS (40% vs. 50.3%, HR=0.75), 2-sided alpha=5%, beta=20%, 381 deaths were required, leading to include 480 pts. Pts were stratified according to centre, ECOG-PS (0-1 vs. 2) and tumor location.

Results: Modified Intent To Treat population was 470 pts, from the 473 pts randomized from 10/2016 to 12/2021 in 19 French centers. Main pts characteristics were: median age= 67.5; 273/470 males; tumour site: oesophagus 39, HER2-negative esogastric 48, pancreas 297, biliary tree 86; ECOG-PS 0/1/2: 104/278/88. The mean number of PC visits was 4.7 and 0.6 in the EPC and SOC group, respectively. Median follow-up was 46m. OS data has already been reported at ASCO-2023. Overall, all dimensions of QoL remained stable along the study course, without any difference between arms. TUDD analysis did not show any difference between treatment arms for any of the QoL dimensions. Anxiety and depressions scores varied over time similarly in both arms. Respectively in EPC and SOC arms, 33% and 28% pts received chemotherapy in their last month of life; 17% and 11% had advanced directive written.

Conclusions: EPC did not improve QoL, anxiety and depression scores versus SOC in mUGIC pts. Whether these unexpected findings are related to our study population, to our study design (including content or number of EPC we provided), or to real facts remains to be determined.

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1518P Zanidatamab (zani) plus chemotherapy (chemo) and tislelizumab (tis) as first-line (1l) therapy for patients (pts) with advanced HER2-positive (+) gastric/gastroesophageal junction adenocarcinoma (GC/GEJC): Updated results from a phase Ib/II study

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Background: Zani, an anti-HER2 bispecific antibody, targets two distinct extracellular domains of HER2 and has shown preliminary antitumor activity and tolerability, with chemo, in pts with HER2+ GC/GEJC. These are updated results from the phase Ib/II study (NCT04276493) for zani plus chemo and TIS, an anti-PD-1 monoclonal antibody. Duration of response is reported for the first time.

Methods: Cohort 2 of this open-label study included pts with untreated, unresectable, locally advanced/metastatic HER2+ GC/GEJC. Cohort 2a received zani 30 mg/kg intravenously (IV), Cohort 2b received zani 1800 mg IV (weight <70 kg) or 2400 mg IV (weight $\geq$70 kg), each with TIS 200 mg IV every 3 weeks. Both cohorts also received standard capecitabine-oxaliplatin (CAPOX). Primary endpoints were safety and investigator (INV)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included INV-assessed progression-free survival (PFS), duration of response, and disease control rate.

Results: As of 22 Nov 2022, 33 pts (median age 64 years [range: 29-80]) were assigned to Cohort 2a (n=19) or 2b (n=14). Overall, 13 (39.4%) pts remained on treatment. Confirmed ORR was 75.8% (95% CI: 57.7, 88.9); median PFS was 16.7 months (95% CI: 8.2, NE). Efficacy data are presented in the table. All pts had $\geq$1 treatment-related adverse event (TRAE), and 22 (66.7%) had grade $\geq$3 TRAEs. Serious TRAEs occurred in 11 (33.3%) pts; TRAEs leading to treatment discontinuation occurred in two (6.1%) pts; and TRAEs leading to death occurred in two (6.1%) pts.

Table: 1518P

	Cohort 2a (n=19)	Cohort 2b (n=14)	Overall (N=33)
Median follow-up, months	19.1	18.0	18.2
Best overall response[a], n (%)			
Complete response	1 (5.3)	0 (0.0)	1 (3.0)
Partial response	14 (73.7)	10 (71.4)	24 (72.7)
Stable disease	4 (21.1)	4 (28.6)	8 (24.2)
ORR[a], n (%) (95% CI)	15 (78.9) (54.4, 93.9)	10 (71.4) (41.9, 91.6)	25 (75.8) (57.7, 88.9)
DCR[a], n (%) (95% CI)	19 (100.0) (82.4, 100.0)	14 (100.0) (76.8, 100.0)	33 (100.0) (89.4, 100.0)
Median DoR, months (95% CI)	15.4 (4.9, NE)	NE (7.4, NE)	22.8 (7.4, NE)
Median PFS, months (95% CI)	8.3 (5.6, NE)	NE (8.8, NE)	16.7 (8.2, NE)

[a]Confirmed. DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

Conclusions: Zani plus TIS and CAPOX produced durable, promising antitumor activity with encouraging PFS as 1L therapy for pts with HER2+ GC/GEJC. Safety was

consistent with previous findings. A phase III trial (NCT05152147) evaluating this regimen is ongoing.

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1519P Fruquintinib plus sintilimab in patients (pts) with either treatment-naïve or previously treated advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Results from a multicenter, single-arm phase II study

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Background: Fruquintinib (F, a highly selective VEGFR inhibitor) plus sintilimab (S, an anti-PD-1 monoclonal antibody) showed promising antitumor activity in both preclinical and clinical studies. Here, we reported the results of F plus S from a gastric cancer (GC) cohort in an open-label, multicenter, single-arm phase II study in China.

Methods: Advanced gastric or GEJ adenocarcinoma pts with PD-L1 status of CPS $\geq$1, who had no prior systemic therapy or had failed at least first-line treatment were enrolled. Eligible pts received F (5 mg, 2 weeks on/1 week off, orally, once daily) plus S (200 mg, IV, every 3 weeks) in 21-day cycles, until disease progression or unacceptable toxicity. Treatment of S was allowed for up to 24 months (mo). The primary endpoint was ORR per RECIST v1.1.

Results: As of February 28, 2023, 27 pts were enrolled and received F plus S, including 20 treatment-naive pts (i.e.: 1st -line pts), and 7 pts with prior treatment (i.e.: $\geq$ 2nd-line pts). Median (range) age was 63.71 (35.8, 74.6) years. There were 8 (29.6%), 9 (33.3%), and 8 (29.6%) pts with PD-L1 status of 1$\leq$ CPS $<$5, 5$\leq$ CPS$<$10, and 10$\leq$ CPS, which was tested by the central lab, respectively. Median duration of treatment of F and S were 6.90 and 7.13 months. Among tumor evaluable pts (N=18 for 1st -line pts, N=6 for $\geq$ 2nd-line pts), confirmed ORRs were 72.2% and 33.3% in 1st -line pts and $\geq$ 2nd-line pts, respectively; clinical responses correlated with level of PD-L1 status. DCRs were 100% and 83.3% in 1st -line pts and $\geq$ 2nd-line pts; median TTR reached 2.7 mo and 2 mo in 1st -line pts and $\geq$ 2nd-line pts. 9-month PFS rates were 63.8% and 50.0% in 1st -line pts and $\geq$ 2nd-line pts. Median PFS and OS were not mature. Common ($\geq$20%) treatment-related treatment-emergent adverse events included proteinuria (48.1%), hypothyroidism (40.7%), aspartate aminotransferase increased (25.9%), alanine aminotransferase increased (22.2%), hypertension (22.2%), and weight decreased (22.2%).

Conclusions: F plus S provided favourable efficacy and manageable toxicity profile in pts with advanced gastric or GEJ adenocarcinoma, especially for pts who cannot tolerate chemotherapy.

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1520P Perioperative treatment in resectable gastric cancer with spartalizumab combined with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT): The GASPAR phase II trial

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Background: Perioperative chemotherapy with FLOT is a standard of care for patients (pts) with resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma, despite a still poor prognosis. This trial evaluates the anti—PD-1 antibody spartalizumab combined to FLOT as perioperative treatment (tt) for resectable pts.

Methods: GASPAR trial is a multicenter, single arm, phase II trial. Pts with untreated localized gastric or GEJ adenocarcinoma considered resectable ($\geq$ cT2 or cN+) were enrolled. Pts received 4 pre- and post-operative cycles of FLOT (Docetaxel 50 mg/m^2, oxaliplatine 85 mg/m^2, leucovorin 200 mg/m^2 and fluorouracile 2600 mg/m^2 24h infusion, q2w) and 2 pre- and post-operative cycles of spartalizumab (fixed dose of 400 mg, q4w). The main endpoint was the rate of pathological complete regression (pCR) assessed using Becker criteria.

Results: In total, 68 pts were included: men (78%), median age 63 yrs [range 31-79], cT3/T4 51%, GEJ 60%, cN+ 18/48 pts. Among 67 pts who started the tt, 64 (96%) received 2 pre-operative cycles of spartalizumab, the 3 others received 1 cycle due to toxicity. Similarly, 64 (96%) pts completed the 4 pre-cycles of FLOT, 1 discontinued after 2 cycles (toxicity), the 2 others received 3 cycles (pt decision). FLOT administration was delayed for 13 pts (19%) due to toxicity, and 26 pts (39%) observed dose reduction. Surgery, performed in 65 pts (97%) within 38 days from the end of preoperative tt in median [range 23-67], was R0 for 62 pts (95%). Among 64 pts assessable for efficacy, pCR was observed for 20 pts (31%), and sub-total regression ($<$10% residual tumor) for 12 pts (19%), meaning a major response rate of 50%. After a median follow-up of 6.9 months, 8 pts are still under adjuvant tt. No toxic death, nor spartalizumab-related grade (G) 4 adverse events (AEs) were observed. 5 pts developed G3 immune-mediated AEs: pancreatitis (2), hepatitis, enterocolitis and encephalitis. 15 pts (23%) experienced post-surgery G3/4 complications.

Conclusions: Spartalizumab combined with FLOT shows high efficacy as perioperative tt in pts with resectable gastric or GEJ adenocarcinoma with a high rate of pathological complete regression and an acceptable safety profile.

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1521P Addition of durvalumab to CROSS in oesophageal adenocarcinoma is feasible and safe

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Background: Anti-PD-(L)1 is effective in esophago-gastric adenocarcinoma (EGA) and appears synergistic with chemoradiotherapy (CRT). The RICE trial aims to evaluate safety, feasibility and efficacy of addition of neoadjuvant durvalumab and adjuvant durvalumab ± tremelimumab to standard CRT.

Methods: In this open-label, randomized phase-2 trial, pts with locally advanced (≥uT3/Nx or uT2/N+) non-metastatic EGA (including EGJ-I and EGJ-II) receive two doses of neoadjuvant durvalumab (1500mg) in addition to CRT according to the CROSS protocol. After a safety-run in of 6 pts, adjuvant therapy was randomized 1:1 to 12 doses of durvalumab monotherapy or 12 doses of durvalumab (1500mg/4w) plus a single dose of adjuvant tremelimumab (300mg d1 of adjuvant treatment). Here we report the results from the neoadjuvant part of the trial including the primary endpoints for safety and efficacy and extensive translational immune monitoring.

Results: In the modified intention to treat analyses 95% (53/56) of pts completed neoadjuvant therapy and 93% (52/56) underwent resection (3 excluded due to peritoneal carcinomatosis, 1 to intraoperatively identified cirrhosis; R0 in all pts), which was not lower than 90.4% as predefined benchmark for feasibility. Regarding the primary endpoints for safety, the rate of anastomotic leakage was 6% (3/52) and significantly lower than the predefined threshold of 22% ($p<0.05$), while the rate of grade 3/4 toxicity exceeded the predefined threshold of 13% (25%, 13/56 G3, 1/56 G4). Clinicopathological evaluation of response revealed 5% (3/56) peritoneal carcinomatosis, 39% (22/56) minor response (>10% vital tumor), 30% (17/56) major response (<10%), 23% (13/56) complete response and 2% not evaluable (1/56, cirrhosis).The primary endpoint for efficacy (35% CR) was not reached, but at least <10% residual tumour was achieved in 53%, which was higher than in patients treated with CROSS during the same period at the same center (38.6%; 56/145; $p<0.05$). Patterns of response and resistance from translational analyses will be presented as well.

Conclusions: The first analyses of the RICE trial demonstrate safety and feasibility of addition of neoadjuvant immunotherapy with durvalumab to CROSS.

Clinical trial identification: NCT04159974.

Legal entity responsible for the study: University of Cologne.

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1522P Camrelizumab plus chemotherapy versus concurrent chemoradiotherapy as neoadjuvant therapy for resectable thoracic oesophageal squamous cell cancer (REVO): A multicenter, randomized, open-label, phase II trial

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Background: Preoperative chemoradiotherapy (CRT) is the current standard treatment for locally advanced oesophageal cancer in the world. In previous single-arm clinical trials, neoadjuvant camrelizumab (anti-PD-1 antibody) plus chemotherapy showed durable antitumor activity with a manageable safety profile in patients with locally advanced oesophageal squamous cell carcinoma (ESCC). In this multicenter, randomized, open-label, phase II REVO trial, we compared immunochemotherapy (ICT) with concurrent CRT as neoadjuvant therapy in patients with resectable thoracic ESCC using a non-inferiority design.

Methods: Patients were randomly assigned to two to four 21-day cycles of intravenous camrelizumab (200 mg, day 1) plus albumin-bound paclitaxel (125 mg/m^2, days 1 and 8) and cisplatin (75 mg/m^2, day 1), or two 21-day cycles of albumin-bound paclitaxel and cisplatin combined with concurrent radiotherapy (36-40Gy in 20 fractions, 5 days per week), followed by surgery. The primary endpoint was pathological complete response (pCR) rate.

Results: Between September 2021 and March 2023, 85 patients had been enrolled, and the enrolment is still ongoing. As of April 6, 2023, 32 of 41 and 28 of 44 patients underwent surgery in the ICT and CRT groups, respectively. All patients achieved R0 resection. The pCR (ypT0N0) and major pathological response (MPR) rates were 40.6% (13/32) and 62.5% (20/32) in the ICT group and 35.7% (10/28) and 71.4% (20/28) in the CRT group, respectively. The incidence of grade ≥3 treatment-related adverse events (TRAEs) was 22.0% in the ICT group and 31.8% in the CRT group. The most common grade ≥3 TRAE was decreased lymphocyte count (14.6%) in the ICT group, and decreased lymphocyte count (18.2%) and decreased platelet count (6.8%) in the CRT group. One patient in the CRT group died due to pneumonia after surgery.

Conclusions: The current results suggest that neoadjuvant camrelizumab plus chemotherapy is non-inferior to concurrent CRT for patients with locally advanced ESCC, with better safety. The final results and long-term survival will be reported in the future.

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1523P Phase II dose optimization results from MOUNTAINEER-02: A study of tucatinib, trastuzumab, ramucirumab, and paclitaxel for HER2+ gastroesophageal cancer (GEC)

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Background: Approximately 12%-23% of pts with GEC have HER2+ tumours. Ramucirumab (R) + paclitaxel (P) is commonly used in the 2L setting for GEC; however, overall response and survival rates remain low. Tucatinib (TUC) is a highly selective, HER2-directed TKI. Here, we report safety and efficacy results from the dose optimization phase of MOUNTAINEER-02 (NCT04499924), a trial evaluating TUC in combination with trastuzumab (T), P, and R.

Methods: MOUNTAINEER-02 is a global trial evaluating TUC 300 mg BID + T (6 then 4 mg/kg D1,15) + P (D1, 8, 15) + R (8 mg/kg D1, 15) every 28 days in pts with previously treated, locally advanced unresectable or metastatic HER2+ GEC. In the open-label phase II dose optimization stage, two P doses were explored (60 mg/m^2 and 80 mg/m^2). HER2+ status was confirmed by ctDNA or IHC/ISH assay. The primary endpoint is safety/tolerability of TUC+T+P+R. Secondary endpoints are ORR, confirmed ORR (cORR), DOR, DCR, PFS (all investigator-assessed), and PK.

Results: As of Jan 20, 2023, 17 pts (median age 59 yrs) received study tx (n=8 in 60 mg/m^2 vs n=9 in 80 mg/m^2). Ten pts (58.8%) remain on study after a median of 8 TUC cycles. All pts treated with 80 mg/m^2 P were DLT-evaluable; 2 experienced a DLT event (1 pt with G3 mucositis and 1 pt with G2 fatigue and diarrhea leading to dose holds). No DLTs were observed in 7 DLT-evaluable pts treated with 60 mg/m^2 P. TEAEs stratified by two P doses are summarized in the table. ORR was 76.5% (95% CI, 50.1-93.2), with cORR of 70.6% (44-89.7) and DCR of 94.1% (71.3-99.9). Median DOR was 10.6 months (95% CI, 6.7-inestimable), and median PFS was 11.9 months (4.1-inestimable) after 7 PFS events. Plasma concentrations of P were not affected by TUC administration.

Table: 1523P Most Common TEAEs (≥30%)

	60 mg/m²		80 mg/m²		Total	
	Any G	G ≥3	Any G	G ≥3	Any G	G ≥3
Any Event	8 (100)	6 (75.0)	9 (100)	8 (88.9)	17 (100)	14 (82.4)
Diarrhea	4 (50.0)	2 (25.0)	7 (77.8)	1 (11.1)	11 (64.7)	3 (17.6)
Nausea	2 (25.0)	0	7 (77.8)	0	9 (52.9)	0
Epistaxis	2 (25.0)	0	6 (66.7)	0	8 (47.1)	0
Fatigue	2 (25.0)	0	6 (66.7)	2 (22.2)	8 (47.1)	2 (11.8)
Peripheral sensory neuropathy	1 (12.5)	0	7 (77.8)	2 (22.2)	8 (47.1)	2 (11.8)
Stomatitis	2 (25.0)	0	6 (66.7)	1 (11.1)	8 (47.1)	1 (5.9)
Constipation	3 (37.5)	0	3 (33.3)	0	6 (35.3)	0
Neutropenia	1 (12.5)	1 (12.5)	5 (55.6)	4 (44.4)	6 (35.3)	5 (29.4)
Pyrexia	3 (37.5)	0	3 (33.3)	0	6 (35.3)	0
Weight decreased	2 (25.0)	1 (12.5)	4 (44.4)	1 (11.1)	6 (35.3)	2 (11.8)

Conclusions: Coadministration with TUC did not impact the PK of P. Based on the preliminary data from MOUNTAINEER-02, the combination of TUC+T+P+R was tolerable with encouraging antitumor activity in pts with previously treated HER2+ GEC.

Clinical trial identification: NCT04499924.

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1524P First-line TST001 plus capecitabine and oxaliplatin (CAPOX) for advanced G/GEJ cancer with CLDN18.2 positive overall survival data from study transtar102-Cohort C

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Background: Phase III studies (SPOTLIGHT and GLOW) showed that combining anti-Claudin18.2 (CLDN18.2) antibody with chemotherapy significantly improved outcomes for first-line treatment for G/GEJ cancer with high CLDN18.2 expression. TST001 is a potential best-in-class antibody with improved CLDN18.2 affinity and enhanced ADCC effect, leading to anti-tumor activity in low to medium CLDN18.2 expression gastric cancer animal models.

Methods: Cohort C from Transtar102 study was designed to explore the safety and efficacy of TST001 plus CAPOX as 1st- line treatment in advanced G/GEJ cancer (NCT04495296—study Transtar102). Positive CLDN18.2 (membranous staining intensity ≥1+ in ≥10% of tumor cells) assessed centrally using the IHC 14G11 LDT assay was required in the expansion phase only.

Results: As of 21 April 2023, 64 patients have been dosed with TST001 plus CAPOX, including 15 patients who received TST001 at doses ranging from 1 to 8 mg/kg Q3W

in the dose escalation phase and 49 patients at 6 mg/kg in the dose expansion phase. The median follow-up is 197.5 days. The most common treatment related adverse events are nausea (70.3%), vomiting (53.1%) and hypoalbuminemia (75%) with grade 3 being 1.6% each. 42 out of the 49 patients in the 6 mg/kg expansion cohort have measurable lesions and had at least one post-treatment tumor assessment, with 28 (66.7%) achieving partial response (confirmed and unconfirmed). Across all doses, the objective response rate (confirmed and unconfirmed) is 65.4%, the estimated median progression-free survival is 9.5 months, and the estimated median duration of response is 9.9 months. 38 of 49 patients are CLDN18.2 positive with no notable difference in efficacy per CLDN18.2 level. Overall survival is immature and will be updated at the time of the conference.

Conclusions: TST001 plus CAPOX as first-line treatment for patients with G/GEJ cancer demonstrated good safety and tolerability. Encouraging anti-tumor activities have been observed regardless of the CLDN18.2 expression levels, including expression as low as ≥10% tumor cells staining ≥1+, <40% tumor cells staining <2+ or 3+. Overall survival data will be presented.

Clinical trial identification: NCT04495296.

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1526P Phase Ib results of bemarituzumab (BEMA)+mfolfox6+nivolumab (NIVO) for advanced gastric/gastroesophageal junction cancer (G/GEJC): Fortitude-102 part 1

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Background: In the phase (ph) 2 FIGHT trial, BEMA+mFOLFOX6 had promising efficacy in patients with FGFR2b-selected G/GEJC. FORTITUDE-102 comprises part 1 (open-label ph1b) evaluated the safety and tolerability of BEMA+mFOLFOX6+NIVO and part 2 (randomized ph3) the safety and efficacy compared with placebo. Here, we present the results of part 1.

Methods: Up to 20 patients (pts) with/without FGFR2b overexpression could be enrolled. The initial dose of BEMA was 15 mg/kg IV Q2W with one 7.5 mg/kg dose on cycle 1 day 8. The dose-limiting toxicity (DLT) period was 28 days. At least 6 pts were treated at a dose level with less than 33% incidence of DLTs to determine the recommended ph3 dose (RP3D). An ad hoc review was performed 6mo after the DLT period.

Results: Eight pts (50-71 y) were enrolled and evaluated for DLTs: 6 pts were men, 4 pts were Asian, and 4 pts were White. No DLTs were reported; no new safety signals were identified. Mean exposures for the first 3 cycles and estimated terminal elimination half-life (7-11 days) were consistent with historical data. No meaningful BEMA exposure changes were observed with the addition of NIVO, indicating no drug interactions. The RP3D was 15 mg/kg Q2W with one 7.5mg/kg dose on cycle 1 day 8. Six mo post-DLT period, the median treatment duration was ∼34 weeks (8-40). Four pts had 6 serious AEs (n=1 AE [hyponatremia] considered BEMA-related); 7 pts had 13 grade ≥3 AEs (n=4 [neutropenia, mucositis, hyponatremia, and delirium] in 2pts considered BEMA-related). Five pts reported 8 ocular AEs of grades ≤2, with a median time to onset of ∼17 weeks. No AEs led to BEMA discontinuation. Treatment was interrupted in 4 pts due to BEMA-related AEs (1 was ocular related). PR was seen in 3 pts, SD in 4 pts, and PD in 1 pt. BEMA was stopped for consent withdrawal in 1pt and PD in 2pts. Updated data will be presented at the congress.

Conclusions: This is the first time a combination of BEMA, mFOLFOX6, and NIVO is assessed. In part 1, consistent safety and PK profiles suggest no negative interaction, with no new safety signals after 6 mo.

Clinical trial identification: NCT05111626.

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1527P Efficacy and safety of infigratinib in locally advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma patients with FGFR2 gene amplification

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Background: The FGFR/FGF cascade is a complex intracellular pathway that controls cellular proliferation, tumor growth, angiogenesis, and dissemination. It is implicated in various human cancers including gastric cancer (GC). The FGFR2-amplification in a proportion ranging from 9% to 1.2% worldwide in GC patients. However, previous studies have demonstrated FGFR2-amplification may have poor PFS and OS survival in GC patients. Infigratinib (BGJ398) is a selective ATP-competitive, FGFR1−3 selective oral TKI. We present the data generated from the LB1001-201 trial **(NCT05019794) Cohort 1** to evaluate the efficacy and safety of infigratinib monotherapy in previously systemic second-line treated patients harbouring FGFR2 gene amplification.

Methods: Population and eligibility criteria - Failed on prior 2nd -lines treatment or above, locally advanced or metastatic GC/EGJ. FGFR2 gene amplification positive was confirmed via central FISH testing. Adequate organ function and laboratory values. MAPK-MEK or selective FGFR inhibitor treatment-naive. Procedures and treatment - Tumor biopsy or FFPE samples will be tested at the central lab for FGFR2 gene amplification orally infigratinib (125mg, QD) for 3 weeks on, 1 week off in each 28-day cycle; Dose adjustment will be based on drug-related AEs and severity per protocol demanded. Outcomes and assessments - ORR and DCR: Descriptive statistics were used, and an accurate 95% CI was provided. Time-to-event endpoints were summarized using K-M analyses. Safety endpoints were analyzed using frequency and percentage distribution in patients who received at least one dose of infigratinib.

Results: cORR 25.0% (95%CI 8.7, 49.1), DCR 80.0% (95%CI 56.3, 94.3), mDoR 3.8 months (mos) (3.6, NE). mPFS 3.3 mos (95%CI 2.3, 4.5), mOS 8.0 mos (95%CI 4.1, NE). 15/19 patients with tumor shrinkage, the maximum from baseline was -78.5%. ≥ Grade 3 TRAE was 42.9%, most were recoverable. No drug-induced death was reported.

Conclusions: Infigratinib in GC/GEJ patients with FGFR2 gene amplification has shown an inspiring clinical improvement, with acceptable tolerance, which is a potential first TKI regimen that precisely targeting in this population.

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1528P A phase I/II trial investigating safety and efficacy of autologous TAC01-HER2 in relapsed or refractory solid tumors

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Background: Despite therapeutic developments for patients with advanced HER2+ solid tumors, significant unmet medical needs still exist. The T-cell antigen coupler (TAC) technology is an approach to modifying T-cells *ex vivo*, which allows recognition and cytotoxicity of tumor cells by co-opting the natural T-cell receptor. TAC T-cells demonstrate a safer profile than chimeric antigen receptor T cells. TAC01-HER2 is an autologous T-cell product comprising T-cells expressing HER2 TAC.

Methods: The ongoing clinical trial (NCT04727151) is evaluating the safety and preliminary anti-tumor activity of TAC01-HER2 treatment of HER2+ solid tumors. Subjects undergo leukapheresis followed by lymphodepletion chemotherapy (LDC) prior to TAC01-HER2 infusion. In phase I dose escalation, TAC01-HER2 is administered at increasing doses (Cohorts 1-4) in adult subjects after $\geq$2 lines of therapy. Dose limiting toxicities (DLT) are assessed up to 28 days from TAC01-HER2 infusion. In phase II, dose expansion groups will further evaluate the safety, efficacy, and pharmacokinetics of the optimal TAC01-HER2 dose in gastric/GEJ tumors.

Results: As of 23 April 2023, 19 patients with solid tumors have been treated in Cohorts 1-4. Three were HER2 1+ or 2+/FISH-. One DLT event of grade (G) 3 pneumonitis has been reported in 1 subject in Cohort 4. No neurotoxicity has been reported. Most subjects treated at Cohorts 3-4 experienced CRS which resolved with supportive therapy. Thirteen subjects have reported a total of 26 serious adverse events, with 1 G3 pneumonitis, 1 G1, 3 G2 and 1 G3 CRS related to TAC01-HER2. A 67% disease control rate (DCR) was observed in Cohorts 2-4 at 4 weeks restaging after TAC01-HER2 infusion. For gastric/GEJ subjects of the same Cohorts, DCR was 83%. Two patients had an unconfirmed partial response (uPR). At Cohort 4, a uPR was observed in a subject with GEJ (HER2 2+, FISH+) with 100% reduction of target lesion. This patient had progressed on 4 prior lines of therapy including trastzumab and trastuzumab deruxtecan.

Conclusions: Treatment with TAC01-HER2 showed manageable safety and promising clinical activity in a heavily pre-treated cancer population. Dose escalation is complete.

Clinical trial identification: NCT04727151.

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1529P Tislelizumab plus chemotherapy sequential neo-chemoradiotherapy therapy as total neoadjuvant therapy in locally advanced esophageal squamous cell carcinoma (ETNT)

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Background: High recurrence and metastasis rates remain the main factors leading to the failure of the current standard treatment of neoadjuvant chemoradiotherapy plus surgery for resectable locally advanced ESCC. Improving the pathological complete response (pCR) rate may significantly benefit the survival of patients with resectable locally advanced ESCC after neoadjuvant therapy.

Methods: Patients aged 18-75 years with untreated, resectable, stage III-IVA ESCC, adequate organ and bone marrow function were eligible for inclusion. patients received neoadjuvant chemoradiotherapy (paclitaxel 135 mg/m2 d1 + carboplatin AUC = 3−5 d1, q3w × 2 cycles + 65 simultaneous radiotherapy (40 Gy/4 W/20F)) treatment, after the end of chemoradiotherapy, Tislelizumab (200 mg intravenously every 3 weeks for 2 cycles, and all patients undergo surgery after 4−6 weeks. The primary outcomes of the pCR rate and the incidence of adverse events will be analyzed completely within months, the secondary endpoints will include major pathological response rate, objective response rate, R0 resection rate, event-free survival, and overall survival. All enrolled patients were included in the activity and safety analyses.

Results: Thirty-two patients were enrolled in the study, among 8 patients are waiting for a surgery, with 24 patients undergoing surgical resection at a 100% R0 resection rate. All patients had stage III-IVA disease. Patients who received tislelizumab plus chemotherapy sequential nCRT achieved 13(54.2%) patients had a pathologic complete response, 16 (66.7%) patients achieved major pathologic response, and 21(87.5%) objective remission rate. Within 30 days after surgery, anastomotic fistula was found in 4 (16.7%) patients, but no deaths occurred, the most common grade 2 or 3 adverse event was leukopenia, hypothyroidism and lymphopenia. The analysis of survival was immature, and patients are still being followed up.

Conclusions: This study explored the safety and efficacy of tislelizumab plus chemotherapy sequential neo-chemoradiotherapy therapy for ESCC patients and provided a total neoadjuvant therapy model that can benefit patients with locally advanced ESCC.

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1530P Health-related quality of life (hrqol) in patients with claudin-18 isoform 2-positive (CLDN18.2+) locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mg/GEJ) adenocarcinoma: Results from SPOTLIGHT and GLOW

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Background: In the randomized, double-blind, global SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) trials, first-line zolbetuximab + chemo (mFOLFOX6 [SPOTLIGHT]; CAPOX [GLOW]) showed improved PFS (SPOTLIGHT, HR 0.75 [95% CI 0.60, 0.94], $P = 0.0066$; GLOW, HR 0.69 [95% CI 0.54, 0.87], $P = 0.0007$) and OS (SPOTLIGHT, HR 0.75 [95% CI 0.60, 0.94], $P = 0.0053$; GLOW, HR 0.77 [95% CI 0.62, 0.97], $P = 0.0118$) compared with placebo + chemo in patients with CLDN18.2+, HER2−, LA

unresectable or mG/GEJ adenocarcinoma at data cutoff. We present key patient-reported outcome (PRO) findings from these trials.

Methods: Patients completed the EORTC QLQ-C30 and QLQ-OG25 at screening, every 3 weeks on treatment, at discontinuation, and 30 and 90 days thereafter. Changes in scores from baseline, time to confirmed deterioration (TTCD), and time to definitive deterioration (TTDD) in PROs based on literature thresholds were evaluated. Least square mean (LSM) changes from baseline were summarized descriptively. TTCD and TTDD were assessed by Kaplan-Meier estimates and Cox hazard models.

Results: Table describes the LSM changes from baseline for SPOTLIGHT (N = 565) and GLOW (N = 507). No clinically meaningful deteriorations in global health status and quality of life (GHS/QoL), physical functioning (PF), abdominal pain and discomfort, or nausea/vomiting (N/V) were observed. Overall TTCD and TTDD results were similar between arms in both studies.

Table: 1530P

	Zolbetuximab + chemo LSM (standard error [SE])	Placebo + chemo LSM (SE)	Zolbetuximab vs placebo arms LSM (95% CI)	*P* value
SPOTLIGHT Cycle 9 Day 1	(N = 283)	(N = 282)		
GHS/QoL	1.65 (1.60)	4.20 (1.77)	-2.54 (-7.02, 1.93)	0.263
PF	-5.68 (1.77)	0.34 (1.88)	-6.02 (-10.85, -1.19)	0.015
Pain	-6.85 (1.86)	-9.12 (2.08)	2.27 (-2.97, 7.51)	0.394
N/V	-3.38 (1.64)	-2.31 (1.80)	-1.07 (-5.61, 3.47)	0.642
GLOW Cycle 17 Day1	(N = 254)	(N = 253)		
GHS/QoL	-0.04 (2.43)	-5.55 (2.89)	5.51 (-1.82, 12.84)	0.139
PF	-2.05 (1.88)	-2.93 (2.19)	0.88 (-4.67, 6.43)	0.753
Pain	-5.39 (2.32)	-7.27 (2.88)	1.88 (-5.30, 9.07)	0.604
N/V	-0.95 (1.89)	2.85 (2.31)	-3.79 (-9.57, 1.98)	0.192

Conclusions: There were not overall clinical HRQoL differences between patients in the zolbetuximab and placebo arms. Zolbetuximab + chemo improved clinical outcomes without negatively affecting HRQoL in key PROs in both SPOTLIGHT and GLOW.

Clinical trial identification: NCT03653507.

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1531P Update results of anlotinib combined with TQB2450 (PD-L1 blockade) as first-line treatment for advanced esophageal squamous cell carcinoma (ESCC): A single-arm, multicenter, open-label phase II clinical trial

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Background: Recent studies have demonstrated encouraging efficacy in patients with ESCC when combining PD-1 blockades with chemotherapy in the first-line setting. However, the safety profile of conventional chemotherapy remains unsatisfactory, suggesting the chemotherapy-free regimen a promising strategy. Anlotinib, a novel multitarget TKI primarily targeting VEGFR1-3, has shown therapeutic activity as first-line combination therapy or second-line monotherapy for ESCC patients in China. TQB2450 is a novel PD-L1 blockade developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. (Nanjing, China). This study aims to investigate the efficacy and safety of anlotinib plus TQB2450 as first-line therapy for patients with advanced ESCC.

Methods: Patients with previously untreated metastatic or locally advanced ESCC, whose age was between 18 and 75 years, with ECOG PS of 0 or 1 score and life expectancy of >3 months were inclusion criteria. Eligible patients were administered with anlotinib (12mg, po, d1∼14, q3w) plus TQB2450 (1200mg, iv, d1, q3w) until disease progression or unacceptable toxicity. The predefined sample size was 46. The primary endpoint was ORR, secondary endpoints included safety, PFS, DCR, DoR and OS.

Results: From Mar 2022 to Sep 2022, a total of 46 patients were enrolled. At the data cut-off date (Mar 2023), the preliminary ORR was 69.6% (95%CI: 54.2%∼82.3%), DCR was 93.5% (95%CI: 82.1%∼98.6%). At the data cut-off date, 9 pts discontinued treatment due to PD, the preliminary prognostic result exhibited that the median PFS of the 46 pts was 9.92 months (95%CI: 8.26∼11.58). Additionally, safety profile exhibited that the regimen was tolerable. The common grade ≥3 treatment-related adverse events in 46 patients were hypertension (7%), hyponatremia (4%), low white blood cell count (2%), neutrophil count decreased (2%), platelet count decreased (2%), intestinal obstruction (2%), haemoptysis (2%) and toothache (2%).

Conclusions: The preliminary results highlighted that anlotinib plus TQB2450 as a first-line therapy for advanced ESCC showed encouraging efficacy and manageable safety profile.

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1532P Phase Ib study of futibatinib plus pembrolizumab in patients with esophageal carcinoma: Updated results of antitumor activity and tolerability results in combination with chemotherapy

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Background: Combination therapy using FGFR inhibitors and Immune checkpoint inhibitors (ICIs) are being explored as a novel strategy for cancer patients (pts). Previously, we reported the preliminary antitumor activity of irreversible FGFR inhibitor futibatinib plus pembrolizumab in pts with advanced (adv) or metastatic

esophageal carcinoma (EC). Here, updated results and tolerability in combination with chemotherapy are presented.

Methods: Pts who are ICI naïve (Cohort A) or ICI refractory (Cohort B) for adv or metastatic EC who have received at least one prior therapy with a fluorouracil and platinum-based drug were administrated with futibatinib plus pembrolizumab. In addition, pts who have not received prior treatment with any systemic chemotherapy received futibatinib 20 mg once daily (QD) plus pembrolizumab 200 mg, fluorouracil 800mg/m^2 on days 1-5 and cisplatin 80mg/m^2 every 3weeks in Cohort D. Primary endpoint was overall response rate (ORR) in Cohort A and B, and dose-limiting toxicity (DLT) in Cohort D.

Results: As of March 15, 2023, 31 pts (Cohort A), 50 pts (Cohort B) and 11 pts (Cohort D) were enrolled. As results of the analysis for the cut-off data, confirmed partial responses (PRs) were observed in 11 pts in Cohort A; ORR was 39% with DCR of 75%. In Cohort B, confirmed PRs were observed in 3 pts; ORR was 6% with DCR of 57%. DLT was observed in one pt (Grade 3, Stomatitis) in Cohort D and the RD of futibatinib in combination with pembrolizumab and chemotherapy was determined as 20 mg QD. In Cohort D, most common TRAEs (N=11; all grade, grade ≥3) were hyperphosphatemia (82%, 0%) and stomatitis (82%, 9.1%). Of the 8 pts evaluated for efficacy in Cohort D, confirmed PRs and unconfirmed PRs were observed in 2 pts and 5 pts (5 pts are ongoing), respectively.

Conclusions: Futibatinib plus pembrolizumab showed encouraging antitumor activity in ICIs naïve adv or metastatic EC pts. Futibatinib plus pembrolizumab and chemotherapy showed no new safety signals and manageable safety profile, with promising antitumor activity in pts with adv or metastatic EC who have not received prior treatment with systemic chemotherapy.

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1533P Advantig-105: Phase Ib dose-expansion study of ociperlimab (OCI) + tislelizumab (TIS) with chemotherapy (CT) in patients (pts) with metastatic oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma (EAC)

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Background: A T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) inhibitor + an anti-PD-1 antibody is a promising combination which shows potent efficacy in solid tumors. AdvanTIG-105 (NCT04047862) is a phase I/1b open-label study designed to assess the safety and preliminary antitumor activity of anti-TIGIT mAb OCI + anti-PD-1 mAb TIS in pts with metastatic unresectable solid tumors. OCI + TIS was well tolerated in the dose-escalation part, preliminary efficacy was observed, and the recommended phase II dose (RP2D) of OCI 900 mg IV Q3W + TIS 200 mg IV Q3W was established. Here we report results from dose-expansion cohorts 6 (C6) and 7 (C7).

Methods: Treatment-naïve adult pts with histologically/cytologically confirmed metastatic ESCC (C6) or EAC (C7) were enrolled. Pts received the RP2D of OCI + TIS with cisplatin + 5-fluorouracil/paclitaxel until disease progression, intolerable toxicity, or consent withdrawal. Primary endpoint: investigator-assessed ORR per RECIST v1.1. Secondary endpoints: efficacy (PFS, DoR, DCR), safety and PD-L1 and TIGIT expression as predictive efficacy biomarkers.

Results: As of Feb 2, 2023, 27 pts (C6: n=21; C7: n=6) with a median age of 63.0 y (range C6: 51-72; C7: 58-69) were enrolled; 24 (C6: n=19; C7: n=5) were efficacy evaluable. Efficacy and safety data are summarized in the table. ORRs by biomarker subgroups: C6, 100% in pts with PD-L1 tumor area positivity (TAP) score ≥10% (n=4) vs 76.9% in pts with PD-L1 TAP <10% (n=13); 80.0% in pts with TIGIT IC score ≥5% (n=10) vs 87.5% in pts with TIGIT IC <5% (n=8). C7 had too few pts for biomarker subgroup analysis.

Table: 1533P Efficacy and Safety Summary

	Efficacy Evaluable Set	
	C6	C7
Parameter	**n=19 % (95% CI)**	**n=5**
ORR	84.2 (60.4-96.6)	80.0 (28.4-99.5)
DCR	94.7 (74.0-99.9)	100 (47.8-100)
	mo (95% CI)	
Median DoR	6.7 (4.7-NE)	3.4 (1.7-NE)
Median PFS	8.1 (6.5-NE)	6.2 (3.0-NE)
	Safety Set	
Parameter	**n=21**	**n=6**
Median study follow-up (range), wks	36.1 (1.7-77.0)	29.3 (8.6-57.1)
	n (%)	
Pts with ≥1 TEAE	21 (100)	6 (100)
Grade ≥3	14 (66.7)	6 (100)
Serious	9 (42.9)	4 (66.7)
imAE	11 (52.4)	2 (33.3)

DCR, disease control rate; DoR, duration of response; imAE, immune-mediate adverse event; mo, months; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Conclusions: These results demonstrate that OCI 900 mg + TIS 200 mg + CT had a safety profile consistent with previous reports and showed encouraging antitumor activity in pts with stage IV ESCC and EAC.

Clinical trial identification: NCT04047862.

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1534P First-line lenvatinib (len) plus pembrolizumab (pembro) and chemotherapy (chemo) for metastatic esophageal squamous cell carcinoma (mESCC): Safety run-in results from the phase III LEAP-014 study

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Background: LEAP-014 (NCT04949256) is a randomized, two-part, open-label, phase III study evaluating the safety and efficacy of len + pembro + chemo vs pembro + chemo in patients (pts) with previously untreated mESCC. Results from part 1 (safety run-in cohort) are reported.

Methods: Eligible pts had confirmed previously untreated mESCC; measurable disease per RECIST v1.1 by investigator; and ECOG PS score $\leq$1. In part 1, pts received induction with IV pembro 400 mg Q6W$\times$2 cycles + oral len 8 mg QD + chemo (cisplatin + 5-FU [FP] Q3W$\times$4 cycles or paclitaxel + cisplatin [TP] Q3W$\times$4 cycles) and consolidation with IV pembro 400 mg Q6W for $\leq$16 doses + oral len 20 mg QD. Pts were treated until disease progression or unacceptable toxicity. Primary end points for part 1 were dose-limiting toxicities (DLTs), adverse events (AEs), and discontinuations due to AEs. DLTs were evaluated for 21 days after the first dose; if $\geq$3 DLTs occurred in the TP or FP cohort, then part 2 could be delayed to further examine safety data and consider study design changes.

Results: At data cut-off (February 2, 2023), 13 pts were treated (FP: 7; TP: 6). Median time from first dose to data cut-off was 16.6 mo (range, 15.9-17.3) and 5.6 mo (4.6-6.2) with len + pembro + FP and len + pembro + TP, respectively. Median (range) age was 64 y (43-77) and 66 y (53-71), respectively. One DLT of grade 3 acute kidney injury associated with increased creatinine level and 1 DLT of grade 3 hypokalemia occurred in the FP cohort; no DLTs were reported in the TP cohort. No pt discontinued because of a DLT. No treatment-related deaths occurred. ORR and DOR will be reported.

Conclusions: Part 1 (safety run-in) of LEAP-014 showed that len + pembro + chemo had acceptable safety and tolerability in pts with previously untreated mESCC, allowing initiation of part 2. Part 2 is ongoing and will evaluate the efficacy and safety of len + pembro + chemo vs pembro + chemo as first-line therapy for mESCC.

Clinical trial identification: NCT04949256.

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1535P Paclitaxel + ramucirumab versus paclitaxel alone in patients with squamous-cell carcinoma of the oesophagus, refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs: Final results from the randomized phase II IKF-S627/RAMOS trial of the AIO

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Background: Ramucirumab (Ram) combined with docetaxel is an approved 2nd-line treatment in patients (pts) with squamous cell carcinoma (SCC) of the lung (REVEL study) and with paclitaxel for esophagogastric adenocarcinoma (RAINBOW study). In SCC of the oesophagus, nivolumab is currently the only evidence-based 2nd-line treatment option. This study evaluates the safety and efficacy of Ram plus paclitaxel.

Methods: This prospective, randomized, open-label, multicentre, phase II trial evaluated paclitaxel plus Ram (Ram 8 mg/kg d1, 15 and paclitaxel 80 mg/m^2 d1, 8, 15) Arm A vs. paclitaxel alone (80 mg/m^2 d1, 8, 15) Arm B, both q4w. Primary endpoint was overall survival rate at 6 months (mos) (OS@6), main secondary endpoints were OS, PFS, objective response rate (ORR) and safety.

Results: From 3/2019 to 4/2021, 21/186 planned pts were treated within the study protocol (Arm A 11 pts; Arm B 10 pts) in 9 German centres. Due to slow accrual, the study was terminated prematurely. Median age was 63y, 71% were male and 86% had relevant concomitant disease. Pts received a median of 9 and 10 cycles in Arms A and B, respectively. Median follow-up was 9 mos (0.7 — 32.4 mos). OS@6 in Arm A was 73% for Ram/paclitaxel and 50% for paclitaxel. However, the study design did not allow for statistical comparison of the arms. ORR (CR+PR 18% vs. 20%) and DCR (CR+PR+SD 55% vs. 60%) were in the same range, as well as median PFS (3.8 vs. 3.5 mos) and OS (12.1 vs. 9.2 mos) for Arms A and B, respectively. The most common treatment related adverse events (AEs) in Arm A were leucopoenia (55%), fatigue (27%) and peripheral sensory neuropathy (18%). Treatment related AEs $\geq$ grade 3 occurred in 27% in Arm A and 50% in Arm B. Serious AEs (SAEs) occurred in 36% and 50% in Arms A and B, respectively.

Conclusions: Ram and Paclitaxel shows an acceptable tolerability and numerically improved OS@6. Due to the small number of pts the current trial must be considered exploratory, and more data are needed in this indication.

Clinical trial identification: NCT03762564.

Legal entity responsible for the study: Institut für Klinische Krebsforschung IKF am Krankenhaus Nordwest.

Funding: Lilly Deutschland GmbH.

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1536P HERIZON: A phase II study of HER-Vaxx (IMU-131), a HER2-targeting peptide vaccine plus standard of care chemotherapy in patients with HER2+ advanced stomach cancer - Dose-dependent anti-cancer antibodies correlating with improved clinical outcome

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Background: HER-Vaxx is a B cell peptide-based anti-Her2 vaccine (IMU-131) comprising B cell epitopes located within trastuzumab's binding site. In the phase Ib HERIZON trial (NCT02795988), HER-Vaxx has been shown to be safe and to prolong progression-free survival in patients with Her2-overexpressing gastric/gastro-oesophageal junction cancer (GC). The present randomized phase II open-label, multicentre study, compared two different doses of HER-Vaxx plus chemotherapy vs chemotherapy alone and aimed to evaluate antibody and clinical responses in patients with advanced or metastatic Her2-overexpressing GC naïve to Her2 therapy.

Methods: Patients were randomized to chemotherapy alone (n=17) or HER-Vaxx (50µg dose, n=19; 100µg, n=7) plus chemotherapy. In both vaccination groups, the patients received the vaccine at days 0, 14, 35, and 77 followed by q. 63 days until disease progression. Chemotherapy consisted of oxaliplatin plus capecitabine and was started at day 0, repeated q. 21 days for a maximum of 6 cycles. Specific anti-Her2 IgG antibody levels in the patient's sera were evaluated by ELISA and clinical responses were assessed by RECIST 1.1 criteria.

Results: Evaluation of the vaccine's two doses showed no difference in the induced Her2-specific IgG and IgG1 antibody responses, which, compared to patients from the chemotherapy-only group, were both significantly elevated ($P<0.001$) at all time points after 3 or more vaccinations. No further reduction of tumour diameters was observed with the vaccine's higher dose, and the induced Her2-specific antibodies following vaccination with either dose significantly correlated with the anti-tumour effect (IgG, $P=0.001$; IgG1, $P=0.016$). Moreover, the vaccine-induced IgG antibodies had the capacity to inhibit intracellular phosphorylation of Her2 and exhibited binding to the gastric cancer cell line N87 overexpressing Her2.

Conclusions: Vaccination with HER-Vaxx in patients with Her2-overexpressing GC at doses of 50µg and 100µg led to an anti-tumour effect that correlated with anti-Her2 IgG antibody levels.

Clinical trial identification: NCT02795988.

Legal entity responsible for the study: Imugene Limited.

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1537P A phase I study of pevonedistat plus capeOX in patients with advanced gastric cancer refractory to platinum (NCCH-1811)

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Background: Pevonedistat (MLN4924/TAK924), which is an inhibitor of NEDD8 (neural precursor cell expressed developmentally down-regulated protein 8)-activating enzyme (NAE), shows synergistic effects with platinum, suggesting possibility of conquest over platinum-resistance, in preclinical studies. This phase I study was conducted to determine the recommended dose (RD) of pevonedistat in combination with capecitabine plus oxaliplatin (CapeOX) and explore its efficacy and safety as third- or later line treatment in patients (pts) with unresectable advanced gastric cancer (AGC).

Methods: This study consisted of two parts: the dose-finding part, and the expansion part at the RD. In both parts, treatment was started as monotherapy with pevonedistat for a week (Lead-in) and followed by 3-drug combination in a 3-week cycle: Capecitabine (1000 mg/m2/day, twice daily, for 14 days), oxaliplatin (130 mg/m2 on day 1) and pevonedistat (20 mg/m2 in level 1, 15 mg/m2 in level 0, on days 1, 3, and 5). Pharmacokinetics (PK) of pevonedistat was compared between its mono and combination therapy. Translational research for pharmacodynamics and genetic biomarkers were performed.

Results: Between April 2019 and September 2021, 12 pts having prior chemotherapy containing fluoropyrimidine plus platinum were enrolled. The initial 2 pts in the level 1 experienced DLTs (grade 3 elevation in ALT and AST, delay of starting cycle 2). After confirming that six pts in the level 0 showed no DLTs, 4 pts were added in the expansion part. Grade3 AEs included AST increased (25%), ALT increased (17%), and platelet count decreased (17%). No obvious difference in the PK of pevonedistat was observed when combined with CapeOX. Two (17%) and 8 (75%) pts achieved partial response and disease control. The median overall and progression-free survival were 9.3 and 4.4 months. Inhibition of NAE by pevonedistat was confirmed in all patients by positive Cdt1 expression in the post-treatment biopsy. No genetic alterations associated with efficacy were identified.

Conclusions: Pevonedistat plus CapeOX was well tolerated and showed promising efficacy in AGC pts previously treated with platinum containing chemotherapy.

Clinical trial identification: jRCT2031190020.

Legal entity responsible for the study: H. Shoji.

Funding: Takeda.

Disclosure: H. Shoji: Financial Interests, Personal, Advisory Board: Ono Pharmaceutical Co., Ltd., Zymeworks Inc.; Financial Interests, Institutional, Local PI: Ono Pharmaceutical Co., Ltd., MSD, Astellas, Amgen, Daiichi Sankyo; Financial Interests, Institutional, Funding: Ono Pharmaceutical Co., Ltd., Takeda Pharmaceuticals. H. Hirano: Financial Interests, Personal, Invited Speaker: Taiho Pharmaceutical, Ono Pharmaceutical, Teijin Pharma, Novartis; Financial Interests, Personal, Writing Engagement: Financial Interests, Institutional, Research Grant: Chugai Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Ono Pharmaceutical, Janssen Pharmaceutical, Merck Biopharma, Bristol Myers Squibb, Pfizer, Eisai, Amgen, Astellas, Seagen, MSD, Incyte, BeiGene, Novartis. K. Yamaguchi: Financial Interests, Personal, Invited Speaker: Taiho Pharm; Financial Interests, Personal, Advisory Board: Daiichi Sankyo, Bristol Myers Squibb, Ono Pharm, Eli Lilly Japan; Financial Interests, Institutional, Funding: Taiho. K. Kato: Financial Interests, Personal, Invited Speaker: Ono Pharmaceutical, Bristol Myers Squibb, Merck and Co; Financial Interests, Personal, Advisory Board: Ono Pharmaceutical, Bristol Myers Squibb, Merck and Co, Bayer, AstraZeneca, BeiGene, Taiho, Merck Biopharma, Amgen, Novartis, Daiichi Sankyo; Financial Interests, Institutional, Coordinating PI: Ono Pharmaceuticals, Merck & Co; Financial Interests, Institutional, Local PI: Bayer, AstraZeneca, BeiGene, Chugai, Taiho, Oncolys Biopharma, Janssen Pharmaceutical. N. Boku: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Eli Lilly, Ono Pharmaceutical, Taiho, Daiichi Sankyo; Financial Interests, Institutional, Research Grant: Takeda Pharmaceutical, Ono Pharmaceutical. All other authors have declared no conflicts of interest.

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1538P A phase II study to evaluate the efficacy and safety of tislelizumab combined with chemotherapy (cis-platinum plus albumin-paclitaxel/paclitaxel) in neoadjuvant treatment of locally advanced oesophageal squamous cell carcinoma

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Background: Neoadjuvant chemoimmunotherapy might benefit pts with locally advanced oesophageal squamous cell carcinoma (ESCC). Herein, we aimed to evaluate the efficacy and safety of Tislelizumab (a humanized anti-PD-1 antibody) combined with cisplatin plus albumin-paclitaxel(nab-PTX)/paclitaxel (PTX).

Methods: A prospective, open, single-arm, two-cohort phase II trial was conducted. ESCC Pts with resectable locally advanced disease were enrolled and randomly allocated into group nab-PTX (group A) or group PTX (group B). Pts received intravenous Tislelizumab (200 mg, day 1) combined with cisplatin (25mg/m2, day 1-3) plus nab-PTX (130 mg/m2, day 1, 8) in group A or PTX (75 mg/m2, day 1, 8) in group B of each 21-day cycle for two cycles before surgery, respectively. The primary endpoint was major pathologic responses (MPR) rate. The Secondary endpoints were pathological complete response (pCR) rate, R0 resection rate, treatment related adverse events (TRAEs), DFS and OS.

Results: From Feb 14, 2022, to Mar 8, 2023, 39 pts were enrolled (n=20 in group A, n=19 in group B). 35 pts received the full two-cycle chemoimmunotherapy successfully and received surgery (n=19 in group A, n=16 in group B), 2 pts in group B didn't receive the second cycle due to intolerance and dropped out, and 2 patients gave up surgery after neoadjuvant therapy for personal reasons (n=1 in each group). Pts underwent surgery within 23-97 days (median 35 days) after neoadjuvant treatment, among others, 2 pts delayed surgery due to TRAEs. All patients achieved radical (R0) resection. No patient died during neoadjuvant therapy and perioperative period. In group A, the MPR rate and pCR rate were 78.9% (15/19) and 36.8% (7/19), respectively. In group B, the MPR rate and pCR rate were 18.8% (3/16) and 0% (0/16), respectively. The most common TRAEs were lymphopenia (45.7%), diarrhoea (34.3.0%) and fatigue (31.4%), and there was no significant difference between groups.

Conclusions: Neoadjuvant treatment with Tislelizumab combined with cisplatin plus nab-PTX demonstrated promising anti-tumor efficacy with acceptable toxicity in pts with locally advanced thoracic ESCC.

Legal entity responsible for the study: Y. Sun.

Funding: BeiGene Pharmaceutical (Shanghai) Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

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1539P Efficacy and safety of perioperative chemotherapy combined with tislelizumab and trastuzumab for HER2-positive resectable gastric/gastroesophageal junction cancer (GC/EGJC): Preliminary results of a phase II, single-arm trial

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Background: Immunotherapy combined with trastuzumab, and chemotherapy have been recommended by the clinical guidelines of many countries as the first-line treatment for advanced HER2-positive G/GEJ adnocarcinoma. Combining chemotherapy with tislizumab and trastuzumab in the neoadjuvant/adjuvant setting may benefit patients with locally advanced, resectable HER2-positive GC/GEJC.

Methods: This study is a multicentre, single-arm, open-label phase II study. Patients with histologically confirmed cT2-4NxM0 or cTxN+M0, (TNM 8th edition), resectable GC/GEJC are eligible for this study. Neoadjuvant therapy will be administered for four cycles. The patients will receive tislelizumab and trastuzumab for 1 cycle (Q3W), followed by tislelizumab and trastuzumab combined with DOS (Docetaxel + Oxaliplatin + S-1) for 3 cycles (Q3W). Surgery is planned 4-6 weeks after preoperative treatment. Patients will receive adjuvant therapy starting within 4−6 weeks after surgery for 9 cycles. The primary endpoint was pathological complete response rate (pCR). Secondary endpoints included R0 resection rate, 1-year and 2-year event-free survival (EFS), overall survival (OS) and safety.

Results: From September 13, 2021, to May 05, 2023, 18 patients were enrolled, and the median follow up time was 9.2 months (0.1-20.0).11 patients completed surgery, and 5 patients were undergoing neoadjuvant therapy, 2 patients required organ preservation therapy. R0 resection rate was 100%, 6 patients (54.5%) achieved pCR, and 7 patients (63.6%) achieved MPR. Postoperative pathology showed that T stage decreased in 9 cases after neoadjuvant therapy, with a decrease rate of 81.8%. Median OS and EFS have not been reached. The most common AEs (grade ≥3) were anaemia in 1 (5.6%) and neutropenia in 1 case (5.6%). The immune-related adverse events were all grade 1. No treatment related deaths were reported.

Conclusions: According to the preliminary results, tislelizumab combined with trastuzumab and standard chemotherapy in the perioperative period of HER2-positive GC / EGJ have a good clinical benefit trend and controllable security.

Clinical trial identification: NCT04819971.

Legal entity responsible for the study: The First Affiliated Hospital of Zhengzhou University.

Funding: BeiGene (Beijing) Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

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1540P Tislelizumab combined with neoadjuvant chemoradiotherapy for resectable locally advanced oesophageal squamous cell carcinoma: A prospective, phase II clinical study

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Background: Neoadjuvant chemoradiotherapy (nCRT) is a standard treatment for resectable locally advanced oesophageal squamous cell carcinoma (ESCC); however, its effectiveness is curtailed by recurrence and distant metastasis. Developing novel therapies, such as combined checkpoint inhibitors, is crucial for improving patient survival. Tislelizumab, an anti-PD-1 monoclonal antibody, has shown promise in various malignancies. This is the first phase II study to assess the efficacy and safety of Tislelizumab combined with nCRT for resectable locally advanced ESCC.

Methods: All subjects underwent nCRT with a 40 Gy total radiation dose given daily for 5 days/week. Paclitaxel albumin (taxanes) with cisplatin/carboplatin were given on days 1 and 22, while Tislelizumab was administered twice on days 8 and 29 concurrently with radiation therapy. Finally, surgery was performed at 6-8 weeks post-treatment.

Results: By April 2023, 26 patients were enrolled in the study, with 21 undergoing surgical resection at a 100% R0 resection rate. Patients who received Tislelizumab combined with nCRT achieved a 100% objective remission rate, with 9 (42.8%) patients had complete response rate and 14 (66.6%) patients achieved major pathologic response, no surgical delay, among 6 patients continue to receive postoperative adjuvant therapy. Common side-effects included leukopenia, thrombocytopenia, neutropenia, anemia, anastomotic leakage, and rash. Most adverse events were grades 1/2, and grades 3/4 adverse events include four cases of grade 3 leukopenia, and one case of grade 3 neutropenia. Regrettably, 2 patients have passed away due to the novel coronavirus. The analysis of survival was immature, and patients are still being followed up.

Conclusions: Tislelizumab in combination with nCRT is a safe and effective treatment strategy for resectable locally advanced ESCC. The high complete response rate and favorable safety profile observed in this study warrant further investigation in larger, randomized controlled trials to confirm the benefit of Tislelizumab in improving treatment outcomes for patients with locally advanced ESCC.

Clinical trial identification: CTR2100051599.

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Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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1541P Neoadjuvant therapy of camrelizumab combined with chemotherapy in patients (pts) with resectable esophageal squamous cell cancer (ESCC)

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Background: The study aimed to evaluate the efficacy and safety of neoadjuvant therapy of camrelizumab, combined with chemotherapy in resectable ESCC pts.

Methods: In this single-center, single-arm, exploratory clinical trial (ChiCTR2100050057), treatment naïve pts with histologically identified resectable ESCC were included. Eligible pts was treated with camrelizumab (200 mg, d1) combined with nab-paclitaxel (100 mg/m^2, d1 and d8) and nedaplatin (75 mg/m^2, d1) for 2 cycles (21 days per cycle). Radical surgery was conducted in the following 4-6 weeks. Primary endpoints were pathological complete response (pCR) rate, and major pathologic response (MPR).

Results: From Aug 13, 2021, to Jul 9, 2022, a total of 70 pts were enrolled in this study. Sixty-eight pts completed the two-cycle neoadjuvant therapy, with two pts discontinued the 2nd cycle therapy for intolerable toxicity. As of March 15, 2023, 61 pts were available for efficacy evaluation, with 6 complete responses (CR), 35 partial responses (PR), and 20 stable diseases (SD) based on RECIST 1.1 criteria, resulting in an objective response rate (ORR) of 67.2%. Then 59 pts underwent surgery, as 11 pts refused. Overall, surgery-related complications occurred in 53 (89.8%) pts after resection. Pulmonary complications occurred in forty-nine pts (83.1%) and cardiac complications were observed in four pts (6.8%). The rate of anastomotic leakage was 20.3%. Vocal cord paralysis and wound infection occurred in 2 pts, respectively. The pCR and MPR rate were 27.1% and 59.3%, respectively. According to tumor regression grade, 19/59 (32.2%) pts had TRG0, 16/59 (27.1%) TRG1, 14/59 (23.7%) TRG2, and 10/59 (16.9%) TRG3. We analyzed the correlation between PD-L1 expression and pathological tumor regression and found no significant correlation between PD-L1 status and pathological reactions in ESCC. The most common AEs were anemia (70.0%) lymphocyte count decreased (67.1%) white blood cell count decreased (52.9%) and neutrophil count decreased (50%). Most AEs were grade 1-2. No grade 4/5 AEs occurred.

Conclusions: Neoadjuvant therapy of camrelizumab combined with chemotherapy has promising efficacy and good safety in ESCC pts.

Legal entity responsible for the study: Affiliated Cancer Hospital of Shandong First Medical University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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1542P Updated results of a phase II clinical trial: Paclitaxel and carboplatin plus PD-1 blockades combined with anlotinib as first-line treatment for advanced oesophageal cancer

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Background: The combination of PD-1 blockades with chemotherapy is the standard first-line therapy for advanced esophageal cancer. Recent studies exhibited that anti-angiogenic drug combined with PD-1 blockades or chemotherapy demonstrated potential synergistic action and bright prospect in the combined application of anti-tumor therapy. We present updated data from the study of paclitaxel and carboplatin combined with anlotinib and PD-1 blockades in the treatment of advanced oesophageal cancer.

Methods: This study was a parallel, open-label, phase II clinical trial. A total of 90 patients (pts) with previously untreated, advanced or metastatic ESCC, with an age ranging from 18-75 years old were planned to be enrolled into three arms with an allocation ratio of 1:1:1. Arm A received TC (paclitaxel + carboplatin) + camrelizumab (200mg, q3w) + anlotinib (8mg, q3w); Arm B received TC with camrelizumab; Arm C received TC only. After 4-6 cycles of induction therapy, arm A and arm B would receive maintenance therapy until disease progression or intolerable adverse events. The primary endpoint was ORR. Secondary endpoints included PFS, OS and safety.

Results: At data cut-off date (Apr. 30, 2023), a total of 90 pts was enrolled. 25 of 30 pts achieved partial response (PR) and 2 pts achieved complete response in arm A, 13 of 30 pts achieved PR in arm B, and 7 of 30 pts achieved PR in arm C. The ORR were 90.0% in arm A, 43.3% in arm B, and 26.7% in arm C. The median PFS (95% CI) were 13.4 months (10.1-16.8) in arm A, 7.2 months (3.6-10.9) in arm B, and 4.8 months (4.0-5.6) in arm C. The median OS was not reached. The rate of treatment related adverse events (TRAEs) of any grade was 100% in all three groups, and grade 3 TRAEs were 30.0%, 23.3% and 13.3%, respectively. The most common grade 3 TRAEs were thrombocytopenia (8.9%), decreased white blood cell count (6.7%), neutropenia (5.6%). No grade 4 or 5 TRAEs were observed.

Conclusions: Addition of anlotinib to immunotherapy plus chemotherapy as first-line therapy showed amazing clinical outcomes in ESCC pts with a manageable safety profile. The study was still ongoing, and the data would be updated to confirm this conclusion subsequently.

Clinical trial identification: NCT04471480.

Legal entity responsible for the study: Daping Hospital, Army Medical University.

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1543P Clinical study of camrelizumab combined with docetaxel and carboplatin in neoadjuvant treatment of locally advanced oesophageal squamous cell carcinoma

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Background: Immunotherapy is effective in treating unresectable oesophageal squamous cell carcinoma (ESCC). This study aims to evaluate the clinical efficacy and safety of neoadjuvant camrelizumab combined with docetaxel and carboplatin in locally advanced ESCC.

Methods: All patients underwent surgery within 4-8 weeks after receiving 2 cycles of neoadjuvant therapy, which was camrelizumab (200mg IV Q3W) combined with docetaxel (75 mg/m^2 IV Q3W) and carboplatin (AUC= 5-6 IV Q3W). The pathological complete response (pCR) rate was the primary endpoint, and the secondary endpoints included R0 resection rate, objective response rate (ORR), disease-free survival (DFS), overall survival (OS) and safety.

Results: A total of 40 patients were included, of which 37 patients were evaluated, including 9 cases of complete response (CR), 18 cases of partial response (PR), 10 cases of stable disease (SD), and the ORR was 73% (27/37). The main adverse events were ALT/AST increase 52.5% (21/40), leukopenia 50% (20/40), nausea and vomiting 47.5% (19/40), bilirubin increase 40% (16/40), all of which were grade 1-2. One patient had Guillain-Barre Syndrome. Among these patients, 31 underwent surgical treatment, pCR rate was 22.6% (7/31), R0 resection rate was 100% (31/31), tumour regression grade (TRG) 0, 1, 2 and 3 were 22.6% (7/31), 16.1% (5/31), 22.6% (7/31) and 38.7% (12/31), respectively. The average operation time (310.0±57.6 minutes). The average intraoperative blood loss (136.1±41.4 ml) and the average hospitalization time after operation (10.9±2.7 days). The average number of resected lymph nodes (24.4±8.2). Surgery-related complications: anastomotic leakage 6.5% (2/31), pleural effusion 6.5% (2/31), cardiac arrhythmia 9.7% (3/31), pneumonia 3.2% (1/31), gastric emptying disorder 3.2% (1/31). The median follow-up time was 12 months (range 1—32 months). One patient had liver metastasis 21 months after surgery. No treatment-related death occurred.

Conclusions: Camrelizumab combined with docetaxel and carboplatin is effective and safe in the neoadjuvant treatment of locally advanced ESCC.

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1544P Camrelizumab plus albumin-bound paclitaxel and S-1 as first-line treatment of advanced gastric/gastroesophageal junction cancer: A phase II clinical trial

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Background: Patients (pts) with advanced gastric/gastroesophageal junction cancer that progresses on chemotherapy have poor outcomes. We investigated the safety and efficacy of camrelizumab combined with albumin-bound paclitaxel and S-1 in first-line treatment of HER-2-negative advanced gastric/gastroesophageal junction cancer.

Methods: This study was a single-arm, open-label, phase II clinical study. Eligible pts were adults with histologically confirmed HER-2 -negative advanced gastric/ gastroesophageal junction cancer. Pts participating in this study were required to detect PD-L1 expression, MSI/MMR status, and EBV virus content. Pts received camrelizumab (200 mg, day 1), S-1 (60mg/m^2 bid, days 1-14), and albumin-bound paclitaxel (125mg/

m^2, days 1, 8) every 3 weeks. The maintenance therapy of camrelizumab (200 mg, day 1, every 3 weeks) was given to pts who did not progress after 4-6 cycles of chemotherapy until disease progression or unacceptable toxicity. Response was assessed every 6 weeks in accordance with RECIST1.1. The primary endpoint was overall response rate (ORR), and secondary endpoints included safety profile, progression free survival (PFS), overall survival (OS), and disease control rate (DCR).

Results: Between December 2020 and March 2023, a total of 28 pts were enrolled in this study. Median age was 57.5 (range: 35-71) years, and most pts were male (75.0%). Among 21 pts who were evaluated, the ORR was 71.4% (15/21) and the DCR was 95.2% (20/21). The median PFS was 9.3 months (95% CI: 7.0-11.6), the Median follow-up time was 14.3 months (95% CI: 9.9-18.7), and the one-year survival rate was 85.7%. The most common treatment-related adverse events of grade 3 or 4 included neutropenia (22.2%), leukopenia (22.2%), erythra (3.7%). There were no treatment-related deaths.

Conclusions: Camrelizumab plus albumin-bound paclitaxel and S-1 demonstrated promising activity and manageable safety in first-line treatment of HER-2- negative advanced gastric/gastroesophageal junction cancer.

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1545P Phase II trial of endostar in combination with concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of esophagus

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Background: To evaluate the efficacy and safety of Endostar combined with concurrent chemoradiotherapy (CCRT) in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: From May 2017 to February 2021, 92 patients with unresectable thoracic ESCC, clinical staged as IB to IVB disease based on the 8th edition of the American Joint Committee on Cancer (stage IVB: Only metastasis to supraclavicular/celiac lymph nodes) and local recurrence, were enrolled and randomly allocated in Endostar plus concurrent chemoradiotherapy (CCRT)(intervention group; n=46) and concurrent chemoradiotherapy (CCRT) (control group; n=48). Five or six cycles of Endostar (7.5mg/m2/24h ×120h, 7 days/cycle) were delivered in intervention group. The primary endpoint was overall survival (OS). The secondary endpoints were progression-free survival (PFS), 1-year and 2-year overall survival rate and adverse events (AE).

Results: The median age was 63(interquartile range, 50-77) years in intervention group and 65(interquartile range, 52-79) years in control group. A total of 68 patients (74%) had stage III and IV disease. The intervention group had a significant higher complete response rate (ORR) than the control group (80% vs. 63.8%; $P<0.05$). The 1- and 2-year overall survival rates were 88.1% and 75.2% in intervention group, 87.4% and 62.3% in control group, respectively ($P>0.05$). The were no significant differences in the incidence of grade 3 or higher toxic effects between the intervention group and control group ($P>0.05$).

Conclusions: The median age was 63(interquartile range, 50-77) years in intervention group and 65(interquartile range, 52-79) years in control group. A total of 68 patients (74%) had stage III and IV disease. The intervention group had a significant higher complete response rate (ORR) than the control group (80% vs. 63.8%; $P<0.05$). The 1- and 2-year overall survival rates were 88.1% and 75.2% in intervention group, 87.4% and 62.3% in control group, respectively ($P>0.05$). The were no significant differences in the incidence of grade 3 or higher toxic effects between the intervention group and control group ($P>0.05$).

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1546P Safety, efficacy, and biomarkers for ONO-4578 plus nivolumab in unresectable advanced or recurrent gastric or gastroesophageal cancer

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Background: Prostaglandin E_2 (PGE_2) and its receptor EP4 showed immunosuppressive activity in cancers. In the ONO-4578-01 phase I study parts A/B, ONO-4578 (4578), which is an antagonist of EP4, alone and in combination with nivolumab (NIV) demonstrated a manageable safety profile in patients (pts) with advanced or metastatic solid tumors (Cancer Sci. 2023;114:211-220). Part C evaluated the safety, preliminary efficacy, and biomarkers of 4578 + NIV in pts with gastric or gastroesophageal (G/GEJ) cancer.

Methods: Part C was conducted at 22 sites in Japan, and it included pts with unresectable advanced or recurrent G/GEJ cancer who previously received at least two regimens. We categorized pts into three groups: IO-treated, pts who received immune-oncology (IO) treatment with anti-PD-(L)1 antibody as the most recent treatment; IO-naïve, pts without IO treatment; UGT1A1p, pts with *UGT1A1* polymorphism. Pts received oral 4578 (40 mg) daily and NIV (480 mg) every 4 weeks. The primary endpoint was safety. We assessed biomarkers with multiple methods including immunostaining and RNA-seq using pts' tumor tissues, and urine PGE_2 metabolite (PGEM) analysis.

Results: The IO-treated, IO-naïve, and UGT1A1p groups included 30, 30, and 6 pts, respectively, with a median age of 65.0 years. Treatment-related adverse events (TRAEs) occurred in 46 (70%) pts, wherein grade ≥3 TRAEs occurred in 17 (26%). No pts died due to TRAEs. Tolerability was confirmed in UGT1A1p. The investigator-assessed objective response and disease control rates were 10% and 73% in IO-treated and 17% and 40% in IO-naïve, respectively. Of note, >50% of the IO-treated pts achieved tumor shrinkage. In biomarker analyses, we observed signs of activated immune status in the tumor microenvironment after treatment, such as increases in T cell signature score and number, and relative increase of the ratio of M1 macrophage signature score to that of M2. Baseline urine PGEM, the potential surrogate marker of tumor PGE_2, was higher in pts with PR or SD than in pts with PD, suggesting the contribution of 4578 to the antitumor activity.

Conclusions: 4578 + NIV demonstrated a manageable safety profile and antitumor activity in pts with G/GEJ cancer.

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1547P SNP discovery based on transcriptome sequencing of whole blood RNA to find predictive biomarkers for nivolumab in gastric cancer

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Background: Nivolumab (Nivo) monotherapy showed a survival benefit for patients (pts) with advanced gastric cancer (AGC), while its efficacy is limited, raising an urgent need to discover biomarkers. Here, we performed SNP discovery based on gene ontology (GO) terms analysis from transcriptome sequencing of whole blood RNA to find predictive biomarkers of Nivo in AGC.

Methods: We analyzed differential gene expression and SNPs data in pts with available pre-treatment blood samples from the DELIVER trial (JACCRO GC-08), an observational/translational study (UMIN000030850) that enrolled 501 AGC pts treated with Nivo alone. The GO-terms analysis was performed to identify genes associated with outcomes (CR/PR vs. SD/PD, non-PD vs. PD, non-hyper progressive disease [HPD] vs. HPD) in the exploratory cohort (the first 200 pts), and then the results were confirmed in the validation cohort (the last 301 pts). For the validated genes, SNP analysis was carried out to further assess genetic relatedness.

Results: When comparing pts with non-PD and PD, 205 genes in metabolic-related GO-Terms were upregulated in pts with non-PD; 12 SNPs in 12 genes (BICD1, PKD2, GOPC, TXK, SYPL1, PAQR8, ZC3H3, RNF138, ZFP90, ZC3H3, DDX60, FAM175B) were correlated to non-PD. In tumor response, 107 genes in nucleic acid-related GO-Terms were upregulated in pts with CR/PR; 5 SNPs in 4 genes (PDE3B, ZNF333, ACACB, ZNF780A) were correlated to CR/PR. In comparison between pts with non-HPD and pts with HPD, 306 genes in immune-related GO-Terms were enriched in pts with non-HPD and the median expression value of this genes set was significantly higher in pts with non-HPD; 16 SNPs in 12 genes (COX10-AS1, PASK, DOCK10, CDS2, PASK, CSGALNACT1, ARHGAP26, HLA-DQA1, DIAPH2, NFATC1, ARHGAP6, LCP2, RASA3) were correlated to non-HPD.

Conclusions: Our translational study demonstrated for the first time that gene expression of whole blood and SNPs as host-related markers can potentially predict response to Nivo in AGC.

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1548P PD-L1 assessment in oesophageal and gastro-oesophageal adenocarcinoma with PD-L1 IHC 22C3 pharmDx and PD-L1 IHC 28-8 pharmDx assays on Autostainer Link 48: The University Hospitals Birmingham experience over a period of 18 months

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Background: In England, the National Institute for Health and Care Excellence (NICE) recommends Nivolumab and Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy, as an option for untreated HER2-negative, advanced or metastatic oesophageal and gastro-oesophageal junction adenocarcinoma in adults whose tumors express PD-L1 with a combined positive score (CPS) of 5 or more (Nivolumab) or of 10 or more (Pembrolizumab).

Methods: Our Department uses both PD-L1 IHC 22C3 pharmDx (Agilent) and PD-L1 IHC 28-8 pharmDx (Agilent) assays on Autostainer Link 48. We report on our experience of testing over a period of 18 months. Both tests are ISO accredited; reporting was performed by 2 expert pathologists and 1 expert scientists, all trained for PD-L1 reporting.

Results: 3892 tumours were tested with the PD-L1 IHC 22C3 pharmDx (Agilent) assay: 31.5% showed CPS more than 10 1209 tumours were tested with the PD-L1 IHC 28-8 pharmDx (Agilent) assay: 25% showed CPS more than 5. 700 tumours were tested with both assays: 95% were eligible for none or both Nivolumab or Pembrolizumab according to the respective guidelines; 13% of tumours showed CPS >5 and <10 with the PD-L1 IHC 28-8 pharmDx (Agilent) and CPS >10 with the PD-L1 IHC 22C3 pharmDx (Agilent) assay.

Conclusions: The rate of positivity of PD-L1 expression with both assays is lower than initially shown in trials (was up to 45%); we do not have a clear explanation for this; we however have ruled out technical artefacts since we used companion diagnostics, validated in our Laboratory and have negative and positive controls in each slide; the interpretation is performed by trained experienced pathologists or scientists. Our audit provides data on the equivalence between both assays; this could help Laboratories to adopt a strategy regarding PD-L1 testing, especially to decide on the need or not to test tumours with both assays.

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1549P A prospective study of circulating tumor DNA (ctDNA) genomic profiling in gastric or gastroesophageal junction (GEJ) cancer patients with recurrence after adjuvant chemotherapy: Liquid-GEAR trial

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Background: The genomic profile of gastric or GEJ cancer is unclear in cases that have recurred after primary adjuvant chemotherapy. We investigated genomic alterations (GA) detected in ctDNA using a liquid biopsy test and compared the results to the those of the primary tumor.

Methods: This prospective observational study was conducted at 17 institutes from Jan 2021 to Dec 2022. Eligible patients (pts) had previously resected stage II or III gastric/GEJ cancer with recurrence after or during adjuvant chemotherapy. Whole blood was collected before chemotherapy for recurrent disease; ctDNA was analyzed

using a next-generation sequencing gene panel (Guardant360). The primary endpoint was the detection rate of actionable GA with at least level 3 evidence by OncoKB for any cancer type. Secondary endpoints included a comparison of ctDNA and primary tumor GA profiles, and biomarkers relevant to clinical outcomes. A binomial test was used to determine with 90% probability that actionable GA were found in ctDNA in more than 5% of cases.

Results: Among 51 enrolled pts, 50 were available for analysis, 14% stage II and 86% stage III. The most common primary site was gastric body (56%) followed by gastric antrum (26%), and GEJ (12%). The number of metastatic sites was 1 for 76%, 2 for 18%, and 3 for 6% pts. Liquid biopsy analysis detected actionable GA in 64% [90%CI: 49.2-77.1] and actionable GA for targeted therapy in 36% pts [90%CI: 22.9-50.8, *P*=0.0075]:*PIK3CA* in 20%, *ARID1A* in 10%, *ERBB2* in 8% (6% amplification and 2% mutation), *ATM* in 6%, and *BRCA2*, *EGFR*, *IDH2*, *RAF1*, and *ROS1* in 2% pts each. MSI-high was detected in one patient. Comparison of primary tumor DNA and ctDNA at recurrence is ongoing.

Conclusions: Using ctDNA analysis, our study demonstrated that potentially actionable GA occur in nearly one-third of pts with recurrence after curative-intent treatment of stage II-III gastric/GEJ cancer. Genomic profiling should be strongly considered in this setting. We will compare these data with genomic analysis of primary tumor tissues.

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Legal entity responsible for the study: The authors.

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1550P Evaluating the novel combination of pressurized intraperitoneal aerosol chemotherapy-oxaliplatin (PIPAC-OX) as an immunomodulator in combination with systemic nivolumab for gastric cancer peritoneal metastases

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Background: Combination therapies with immunomodulators and systemic immune checkpoint inhibitors (ICIs) may overcome cancer resistance to immunotherapy. In gastric cancer patients with peritoneal metastases (GCPM), PIPAC-OX has been shown to induce direct DNA-damage and immunogenic cell death but has not been evaluated in combination with ICIs. We conducted a phase I study, evaluating the safety and efficacy of PIPAC-OX in combination with systemic nivolumab.

Methods: Patients with predominant GCPM who had progressed on at least 1st -line systemic chemotherapy were recruited across 3 centers in Singapore and Belgium. After initial staging laparoscopy, patients received PIPAC oxaliplatin at 90mg/m2 every 6 weeks with intravenous nivolumab at 240mg every 2 weeks, up to disease progression or death. Response was evaluated clinically by Peritoneal Carcinomatosis Index (PCI) and Response Evaluation Criteria in Solid Tumors (RECIST), while histological response was determined with the Peritoneal Regression Grading Score (PRGS).

Results: In total, 18 patients with GCPM were prospectively recruited and underwent a combined total of 32 cycles of PIPAC with a median follow-up of 7.1 months. The first cycle of PIPAC was successfully administered in all patients while 50% (9/18), and 28% (5/18) received 2 & 3 cycles respectively. Common adverse events included abdominal pain and diarrhea while three (9.4%) PIPAC-related severe adverse events including diarrhea and transaminitis were reported. Objective response was seen in 7.1% while disease control was achieved in 57.1% of patients. The median PCI decreased by 5 and 7 points, while PRGS grade 1-2 response was seen in 67% and 100% at 2nd & 3rd PIPAC respectively. Those that received 3 PIPACs had a median OS of 19.8m (vs 2.9m for 1 PIPAC, p = 0.01).

Conclusions: PIPAC-OX in combination with systemic nivolumab was safe and tolerable, with some responses seen. Ongoing biomarker and translational analyses may yield further insights into the unexpected long-term responders and define the subgroup most likely to benefit from combination locoregional and systemic therapy for GCPM.

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1551P Clinicopathologic characteristics and genomic profiling of HER2-low advanced gastric cancer

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Background: Recent advances in HER2-targeting agents, including HER2 antibody-drug conjugates have shown promising results in targeting HER2-low expressing cancers. We performed retrospective study to characterize clinicopathologic features and genomic profiling of HER2-low advanced gastric cancer (AGC) compared to HER2-high or HER2-none expressing tumors.

Methods: We retrospectively analyzed patients with stage IV AGC with known HER2 status who were systemically treated in Yonsei Cancer Center, Korea. HER2-low tumors were defined as HER2 IHC 2+/ISH- or HER2 IHC 1+. Patients whose pre-treatment tumors were molecularly profiled with in-house next-generation sequencing (NGS) were further evaluated. Clinicopathologic characteristics including biomarker distribution and survivals, and genomic profiling including oncogenic signalling pathways were analyzed according to HER2 status.

Results: Among total 953 patients diagnosed as recurrent/metastatic AGC from August 2008 to February 2022, HER2-high, HER2-low, and HER2-none (HER2 IHC 0) patients were 122 (12.8%), 244 (25.6%), and 587 (61.6%), respectively. For HER2-low tumors compared to HER2-high and HER2-none, there was no statistical difference in distribution of pathology, EBV, MSI, or PD-L1 expression status. HER2-low patients showed similar survival as HER2-none, but shorter survival compared to HER2-high, in terms of progression-free survival of palliative first-line chemotherapy (6.3 vs 6.0 vs 8.5 months, *P*=0.0002) and overall survival (14.8 vs 14.4 vs 20.7 months, *P*=0.0001). There was no difference in survival between HER2 IHC 2+/ISH- and IHC 1+. HER2-low tumors had enhanced survival with the first-line chemotherapy when combined with immunotherapy. Among patients who have undergone in-house NGS excluding EBV-positive or MSI-H tumors (n=183), HER2-low tumors showed similar TMB compared to HER2-high and HER2-none tumors, but highest genetic alteration rates in PI3K pathway (62 vs 54 vs 54%), TGF-ß pathway (32 vs 22 vs 29%), and JAK/STAT pathway (15 vs 9 vs 8%).

Conclusions: We observed that HER2-low AGC patients showed similar but distinct clinicopathologic and genomic profile compared to HER2-none patients. Further strategies to target HER2-low AGC patients are warranted.

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1552P Clinical multi-omics analysis of gastric cancer (GC) in Europe (EU) and Latin America (LatAm): The LEGACy project

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Background: Gastric cancer is heterogenous with poor prognosis. The LEGACy project aimed to deepen GC molecular understanding through multi-omics analysis of tumours from EU and LatAm. We present partial results including histopathology, immunohistochemistry (IHC) + in-situ hybridization (ISH) markers, immune cell infiltration pattern, broad multi-gene sequencing panel and targeted transcriptomics of stage IV GC paraffin-embedded tissues.

Methods: After the central pathological confirmation of GC, standard IHC/ISH was performed, nucleic acids were extracted for DNA sequencing of 435 genes (covering mutations, copy number, fusions, MSI + TMB), and mRNA was profiled with custom Nanostring gene expression assay. The primary aim was to explore a clinically feasible diagnostic classification of GC: a. MSI; b. EBV+; c. HER2+; d. other intestinal-type (IT); and e. other poorly cohesive-type (PCT) f. and mixed. Only significant associations (P values <0.05) in non-parametric tests adjusted for multiple testing are reported.

Results: Out of 334 GC patients were enrolled in the project, 148 were eligible for molecular analysis Prevalence of GC subtypes: MSI 11%, EBV+ 4%; HER2+ 9%, IT 41%, PCT 31% and mixed 4%. We found higher HER2+ and IT tumors in EU vs. LatAm (14% vs. 6% and 46% vs. 30%, respectively). MSI tumors had highest TMB (median 38 mut/Mb) enriched for KMT2D, KRAS, PIK3CA and RNF43 mut, but no differences in immune cell infiltration/activation. EBV+ tumors had intermediate TMB (median 14 mut/Mb), highest PIK3CA mut, highest CD3/CD8 infiltration, cytotoxic and apoptotic signatures. HER2+ tumors were enriched for TP53 mut. While both IT and PCT samples had low TMB (median $<$ 7 mut/Mb) and higher dendritic cell/mast cell infiltration, IT tumors had high cell cycle activation + TP53 mut, and PCT tumors had low Ki67, highest Hedgehog + Notch + Wnt activation scores. Interestingly, PCT tumors from LatAm had higher median TMB (7 mut/Mb) when compared to EU (4 mut/Mb). Overall, PDL1 expression was similar across the groups.

Conclusions: Our pathological-molecular classification of GC is comparable with TCGA and others, with potential differences in prevalence and mutational signatures for EU and LatAm populations that will be further explored.

Clinical trial identification: NCT04015466.

Legal entity responsible for the study: INCLIVA Biomedical Research Institute, Valencia, Spain.

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1553P Blood-borne assessment of stromal activation in esophageal adenocarcinoma to guide tocilizumab therapy: A randomized phase II proof-of-concept study

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Background: Production of IL6 by the tumor stroma of esophageal adenocarcinoma (EAC) causes epithelial-to-mesenchymal transition of tumor cells and resistance to chemoradiation (Ebbing *et al.* 2019). Serum ADAM12 protein levels measure stroma activity (Veenstra *et al.* 2018) whilst IL6 and IL6R monitor IL6 inhibition (Nishimoto *et al.* 2008). Here, we aim to demonstrate that targeting stroma with tocilizumab in EAC patients increases efficacy of chemoradiation.

Methods: This was a multicenter, randomized, open label, phase II proof-of-concept trial in 48 patients with resectable EAC. Patients were stratified for serum ADAM12 (cutoff of 203 pg/mL) and randomized for standard of care chemoradiation according to the CROSS regimen or addition of tocilizumab to standard of care, followed by surgery. Tocilizumab 8 mg/kg with a maximum of 800 mg was given intravenously for three cycles. Serum ADAM12, IL6 and IL6R was measured at baseline, during treatment, at resection and three months thereafter. Primary endpoint was histopathological response to chemoradiation according to the Mandard score.

Results: After inclusion of 36 patients, the trial was discontinued due to safety concerns. Perforation of the esophageal wall was observed in 3/20 (15%) of patients in the intervention arm compared to 0/16 (0%) in the control arm. There was no significant difference in Mandard score between treatment arms ($p = 1.000$). Patients treated with tocilizumab had significantly higher serum levels of IL6 and IL6R during treatment ($p < 0.0001$). Baseline ADAM12 was not associated with histopathological response to tocilizumab ($p = 0.672$). There was no difference in serum ADAM12 levels over time between treatment arms.

Conclusions: Addition of tocilizumab to neoadjuvant chemoradiation in patients with EAC is unsafe and should not be considered for clinical practice. Potentially, concurrent inhibition of IL6 impairs wound healing whilst chemoradiation obliviates the tumor in the esophageal wall, increasing the risk for perforation. We plan to investigate this hypothesis with RNA sequencing, immunohistochemistry, cytokine profiling, and flow cytometry of peripheral blood mononuclear cells and tumor biopsies.

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Legal entity responsible for the study: Amsterdam UMC, location AMC.

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Institutional, Advisory Role, Unrelated to the present study: Bristol Meyers Squibb; Financial Interests, Institutional, Funding, Unrelated to the present study: Incyte; Financial Interests, Institutional, Invited Speaker, Unrelated to the present study: Benecke, Medtalks, Novartis, Servier. M.F. Bijlsma: Financial Interests, Institutional, Funding, Unrelated to present study: Celgene, Lead Pharma; Financial Interests, Institutional, Advisory Role, Consultant: Servier. H.W.M. Van Laarhoven: Financial Interests, Institutional, Advisory Board: BMS, MSD; Financial Interests, Personal, Invited Speaker: Lilly; Financial Interests, Institutional, Writing Engagement: Nordic Pharma; Financial Interests, Institutional, Invited Speaker: Servier; Financial Interests, Institutional, Research Grant, REPEAT study: Bayer; Financial Interests, Institutional, Research Grant: BMS, Philips; Financial Interests, Institutional, Local PI, FRACTION study: BMS; Financial Interests, Institutional, Research Grant, ACTION study: Celgene; Financial Interests, Institutional, Research Grant, DECO study: Janssen; Financial Interests, Institutional, Local PI, RAINFALL study: Lilly; Financial Interests, Institutional, Local PI, KEYNOTE 062 and KEYNOTE 181 study: Merck/MSD; Financial Interests, Institutional, Research Grant, SOX study: Nordic Pharma; Financial Interests, Institutional, Research Grant, TRAP study, PERFECT study; local PI of JACOB study: Roche; Financial Interests, Institutional, Research Grant, LyRICX study: Servier; Financial Interests, Institutional, Research Grant, TAPESTRY study: Merck; Financial Interests, Institutional, Research Grant, Research money and investigational product: Incyte; Non-Financial Interests, Institutional, Product Samples, For all clinical study mentioned, study medication is provided: See 'research funding'. All other authors have declared no conflicts of interest.

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1554P Clinical Impact of ERBB2 copy number and tumor mutation burden (TMB) in patients with HER2- positive advanced gastric cancer treated by nivolumab (N-mab) plus trastuzumab (T-mab) and standard chemotherapy

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Background: We conducted a clinical trial evaluating safety and efficacy of T-mab plus N-mab with S-1/Capecitabine plus oxaliplatin (UMIN000034222). The aim of this study was to investigate the clinical significance of *ERBB2* amplification (amp.) and TMB-H for this new combination therapy.

Methods: Patients were treated with S-1 80 mg/m2/day or Capecitabine 2000 mg/m2/day on days 1-14 with oxaliplatin 130 mg/m2, N-mab 360mg, and T-mab 8mg/kg for initial treatment, and subsequently with 6 mg/kg on day, repeated every 3 weeks. Pretreatment primary tumor samples were collected for whole exome sequencing (WES) and immunohistochemistry (IHC).

Results: Among 42 patients enrolled in this clinical trial, WES was performed on 23 patients. ERBB2 amp. ($\geq$ 6 copies) was observed in 15 patients (65%). Fourteen (93.3%) of these 15 patients with ERBB2 amp. and 2 (25%) of 8 patients without ERBB2 amp. were IHC3+, respectively ($p = 0.002$). There was a weak positive correlation between ERBB2 copy number and PFS ($r = 0.449$, $p = 0.032$). Patients with ERBB2 amp. showed longer PFS than those without ERBB2 amp. (mPFS: 16.3 vs 5.8 months, HR = 0.70 [95%CI 0.24-2.09], $p = 0.522$). In particular, 7 patients with high ERBB2 copy number ($\geq$ 50) showed remarkably longer PFS and a higher response rate than 16 patients with $<$ 50 (mPFS: 20.8 vs 6.7 months, HR = 0.40 [95%CI 0.12-1.30], $p = 0.117$, response rate: 100% vs 63%, $p = 0.124$). TMB-H ($\geq$ 10 muts/Mb) was observed in 6 patients (26%), and these patients also showed substantially longer PFS than those with TMB-L (mPFS: 16.3 vs 9.2 months, HR = 0.43 [95%CI 0.12-1.51], $p = 0.172$) with a comparable response rate (83% vs 73%). Eleven patients with ERBB2 copy number $\geq$ 50 or TMB-H showed significantly longer PFS (mPFS: 20.8 vs 5.8 months, HR = 0.28 [95%CI 0.09-0.88], $p = 0.021$) and OS (mOS: not reached vs 15.0 months, HR = 0.10 [95%CI 0.01-0.78], $p = 0.007$) and a higher response rate (91% vs 58%, $p = 0.155$) than the remaining 12 patients.

Conclusions: High ERBB2 copy number and TMB-H may be a candidate biomarker for this new combination therapy including T-mab and N-mab in patients with HER2-positive advanced gastric cancer.

Clinical trial identification: UMIN000034222.

Legal entity responsible for the study: Daisuke Takahari.

Funding: Ono Pharmaceutical Co., Ltd.

Disclosure: H. Shoji: Financial Interests, Personal, Advisory Board: Ono Pharmaceutical Co., Ltd., Zymeworks inc.; Financial Interests, Institutional, Local PI: Ono Pharmaceutical Co., Ltd., MSD, Astellas, Amgen, Daiichi Sankyo; Financial Interests, Institutional, Funding: Ono Pharmaceutical Co., Ltd., Takeda Pharmaceuticals. K. Minashi: Financial Interests, Institutional, Research Grant: Amgen, Taiho Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd., Astellas Pharmaceutical Co., Ltd. H. Hara: Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, Boehringer Ingelheim, MSD; Financial Interests, Personal, Invited Speaker: Daiichi Sankyo, MSD, Ono, Bayer, Chugai, Lilly, Merck Biopharma, Taiho, Takeda, Yakult, Bristol Myers Squibb; Financial Interests, Institutional, Invited Speaker: Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Janssen, Merck Biopharma, MSD, Ono, Taiho, ALX oncology. N. Boku: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Eli Lilly, Ono Pharmaceutical, Taiho, Daiichi Sankyo; Financial Interests, Institutional, Research Grant: Takeda Pharmaceutical, Ono Pharmaceutical. K. Yamaguchi: Financial Interests, Personal, Invited Speaker: Taiho; Financial Interests, Personal, Expert Testimony: Daiichi Sankyo, Bristol Myers Squibb, Ono, Eli Lilly Japan; Financial Interests, Institutional, Funding: Taiho. All other authors have declared no conflicts of interest.

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1555P Cell-free DNA analysis in patients with metastatic gastroesophageal adenocarcinoma: Preliminary results of the REGIRI - PRODIGE 58 ancillary study

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Background: Cell-free DNA (*cfDNA*) analysis has shown promising results for the management of patients with cancer, but few data exist in patients with metastatic gastro-esophageal adenocarcinomas (mGEA). In this study, we analyzed *cfDNA* extracted from blood of patients included in the REGIRI - PRODIGE 58 trial (Regorafenib + irinotecan as 2nd line in patients with mGEA).

Methods: 239 samples from 34 patients with mGEA included in the Regiri arm were available for analysis. Plasma samples were taken before treatment's initiation, then at days 1, 2, 8 and 15 of Cycle 1 and days 1, 8 and 15 of Cycle 2. *cfDNA* was extracted from plasma, concentrations and fragments sizes determined by fragment analysis. First and last time points were selected to estimate concentration's evolution for each patient.

Results: A cfDNA threshold concentration (tc) of 0.55 ng/µL was settled as the best threshold at baseline to separate patients into 2 groups "low" and "high" corresponding to concentrations lower or greater than tc respectively. Among the 34 patients analyzed, 1 patient was excluded because of genomic DNA contamination in plasma at baseline. 16 patients (48.48%) were in the "low" group and 17 (51.52%) in the "high" group. For *cfDNA* concentration at baseline and PFS, a trend non-statistically significant difference (HR=0.53; CI95[0.2595;1.085]; p=0.0564) was found: Low cfDNA concentration at baseline was associated with a better PFS (2.6 vs 1.7 months). 4 distinct subgroups emerged: Patients with low concentration at baseline that remains low (low-low), low at baseline with an increase during follow-up (low-high), high at baseline with a decrease during follow-up (high-low) and high at baseline that remains high (high-high). A statistically significant difference was found for PFS (4.55 vs 2.11 months) between the low-low and high-high subgroups respectively (HR=0.4139; CI95[0.1652;1.037]; p=0.022).

Conclusions: Our findings suggest that cfDNA concentration at baseline and cfDNA clearance might have an interest to predict PFS in patients with mGEA. Further investigations are ongoing to decipher if genomic signatures can be predictive of PFS in patients with mGEA.

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1556P Pharmacokinetics, pharmacodynamics and exposure response analyses of osemitamab in patients with locally advanced or metastatic solid tumors

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Background: Osemitamab, a humanized Claudin18.2 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC) via improved binding affinity and reduced fucosylation, is being developed to treat metastatic gastric/gastroesophageal junction (G/GEJ) adenocarcinoma. Pharmacokinetics (PK), pharmacodynamics (PD) and exposure-response (ER) relationship of Osemitamab were evaluated in two phase I/IIa studies.

Methods: Osemitamab was administrated as monotherapy or in combination with standard of care (SOC) in patients. PK profiles of osemitamab were determined using non-compartmental analysis and population PK. The ADCC capacity of circulating osemitamab was tested in a subset of patients who received 3-10mg/kg Q3W. Relationships between PK and objective response rate (ORR) and safety were explored.

Results: A total of 2401 PK data were obtained from 248 patients from two clinical trials. Similar PK was observed between the US and Chinese patients. PK is dose proportional between 0.3 to 15 mg/kg. A two-compartment model with first-order elimination described the PK profile of osemitamab. Clearance (CL) was affected by body weight and gastrectomy history. Model simulated steady state trough concentration will achieve in vitro ADCC assay EC95 and in vivo MKN45-CLDN18.2 tumor growth inhibition model EC50 in most subjects following 6mg/kg Q3W and 4mg/kg Q2W. ADA incidence is less than 10%. Serum ADCC response remained at $\sim$ 50% of the maximum lysis up to 21 days following osemitamab 6 mg/kg Q3W. Anti-tumor activity data from 58 patients with 1L G/GEJ adenocarcinoma treated with osemitamab and capecitabine and oxaliplatin (CAPOX) showed patients with average concentration in 56 days above 24 µg/mL tended to have a better ORR. Grade 2+ nausea/vomiting are found to be associated with osemitamab exposure; however, simulations demonstrated the proportion of patients that developed Grade 2+ nausea or vomiting by 6 months were just slightly higher ($<$ 10% in difference) following 6 mg/kg Q3W than 3 mg/kg Q3W.

Conclusions: Osemitamab at 6mg/kg Q3W or 4mg/kg Q2W are predicted to have favorable PK/PD/safety profiles and might be associated with better ORR in combination with SOC compared to the lower doses.

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1557P Single-cell RNA-seq dissecting the initiating liver metastasis cells and liver metastatic microenvironment in gastric cancer

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Background: Liver metastasis (LM) frequently occurs in patients with advanced gastric cancer; yet our understanding of the underlying salient biology is preliminary. Here, we performed single-cell RNA-seq in two patients with LM of gastric cancer to explore the initiating liver metastasis cells and liver metastatic microenvironment in gastric cancer.

Methods: Single cell RNA sequencing was performed on tissues from LM of gastric cancer. Also, we downloaded the single-cell RNA-seq of hepatocellular carcinoma (HCC) and primary gastric cancer from GEO database. Seurat were applied to sort single-cell RNA-seq of LM in gastric cancer and primary gastric cancer into different clusters via feature dimension reduction and then we investigated their expression profiling, stemness initiating and enrichment pathways. Furthermore, CellChat and monocle2 were used to explore the cellular communication and regulatory network of liver metastatic microenvironment.

Results: The transcriptomes of 13305, 26373, 20207 single cells among LM of gastric cancer, HCC, and primary gastric cancer were extracted respectively. There were 14 clusters divided into epithelial cells of liver metastasis single cells. Differential gene analyses and ratio analyses in LM and corresponding primary cancers groups showed that C10 and C12 might be the LM initiating cells clusters. And they were both enriched in the positive regulation of cell migration. $SOX6^+$ $MMP7^+$ epithelial cells might be the LM initiating cells in gastric cancer. Cell communication and inverse temporal analysis showed that $SEPP1^+$ macrophage and $CXCL2^+$ cancer associated fibroblasts (CAFs) might regulate metastatic microenvironment, of which promoted cancer stem cells migration.

Conclusions: The initiating liver metastasis cells and liver metastatic microenvironment in gastric cancer have been investigated in this study, which provided a further understanding of the potential biological mechanisms of LM in gastric cancer.

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1558P Preoperative pembrolizumab plus chemotherapy for resectable esophageal squamous cell carcinoma (ESCC): The phase II Keystone-001 trial

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Background: The Keystone-001 study was designed to prospectively evaluate the efficacy and safety of preoperative treatment with pembrolizumab plus paclitaxel and cisplatin followed by Da Vinci robotic radical surgery in patients with locally advanced (stage III) ESCC. The study also explored the potential mechanism of this treatment strategy (NCT 04389177, 5/15/2020).

Methods: The full study methods for this prospective, single-arm, single-center, open-label, phase-II study have been published previously. For further investigating the immune cell subpopulations that determine the efficacy, we performed single-cell sequencing on peripheral blood and tumor tissues after neoadjuvant therapy, and validated using flow cytometry.

Results: Of the 49 patients enrolled between July 8, 2020, and February 10, 2022, 47 received neoadjuvant therapy and were included in the ITT analysis. Among all patients who received neoadjuvant therapy, no grade $\geq$3 AEs were reported. Improvements from baseline nutritional status were observed with increases in patients' median body weight and NRI. QoL evaluations showed improvements from baseline to post-adjuvant therapy in all functional scales and symptom scales of EORTC QLQ-C30 and in all items of the EORTC QLQ-OES18 questionnaire. Among all 45 patients in the efficacy analysis, the MPR rate was 73.3%, the pCR rate was 42.2%, the ORR was 95.6%, and the DCR was 100%. After a median follow-up of 23.3 months (95% CI 20.6, 24.9; maximum follow-up 34 months), the 1- and 2-year OS and DFS rates were 95.6 and 90.5% and 95.6 and 86.3%, respectively. The single-cell sequencing results showed that the main cell populations that affect the response of this treatment strategy were NKT and NK cell subpopulations in peripheral blood. Further analysis

results showed that the TRGC2+NKT and FGFBP2+NK cell subpopulation in peripheral blood were more significantly increased in peripheral blood from patients with a good response.

Conclusions: The preliminary findings of this trial were safe and effective, and further phase III studies (Keystone-002) have begun to recruit participants.

Clinical trial identification: NCT 04389177.

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1559P PD-L1 expression as a negative predictive biomarker in advanced esophageal squamous cell cancer treated with chemotherapy alone: A KMSubtraction derived analysis

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Background: Prognosis for aESCC (advanced esophageal squamous cell carcinoma) remains poor. Programmed death-ligand 1 (PD-L1) expression is a well-established positive predictive biomarker for response to immunotherapy in aESCC. However, the association between PD-L1 and response to chemotherapy alone remains unclear. This study aims to determine the prognostic significance of PD-L1 expression in patients treated with first-line chemotherapy alone in aESCC.

Methods: First-line phase III randomized trials that included PD-L1 expression as a biomarker in aESCC were extracted after a systematic search of Embase and PubMed from inception until September 24, 2022. Only trials that reported PD-L1 stratified Kaplan-Meier (KM) curves of chemotherapy arms were included. A graphical reconstructive algorithm was used to estimate time-to-event outcomes from reported KM plots in all overall and reported subgroup cohorts. Where unavailable, KMSubtraction was utilized to derive KM plots of unreported PD-L1 subgroups. Thereafter, individual patient data meta-analysis was conducted. Survival analyses for overall and progression-free survival (OS, PFS) were conducted with Cox proportional hazards models with a shared-frailty term incorporated to account for inter-study differences.

Results: Chemotherapy arms from 5 randomized phase III trials - CheckMate-648, ESCORT-first, KEYNOTE-590, RATIONALE306 and ORIENT-15 — comprising 1,517 patients were included in the OS analysis. Compared to PD-L1 low expressing tumors, patients with PD-L1 high expressing tumors were at a significantly higher risk of mortality (PD-L1 high [n=769] vs PD-L1 low [n=748], HR=1.152, 95%-CI: 1.018 — 1.305, p=0.025). Three trials — CheckMate-648, ESCORT-first and ORIENT-15 — comprising 949 patients treated with chemotherapy alone were included in the PFS analysis. Likewise, patients with PD-L1 high expressing tumors were at a higher risk of tumor progression, although this was not significant (PD-L1-high [n=513] vs PD-L1-low [n=436], HR=1.076, 95%-CI: 0.923 - 1.253, p=0.35).

Conclusions: Our study found PD-L1 expression is a negative predictor of overall survival in aESCC treated with first-line chemotherapy.

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1560P Osemitamab (TST001): An ADCC enhanced humanized anti-CLDN18.2 mab, demonstrated improved efficacy in combination with anti-PD-L1/PD-1 mab and oxaliplatin/5-FU in preclinical tumor models

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Background: Osemitamab (TST001) is a best-in-class humanized antibody with improved CLDN18.2 binding affinity and ADCC activity. Here, we evaluated the dynamics of on-treatment PD-L1 expression on the tumor cells in both *in vivo* tumor models and *in vitro* tumor cells and studied preclinical efficacy of the combination of Osemitamab and anti-PD-L1/PD-1 mAb +/- oxaliplatin/5-FU (Oxa/5-FU) in both CLDN18.2+/PD-L1+ and CLDN18.2+/PD-L1- tumor models.

Methods: For *in vitro* cell assay, we co-cultured the CLDN18.2-expressing GC cells w/wo human PBMC and 30 μg/ml Osemitamab for 72hr, and then transferred the supernatant to the matched tumor cells for another 72hr incubation. PD-L1 expression on the tumor cells was detected by using FACS analysis. The mouse with CLDN18.2-expressing tumors were injected intraperitoneally with Osemitamab or in combination with anti-PD-L1/PD-1 mAbs twice a week and injected intravenously with oxa/5-FU weekly in *in vivo* efficacy studies. CLDN18.2 and PD-L1 expression on the tumors was detected by using IHC analysis.

Results: We found that in the presence of human immune cells, PD-L1 expression on the CLDN18.2-expressing GC cells *in vitro* and tumors *in vivo* was upregulated after Osemitamab treatment. In two CLDN18.2+/PD-L1+ mouse syngeneic models, Osemitamab combined with Atezolizumab exhibited significantly higher tumor growth inhibition (TGI) than the single agents. Furthermore, in the same tumor model, the triplet [Osemitamab in combination with anti-mouse PD-1 (RMP1-14) + Oxa/5-FU] showed even better TGI than the doublet [Osemitamab + Oxa/5-FU or RMP1-14 + Oxa/5-FU]. Additionally, in a CLDN18.2+/PD-L1- GC PDX model with human PBMC reconstruction on B-NSG-hIL-15 mice, the Osemitamab in combination with Oxa/5-FU was also superior to either Oxa/5-FU or Oxa/5-FU + nivolumab.

Conclusions: PD-L1 upregulation after Osemitamab treatment provides a rationale for combination of Osemitamab and anti-PD-L1/PD-1 mAb. And the potential synergistic effect of Osemitamab and GC standard of care (SoC: anti-PD-1 mAb + Oxa/5-FU) in preclinical tumor models supports Osemitamab in combination with SoC chemotherapy +/- nivolumab in G/GEJ patients.

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1561P APC mutation (mt.), MYC, and GATA6 amplifications (amp.) were associated with worse survival in HER2-positive advanced gastric cancer patients treated with S-1/capecitabine plus oxaliplatin combined with trastuzumab (T-mab) and nivolumab (N-mab)

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Background: Recently, we reported safety and efficacy of T-mab plus N-mab with S-1/Capecitabine plus oxaliplatin (UMIN000034222). The aim of this study was to explore a candidate biomarker for this new combination therapy.

Methods: Patients were treated with S-1 80 mg/m2/day or Capecitabine 2000 mg/m2/day on days 1-14 with oxaliplatin 130 mg/m2, N-mab 360mg, and T-mab 8mg/kg for initial treatment, and subsequently with 6 mg/kg on day 1, repeated every 3 weeks. Pre-treatment primary tumor samples were collected for whole exome sequencing (WES).

Results: 42 patients enrolled in this clinical trial, and WES was performed on 23 patients. In the copy number analysis, *ERBB2* amp. was observed most frequently in 15 patients (65%). Subsequently, *GATA6*, *MYC* and *CCNE1* amp. were observed in 8 (35%), 6 (26%), and 5 (22%) patients, respectively. In the mutation analysis, *TP53* was observed most frequently in 20 patients (87%). Subsequently, mutations in *APC*, *ERBB3*, and *PIK3CA* were observed in 6 (26%), 3 (13%), and 3 (13%) patients, respectively. Among them, *APC* mut., *MYC*, and *GATA6* amp. were associated with worse survival. Patients with *APC* mut. showed significantly shorter PFS (median 5.6 vs 20.8 months, HR 3.47, 95%CI 1.16-10.44, p = 0.018), but not for OS (median 21.0 vs 26.5 months, HR 1.19, 95%CI 0.31-4.60, p = 0.806). Patients with *MYC* amp. showed significantly shorter PFS (median 4.2 vs 18.0 months, HR 3.48, 95%CI 1.09-11.12, p = 0.024) and OS (median 13.9 months vs not reached, HR 3.97, 95%CI 0.95-16.54, p = 0.042), respectively. Patients with *GATA6* amp. showed significantly shorter PFS (median 5.8 vs 32.0 months, HR 3.53, 95%CI 1.25-9.99, p = 0.011) and OS (median 13.9 months vs not reached, HR 3.74, 95%CI 1.04-13.40, p = 0.030). As for objective response rates (ORRs), patients with *APC* mut. and *MYC* amp. showed lower

response rates (50% vs 82% for *APC* mut., 67% vs 77% for *MYC* amp.), whereas comparable ORR was shown for *GATA6* amp. (75% vs 73 %).

Conclusions: *APC* mut., *MYC,* and *GATA6* amp. may have negative clinical impacts on the effects of the new combination therapy including T-mab and N-mab.

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1562P Claudin 18.2 expression in resected gastric cancer

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Background: Zolbetuximab showed efficacy for gastric cancer with Claudin (CLDN) 18.2 expression. CLDN18.2 is reported to be expressed in about 20-50% of gastric cancer, but the definitions varied in previous reports and the relationship with prognosis is controversial. The present study aimed to examine the expression of CLDN18.2 based on SPOTLIGHT/GLOW study and the relationship with prognosis and clinical/molecular characteristics in resected gastric cancer.

Methods: We used a tissue microarray set including gastric cancer samples resected in our institution between July 1989 and September 2009. VENTANA CLDN18 (43-14A) assay was used for immunohistochemistry (IHC) of CLDN18.2. CLDN18.2 expression was judged as positive when $\geq$75% of the tumor cell membrane was stained in moderate-to-strong intensity by IHC. The Combined Positive Score (CPS) was evaluated using Dako PD-L1 28-8 pharmDx assay.

Results: CLDN18.2 was evaluable in 366 samples and expressed in 139 samples (38%). Clinical data was available in 129 patients (pts) with CLDN18.2+ vs 191 CLDN18.2- pts. Patient characteristics in the CLDN18.2+ group vs the CLDN18.2- group were as follows; median age (range), 64 (27 - 85) vs 66 (35 - 83); gender male 94 (73%) vs 139 (73%); HER2 positive 11 (10%) vs 19 (10%); CPS $\geq$5, 64 (50%) vs 88 (46%); dMMR, 4 (3.1%) vs 5 (2.6%); Lauren classification diffuse, 71 (55%) vs 107 (56%); pTstage 1/2/3/4, 13/15/17/84 vs 17/34/28/112; pNstage 0/1/2/3, 27/31/32/39 vs 41/39/50/61; pStage I/II/III, 13/36/80 vs 14/68/109; and adjuvant S-1, 43 (33%) vs 54 (28%). Three-year RFS was 56.8% in the CLDN18.2+ group vs 60.3% in the CLDN18.2- group (HR = 1.07 [95% CI 0.77-1.49], p = 0.68). Three-year OS was 66.9% in the CLDN18.2+ group vs 68.7% in the CLDN18.2- group (HR = 1.13 [95% CI 0.80-1.59], p = 0.49).

Conclusions: CLDN18.2 expression was observed in 38% of resected gastric cancer samples, which was consistent with previous reports. CLDN18.2 expression was not related to prognosis and specific relationship was not observed in clinical/molecular characteristics of resected gastric cancer.

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1563P Tumor-intrinsic subtypes of esophageal adenocarcinoma associate cellular phenotypes with responses to therapy

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Background: Effective treatment of esophageal adenocarcinoma (EAC) is hampered by a high degree of mesenchymal plasticity that contributes to acquired therapy resistance and disease recurrence. Many trials are or have been investigating new treatments, such as additional epidermal growth factor signaling inhibition, to improve patient outcome. However, patient selection methods are limited. The existence of a tissue-level molecular subtype that could be used to stratify patients has remained elusive, in large part due to an abundance of non-tumor cells confounding bulk gene expression data.

Methods: We profiled gene expression from 186 esophageal cancer samples and applied non-negative matrix factorization to identify tumor-intrinsic features. Subgroups were discovered using consensus clustering of the tumor-intrinsic gene expression signatures and single-nucleus RNA sequencing analysis.

Results: Two subtypes were identified; intestinal-like (IL) and mesenchymal-like (ML). The latter enriched following neoadjuvant treatment and during disease progression. In a separate cohort of RNA-sequenced metastatic EAC, the ML subtype was found to predict poor response to treatment. Conversely, IL subtype cancer cells were highly dependent on epidermal growth factor signalling, and sensitive to receptor tyrosine kinase inhibition. Mechanisms behind the dependence on epidermal growth factor signalling are currently elucidated using comprehensive analyses.

Conclusions: Targeting of epidermal growth factor signaling is currently only available for HER2-positive patients, about 15% of all cases. Based on our tumor-intrinsic subtypes, a larger fraction of EAC patients seem to benefit from epidermal growth factor inhibition. Therefore, the ability to assign subtype labels in the clinic will be an important step forward to identify patients who may benefit from additional epidermal growth factor inhibition.

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1564P Gut microbiome and metabolome are associated with the response to chemoradiotherapy in patients with esophageal cancer

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Background: To explore the dynamic change of gut microbiota and metabolites and its predictive role in progression-free survival (PFS) in esophageal cancer (EC) after concurrent chemoradiotherapy (CCRT).

Methods: In this prospective study, 94 newly diagnosed EC patients were recruited. A total of 282 fecal samples were collected at 3 time points (T0, before CCRT; T1, 2 weeks after the initiation of CCRT; and T2, the end of CCRT). Gut microbiota and its metabolites were analyzed by 16S rRNA sequencing and untargeted metabolomics, respectively. Microbe-metabolite correlation networks were compared between patients in the long-PFS group (PFS $\geq$18.0 months) and short-PFS group (PFS $<$18.0 months). A random forest classifier was constructed to identify microbial signature related to PFS. Clinical and microbial factors potentially predictive of PFS were assessed in the univariate and multivariate Cox regression analysis.

Results: At baseline, there was no significant difference in the distribution of microbial species or pathway abundance between the two groups. The abundance of Bacteroidota and Acidobacteria increased, while the abundance of Firmicutes decreased after CCRT. Shannon index (P = .016) and PD index (P = .007) were significantly higher in the long-PFS group than for those in the short-PFS group at T1. These distinct changes in gut microbiota were accompanied by functional alterations in tryptophan, fatty acid, and bile acid metabolism and nucleotide biosynthesis pathways during CCRT. Further metabolomic analyses revealed that the distributions of metabolites from these four essential metabolic pathways varied in the two groups at T1. The PFS-prediction microbial signature at T1 included members of the *Ruminococcus*, and various strains from within the *Blautia* and *Prevotella*. The machine learning classifier based on gut microbiota and metabolites yielded an area under the ROC curve of 0.93. Multivariate analysis indicated PD index (P = .027), the abundance of *Blautia* (P = .033) and deoxycholic acid (P = .025) at T1 were independent predictors of PFS.

Conclusions: Gut microbiota and metabolites composition at 2 weeks after the initiation of CCRT were associated with PFS in EC. Further research is needed to confirm these results.

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1565P ERCC1 gene polymorphism influences overall survival in early oesophageal cancer: Results from the phase III MRC OEO2 randomised controlled trial

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Background: Germline polymorphisms may have an association with survival and response to chemotherapy. We examined the gene polymorphism data from the landmark OEO2 trial which compared chemotherapy plus surgery vs surgery alone in early oesophageal cancer. We reviewed common DNA repair genes polymorphisms and selected a subset that has been validated as predictors of survival or chemotherapy toxicity across different tumor types.

Methods: DNA formalin-fixed paraffin embedded normal tissue was available for 515/802 OEO2 patients and successfully extracted in 90% (464/515) of samples. Gene polymorphisms were investigated for *GSTP1, TS 3'UTR, TS 5'UTR, OPRT, DYPD, ERCC1, ERCC2, XRCC1* using Sequenom or multiplex PCR and gel electrophoresis. We investigated these polymorphisms and their relationship with clinicopathological variables including overall survival (OS) and progression free survival (PFS).

Results: All patients with the ERCC1_rs116115 CT genotype had superior OS and PFS when compared to those with a non CT genotype, OS HR 0.790 95% CI 0.642-0.972 (p=0.026), PFS HR 0.80 95% CI 0.656-0.979 (p=0.03). When stratified into chemotherapy + surgery (C+S) vs surgery alone (S), OS for those in the C+S arm was statistically significantly better in the CT genotype (OS 1.975 vs 1.547 years p=0.047) (HR 0.744 95% CI 0.55-0.998 p=0.048). In the S arm there was no significant difference in OS in the CT vs non CT genotype (1.339 vs 1.258 years p=0.275) (HR=0.849 95%CI 0.633-1.140 p=0.276). Test of interaction between treatment groups and ERCC1 polymorphisms was not significant for OS (p=0.58) and PFS (p=0.17). In patients who received preoperative chemotherapy, those with ERCC1 CT genotype were more likely to have any response to chemotherapy (Mandard TRG 1-4) than patients with non CT genotypes (CT vs non CT, 63% vs. 37%, p=0.031).

Conclusions: Patients with ERCC1 CT genotype had superior OS and PFS when compared to those with non CT genotype. Patients with ERCC1 CT genotype receiving preoperative chemotherapy had a better response compared to those with non CT genotype. ERCC1 polymorphisms have prognostic implications and may serve as biomarkers for preoperative chemotherapy response.

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1566P Clinical relevance of circulating tumor DNA in HER2 -positive advanced gastric cancer: Results from phase Ib trial of HER2 and PD-1 dual targeted therapy (Ni-High)

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Background: Anti-PD-1 antibody in addition to HER2-targeted therapy and chemotherapy may enhance antibody-dependent cell-mediated cytotoxicity and add further chemotherapeutic efficacy for HER2 -positive advanced gastric cancer (AGC). On the other hand, it remains unclear molecular profiles related to efficacy and resistance to this dual targeted therapy. Real-time tracking of these changes of the alteration using ctDNA may contribute to the treatment optimization.

Methods: We enrolled tissue-confirmed HER2 -positive AGC who received chemotherapy with HER2 and anti-PD-1 dual targeted therapy from phase Ib clinical trial. Genomic profiling of 74 genes of their plasma by next-generation sequencing was carried out using ctDNA panel (Guardant 360®) to compare with their clinical parameters, clinical outcomes of dual targeted therapy and *HER2* gene amplifications in matched tissue samples.

Results: Twenty-one patients were eligible in this study. *HER2* gene amplification and single nucleotide variant (SNV) / Indels were detected in 12 (57.1%), 3 (14.3%) patients, respectively. Maximum mutant allele frequency (mMAF) in diffuse type histology were significantly lower than intestinal type histology (P = 0.01), and mMAF were associated with tumor diameter (r = 0.626, P = 0.0032). Tissue and ctDNA *HER2* copy numbers were significantly correlated (r = 0.662, P = 0.019). Patients without *HER2* SNV / Indels (n=17) had significantly longer PFS and OS than patients with *HER2* SNV / Indels (n=3) (median PFS: 20.8 vs 8.4 months; P = 0.04; HR, 0.24, median OS: NA vs 14.0 months; P = 0.037; HR, 0.18). Moreover, patients with focal *HER2* gene amplification (n = 9) had significantly longer PFS and OS than patients with *HER2* aneuploidy (n=3) (median PFS: 20.8 vs 8.4 months; P = 0.007; HR, 0.08, median OS: NA vs 14.8 months; P = 0.0046; HR, 0.077). In patients achieving CR or PR (n=16), mMAF 3 weeks after initiation of chemotherapy was significantly lower than those in patients achieving SD (n=4) (P = 0.0087).

Conclusions: Our data confirmed that *HER2* SNV / Indels and gene amplification status may be predictor of treatment efficacy in patients with HER2- positive AGC who received chemotherapy with HER2 and PD-1 dual targeted therapy.

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1567P The effect of SGLT2i and DPP4i on new-onset gastric cancer and gastric diseases in type 2 diabetes mellitus: A population-based cohort study

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Background: The effects of sodium-glucose cotransporter 2 inhibitors (SGLT2I) and dipeptidyl peptidase-4 inhibitors (DPP4I) on the risk of gastric cancer remains unknown. This study aims to compare the effects of SGLT2I and DPP4I on gastric cancer and other gastric diseases.

Methods: This was a retrospective population-based cohort study of patients with type-2 diabetes mellitus (T2DM) on either SGLT2I or DPP4I between 1st January 2015 and 31st December 2020 in Hong Kong. The primary outcome was new-onset gastric cancer, peptic ulcer (PU), acute gastritis, non-acute gastritis, and gastroesophageal reflux disease (GERD). Propensity score matching (1:1 ratio) using the nearest neighbour search was performed. Univariable and multivariable Cox regression was applied to identify the associations.

Results: This cohort included 62858 T2DM patients (median age: 62.2 years old [SD: 12.8]; 55.93% males). 23442 patients used SGLT2I, and 39416 patients used DPP4I. After matching, the incidence of gastric cancer (incidence rate ratio, IRR: 0.26; 95% confidence interval, CI: 0.18-0.37) was significantly lower in SGLT2I users than in DPP4I. SGLT2I was associated with lower risks of gastric cancer (Hazard ratio, HR: 0.30; 95% CI: 0.19-0.48). SGLT2I was also associated with lower risks of PU (HR: 0.66; 95% CI: 0.47-0.91), acute gastritis (HR: 0.31; 95% CI: 0.20-0.48), non-acute gastritis (HR: 0.35; 95% CI: 0.25-0.49), and GERD (HR: 0.62; 95% CI: 0.50-0.76) compared to DPP4I after adjustments. In the subgroup analysis, the results remained consistent across different age groups and genders. SGLT2I was associated with lower risks of gastric cancer amongst patients without prior H. pylori infection (HR: 0.26; 95% CI: 0.18-0.37) but not those with prior infection (HR: 0.28; 95% CI: 0.08-1.01). The results were consistent in the competing risk models and the different matching approaches in the sensitivity analysis.

Conclusions: SGLT2I was associated with lower risks of new-onset gastric cancer than DPP4I. SGLT2I was also associated with lower risks of PU, acute gastritis, non-acute gastritis, and GERD after matching and adjustments compared to DPP4I.

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1568P Establishment of a platform to predict radiation sensitivity in organoids derived from esophageal cancer patients

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Background: To increase the effectiveness of the treatment, radiotherapy (RT) is frequently combined with chemotherapy, immunotherapy, or radiosensitizer medications. Identifying a patient's radiosensitivity can be important for determining patient's therapy strategy. But there isn't a reliable and pertinent radiation sensitivity prediction model for assessing radiation sensitivity. Here, we propose the cancer organoid-based platform for predicting the individual RT response evaluation and recurrence.

Methods: Eighteen Esophageal cancer biopsy tissues were dissociated to single cells and then disposed with BME on pillar plate (MBD co., Korea) to make the cancer organoids. After forming the organoids, these were exposed to radiation doses of 2, 4 and 8Gy. We are staining live organoid with calcein AM after radiation and obtain organoid viability. From viability, AUC (area under curve) and growth rate were calculated to predict patient's radiation sensitivity. With these two variables, the patient's cancer stage score was also used to predict patient's radiation sensitivity. CODRP (cancer organoid-based diagnosis reactivity prediction), radiosensitivity predication index, were calculated by patient's AUC, growth rate, and cancer stage.

Results: Radiation sensitivity prediction model using each single-factor (patient's AUC, growth rate and cancer stage) showed about 62% specificity, 72% sensitivity and positive predictive value (PPV) was 69%. However, when applying multi-factor model (CODRP), the specificity was 81.8%, the sensitivity was 85.7%, and the PPV was 90%. In the CODRP model, the radiation sensitive group showed 11.1% recurrence rate, while the radiation resistive group showed 72.7% recurrence rate. Therefore, there was a significant difference in recurrence-free survival rate between the sensitive group and the non-responder group based on the CODRP model.

Conclusions: Our proposed CODRP models using patient derived cancer organoid successfully predict clinical response of patient's radiation treatment. Thus, this platform has promise as a novel prognostic indicator for people with esophageal cancer and can support precision treatment.

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1569P The CODRP model for predicting drug sensitivity in patient-derived 3D gastric cancer cells

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Background: Recently, cancer organoid-based drug sensitivity tests have been studied to predict patient responses to anticancer drugs. This study proposes a multi-factor analysis method (cancer organoid-based diagnosis reactivity prediction, CODRP) that considers the cancer stage and cancer cell growth rate, which represent the severity of cancer patients, in the sensitivity test for gastric cancer patients.

Methods: Primary cells were isolated from surgical tissues from 143 gastric cancer (GC) patients and mixed with matrigel to make patient derived 3D cultured cells. Due to small number of patient's cells, we used 384 pillar plate (MBD, Korea) for high throughput screening. 1.5ul spots dispensed on pillar and, the cells were stabilized in a culture medium optimized for GC cells for 3days and the drug response was observed for 7days. 3D cell morphology was scanned after calcein staining and cell viability was quantified using ATP assay. The primary characteristics of GC 3D cultured

cells were confirmed by IHC. The drug responses were calculated by a sigmoidal dose response curve and compared to clinical case report form.

Results: Evaluation of drug response was established for various drugs in 143 patients and success rate was 71%. We analyzed drug response through CODRP analysis method using multi-factor (cell growth rate, TNM stage, AUC). In clinic, 56 patients were treated by oxaliplatin after surgery, the CODRP index about oxaliplatin compared with clinical response. Although the clinical recurrence rate was low due to the 1 year follow up, the early recurrence rate by CODRP analysis in the resistant group was 10% p higher than AUC analysis, while there was almost no difference in the sensitive group. When we analyze the 1-year recurrence-free survival rate in the CODRP model, the sensitive group showed 78% survival, while the resistant group showed 38.2% survival. Therefore, there was a significant difference in 1 year recurrence-free survival rate based on the CODRP model.

Conclusions: This study proposes a novel drug sensitivity prediction model using patient derived 3D cultured cells. In 56 gastric cancer patients, CODRP models based on the drug sensitivity AUC, growth rate, and cancer stage successfully predict clinical response of patient's drug treatment.

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1570P Dynamic changes in imaging biomarkers on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) are associated with survival outcomes in patients with concurrent chemoradiotherapy for esophageal cancer

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Background: Patients with Esophageal Cancer (EC) have variable responses to (chemo)radiotherapy. A reliable early prediction of outcomes allows for enhancing treatment efficacy and follow-up monitoring. DCE-MRI can provide information regarding tumor perfusion and permeability and has shown prognostic value in certain tumor types. Our aim was to investigate the potential application of DCE-MRI parameters as predictors for progression-free (PFS) and overall survival (OS) in-patients with EC treated with concurrent chemoradiation (CRT).

Methods: This study involved fifty-two patients with esophageal cancer and treated with CRT. The patients underwent DCE-MRI before CRT (pre-CRT) in three weeks and three weeks after starting CRT (post-CRT). Patients were grouped into high and low risk groups according to the cut-off value of best OS and PFS respectively. The correlations between quantitative parameters of DCE-MRI (pre-K^{trans}, post-K^{trans} and the changes and ratios of parameters (ΔiK^{trans}, riK^{trans}), and OS/PFS were calculated and compared between two-time frames in two groups, respectively. The K-M method was used to calculate the survival curve, and the log-rank method was used to compare differences in the survival curves.

Results: The level of pre-CRT K^{trans} was positively associated with OS (cutoff value=70.53/min, p=0.113) and PFS (cutoff value=70.53/min, p=0.026). The level of post-CRT K^{trans} was impaired associated with OS (cutoff value=45.60/min, p=0.001) and PFS (cutoff value=45.60/min, p=0.003). Level of riK^{trans} was impaired associated with OS (cutoff value=0.374, p=0.024) and PFS (cutoff value=0.374, p=0.040). The level of ΔiK^{trans} was impaired associated with OS (cutoff value=4.5/min, p=0.048) and PFS (cutoff value=0.595/min, p=0.056).

Conclusions: This study suggests an important role for DCE-MRI parameter K^{trans} as a predictor of outcome in Esophageal Cancer patients treated with CRT.

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1571P Exploration of immune and metabolism gene signature for prognosis of esophageal carcinoma and establishment of a combined prediction model

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Background: Esophageal carcinoma (EC) a high rank common and death cancer. The intricate tumor microenvironment of EC necessitates a better performance signature to distinguish different tumor prognoses, which may facilitate enable appropriate treatment selection for patients. This is the first study aimed to identify the immune and metabolism gene signature for prognosis prediction of EC and constructing a prediction model, from EC transcriptional data.

Methods: Using differential expression analysis to compare the transcriptomic data associated with immune and metabolism from TCGA dataset between 10 normal population and 162 EC patient samples. Screen the differentially expressed genes (DEGs) related to prognosis by univariate Cox regression, the subtype clusters were identified, and the characteristics were analyzed. Through multivariate Cox and LASSO regression, a prediction model of the EC prognostic risk score (RS) was established and validated.

Results: Compared with the normal population, there were 568 immune-related genes of differential expression in EC, with 369 up-regulated and 199 down-regulated; and 810 metabolism-related genes, including 428 up-regulated and 382 down-regulated. Based on these immune and metabolic DEGs, 12 prognosis-related genes identified that could be clustered patients into three subtypes. The prognosis of the three subtypes was significantly different (P= 0.0016). Furthermore, the prediction model of prognostic RS was constructed based on six genes included STC2, APLN, GPER1, FMO1, SNRPB, and FABP3 from above DEGs. The patients with low RS had significantly higher OS ($P < 0.001$) than those in the high RS group, and it had a certain predictive accuracy (AUC of 5 years OS = 0.818). Those were verified in the GSE53625 cohort.

Conclusions: Immune and metabolism gene were significantly correlated with the prognosis of EC patients, and the prognostic model by six DEGs had good prediction efficiency. These were expected to help clinical diagnosis and therapy, and provides a new perspective to explore the molecular mechanisms of EC.

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1572P Impact of HER2 and PD-L1 co-expression in Claudin18.2 positive resectable gastroesophageal cancers

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Background: The identification of CLDN18.2, HER2, and PD-L1 as targetable biomarkers has contributed to defining different molecular subsets of gastroesophageal adenocarcinoma (GEA) and developing tailored treatments in the unresectable space. However, the prevalence and significance of their co-expression in the resectable stages remain unclear.

Methods: We evaluated CLDN18.2, HER2 and PD-L1 in a cohort of resectable GEA with paired clinical and WGS data. CLDN18.2 (ab222512, Abcam), HER2 (ab16662, Abcam) and PD-L1 (E1L3N, Cell Signaling) were assessed by immunohistochemistry (IHC) on adjacent slides from FFPE tumor samples. Positivity was defined as 2+/3+ staining in ≥40% of tumor cells for CLDN18.2, in ≥10% (surgical samples) or any percentage of tumor cells (biopsies) for HER2, and as a combined positive score (CPS)≥1 for PD-L1. Tumor mutational burden (TMB) was calculated as the number of non-synonymous somatic mutations per mega-base from WGS. Fisher's exact test or Mann-Whitney test was used to compare baseline characteristics and log-rank test to compare survival curves, with statistical significance set at p=0.05 (two-sided).

Results: Eighty-four patients with resected GEA (71% GEJC/20% GC; 77% after neo-adjuvant chemotherapy) were evaluated. CLDN18.2 was overexpressed in 18%, HER2 in 19%, and PD-L1 in 31% of the cases. Clinicopathological characteristics and OS were similar across subgroups (all p>0.05), except for significantly more stage III disease at diagnosis in HER2+ve (OR 6.07, p=0.02) and PD-L1+ve (OR 7.91, p<0.01) compared to their negative counterpart. Among CLDN18.2+ve cases, 4 patients (27%) co-expressed HER2 and 6 (40%) PD-L1. CLDN18.2+ve/HER2+ve cases were all MSS, mostly PD-L1-ve (n=3/4), and their TMB was significantly higher compared to CLDN18.2+ve only (10.46 vs 5.62, p=002). TMB was not significantly different by PD-L1 status in the CLDN18.2+ve subgroup nor between CLDN18.2+ve and HER2+ve subgroups, taking co-expressors out.

Conclusions: Biomarker co-expression may be frequent in the CDLN18.2+ve subset, and CLDN18.2+ve/HER2+ve may reveal a genomically more complex subgroup. Evaluation in larger datasets is required to understand its biological significance and potential therapeutic implications.

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1573P Involved field and elective nodal irradiation presented similar treatment efficiency in concurrent chemoradiation for locally advanced ESCC

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Background: Concurrent chemoradiation is standard treatment for locally advanced esophageal squamous cell carcinoma (ESCC), while the optimal regimen of radiotherapy, especially in terms of total dose and planned range of target field, remained unclear. We performed this phase III clinical trial (ChiCTR-IPR-15007172) to compare the survival benefits between different radiation dose and different target field.

Methods: This trial compared two radiation treatment aspects of total dose and field under two-by-two factorial design. The involved field irradiation (IFI) group and elective nodal irradiation (ENI) group adopted different radiation plans of clinical target volume. The high radiation dose group (HD) totally received 59.4Gy radiation and standard dose group (SD) received 50.4 Gy. The participants were assigned to one of the four groups (HD+ENI, HD+IFI, SD+ENI and SD+IFI) by simple randomization (1:1:1:1 ratio). The planned sample size was 147 in each arm (588 totally) and the primary endpoint was overall survival (OS). All statistical analysis was performed according to intention-to-treat principle.

Results: The median follow-up time reached 64.6 months up to April 2023. In comparison of target field, patients in IFI or ENI presented similar OS (HR=0.99, log rank test p =0.93) and PFS (HR=1.02). The HD treatment did not present significantly prolonged OS (HR=0.90, log rank test p value=0.318) compared with SD but suggested improved PFS (25.2 months to 18.0 months, HR=0.76). No significant synergistic effect was detected between dose and radiation field in interaction analysis (p=0.11). In subgroup analysis, the HD radiation suggested benefits in T4 tumors, and the ENI treatment was associated with better OS in N0 patients. No significant difference in occurrences of severe adverse events was detected in dose or field comparisons.

Conclusions: The IFI has similar treatment efficiency to ENI, which indicated a reasonable choice for locally advanced ESCC. HD radiation did not suggest significant benefits in OS, but associated with better PFS compared to SD.

Clinical trial identification: ChiCTR-IPR-15007172.

Legal entity responsible for the study: The authors.

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1574P Trastuzumab deruxtecan versus ramucirumab and paclitaxel as second-line therapy for patients with her2-positive gastric or gastro-esophageal junction adenocarcinoma: A propensity score matched comparison

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Background: The single arm phase II DESTINY-Gastric02 (DG-02) study investigated the objective response rate, overall survival (OS) and safety of patients treated with Trastuzumab Deruxtecan (T-DXd) as second-line therapy in Western patients with HER2+ unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma who progressed during or after trastuzumab-based first-line therapy. As the DG-02 study had no control group, the aim of the current study was to compare patients in the DG-02 study to a real-world reference group treated with Ramucirumab and Paclitaxel (Ram+Pac) as second-line therapy.

Methods: DG-02 patients who received trastuzumab in a non-metastatic setting (N=8) were excluded, due to absence of similarly treated patients in the Netherlands Cancer Registry (NCR). All other DG-02 patients (N=71) were included. A comparable set of patients with HER2+ esophageal, gastric or GEJ adenocarcinoma who received trastuzumab in first-line and Ram+Pac in second-line settings were identified from the NCR (N=120). Propensity score trimming (exclusion of patients at the extremes of the propensity score) and propensity score matching based on sex, age, performance status, primary tumor location, BMI, renal function, number of metastatic sites, presence of liver metastases, and duration of first-line treatment were used to select a reference group for the DG-02.

Results: Propensity score trimming resulted in exclusion of 12 DG-02 and 33 NCR patients. Thereafter, propensity score matching resulted in a balanced group of patients from the NCR (N=78) and DG-02 (N=58). Median OS was significantly longer among patients treated with T-DXd (11.6 months, 95%CI: 9.0-20.5) compared to the Ram+Pac group (6.2 months, 95%CI: 4.5 − 10.0) (HR: 0.39, 95%CI: 0.26 −0.59, $p<0.0001$).

Conclusions: Compared to propensity score-matched patients with metastatic, trastuzumab-pretreated HER2+ gastric or GEJ adenocarcinomas who received Ram+Pac in the real-world as a second -line therapy, overall survival was better for patients who received T-DXd. Due to the nature of the comparison, the results should be interpreted with caution.

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1575P Factors associated with uptake of adjuvant nivolumab in a nationwide esophageal cancer patient cohort

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Background: Adjuvant nivolumab is approved and reimbursed for resected patients with esophageal or gastro-esophageal junction (GEJ) cancer with incomplete response to neoadjuvant chemoradiation (nCRT) in the Netherlands since January 2022. This study investigated factors associated with uptake of adjuvant nivolumab in a nationwide population.

Methods: Patients were selected from the Netherlands Cancer Registry based on the EMA indication (non-metastasized esophageal or GEJ cancer treated with nCRT plus surgery and residual pathological disease). Following the Checkmate-577 inclusion criteria, we also investigated a subpopulation using additional criteria: R0 resection and WHO performance status 0-1. Treatment with nivolumab is presented according to time of surgery. The association of not administering nivolumab with patient, disease and treatment characteristics was assessed with multivariable logistic regression.

Results: Of 275 eligible patients in the EMA-indicated population, 177 (64%) were treated with adjuvant nivolumab. Uptake increased from 51% in November-December 2021 to 72%, 68%, and 66% in Q1, Q2 and Q3 of 2022, respectively. According to the Checkmate-577 criteria, 215 patients were eligible, of whom 147 (68%) were treated with nivolumab, with a similar pattern over time (49%, 78%, 67% and 76%, respectively). In the EMA-indicated population, nivolumab was administered less often to patients with ypN0-1 nodal status, irradical resection, post-operative grade 3-4 complications and patients undergoing a gastrectomy (Table).

Table: 1575P Factors associated with nivolumab treatment

Variable	*N*	Univariable proportion treated with adjuvant nivolumab	Multivariable odds ratios on not starting with adjuvant nivolumab (95% confidence interval)	P-value
Age (continuous)	275	*Not applicable*	1.02 (0.99 − 1.05)	0.28
ypN				
- ypN0	130	56%	3.54 (1.57 − 7.98)	<0.01
- ypN1	92	66%	2.43 (1.04 − 5.69)	0.04
- ypN2-3	53	79%	Ref	
Type of surgery				
- Esophagectomy	267	65%	Ref	
- Total gastrectomy	8	12%	12.13 (1.41 − 105.6)	0.02
Surgical radicality				
- R0	222	67%	Ref	
- R1-2	49	49%	2.91 (1.45 − 5.87)	<0.01
- Unknown	4	75%	0.81 (0.08 − 8.83)	0.86
Post-operative grade 3-4 Clavien-Dindo complications				
- No grade 3-4 complication	217	68%	Ref	
- Grade 3-4 complication	58	50%	2.11 (1.13 − 3.96)	<0.01

Conclusions: Treatment with adjuvant nivolumab has been implemented in the Netherlands, reaching a quarterly maximum of 72-78% of theoretically eligible patients. Small differences in uptake were found between eligible populations based on EMA indicated and Checkmate-577 criteria. Specific disease and treatment characteristics were associated with administration of nivolumab.

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1576P Comparison of efficacy and safety of first-line systemic therapy combined with or without radiotherapy for stage IVb esophageal squamous cell carcinoma: A propensity score matching analysis

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Background: The role of additional radiotherapy (RT) to systemic therapy including chemotherapy plus anti-PD-1 for metastatic esophageal squamous cell carcinoma (ESCC) is not clear. This analysis aims to compare the survival and safety profile of stage IVB ESCC treated by first-line systemic therapy combined with or without radiotherapy.

Methods: We retrospectively enrolled 155 patients with metastatic ESCC who were treated with first-line systemic therapy including chemotherapy plus anti-PD-1 combined with or without radiotherapy of primary tumor. Propensity score matching (PSM) was performed to minimize the effects of confounding factors. Kaplan-Meier analysis and the log-rank test were conducted to analyze the survival. Prognostic factors were identified by univariate and multivariate cox regression analyses.

Results: The median follow-up period was 22.1 (interquartile range [IQR]: 17.5-27.7) months in the whole cohort. OS and PFS were significantly longer in additional RT group ($P = 0.017$ for OS, $P = 0.04$ for PFS). One hundred and twenty-four patients were enrolled after PSM. Additional RT group has superior OS compared to no RT group ($P = 0.026$). Additional RT group has higher 1-year OS and PFS rates compared to no RT group (1-year OS: 74% vs 52.4%, $P = 0.027$; 1-year PFS: 61.4% vs 44%, $P = 0.046$). Multivariate analyses suggested that RT was an independent prognostic factor for OS (hazard ratio [HR]:0.52, 95 % confidence interval [CI]: 0.3-0.91, $P = 0.022$) and tumor length was an independent predictor for unfavorable PFS (HR: 1.9, 95% CI: 1.06-3.38, $P = 0.03$). Grade 3-4 lymphocytopenia (83.5% versus 11.1%, $P < 0.001$) and grade 3-4 esophagitis (21.5% versus 6.7%, $P = 0.031$) were more frequently observed in additional RT group. Regarding fistula, no significant difference was found between two groups (13.3% versus 8.9%, $P = 0.544$).

Conclusions: Radiotherapy combined with first-line systemic therapy including chemotherapy plus anti-PD1 has superior survival and tolerable toxicities compared to systemic therapy alone for stage IVB ESCC.

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1577P Prior antibiotic administration disrupts outcomes of PD-1 blockade in advanced gastric cancer by altering gut microbiome and systemic immune response

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Background: Antibiotic therapy has been known to disrupt microbiota homeostasis and systemic immune responses, both of which are linked to response to immune checkpoint blockade. We aim to investigate whether prior antibiotics (pATB) administration influences outcomes following treatment with programmed cell death protein-1 (PD-1) inhibitors or chemotherapy in patients with advanced gastric cancer (AGC).

Methods: We analysed data of patients with AGC who were treated with PD-1 inhibitors (retrospective exploratory cohort; n=152) or irinotecan (chemotherapy cohort; n=101). Patients were classified into two groups based on whether they had received pATB within 28 days prior to the treatment. Another independent retrospective validation cohort (n=123) and prospective validation cohort (n=30) treated with PD-1 inhibitors were further analysed. Distinct features in gut microbiome and circulating immune cells were analysed (experimental cohort; n=24).

Results: In the retrospective exploratory cohort, pATB administration was associated with poor 17 progression-free survival (PFS; hazard ratio [HR]=2.897, 95% confidence interval [CI]=2.043−4.109) and overall survival (OS; HR=2.294, 95% CI=1.622−3.242) but did not affect outcomes among patients treated with irinotecan. In the validation cohorts, pATB administration was associated with poor treatment outcomes following PD-1 blockade. Multivariate analysis of the overall patients treated with PD-1 inhibitors confirmed that pATB was an independent predictor of poor PFS (HR=3.243, 95% CI=2.427−4.333) and OS (HR=3.046, 95% CI= 2.358−3.935). Administration of pATB was associated with diminished gut microbiome diversity, reduced abundance of *Lactobacillus gasseri*, and disproportional enrichment of circulating exhaustive $CD8^+$ T cells, all of which can hinder the efficacy of PD-1 blockade.

Conclusions: Considering the inferior treatment response and poor survival outcomes by pATB followed by PD-1 blockade, antibiotics should be prescribed with caution in patients with AGC planned to receive PD-1 inhibitors.

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1578P Effect of immune checkpoint inhibitors in metastatic gastric cancer: A real-world evidence study

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Background: Despite the beneficial findings from different clinical trials, targeted immunotherapy is still debated in advanced gastric cancer care. Immune checkpoint inhibitors (ICIs) of programmed cell death protein 1 (PD-1) have emerged as a promising therapeutic option, demonstrating clinical activity in gastric cancer. This study aims to analyze the impact of PD-1 inhibition overall survival of a large-scale series of patients treated for metastatic gastric cancer.

Methods: A retrospective study was designed by using TriNetX Platform for a large-scale search of patients with metastatic gastric cancer, who underwent immunotherapy at large healthcare organizations collaborating through TriNetX-mediated network at both European (EMEA collaborative group) and international (GLOBAL) levels. Propensity score matching was used to balance these cohorts against the cohort of metastatic gastric cancer patients not treated with PD-1 inhibitors, to remove possible confounding effect of age and gender. Kaplan Meier analysis was used to compare the 2-year overall survival of these two cohorts, after propensity score matching was used.

Results: From a total of 15.318 patients affected by metastatic gastric cancer, a cohort of 1.425 patients treated with PD-1 inhibitors was identified, including 1.372 from TriNetX healthcare organization network at a global level (TNX-GLOBAL) and 53 from the EMEA group (TNX-EMEA). When compared to the propensity score matched control patient's cohort with no PD-1 treatment, anti-PD-1 treated patients had significantly better overall survival in both TNX-GLOBAL, 44.73% vs 41.26% ($p<0.01$), and in TNX-EMEA, 39.31% vs 21.47% ($p<0.01$).

Conclusions: The evidence from the present retrospective cohort study using real-world data from TNX-GLOBAL and TNX-EMEA collaborative networks created the unique opportunity to analyze a large-scale series of patients with metastatic gastric cancer. Positive effects of anti-PD-1-targeted therapy on survival of such a frail cohort demonstrated the clinical relevance of prevalence of PD-1 expression and supported the effectiveness of new therapies based on ICI's for metastatic disease. Given these results, further studies on the role of ICI's also in perioperative setting are awaited.

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1579P Gender differences and worse metastatic survival outcomes in young adult patients with oesophagogastric cancer: 12-year data from a Czech comprehensive cancer center

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Background: The US Surveillance, Epidemiology, and End Result (SEER) data indicated an increasing incidence of early-onset GI tract cancers. According to published data, the treatment outcomes of young adults (YA) are comparable to the general population. We aimed to analyze the clinicopathological characteristics and overall survival (OS) of YA treated in a comprehensive cancer center.

Methods: Patients diagnosed with oesophagal (OC), oesophagogastric junction (OGJ), or gastric (GC) cancer between 2010 and 2022 were retrospectively identified from the Masaryk Memorial Cancer Institute database. Inclusion criteria were 1) age 18-50 years, 2) histology, and 3) treatment according to international recommendations.

Results: The consecutive patient cohort included 1725 patients, of which 162 met the inclusion criteria, representing approximately 10% of YA patients from the Czech Republic. In 63% of cases, the patients were men, significantly older than women (84% vs 65% in the age group 40-49 years, p=0.005). In women, tumors were more often located in the stomach (78% vs 53%, p=0.001) and primary metastatic (67% vs 50%, p=0.039). Six patients had localized disease (stage I), 36 (16 OC/OGJ, 20 GC) underwent radical resection, 31 (15 OC/OGJ, 16 GC) were unresectable, and 86 metastatic (25 OC/OGJ, 61 GC). With a median follow-up of 67 months, 131 (81%) deaths were recorded. Radically resected patients achieved a median OS of 54 mo with a 5-year OS of 42%, whereas the median OS for the unresectable and metastatic disease was 11 mo, and 8.6 mo, respectively.

Conclusions: In our YA cohort, men were older, while women were more likely to have metastatic gastric cancer. OS for the locally advanced disease was comparable to published studies observing the general population but noticeably shorter for metastatic disease.

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1580P Early onset oesophageal adenocarcinoma: A separate biological entity?

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Background: There is concern that the incidence of oesophageal adenocarcinoma (OAC) in patients under 50, described as early onset (EO) OAC, may be rising steadily. Epidemiological studies suggest that EO-OAC patients present with higher-stage disease compared to late-onset patients, receive more aggressive treatment but may have poorer survival outcomes. We utilised Whole Genome Sequencing (WGS) and

RNA-seq to investigate if EO-OAC represents a distinct biological entity compared to late-onset disease.

Methods: We obtained WGS and clinical data for stage and treatment matched OAC patients who received neoadjuvant chemotherapy prior to surgical resection (n=29 patients ≤50 years and n=144 patients ≥70 years) from the OCCAMS consortium. We performed statistical analysis between age groups using chi-squared testing with FDR correction for copy number aberrations (CNA), insertions and deletions (INDELS) and single nucleotide variants (SNV), assessing gene-level mutations and mutational burden considering coding genes only, prior to assessing 76 OAC driver genes as described by Frankell et al., 2019. Biological pathways between age groups were assessed for n=66 patients using available RNASeq data and Gene Set Enrichment Analysis (GSEA).

Results: Our results indicate that EO-OAC had a lower combined mutational burden (Wilcoxon p=0.0204) and lower indel counts (Wilcoxon p=0.0031) compared to late-onset patients. When considering gene-level mutations for SNV, CNA, INDELS and 76 OAC driver genes (Frankell et al., 2019), multiple analyses showed genes at a nominal p-value <0.05 between age groups yet none reached significance at FDR p-value <0.25. GSEA indicated 179 enriched pathways, several related to immune signalling for EO-OAC at nominal p-value <0.05 and a higher DNA Damage Immune Response (DDIR) assay score in EO-OAC (p=0.012).

Conclusions: Our comparison of early and late-onset OAC using WGS and RNA-seq data highlights the possibility of EO-OAC as a separate biological entity, with potentially enhanced immune signalling. Future work in larger sample cohorts and the investigation of clinically relevant gene and mutational signatures is required to further assess molecular differences between early and late onset OAC.

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1581P Total neoadjuvant chemotherapy with FOLFIRINOX regimen in patients with resectable locally advanced gastric and gastroesophageal junction cancer

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Background: Surgery with perioperative chemotherapy has been standard of care in patients with locally advanced gastric and gastroesophageal junction (GEJ) cancer since FLOT4-AIO trial. However, less than half of patients complete all adjuvant cycles. We studied total neoadjuvant chemotherapy with FOLFIRINOX regimen followed by surgery in this setting.

Methods: We conducted non-randomized, open-label, single-center phase II study in 119 patients with locally advanced resectable gastric and GEJ cancer. Sixty patients were enrolled to received 8 cycles of FOLFIRINOX preoperatively. This prospective cohort was compared to the retrospective cohort (n = 59), that received standard perioperative FLOT regimen (4 cycles before and 4 cycles after surgery). The primary endpoint was disease-free survival (DFS). Secondary endpoints were safety profile and pathological complete response rate (pCR).

Results: In the FOLFIRINOX and FLOT groups 78,6% and 77,8% of patients completed all planned cycles and underwent surgery, respectively. Dose reductions and drug withdrawal rates were higher in the FLOT group. More patients achieved pCR and near-pCR in the FLOT group by three different tumor regression grading systems (TRG 1a/b by Becker, 1/2 by Mandart, and 3/4 by Lavnikova): 47,7%, 40,5%, and 35,7% in the FLOT group and 25%, 27,3%, and 29,6% in the FOLFIRINOX group, respectively, though statistically insignificant. pCR or partial pathological response by any of TRG systems did not predict one-year DFS regardless of the treatment regimen. One-year DFS was numerically higher in the FOLFIRINOX group - 90,4% vs 67,5 % in the FLOT group (hazard ratio [HR] 0,65, 95% CI 0,29 — 1,45, p=0,29). The risk of recurrence in the FOLFIRINOX group was lower than in the FLOT group (odds ratio [OR] 0,40, 95% CI 0,16-0,97, p=0,047). Regional lymph node involvement (ypN2), lymphatic, vascular and perineural invasion negatively affected DFS (p=0,046; p=0,014; p=0,0021; p=0,04, respectively).

Conclusions: The total neoadjuvant chemotherapy with FOLFIRINOX regimen in patients with locally advanced gastric and GEJ cancer demonstrated comparable to the perioperative FLOT one-year DFS rate regardless of pCR and manageable safety profile.

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1582P Gastroesophageal adenocarcinoma in young adults: Retrospective analysis of clinical and molecular features

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Background: Gastroesophageal adenocarcinoma (GEA) in young patients presents poor prognosis due to heterogeneity of the disease and lack of dedicated treatment resulting in high socioeconomic impact. Objective was to explore clinical and molecular features.

Methods: Included patients had diagnosis of GEA at an age of ≤50 years evaluated at Vall d'Hebron University Hospital between 2015 and 2023. Clinical data was obtained retrospectively from the electronic medical history. ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) was used to classify biomarkers. Survival was calculated by the Kaplan-Meier method.

Results: We identified 170 patients with GEA under 50 years. Clinical characteristics are outlined in the table. Median overall survival (OS) was 15.9 months (m) (95% CI 14.7 — 18.1) since diagnosis of advanced disease (n=159). Patients with esophagogastric junction (EGJ) tumors had better OS compared to esophageal (HR 0.29 (95% CI 0.15-0.58) 20.1 vs 13.3 m p= 0.0003) or gastric (HR 0.48 (95% CI 0.26-0.86) 20.1 vs 15.9 m p=0.01). Survival analysis didnt show statistically significant differences in OS regarding sex, *HER2* status, ascites or signet ring cells. We found ESCAT I, II and III alterations in 52, 5 and 10 cases respectively. Most tier I (38) were *HER2* overexpression/amplification, all received matched therapy with trastuzumab. Other were: MSI (10), TMB-H (3) and *FRFR2* amp (1). Among Tier II: *BCRA1* mut (1), *BRCA2* mut (1) and *EGFR* amplification (3) and Tier III: *PIK3CA* mut (5), *HER2* mut (3) and *ATM* mut (2).

Table: 1582P

	N = 170 (100%)
Sex	
Male:Female	91 (53,5): 79 (46,5)
Age	Median 42 (18-50)
Localization	
Esophageal	20 (11,8)
EGJ	44 (25,9)
Gastric	106 (62,4)
Histology	
Diffuse	33 (19,4)
Intestinal	17 (10)
Poorly cohesive	29 (17,1)
Undifferentiated	18 (10,6)
Others	73 (43)
Signet ring cells	
Yes	67 (39,4)
No	103 (60,6)
Stage	
I-III	53 (31,2)
IV	117 (68,8)
Metastatic site	
Peritoneal	85 (50)
Liver	35 (20,6)
Ascites at diagnosis	
Yes	38 (22,4)
No	118 (69,4)
Not applicable	14 (8,2)
NGS	
Yes	82 (48,2)
No	88 (51,8)

Conclusions: Our results indicate that young patients present poor prognosis features (localization, advanced stage, histology) but a significant number of them presented ESCAT I alterations, being candidates to receive a matched therapy as standard of care.

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1583P Intraperitoneal chemotherapy for peritoneal metastases of gastric origin: A systematic review and meta-analysis

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Background: Gastric cancer with peritoneal metastases is associated with a dismal prognosis. Catheter-based intraperitoneal (IP) chemotherapy and pressurized intraperitoneal aerosol chemotherapy (PIPAC) are methods to deliver chemotherapy intraperitoneally leading to higher intraperitoneal concentrations of cytotoxic drugs, compared to intravenous administration. We reviewed the effectiveness of palliative intraperitoneal chemotherapy for patients with peritoneal metastases of gastric origin.

Methods: Embase, MEDLINE, Web of Science, and Cochrane were searched for articles on chemotherapy with palliative intent in patients with peritoneal metastases of gastric origin published up to April 2023. The primary outcome was overall survival. Secondary outcomes included toxicity and clinicopathological outcomes in patients that underwent conversion surgery. A Bayesian random effect model was used to calculate the pooled median overall survival (mOS).

Results: 21 studies including 904 patients were retrieved, categorized in 3 treatment groups (IP docetaxel, IP paclitaxel and PIPAC). The pooled mOS for all intraperitoneal chemotherapy treatments was 14.2 months (95% CI: 10.8 — 17.7 months). The pooled hazard ratio of IP paclitaxel and docetaxel favored the combination of IP and systemic chemotherapy compared to systemic chemotherapy only (0.64, 95% CI: 0.47 — 0.86). mOS of IP paclitaxel, IP docetaxel and PIPAC with cisplatin and doxorubicin were respectively 18.3 months (95% CI: 14.0 — 22.7 months), 13.2 months (95% CI: 3.6 — 25.1 months) and 9.0 months (95% CI: 2.3 — 16.5 months). All treatment methods had a relatively safe toxicity profile. Conversion surgery was performed in 14% of the patients and a radical resection was achieved in 69%, with a mOS ranging from 24 to 33 months.

Conclusions: Patients with peritoneal metastases of gastric origin treated with intraperitoneal chemotherapy had a pooled median overall survival of 14.2 months and a pooled hazard ratio of 0.64 compared to systemic chemotherapy. Intraperitoneal chemotherapy, regardless of method of administration, is a safe treatment and conversion surgery is possible in a selected subset of patients.

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1584P Conversion effect of PD-1 antibody camrelizumab (Cam) combined with modified FLOT (mFLOT) regimen in patients(pts) with initially unresectable locally advanced or limited metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma

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Background: The AIO-FLOT3 Trial suggested that conversion therapy might improve outcome in pts with metastatic gastric cancer (GC). We conducted this prospective, single-arm, phase II trial to improve conversion efficacy of ICIs combined with mFLOT regimen (fluorouracil, oxaliplatin, and nab-PTX) in pts with initially unresectable locally advanced or limited metastatic GC or GEJ adenocarcinoma.

Methods: Eligible pts received Cam 200mg, oxaliplatin 85 mg/m^2, nab-PTX 125 mg/m^2 or with trastuzumab if Her2 positive, each was an IV followed by fluorouracil 2400 mg/m^2 as a 48-h continuous iv on day 1, every 2 weeks. Pts were assessed for tumor response and surgical feasibility every 3 cycles. The primary endpoint was R0 conversion rate.

Results: 35 pts were enrolled up to 04/2023. 30 pts were evaluable. The median age was 50y. Male was 76.7%. The metastatic sites included liver 50.0% (15), retroperitoneal lymph nodes (LNs) 33.0% (10), axillary and supraclavicular LNs 6.7% (2), Krukenberg 3.3% (1), adrenal gland 3.3% (1), and locally advanced unresectable 10% (3). 7(23.3%) pts had two or more unresectable lesions. 4 pts were dMMR/MSI-H and 4 were Her2 positive. ORR was 86.7% and DCR was 96.7%. 25(83.3%) pts were assessed as resectable after conversion therapy. One pt refused surgery and 2 were cCR under observation. 22 pts (73.3%) received operation with R0 resection and no perioperative mortality. With 2 cCR included, R0 conversion rate was 80.0% (24/30). 5 pts (22.7%) achieved pCR and 12(54.5%) achieved MPR. Grade 3 AEs included 2 cases of rash, 1 case of adrenal insufficiency, 1 case each of ALT, AST elevation and febrile neutropenia. 1 pt was Grade 4 Neutrophil count decreased. (Table)

Table: 1584P

Response and surgical conversion, n (%)		N = 30
ORR		26 (86.7)
	CR	2 (6.7)
	PR	24 (80.0)
DCR		29 (96.7)
	SD	3 (10.0)
	PD	1 (3.3)
R0 conversion rate		24 (80.0)
Pathological response	pCR	5/22 (22.7)
	MPR	12/22 (54.5)
cCR+pCR		7 (23.3)

Conclusions: Cam combined with mFLOT regimen safely induced a high conversion rate, with very high R0 resection, pCR and MPR. The findings warrant further prospective investigations.

Clinical trial identification: NCT04510064.

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1585P The impact of platinum-induced peripheral neuropathy (PN) in first-line treatment on PN and efficacy in second-line paclitaxel (PTX)-based chemotherapy for unresectable advanced gastric cancer (AGC): A prospective observational multicenter study - IVY study

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Background: The IVY study (UMIN000033376) investigated the impact of first-line platinum-induced PN on the incidence of PN during second-line PTX-based chemotherapy and its efficacy in patients with unresectable AGC.

Methods: The study utilized the Common Terminology Criteria for Adverse Events (CTCAE), the Patient Neurotoxicity Questionnaire (PNQ), and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) to assess PN. The primary endpoint was to determine the incidence of grade 3 or greater PN during second-line treatment in patients with and without PN at the start of treatment. The secondary objective was to examine the relationship between PN and the efficacy.

Results: Of 162 patients enrolled in this study, 156 received second-line PTX-based chemotherapy and were divided into two groups based on their PN status at the start of the treatment. The characteristics of 156 patients are as follows: the median age was 69 years, 72% were male, 90% were ECOG PS: 0 or 1, 81% used oxaliplatin in their first-line chemotherapy regimen. Of the 156 patients, 90 patients (58%) were in the group with PN (CTCAE grade: 1 to 3), and 66 were in the group without PN (grade: 0). The group with PN had a higher incidence of grade 3 or greater PN than the group without PN (16.7% vs. 4.6%, p=0.02). The progression-free survival and the overall response rate were not significantly different between the two groups (4.0 months in the group with PN vs. 3.5 months without PN, p=0.20; and 23% vs. 19%, p=0.69). However, the median overall survival was significantly better in the group with PN (10.3 months vs. 8.1 months, p=0.04). The quality-of-life scores, as assessed by PNQ and FACT/GOG-Ntx, were lower in the group with PN than the scores of the group without PN during two months of treatment.

Conclusions: Starting second-line PTX-based chemotherapy with existing PN increased the severity of PN during treatment. However, this adverse effect did not impact the effectiveness of second-line PTX-based chemotherapy for patients with unresectable AGC.

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1586P Characteristics, treatment (Tx) patterns and outcomes of patients with advanced/metastatic gastric cancer (GC) or gastro-esophageal junction (GEJ) adenocarcinoma previously treated with anti-HER2 therapy in an English national registry

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Background: Understanding the natural history of patients with GC/GEJ adenocarcinoma treated previously with anti-HER2 regimens is useful for understanding the disease burden and selecting the optimal Tx for this population. This study reports Tx patterns and outcomes of patients with GC/GEJ adenocarcinoma treated previously with anti-HER2-based regimens.

Methods: Adults with advanced/metastatic GC/GEJ adenocarcinoma who received first-line (1L) trastuzumab-containing regimens were identified in the English Cancer Outcomes and Services Dataset (Jan 2010—Dec 2019). Tx pathways and outcomes were obtained from the Systemic Anti-Cancer Therapy Dataset, which captured nearly all treatments in England. A novel regimen-based algorithm for reporting Tx sequencing and outcomes was developed since line of therapy was not in the database. Descriptive statistics were reported. Overall survival (OS) and time to Tx discontinuation or death (TTD) underwent Kaplan—Meier analysis.

Results: A total of 948 patients were identified. At the start of their 1L trastuzumab-containing Tx, median age was 67 years (interquartile range [IQR] 57—73]); 82.1% were male; 90.4% were White; 85.4% had an ECOG status of 0—1; 26.0% had liver metastases; 1.0% had brain metastases; and 81.2% had a Charlson Comorbidity Index of 0—1. Three hundred and sixteen patients (33.3%) received 2L onward; 63 (6.6%) received 3L onward. The most common 2L regimens were paclitaxel (n=115 [36.4%]), docetaxel (n=98 [31.0%]), and 5-fluorouracil (5FU) + irinotecan (n=19 [6.0%]). Common 3L regimens included 5FU + irinotecan (n=12 [19.1%]), paclitaxel (n=11 [17.5%]) and capecitabine + irinotecan (n=10 [15.9%]). Median TTD was 2.8 months from the start of 2L. Median OS was 6.1 months (IQR, 3.4—11.2) from the start of 2L and 5.9 months (IQR, 3.2—9.5) from the start of 3L.

Conclusions: Survival of patients with GC/GEJ adenocarcinoma previously treated with 1L anti-HER2 regimens remains poor after 2L and 3L therapy, which is limited mainly to chemotherapy. These findings reflect an urgent need to improve 2L and 3L options.

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1587P Analysis of survival outcomes according to start timing of adjuvant chemotherapy in patients with gastric cancer: A retrospective nationwide cohort study

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Background: Gastrectomy with D2 lymph node dissection followed by adjuvant chemotherapy (AC) has been the standard treatment for patients with stage II and III gastric cancer (GC). Especially, 1-year S-1 and 6-month capecitabine/oxaliplatin (CAPOX) are the standard chemotherapeutic regimens for AC. However, there is no established guideline for start timing of AC for GC. We aimed to investigate treatment outcomes according to start timing of AC using big-data analysis from Korean Health Insurance and Review Assessment (HIRA).

Methods: A total of 19,140 patients with GC who underwent AC with S-1 (n=10,442) or CAPOX (n=8,698) after gastrectomy were identified from January 2014 to December 2018 in the database of HIRA. Disease-free survival (DFS) and overall survival (OS) were analyzed according to the start timing of AC from surgery classified into within 6 weeks (group A, n=12,843), from 6 to 8 weeks (group B, n=5,386), and more than 8 to 16 weeks (group C, n=911).

Results: The median follow-up duration of all patients was 3.6 years. Five-year DFS and OS were significantly inferior in group B (57%, 66%) and group C (47%, 53%) compared with group A (63%, 72%) (all $p<0.0001$), which were consistently observed in either S-1 or CAPOX group (all $p<0.005$). In multivariate analysis, group B and C were independently associated with poor DFS and OS (all $p<0.0001$). Moreover, DFS and OS were inferior in group B (n=5386) compared with group A (n=5386) even after propensity score matching (both $p<0.0001$).

Conclusions: AC for GC with S-1 or CAPOX showed the best outcomes when initiated within 6 weeks following surgery. Therefore, AC for GC should be started within 6 weeks after gastrectomy if patients have fully recovered.

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1588P Analysis of risk factors of anastomotic leakage after minimally invasive esophagectomy with circular cervical anastomosis

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Background: Esophagectomy is a high-risk surgical procedure with significant postoperative morbidity and mortality. Anastomotic leakage is still one of the most serious complications after anterior resection for esophageal carcinoma. This study aimed to analyze the risk factors after minimally invasive cervical anastomosis of esophageal cancer and postoperative mortality.

Methods: This was a retrospective study of 312 minimally invasive cervical anastomosis of esophageal cancer in a single institute between 2013 and 2016. The anastomotic level and perioperative confounding factors were analyzed by univariate and multivariate logistic regression to identify potential risk factors for postoperative leakage.

Results: Total 312 patients were evaluated. Overall leak rate was 10.6%. In-hospital or 30-day mortality was 0%. Only 3 patients received intensive care unit due to postoperative complications and mean hospital stay was 14.22 ($\pm$7.70) days. Univariate analysis showed that the following variables were related to the incidence of anastomotic leakage: neoadjuvant chemotherapy before operation ($p=0.007$); body mass index (BMI) ($p=0.000$); diabetes ($p=0.001$); operation time ($p=0.006$). Multivariable analysis identified diabetes [$P = 0.032$, odds ratio (OR) 2.637, 95% confidence interval (CI): 1.087-6.393], BMI [$P = 0.003$, odds ratio (OR) 1.223, 95% confidence interval (CI): 1.070-1.399] and operation time [$P = 0.033$, odds ratio (OR) 1.012, 95% confidence interval (CI): 1.001-1.024] as the risk factors of anastomotic leakage.

Conclusions: Diabetes, operation time and BMI are independent prognostic factors for cervical anastomotic leakage of minimally invasive esophageal cancer. Cervical anastomotic leakage will not affect the short-term survival of the patients.

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Disclosure: All authors have declared no conflicts of interest.

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1589P Systemic treatment strategies and outcomes of patients with peritoneal metastases of gastric origin

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Background: Patients with peritoneal metastases of gastric origin are often underrepresented in clinical studies due to unmeasurable radiological disease. In theory, the efficacy of systemic treatment might be hampered by the peritoneal-plasma barrier. Here, we describe the outcomes of systemic treatment strategies in patients with peritoneal metastases in a real-world setting.

Methods: Patients with gastric adenocarcinoma and peritoneal metastases (with or without other metastases) treated with systemic therapy in the Netherlands between 2015 and 2020 were identified from the Netherlands Cancer Registry. Treatment regimens were classified into groups with one, two or three agents. Median overall survival (mOS) was determined, and multivariable Cox regression analyses were used to compare treatment groups, corrected for relevant tumor and patients' characteristics.

Results: In 909 patients, a total of 36 different treatment regimens were administered as first-line therapy. Local peritoneal therapies (i.e., HIPEC) was not observed. 5-FU or derivate combined with oxaliplatin (62%) was used most frequently, followed by epirubicin/oxaliplatin/capecitabine (9%) and capecitabine monotherapy (5%). mOS after first-line treatment was 8.1 months. Triplets containing docetaxel (mOS: 10.7 months, HR: 0.68, 95% CI 0.52-0.89) and trastuzumab-containing regimens (mOS: 11.4 months, HR: 0.65, 95% CI 0.50-0.85) had superior mOS compared to doublet therapy with 5-FU/capecitabine + oxaliplatin (mOS: 7.6 months) in multivariable analysis. Monotherapy was associated with a significantly lower mOS of 3.9 months (HR: 2.33, 95% CI 1.69-3.20). Best supportive care had a mOS of only 1.7 months.

Conclusions: In this real-world study, heterogeneity in the first-line treatment for patients with peritoneal metastases of gastric cancer was seen. Triplet therapy with docetaxel and trastuzumab-containing regimens were associated with longer survival. For docetaxel, this result is in contrast to previous meta-analyses in patients with metastases at any location. Whether this is caused by better exposure of peritoneal metastases to docetaxel or results from bias by indication should be the subject of further research.

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1590P Real-world gastric cancer (GC) in Latin America (LATAM) and Europe (EU)

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Background: The LEGACy project aims to improve personalized medicine for gastric cancer in EU and LATAM populations. A hospital-based registry was implemented to compare these populations as a potential tool to plan prevention and treatment strategies providing real-world data.

Methods: A retrospective observational cohort design was used. Survival estimates were determined using actuarial Kaplan-Meier curves. Comparison was performed with the loge-rank test, and differences were considered statistically significant for P values .05.

Results: A total of 689 patients diagnosed with GC from 11/2018 to 04/2021 were included. Country and clinical characteristics are shown in the table. Both cohorts had the body as the most common site reported (34.4% for EU and 51% for LATAM). The most used method for staging was computed tomography for both cohorts, but 6.9% of the LATAM population had a PET/TC instead. The staging at diagnose for LATAM was lower than for the EU population (2.8% and 17.4% respectively). Intestinal histological subtype was the most common (41.9% and 46.3% reported by EU and LATAM), while diffuse subtype was 44.9% for LATAM and 21.3% for EU population. Among patients tested for HER2, 12.5% were positive in the EU cohort and 13.8% in the LATAM cohort. For both cohorts, the most common site of HER2 positive was the GOJ. Surgery was reported in 43.4% of EU population and 48.9% in the LATAM cohort. Systemic treatment with curative intention was indicated in 50.7% in the EU cohort and 46.4% of the LATAM cohort. The most frequent scheme indicated was platinum-based (42.6% and 84.8% for EU and LATAM). Considering both cohorts only 14.4% of the patients got a 2° line of treatment and 3% of the patients received a 3° line. After using cox regression analysis, no difference in overall survival was reported, with a median of 10.9 months.

Table: 1590P

Characteristic	EU Cohort (n: 407)	LATAM Cohort (n: 282)
Age - Median y [IQR]	70.50 [61.00, 78.00]	63.00 [53.00, 71.00]
Sex - n (%)		
Male	243 (59.9%)	166 (59.1%)
Country - n		
Argentine		67
Chile		112
Mexico		70
Netherlands	159	
Paraguay		31
Portugal	124	
Spain	121	
ECOG n (%)		
0	45 (21.1%)	61 (27.7%)
1	110 (51.6%)	116 (52.7%)
≥2	47 (22.1%)	43 (19.9%)

Conclusions: Although the limitations of hospital-based registry analysis, this study have provided valuable insights into clinical characteristics and treatment approaches of EU and LATAM populations.

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1591P Gastric cancer in young patients under 40 years: 5-year analyses of Georgian cancer registry

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Background: Gastric cancer (GC) is 5th most common cancer and 4th most common cause of cancer death worldwide. The rate of GC in patients < 40 years in different countries is ∼ 5%. The incidence and characteristics of GC in <40 patients were not studied in Georgian population. We analyzed clinicopathologic features of early onset GC in Georgia.

Methods: In this study we analyzed data from national cancer registry of Georgia 2015-2021. The data included number of cases, age, sex, anatomic location, stage, pathology and treatment types of GC. Aim of the study was to investigate clinicopathologic characteristics, treatment approaches and survival rates of GC in patients <40 compared to entire cohort. Survival was summarized by Kaplan-Meier method.

Results: A total of 1775 patients with GC were included in the study during 2015-2021. Out of 1775 patients 52 (2,9%) were < 40 years. Median age 34 (17-39). In <40 patients 50% were female, while in entire cohort 62% were male. No differences were seen in anatomic location, tumor grade, stage. Stage III (25 % in <40 patients vs 29% in entire cohort) and IV (40% vs 43%) were most common. Differences were seen in pathologic types - not otherwise classified adenocarcinoma 31% in <40 patients vs 25% in entire cohort (P value 0.3367), not otherwise classified carcinoma 26 % vs 2% (P value <0.0001), signet ring carcinoma 17% vs 6% respectively (P value 0.0004). In entire cohort rate of undifferentiated carcinoma was 30% and tubular adenocarcinoma 16%, which were not seen in <40 patients. 23% of <40 patients vs 30% entire cohort had surgery (P value 0.2294) and 42% vs 30% chemotherapy (P value 0.0714). Median overal survival (OS) for patients <40 was 20 months (95% CI 9,0-30,0) and 13 months for entire cohort (95% CI 12,0-15,0) (p value — 0,1488).

Conclusions: This study showed, that in Georgian <40 patients GC is equally distributed between both sexes, while in the entire cohort it is slighlty more common in males. Pathologic types as not otherwise classified carcinoma and signet ring carcinoma were seen most frequently in <40 patients. <40 patients were slightly more likely to receive chemotherapy and surgery. However, median OS was <2 years for patients <40. Further studies are required to understand causes of early onset GC in Georgian patients and to improve survival.

Legal entity responsible for the study: T. Esakia.

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Disclosure: E. Smyth: Financial Interests, Personal, Invited Speaker: Amgen, Bristol Myers Squibb, Imedex, Merck, Novartis, Prova Education, Servier, TouchIME, Elsevier, PeerVoice, Cor2Ed, Daiichi Sankyo; Financial Interests, Personal, Other, TSC: Amgen; Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Bristol Myers Squibb, Bristol Myers Squibb, My Personal Therapeutics, Novartis, Roche, Servier, Zymeworks, Viracta; Financial Interests, Personal, Other, IDMC: BeiGene, Zymeworks; Financial Interests, Personal, Other, IDMC chair: Everest Clinical Research; Financial Interests, Personal, Officer: EORTC GI Clinical Trials Group; Financial Interests, Institutional, Local PI: Daiichi Sankyo, Merus, Basilea, MSD, Mirati; Financial Interests, Institutional, Coordinating PI: Roche, AstraZeneca, Amgen; Financial Interests, Institutional, Research Grant: Bristol Myers Squibb; Non-Financial Interests, Leadership Role, Trustee: UK & Ireland Oesophagogastric Group (UKIOG). All other authors have declared no conflicts of interest.

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PALLIATIVE CARE

1592MO Anticancer therapy at the end-of-life: A cluster-randomized trial

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Background: Early palliative care (PC) and regular use of patient self-reported symptoms at End-of-Life (EoL) have shown beneficial results on diverse quality of life (QoL) outcomes and survival. Effect on anticancer therapy (ACT) use is rarely investigated. The primary outcome in this cluster-randomized trial was use of ACT at EoL, i.e., last 3 months of life following a complex intervention in one arm (INT) versus conventional care in the other (CTR).

Methods: Hospitals were stratified on size prior to randomization. Patient eligibility was age $\geq$18, advanced stage solid tumours, starting last ACT line, estimated life expectancy $\leq$12 months. The intervention consisted of a physician educational program, compulsory PC referrals at inclusion, and patient symptom reporting (paper/digitally) prior to all consultations. Clinical data were recorded, and all patients completed postal QoL forms bimonthly. Follow-up was 1 year/till death, whichever came first.

Results: 616 (93%) patients were eligible (INT:309/CTR:307); 63% male, median age 69 (IQR 62-75), 71% with Karnofsky score (KPS) 80-100. 77% had gastrointestinal (GI) cancers. Median survival time from inclusion was 8 (IQR 3-14) and 7 months (IQR 3-12) (INT/CTR). Median number of days between ACT start and death was 188 (OQR 77-370). Median number of days between diagnosis, ACT start or stop, and death did not differ by group. 177 (28.7 %) patients received ACT in the last 3 months, 75 (12.1%) in the last month. Adjusted model for the time from ACT cessation to death was longer in INT (p=0.25; HR=0.81 95% CI 0.57-1.15) and in patients with high KPS at inclusion (p<0.001). No QoL differences across groups was found for those with complete measures at 2, 4 and 6 months (n=215). Physical function was significantly lower at 6 months, while insomnia improved (p <.05).

Conclusions: The intervention did not have the desired effect. This may be due to a relatively low national use of ACT at EoL in Norway. A lower proportion of GI cancers had been desirable. Additionally, the intervention was too general and maybe too focused on communication skills to exert a substantial influence on conventional clinical practice. We recommend close, continuous monitoring to secure adherence to study procedures.

Clinical trial identification: NCT01362816.

Legal entity responsible for the study: M. J. Hjermstad, N. Aass, S. Kaasa.

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Disclosure: All authors have declared no conflicts of interest.

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1593MO Combined early palliative care in patients with non small cell lung cancer: A randomised controlled trial in Chongqing, China

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Background: Effective interventions to improve prognosis in non-small-cell lung cancer (NSCLC) are urgently needed. We assessed the effect of the early integration of interdisciplinary palliative care (based on Ewarm model) for patients with NSCLC on the quality of life (QoL), psychological state, cancer pain and nutritional status.

Methods: In this randomised controlled trial, 280 newly diagnosed NSCLC patients were enrolled and randomly assigned (1:1) to the combined early palliative care (CEPC) group integrated with standard oncologic care or standard oncological care (SC) group. QoL and psychological state were assessed at baseline and at 24 weeks by Functional Assessment of Cancer Therapy-Lung (FACT-L) scale, the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire-9 (PHQ-9), respectively. Cancer nutritional and pain status were assessed with the use of the Patient-Generated Subjective Global Assessment (PG-SGA) and Numerical Rating Scale (NRS), respectively. The primary end point was overall survival (OS). The second end point was the change in the quality of life, psychological state, pain and nutritional status at 24 weeks. Analysis was by intention to treat.

Results: 280 patients were enrolled: 140 in CEPC group (102 completed) and 140 in the SC group (82 completed). CEPC group had a better QoL than SC group (all $P <$ 0.05). In addition, fewer patients in the CEPC group than in the SC group had depressive ($P <$ 0.05) symptoms. Furthermore, patients in CEPC group had a better nutritional status and pain than SC group (P =0.007 and P =0.003). Patients in the CEPC group had significantly longer survival than those in the SC group (median OS, 24.6 vs. 20.4 months; P=0.042) (HR, 0.19; 95% CI, 0.04 to 0.85; P=0.029).

Conclusions: Among patients with non-small-cell lung cancer, early palliative care led to significant improvements in longer survival, quality of life, psychological state, pain and nutritional status.

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1594P End-of-life hospital cancer care in the COVID-19 era: A retrospective population-based study in the Netherlands

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Background: The COVID-19 pandemic impacted cancer diagnosis and treatment. However, little is known about end-of-life (EOL) cancer care during the pandemic. Therefore, the aim of this study was to investigate potentially inappropriate EOL hospital care in patients dying with cancer before and during the COVID-19 pandemic.

Methods: This population-based study used linked data from the Netherlands Cancer Registry and the Dutch National Hospital Care Registration. Patients deceased between January 2018 and May 2021, who were diagnosed with cancer or received hospital care for cancer in the year preceding death were included. Potentially inappropriate EOL care was compared between four periods during the COVID-19 pandemic and corresponding periods in 2018/2019. Six international indicators of potentially inappropriate care in the last month of life were used: chemotherapy

administration, >1 emergency room contact, >1 hospitalization, hospitalization >14 days, intensive care unit admission and hospital death.

Results: In total, 112,919 patients were included. Less patients received potentially inappropriate EOL hospital care during the COVID-19 pandemic compared to the preceding years, most pronounced during the first COVID-19 peak (22,4% vs 26,0%). Regression analysis showed lower odds of potentially inappropriate EOL care during all COVID-19 periods (ranging between OR 0.81; 95%CI:0.74-0.88 and OR 0.92; 95%CI 0.87-0.97) after adjusting for age, gender and cancer type. For the separate indicators, less patients experienced multiple or long hospitalizations, intensive care unit admission or a hospital death during the pandemic.

Conclusions: Cancer patients experienced less potentially inappropriate EOL hospital care during the COVID-19 pandemic. Because lack of capacity, patients avoiding hospital and increased awareness for triaging and advance care planning (ACP) may all have contributed, it is unclear whether this reflects better quality care. Nevertheless, retaining awareness for triaging and ACP is important because it may help provide appropriate EOL care to an increasing number of patients in the context of limited resources.

Legal entity responsible for the study: COVID and Cancer NL Consortium.

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1595P Incidence and characterization of end-of-life (EoL) systemic anticancer therapy (SACT) in melanoma patients (pts): A monocentric experience

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Background: The administration of SACT in the last month of life represents an indicator of poor quality of care and exposes subjects to unbalanced side effects with limited therapeutic benefit. As a result, the overuse of SACT at the EoL is associated with higher rates of downstream acute care, delayed hospice care and higher costs. A recent evaluation on a cohort of unselected cancer pts showed an increased use of target agents (TA) and immunotherapy (IT) at the EoL, while chemotherapy (CT) has declined since 2015. Overall, SACT use rate was 39% within 30 days of death. Few data are available in melanoma population.

Methods: We retrospectively retrieved data on date of death and last SACT in a cohort of stage IV melanoma pts treated between January 2013 and December 2022 at the Oncology Unit of the University Hospital of Udine. Type of last SACT, occurrence of acute event (AE) and incidence of Hospital admission in the last 30 days were recorded.

Results: Overall, 140 pts treated with SACT for stage IV melanoma were included, with prevalence of male (64%) and BRAF mutated pts (60%). Fifty-five pts (39%) started a new SACT in the last three months of life and 36% of pts (51/140) received the last dose of SACT during the last 30 days. As last therapy, mono-IT was administered in nearly one third of pts (35%), TA in 41% and CT in 14% of pts. Twenty-seven (53%) patients had brain metastasis and 63% presented with more than 2 metastatic sites at last SACT administration. With regards to hospitalization rate, 70% (36/51) of pts treated in the last month was hospitalized with only 3 pts (8%) referred to the Palliative care Unit. The majority of subjects was admitted due to an AE (77%). Overall, the median survival from the last dose of SACT was 1,7 months.

Conclusions: In our cohort of melanoma pts the rate of SACT within the last 30 days of life was consistent with the historical literature data across all cancer type. However, we found a higher rate of hospital admission in the population who received a dose of SACT in the last months of life, compared to untreated population in that period (70% vs 42%). In accordance with the current therapeutic scenario, chemotherapy has been playing a limited role in advanced stage melanoma pts, as well in the EoL setting.

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1596P Exploring the economic impact of palliative care in oncology at the end of life

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Background: Palliative care has shown a positive economic impact in oncology. However, research on its financial viability in oncology, especially in developing countries, is lacking. This study estimates hospitalization costs for cancer patients in the southeast region of Brazil.

Methods: We used a retrospective analysis of electronic medical records for cancer patients treated at a Cancer Center in the southeast region of Brazil. Inclusion criteria were adult patients with any type of cancer who had died at a hospital setting between January 2022 and March 2023. Patients were divided into two groups: those who received outpatient palliative care (OPCT) and those who did not receive any OPCT. Based on the available clinical outcomes of the sample, data was collected on the hospital admission date, length of stay until death, and the type of accommodation until death [admission at intensive care unit (ICU) versus general ward]. To estimate the costs, we used real-world data from private hospitals in the southeast region, measuring the general amounts spent on daily hospitalization and ICU stays, and their respective lengths of stay, without reference to any specific patient or procedures. We performed univariate comparisons using Linear Regression.

Results: Out of the 72 patients with cancer, 29 were followed by the OPCT team, while 43 were not. The average cost of hospitalization for patients who did not receive the OPCT was found to be R$ 20,000.00 (€ 3,651.00; SD = 9.19) higher than those who received OPCT ($p = 0.03$). We observed that patients who were admitted to the ICU had hospitalization cost, on average, R$ 17,800.00 (€ 3,249.00; SD = 9.61) more than those who stayed in general ward ($p = 0.06$).

Conclusions: Our study highlights the economic benefits of providing OPCT in a developing country. Based on this analysis, OPCT can reduce healthcare costs by decreasing the length of hospital stay and preventing unnecessary ICU admissions. Our study suggest that policymakers and healthcare providers should prioritize the provision of OPCT in Brazil, and this type of support should be considered as an essential component of end-of-life care.

Legal entity responsible for the study: Oncoclinicas.

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1597P Improving in-hospital end-of-life care (EOLC) for oncology patients in a tertiary cancer centre

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Background: Cancer is the leading cause of death in Ireland, accounting for 28.5% of all deaths in 2021. Our aging population is predicted to drive a significant increase in new cancer cases in the coming decades. As such, high quality end-of-life care (EOLC) for patients dying in the acute hospital setting is an essential part of delivering holistic care to patients with cancer and their families. This is the second audit cycle to examine the quality of EOLC in one of the largest university teaching hospitals in Ireland. The first audit cycle, during the COVID-19 pandemic, identified several shortcomings in EOLC (ESMO 2022 : S1134).

Methods: A care of dying patients guidance document, EOLC quality checklist, and staff education huddles facilitated by the Hospital Palliative Care Team were introduced in July 2022. A second retrospective chart review of patients who died under the care of the medical oncology service between 11th July 2022 and 30th April 2023 was performed. Data on the quality of EOLC delivered was collected and assessed using the published Oxford Quality Indicators for mortality review. An overall score for EOLC between 1 (very poor) and 5 (excellent) was assigned to each patient. These were compared with the previously presented 2021 cohort.

Results: We identified 72 patients (41 female). The median age at death was 65 years [23-89]. The mean length of admission resulting in death was 15.2 days [0-118]. The mean quality score for EOLC was 4.0, compared to 3.5 pre-intervention. Exploration of patient wishes, and spiritual care were documented in 45.8% and 58.3% of cases

respectively, compared to 24.2% and 10.6% in the initial audit. 42 patients (58.3%) had care of the dying patient documents completed. The mean quality score for EOLC for these patients was 4.6, versus 3.2 for those without the document.

Conclusions: The quality of EOLC in our organisation has improved numerically in the second audit cycle. Areas of ongoing non-compliance to the Oxford Quality Indicators include exploration of patient wishes and spiritual care. The end-of-life committee, which now includes doctors in training, is committed to continuing to address deficits in the quality of EOLC in our institution, as an ESMO Designated Centre of Integrated Oncology and Palliative Care.

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1598P Differences in referral patterns to the palliative care team among specialized physicians in patients with terminal cancer

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Background: The importance of Hospice & Palliative care for patients with terminal cancer is well established. Although hospice use is increasing, the use of hospice services is still suboptimal. Previous studies reported that surgeons tend to underuse palliative care (PC) consultation. This study aimed to investigate potential variations in referral patterns to the PC team and differences in end-of-life care among specialized physicians in patients with terminal cancer.

Methods: A single-institution retrospective observational study of consecutive PC consultations within a National Cancer Institute-designated cancer center in 2020-2021 was conducted. We categorized specialized physicians into medical oncologists (MO) and non-medical oncologists (NMO), which include hematologists, gastroenterologists, surgical and radiation oncologists.

Results: We analyzed 1710 patients, 1130 were referred from MO and 580 from NMO. Patients in the NMO group had lower levels of prognostic awareness (PA) regarding their terminal cancer status compared to those in MO. 44.7 % of patients in the MO group and 16.2 % of patients in the NMO group had accurate PA ($p<0.01$). The median survival from a day of PC consultation was 40.7 days for all, 47.3 days for the MO group, and 28 days for NMO group ($p = 0.00$). The survival time after planning Advance Directives was 100 days for all, significantly longer in the MO group (131.2 vs. 54.9 days, $p=0.00$). The median time from notification of discontinuation of active cancer treatment to PC consultation was 40 days. The interval to PC consultation was significantly longer in patients referred from the NMO group (92.6 days in the NMO group vs. 13.5 days in the MO group, $p=0.00$). The rate of discharge to specialized inpatient hospice facilities or home hospice was higher in the MO group. However, the discharge rate to acute-stage hospital, ICU was higher in the NMO group.

Conclusions: There was significant variation in referral patterns to the PC team according to a division of physicians. NMO patients had a lower level of prognostic awareness (PA) compared to MO patients. Late referrals to the PC team were observed in the NMO group. This suggests a need for increased education and training in palliative care for the NMO.

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Disclosure: All authors have declared no conflicts of interest.

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1599P Clinical predictors of 30-day mortality in hospitalized patients with lung cancer: A retrospective single-center observational study

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Background: Lung cancer patients experience high rates of hospitalization, mainly due to the high risk of complications that emerge during the natural history of disease. We designed a retrospective single-center observational study aimed at defining clinical predictors of 30-day mortality in hospitalized lung cancer patients.

Methods: Clinical records from the first admission of lung cancer patients to the Oncology ward of University Hospital of Parma from January 1st, 2017, to January 1st, 2022, were collected.

Results: 251 patients were consecutively enrolled. Median age was 66 years (Range, 29-85). 161 (64.1%) patients were men and 217 (86.5%) current/former smokers. ECOG PS was 0-1 in 182 (72.5%) cases. The most frequent histology was adenocarcinoma (n=120, 47.8%), followed by small-cell carcinoma (n=73, 29.0%), and the majority of patients had stage IV disease (n=209, 83.3%). Main reasons for hospital admission were anticancer treatment start (n=146, 58.2%) and cancer-related complications (n=75, 29.9%). The most frequently symptoms at admission were pain (n=131, 52.2%) and dyspnea (n=92, 36.7%). Median Blaylock Risk Assessment Screening Score (BRASS) was 7 (Range, 1-28). Clinical deterioration (n=102, 40.6%) was the main complication during the hospital stay. Baseline clinical predictors of 30-day mortality were poor ECOG PS ($\geq$ 2 vs 0-1: 27.5% vs 14.8%, $p=0.028$), high BRASS (High vs Intermediate-Low: 34.3% vs 11.9%, $p<0.001$), high number of metastatic sites ($\geq$ 3 vs $<$ 3: 26.5% vs 13.4%, $p=0.017$), presence of bone metastases (Yes vs No: 29.0% vs 10.8%, $p=0.001$) and presence of pain (Yes vs No: 24.4% vs 11.7%, $p=0.009$). At multivariate analysis, only high BRASS remained significantly associated with higher 30-day mortality (BRASS High vs Intermediate-Low Odds Ratio 2.87, 95% CI 1.21-6.78, $p=0.016$).

Conclusions: Baseline poor ECOG PS, high BRASS, high tumour burden, presence bone metastases and pain were associated with increased 30-day mortality in hospitalized lung cancer patients, with high BRASS being statistically significant at multivariate analysis. Our study draw attention on BRASS as a new feasible potential indicator of 30-day mortality in hospitalized lung cancer patients.

Legal entity responsible for the study: University Hospital of Parma.

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1600P Sarcopenia, depression, and poor health perception among cancer patients registered in an oncology center in Pakistan

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Background: Sarcopenia is a disorder that causes muscle mass and strength loss, which can result in diminished mobility and functional limits. Depression and a bad assessment of one's own health are common results among cancer patients. As a result, this study aimed to look at the association between sarcopenia, depression, and health perception.

Methods: Cancer patients were the subject of a retrospective study from January to April 2023. The study included 150 patients who had different forms of a verified cancer diagnosis. These individuals were admitted to Mayo Hospital's Palliative Care Cancer Department. The presence of depressive symptoms was assessed using the Patient Health Questionnaire (PHQ-9). SARC-F was used to measure all the five dimensions of sarcopenia. To examine self-perceived health, a self-report questionnaire was used. The relationships between sarcopenia, depression, and health perception were investigated using correlation analysis.

Results: We observed a significant and positive association between depression and the dimensions of sarcopenia. Specifically, we found a positive correlation between depression and SARC1=Strength ($r = 0.378$, $p<0.01$), SARC2=Assistance in walking ($r = 0.390$, $p<0.01$), SARC3=Rise from a chair ($r = 0.488$, $p<0.01$), and SARC4=Climb stairs ($r = 0.392$, $p<0.01$). However, we found a positive but insignificant relationship between depression and SARC5=Falls ($r = 0.150$, $p>0.05$). In addition, we discovered that patients' perception of poor health was correlated with depression ($r = -0.391$, $p<0.01$), SARC2=Assistance in walking ($r = -0.235$, $p<0.01$), SARC3=Rise from a chair ($r = -0.259$, $p<0.01$), and SARC4=Climb stairs ($r = -0.277$, $p<0.01$). However, we did not find a significant relationship between health perception and two dimensions of sarcopenia (i.e., SARC1=Strength and SARC5=Falls).

Conclusions: Sarcopenia adversely affects the physical and mental health of cancer patients. They feel depressed and perceive their health as bad which imparts a negative impact on the outcome of these patients.

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1601P Relationship between CT and ultrasonography-based sarcopenia and hematologic toxicity in patients with cancer receiving chemotherapy

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Background: Sarcopenia is a common condition among cancer patients. The aim of this study is to investigate the potential relationship between sarcopenia and hematologic toxicity in cancer patients by evaluating skeletal muscles with computed tomography (CT) and ultrasound (US) before chemotherapy.

Methods: A prospective cohort study was conducted on cancer patients who received anthracycline-based chemotherapy between 2018 and 2020 and had baseline abdominal CT containing L3 level for measuring skeletal muscle index (L3 SMI) and/or muscle US were included. Sex-specific cut-offs for L3 SMI were used for diagnosis of sarcopenia. Sex- and body mass index—adjusted sonographic thigh adjustment ratio (STAR) values (cut-off values 1.0 for female patients and 1.4 for male patients) were used for US assessment of sarcopenia.

Results: A total of 65 patients (14 male, 51 female) were included; 40 (61.5%) with breast cancer, 17 (26.2%) with lymphoma, and 8 (12.3%) with sarcoma. Mean age was 46.3 $\pm$ 14 years. Sarcopenia was determined in 13 patients (20%) according to CT, and in 10 patients (15.4%) according to US assessment. Regarding acute toxicity, patients with sarcopenia according to CT L3-SMI value had a significantly higher incidence of grade $\geq$ 3 neutropenia (39% vs 12%, p = 0.045) but similar level of thrombocytopenia (%3 vs %0, p > 0.9) after the first cycle of chemotherapy compared to non-sarcopenic patients. Patients with sarcopenia based on STAR values also had a significantly higher incidence of grade $\geq$ 3 neutropenia (50% vs 16%, p = 0.03) and higher incidence of grade $\geq$ 3 thrombocytopenia (10% vs 0%, p = 0.15) after the first cycle of chemotherapy compared to non-sarcopenic patients.

Conclusions: We found a significant association between sarcopenia diagnosed by CT and US and hematologic toxicity. Routine CT scans performed for cancer staging may help clinicians identify high-risk patients and facilitate closer monitoring of side effects and earlier introduction of supportive measures. US based assessment of sarcopenia also has high diagnostic accuracy and may predict neutropenia risk. US may serve as an easy-to-use, point of care tool for assessing sarcopenia with the advantage of repeated sequential assessment.

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1602P Simulation training for compassionate extubation in the pediatric intensive care unit

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Background: When a child has a life-limiting, irreversible condition such as advanced cancer, a healthcare team and family may decide to limit care lacking clear benefit. In such circumstances, a compassionate extubation, or discontinuation of life-sustaining ventilator support allowing natural death, may be pursued. Compassionate extubations are an infrequently performed procedure with complexities that include difficult conversations and dynamic symptom management which can lend to this being a challenging process to execute, particularly without opportunity for practice. Simulation can be a helpful tool to enhance knowledge, confidence, and preparedness with unfamiliar or uncommon scenarios in a safe environment. A compassionate extubation simulation training experience focusing on the conversational and technical skills was implemented within the Pediatric Intensive Care Unit at an academic medical center in New York City. The aim of the project was to determine whether participation in one simulation training improved healthcare providers' confidence with performing a compassionate extubation.

Methods: A one group pretest-posttest design project was implemented using The Confidence Scale to evaluate RN and APRN confidence with performing a compassionate extubation before and after the simulation. The sample was described using descriptive statistical analysis and the Wilcoxon signed-rank test was used to evaluate for differences between first and second observations.

Results: A Wilcoxon signed-rank test determined that the compassionate extubation simulation elicited a statistically significant median increase in C-Scale scores after participation in the simulation (*median* = 20) compared to C-Scale scores prior (*median* = 12), $W = 45$, $p = 0.007$.

Conclusions: Affording opportunity for healthcare providers to sculpt and refine their practice with certain challenging clinical scenarios has been shown to improve their confidence navigating these situations. All efforts to improve confidence related to sensitive situations such as with a compassionate extubation are made with the intention of improving the experience of children at the end of their lives as well as the experiences of the families and loved ones who walk this journey with them.

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Disclosure: All authors have declared no conflicts of interest.

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1603P The ability of the LACE index to predict 30-day readmissions in oncology patients

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Background: The LACE index predicts readmission within 30 days. We evaluated the success of this score in oncological patients for whom hospitalisation is a common condition.

Methods: Between February and July 2022, 188 patients hospitalised in the oncology service of a tertiary referral university hospital were retrospectively screened. Patients admitted for chemotherapy and day care procedures, patients who died during hospitalisation, and subsequent hospitalisation within a month were excluded. LACE scores of the patients were calculated using the length of stay, acuity of the admission, Charlson comorbidity index and emergency Department use six months before admission.

Results: A total of 60 patients were included in the study. Thirty-six (60%) of the patients were under 65 years of age. Most of the patients admitted had gastrointestinal system cancer (n=27, 45%) and lung cancer (n=14, 23.3%), respectively. Twenty-two (36.7%) patients were hospitalised due to infection, and 38 (63.3%) were for palliative care. The median hospital stay of the patients was ten days (min-max: 2-65). The median LACE score of the patients was 11.5 (min-max: 6-16). Fifty-two (% 86.7) patients had a high LACE score, eight were in the moderate group, and none were in the low-risk group. Thirty-three (63.5%) of 52 patients with high LACE scores were readmitted to the hospital within 30 days. This rate was statistically significantly higher (p = 0.040) than the moderate group (n=2, 25%). While 55.8% of the patient group with a high LACE score died within 90 days, this rate was (37.5%) in the moderate patient group (p = 0.33).

Conclusions: The LACE index predicted one-month readmission in oncology patients but was insufficient to predict one-month death.

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1604P A comparative study of symptom prevalence between adults and elderly patients with advanced cancer diagnosis under palliative care: A single institution experience

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Background: Analysis of the most common prevalent symptoms among patients with advanced cancer diagnosis is needed in order to reach the most appropriate interventions leading to improved quality of life of these patients. The aim of this study is to report on the overall symptom prevalence among patients with advanced cancer diagnosis under palliative care and to analyze the difference of symptom prevalence between elderly ($\geq$ 65 years) and adult (<65 years) patients.

Methods: A retrospective cohort study of 400 patients with advanced cancer who were admitted under palliative care between 1st January 2017 to December 31st, 2021. Data were retrieved from electronic medical records.

Results: Anorexia (91%), fatigue (98%), drowsiness (84%) and pain (83%) were the highest 4 prevalent symptoms for the whole group, followed by depression (76%) and anxiety (72%). Adult patients had significant higher pain (80% versus 76%), depression (83% versus 68%) and anxiety (77% versus 65%), compared to elderly ($\geq$ 65 years) patients. On multivariate analysis, pain only was significantly higher in adult patients (p=0.021). The reported percentage of symptom prevalence for the whole group is higher than that in the literature, indicating late referral to palliative care.

Conclusions: There is a high percentage of symptom prevalence among our patients and a short median overall survival that indicates late referral to palliative care. Adult patients had significantly higher pain, depression, and anxiety compared to elderly

patients. An earlier integration of palliative care is recommended in the overall management of our patients.

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1605P The impact of cancer pain on survival of lung cancer patients receiving immune checkpoint inhibitors

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Background: Pain is one of the most common symptoms experienced by cancer patients. Previous studies have shown that unrelieved cancer pain can affect the quality of life dramatically and is associated with worse survival in patients with cancer, including lung cancer. Non-opioid analgesics are often used in the management of cancer pain. Yet whether the usage of non-opioid analgesics can affect the survival of lung cancer patients receiving immune checkpoint inhibitors (ICIs) remains undetermined.

Methods: We identified 910 patients with records of at least two cycles of ICI prescription with or without records of non-opioid analgesics prescription between 2018 and 2020 within the Clinical Data Analysis and Reporting System of Hong Kong. Kaplan-Meier curves and Cox proportional hazards regression analysis were used to compare the overall survival (OS) of patients who received ICI with non-opioid analgesics versus those without.

Results: In total, 765 (84.1%) and 145 (15.9%) patients with lung cancer received ICI with or without non-opioid analgesics, respectively. The median follow-up time was 35.9 months (95% CI: 34.7-37.3 months). Patients with records of non-opioid analgesics prescriptions had significantly shorter OS than those without (13.4 vs 40.5 months, $p < 0.0001$). In Cox regression analysis, ICI with a history of non-opioid analgesics usage was associated with a significantly worse prognosis. (HR = 2.42, 95% CI: 1.86-3.10, $p < 0.001$).

Conclusions: Lung cancer patients who received ICI with a history of non-opioid analgesics usage had shorter survival than those without. Patients with a history of non-opioid analgesics usage are likely to have cancer pain or suboptimal tumour control, which were associated with a worse prognosis.

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1606P Sarcopenia, depression, and modes of feeding among cancer patients

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Background: Sarcopenia refers to the loss of muscle mass and strength that occurs with aging and due to some medical conditions like cancer. Depression and inability to eat without assistance are common effects documented in cancer patients with sarcopenia. As a result, the goal of this study was to look into the relationship between sarcopenia, depression, and modes of feeding.

Methods: During the period beginning in January 2023 and ending in April 2023, cancer patients participated in a retrospective study. There has been a total of 150 participants enrolled in the trial, all of whom have been diagnosed with cancer. These people were enrolled in Mayo Hospital's Palliative Care Cancer Department in order to receive treatment. The Patient Health Questionnaire (PHQ-9) was used to determine the presence of depressive symptoms. The SARC-F was utilized to assess sarcopenia across all five dimensions. A self-report measure was utilized to assess modes of feeding [options include: 1) unable to eat without assistance 2) (self-fed with some difficulty, and 3) self-fed without any problem]. Sarcopenia, major depressive disorder, and feeding modes were studied using correlation analysis.

Results: We have observed a significant and negative association between modes of feeding and depression ($r=-0.459$, $p<0.01$), SARC1=Strength ($r = -0.326$, $p<0.01$), SARC2=Assistance in walking ($r = -0.196$, $p<0.05$), and SARC3=Rise from a chair ($r = -0.238$, $p<0.01$). These findings show that cancer patients are unable to eat without assistance when they suffer from sarcopenia which ultimately leads to more depressive symptoms.

Conclusions: Sarcopenia has a negative impact on the quality of life of patients, leading to depression and dependence on daily activities like self-eating which further complicates management.

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1607P Patient perceptions of the efficacy, safety, and quality of the evidence available on medicinal cannabis: A survey of Australian cancer patients - comparing users to non-users

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Background: Despite the increased demand [8], and accessibility [5], to medical cannabis (MC) there is a general consensus among physicians that evidence on its efficacy [10,12,13], and safety [4,11], is lacking. Although research has been undertaken to explore medical professionals' perceptions of the: benefits, risks, and evidence of MC in general [10], and specifically in a cancer setting [12,13]; there is minimal research exploring patients' perceptions, particularly in a cancer setting [14,15,16].

Methods: We conducted a prospective cross-sectional questionnaire of Australian cancer patients' attending adult oncology outpatient clinics between April 2019 to March 2020.

Results: 350 patients completed the survey; 19% being MC users. Demographics significantly associated with use were male gender ($P <.05$) and tobacco smoking ($P<.01$). The most common indication for use was pain (61%). Over 85% of all patients, regardless of using, had accessed some form of information on MC, but only a minority received such information from their healthcare team; relying instead on resources like: friends, TV, and social media. Interestingly, despite using MC, and generally scoring it as highly beneficial, most users "disagreed", that there was high quality evidence to support this.

Conclusions: To our knowledge, this is the first study exploring cancer patient's perceptions of: the evidence for MC, the sources of information used to shape their health beliefs, and which directly compares users to non-users. Surprisingly, our results showed that despite using MC, and believing it worked for them as individuals, the majority of users felt the evidence was not high quality. Concerningly, a high proportion of patients believe MC has anti-cancer activity; and are relying on information provided by resources other than traditional healthcare providers, which are considered unreliable [23, 24]. We hope that our results highlight the need for the treating team to combat potential misinformation that patients may be receiving on MC and link them to the palliative care team for treatments with greater evidence.

Legal entity responsible for the study: University of Newcastle ethics committee.

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1608P Albumin-myosteatosis gauge as a prognostic factor in patients with advanced pancreatic cancer undergoing first-line chemotherapy

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Background: Sarcopenia and myosteatosis have been associated with a poor prognosis for certain cancers. The albumin-myosteatosis gauge (AMG) is a novel integrated measure proposed to assess myosteatosis along with serum albumin level as a surrogate of systemic inflammation. The aim of this study was to investigate the prognostic value of AMG in patients with advanced pancreatic cancer (APC).

Methods: Patients with APC treated with chemotherapy between 2013 and 2022 were evaluated. Skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) were calculated using computed tomography at the L3 level. The AMG was defined as SMD $\times$ albumin and expressed as an arbitrary unit (AU). Patients were categorized

into two groups by sex-specific cut-off value according to the AMG. Univariate and multivariate Cox analyses were performed for survival analysis.

Results: A total of 196 patients were included. The median age (interquartile range) was 62 (54-67), and 128 (65.3%) were male. ECOG PS was 0/1/2 in 48%/46%/6% of the patients, respectively. At presentation, 79% of patients had metastatic disease, and 21% had locally advanced disease. With regard to AMG, 142.86 and 114.15 AU were identified as cut-off values for males and females, respectively. The patients with low AMG had significantly poorer OS than those in high AMG group (median: 8.33 vs. 12.93 months, p=0.040). In multivariable analyses, lower AMG values (HR: 1.61, 95% CI: 1.17-2.21, p=0.003), higher ECOG performance score (>0 vs 0) (HR: 1.51, 95% CI: 1.10-2.06, p=0.009) and metastatic disease (vs. locally advanced) (HR: 1.88, 95% CI: 1.27-2.79, p=0.001) were associated with decreased OS (see table).

Table: 1608P

Variable	Multivariate analysis		
	HR	95%CI	p value
ECOG status (>0 vs. 0)	1.51	1.10-2.06	0.009
Stage at diagnosis (metastatic vs locally advanced)	1.88	1.27-2.79	0.001
Sarcopenia	1.33	0.96-1.83	0.081
Albumin-myosteatosis gauge (G1-G2 vs. G3-G4)	1.61	1.17-1.21	0.003

Conclusions: This study suggests strong prognostic value for AMG in patients with APC undergoing first-line chemotherapy. Further studies are warranted to validate these findings and assess potential predictive role in guiding treatment.

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Disclosure: All authors have declared no conflicts of interest.

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1609P A machine learning-based prognostic model to predict survival in patients with advanced cancer admitted to an acute palliative care unit

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Background: Although accurate prognostication is very important to assist with patients with advanced cancer at the end-of-life (EOL), current prognostic models have several limitations. We aimed to develop a machine learning (ML)-based prognostic model to predict survival at 2 weeks, 1 month, and 2 months in patients with advanced cancer referred to palliative care specialists.

Methods: A total of 2,104 consecutive patients admitted to the acute palliate care unit (APCU) in a single tertiary cancer center between April 2015 and December 2019 were selected for analysis. Variables for developing the ML algorithm included age, gender, performance status, cancer type, body mass index, laboratory findings, and Edmonton Symptom Assessment System scores. Analysable patients (N=2,084) were divided into training set (N=1,667) and validation set (N=417), and the performance of the ML algorithm model was evaluated by accuracy, sensitivity, precision, specificity, area under the receiver-operating characteristic curve (AUROC), and area under the precision-recall curve (AUPRC).

Results: Among 2,084 patients, the median age was 67 years, 865 (41.5%) patients were female, and the most common cancer type was lung cancer (20.4%). As for the final performance of the ML algorithm, the ensemble model using gradient boosting, random forest, and logistic regression was the best in terms of AUROC and AUPRC. The AUROC and AUPRC for predicting 2-week, 1-month, and 2-month survival were 0.84, 0.79, 0.79, and 0.66, 0.77, 0.92, respectively. Because our data cannot reflect all characteristics of patients with imminent death, AUPRC was relatively low in 2-week mortality model. More precise results could be obtained by deep learning with multilayer perceptron using soft labelling (AUPRC 0.90).

Conclusions: Our study demonstrated ML-based prognostic models capable of predicting short-term survival of 2 weeks, 1 month, and 2 months in patients with advanced cancer admitted to an APCU. Integrating these models in the real-world may help patients nearing the EOL to make timely clinical and personal decisions.

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1610P A new updated prognostic index for patients with brain metastases (BM) treated with palliative whole brain radiotherapy (WBRT) in the era of precision oncology: METASNCore project

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Background: Palliative WBRT is the main treatment for multiple brain metastases. Recent studies report no benefit in survival after WBRT compared to palliative supportive care in patients (pts) with poor prognosis. The purpose of this study is to develop and statistically validate a prognostic score in palliative pts with BM who undergo WBRT and compare it with previous scores.

Methods: 239 pts with BM who received palliative WBRT between 2013-2022 in our center were analyzed retrospectively. The score was designed according to the value of the β coefficient of each variable with statistical significance in the multivariate model. Once the score was established, a comparison was performed according to Kaplan-Meier and was analyzed by log-rank test. We also studied the concordance between MetaSNCore and the RPA scale (gold standard). Finally, METASNcore was validated in a different sample of 100 patients.

Results: 149 pts (62.3%) were male and median (m) age was 60 years. 139 (58,2%) were lung cancer and 35 (14,6%) breast cancer. All patients received 30Gys in 10 sessions. 37 pts (15,5%) had a specific target mutation and mOS was 3,74 months. Each point in the score is associated with a HR 1.243 (CI 95% 1.164 - 1.329) (p<0.001) (Table). 144 pts were in group "good prognosis" (up to 7 points) with mOS 4.9ms (CI 95% 3.94 - 5.8); 92 in group "bad prognosis" (above 7) with mOS 2.73ms (CI 95% 1.93 - 3.5) (p<0.001). After RPA concordance analysis, METASNcore had a specificity of 88.5% (CI 95% 82.9-94.2) and a sensitivity of 68.4% (CI 95% 59.9-77). We also found statistically significant differences in the validation sample (mOS 4.6ms (CI 95% 3 - 6.2) versus mOS 1.45ms (CI 95% 1.16 - 1.74)) (p<0,05).

Table: 1610P

VARIABLE	SCORE
ECOG >= 2	1
Gastrointestinal cancer	3
Urothelial cancer	2
Progression on known BM	2
No indication of systemic treatment after WBRT	3
Target mutation treatment received before WBRT	2
Protein C reactive (>20)	2

Conclusions: The variables in our cohort included in METASNCore are independently associated with OS and could be useful for selecting palliative patients who are candidates for WBRT. Further studies are needed to corroborate our findings.

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1611P Family carers' experiences with brain metastases: A longitudinal qualitative study

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Background: Living with brain metastasis (BM) causes distress for patients and family carers. Patients report a wide range of physical, social and psychological problems that affect daily life for them and their families. Despite the high prevalence of BM, little is known about the experiences of family carers. This qualitative study explores how family carers of BM patients perceive the information and communication about diagnosis, the health care services provided, and how their lives are affected by the BM.

Methods: This was a prospective qualitative study with individual semi-structured interviews. Participants were interviewed three times; shortly after the BM diagnosis, and then after two and four months. A total of 40 interviews with 18 adult family carers (13 spouses, 2 adult children, 2 siblings) were conducted. Transcripts were analysed using a reflexive thematic analysis. A trajectory matrix was developed for the longitudinal design, searching for overarching themes over time as well as changes in the themes identified.

Results: For many family carers the BM diagnosis was experienced as particularly frightening, given that the metastases were located in the brain. Family carers felt that they lived in a rapidly changing, chaotic and unpredictable situation. They reported working nonstop to coordinate family life, the patient's health care follow-up, and to maintain a sort of normality in daily life. The situation affected their relationship with the patient, especially daily life activities and communication. The need for information was extensive among most family carers. They emphasized a need for more information about treatment and prognosis to be able to plan for the future. This information need remained high through all interviews.

Conclusions: Being a family carer of a patient with BM implies extensive practical, emotional and psychosocial challenges. The need for continuous information is particularly high, and health care providers should tailor their information to the individual recipient. Palliative care, with a person-centred approach and systematic follow up of the needs of family carers, should be introduced in an early stage.

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1612P Demonstrating the complexity of need and the effectiveness of integrated palliative care: An analysis of routinely collected patient centred outcome measures

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Background: Patient centred outcome measures (PCOMs) are increasingly used to structure proactive symptom assessment and help centre care around the specific needs of the patient. This study aimed to review the use of PCOMs as part of the routine care of inpatients reviewed by the integrated palliative care team in a specialist cancer centre.

Methods: Anonymised electronic palliative care PCOM data were retrieved for inpatients between 7/4/2021 to 31/01/2023, including Integrated Palliative Outcome Scale (IPOS), ECOG performance status, Australian Karnofsky Performance Status (AKPS) and Phase of Illness (POI). Descriptive statistics were used to define the complexity of palliative care needs based on IPOS, PS and POI. The effectiveness of the integrated palliative care service was evaluated by examining the difference between PCOM at initial and follow up assessment.

Results: Digital PCOM records for 1115 episodes of inpatient care were included, of which 391 had follow up data. On initial assessment 63% (703) patients had ECOG PS of 3 or 4 and 77% (864) had AKPS of less than 70. The most prevalent physical symptoms were weakness (84%, 1265), pain (80.7%, 1215), and poor mobility (72.3%, 1089). The most prevalent psychosocial symptom was family or friends feeling anxious or worried (85.8%, 1292). 83% (1250) had at least one palliative care need of severe or overwhelming intensity on initial assessment. 67.5% (753) were in an unstable POI on initial assessment, requiring urgent input. On follow up 92% (328) patients were in a stable, deteriorating or dying POI with no change to the care plan required. In patients with initial moderate to overwhelming symptoms, pain improved in 74%, nausea improved in 84%, vomiting improved in 93%, and constipation improved in 68% at follow up.

Conclusions: The high prevalence of physical and psychosocial symptoms demonstrates the complexity of needs and provides evidence of the requirement for integration of specialist palliative care services in cancer centres. The improvement in symptom scores between initial and follow up assessment demonstrates the effectiveness of integrated palliative care for cancer centre inpatients.

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1613P The BreakThrough cancer malnutrition

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Background: The BreakThrough Cancer Pain (BTCP) is a symptom that affects different aspects of the daily life of the patient. The aim of this research was to assess the impact of BTCP on the nutritional status of cancer patients initiating a palliative care program in home and hospital setting.

Methods: In this Italian observational, multicentre study "NO PAIN", cancer patients, affected by BTCP, were included. ECOG PS, MNA, BMI, EORTC QLQ-C15-PAL, PSQI, ESAS, PGIC, HADS, BRASS were assessed. Cancer Malnutrition is defined as patient who experienced weight loss >5% of their usual weight over 3 months, combined with BMI <20 kg/m2 if <70 years old, or < 22 kg/m2 if >70 years old (ESPEN guidelines).

Results: In total, 61 patients (57.6%) male, median age (range) 70 (42-92) were accrued. The majority [40 (65%)] of them had metastatic primaries of the lung and liver, PS of 2 [39 (64%)]. Patients reported 2.4 ± 0.9 BTCP episodes/day with a mean intensity of 6.96 ± 1 NRS; 45 patients (73.7%) had incident BTCP, and 44 patients (72.1%) reported rapid onset pain (<10 min).

We observed a short "time lag" (median 30 days) between the onset of pain and the diagnosis of BTCP and severe malnutrition. We proposed the term BreakThrough Cancer Malnutrition (BTCM) as the exacerbation of rapidly progressive malnutrition that occurs in cancer patients with uncontrolled BTCP. Weight loss was reported by 88% and BMI <21 by 62%. There was a decrease in food intake in 66% of patients. BTCP was statistically significant associated with anorexia, weight loss and MNA.

Conclusions: BTCP, if left untreated, can lead to weight loss and severe malnutrition. The BTCM is the new concept of cancer malnutrition defined as the exacerbation of rapidly progressive malnutrition that occurs in cancer patients with uncontrolled BTCP. The prospective study "NO PAIN" confirmed that BTCP has deleterious consequences for the nutritional status, this information may have important significance in early palliative care.

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1614P Integrated palliative care for patients referred for Chimeric Antigen Receptor T-cell (CAR-T) therapy: A service evaluation

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Background: CAR-T therapy is potentially lifesaving for patients with certain types of refractory or relapsed lymphoma. However, patients face uncertainty about treatment outcomes and are at risk of severe toxicity. A novel integrated service was developed at our cancer centre offering patients with lymphoma being considered for CAR-T therapy a review by the Palliative Care team. The aims of this study were to describe the uptake of this service and the nature of the palliative care interventions.

Methods: Health record data was analysed for all patients with lymphoma referred for consideration of CAR-T therapy at a tertiary referral cancer centre between January 2020 and March 2022. Outcomes were recorded up to 1 year. This service evaluation was approved by the local Committee for Clinical Research.

Results: 37 patient records were included. 83.8% (n=31) proceeded with CAR-T therapy. All patients had 2 or more previous lines of systemic treatment. 97.3% had an ECOG performance status of 0-1 at time of referral and median age was 66 years. Post CAR-T therapy, 35.5% had disease progression or relapse. 35.5% developed a grade 3 or 4 toxicity. 5 patients (16.1%) died, 4 due to disease progression and 4 of whom were seen by palliative care. The median time between first palliative care review and death was 133 days (range 78 - 309). Of the patients who did not proceed with CAR-T therapy, 100% (n=6) died, all due to disease progression, of whom 5 were seen by palliative care. The median time between first palliative care review and death was 18 days (range 1 - 99). In total 25 patients (67.6%) were seen by the palliative care team, of whom 40% had more than 1 consultation. The most frequent interventions were information provision (n=25), symptom control (n=13),

communication (n=10) and advance care planning (n=9). Pain was the most common symptom, followed by constipation, nausea and vomiting and anxiety.

Conclusions: An integrated palliative care service is feasible within a CAR-T oncology service and is an opportunity to provide patients with information about palliative care. Development of an earlier and more integrated service can be explored. Specialist palliative care input may be required to support symptom control and advance care planning.

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1615P Investigation of status of lung cancer palliative care management and concept and practice in Chinese medical providers

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Background: This study aimed to investigate the current situation of lung cancer palliative care and the awareness of related issues among Chinese medical providers.

Methods: Doctors, nurses, pharmacists were investigated using an electronic questionnaire from January 14 to March 1,2022. The questionnaire addressed the current situation of lung cancer palliative care, most common accompanying symptoms in patients with lung cancer, the incidence of lung cancer-refractory cancer pain, the assessment of treatment satisfaction, usage of patient-controlled analgesia (PCA) drugs.

Results: Questionnaires from 2093 medical provides were collected from 706 hospitals in 28 provincial administrative units. 84.2% p of physicians believed that anti-tumor therapy and palliative care are equally important, while less than 50% of lung cancer patients received palliative care in most hospitals. The main obstacle affecting the palliative care of lung cancer patients is that patients and their families have concerns about the safety of long-term use of palliative care related drugs. Pain is the most common concomitant symptom of lung cancer. There were statistically significant differences in the proportion of obstacles to the treatment of cancer pain by PCA in different levels of hospitals (goodness-of-fit test result was: χ^2=620.022 , $P<0.001$). The top three ranking of response rate and penetration rate of secondary and tertiary hospitals were: worry about adverse reactions of drug overdose, worry about opioid addiction and increase the economic burden of patients. There is a serious lack of training for Chinese medical providers in terms of the timing of palliative care initiation, pain relief for refractory cancer pain by PCA, and basic understanding of symptom management.

Conclusions: The proportion of patients who were satisfied with the effect of palliative care is low. The medical staff have insufficient awareness of this. There was an urgent need to develop a consensus and standardize lung cancer palliative care and symptoms management in China.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

PANCREATIC CANCER

1616O Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): A multicentred, randomized, open-label, three-arm, phase II/III trial

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Background: Both nab-paclitaxel plus gemcitabine and modified FOLFIRINOX are equivalently recommended as first-line treatment for metastatic pancreatic cancer in patients with good performance status. S-IROX (S-1, irinotecan, and oxaliplatin) showed activity in a phase Ib study in this population. We therefore aimed to compare the efficacy and safety of these three regimens directly.

Methods: This multicentred, randomized, open-label, phase II/III trial was done in 45 centres in Japan. Eligible patients were aged 20—75 years and an Eastern Cooperative Oncology Group performance status of 0 or 1 with pathologically confirmed metastatic or recurrent pancreatic cancer. Patients were randomly assigned (1:1:1) to receive nab-paclitaxel (125 mg/m^2) plus gemcitabine (1,000 mg/m^2) on days 1, 8, 15, every 4 weeks, modified FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, l-leucovorin 200 mg/m^2, and fluorouracil 2,400 mg/m^2 on days 1—3, every 2 weeks), or S-IROX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, and S-1 80 mg/m^2/day on days 1—7, every 2 weeks). The primary endpoint of the phase III portion was overall survival.

Results: Between Apr 2019, and Mar 2023, 527 patients were enrolled, and 426 patients were analyzed at the planned interim analysis in Mar 2023. The median overall survival was 17.1 months in the nab-paclitaxel plus gemcitabine arm, 14.0 months in the modified FOLFIRINOX arm (HR 1.31, 95% CI 0.97—1.77), and 13.6 months in the S-IROX arm (HR 1.35, 95% CI 1.00—1.82). The predictive probability for achieving superiority at the final analysis was 0.73% for the modified FOLFIRINOX arm and 0.48% for the S-IROX arm. Therefore, the study was terminated for futility. The most common grade 3—4 non-hematological toxicity of anorexia was more frequent in the modified FOLFIRINOX (23.3%) and S-IROX (27.5%) arm than the nab-paclitaxel plus gemcitabine arm (5.0%).

Conclusions: Nab-paclitaxel plus gemcitabine is recommended as the first-line treatment for patients with metastatic or recurrent pancreatic cancer compared to modified FOLFIRINOX or S-IROX.

Clinical trial identification: jRCTs031190009.

Legal entity responsible for the study: Japan Clinical Oncology Group (JCOG), Hepatobiliary and Pancreatic Oncology Group (HBPOG).

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1617P PRODIGE 29-UCGI 26 (NEOPAN): Quality of life results of a phase III randomised trial comparing chemotherapy with folfirinox (FFX) or gemcitabine (gem) in locally advanced pancreatic carcinoma (LAPC)

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Background: Pancreatic carcinoma (PC) is an aggressive malignancy and the 4th cause of all cancer deaths worldwide. More than 30% of patients (pts) with PC are unresectable because of the local extension with a median overall survival (OS) of less than 1 year. FFX is superior to gem in the treatment of metastatic PC, in terms of OS and progression-free survival (PFS) but standard of care remains gem for LAPC.

Methods: Pts with histologically proven LAPC not suitable for surgery, WHO PS $\leq$1, no cardiac ischemia were eligible. Randomization was stratified by center, tumour localization (pancreas head yes/no), WHO PS (0 vs 1) and age ($\leq$60 vs $>$ 60 years [yrs]). Pts received FFX (every 14 days for 12 cycles) or Gem 1000 mg/m^2 on days 1, 8, and 15 for six 28-day cycles excepted for cycle 1 with an infusion at D22. Primary

endpoint was PFS. Secondary endpoints were OS, rate of secondary curative-intent surgery, objective response rate, disease control rate, time to treatment failure, quality of life (QoL) and safety. QoL outcomes and updated survival results since ESMO 2022 are presented here in the intent-to-treat population.

Results: A total of 171 pts aged 35-84 yrs were included and followed for maximum 5 yrs. With a median follow-up of 47.8 mo, 159 PFS events were observed. Median PFS was 9.7 mo (95% CI: 7.0; 11.7) vs 7.7 mo (95% CI: 6.2; 9.2) in FFX and gem arm respectively, stratified HR=0,71 (95% CI: 0.5; 1.00), p=.04 and median OS was 15.7 mo (95% CI: 11.9; 20.3) vs 14.9 mo (95% CI:11.7; 18.3), stratified HR=1.03 (95% CI: 0.73; 1.46), p=0.71. QoL was evaluated on 141 pts (68 in gem arm and 73 pts in FFX arm). No significant difference was observed between the two arms except on the diarrhea scale: rate of patients without deterioration was 50.4% (95% CI: 37.6.; 63.2) and 37.8% (95% CI: 25.9.; 51.5) in FFX arm vs 89,3% (95% CI: 78.5.; 95) and 63,2% (95% CI: 48.3.; 76) in Gem arm, at 3 and 6 mo respectively, p=0.002.

Conclusions: PRODIGE 29/NEOPAN trial results show that FFX yields significantly longer PFS compared to Gem and was well tolerated. No significant difference in OS and QoL was observed between both groups. More analysis are ongoing on QoL, and will be presented during ESMO meeting.

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Legal entity responsible for the study: UNICANCER.

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1618P Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion positive (NRG1+) pancreatic ductal adenocarcinoma (PDAC)

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Background: *NRG1* fusions are rare oncogenic drivers of PDAC and other solid tumours. These chimeric proteins bind HER3, leading to HER2/HER3 heterodimerization and oncogenic transformation. Zenocutuzumab (MCLA-128; Zeno) is a bispecific antibody that overcomes HER3 mediated NRG1 signalling in NRG1+ cancer. Zeno is being evaluated in the ongoing pivotal phase II eNRGy study and early access program (EAP). Updated NRG1+ PDAC data are presented.

Methods: Patients (pts) with advanced NRG1+ PDAC determined by NGS, previously treated with or not candidate for standard therapy, age $\geq$ 18 y, ECOG PS $\leq$ 2, and measurable (RECIST v1.1) or evaluable disease were enrolled. Zeno (750 mg IV Q2W) was administered until disease progression or unacceptable toxicity. Tumour imaging was conducted Q8W. The primary endpoint is investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints include duration of response (DOR) and safety.

Results: As of 01 Feb 2023, 38 pts with NRG1+ PDAC (33 eNRGy/5 EAP) were enrolled. Efficacy was assessed in 27 pts who received $\geq$ 1 dose of Zeno and were enrolled by 01 Aug 2022 to allow for the opportunity for $\geq$ 6 months (mo) follow-up and met the criteria for the primary efficacy population. The median age was 49 y (range 21—72), 52% were male, 44%/52%/4% pts had ECOG PS 0/1/3. Pts had a median of 2 prior systemic therapies (range 0-5), 93% with FOLFIRINOX and/or gemcitabine-based therapy. All had liver metastases and measurable disease. Common fusion partners were *ATP1B1* (52%) and *SLC4A4* (11%). The confirmed ORR was 44% (95% CI 26-65), with 1 CR and 11 PRs. Most (22/27; 81%) pts had target lesion reduction and 16/19 (84%) pts had CA 19-9 decline $\geq$ 50% from baseline. Median DOR was 9.1 mo with responses ongoing in 4/12 (33%) pts. Kaplan Meier estimate of 6-mo DOR rate was 64%. Among 38 pts treated with Zeno, Grade $\geq$ 3 individual AEs irrespective of causality occurred in $<$ 5% pts. No pt discontinued Zeno for a treatment related AE.

Conclusions: In this updated analysis, Zeno continues to demonstrate unprecedented efficacy in pts with previously treated advanced/metastatic NRG1+ PDAC with robust and durable responses and a well-tolerated safety profile.

Clinical trial identification: NCT02912949.

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1619P Health-related quality of life with nalirifox versus nab-paclitaxel + gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): EORTC QLQ-C30 results from the NAPOLI 3 trial

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Background: The phase III NAPOLI 3 trial (NCT04083235) included 770 patients with mPDAC who were randomized (1:1) to receive liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) or nab-paclitaxel + gemcitabine (Gem+NabP) in 28-day cycles. As previously reported, at a median follow-up of 16.1 months, NALIRIFOX demonstrated statistically significant improvements in overall survival and progression-free survival versus Gem+NabP. Here, we report EORTC QLQ-C30 results from NAPOLI 3.

Methods: The EORTC QLQ-C30 was completed at baseline, day 1 of each 28-day cycle and at the end of treatment. A mixed model repeated measures (MMRM) model was used to describe the global health status (GHS) evolution over time between treatment arms. Time until definitive deterioration (TUDD) was defined as the time between randomization and first occurrence of a decrease $\geq$ 10 points in QLQ-C30 score without further improvement of $\geq$ 10 points or further data due to discontinuation.

Results: Mean GHS scores at baseline were similar between treatment arms (NALIRIFOX 62.1; Gem+NabP 61.2); from week 16, there was a trend towards improvement in GHS scores in the NALIRIFOX arm relative to the Gem+NabP arm. The median TUDD of GHS was 15.7 months with NALIRIFOX and 12.2 months with Gem+NabP (stratified Cox hazard ratio 0.74 [95% confidence interval: 0.53−1.04]; nominal $p = 0.08$). At 6 months, 26.4% and 31.7% of patients NALIRIFOX and Gem+NabP arms, respectively, experienced definitive deterioration in GHS. The TUDD of physical, role and emotional functioning, pain, dyspnea and constipation were longer, with nominal $p \leq 0.05$, in patients who received NALIRIFOX versus Gem+NabP.

Conclusions: NALIRIFOX was associated with a trend towards improvement in GHS scores and longer TUDD in several EORTC QLQ-C30 subscales compared with Gem+NabP. However, these results should be interpreted with caution owing to the number of missing assessments.

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1620P A phase II study of perioperative nalirifox in patients with resectable pancreatic ductal adenocarcinoma (rPDAC): Survival update and biomarkers analysis of the NITRO trial

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Background: The risk of positive surgical margins, poor recovery after surgery that impairs postoperative treatments, and a high risk of recurrence might limit the current standard treatment for rPDAC. This study evaluated the safety and the activity of perioperative liposomal irinotecan 50 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 + oxaliplatin 60 mg/m^2 (NALIRIFOX) for patients with rPDAC.

Methods: nITRO was an investigator-initiated, Simon's two-stages, single arm study. Eligible patients had newly diagnosed rPDAC with $<180^\circ$ interface with major veins' wall and a Karnofsky status $\geq$60. Patients received 3 cycles before and 3 cycles after resection with NALIRIFOX, day 1 and 15 of a 28 day cycle. The primary endpoint was the proportion of patients undergoing an R0 resection. Plasma concentration of 25 different cytokines was measured by a multiplex xMAP/Luminex technology.

Results: 107 patients were enrolled and began preoperative treatment (ITT population). 9 patients discontinued the treatment in the preoperative phase because of treatment related or unrelated adverse events (AEs). The disease control rate was 92.9%. 87 (81.2%) patients underwent surgical exploration, 11 (10.3%) had intraoperative evidence of unresectable or metastatic disease, and 1 died due to surgical complications. 49 patients achieved an R0 resection, accounting for a rate of 65.3%, which largely exceeded the alternative hypothesis of 55%. The most common grade $>$3 AEs were neutropenia and diarrhea (10.3% and 13.1% in the preoperative, 10.2% and 5.1 in the postoperative phase). With an updated median follow-up time of 33·1 months (IQR 23·1-43·6), the median overall survival (OS) of the ITT population was 32.3 months (95% CI 27.8-44.3). The median disease-free and OS of resected patients were 19.3 (95% CI 12.6-34.1) and 44.3 months (95% CI 33.2-NA), respectively. TNF-α, a potent activator of the chemoresistance pathway TAK1/NF-κB, was the circulating factor most significantly correlated with response and survival outcomes.

Conclusions: NALIRIFOX was manageable and active for patients with rPDAC. Plasmatic TNF-α level allows for the selection of patients who may benefit the most from this perioperative strategy.

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1621P Efficacy and safety of erdafitinib in adults with pancreatic cancer and prespecified fibroblast growth factor receptor alterations (FGFRalt) in the phase II open-label: Single-arm RAGNAR trial

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Background: Erdafitinib (erda) is an oral selective pan-FGFR tyrosine kinase inhibitor approved for treatment of locally advanced or metastatic urothelial carcinoma in adults with susceptible FGFR3/2alt who have progressed during or after ≥1 line of platinum-based chemotherapy. Interim results from the RAGNAR study demonstrated tumor agnostic efficacy in patients (pts) with advanced solid tumors with predefined FGFRalt after failure of standard therapies (tx) (Loriot et al, ASCO 2022). Here we report results on pts with pancreatic cancer in RAGNAR.

Methods: Pts with advanced or metastatic pancreatic cancer with prespecified FGFR1-4alt (mutations or fusions), disease progression after ≥1 line of systemic tx, and who exhausted standard tx received oral erda until disease progression or intolerable toxicity. Primary end point is objective response rate (ORR) by independent review committee (IRC). Secondary endpoints include duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: At data cutoff (median survival f/u 15.24 mo), 18 pts with pancreatic cancer received erda. Median age was 60.5 y (range 34-78); 17 (94.4%) had visceral metastases; median 3 prior lines of systemic tx (range 1-9); 1 (5.6%) responded to last line of tx. All 18-pts had FGFR fusions (14 FGFR2, 4 FGFR1); none had FGFR mutations. None of the pts had KRAS co-alterations. ORR by IRC was 55.6% (95% CI 30.8-78.5). Median time to onset of response was 1.45 mo. Responses were observed in pts with FGFR1 and FGFR2 fusions. Median DCR was 94.4%. Median DOR, PFS and OS were 7.1 mo, 7.0 mo, and 19.7 mo respectively. Investigator-assessed efficacy data were comparable to IRC. The most common adverse events (AEs) were dry mouth (72%), diarrhea (67%), stomatitis (67%), dry skin (67%), hyperphosphatemia (56%), and fatigue (50%); 5 (28%) had serious AEs; 2 (11%) discontinued erda due to AEs. No treatment-related deaths were observed.

Conclusions: Erda demonstrated robust and clinically meaningful activity in pancreatic cancer pts with FGFRalt. Safety data were consistent with erda safety profile.

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1622P D-1553 in patients with KRAS G12C mutated advanced pancreatic cancer (pca)

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Background: KRAS mutations are found in approximately 90% of PCa, of which 1-2% are KRAS G12C. D-1553 has shown clinical activity in patients (pts) with KRAS G12C mutated non-small cell lung cancer and colorectal cancer. Here, we report preliminary data of D-1553 in KRAS G12C mutated advanced PCa.

Methods: Pts with KRAS G12C mutated advanced PCa (with no standard treatment available or refractory or intolerant to existing standard treatment) were enrolled and received D-1553 at the recommended phase II dose of 600 mg BID orally. Study endpoints included safety, pharmacokinetics (PK), and efficacy (RECIST, v1.1). Efficacy endpoints included objective response, disease control (defined as an objective response or stable disease) and progression-free survival. Safety was also assessed.

Results: As of 01 March 2023, a total of 10 pts with advanced PCa (median age 67.5 years [range 48—78]; 60% female; 70% Asian; 80%/20% ECOG PS 0/1; 100% stage IV disease at baseline; 40% with ≥ 2 prior lines of therapy [median 1]) were enrolled and treated with D-1553. At data cutoff, 5 (50%) pts remained on treatment. The median duration of treatment and follow-up were 7.15 months (range 1.22-8.94) and 8.10 (range 4.47-9.23) months, respectively. The objective response rate was 50.0% (5/10, including 1 confirmed complete response, 3 confirmed partial response [PR], and 1 unconfirmed PR) and disease control rate was 80.0% (8/10). Median progression-free survival was 8.54 (95% CI 1.25-NA) months. Treatment-related adverse events (TRAEs) of any grade occurred in 7 (70.0%) pts, with the most commonly (≥ 20%) reported as increased ALT, increased AST, decreased appetite, and diarrhoea. Grade 3 TRAEs occurred in 2 (20%) pts, including increased ALT, increased AST and increased alkaline phosphatase. There was no grade > 3 TRAEs, nor TRAEs leading to death or D-1553 permanent discontinuation.

Conclusions: D-1553 is well tolerated and has shown promising anticancer activity in pts with pre-treated KRAS G12C mutated advanced PCa. This study is ongoing, and more results will be presented at the meeting.

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1623P Pelareorep (pela) + atezolizumab (atezo) and chemotherapy in first-line (1L) advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) patients: Results from the GOBLET study

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Background: Pela is an intravenously delivered unmodified oncolytic reovirus that selectively replicates in cancer cells and induces innate and adaptive immune responses. The GOBLET study assesses the safety and efficacy of pela in combination with atezo +/- chemotherapy in multiple gastrointestinal cancers. Here, we report clinical and translational results for the PDAC cohort.

Methods: GOBLET is a phase I/2 Simon 2-stage basket study. PDAC patients must have locally advanced and/or metastatic disease evaluable by RECIST and be eligible for 1L therapy. Patients received pela, atezo and gemcitabine/nab-paclitaxel. The first stage enrolled 13 evaluable patients (at least one post-baseline tumor assessment). Primary objectives are safety and efficacy (objective response rate [ORR]). The Stage 1 success criterion for PDAC is $\geq$3 confirmed responses. T cell receptor sequencing (TCR-seq) was performed on blood samples collected at baseline (cycle 1 day 1 [c1d1]), c2d1 and c4d1 to assess treatment effects on the T cell repertoire.

Results: No safety signals were observed in treated patients. Median age was 61 years; 92% had metastatic disease (69% liver). Eight of 13 evaluable patients had a partial response and 3 had stable disease for an ORR of 62% (confirmed ORR 53%) and a CBR of 85%. At the data cut-off (January 19, 2023), median duration of response was 6.0 month; 6-month progression-free survival (PFS) rate was 72.9% (95% CI 36.8-90.5), and 6-month overall survival (OS) rate was 82.1% (95% CI 44.4-95.3). Final PFS/OS are pending. TCR-seq revealed an expansion of new and preexisting T cell clones. Updated efficacy and TCR-seq results will be presented.

Conclusions: Pela combined with atezo and chemotherapy was well-tolerated. The ORR exceeded the pre-specified success criteria and compares favourably to ORRs from prior PDAC clinical trials in 1L PDAC. The changes in T cell repertoire observed by c2d1 are consistent with previous pela/checkpoint inhibitor studies and will be evaluated at later study timepoints.

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1624P Predictive factors for treatment success of second-line Nal-IRI/5-FU/FA in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) (AIO-PAK-0216)

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Background: Second line nanoliposomal irinotecan/5-FU/folinic acid (Nal-IRI/5-FU/FA) increases survival of unselected patients (pts) with metastatic PDAC after gemcitabine-based 1st-line therapy. It is not well defined, which parameters are predictive for the efficacy of a 2nd-line treatment.

Methods: In this prospective trial, 151 pts with locally advanced or metastatic PDAC were enrolled for treatment with biweekly Nal-IRI/5-FU/FA (70 mg/m^2, 2400 mg/m^2, 400 mg/m^2) after failure of gemcitabine/nab-paclitaxel. Primary end point was the time to treatment failure of the 2nd-line therapy (TTF2). Secondary endpoints were overall survival (OS) and quality of life. To evaluate the impact of 1st-line treatment, pts was divided into three cohorts: TTF1low, -medium and -high. Comparative analyses were performed for the TTF1low and TTF1high cohorts, and for a comprehensive set of potential predictive factors.

Results: 146 (97%) pts have received at least one dose of medication. Median treatment duration of 2nd-line treatment was 3.71 [95% CI: 2.50, 4.11] months, with 28.3% on treatment after 6 m. Analyses of the TTF1 low ($\leq$ 120 d, n=50) and TTF1high ($\geq$ 210 d, n=49) cohorts and predictive factors for TTF2 are summarized in the table.

Table: 1624P Selected predictive factors for TTF2 and OS

		TTF2 months (95% CI)	p-value	OS months (95% CI)	p-value
Baseline					
TTF1	high (N=50)	3.22 [1.77, 4.01]	0.790	6.41 [4.76, 9.99]	0.746
	low (N=49)	2.83 [2.10, 4.86]		8.08 [4.73, 10.02]	
CA19-9	<100 U/ml (N=36)	5.95 [2.10, 7.06]	0.005	9.26 [6.08, 11.89]	0.035
	≥100 U/ml (N=104)	2.86 [2.17, 3.91]		6.67 [5.45, 8.08]	
Leukocyte level	normal (N=111)	4.07 [3.45, 5.06]	<0.001	-	-
	abnormal (N=35)	2.14 [1.28, 2.69]		-	
Metastases	liver (N=106)	2.79 [2.17, 4.01]	0.047	-	-
	non liver (N=40)	4.40 [2.92, 6.24]		-	
During treatment					
CA 19-9 decrease (response)	≥ 50% (N=32)	6.05 [4.14, 8.94]	<0.001	-	-
	< 50% (N=81)	2.14 [1.84, 2.83]		-	

Conclusions: Duration, efficacy, or dose of 1st-line treatment did not correlate with the success of 2nd-line therapy. Significant predictive factors are CA19-9 levels and leucocytes, which correlated with TTF2 and OS. During 2nd line treatment CA19-9 response and reduced pain indicate a benefit from treatment.

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1625P Multicenter, randomized, parallel group, phase II study to establish the efficacy and safety of CBP501, cisplatin, and nivolumab for ≥ third-line treatment of patients with exocrine pancreatic cancer and WBC <10,000/mm3

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Background: Metastatic pancreatic adenocarcinoma (PDAC) is an aggressive disease without third line standard-of-care treatment option. CBP501, a 12-amino acid G2 checkpoint abrogator and calmodulin-modulating peptide increases platinum influx into tumour cells, suppresses platinum-induced macrophage cytokine release and enhances anti-tumor activity with anti-programmed cell death-1 (anti-PD-1).

Methods: Patients with metastatic PDAC, who failed two lines of systemic therapy, with white blood cell count <10,000/mm^3 were stratified by ECOG (0 vs 1) and liver metastasis (present vs absent) and randomized 1:1:1:1 to arm 1 - CBP501 25 mg/m^2 + cisplatin 60 mg/m^2 + nivolumab 240 mg; arm 2 - CBP501 16 mg/m^2 + cisplatin 60 mg/m^2 + nivolumab 240 mg; arm 3 - CBP501 25 mg/m^2 + cisplatin 60 mg/m^2; or arm 4 - cisplatin 60 mg/m^2 + nivolumab 240 mg. Patients received 4 cycles of combination therapy then 6 cycles of nivolumab every 21 days if without disease progression (nivolumab arms only). The primary endpoint was 3-month progression-free survival rate (3M PFSR) in the ITT population. Secondary endpoints were safety, PFS, objective response rate (ORR) and overall survival (OS).

Results: As of October 17, 2022, efficacy was evaluable in 36 patients. 3M PFSR were 44%, 22%, 11% and 33% in arms 1, 2, 3 and 4, respectively. ORR were 22% in arm 1 (2 partial responses), 0% in arms 2, 3 and 4. Median PFS were 2.8, 2.1, 1.5 and 1.5 months, respectively. Median OS was not reached in arm 1 and 7.0, 2.7 and 3.8 months in arms 2, 3 and 4. Most common AEs were infusion-related reaction in 18/25 (72%; grade 1-2) during CBP501 infusion, and anemia in 2/33 (6%; both grade 3). SAEs occurred in 14/33 (42%); 13 SAEs were unrelated to CBP501. SAE acute renal failure (arm 3, after 1 cycle) was assessed as possibly related to CBP501 and definitely related to cisplatin.

Conclusions: Preliminary results indicate clinically meaningful improvement and tolerable safety of CBP501, cisplatin and nivolumab as 3rd line treatment for metastatic PDAC.

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1626P A novel endoscopic ultrasound guided extended-release siRNA implant targeting KRASG12D/V in localized pancreatic cancer

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Background: Locally advanced pancreatic cancer (LAPC) accounts for 30% of pancreatic cancer (PC). LAPC incurs high mortality. We evaluated a novel extended-release siRNA targeting $KRAS^{G12D/V}$ (G12D/V) mutations (Loder) in combination with standard chemotherapy.

Methods: A two-cohort, phase II multicenter, open-label trial was conducted. Cohort 1: Patients (pts) with LAPC randomized to: Loder + gemcitabine/nab-paclitaxel (GnP); or GnP. Cohort 2: pts with Borderline Resectable (BR) PC or LAPC single arm, Loder + (modified)FOLFIRINOX ((m)FFX) or GnP. The Loder was inserted into primary tumor via endoscopic ultrasound (EUS 19G needle) q3 mo. for 2-3 doses. mITT, all patients $\geq$ 1 treatment. Key study endpoints: overall survival (OS), safety.

Results: N= 49 pts in mITT (6 BRPC, 43 LAPC, Loder n=38, control n=11). KRAS known for n=35: G12V, n=12; G12D, n=11; G12R, n=7; Q61R, n=2; wild-type, n=1. For mITT: no difference in OS for Loder + chemo vs. chemo (OS=21.1 vs. 22.2 mo.). However, in pts with G12D/V a non-statistically significant numerical advantage was seen in Loder + (m)FFX or GnP arm (n=18, Cohorts 1,2) median OS = 19.4 mo. vs. 13.8 mo. GnP arm.

Table: 1626P

Cohort/Arm	Median OS mo. (HR (95% CI))	RR (partial or complete)
All Patients, mITT n=49		
Arm 1: Loder + Chemo, n=38	21.1 (1.64 (0.78,3.8))	9/38 23.2% 2/11
Arm 2: GnP, n=11	22.1	18.2%
Cohort 1 (Randomized, LAPC)	22.8 (1.47 (0.64,3.4))	3/18 16.7% 2/11
Arm 1: Loder + GnP, n=18	22.1	18.2%
Arm 2: GnP, n=11		
Cohort 2 (Single arm, LAPC+BRPC)	17.4	6/20 30.0%
Loder + (m)FFX or GnP, n=20		
G12V and G12D Exploratory Subgroup		
Cohort 1+Cohort 2	19.4 (0.65 (0.21,2.0))	4/18 22.2% 0/5 0.0%
Arm 1: Loder + (m)FFX or GnP	13.8	
n=18 Arm 2: GnP, n=5		
Cohort 1 (Randomized, LAPC) Arm	22.8 (0.63 (0.19,2.1))	2/11 18.2% 0/5 0.0%
1: Loder + GnP, n=11 Arm 2: GnP,	13.8	
n=5		

Loder treatment was well tolerated. Safety events were primarily related to procedure, mainly reversible abdominal pain. Four Grade 5 events (visceral arterial ischemia, sepsis; 2 progression of disease), assessed as unrelated.

Conclusions: Loder with chemotherapy is feasible, safe, and shows a promising signal in KRASG12D/V BR, LAPC. Further evaluation is warranted.

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1627P First-line (1L) fuzuloparib plus mfolfirinox followed by maintenance fuzuloparib in patients (pts) with unresectable locally advanced or metastatic (LA/M) pancreatic cancer (PC): A phase Ib study

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Background: Chemotherapy regimens remain the standard 1L treatment for PC, but with limited anti-tumor activity. We amid to explore the feasibility of adding the PARPi fuzuloparib to mFOLFIRINOX in pts with LA/M PC.

Methods: This was a dose escalation (ESC) and expansion (EXP) phase Ib study. Pts were given oral fuzuloparib at escalating doses starting at 30 mg bid plus intravenous mFOLFIRINOX q2w for 8–12 cycles, followed by maintenance fuzuloparib at 150 mg bid. Dose-limiting toxicities (DLTs) were observed during the first 2 cycles. At least 1 dose cohort would be selected for EXP to collect data supporting the determination of recommended phase II dose (RP2D). Primary endpoints were DLT, maximal tolerated dose (MTD), and RP2D.

Results: As of Jan 15, 2023, 39 pts were recruited. Of them, 12 pts were enrolled in ESC phase (30 mg [n=4]; 60 mg [n=6]; 100 mg [n=2]). DLT occurred in 1 pt in 60 mg cohort (grade 4 decreased platelet count and grade 4 decreased neutrophil count lasting for $\geq$5 d) and 1 pt in 100 mg cohort (grade 4 decreased neutrophil count lasting for $\geq$5 d). Based on the tolerability and safety data during ESC, 60 mg bid was determined to be the MTD. 60 and 30 mg cohorts were expanded to 22 and 15 pts, respectively. Overall, grade $\geq$3 treatment-related adverse events (TRAEs) were reported in 34 (87.2%) of 39 pts; the most common were decreased neutrophil count, decreased platelet count, decreased white blood cell count, and anemia. TRAEs led to discontinuation of any study agent in 5 (12.8%) pts. Efficacy in 60 mg cohort seemed to be most favorable, with ORR of 50.0%, DCR of 94.4%, median PFS of 7.2 mo, and median OS of 12.5 mo (Table).

Table: 1627P Efficacy outcomes

	30 mg	60 mg	100 mg	Overall
Confirmed ORR*, n/N (%; 95% CI)	2/12 (16.7%; 2.1—48.4)	9/18 (50.0%; 26.0—74.0)	0/2 (0.0%; 0.0—84.2)	11/32 (34.4%; 18.6—53.2)
Confirmed DCR*, n/N (%; 95% CI)	10/12 (83.3%; 51.6—97.9)	17/18 (94.4%; 72.7—99.9)	1/2 (50.0%; 1.3—98.7)	28/32 (87.5%; 71.0—96.5)
PFS#				
Events, n/N (%)	10/15 (66.7%)	12/22 (54.5%)	2/2 (100.0%)	24/39 (61.5%)
Median (95% CI), mo	7.5 (1.9—10.1)	7.2 (5.1—13.9)	7.2 (1.6—NR)	7.3 (5.3—10.1)
OS#				
Events, n/N (%)	10/15 (66.7%)	15/22 (68.2%)	1/2 (50.0%)	26/39 (66.7%)
Median (95% CI), mo	11.5 (4.0—NR)	12.5 (7.8—NR)	NR (2.0—NR)	11.5 (7.8—14.2)

*tumor response evaluable set;#full analysis set.

Conclusions: 1L fuzuloparib plus mFOLFIRINOX followed by maintenance fuzuloparib was generally safe, with no unexpected toxicities, and showed encouraging efficacy in pts with LA/M PC. The RP2D of fuzuloparib combination was 60 mg bid.

Clinical trial identification: NCT04228601.

Legal entity responsible for the study: Jiangsu Hengrui Pharmaceuticals.

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1628P Anlotinib plus chemotherapy as first-line therapy for gastrointestinal tumor patients with unresectable liver metastasis: Preliminary results from a multi-cohort, multi-center phase II trial (ALTER-G-001)

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Background: Advanced gastrointestinal (GI) tumors, such as colorectal, gastric and pancreatic cancers (CRC, GC and PC), and esophageal squamous cell carcinoma (ESCC), 20%-50% with liver metastases (LMs) and have poor prognosis. Previous trials showed anlotinib plus chemotherapy (CT) has promising clinical activity and a tolerable safety profile for advanced CRC and ESCC, especially with LMs. In this phase II trial, we assessed the efficacy and safety of anlotinib plus CT as first-line (1L) treatment for LMs GI tumors.

Methods: Previous untreated pts with unresectable LMs GI tumors received induction therapy (6 cycles, q3w) in 3 cohorts: cohort A (CRC): anlotinib (12 mg, po, qd, d1-d14), oxaliplatin (130 mg/m^2, iv, d1), capecitabine (850 mg/m^2, po, bid, d1-14). B (ESCC): anlotinib, cisplatin (60-750 mg/m^2, iv, d1/d1-3), paclitaxel (135 mg/m^2, iv, d1) or docetaxel (75 mg/m^2, iv, d1). C (other GI tumors, e.g., PC, GC): anlotinib plus standard CT. Pts without PD and radical resection received anlotinib and metronomic capecitabine (500 mg, po, bid, d1-21, q3w) maintenance until PD or unacceptable toxicity. The primary endpoint was ORR (RECIST 1.1). Secondary endpoints were DoR, PFS, OS, DCR, radical resection rate for LMs and safety.

Results: As of May 8th, 2023, 74 pts were enrolled, 33 in cohort A, 3 in B and 38 in C (26 PC, 6 GC, 5 biliary tract cancer (BTC) and others), median age was 64 years (34-75), 70.3% male, 91.9% ECOG-PS 1 and 59.5% had LMs only. After induction therapy, 8 pts (5 CRC, 1 PC, 1 GC, 1 BTC) received surgical resection. Of 19 evaluable pts in cohort A, ORR and DCR were 57.9% and 100% (PR, n=11; SD, n=8, 5 SD had reduced tumor size). All 3 pts in cohort B were PR. Of 28 evaluable pts in cohort C, ORR and DCR were 39.3% and 85.7% (PR, n=11; SD, n=13, 6 SD had reduced tumor size). Of 16 evaluable PC pts, 7 had PR, 7 had SD, ORR 43.8%. The mPFS was not reached. 50 pts had TEAEs and grade 3/4 TEAEs (28.4%) mainly included neutropenia (13.5%), hypertension (6.8%) and white blood cell decreased (5.4%).

Conclusions: Anlotinib plus chemotherapy as 1L treatment has shown promising efficacy and acceptable safety and may be a favorable option for advanced LMs GI tumors, especially for PC.

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1629P Modified-FOLFIRINOX-losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: A phase II study

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Background: The management of pancreatic adenocarcinoma continues to be challenging. Surgical resection is the only modality for a cure, with an overall survival rate of 10—20% at 5 years. However, only 20% of the patients are surgical candidates because of locally advanced disease or systemic stage at presentation.

Methods: A phase II clinical trial was carried out on 50 patients with previously untreated locally advanced, surgically unresectable pancreatic adenocarcinoma. Patients had ECOG PS 0 or 1 and adequate hematologic, renal, and hepatic function. They arranged to receive 3 cycles of modified FOLFIRINOX prior to CCRT, with losartan taken orally every day followed by chemoradiotherapy.

Results: Response after completion CCRT was assessed. 6% of patients achieved complete response. 38% of the patients had a partial response, while twenty-four patients (48%) had stable disease and 8% had progressive disease. Of the 50 patients, thirteen (26%) underwent surgery, with R0 resection achieved in 6 of 13 patients. Median follow-up period was 20.25 months (range, 6.0-34.5). The median PFS was 12 months (95% CI, 9.647 — 14.353), while Median OS was 21 months (95% CI, (10.200—31.800). The patients who underwent resection had longer survival 24 months (95% CI, (16.363 — 27.637) compared to those who did not undergo resection; mean OS was 14 months (95% CI, (9.205 — 18.795)). (P=0.271). The patients who achieved CR after modified Folforinox-losartan had a longer median OS of 33 months (95% CI, 19.918 — 46.082) compared to patients who had PR and SD, each had median OS of 13 months (95% CI, 6.768 — 19.232), (11.718 — 14.282) respectively (P=0.040*). The patients who achieved CR after CCRT had longer OS (NR) compared to those who had PR, SD and PD. median OS was 24, 14 and 8 months, respectively (95% CI, 6.761 — 41.239), (11.022 — 16.978), and (95% CI, 4.080 — 11.920) (P=<0.001*). The patients who achieved CR after CCRT had longer PFS (NR) compared to those who had PR, SD and PD. Median PFS was 24 (95% CI, 13.191 — 34.809), 10(95% CI, 4.973 — 15.027) and 5 (95% CI,4.823-5.124) months, respectively (P=<0.001*).

Conclusions: Induction chemotherapy with modified-FOLFIRINOX-losartan, followed by CCRT improved patient outcomes.

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1630P Phase I/Ib study of SHP2-ERK inhibition in KRASm pancreatic cancer (SHERPA trial) and preclinical identification of potential resistance markers

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Background: Pancreatic ductal adenocarcinoma (PDAC) patients have a 5-year survival rate of < 5%. Therapy options are limited. *KRAS* is mutated in >85% of PDAC and could be a key target. Preclinical studies have shown that SHP2 and ERK inhibition in *KRAS* mutant (*KRAS*m) PDAC models results in inhibition of proliferation. The aim of this phase I/Ib trial is to assess safety and efficacy of treatment with SHP2 inhibitor RMC-4630 and ERK inhibitor LY3214996 in *KRAS*m PDAC, non-small cell lung carcinoma (NSCLC) and colorectal carcinoma (CRC) patients. In the expansion phase, only PDAC patients will be included. In preclinical setting, potential resistance markers will be investigated to anticipate patient response.

Methods: In the dose escalation phase, patients with *KRAS*m PDAC, NSCLC or CRC were treated in a 28-day cycle with RMC-4630 on day 1 and 2 every week and LY3214996 daily. The main objective was to determine the Recommended Phase II Dose (RP2D). Other objectives included safety and tolerability assessed by the incidence of adverse events, efficacy determined by objective response rate (ORR) according to RECIST 1.1, pharmacokinetics (PK), and pharmacodynamics assessed by MAPK downstream protein expression levels. Resistance markers were explored by CRISPR.

Results: Eleven patients were enrolled in 2 cohorts: Cohort 1a 140 mg RMC-4630 and 100 mg LY3214996; cohort 1b 100 mg RMC-4630 and 200 mg LY3214996. Eight patients were evaluable for dose limiting toxicity (DLT). In cohort 1a, 2 out of 5 patients developed a DLT: grade 3 thrombocytopenia and renal insufficiency. No DLTs occurred in cohort 1b. PK analysis showed high interpatient variability. The exposure of LY3214966 was dose proportional. The ORR in both cohorts was 0%. In *KRAS*m tumor cell lines, PTEN downregulation, c-JUN hyperactivation and increased PI3K/AKT/mTOR pathways activation were identified as mechanisms of resistance.

Conclusions: Two DLTs out of 5 patients limited the tolerability of the combination in cohort 1a, no DLTs were identified in cohort 1b. Patient enrolment is ongoing in the next dose level. The RP2D has not been determined yet. Alterations in the PI3K/AKT/mTOR and the c-JUN pathways could be markers for drug resistance, which data are pending.

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Legal entity responsible for the study: The authors.

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1631P Phase I study of endoscopic ultrasound (EUS)-guided NBTXR3 delivery activated by radiotherapy (RT) for locally advanced or borderline resectable pancreatic cancer (LAPC or BRPC)

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Background: Patients with LAPC or BRPC often receive RT after chemotherapy (chemo) if no metastatic progression has occurred, and CA19-9 historically normalizes ~20% after all therapy. While escalated dose RT (EDR) has shown promising survival in selected patients, RT dose limitations of the bowel often prevent safe EDR. To overcome this challenge, we are investigating NBTXR3, a functionalized hafnium oxide radio enhancer administered by a single intratumoral injection, locally amplifying the RT dose. The primary objective is to determine NBTXR3 recommended phase II dose (RP2D) and secondary objective is to measure anti-tumor effects.

Methods: The study uses a Bayesian optimal interval design (BOIN) with two parts: dose-finding for RP2D (NBTXR3 at [level 1] 33% of gross tumor volume [GTV] or [level 2] at 42% of GTV) and cohort expansion at RP2D. In part 1, eligibility criteria included only LAPC patients with no evidence of metastatic disease after 2-6 months of chemo, part 2 allows BRPC. NBTXR3 is given once prior to RT via EUS-guided intratumoral injection. All patients receive 45 Gy in 15 fractions to GTV. Target tumor response is per RECIST v1.1 criteria. CA19-9 is measured serially.

Results: As of January 12, 2023, 12 LAPC patients (median age 61 years [range 43-81], 8 males, 4 females) received protocol therapy. The first patient (level 1) and subsequent 11 patients (level 2) had no dose limiting toxicities (DLTs). At 4 weeks post RT, 11 had stable disease (SD) locally (1 had progressive disease [PD] overall) and 1 had radiographic complete response (CR). At 3 months post RT, 11 had SD locally (1 PD overall), and 1 had surgery with negative margins and no residual viable tumor. 6 patients had elevated CA19-9 before NBTXR3/RT, 5 of these 6 (83%) had a decrease in CA19-9 subsequently, and 2 of these 6 (33%) had CA19-9 normalization eventually. 9 patients had elevated CA19-9 at diagnosis, and 5 out of 9 patients (56%) had normalization of CA19-9 after all therapy.

Conclusions: The RP2D of NBTXR3 for LAPC is 42% of GTV. The successful CR and shift to resectability in this patient population, along with the response and CA19-9 decrease and normalization suggest promising anti-tumor efficacy of NBTXR3/RT.

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Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

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1632P Organoids as tools for functional precision oncology in advanced pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a steadily increasing incidence and a poor prognosis. Patient (pts) tumors' derived organoids (PDO) are promising models for functional precision oncology (FPO). This study aims to evaluate whether PDO can be implemented in clinical practice for the management of PDAC pts.

Methods: During 2021-2022, pts were prospectively enrolled in an IRB-approved protocol (NCT04932525). Main inclusion criteria were histologically confirmed PDAC, at least one tumor accessible site (biopsy, surgery or effusions) and ECOG performance status 0-1. The efficacy of 25 antitumor therapies was tested (=chemogram) (ATP luminescence test). A scoring system was developed to rank drugs and to find hits.

Results: Overall, 81 patients were included (median age 61 years; median previous treatment lines 2 [range: 0-5]). 91% pts had previously received FOLFIRINOX, 61% gemcitabine and 49% (nab)-paclitaxel. PDO take-on rate was 62% (n=50/81) (notably, liver biopsy: 64%, ascites: 93%). Mean turnaround-time to chemogram was 6.7 weeks. Main PDO molecular alterations were *KRAS* (98%), TP53 (72%), CDKN2A/B (17%) and SMAD4 (17%) with good concordance rate (88%) with initial tumor. Median patients' overall survival from PDO sampling was shorter when PDO were established ($p<0.01$). Median number of hits was 3 (range 0-12). In 89% of cases, at least 1 hit

was identified, and in 84% of cases, at least one of the hits was not a Standard-of-Care (SOC, i.e., 5-FU, irinotecan, oxaliplatin, gemcitabine, or paclitaxel). Main identified hits were gemcitabine (n=17/50), docetaxel (n=16/50), olaparib (n=15/50), and vinorelbine (n=15/50). Evaluable pts that received a treatment that was a hit after PDO biopsy had a longer growth modulator index (GMI) (p= 0.0007) disease control rate (p=0.001) and progression-free survival (p=0.07, NS) than others. Sensitivity and specificity of PDO to predict pts response were 80% and 95.7% respectively.

Conclusions: We report a large prospective study that aims to implement PDO-based FPO for PDAC. In a clinically relevant turnaround time, at least one putative hit was identified in 89% of cases with good sensitivity and specificity. The benefit of PDO-based FPO warrant to be confirmed in a prospective randomized trial.

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Legal entity responsible for the study: The authors.

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1633P Development and clinical validation of news transcriptomic tools for predicting the response to individual drug of the mfolfirinox regimen in patients with pancreatic ductal adenocarcinoma

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Background: Current therapeutic options for patients with a pancreatic ductal adenocarcinoma (PDAC) implicate monotherapy (gemcitabine) or combined therapies (modified FOLFIRINOX). mFFX treatment is accompanied by a high toxicity and therefore, administration of mFFX is conditioned by the performance of the patients, rather by rational criteria. In this work, we developed transcriptomic signatures for each drug of the mFFX regimen and validate their clinical interest.

Methods: To extract biologically relevant signatures for 5FU, oxaliplatin and irinotecan, we integrated transcriptomic data from patient-derived primary cell cultures (PDC), patients-derived organoids (PDO) and patient-derived xenografts (PDX) with their corresponding chemo-response profiles to capture the biological components responsible for the response to each drug. The genes displaying the highest levels of contribution defined the signatures 5FUCore, OxaCore and IriCore. We further validated the signatures in a pooled cohort of 167 patients with advanced and metastatic PDAC (94 patients from the COMPASS cohort and 73 from the Angers-Strasbourg cohort).

Results: All three signatures captured high responder patients for overall survival (OS) and progression-free survival (PFS) in the mFFX arm exclusively. We then studied the response of patients to 0, 1, 2 and 3 drugs and we identified a positive correlation between the number of drugs predicted as sensitive and the OS and PFS, and with the objective response rate. We next evaluated the level of association between the PurIST classifier and our signatures. We found an association between both OxaCore and IriCore and the classical subtype, but none with 5FUCore. However, we observed in a multivariate Cox regression that our model based on independent signatures displayed higher predictive value for the OS and PFS.

Conclusions: We developed three novel transcriptome-based signatures which define sensitivity for each mFFX components that can be used to rationalize the administration of the mFFX regimen and could help to avoid unnecessary toxic effects.

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1634P Extensive molecular profiling of KRAS wild-type versus KRAS mutant pancreatic ductal adenocarcinoma on 233 patients

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Background: Molecular profiling is increasingly implemented to guide treatment of pancreatic ductal adenocarcinoma (PDAC), especially if enrolment in clinical trials is considered. The aim of our study was to describe actionable alterations detected in *KRAS* mutant (*KRASm*) versus *KRAS* wild-type (*KRASwt*) PDAC, as the latter is considered as harboring more molecular alterations.

Methods: This monocentric prospective study included patients with locally advanced or metastatic PDAC who underwent next-generation sequencing (NGS) on liquid biopsy and/or tissue sample between 2015 and 2022 (FoundationOne® CDx, Liquid CDx or Oncomine Comprehensive Assay), as part of the BIP study (NCT02534649).

Results: 233 patients with a PDAC underwent NGS: 63 on tissue samples alone, 95 on liquid biopsies alone, and 75 on both tissue and liquid. Among 170 liquid biopsies, 90 were informative (52.9%). Among 196 patients with informative NGS, 172 patients (87.8%) had a *KRASm* PDAC, and 24 a *KRASwt* PDAC (12.2%). Median overall survival (OS) in the *KRASwt* group was 27.8 versus 20.3 months for *KRASm* patients (HR 0.58, CI (0.39-0.87), p=0.02). ESCAT alterations were found in 17.3% of total population, 25.0% in *KRASwt* group and 16.3% in *KRASm* group. All 7 *BRCA1/2* germline mutations were detected in the *KRASm* group. 1 *NTRK* fusion was found in a *KRASwt* PDAC. *BRCA1/2* somatic mutations, *PIK3CA* hotspot mutations, *MDM2* amplifications and *ERRB2* alterations were found similarly in both groups. We detected 5 *KRAS* G12C mutations. Patients harboring ESCAT alterations had a median OS of 25.0 versus 19.6 months for those without (HR 0.85, 95%CI (0.58 − 1.23), p=0.40). 66 patients (33.7%) were eligible to early-phase trials according to the molecular tumor board and 10 patients (5.1%) were effectively enrolled, with a range of time to progression between 22 days and 11 months.

Conclusions: Although actionable mutations are more prevalent in the *KRASwt* group, 16.3% of *KRASm* patients harbored ESCAT alterations, underlying the need for molecular profiling regardless of *KRAS* status.

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1635P Germline pathogenic variants of cancer predisposition genes in a multicentre Italian cohort of pancreatic ductal adenocarcinoma patients

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Background: Assessment of germline BRCA1-2 pathogenic variants (gPV) is routinely recommended in Pancreatic Ductal Adenocarcinoma (PDAC) patients (pts), due to clinical-epidemiological relevance. Limited data are available on the prevalence of gPV

in other cancer predisposition genes, including the DNA Damage Response (DDR) system.

Methods: Clinical data of consecutive PDAC pts, of any age and stage, tested with a multigene germline panel between January 2018 and March 2023 in five Italian Institutes were collected. A descriptive analysis of gPV (class 4 and 5) frequency, clinical variables and risk factors, was performed. Since gene panels did not overlap across all Institutes, it was difficult to properly estimate the real prevalence of gPV and to compare the clinical characteristics of all wild type with any-PV population, as screened pts/gene also varied (291-1200). Herein we report the best scenario that may result in rates underestimation.

Results: Among the 1200 pts included in the analysis, 169 (14%) had a gPV (any-PV). 23/73 genes had a gPV in $\geq$ 1 patient. Genes with a gPV in >1% of tested pts were ATM (36/1200 - 3.0%), BRCA2 (35/1200 - 2.9%), CDKN2A (23/942 - 2.4%), BRCA1 (18/1200 - 1.5%), CHEK2 (11/838 - 1.3%), and COL7A1 (5/447 - 1.1%). Characteristics of the main cohorts are shown in the table. The risk of having a genomic gPV was $\geq$9% in all the subgroups of pts considered for the different variables, including >73 years old pts (11%). Moreover, 25% of pts with age 41-50, 18% of obese pts and 21% of pts with PDAC/breast/ovarian/prostate cancer/melanoma family history harbored a gPV.

Table: 1635P Patients' characteristics [N (%)]

	Wild Type 1031	Any Pathogenic Variant 169	BRCA1-2 53	ATM 36	CDKN2A 23
Age					
Median	66	63	60	63	64
Range	28-89	26-83	44-79	38-83	51-83
$\leq$50	84 (8)	24 (14)	10 (19)	5 (14)	0
51-73	753 (73)	122 (72)	41 (77)	25 (69)	18 (78)
$\geq$74	194 (19)	23 (14)	2 (4)	6 (17)	5 (22)
Gender					
Female	525 (51)	79 (47)	26 (49)	14 (39)	10 (43)
Stage					
I-II	256 (27)	32 (21)	6 (12)	12 (38)	5 (26)
III	192 (20)	31 (20)	10 (19)	8 (26)	2 (11)
IV	511 (53)	92 (59)	36 (69)	11 (36)	12 (63)
NA	72	14	1	5	4
CA19.9					
Median	648	738	983	388	103
$\leq$35	191 (22)	24 (17)	8 (18)	2 (6)	7 (44)
>35	666 (78)	113 (83)	36 (82)	29 (94)	9 (56)
NA	174	32	9	5	7
Family history					
Yes	383 (41)	103 (65)	38 (75)	21 (64)	15 (79)
No	554 (59)	55 (35)	13 (25)	12 (36)	4 (21)
NA	94	11	2	3	4

NA: not available

Conclusions: Our study highlighted a remarkable prevalence of gPV in cancer predisposition and DDR genes in a large cohort of PDAC pts. These findings endorse the implementation of an extended multigene germline panel to be offered to all PDAC pts, irrespective of age, stage, and personal/family history.

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1636P Circulating tumor DNA (ctDNA) profile in patients (pts) with pancreatic cancer (PC): A multicenter experience and challenges for clinical application

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Background: Pts with advanced PC have limited treatment (Tx) options. Research has focused on identifying a subset of pts who may benefit from targeted therapies. ctDNA genomic profiling by NGS is an emerging non-invasive diagnostic tool. We show the genomic landscape of advanced PC pts using ctDNA.

Methods: We conducted a retrospective multicentre analysis of PC pts that underwent ctDNA blood sample testing 10 days after any Tx line progression. Samples were analysed by standardised Guardant360 assay covering microsatellite instability (MSI) evaluation and somatic alterations among 74 genes reported as pathogenic or non-pathogenic. Hereditary syndromes genes with VAF $\geq$ 30% were confirmed by Sanger. Demographic data were obtained from medical records. Potential therapeutically relevant alterations (pTRA) were classified according to OncoKB and ESCAT levels of evidence (LE), consulted 05/2023. Negative ctDNA reports were interpreted as absence or low levels of detectable mutations (mut).

Results: We collected blood samples of 242 PC pts from 07/2017 to 08/2022 from 7 hospitals in Spain. Most pts were diagnosed with metastatic PC; 52% were male, 56% were <65 yrs. old and 45% were Tx naïve. Median turnaround for molecular reports was 6 days. A total of 736 gene alterations were detected, 78% pathogenic and 18% pTRA. Negative ctDNA was reported in 48 pts (20%). *TP53* (67%) was the most frequently altered gene, followed by *KRAS* (62%). Additionally, we identified incidental germline cancer predisposition mut detected in 9 pts (4%), 3 *ATM* and 6 *BRCA2*. Description of pTRA according to OncoKB and ESCAT LE in the table. Only 4 (2%) pts with *BRCA2* mut received PARP inhibitors Tx.

Table: 1636P Number of potential therapeutically relevant alterations according to OncoKB and ESCAT levels of evidence

	Pathogenic	Non-Pathogenic	OncoKB	ESCAT
MSI-High	2	0	1	IC
BRAF^{V600E}	1	0	1	IIIA
BRCA1 BRCA2	3 13	8 6	2	Germline IA Somatic IIIB
KRAS^{G12C} *KRAS*^{G12D}	2 18	0 0	3 4	IIB IIIA
ARID1A	15	9	4	IVA
CDKN2A	34	3	4	IIIA
PIK3CA	8	1	4	IIIA
TP53^{Y220C}	6	0	3	IIIA
Others	474	133	-	-

Conclusions: ctDNA is a feasible and non-invasive tool for identifying pTRA in advanced PC pts and adds value by detecting hereditary syndromes. Even though very few pts receives molecular targeted therapy. We highlight a clinical practice gap and the unmet medical need for new treatment options.

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1637P Early retention of KRAS mutations in cfDNA is an ominous sign for pancreatic cancer patients during chemotherapy: A prospective cohort study

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a notoriously poor prognosis after treatments without precise biomarkers. The traditional biomarker, carbohydrate antigen 19-9 is not suitable for timely checking treatment responses for all PDAC patients. The usage of low-invasive liquid biopsies, e.g., cell-free DNA (cfDNA) from blood, has shown to improve prognostication for several cancers, but not precisely for PDAC, especially for predictive prognosis by longitudinal sampling. This study aims to address the issue that the dynamic occurrence of oncogenic mutations in cfDNA from serial monitoring could be served as a predictive indicator of disease outcomes in PDAC patients after chemotherapy.

Methods: A total of 65 advanced-staged PDAC patients were enrolled. The plasma cfDNA were subjected to next generation sequencing with a panel of tumor-associated genes and confirmed by digital PCR. Patients were grouped by three risky levels which were designated by the quantities of cfDNA and presence of the oncogenic mutations in cfDNA after treatment (post-cfDNA). Association of different risk factors with progression-free survival (PFS) and overall survival (OS) was assessed in Kaplan-Meier curves and Cox regression analyses.

Results: In the prospective cohort, high-risk patients who had high levels of cfDNA over the threshold showed the worst PFS and OS [HR= 8.83 (3.99-19.51) in PFS, $p<0.001$; HR=4.25 (2.24-8.06) in OS, $p<0.001$]. The medium-risk patients, whose cfDNA levels were lower than the threshold but contained KRAS mutants in post-cfDNA, demonstrated moderately worse PFS and OS than low-risk patients without elevated levels and KRAS mutants in post-cfDNA [low risk as reference, HR= 6.08 (2.42-15.27) in PFS, $p<0.001$; HR=2.64 (1.18-5.91) in OS, p=0.018]. However, patients with TP53 mutants in cfDNA after treatments showed no significance correlations to either PFS (p=0.144) or to OS (p=0.098), respectively.

Conclusions: Early retention of oncogenic KRAS mutants in cfDNA after chemotherapy is an independent factor in predicting worse OS and PFS in PDAC patients. The serial molecular response of oncogenes in post-cfDNA could serve as a leading biomarker in monitoring clinical outcomes in PDAC patients.

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1638P The prognostic and predictive role of class III β-tubulin and hENT1 expression in patients with advanced pancreatic ductal adenocarcinoma

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Background: FOLFIRINOX and gemcitabine-nabpaclitaxel (GnP) are both standard first-line treatment regimens for advanced pancreatic ductal adenocarcinoma (PDAC), however, predictive biomarkers are currently lacking to guide treatment selection. We aimed to investigate the prognostic and predictive value of class III β-Tubulin (TUBB3) and human equilibrative nucleoside transporter 1 (hENT1) expression, which have previously been shown to be associated with taxane and gemcitabine resistance in advanced PDAC.

Methods: We conducted a retrospective analysis of 106 patients with advanced PDAC at Hacettepe University Cancer Institute. TUBB3 and hENT1 immunohistochemical staining were analyzed in tumor specimens and scored jointly according to the intensity of expression: high score ($TUBB3^{low}/hENT1^{high}$) and low score ($TUBB3^{high}/hENT1^{high}$, $TUBB3^{low}/hENT1^{low}$ or $TUBB3^{high}/hENT1^{low}$). Response rates and progression-free survival (PFS) rates were compared based on TUBB3 and hENT1 expression.

Results: The median age was 60 years (range; 38-80 years) and 65% were male patients. The median progression-free survival (PFS) and overall survival (OS) of patients were 6.83 and 12.06 months, respectively. In patients who received the GnP regimen (n=68), a high combined score ($TUBB3^{low}/hENT1^{high}$) was associated with a higher disease control rate (DCR) (84.2% vs. 39.6%, p=0.001) and longer PFS (8.76 months vs. 3.1 months, $p<0.001$) compared to those with low score. In the multivariate analysis, a high combined score was an independent predictor of higher DCR (OR: 11.96; 95% CI: 2.61-54.82; p=0.001) and longer PFS (HR: 0.33; 95%CI: 0.18−0.60; $p<0.001$). However, there was no difference in response rates or PFS based on TUBB3 and hENT1 expression among patients receiving FOLFIRINOX regimen.

Conclusions: Our findings suggest that tumor TUBB3 and hENT1 expression may predict the efficacy of GnP regimen, and low TUBB3 and high hENT1 expression are associated with a higher DCR and longer PFS in patients with advanced PDAC.

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1639P Feasibility of tumor genomic sequencing on tissue obtained from endoscopic ultrasound in patients with pancreatic cancer

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Background: Endoscopic fine needle biopsy (EUS-FNB) is an effective tissue sampling modality for diagnosing pancreatic cancer. Genomic sequencing is becoming essential with the emerging targeted therapies in pancreatic cancer. However, the feasibility of commercial comprehensive next-generation sequencing on tissue obtained from EUS-FNB is unknown. We aimed to examine the success rate of genomic sequencing utilizing tissue from EUS-FNB and correlate it with procedural characteristics.

Methods: We retrospectively reviewed a consecutive cohort of patients who underwent a diagnostic EUS-FNB during the workup of a pancreatic mass, over five years, at our institution. Genomic results, patient demographics, tumor characteristics, and technical aspects of the EUS-FNB were reviewed. The successful completion of sequencing was defined as the generation and reporting of DNA sequencing results.

Results: A total of 396 patients underwent endoscopic ultrasound with pancreatic mass biopsy as part of the routine diagnostic workup. Tumor sequencing from the pancreatic EUS-FNB was requested from 101 patient samples. The remaining samples had no sequencing performed, or sequencing was requested on pancreatectomy samples and/or metastatic sites. Of the 101 patients, sequencing was successful in 88 samples (87%). The median number of needle passes to obtain sufficient tissue for completion of sequencing was 3 (range 1-5). Tumor purity information was available in 71 samples; the average purity was 32% (range 20-90%). Genomic sequencing was unsuccessful in the remaining 13 samples (13%) due to inadequate tissue. The median number of needle passes for these patients was 2 (range 1-5). The cancer stage distribution for patients whose tumor sequencing was requested from pancreatic biopsies was the following: I (9%), II (10%), III (14%), and IV (67%). Genomic sequencing results will be presented at the meeting.

Conclusions: Comprehensive genomic sequencing of all stages of pancreatic cancer is feasible on EUS-FNB. Increasing the number of needle passes can increase the yield for tumor genomic sequencing. This is particularly important for locally advanced, unresectable pancreatic cancers without alternative sites for tissue sampling.

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1640P Response monitoring with ctDNA in metastatic pancreatic cancer

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Background: Various studies about clinical usefulness of serial monitoring with liquid biopsy are being conducted actively in many types of cancer. However, there is not much in pancreatic cancer. We explored whether serial ctDNA monitoring in metastatic pancreatic cancer (MPC) can be beneficial for evaluating treatment response and predicting prognosis.

Methods: A total of 76 MPC patients were prospectively enrolled. Blood samples were collected at every response evaluation until progression of disease (PD) or 5th evaluation. Quantitative ctDNA were measured by droplet digital polymerase chain

reaction using *KRAS G12/G13* screening multiplex Kit (Bio-Rad) and reported as variant allele fraction (VAF). Percent change of ctDNA VAF (DctDNA(%) = (current VAF - previous VAF)/previous VAF*100) were correlated to radiographic responses by RECIST 1.1 and tumor volume. Furthermore, Progression free survival (PFS) and overall survival (OS) were analyzed by DctDNA.

Results: Among the 76 enrolled patients, baseline ctDNA were detected in 65 patients. Patients with hepatic metastasis had higher baseline ctDNA level than other metastasis (p=0.038). During a median follow-up of 11.3 months, PD by radiographic response was observed in 43 patients. As expected, PD group showed higher DctDNA compared with non-PD group (p=0.013). The group with increased tumor volume exhibited higher DctDNA levels than the other groups (p=0.028). DctDNA for PD yielded Area Under Curve of 0.839 (p<0.001) with 73.3% sensitivity at 90% specificity. Patients who showed early ctDNA clearance had longer PFS (8.2 m vs 4.8 m; HR 0.45; 95% CI 0.20 to 1.03; p=0.059) and OS (16.6 m vs 10.8 m; HR 0.22; 95% CI 0.07 to 0.75; p=0.013) than those who did not. In multivariable analysis, early ctDNA clearance was still associated with significantly longer PFS (HR 0.29; p=0.036) and OS (HR 0.11; p=0.014).

Table: 1640P

Prognostic Factor	PFS HR	P value	OS HR	P value
ctDNA clearance	0.29 (0.11-0.93)	0.036	0.11 (0.04-0.57)	0.014
Age	0.97 (0.92-1.03)	0.326	1.02 (0.95-1.10)	0.629
Sex male	1		1	
female	0.58 (0.18-2.04)	0.410	0.24 (0.03-1.85)	0.171
Primary site Head	1		1	
Body	1.92 (0.62-5.97)	0.260	7.80 (1.17-51.87)	0.034
Tail	1.08 (0.30-3.91)	0.906	0.44 (0.04-5.54)	0.525
Metastatic site Liver	1		1	
Lung	0.81 (0.08-8.19)	0.859	0.78 (0.05-13.23)	0.860
Peritoneum	1.15 (0.34-3.91)	0.823	5.87 (0.79-43.64)	0.084
Multiple	1.03 (0.36-2.95)	0.962	1.38 (0.22-8.78)	0.081
Chemotherapy FOLFIRINOX	1		1	
GNP	1.43 (0.51-4.03)	0.495	4.09 (0.84-19.95)	0.081
CA 19-9 < 1900	1		1	
≥ 1900	1.08 (0.45-2.60)	0.873	1.44 (0.27-7.87)	0.671

Conclusions: Serial monitoring with ctDNA in MPC has considerable clinical potential in monitoring treatment response and predicting prognosis.

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1641P ABCG transporter and SRPK1 kinase inhibition of chemotherapy resistance: A phase Ib clinical trial of safety and maximum tolerated dose for SCO-101 in combination with gemcitabine and nab-paclitaxel in inoperable pancreatic cancer

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Background: Gemcitabine (Gem) and nab-paclitaxel (Nab) is a standard treatment for pts with inoperable pancreatic cancer (iPC), but a high frequency of chemoresistance is observed clinically. SCO-101 is a compound for oral use that was shown to revert drug resistance in preclinical studies: In taxane-resistant cancer cells SCO-101 resensitized tumor cells to taxane and reduced the active efflux of ATP Binding Cassette G2 substrate molecules from irinotecan resistant colon cancer cells. Moreover, SCO-101 inhibits Serinine-Arginine Protein Kinase 1, which may increase sensitivity of tumor cells to Gem. In clinical phase I studies, SCO-101 was well tolerated after single (up to 200 mg) and multiple (up to 150 mg daily for 14 days) doses.

Methods: This open-label, phase Ib study was conducted at four centers in Denmark and Germany as a standard 3+3 dose escalation study with increasing doses of SCO-101 and 80% dose of Gem-Nab in pts with iPC. Here we report on the primary objective to determine safety and Maximum Tolerated Dose (MTD) by evaluation of Dose-Limiting Toxicities (DLTs) related to SCO-101 during the first treatment cycle.

Results: 22 pts were included. Median age was 65 years (range 51-77) and 16 had ECOG PS=0. 11 pts had prior PC-related surgery and 19 had previously received chemotherapy. SCO-101 was dosed once daily for 6 days on days 1-6 and 15-20 on a bi-weekly schedule and chemotherapy given on day 6, 13 and 20. MTD was determined to be 200mg (Table). DLTs included increased conjugated bilirubin and decreased platelet count.

Table: 1641P Results of dose escalation

Cohort	No of pts	No of DLTs	*Type and grade of DLT (*Graded according to CTC ver. 5.0)
50 mg of SCO-101	3	0	
100 mg SCO-101	3	0	
150 mg SCO-101	6	1	Conjugated bilirubin gr. 3
200 mg SCO-101	6	0	
250 mg SCO-101	4	2	Decreased platelet count gr. 4
Total	22	3	

Conclusions: The combination of SCO-101 and Gem-Nab was generally well tolerated. DLTs were observed in 2 pts in the cohort treated with 250mg of SCO-101, hence MTD for SCO-101 concurrent with Gem-Nab was determined to be 200mg once daily for 6 days on a bi-weekly schedule. A full description of toxicities is pending.

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1642P Prognostic impact of an immunomorphological signature integrating immune, fibroblastic and tumor markers in a series of 217 resected pancreatic adenocarcinoma patients

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Background: Pancreatic ductal adenocarcinoma (PDAC) is marked by a desmoplastic stroma and poor prognosis. Current pathological or molecular classifications are discordant and not applied in routine clinical practice. In order to predict relapse-free survival (RFS), we aimed to develop an immunohistochemical (IHC) signature involving immune, fibroblastic, tumor markers in a cohort of 217 resected PDAC patients.

Methods: Tumors were collected for tissue microarrays construction and characterized by digital pathology with 13 IHC stains at the tumor epithelial, immune and stromal compartments. Cox proportional hazard models were performed to estimate hazard ratio and CI95% for factors associated with RFS.

Results: Multivariate Cox analysis showed that loss of membrane localization of β-catenin on tumor cells (HR=1.54, 95%CI=1.08-2.20, p=0.02), a low density of tumor infiltrating CD8+ T-cells (HR=1.72, 95%CI =1.23-2.41, p<0.01) and a high percentage of HSP47-positive Cancer-Associated Fibroblasts (CAF) (HR=1.41, 95%CI =1.03-1.96, p=0.03) were independent predictors of reduced RFS. Based on the expression of these three markers, we constructed a scoring system to classify resected PDAC into three distinct prognostic groups (p<0.001): 0/1+ (mRFS=8.4, 95%CI=6.7-9.9), 2+ (mRFS=13.1, 95%CI=10.7-16.4) and 3+ (mRFS=22.5, 95%CI=17.1-131.7). The discriminative ability of the three-group model was confirmed in overall survival analysis. Furthermore, with the exception of neoadjuvant therapy (p=0.03) and the presence of lymphovascular invasions (p=0.04), the score developed was not related to other clinicopathological data.

Conclusions: We propose a novel RFS prediction model based on three independent prognostic IHC markers evaluating tumor epithelial, immune and fibroblastic compartments. These results highlight considerable heterogeneity in the survival of patients with resected PDAC. Moreover, this is the first demonstration of the prognostic character of HSP47 by IHC in PDAC.

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1643P Clinical outcomes of FOLFIRINOX as front-line therapy in patients with localized pancreatic adenocarcinoma: Asian retrospective study of 781 patients

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Background: Neoadjuvant (m)FOLFIRINOX has been established as one of standard therapy for borderline resectable (BRPC) and locally advanced pancreatic cancer (LAPC). Recently, its use has been expanded to resectable pancreatic cancer (RPC), but large pragmatic studies, particularly in Asia, to show the implication of localized pancreatic adenocarcinoma are still lacking.

Methods: This retrospective study included 781 patients with localized pancreatic adenocarcinoma who received (m)FOLFIRINOX as initial therapy in Asan Medical Center, Seoul, Korea, between DEC 2017 and DEC 2020.

Results: The median age was 62 years, and 341 (43.8%) patients were female. According to the NCCN criteria, 131 (16.8%), 326 (41.9%), and 321 (41.3%) patients had RPC, BRPC and LAPC, respectively. The objective response rates were 22.1%, 16.3%, and 15.0%, respectively. The curative-intent resection (R0 or R1) was performed in 94 (71.8%) patients of the RPC group, 137 (42.0%) patients of the BRPC group, and 40 (12.5%) patients of the LAPC group; patients who underwent curative resection, the R0 resection rates were similar among three groups (86.2%, 86.1%, and 80.0%, respectively). There were 11 patients who achieved surgery following salvage chemotherapy after progression on initial (m)FOLFIRINOX. The median overall survival (OS) was 28.1 months (95% CI, 22.7—33.5) for RPC, 22.0 months (95% CI, 19.8—24.1) for BRPC, and 20.3 months (95% CI, 18.7—21.9) for LAPC ($p<0.001$). In each resectability group, median OS was significantly better in patients with surgical resection (RPC, 41.6 *vs* 14.5 months, $p<0.001$; BRPC, 37.3 *vs* 14.7, $p<0.001$; LAPC, 51.4 *vs* 18.5 months, $p<0.001$). In multivariate analysis, female gender, RPC, baseline CA 19-9 $<$ median (118.7 U/mL), objective response (CR or PR), and curative-intent surgery were significantly associated with better OS.

Conclusions: This large retrospective cohort study provides the realistic key clinical outcome data such as resection rates, survival outcomes and prognostic factors in RPC, BRPC and LAPC treated with front-line (m)FOLFIRINOX.

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1644P The mutation landscape and evolution pattern of liver or peritoneal metastasis in pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) has been found to metastasize in more than 50% of patients at the time of their initial diagnosis. This is considered to be the main reason for mortality. The liver and peritoneum are frequently observed as metastatic locations in cases of PDAC. The mutational profile and evolutionary patterns of metastatic lesions in the liver and peritoneum in pancreatic cancer remain poorly understood.

Methods: Whole exome sequencing (WES) was performed on 47 samples from 30 treatment-naïve, synchronously resected hepatic or peritoneal metastatic PDACs. The present study examined 10 primary tumours that did not metastasize within a year after surgery (non-PTs), 8 matched pairs of liver-metastatic primary (LiM-PTs) and metastatic (LiM-MTs), 9 matched pairs of peritoneal-metastatic primary (PeM-PTs), and 3 unpaired primary and metastatic tumours.

Results: KRAS mutations were found in 89.65% (26/29) of primary tumours, 70% (7/10) of liver metastases, and 100% (8/8) of peritoneal metastases. Interestingly, PCDHB14 and PXDN mutations were only detected in non-PTs, MUC16 were only detected in LiM-PTs, and ZNF594 were only detected in PeM-PTs, although there was no statistical difference. Meanwhile, the LiM-MTs group had higher TMB than PeM-MTs group (P=0.048). Mutation pattern analysis found that transitions outnumbered transversions in all samples. The paired LiM-PTs and PeM-PTs samples underwent GO and KEGG analyses. The ECM-receptor interaction signaling pathway that has been linked to metastasis in other cancer types was found to be distinct in LiM-PTs as compared to other groups. On the other hand, the proteoglycans and calcium signaling pathway was found to be unique to LiM-MTs when compared to PeM-MTs. Phylogenetic relationships analysis found that neither the LiM group nor the PeM group has a unified evolutionary pattern.

Conclusions: This research reveals that PDAC liver metastasis and peritoneal metastasis differ in mutated genes and evolutionary pattern. These results suggest that different biological mechanisms may exist in metastasis to different sites, and also highlights the need for more precise personalized treatment for PDAC in clinical practice.

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1645P STAT3, ACTA2, and SPARC stromal markers predict response to Gemcitabine/Cisplatin/Nab-paclitaxel (GCN) in patients with advanced pancreatic adenocarcinoma (apdac)

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Background: GN is front-line therapy for aPDAC. Addition of Cisplatin showed high overall response rate, progression free survival (PFS), and median overall survival (mOS) in aPDAC patients in a phase II study. However, biomarkers predicting response or resistance to GCN are lacking. We hypothesize that addition of cisplatin alters the aPDAC tumor microenvironment.

Methods: Analysis of 1379 aPDAC patients using Next-Gen sequencing (NGS) of the DNA (NextSeq, 592 genes or NovaSeq, WES) and RNA (NovaSeq, WTS) (Caris Life Sciences, Phoenix, AZ) was done to determine biomarkers of response to GCN versus GN (DNA damage repair mutations/DDRMs and stromal gene markers). Real-world mOS was extracted from insurance claims data and calculated using Kaplan-Meier estimates for molecularly defined cohorts from first treatment of GN or GCN to last contact. Time on treatment (ToT) was obtained similarly as the time of first treatment of GN or GCN to last treatment.

Results: 1204 aPDAC patients received GN therapy among which 47% were female. 175 aPDAC patients received GCN regimen (47.5% were female). GCN was associated with higher mOS (534 vs 275 days(d), HR:0.61, $p<0.001$) and longer ToT (238 vs 105 d, HR:0.43, $p<0.001$) compared to GN. No difference in mOS and ToT was seen with either regimen in patients harboring somatic DDRMs (BRCA, CHEK, FANC, MSH, MLH and others). High STAT3 (957 vs 421 d, HR:0.44, p=0.017), ACTA2 (957 vs 421 d, HR:0.45, p=0.019) and SPARC (1029 vs 421 d, HR:0.49, p=0.038) gene expressions were associated with improvement in mOS on GCN whereas STAT2 had no association. Several stromal genes including TGFB1, TGFB2, HAS-2 and IL-6 correlated with worse mOS following GN therapy. High MMP-2 expression was associated with better mOS (p=0.007) and longer ToT (p=0.006) in patients who received GN.

Conclusions: GCN demonstrated higher mOS and ToT compared to GN. There was no difference in outcome among patients with somatic DDRMs. High expression of STAT3, ACTA2, and SPARC was associated with significant mOS benefit in patients who received GCN. In patients who received GN, MMP-2 was associated with better outcome. Analysis of stromal markers STAT3, ACTA2, and SPARC in a prospective trial is ongoing.

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1646P Genomic and prognostic differences in patients with different KRAS mutations in pancreatic cancer

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Background: Approximately 90% of pancreatic cancer patients carry *KRAS* mutations, and about 80% of pancreatic cancer patients are diagnosed at advanced stage with poor efficacy of first-line treatment. Currently, several anti-tumor small molecule drugs targeting *KRAS* are under clinical investigation. Exploring the genomic and prognostic information of *KRAS*-mutated patients can help identify suitable pancreatic cancer patients for targeted therapy.

Methods: From 2017 to 2020, a total of 487 tumor samples were collected from pancreatic cancer patients across China. The laboratory Origimed, certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), conducted next-generation sequencing (NGS) of 450 cancer-related genes (YUANSU™) in Shanghai, China.

Results: In this study, we found that among 487 patients with pancreatic cancer, the percentages of *KRAS* G12, non-G12 *KRAS* mutations, and *KRAS* wild-type were 79.9%, 7.8%, and 12.3%, respectively. Furthermore, we found that pancreatic cancer patients with *KRAS* mutations were more likely to have *TP53* mutations (82.2% vs 78.4% vs 48.3%, $p=9.7x10^{-8}$), while *BRAF* (23.3% vs 2.6% vs 0.5%, $p=3.0x10^{-11}$) and *CTNNB1* (21.7% vs 5.3% vs 1.3%, $p=1.2x10^{-8}$) were more common mutated genes in *KRAS* wild-type patients. We found that patients with non-G12 mutations had significantly higher TMB than those with G12 mutations and *KRAS* wild-type (4.1 vs 2.3, p=0.0008), and this group of patients had significantly lower OS after receiving first-line chemotherapy in our cohort (249 days VS 352 days VS NA, p=0.013), but no difference was observed in PFS.

Conclusions: In this study, we elucidated the genomic differences among pancreatic cancer patients with *KRAS* G12, non-G12, and KRAS wild-type mutations. Furthermore, we found that patients with non-G12 KRAS mutations had lower OS after receiving first-line chemotherapy compared to other patients, and these patients had higher TMB levels.

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1647P Cancer-associated endocrine cell: A novel component of tumor microenvironment in pancreatic cancer

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Background: Pancreatic cancer is a highly fatal and aggressive disease due to its discouraging mortality and clinical treatment efficacy. Pancreas is composed of endocrine and exocrine parts, and the interlacing structure of them reminds us of the potential interaction between endocrine and exocrine cells in the oncogenesis and development of pancreatic cancer.

Methods: We depicted the changes of pancreatic endocrine cells in pancreatic cancer tissues by single-cell transcriptome sequencing, spatial transcriptome sequencing and multiplexed immunohistochemistry in human as well as in mouse models. After that, the interaction and sequence between pancreatic cancer oncogenesis and endocrine changes was explored in orthotopic transplantation mice and KPC mice. Finally, we proved the mechanism of the interaction between endocrine and exocrine parts of the pancreas through islet isolation, co-culture in vitro and co-injection in vivo.

Results: We found that, compared with normal pancreatic tissue, pancreatic endocrine cells displayed significantly different transcriptomic characteristics and increased interaction with exocrine part in pancreatic cancer tissues. Specifically, pancreatic polypeptide positive (PP+) cells showed a sharp increment accompanied with the progression of the cancer lesion. From an evolutionary perspective, the increased PP+ cells might be derived from the trans differentiation of α and β cells. Interestingly, in vivo and in vitro experiments proved that pancreatic cancer cells were able to induce the trans differentiation of α cells and β cells into GCG+PP+ and INS+PP+ double-positive cells, which further promoted pancreatic cancer proliferation in a paracrine-dependent manner and formed a positive feedback loop.

Conclusions: Our study systematically mapped the changes of pancreatic endocrine cells in pancreatic cancer and elucidated their relationship with pancreatic cancer oncogenesis and development. Meanwhile, we first time defined and characterized cancer-associated endocrine cells (CAE), which indicated that pancreatic endocrine cells should be an important component of pancreatic cancer microenvironment, thereby providing novel ideas for early diagnosis and targeted therapy of pancreatic cancer.

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1648P Association between circulating tumor cell count and thrombosis in pancreatic cancer

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Background: Cancer patients have a risk up to nine times higher of suffering from venous thromboembolism (VTE) compared to those without cancer, which makes VTE the second preventable cause of mortality in cancer patients. Pancreatic carcinoma is a high thrombotic risk tumor, being its incidence of thrombosis of up to 30% in outpatient patients. It has been suggested that circulating tumor cells (CTC) may be related to thrombosis, as they can alter blood coagulation and due to their pro-inflammatory and pro-coagulant properties.

Methods: We conducted an observational, prospective, cohort study in a two Spanish centers. CTC were isolated from a blood sample of newly diagnosed patients of pancreas carcinoma before starting chemotherapy treatment. CTC count was determined by using Isoflux® technology followed by counting via confocal microscopy. Patients were followed up according to routine practice. Clinical and analytical data were collected up to death. We analyzed the relation between CTC and VTE, and between CTC and VTE scores.

Results: This analysis included a total of 63 patients newly diagnosed before chemotherapy was given. 39 (61,9%) patients were metastatic, 16 (25,4%) locally advanced and 8 (12,7%) borderline tumors. Median follow up was 11,63 months. 25 episodes of VTE occurred in 23 patients during follow up (11 pulmonary embolism, 5 deep vein thrombosis, 6 visceral thrombosis, 3 catheter-related thrombosis). Median value of CTC was 397 (range 33-21697). For a cut off of CTC 500, we found no relation between CTC and VTE (p=0,298). However, when we analyzed CTC>500 and VTE excluding visceral and catheter-related thrombosis, it was found to be associated (p=0.006, p=0.002 in those metastatic). We found no relation between CTC and thrombosis scores (Khorana, Viena, Protech, Conko nor CAT).

Conclusions: This study shows that CTC detection before first-line chemotherapy could be a predictor marker for VTE.

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1649P Comprehensive genomic profiling contributes to the prognosis of patients with advanced pancreatic cancer

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Background: Precision medicine for pancreatic cancer (PC) is one of the promising treatment strategies. However, only a few patients can receive genotype-matched treatments for the low detection rate of actionable genomic alterations, therefore the clinical utility of comprehensive genomic profiling (CGP) is still unknown. On the other hand, CGP gives us a lot of information such as prognosis, future eligibility for genotype-matched clinical trials, and it may affect physician's treatment strategies. The present study was to investigate the contribution to prognosis of CGP, and its appropriate timing in the treatment of advanced PC.

Methods: This was a single-center, retrospective cohort study. Patients who were diagnosed as recurrent or metastatic PC with adenocarcinoma or adenosquamous carcinoma and underwent systemic chemotherapy between April 2018 and March 2022 were recruited. We reviewed the medical records and collected data of patient characteristics, survivals, and genomic information. We compared overall survival (OS) according to those who had received CGP (CGP group) or not (non-CGP group), and those who had performed CGP before or after initial chemotherapy.

Results: A total of 107 patients were eligible, in which 47 patients had received CGP. Patient characteristics were not statistically different between two groups except for age. OS was significantly longer in CGP group than non-CGP group (median, 29.7 vs 13.4 months; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.30—0.89; $P < 0.017$). OS tended to be longer in patients who had received CGP before the initiation of systemic chemotherapy than those who had received CGP after initial chemotherapy (median, 40.1 vs 24.0 months; HR, 0.29; 95% CI, 0.085—1.02; P=0.054). Actionable genomic alterations were detected in 16 patients (34.0%), whereas genotype-matched treatments were implemented for five patients (10.6%).

Conclusions: In the present study, OS was prolonged in patients who had undergone CGP irrespective of implementation of genotype-matched treatments, suggesting that CGP could help physicians to select the optimal treatment strategies for advanced PC in clinical practice. Given the extremely poor prognosis of the disease, earlier timing of CGP is considered.

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1650P Identification of potential targets in pancreatic adenocarcinoma: The KRAS Wild-Type subset

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with limited treatment benefits. However, about 10% of cases are *KRAS* wild-type (WT) which are enriched in potentially actionable molecular alterations (MA). We aim to shed light on the clinical and molecular features and explore the survival benefit from precision medicine in these patients (pts).

Methods: We conducted a comprehensive retrospective analysis of PDAC pts treated at Vall d'Hebron University Hospital from 2016 to 2022 and included those with *KRAS* WT and a molecular profile using next-generation sequencing (NGS). We classified MA using the ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) and compared those in Tiers I-III treated with matched therapy to those who did not or without actionable MA. We used the Kaplan-Meier method and the log-rank test to compare overall survival (OS).

Results: We identified 45 *KRAS* WT pts with a median age of 57 years (range 29 - 75), 69% were male and 56% were metastatic at diagnosis. Among metastatic cases (n=36) median OS was 23.7 months (95% confidence interval (95CI) 18.4-43.4). Ten pts presented DNA damage repair (DDR) gene alterations (24%) and two presented deficient mismatch repair alterations (4.4%). Moreover, we identified pathogenic germline mutations in 8 pts and gene fusions in 8 pts (18%). The table outlines MA according to the ESCAT and matched therapy. Metastatic pts who received matched therapy (n=9) had longer OS compared to those who did not receive matched therapy (n=9) [(HR 0.49 (95CI 0.17-1.45) 34,3 vs 19 months p=0.2] or those without actionable MA (n=18) [(HR 0.86 (95CI 0.31-2,32) 21,8 months p=0.76].

Table: 1650P

ESCAT (n)	Genomic alteration	Therapy (n)	Non-therapy (n)
IA (5)	g*BRCA*1, g*BRCA*2	PARPi (3)	2
IB (3)	s*BRCA*1, s*BRCA2*, s*PALB2*, g*PALB2*	PARPi (1), ATMi (1)	1
IC (3)	MSI	AntiPD1(0)	1
	RET fus	RETi (1)	1
IIB (5)	*NRG1* fus	Anti-HER2/HER2 (3)	1
	BRAF V600E	BRAFi+MEKi (0)	1
IIIA (8)	Other DDR	PARPi (0)	3
	ALK fus	ALKi (0)	1
	*HER*2 mut	AntiHER2 (0)	1
	PIK3CA mut	PIK3CAi (0)	3
IV (1)	*BRAF* fus	NA	NA
X (10)		NA	NA

Conclusions: Our findings suggest that *KRAS* WT PDAC tumours are enriched in potentially targetable MA and could benefit from precision-oncology approaches. These results highlight the relevance of performing a complete NGS analysis in these pts.

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1651P Comparison of surgical outcome and prognostic factors between pancreaticobiliary and intestinal types of periampullary adenocarcinoma following pancreaticoduodenectomy

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Background: The exact origin and associated prognosis of periampullary adenocarcinoma might be challenging to determine, especially in bulky tumours, due to the destruction of normal periampullary anatomy and the extension of the tumour beyond a single periampullary structure. Periampullary carcinomas are typically divided into pancreatobiliary and intestinal types according to histological differentiation. The aim of this study was to determine the prognostic value of this histological differentiation by comparing various clinic-pathological prognostic factors and surgical outcome in periampullary carcinoma cases that underwent pancreaticoduodenectomy.

Methods: From May 2018 to April 2021, 60 consecutive cases of periampullary carcinoma who underwent pancreaticoduodenectomy were included in this study. Cases were divided into two groups: pancreatobiliary and intestinal types. Various clinical and histopathological prognostic variables were analysed, and the association of these variables with pancreatobiliary and intestinal variants of periampullary carcinoma was determined using Chi-square and Fischer's exact tests.

Results: 20 cases were included in the pancreatobiliary group, and 40 cases were included in the intestinal group. These groups were comparable in terms of age, sex, nutritional status, and bilirubin levels. Pancreatobiliary type was more frequently associated with nodal disease (**p<0.01**), lymphovascular invasion (**p<0.01**) and perineural invasion (**p = 0.018**). Post-operative morbidity was significantly higher in the pancreatobiliary group (**p = 0.043**).

Table: 1651P

S.No.	Variable		Periampullary Carcinoma		x2	p-value
			Pancreatobiliary Type	Intestinal Type		
1	Age (years)	<60	15	32	0.196	0.658
		>60	5	8		
2	Sex	Male	12	19	0.834	0.361
		Female	8	21		
3	Comorbidity	Yes	6	16	0.574	0.449
		No	24	24		
4	Bilirubin (mg/dl)	<5	8	8	2.73	0.099
		>5	12	32		
5	Albumin (g/dl)	< 3	8	11	0.96	0.326
		> 3	12	29		
6	Pancreas Texture	Firm	10	21	0.03	0.855
		Soft	10	19		
7	MPD	<3mm	6	5	2.73	0.99
		>3mm	14	35		
8	Tumor size	>2cm	8	21	0.834	0.361
		<2cm	12	19		
9	Nodal status	Positive	12	10	7.03	0.008
		Negative	8	30		
10	Lymphovascular Invasion	Present	12	9	8.24	0.004
		Absent	8	31		
11	Perineural Invasion	Present	7	4	5.57	0.018
		Absent	13	36		
12	Grade	1	10	15	0.857	0.355
		2/3	10	25		
13	Post-operative Morbidity	Yes	11	08	4.10	0.043
		No	9	32		

Conclusions: After pancreaticoduodenectomy, periampullary cancer of the pancreatobiliary type is linked to worse post-operative outcome and unfavourable histopathological prognostic markers. Therefore, after surgery, these cases should follow management algorithms with aggressive adjuvant therapy protocols.

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1652P Interaction between enhanced cytokine signalling and ferroptosis defence fuels obesity-associated pancreatic ductal adenocarcinoma oncogenesis

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Background: Obesity amplifies the risk for various cancers, including pancreatic cancer (PC). Due to limited early screening methods, this study seeks to investigate the effects of obesity-related metabolic disorders on PC initiation and offer novel insights into early detection and diagnosis in obese populations.

Methods: Human pancreatic Nestin-expressing ductal cells (HPNE) were cultured with human serum obtained from obese patients and healthy individuals. Transcriptomics, untargeted metabolomics, and joint-pathway analyses were conducted to examine the impacts of obesity-related metabolic disorders on pancreatic carcinogenesis. Multiomics analysis results were validated using cells of varying genetic backgrounds, while their mechanisms and roles in PDAC development were explored in obese transgenic mouse models. Clinical relevance and translational value were also corroborated using public databases and human samples.

Results: Multiomic assessment revealed heightened cytokine signalling and ferroptosis defence in HPNE cells exposed to obesity serum. *In vitro* tests showed that upregulated interleukin 34 (IL-34) strengthens ferroptosis defence through oxidative stress, while the enhanced ferroptosis defence reciprocally raises IL-34 levels. Our study demonstrated that augmented IL-34 signalling and ferroptosis defence hasten PDAC initiation in diet-induced obese mice by increasing immunosuppressive macrophages infiltration. Public databases revealed a strong correlation between elevated IL-34 and glutathione peroxidase 4 (GPX4) expression in pancreatic tumors vs. normal tissues. Gene signature expression displayed substantial correlations as well. Cohort validation and single-cell analysis suggested a positive association between IL-34 signalling and ferroptosis defence enhancement with PDAC patients' body mass index (BMI).

Conclusions: Obesity elevates IL-34 signalling and ferroptosis defence, thereby promoting PDAC development via macrophage-induced immunosuppression. The observed positive correlations between IL-34 and BMI, as well as GPX4 and BMI in PDAC patients underscore their potential roles in early PC screening among the obese population.

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1653P The activated thermogenesis of intra-pancreatic fat fuels the progression of pancreatic cancer

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Background: The presence of minimal intra-pancreatic fat deposition (IPFD) in the healthy human pancreas has been demonstrated in numerous studies. But excess IPFD, leads to a wide array of diseases, including but not limited to diabetes, pancreatitis, and pancreatic cancer (PC). Remarkably, PC patients with excessive intra-pancreatic fat accumulation are commonly associated with a poor prognosis compared to those with minimal IPFD. However, the interaction between tumor and IPFD remains elusive. Here, we evaluated the pancreatic fat infiltration in normal people and patients with PC respectively, and explored how intra-pancreatic fat accelerates tumor progression.

Methods: Magnetic resonance imaging (MRI) and clinical biopsy specimens were used to assess the degree of pancreatic fat infiltration in PC patients and healthy control individuals. The KC, KPC, KCO, and AAV8-ADIPOQ-DTA mice were established to demonstrate that IPFD promoted tumor progression. The single-nucleus sequencing of pancreatic fat tissue and proteomic of PC cell lines were performed to identify the mechanism of interaction between cancer cells and adipocytes.

Results: We found that patients with PC presented excess intra-pancreatic fat deposition more frequently than control individuals, and the degree of fat infiltration was positively correlated with the tumor size of PC patients. High-fat diet KPC mice or KCO mice showed a higher degree of IPFD, which contributed to tumor growth and low survival rates of mice. Besides, the expression of uncoupling protein 1 (UCP1) was upregulated in PC patients or spontaneous tumor mice compared to normal controls. Constantly, the single-nucleus sequencing of pancreatic fat tissue of PC patients demonstrated the increase in thermogenesis features. Specifically, we revealed that PC cells improved the thermogenesis of intra-pancreatic adipose tissue, which in turn promoted PC cell proliferation.

Conclusions: We demonstrated that excess intra-pancreatic fat infiltration fuels the progression of PC, and selectively eliminating fat in the pancreas inhibits tumor growth. Mechanistically, PC cells promote the browning of adipocytes, and then the activated adipocytes enhance the proliferation and migration of cancer cells in response.

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1654P Circulating tumor cells (CTCs) as prognostic factor for pancreatic cancer: Updated of a prospective study

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Background: CTCs have been extensively studied in different neoplasms. There are several techniques for their identification, however, it is not clear which is the most effective. In pancreatic cancer (PC) their significance in different stages of the disease and correlation with tumor markers are poorly understood.

Methods: Prospective, observational, cohort study in two Spanish centers. We analyzed CTCs at day 0 (before chemotherapy). Isolation was carried out with Isoflux technology, combining cell separation by immunomagnetic particles (positive selection) with a microfluidic system. Four different markers were used, including two mesenchymal markers, EpCAM and EGFR. The count of CTCs was done in a confocal microscope using the iMSRC (intelligent Matrix Screen Remote Control). Primary endpoint was the correlation of CTCs with overall survival (OS). Secondary endpoints: correlation between CTCs with Ca19.9/CEA values and the difference in the median value of CTCs in metastatic compared to locally advanced disease were secondary endpoints.

Results: Sixty-three patients were analyzed. Clinical characteristics: (Table) Median follow up was 11.6 months. Median value of CTC-0 was 343 (range 33 - 6259) for metastatic patients while it was 436 (81 - 1082) for locally advanced patients ($p = 0.380$). Correlation coefficient for Ca 19.9 was 0.03 ($p = 0.824$); CEA correlation coefficient was 0.121 ($p = 0.366$). Kaplan-Meier analysis showed an estimated median OS of 9.9 months for > 500 CTCs (95% confident interval [95% CI] 8.1 — 11.6) vs 14.7 (95% confident interval [95% CI] 6.7 — 22.6) for < 500 CTCs ($p = 0.021$).

Table: 1654P

Clinical characteristics	Results
Median age (range) - yr	65 (45 — 85)
Sex — no. (%) Male Female	35 (55.67) 28 (44.4)
Stage at diagnosis — no. (%) Borderline Locally advanced Metastatic	8 (12.7) 16 (25.4) 39 (61.9)
BMI — no. (%) Underweight Normal Overweight Obesity	2 (3.1) 34 (54) 21 (33.4) 6 (9.5)
PS - no. (%) 0 1 2	12 (19) 43 (68.3) 8 (12.7)
CEA — median (range)	4.8 (0.5 — 381)
Ca 19.9 — median (range)	1131 (2 -6627800)

Conclusions: With an increased number of patients there is still absence of differences of CTC-0 between metastatic and non-metastatic patients as well as no correlation of CTCs with tumor markers at diagnosis. 500 CTCs continues to be a significant cutoff for overall survival.

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1655P Nampt inhibitors re-sensitize MAP17 expressing pancreas tumors

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Background: The overexpression of MAP17, a small non-glycosylated membrane protein, has been described in a wide variety of human carcinomas, correlating with worse prognosis and response to different therapies. Pancreatic cancer (PC) has been the seventh major cause of cancer-related deaths worldwide in 2020, associated to a high mortality with a life expectancy of ∼5% at 5 years. Its aggressiveness makes necessary to identify new targets/biomarkers of response. The aim of this study was to assess the prognostic and predictive value of MAP17 expression in PC.

Methods: We evaluated MAP17 expression by immunohistochemistry in a cohort of 97 paraffin-embedded tissue samples of patients. We overexpressed MAP17 in two PC cells lines and tumorigenesis was analyzed using different functional assays and measuring several stem cell markers. We performed IC50 assays with different drugs and correlated them with MAP17 expression. Finally, we explored the effect of some of those treatments in vivo.

Results: High expression of MAP17 was detected only in pancreatic tumor cells. Also, we found that the overexpression of MAP17 increased the tumorigenic and stemness properties of cells as PC cell lines with high levels of MAP17 grew faster, formed higher number of colonies, holoclones, tumorspheres and a higher proportion of CD133+ cells. We explored whether the response to different antitumoral agents could be dependent on MAP17 expression, detecting that MAP17-expressing PC cells showed better response to gemcitabine, 5-FU, cisplatin and osimertinib, as well as resistance to docetaxel, bortezomib and ixazomib. However, in tumor xenografts in vivo, MAP17 expression confers resistance to all treatments. Next, we detected that the levels of total NAD, an essential metabolite implicated in many cellular processes, were higher in cells that overexpress MAP17. Finally, we found that the use of different inhibitors of NAMPT, the limiting enzyme of the synthesis of NAD, re-sensitize pancreatic tumor xenografts to classic chemotherapy.

Conclusions: MAP17 could serve as a prognostic and predictive biomarker in PC. Moreover, our findings could open new options of coadjuvant to current therapy with cisplatin or gemcitabine in PC that may eventually improve patients' outcomes.

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1656P Targeting NPC1L1 rescues anti-tumor immunity and improves immunotherapeutic efficacy in pancreatic cancer

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Background: The dysfunction of anti-tumor immunity of pancreatic adenocarcinoma (PAAD) is critically attributable to the failure of multi-therapies. Cholesterol is an essential component of mammalian cell membranes essential to the proliferation and TCR activation of $CD8^+$T cells, and it has been revealed that cholesterol metabolism plays an important role in sustaining the antitumor activity of $CD8^+$T cells. Although the cholesterol metabolism reprogramming has been implicated in carcinogenesis, including PAAD, how tumors reprogram cholesterol metabolism to sustain their survival and suppress anti-tumor immunity remains largely unknown.

Methods: RNA-seq, CyTOF, $CD8^+$ T cell isolation and cultivation, flow cytometry analysis etc. biological experimental techniques.

Results: PAAD cells ectopically express NPC1L1 to suppress the activation and proliferation of antitumor $CD8^+$ T cells in tumor microenvironment. NPC1L1 overexpression promotes PAAD cells to evade the immunosurveillance of $CD8^+$T cells and

is responsible for PAAD development and progression. And pancreatic npc1l1-silencing KPC mice led to a marked decrease in late-stage intraepithelial neoplasia lesions and malignant tumor formation. Our findings demonstrated that PAAD cell-expressed NPC1L1 functions as a checkpoint molecule to suppress the cytotoxicity of antitumor $CD8^+$T cell via NPC1L1-ITGAL interaction. Moreover, NPC1L1-ITGAL interaction promotes the efflux of intracellular cholesterol from antitumor $CD8^+$ T cells, consequently leading to a suppression of TCR activation and proliferation of antitumor $CD8^+$ T cells. The NPC1L1 inhibitor ezetimibe promotes the antitumor response mediated by $CD8^+$ T cells and synergizes with PD-1 blockade to enhance its therapeutic efficacy in PAAD.

Conclusions: Ectopically overexpressed NPC1L1 on cell membrane as a metabolic-immunologic two-pronged checkpoint is an ingenious trick of pancreatic cancer cells to gain at the expense of $CD8^+$ T cells.

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1657P Understanding the role of SAGA and mediator in the resistance to Pdk1 deletion in PDAC

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Background: Pancreatic ductal adenocarcinoma (PDAC) represents the fourth highest rate of cancer-related deaths worldwide. The absence of early symptoms, early metastasis, and inefficient systemic therapies lead to a fatal prognosis for PDAC patients. Currently, surgical resection is the only curative option. However, it is often linked to severe postoperative complications and a considerable tumor recurrence rate. Therefore, identifying the resistance mechanisms of PDAC and developing targeted therapies is crucial.

Methods: Mutant KRAS and its effector Pdk1 play a major role in PDAC carcinogenesis. Previous works showed that Pdk1 deletion causes impairment of PDAC cell proliferation in vitro and in vivo. However, a minor subpopulation of cells continues to proliferate. To investigate this resistance, a genome wide CRISPR/Cas9 knockout screen was performed. Members of SAGA and Mediator complexes were among the top hits of the screen. The CRISPR knockouts of these genes were generated in the bulk PDAC epithelial cell line and in two single cell clones - one resistant and one sensitive to Pdk1 deletion. Clonogenic assays were performed to analyze the proliferation of the knocked-out cells, while RNA sequencing was conducted to investigate the differentially expressed genes.

Results: In the CRISPR/Cas9 knockout screen, members of SAGA and Mediator complexes showed enrichment in Pdk1 deletion resistant clones. Amongst all hits, significant proliferation of the Usp22- and Atxn7L3- as well as Med13- and Med16-knockout in the Pdk1 deleted PDAC cells was observed, with the strongest effect in the resistant clone. Several enhanced or downregulated hallmark pathways were observed in the knocked-out cells, providing insight into possible resistance mechanisms of the PDAC.

Conclusions: The results of the RNA sequencing of both SAGA and Mediator knocked-out cells showed an enhancement of the Hedgehog signalling, a pathway reported in the initiation of a growing number of cancers. The results of this research suggest furthermore, that the loss of the connecting units Atxn7L3 and Med16 promotes an unhinged transcription activity of the enzymatically active SAGA and Mediator complexes and leads to an enhanced PDAC cell proliferation.

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1658P Molecular subtyping of familial pancreatic ductal adenocarcinoma identifies novel pathogenic germline variants

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Background: The 5-year survival rate of pancreatic ductal adenocarcinomas (PDAC) is around 7.2% in spite of recent advances in therapeutics, as most patients are diagnosed at an advanced stage. 10-15% of pancreatic ductal adenocarcinoma (PDAC) cases cluster in families with an unknown genetic basis, known as familial pancreatic cancer (FPC). Targeted panel and exome sequencing of FPC cases was performed to identify new variants related to PDAC risk.

Methods: Targeted panel sequencing of 60 genes associated with hereditary cancer was performed in germline from 85 PDAC cases, 53 from families with an apparent familial pancreatic cancer syndrome and 32 cases with sporadic PDAC. Exome sequencing was also performed in 11 PDAC cases that were negative for a germline mutation by panel sequencing. The presence of a somatic mutation in KRAS codons 12, 13, 59, 61, 117 and 146 was determined in cfDNA in 54 PDAC cases.

Results: By panel sequencing, pathogenic variants were identified in 4 FPC cases (7.5%) in the MLH1 and CDKN2A and none of the sporadic cases via panel sequencing. Likely pathogenic variants were found in 5 FPC cases (5.7%) in POLQ, CHEK2 and FANCM and in 3 sporadic cases (9.4%) in MUTYH, TERT and ATM. By exome sequencing, missense variants with a damaging effect were found in all 11 FPC cases tested. However, stop gain, stop loss or frameshift variants were found in 5 FPC cases (45.45%), affecting WWOX, C2orf83, CYP3A5 and TANGO2. KRAS somatic mutations in codons 12 and 13 were more frequently detected in sporadic PDAC cases (70%) compared to familial cases (16%). Interestingly, the median overall survival for sporadic and familial PDAC cases was 10.2 vs. 21.7 months ($p=>0.01$), respectively, even though all patients are treated the same in the clinic.

Conclusions: Familial pancreatic cancer cases harbor pathogenic germline mutations in DNA repair genes and other genes related with tumorigenesis that could explain the aggregation of PDAC in these families. FPC seems to show a different molecular and clinical profile to the sporadic form of the disease.

Legal entity responsible for the study: IRYCIS.

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1659P The use of liquid biopsy in patients with advanced pancreatic cancer (PDAC) to guide enrollment in phase I clinical trials

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Background: Therapeutic possibilities in PDAC remain poor and access to tumor tissue for molecular profiling is still a challenge. The era of circulating tumor DNA (ctDNA) or liquid biopsy facilitated molecular screening and treatment orientation in selected patients (pts).

Methods: Data from PDAC pts who underwent liquid biopsy at the Drug Development Department (DITEP) at Gustave Roussy were collected. The primary objective was to assess the ability of liquid biopsy to find molecular alterations (MA), orient and include pts in early phase clinical trials. We evaluated the progression-free survival (PFS) on matched therapy (PFS2) compared to PFS on prior therapy (PFS1). Treatment efficacy was considered by focusing on the percentage of patients with a PFS2 that was 1.5 times greater than the PFS1, based on a standard calculation (PFS2/PFS1), and a modified formula (mPFSr) with mPFSr = postPFS/prePFS with postPFS = PFS2 if PFS2 $<$ 6 months and postPFS = 24 months if PFS2 $>$ 6 months; prePFS = PFS1 if PFS1 $>$ 2 months and prePFS = 2 months if PFS1 $<$ 2 months.

Results: Between January 2020 to November 2022, a total of 31 pts were included in the study. The main characteristics were as follow: median age of 62 years (32-81), median number of previous lines of treatment of 2 (0-4) and median ECOG Performance Status of 0 (0-2). Finally, 30 patients had a liquid biopsy at progression on their

last treatment line. Targetable MA (FGFR, KRAS…) were found in 8 pts (27%), and 5 patients (17%) received a matched targeted therapy in an early phase clinical trial. FGFR alterations were the most frequent and 3 patients (60%) received FGFR inhibitors. From the 5 patients matched and treated, one patient (20%) had a PFS2/PFS1 ratio > 1.5 and three pts (60%) had an mPFSr > 1.5. With a median follow-up time of 12.3 months (9.2-NR), the overall response rate was 20%, the overall control rate was 100% and the median overall survival was not reached (8.5-NR months).

Conclusions: These results suggest that molecular profiling-matched therapy assessed by liquid biopsy could improve the therapeutic field in pancreatic cancer. However, only a small proportion of patients are matched and treated. Randomised trials are needed to confirm the value of this treatment method in pancreatic cancer.

Legal entity responsible for the study: Dr. S. Ponce Aix (DITEP, Gustave Roussy, Villejuif).

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1660P Squalene epoxidase promotes pancreatic cancer growth by attenuating ER stress and activating lipid rafts-regulated Src/PI3K/Akt signalling pathway

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Background: Pancreatic cancer (PC) is among the deadliest malignancies with a 5-year survival rate of nearly 12%. Malignant proliferating cancer cells usually exhibit metabolism reprogramming, which is distinct from their normal counterparts, resulting in therapeutic vulnerabilities. However, the underlying mechanisms of aberrant cholesterol metabolism regulating PC progression are poorly understood. In the present study, we aimed to identify and investigate the role of a key cholesterol metabolic enzyme squalene epoxidase (SQLE) in tumorigenesis of PC.

Methods: Integrating analysis of The Cancer Genome Atlas (TCGA) cohort and multiple Gene Expression Omnibus (GEO) datasets was used to find the top up-regulated cholesterol homeostasis-related gene in PC. The IHC staining of tissue microarray composed of human PC samples were used to identify the clinical significance of SQLE in PC patients. The biological functions of SQLE and the potential therapeutic efficiency of SQLE inhibitors were assessed both in vitro and in vivo. Transcriptome analysis, untargeted metabolomics analysis, and related lipid detection were further performed to clarify the molecular mechanism of SQLE on PC development.

Results: We found *SQLE* expression was highly expressed in PC tissues compared with normal pancreatic tissues, and the upregulated *SQLE* predicted poor outcomes in PC patients. Additionally, we demonstrated that SQLE promoted the growth of PC both in vitro and in vivo. Mechanistically, inhibition of SQLE caused squalene accumulation-induced endoplasmic reticulum (ER) stress occurrence and subsequent cell apoptosis. Moreover, SQLE increased cholesterol de novo biosynthesis and maintained the stability of lipid rafts, which in turn activated Src/PI3K/Akt signalling. Finally, we found that pharmacological blockade of SQLE with terbinafine or NB-598 profoundly suppressed PC cell proliferation and xenograft tumor growth.

Conclusions: Our findings demonstrated the oncogenic role and tumor promoting mechanism of SQLE in PC. SQLE promotes PC growth by attenuating ER stress and promoting lipid rafts-regulated Src/PI3K/Akt signaling pathway, suggesting SQLE as a potential therapeutic target for PC.

Legal entity responsible for the study: The authors.

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1661P Precision medicine for pancreatic cancer: A clinical study validating EUS biopsies

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Background: Pancreatic cancer (PC) has a high mortality rate and treatment options remain very limited. While there is great appeal in improving patient outcomes by implementing precision medicine in this disease, there are significant barriers including challenges in accessing adequate biopsy material to analyse. Endoscopic ultrasound (EUS) biopsy is a common diagnostic procedure and often the only source of tissue for patients with PC, but the utility of these biopsies to provide high quality biopsy material for clinically relevant molecular profiling remains lacking.

Methods: This study enrolled 135 patients undergoing diagnostic EUS biopsy as standard of care in PC to perform molecular analysis using a commercial 500-gene panel which also provides data on clinically relevant gene fusions, tumour mutation burden (TMB) and microsatellite status. No interventions were provided, but data was analysed and discussed at a Molecular Tumour Board meeting and relevant findings fed back to treating oncologists. Patients were followed for treatment data and survival.

Results: 7 patients were unable to be analysed due to a lack of available biopsy material (n=2), withdrawal of consent (n=1) or inadequate QC metrics (n=4). We detected common oncogenes at expected frequencies, with KRAS in 114 (90%), TP53 in 85 (66%), SMAD4 in 13 (10%) and CDKN2A in 11 (9%). Targetable molecular findings were detected in 28 (22%), with RNF43 variants in 11 (9%), high TMB in 10 (8%), BRCA1/2 mutations in 4 (3%), BRAF V600E mutations in 2 (2%), CHEK2 mutation in 1 (1%) and BARD1 mutation in 1 (1%). No microsatellite instability was detected. Median TMB in this cohort was low, as expected, at 3.1Mut/Mb. However, of the 10 patients with high TMB (>10Mut/Mb), 5 of these had markedly hypermutated profiles (TMB >150Mut/Mb). To date, 8 patients (6%) have commenced targeted therapies and survival follow up is ongoing.

Conclusions: This study validates EUS as a reliable and accurate source of biopsy material for clinically relevant tumour profiling and adds to the body of literature highlighting the potential to improve patient outcomes in PC through routine genomic analysis, despite the many challenges.

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1662P Targeting stress granule formation as a synthetic lethality strategy for kras-induced pancreatic cancer initiation

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Background: Stress granules (SGs) are membrane-less organelles formed by liquid-liquid phase separation (LLPS) that play a critical role in regulating RNA metabolism, and protein synthesis, in a wide range of stress responses. These granules are required to support pancreatic cancer (PDAC) transformation, cell survival, growth, and chemotherapy resistance, making them an attractive target for new cancer therapies. Here we report a novel mechanism for SG formation, which is induced by NUPR1 (an intrinsically disordered stress-associated protein), in response to *Kras*^{G12D} oncogenic stress. We provide a preclinical proof of concept for using SG inhibition as an efficient strategy for targeting PDAC initiation and development, by using NUPR1 inhibitors.

Methods: We have used recombinant proteins for in vitro tests (LLPS tests), PDAC-derived cell lines, and doxycycline-inducible transgenic cell lines (cell viability tests, evaluation of gene expression, and SGs quantification), a transgenic *Pdx1*-Cre; LSL-*Kras*^{G12D} mouse model.

Results: In this study, we show that NUPR1, has the capacity to produce droplets through LLPS, but not its mutants or under the treatment of its inhibitor (ZZW-115). We observed that LLPS induced by rNUPR1 is essential for SGs formation since genetic or pharmacological inhibition of NUPR1 activity hampers SGs formation in pancreatic cancer cells. In addition, we found that *Kras*^{G12D} mutation causes significant oncogenic stress which in turn induces a strong overexpression of NUPR1, promoting the formation of SGs as a stress-dependent mechanism of cell survival.

Consistently, forced Kras^{G12D} expression in pancreatic cells elicits a strong sensitivity to NUPR1 inactivation by genetic or pharmacological means. Finally, inhibition of SGs formation with the NUPR1 inhibitor ZZW-115 in *Pdx1*-Cre; LSL-*Kras^{G12D}* mice blocks the transformation process indicating that SGs formation is necessary for PDAC development.

Conclusions: In this work, we provide a preclinical proof of concept showing that SG formation is a targetable step in the *Kras^{G12D}*signaling pathway, thus suggesting that inhibiting NUPR1 or SG formation can be utilized as a synthetic lethality therapeutic strategy for *Kras^{G12D}*-dependent tumors.

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1663P Role of next-generation sequencing somatic assays in patients with advanced pancreatic cancer

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Background: Recently, the use of Next-Generation Sequencing (NGS) somatic assays has increased aiming the identification of potentially targetable molecular alterations for the treatment of advanced malignancies that progressed after standard therapies. Pancreatic cancer (PC) remains a challenging disease, with poor outcomes, for which novel therapeutic strategies, are largely warranted. Nevertheless, the impact of NSG for the treatment and outcomes of this neoplasia is unclear. The aimed to assess the impact of NGS somatic assays for patients (pts) with advanced pancreatic cancer.

Methods: In this cohort, we evaluated pts with advanced PC (metastatic or locally advanced unresectable) treated in a private cancer network from 2014 to 2021. Electronic records were reviewed for data collection. The study endpoints were the pattern of somatic alterations, the frequency of potentially targetable alterations and the use of targeted therapy directed by the NGS somatic assay.

Results: Among 446 pts with advanced PC, 51 underwent a NGS somatic panel; 44 of them had the panel results available and were evaluated in this study. All pts with panel available had at least one somatic alteration. Most pts (95%) had KRAS mutations; the most common were KRAS G12D (52%), KRAS G12V (17%), KRAS G12R (9%), KRAS G12A (7%), and KRAS Q61H (5%). No patient had a KRAS G12C mutation that could be targeted with anti-KRAS G12C agents. Other frequent molecular alterations were found in the following genes: TP53 (52%), CDKN2A/B (41%), SMAD4 (18%), ARID1A (11%), PTEN (7%), and ATM (4%). Two pts had a BRCA2 mutation that was known to be germline. No patient had microsatellite instability-high or high tumor mutational burden. Overall, 11% had potentially drugable alterations. Only one patient (2%) received a treatment guided by the result of the somatic panel, with a median progression-free survival of 1.6 months.

Conclusions: Unfortunately, NGS somatic panel seems to have limited role for the PC treatment nowadays, with few pts receiving treatment guided by the panel. The development of new targeted therapy directed to the most frequently molecular alterations, including KRAS-directed therapy other than KRAS G12C, are urgently needed to improve outcomes.

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1664P Italian Association for Medical Oncology (AIOM) guideline application in real-world: Multi-institutional based survey of adjuvant and first-line pancreatic ductal adenocarcinoma treatment in Italy (GARIBALDI) - survival analyses in the metastatic cohort

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Background: The present analyses from the GARIBALDI was aimed to addressing the role of oncology center volume, type and accrual rate on the prognosis of patients (pts) with metastatic Pancreatic Ductal Adenocarcinoma (mPDAC).

Methods: Consenting treatment-naïve pts $\geq$ 18-year with pathological diagnosis of mPDAC were enrolled. Participating centers were categorized according to the self-declared expertise, the type and the accrual rate. Survival curves were estimated by the Kaplan—Meier method and compared by the log-rank test. Overall Survival (OS) was defined as the time from the date of medical therapy start to death for any cause.

Results: Between July 2017 and October 2019, 475 pts enrolled in 44 centers were eligible for these analyses. Median age was 69 (range 36-90); 46% females; 90% ECOG PS 0-1; 38% overweight/obese; 66% with liver metastases; median CA19.9 789 (range 0-1,374,500); 8% with prior PDAC resection; 17% with prior cancer history. Median time from diagnosis to treatment was 33 days. 65.2% of pts started therapy >25 days from baseline CT; 70.7% of pts received nab-paclitaxel+gemcitabine; 16.7% gemcitabine alone; 7.7% FOLFIRINOX; 37% received a second-line therapy. The median follow-up was 50 months and 405 pts died. The table provide the median OS estimates.

Table: 1664P

	Deaths/N	Overall survival (Median [95%CI])	Log-rank p-value
Self-declared expertise			0.24483
Low-volume (<25 pts/year)	50/58	7.3 [5.6-9.0]	
Medium-volume (25-50 pts/year)	101/125	8.8 [6.7-11.5]	
High-volume (>50 pts/year)	234/267	10.1 [9.1-11.2]	
Type			0. 3610
Community hospitals	183/224	7.9 [6.7-9.6]	
Academic centers	222/251	10.1 [9.1-11.2]	
Accrual rate			0.6348
Low-accrual (<10 pts/year)	173/210	7.9 [6.7-9.5]	
Medium-accrual (10-50 pts/year)	173/201	9.6 [8.5-11.2]	
High-accrual (> 50 pts/year)	59/64	12.0 [9.7-14.9]	

Conclusions: Although not statically significant, the GARIBALDI survey detected a clinical difference in OS based on center volume, type, and accrual rate.

Legal entity responsible for the study: Associazione Italiana di Oncologia Medica (AIOM), Milan.

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Disclosure: M. Reni: Financial Interests, Advisory Board: AstraZeneca, Eli Lilly, Panavance, Celgene, Viatris, Merck Sharp& Dohme, Sotio, Baxter. E. Giommoni: Financial Interests, Invited Speaker: Viatris, Amgen, AstraZeneca; Financial Interests, Other, Support for attending meetings and/or travel: Viatris, Amgen, AstraZeneca. F. Bergamo: Financial Interests, Personal, Invited Speaker: Lilly, BMS, MSD, EISAI, Bayer; Financial Interests, Personal, Advisory Board: Servier, AAA; Other, Other, congress: Bayer, Ipsen, AAA. L. Cavanna: Financial Interests, Other, Consulting fees: AstraZeneca, Merck; Financial Interests, Other, Support for attending meetings and/or travel: Pfizer, Ipsen, Celgene. M. Spada: Financial Interests, Invited Speaker: Eli Lilly, Roche, Pfizer, Janssen, Italfarmaco, BMS; Financial Interests, Advisory Board: Eli Lilly, Merck, Pfizer, Janssen, BMS. S.S. Cordio: Financial Interests, Invited Speaker: Amgen, Merck, Merck Sharp & Dohme, Servier, Bayer, Sanofi; Financial Interests, Other, Support for attending meetings and/or travel: MSD, Merck, Servier. A. Spallanzani: Financial Interests, Advisory Board: Pierre Fabre, Lilly, Merck, Viatris, MSD; Financial Interests, Invited Speaker: Pierre Fabre, Lilly, Merck, Viatris, MSD. M.C. Di Marco: Financial Interests, Advisory

Board: Oncosil Olaparib. L. Procaccio: Financial Interests, Personal, Other, scientific consultancy: AstraZeneca. All other authors have declared no conflicts of interest.

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1665P Prognostic impact of diabetes and antidiabetic medication in pancreatic cancer patients

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Background: Diabetes mellitus (DM) is associated with pancreatic cancer (PC) as insulin is produced in the pancreatic beta cells. Whereas large epidemiological studies are available investigating the risk and prevalence of DM patients developing PC, only little is known about the impact of DM on the outcome of PC patients.

Methods: PC patients treated at the Medical University of Vienna between 1997 and 2020 with available information about their diabetic status at initial diagnosis of PC were identified from the PC database of our institution. We investigated the association of DM, antidiabetic drugs as well as random blood glucose and HbA1c levels with overall survival (OS, interval from initial diagnosis to death or last date of contact) in the overall patient cohort and subgroups of early and metastatic PC patients.

Results: Among 667 patients included into this analysis, 221 (33.1%) presented with DM at PC diagnosis, 53 (8.0%) developed DM later during the course of disease and 393 (58.9%) never developed DM. Presence of DM at initial diagnosis was significantly associated with a shorter OS in the overall patient population (13 vs. 17 months, hazard ratio (HR): 1.23, 95% confidence interval (CI 9.3 - 12.8; 6.6 - 11.3), $p=0.024$) as well as in patients with resectable disease (20 vs. 29 months, HR: 1.44, CI (13.4 - 31.1; 22.2 - 35.1), $p=0.034$). but showed no association in metastatic patients (8 vs. 11 months, HR: 1.21, CI (6.6 - 11.3; 9.3 - 12.8), $p=0.200$). Median OS was comparable between DM PC patients receiving metformin, insulin or other antidiabetic drugs (13 vs 15 vs 8 months, $p=0.221$, log-rank test). A random blood glucose at diagnosis of >300mg/dl compared to <200mg/dl (HR 2.29, 95%CI 0.06-3.53; $p=0.005$) as well as an HbA1c of >8% compared to <6.5% (HR 1.88, 95%CI 1.03-3.44; $p=0.040$) was associated with a significantly shorter OS.

Conclusions: Within this large cohort of PC patients, one third presented with DM at initial diagnosis. We observed a negative prognostic impact of DM especially in the subgroup of early PC patients. Different antidiabetic drugs thereby did not influence prognosis substantially. Only highly elevated levels of blood glucose and HbA1c seem to impact prognosis, whereas moderately elevated levels did not.

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1666P Non-metastatic cohort of the Italian Association for Medical Oncology (AIOM) guideline application in real-world: Multi-Institutional based survey of adjuvant and first-line pancreatic ductal adenocarcinoma treatment in Italy (GARIBALDI)

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Background: The GARIBALDI study investigated the impact of oncology center volume, type, and accrual rate on the prognosis of the overall therapeutic management of patients (pts) with non-metastatic Pancreatic Ductal Adenocarcinoma (nmPDAC).

Methods: Consenting treatment-naïve pts ≥ 18-year with pathological diagnosis of nmPDAC were eligible. Participating centers were categorized according to the self-declared expertise, the type and the accrual rate. Survival curves were estimated by the Kaplan—Meier method and compared by the log-rank test. Overall Survival (OS) was defined as the time from the date of medical therapy start to death for any cause.

Results: Between July 2017 and October 2019, 402 pts with nmPDAC from 44 centers were enrolled. Median age was 69 (range 36-89); 50% females; 93% ECOG PS 0-1; 33% overweight/obese; 17%, 38.7%, 44.3% with stage I, II, III, respectively; median CA19.9 177 (range 0-350,933); 17% with prior cancer history. Median diagnosis to treatment interval was 26 days. 68.4% had baseline CT >25 days before treatment start. 64% received chemotherapy upfront mainly consisting of nab-paclitaxel+gemcitabine (55%), gemcitabine alone (12%) or FOLFIRINOX (27%); 50% were submitted to surgery; 32% received radiotherapy. The median follow-up was 43.7 months and 274 pts died. The table provides the median OS estimates.

Table: 1666P

	Deaths/N	Overall survival (Median [95%CI])	Log-rank p-value
Self-declared expertise			0.0036
Low-volume (<25 pts/year)	46/61	15.5 [11.7-21.8]	
Medium-volume (25-50 pts/year)	48/69	21.6 [16.9-24.5]	
High-volume (>50 pts/year)	174/260	23.2 [19.2-27.1]	
Type			0.0714
Community hospitals	108/154	20.6 [16.6-23.2]	
Academic centers	166/248	22.0 [18.7-26.9]	
Accrual rate			0.0238
Low-accrual (<10 pts/year)	114/161	18.7 [15.8-23.6]	
Medium-accrual (10-50 pts/year)	107/149	21.6 [18.6-25.1]	
High-accrual (> 50 pts/year)	53/92	29.3 [18.1-35.6]	

Conclusions: A statistically significant difference in OS was found based on center volume and accrual rate, while a clinical difference was highlighted based on center type.

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1667P Clinical and molecular features of young onset pancreatic adenocarcinoma

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Background: Pancreatic adenocarcinoma (PDAC) has a poor prognosis and a growing incidence, especially in patients (pts) $\leq$ 50 years (e.g., young onset YoPA). We aim to describe clinical and molecular features (genomic and transcriptomic) of YoPA.

Methods: A retrospective chart review (demographics, systemic therapies, and outcomes) was performed in consecutive PDAC pts followed in our institution between 2012-2022. Tumor molecular profiling was performed as part of MATCH-R (NCT02517892) or STING (NCT04932525) trial (mostly Foundation Medicine® on tumor tissue (56.4%) or liquid biopsy (43.6%)). RNA sequencing was performed as part of MATCH-R trial.

Results: Overall, 878 pts were included, of them 113 were YoPA, with similar performance status at diagnosis. YoPA were more often diagnosed at metastatic (met) stage (69.7% vs 58.3%, p=0.024). In particular, hepatic mets were more present at diagnosis in YoPA (60.2% vs 43.9%, p=0.002). Conversely, lung and bone mets tended to be less frequent in YoPA. Location of the primary tumor (head vs tail) was not different between groups. Regarding treatment outcomes, among the 239 pts with resectable or borderline disease, 217 (91%) underwent surgery (22 YoPA and 195 nYoPA). The median recurrence-free survival (RFS) was 12.0 months (mos) (95CI: 10.6-14.8) (similar between YoPA and nYoPA). Among the 746 pts with mets, 96% received at least 1 line of systemic therapy. YoPA received more lines (41.6% vs 31.0% received $\geq$ 3 lines, p = 0.045). 1st line PFS was not different between groups. The median overall survival (OS) was 18.2 mos, with no difference between YoPA and nYoPA (HR=1.01, 95%CI= 0.81-1.26). In mets, OS was 12.8 mos (95%CI: 11.8-14.0) and was similar between groups. 312 pts had molecular profile including 49 YoPA. Mean TMB was lower in YoPA (1.42 vs 2.95 mut/Mb, p<0.002). YoPA and nYoPAs had similar prevalence of mutations in *KRAS (*88%) and *BRCA1/2* (6.3%). Conversely, YoPA displayed fewer alterations in *CNKN2A/B* (p=0.03). RNA sequencing data is available for 84 pts and the analysis is in progress.

Conclusions: YoPA were more often diagnosed at the metastatic stage with a higher prevalence of hepatic mets and had similar OS to nYoPA. They displayed a different molecular profile with lower TMB and fewer alterations in *CDKN2A/B*.

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1668P Prevalence and management of pancreatic ductal adenocarcinoma (PDAC) over a decade in France: A population-based study

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Background: Significant progress has been made in the management of PDAC in recent years, with the development of new chemotherapy regimens validated in both adjuvant and metastatic settings, as well as neoadjuvant/induction therapy (N/IT). In this population-based study, we aimed to compare prevalence, therapeutic strategies, and survival outcomes of PDAC patients in France over a decade encompassing these advances.

Methods: This study was performed on SNDS (Système National des Données de Santé) data, including nationwide French data on the consumption of medical care. All patients managed for PDAC during years 2009, 2014 and 2018 were included. Treatment modalities and survival outcomes were analyzed.

Results: A total of 8143/10267/12089 patients were included during years 2009/2014/2018, respectively. Prevalence increased mainly among patients aged 60-75 (62% over the study period) and >75 (53%) while a lesser trend was seen in patients <60 (13%). In localized PDAC, the proportion of patients receiving best supportive care (BSC) decreased at 43.6/37.7/33.5%. More patients received chemotherapy +/- radiotherapy alone over time (27.8/28.5/33.4%), and surgical resection after N/IT increased at 0.9/2.5/5.5%. The rate of upfront surgery remained stable at about 28%. Among metastatic patients, 45.0/49.2/51.3% received BSC. In the overall population, no relevant difference in survival outcomes were seen over time, but median overall survival (OS) and 1-year OS improved significantly both in localized patients and treated metastatic patients (Table). The 1-year OS was 85.7/85.9/91.7% among patients receiving N/IT before surgery, vs 76.3/79.0/80.0% for upfront resection.

Table: 1668P Survival outcomes

Population	Median OS (months) / 1-year OS (%)			p-value log-rank
	2009	2014	2018	
Overall	7.0 / 36.1	6.9 / 36.9	7.5 / 39.4	0.0067
Localized	11.4 / 48.4	12.5 / 51.3	Not reached / 55.0	<0.0001
Metastatic (treated)	7.3 / 30.3	8.4 / 36.1	8.9 / 38.2	<0.0001

Conclusions: This study confirms an increase in the prevalence of PDAC in France. Improved survival outcomes were seen in localized PDAC, with a wider use of chemotherapy and an increase in neo-adjuvant/induction strategies, and in treated metastatic patients.

Legal entity responsible for the study: ACOBIOM.

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1670P Tumoral and non-tumoral thrombosis associated with pancreatic ductal adenocarcinoma (PDAC): Survival impact, assessment of predictive scales and rethrombosis

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Background: PDAC is highly associated with thrombotic risk, with reported incidences up to 40%. Although tumoral (TT) and non-tumoral thrombosis (nonTT) are frequently treated equally, they might have different impact in prognosis and survival. Khorana and ONKOTEV score can predict thrombotic risk in this scenario.

Methods: Retrospective study that includes 204 patients with PDAC treated with chemotherapy and visited in the Medical Oncology Department of a third-level hospital in Barcelona between January 2014 and December 2021. The main objective was to describe the frequency of TT and nonTT, the ability to predict thrombotic risk by predictive scores using ROC curve and to analyze survival associated with thrombosis and rethrombosis.

Results: We identified 62 patients with thrombosis (30.4%) of a total of 204. Median age was 70 years (48-92), 54.8% were males, and 62% presented stage IV at diagnosis. TT involved 71% of thrombotic events being the most frequent in all stages (80% in

resectable, 83.3% in borderline, 75% in locally advanced and 66.7% in metastatic disease). Predominant thrombotic events were splenic (39%) and superior mesenteric vein (32%) for TT and deep vein thrombosis (DVT) in lower extremities and pulmonary embolisms in non-tumoral scenario (56% and 22.2% respectively). The ONKOTEV score presented better predictive capacity compared to Khorana for nonTT (AUC 0.731 vs 0,670 in ROC curves). Neither of both scores demonstrated predictive capacity for TT (AUC 0.540 vs 0.495). Thromboembolic events were associated with reduced overall survival (OS; HR 0.71, p 0.034). Median OS was 12.5 months in patients who presented nonTT vs 7.2 months for those with TT (HR 0.48, p=0.326). Rethrombosis occurred in 8% (5 cases), 2 of them being on anticoagulant therapy. All were in the same location as previously.

Conclusions: TT was more frequent than nonTT in our cohort. Thromboembolic events, including TT and nonTT, were detrimental for survival without statistically significant differences between them. ONKOTEV score has a greater capacity to predict nonTT compared to Khorana, in order to identify patients who could potentially benefit from prophylactic anticoagulation.

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1671P Treatment patterns and efficacy in patients (pt) with pancreatic cancer (PC) from the Spanish RETUD registry

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Background: Pancreatic carcinoma (PC) remains one of the deadliest cancers, with late detection and a complex, still unknown biology as the main factors driving its lethality. Chemotherapy and surgery are the primary options for PC, however, only 15-20% are eligible for surgery and two thirds relapse after. Novel diagnostic strategies are an urgent need for an earlier diagnosis, particularly in pt at higher risk for PC. We aimed to characterize real-world pt management for PC and the prevalence of molecular profiling in routine oncology practice.

Methods: A retrospective chart review of pt from the Spanish RETUD registry diagnosed with PC between 1 January 2019 and 31 December 2022 was conducted. Demographic, clinical characteristics, molecular profiling, systemic treatments, and outcomes were described.

Results: The registry included 1,438 evaluable pt. The median age was 66.8 years, 55.4% were men. Cancer family history was reported in 53.1% of pt. Main histology was ductal adenocarcinoma (97.8%). It was located in the head (59.5%) or body/tail (39.4%). Overall, 56.1%,19.0%,18.5% and 6.5% pt were diagnosed metastatic (met) locally advanced (LA), resectable and borderline PC respectively. Only 24.1% of pt underwent pancreatic surgery. Germline molecular analysis was performed in 135 pt where 17.8% had *BRCA1* or *BRCA2* mutations. *KRAS* mutation in tissue was assessed in 264 pt, and it tested positive in 68.9%. Most (70.2%) pt received first-line systemic treatment, mainly the gemcitabine-based combination NabPGEM (65.9%) or FOLFIRINOX (26.0%). At the database cut-off, 81.3% pt died. Median overall survival (OS) was 24.3 (95% confidence interval [95CI] 20.3-28.7), 13.4 (95CI 12.1-15.0) and 6.4 (95CI 5.7-7.3) months (m), for resectable, LA and met setting, respectively. Met PC median OS was 11.3 m (95CI 10.0-12.3) when treated with frontline NabPGEM and 13.1 m (95CI 11.5-16.5) with FOLFIRINOX (p=0.01).

Conclusions: Our study provides an overview of routinely recommended treatments and their effectiveness in a large multicenter real-world cohort of PC in Spain. Our findings suggest that FOLFIRINOX improves clinical outcomes of pt with met disease, when compared to NabPGEM. Molecular assessment must be enhanced at diagnosis in our environment.

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1673P Trajectories of immune-related serum proteins and quality of life in patients with pancreatic and other periampullary cancer: The champ study

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Background: There is still a profound lack of efficient therapeutic strategies against pancreatic or other periampullary adenocarcinoma. Surgery is seldom possible, leaving palliative chemotherapy the only option for most patients. Chemotherapy treatment is however often accompanied by serious side-effects, and the identification of biomarkers for early prediction of disease and treatment-associated symptoms could help alleviate patient suffering. This study investigated the dynamic interrelationship between immune-related serum proteins, routine biomarkers and health-related quality of life (HRQoL) factors during chemotherapy treatment of patients enrolled in the prospective, observational study Chemotherapy, Host response And Molecular dynamics in Periampullary cancer (CHAMP).

Methods: Proximity extension assay was applied to analyse 92 immune-associated proteins in longitudinal serum samples from 75 patients, 18 being treated with adjuvant and 57 with palliative intent. HRQoL data were available from all patients at baseline (BL), from 41 patients at three months, and from 23 patients at six months.

Results: Levels of 8 proteins; CCL23, CD4, CD28, DCN, Gal-1, GZMB, GZMH and MMP7 were strongly correlated (Spearman's Rho $\leq$-0.6 or $\geq$0.6) with various symptoms (insomnia, dyspnea, cognitive and emotional functioning) during treatment. Associations between routine laboratory parameters albumin, CA19-9, CEA and CRP and HRQoL were overall weaker. None of the investigated proteins were associated with pain.

Conclusions: This is, to our knowledge, the first study exploring associations between serum biomarkers and HRQoL in patients with pancreatic or other periampullary cancer, and some findings merit further validation. The proteoglycan decorin (DCN) is of particular interest as it has been linked to conditions such as Alzheimer's disease and schizophrenia. Chemotherapy is known to cause persistent cognitive dysfunction with effects on memory and executive function, referred to as "chemo brain". It would therefore be of great value to identify biomarkers for early detection and management of this debilitating condition.

Clinical trial identification: NCT03724994.

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1674P VILP registry of patients with metastatic pancreatic cancer treated with pegylated liposomal irinotecan plus 5-fluoroucil and leucovorin in the Czech Republic

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Background: Following the NAPOLI-1 trial, pegylated liposomal irinotecan (nal-IRI), in combination with 5-fluorouracil (5-FU) and leucovorin (LV) (nal-IRI + 5-FU/LV), is a standard treatment for advanced pancreatic ductal adenocarcinoma (PDAC) patients progressing after gemcitabine-based chemotherapy. The VILP registry captured real-world data on metastatic PDAC patients in Czech Republic receiving nal-IRI + 5-FU/LV.

Methods: Data were collected on all metastatic PDAC patients that received nal-IRI + 5-FU/LV, had an Eastern Cooperative Oncology Group performance status 0 or 1, and had progressed on gemcitabine-based chemotherapy, first line or (neo)adjuvant. Treatment was until progression or unmanageable toxicity. For the final evaluation of data, endpoints correspond to those published in the NAPOLI-1 trial; primary endpoint was overall survival (OS), calculated as the time from the treatment initiation to the date of death. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR) and treatment toxicity.

Results: As of April 6, 2023, 142 PDAC patients were enrolled, of which 129 were evaluable. Patients had a median age of 66 years, 95 (73.6%) received nal-IRI + 5-FU/LV as second line therapy and 101 (78.3%) had ECOG PS 1. A total of 93 (72.1%) patients discontinued treatment and median treatment duration was 2.3 months (range: 0.0-18.8) with the principal reason for discontinuation being disease progression (n=45, 48.4%). Median and 6-months OS were 10.1 months (95% CI 6.0—not reached) and 57.1% (95% CI 47.4—68.7), respectively. Median and 6-months PFS were 3.5 months (95% CI 3.1—5.7) and 35.5% (95% CI 27.1—46.6), respectively. ORR was 10.1% (12 cases of partial response and 1 complete response). A total of 19 adverse events (AEs) occurred in 17 (13.2%) patients, with the most frequent AEs being diarrhoea (n=9; grade 3 n=3) and fatigue (n=3; grade 3 n=1).

Conclusions: The VILP register confirms the effectiveness of nal-IRI + 5-FU/LV as a well-tolerated treatment option for patients with PDAC in real-world practice.

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1675P Diagnostic performance of blood-based DNA methylation assay using epigenetic-specific peptide nucleic acid in pancreatic adenocarcinoma

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Background: Pancreatic adenocarcinoma (PA) is an aggressive tumor with a poor prognosis and is difficult to diagnose with traditional tissue-based techniques. Cancer-associated DNA methylation biomarkers are promising for cancer diagnosis and have potential as non-invasive methods, as they can be detected not only in tissues but also in the blood. In the present study, we aimed to evaluate the diagnostic performance of a DNA methylation assay using epigenetic-specific peptide nucleic acid (Epi-sPNA) for PA.

Methods: An Epi-TOP pancreatic assay (Seasun Biomaterials, Daejeon, Korea) was used to detect PA-specific epigenetic and genetic biomarkers. The assay using Epi-sPNA enabled the accurate and quick analysis of methylation without sample processing using bisulfate. A total of 92gDNA samples collected from normal pancreatic and PA tissues of 46 patients who underwent surgical resection for PA were tested to evaluate the diagnostic performance of epigenetic biomarkers for PA. Further validation was performed on cell-free DNA isolated from the plasma samples of 10 individuals each from the PA, benign pancreatic disease, and normal groups.

Results: The combination of seven epigenetic biomarkers, *HOXA9*, *TWIST*, *WT1*, *RPRM*, *BMP3*, *NPTX2*, and *BNC1* showed high sensitivity of 93.5% and specificity of 96.7% in discriminating between normal pancreatic and PA tissues. There were no significant differences in the methylation levels according to age, sex, or cancer stage. Plasma cell-free DNA collected from patients with PA and benign pancreatic disease and normal individuals was tested using a combination of epigenetic seven biomarkers with *KRAS* somatic mutations in codons 12, 13, and 61. Plasma-based DNA methylation analysis confirmed the diagnostic performance, with a sensitivity of 90.0%, specificity of 95.0%, and accuracy of 93.3%, whereas the accuracy of traditional serum biomarkers cancer antigen 19-9 and carcinoembryonic antigen was both 90.0%.

Conclusions: Our study suggests that seven differentially methylated genes, in combination with *KRAS* somatic mutations using Epi-TOP pancreatic assay, can be used as potential blood-based biomarkers for the diagnosis of PA.

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1676P Clinical outcomes of first-line chemotherapy in locally advanced and metastatic pancreatic adenocarcinoma patients: Real-world experience

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Background: Pancreatic cancer has a poor prognosis compared to many other malignancies. This study evaluated the clinical outcomes of systemic chemotherapy (CMT) in patients with locally advanced and metastatic pancreatic ductal adenocarcinoma (LA/M-PDAC).

Methods: A retrospective, observational chart review was conducted on patients with LA/M-PDAC who underwent CMT between January 2012 and November 2022. The efficacy data (objective response rate [ORR], disease-control rate [DCR], progression-free survival [PFS], and overall survival [OS]) were evaluated and compared using Pearson's chi-square tests, Kaplan—Meier plots, and log-rank tests.

Results: Out of the 998 patients diagnosed with LA/M-PDAC, 332 (33.3%) received systemic CMT. Among the treatment regimens used, gemcitabine (GEM) was administered most frequently (33.7% of cases). The next most commonly utilized therapies were (m)FOLFIRINOX and GEM plus capecitabine (GEMCAPE), accounting for 27.4% and 26.2% of cases, respectively. Platinum doublets (PlatD) were administered in 9.3% of cases. The ORRs and DCRs of the four regimens differed significantly (for GEM, GEMCAPE, (m)FOLFIRINOX, and PlatD, the ORRs were 4.5%, 10.3%, 23.1%, 19.4%, respectively, with $P < 0.0001$; the DCRs were 38.4%, 52.9%, 73.6%, and 54.8%, respectively, with $P < 0.0001$). Patients who received combination CMTs had significantly longer median PFSs than those who received GEM alone (PFS = 4.93 months for GEMCAPE, 9 months for (m)FOLFIRINOX, 9.43 months for PlatD, and 3.87 months for GEM). When comparing GEMCAPE with (m)FOLFIRINOX, the median PFS was significantly lower in the GEMCAPE group (PFS = 4.93 vs 9.0 months; HR = 0.53; $P < 0.0001$). However, no significant differences were observed in the median OS rates of the four regimens in a multivariate Cox proportional-hazards model analysis. The frequency of treatment-related grade 3 or 4 adverse events was higher in the (m)FOLFIRINOX group, followed by the GEMCAPE group.

Conclusions: This study revealed that FOLFIRINOX exhibited higher ORR, DCR, and PFS rates than GEM or GEMCAPE. Nevertheless, no survival advantage was detected in the FOLFIRINOX groups, suggesting the influence of subsequent therapies.

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1677P Pancreatic enzyme replacement therapy improves survival in patients receiving nab-paclitaxel plus gemcitabine as first-line treatment for advanced pancreatic adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the big killers with a 5-year-survival rate of less than 2% in metastatic disease. Limited treatment options and early clinical deterioration often affect outcome. Exocrine pancreatic insufficiency (EPI) is often underestimated in patients with advanced PDAC and a large proportion of patients (60-80%) does not receive pancreatic enzyme replacement therapy (PERT). This study aims to optimize the clinical selection of patients with advanced PDAC treated with gemcitabine/nabpaclitaxel and to develop models to predict benefit from first-line therapy and duration of second-line therapy.

Methods: In this observational study we prospectively enrolled patients with advanced PDAC treated with gemcitabine/nabpaclitaxel as first-line therapy at the Medical Oncology Unit of Careggi University Hospital from 2015 to 2022. Clinical and laboratory data were collected and associated with survival outcomes, duration of second-line therapy and treatment exposure.

Results: A total of 107 patients were enrolled, 54 (50.5%) were women and 53 (49.5%) were men. Disease stage was classified as locally advanced in 42 (39.3%) and metastatic in 65 (60.7%). Median progression-free survival (PFS) was 5.6 months and median overall survival (OS) was 7.4 months. Among the baseline clinical variables, a trend towards a worse prognosis was observed in patients with a high tumor burden (OS p=0.065). Overall, 66.0% of patients received PERT at baseline or within 3 months from first-line treatment start. PERT-users had a significantly longer OS than non-PERT-users (9.5 months vs 5.5 months, respectively, HR 95%CI 2,1 [1,2-3,7], p=0.008). In addition, the probability to receive a second-line treatment for at least 2 months was higher in the PERT-user group than in the non-PERT-user group (X-squared=7.6558, p-value=0.005659).

Conclusions: The clinical management of patients with advanced PDAC is challenging and requires a multidisciplinary strategy to prevent EPI-related symptoms and optimize treatment adherence. PERT could play a crucial role in preventing weight loss, maintaining dose intensity and improving survival.

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1678P A retrospective real-world study of nimotuzumab combined with chemotherapy for first-line treatment of advanced pancreatic cancer: A single center propensity score matched analysis

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Background: Chemotherapy alone has limited efficacy in treating advanced pancreatic cancer (APC). The addition of nimotuzumab (nimo) to gemcitabine had been shown to be more effective in our previous studies: the progression-free survival (PFS) was up to 5.1 months, 1.5 months longer than gemcitabine alone for 1st line treatment of APC, but its efficacy and safety in combination with other chemotherapy regimens are unknown.

Methods: In this study, patients with APC were treated with standard of care (routine chemotherapy) combined with or without nimo in a real-world data setting. Demographic and clinical data were collected from electronic medical records of First Affiliated Hospital of Xi'an Jiaotong University from April 2018 to May 2023. The primary efficacy endpoint was progression-free survival (PFS).

Results: We identified 282 APC patients, of which 36.8% received nimo combined with routine chemotherapy. After 1:1 propensity score matching (PSM), we created 65 pairs patients (median age was 62 years, range, 55-69) who received routine chemotherapy with or without nimo as first-line treatment. Among them, 55 pairs were treated with albumin paclitaxel-gemcitabine (AG), 3 pairs with gemcitabine-tegafur (GS) and 7 pairs with others. The median dosage of nimo was 400mg weekly. Up to May 2023, the median follow-up time was beyond 24 months. Survival analysis showed that nimo was associated with longer PFS (10.9 months vs 9.1 months; $p<0.05$, HR=0.5(95%CI, 0.29-0.88) after matching), but the OS was not evaluated due to the missing date of death. No grade 3 or above toxicities were observed.

Conclusions: Gemcitabine-based combination chemotherapy (eg, AG regimen, GS regimen) were commonly used as first-line treatment for APC in China. The addition of nimotuzumab to combination chemotherapy was a strong regimen and found to prolong the survival time for APC, with a manageable safety profile.

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1679P Comparison of first-line chemotherapy regimens in unresectable locally advanced or metastatic pancreatic cancer: A systematic review and network meta-analysis

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Background: In patients with unresectable locally advanced (LAPC) or metastatic pancreatic cancer (MPC) gemcitabine-nab-paclitaxel (GEM-NAB) and FOLFIRINOX are standard first-line treatments. Recently, other combinations have shown to be associated with a survival advantage.

Methods: PubMed, CENTRAL, Embase and oncology meetings websites were searched to March 1st, 2023. We included phase II and III randomized controlled trials (RCTs) enrolling patients with unresectable LAPC or MPC which investigated gemcitabine-based (GEM) regimens, FOLFIRINOX, NALIRIFOX, PAXG or other first-line combinations. Efficacy outcomes were progression-free survival (PFS) and overall survival (OS). Hazard ratios (HRs) and 95% confidence intervals (95% CI) were computed using a random effects model. A frequentist network meta-analysis was conducted, and P-scores were used to rank treatments.

Results: 4412 records were screened, and 45 studies were included; 37 studies were evaluable for PFS and 43 for OS. Considering PFS, PAXG (P-score 0.9410), NALIRIFOX (P-score 0.8723) and FOLFIRINOX (P-score 0.8696) were among the top-ranked strategies, while GEM-NAB had a P-score of 0.6388. In terms of OS, PAXG (P-score 0.9585), GEM-NAB sequential strategies (GEM-NAB > FOLFOX, P-score 0.9350 and GEM-NAB > FOLFIRI, P-score 0.9117), FOLFIRINOX (P-score 0.8512) and NALIRIFOX (P-score 0.8461) were among the top-ranked strategies, while the P-score of GEM-NAB was 0.6998. No difference was observed between NALIRIFOX and FOLFIRINOX (PFS HR: 1.01, 95% CI 0.68-1.50; OS HR: 0.99, 95% CI 0.74-1.31). A significant difference was observed between FOLFIRINOX and GEM+NAB in terms of PFS (HR 0.71, 95% CI 0.53-0.95), while a non-significant trend was observed in OS (HR 0.82, 95% CI 0.66-1.04). No difference was observed between NALIRIFOX and PAXG (PFS HR 1.25, 95% CI 0.72-2.17; OS HR 1.40, 95% CI 0.87-2.24) and between FOLFIRINOX and PAXG (PFS HR: 1.26, 95% CI 0.72-2.22; OS HR: 1.38, 95% CI 0.84-2.27).

Conclusions: With the limitations of a network meta-analysis, our results suggest that combinations with three or four drugs, when feasible, could provide a greater survival benefit compared to GEM-NAB in unresectable LAPC or MPC.

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1680P Meta-analysis of real-world survival outcomes of liposomal irinotecan in advanced pancreatic cancer patients with prior irinotecan exposure

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Background: Liposomal irinotecan (nal-IRI) plus 5-fluorouracil (5-FU)/leucovorin (LV) demonstrated survival benefits in advanced pancreatic cancer (APC) patients (pts) who progressed on gemcitabine-based therapy. The NAPOLI-1 demonstrated greater survival benefits from nal-IRI+5-FU/LV in IRI-naïve pts. Nal-IRI may be less effective in pts with prior irinotecan (IRI) exposure due to a potential cross-resistance to SN-38. This raised concerns about the relevance of nal-IRI + 5-FU/LV in clinical practice, as FOLFIRINOX is the recommended first-line regimen for APC pts with good performance status. Therefore, we evaluated the real-world survival outcomes of nal-IRI in patients with prior IRI exposure.

Methods: Real-world studies evaluating the outcomes of nal-IRI in pts with prior IRI exposure published up to April 2023 were searched using electronic databases including PubMed, Scopus, Cochrane CENTRAL, Web of Science, EBSCOhost. The meta-analysis was conducted using the R package v4.3.0 and RevMan v5.4.1. Random effects model was used to estimate the pooled hazard ratio (HR) and the 95% confidence interval (CI). I^2 statistics was obtained to evaluate the heterogeneity of the studies.

Results: Out of the total 470 pts from seven studies that are included in the meta-analysis, most pts with prior IRI exposure received nal-IRI at the third or later lines. The pooled median progression-free survival (PFS) and overall survival (OS) were 1.9 (95% CI: 1.4-2.4) and 4.1 months (95% CI 3.4-4.7), respectively. The pts with prior IRI exposure had comparable PFS (pooled HR 1.20, 95% CI 0.67-2.14, p= 0.53, I^2= 0%) and OS (HR 1.13, 95% CI 0.69-1.84, p= 0.63, I^2= 0%) to pts without prior IRI exposure. Pts who discontinued prior IRI due to progressive disease had comparable PFS (HR 1.60, 95% CI 0.34, 7.58, p=0.55, I^2= 0%) and OS (HR 2.09, 95% CI 0.29, 14.87, p=0.46, I^2= 0%) to pts with no progressive disease. Nal-IRI had a manageable safety profile across the included studies.

Conclusions: Prior IRI exposure had no impact on the survival outcomes of nal-IRI-containing regimen in APC pts. Thus, it is feasible to introduce nal-IRI in later lines of treatment in patients with prior IRI exposure. Further prospective studies are warranted.

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1681P A retrospective real-world study for nimotuzumab plus postoperative adjuvant chemotherapy for resectable pancreatic cancer

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Background: Adjuvant chemotherapy offers patients an improved chance of long-term survival, especially for those with R0/R1 resection. In APACT study, the median overall survival (mOS) of adjuvant chemotherapy for resectable pancreatic cancer (RPC) patients ranged from 36.2 to 40.5 months, but further improvement is still needed. As targeted therapy is still a blank in the treatment of RPC, we conducted this study, aiming to explore the clinical benefit of the addition of nimotuzumab to standard adjuvant chemotherapy.

Methods: RPC patients were treated with surgery, postoperative chemotherapy with or without nimotuzumab. Demographic and clinical data were collected from electronic medical records of Ruijin Hospital from May 2016 to July 2022. The primary efficacy endpoint was OS.

Results: We identified 795 patients who underwent surgical resection, of which 57 RPC patients received nimo. Propensity score matching (PSM) was performed to reduce the bias. After 1:1 PSM, we created 32 pairs RPC patients (stage I and II) who received adjuvant chemotherapy with nimo (study arm, Nimotuzumab 400mg, weekly, median exposure was 4 weeks) or without (control arm). Baseline characteristics were balanced after PSM. Median age was 63y, with 66% males. Barthel score 80-100. Median follow-up time was 35.2 (95%CI, 24.8-57.4) months and 37.3 (95%CI, 21.6-42.8) months in the control arm and study arm respectively. Survival analysis showed that study arm with a prolongation survival trend in OS (mOS: 24.5 months vs. 45.1 months) and disease-free survival (mDFS: 13.4 months vs. 15.4 months). Adverse events (AEs, Grade 1-2) were reported by 67% of patients (44 out of 64). The most frequently reported AEs were anemia (37.5%), leukopenia (7.8%), and diarrhea (4.7%), and there were no differences between the two groups. No Grade 3 or above adverse events were observed.

Conclusions: RPC patients were with a prolongation survival trend by the addition of nimotuzumab into current regimens in the postoperative program with good safety profile.

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1682P Impact of metastatic site on survival in patients with synchronous metastatic pancreatic adenocarcinoma (PDAC): A national prospective BACAP study

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Background: Advanced PDAC carries a dismal prognosis with a 5-year survival rate of 3%. While treated as an even population, previous retrospective studies suggested significant different survival rates for patients (pts) with lung-only metastases (mets) when compared to other pts. This study aims to explore prospectively the difference in survival outcome based on initial site of metastases in synchronous metastatic PDAC.

Methods: This is a prospective observational study including all adult pts with synchronous metastatic PDAC in BACAP (national Anatomo-Clinical Database on Pancreatic Adenocarcinoma). Data regarding pts demographics, tumor characteristics, and survival outcomes were analyzed. Primary endpoint was overall survival (OS), defined as the time from diagnosis to death or most recent follow-up.

Results: Overall, 504 pts were included [52.4% male, mean age 69 years] of which 31 (6.2%), 58 (11.5%), 363 (72%) and 51 (10.1%) pts had lung-only, peritoneal-only, liver-only and multi-site mets at diagnosis, respectively. Most patients (79.2%) received at least one line of chemotherapy. Patients with lung-only mets were older (38.7% were > 75 years old), mostly male (61.3%) and 22.6% received at least 3 lines of chemotherapy (vs 15.5% for other patients). Median OS was significantly different according to mets site (p=0.003) (Table), with a trend towards better PFS when lung-only mets: 6.3 vs 5.4, 4.5 and 2.4 mo when peritoneal-only, liver-only and multi-site mets, respectively (p=0188).

Table: 1682P

Group	N	Event (%)	OS (mo)	95% CI
Lung-only	29	25 (86.2)	11.7	[9.3; 14.6]
Peritoneal-only	58	49 (84.5)	9.2	[5.5; 12.9]
Liver-only	362	334 (92.3%)	7.2	[6.1; 8.1]
Multi-site	52	50 (96.2%)	4.1	[2.3; 5.0]
Total	501	458 (91.4%)	7.2	[6.1 ;8.1]

p=0.003

Conclusions: Pts with lung-only mets represented 6.2% of synchronous metastatic PDAC pts and exhibited improved survival. These results suggest that a subset of pts with synchronous metastatic PDAC could benefit from more aggressive locoregional treatments. Underlying biological mechanisms contributing to survival difference are under investigation.

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1683TiP Trial in progress: NEO-adjuvant chemo-IMmunotherapy in PAnCreaTic cancer-NEO-IMPACT

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Background: Pancreatic cancer has one of the worst outcomes of any tumor type, with a five-year survival rate of 12%. In patients undergoing upfront resection, up to 30% do not receive adjuvant chemotherapy due to surgical complications. The success of neoadjuvant chemotherapy in converting inoperable patients into operative candidates has resulted in more widespread use of it in early disease. In other cancer types, the addition of neoadjuvant immunotherapy has resulted in increased pathological response rates. The aim of the NEO-IMPACT study is to assess the safety and tolerability of neoadjuvant chemo-immunotherapy in pancreatic adenocarcinoma patients prior to definitive surgery.

Trial design: NEO-IMPACT is a phase II multi-centre, single arm, investigator-initiated trial in patients with upfront or borderline resectable pancreatic adenocarcinoma. This trial is sponsored by the Australasian Gastro-Intestinal Trials Group. Patients receive neoadjuvant durvalumab 1500mg iv q4weekly in combination with mFOLFIRINOX (5- fluorouracil, leucovorin, irinotecan and oxaliplatin) q2weekly over 12 weeks, followed by restaging and multidisciplinary team (MDT) review. Patients who remain surgical candidates will proceed to resection within 6-8 weeks of neoadjuvant therapy. A further 6 cycles of mFOLFIRINOX will be given in the adjuvant setting. The primary endpoint is the proportion of patients receiving 80% of planned neoadjuvant treatment. Secondary objectives include R0 resection rate, pathological complete response rate, objective response rate and treatment tolerability. Exploratory objectives include analysis of pre-treatment and post-treatment tumour tissue for gene expression profiling. A translational sub study is planned to investigate the evolution of the pancreatic microbiome when exposed to neoadjuvant chemo-immunotherapy. Trial recruitment commenced May 2022. 11 of a planned 20 patients are enrolled. ANZCTR registration number: ACTRN12622000378729. This study was awarded the 2018 AGITG 'New Concepts' award. Trial conduct is funded through AGITG Philanthropic Major Donor funding, with Study Drug support from AstraZeneca Pty Ltd.

Clinical trial identification: ACTRN12622000378729.

Legal entity responsible for the study: Australasian Gastrointestinal Trials Group.

Funding: Funded through AGITG Philantrophic Major.

Disclosure: N. Tebbutt: Other, Personal, Other, Consultant: AstraZeneca. J. Tie: Financial Interests, Personal, Advisory Board: AstraZeneca, BMS, Pierre Fabre, Inivata, BeiGene; Financial Interests, Personal, Invited Speaker: Servier, Merck; Financial Interests, Personal, Other, Consultancy: Haystack Oncology; Financial Interests, Institutional, Advisory Board: Daiichi Sankyo, Gilead. L. Christopherson: Financial Interests, Personal, Other, Family member: IMU, DXB, PIQ, IXC. L. Chantrill: Non-Financial Interests, Personal, Advisory Board: Amgen. All other authors have declared no conflicts of interest.

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1684TiP PARPiPANC: A multicentric, single arm, phase II assessing niraparib as first line therapy for patients with metastatic homologous repair-deficient pancreatic cancer

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Background: PARP inhibitors are active in tumors with defect in homologous DNA repair by a mechanism known as synthetic lethality defined as defects in two or more separate proteins/pathways that induce cell death only when combined. Most studies of PARP inhibitors in pancreatic cancer have shown response rates of 20 to 25% in BRCA1/2 mutation carriers previously exposed to cytotoxic chemotherapy. Since mechanisms of resistance to platinum-based chemotherapy share some similarities with the mechanisms of resistance to PARP inhibitors, we hypothesize that PARP inhibitors may be significantly more active when used in chemotherapy-naïve patients and could represent a chemotherapy-free alternative for pancreatic cancers bearing defects in homologous recombination.

Trial design: This investigator initiated, multicentric, single arm, open-label, phase II aims to assess niraparib in chemotherapy-naïve biomarker-selected pancreatic cancer pts. Only pts with mutation and/or rearrangement, detected locally on tumor or liquid biopsy, leading to inactivation in at least one of the following genes BARD1, BRCA1, BRCA2, BRIP1, FANCA, FANCD2, FANCL, MRE11, NBN, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L are eligible. Included pts are treated with niraparib (300mg/d, orally) until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, pt or investigator decision. Primary endpoint is objective response rate after 16 weeks of treatment according to RECIST V1.1 (ORR_{16W}). Secondary endpoints include duration of response, disease control rate, progression free survival, overall survival and safety. Using a Fleming-A'Hern single stage design with a target ORR_{16w} of 60% and an inefficacy bound of 30% (α=5% one sided and 90% power) a total of 25 evaluable pts are required. If at least 16 successes (CR or PR at 16 weeks) are observed, niraparib will deserve further investigation. Correlative studies include documentation of HR alteration at time of progression on optional *de novo* tumor biopsy as well as assessment of predictive value for niraparib resistance of existing or new variants using liquid biopsies. To date, 4 French hospitals are participating.

Clinical trial identification: NCT05442749.

Legal entity responsible for the study: Léon Bérard Center.

Funding: GSK.

Disclosure: All authors have declared no conflicts of interest.

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1685TiP Perioperative or adjuvant mFOLFIRINOX for resectable pancreatic cancer (PREOPANC-3): A multicenter randomized controlled trial

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Background: Surgical resection followed by adjuvant mFOLFIRINOX is the current standard of care for patients with resectable pancreatic cancer. The main concern with adjuvant chemotherapy is that only half of patients actually receive adjuvant treatment. Neoadjuvant chemotherapy, on the other hand, guarantees early systemic treatment and may increase chemotherapy use and thereby improve overall survival. Furthermore, it may prevent futile surgery in patients with rapidly progressive disease. However, some argue that neoadjuvant therapy delays surgery, which could lead to progression towards unresectable disease and thus offset the potential benefits. Comparison of perioperative (i.e., neoadjuvant and adjuvant) with (only) adjuvant administration of mFOLFIRINOX in a randomized controlled trial (RCT) is needed to determine the optimal approach.

Trial design: This is a multicentre, phase III, RCT that will include 378 patients with resectable pancreatic ductal adenocarcinoma with a WHO performance status of 0 or 1. Patients are recruited from 20 Dutch centres and three centres in Sweden. Resectable pancreatic cancer is defined as no arterial contact and $\leq$90 degrees venous contact. Patients in the intervention arm are scheduled for 8 cycles of neoadjuvant mFOLFIRINOX (2-week cycle of oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 at day 1, followed by 46 hours continuous infusion of 5-fluorouracil 2400 g/m^2) followed by surgery and 4 cycles of adjuvant mFOLFIRINOX. Patients in the comparator arm start with surgery followed by 12 cycles of adjuvant mFOLFIRINOX. The primary outcome is overall survival by intention-to-treat. Secondary outcomes include progression-free survival, resection rate, quality of life, adverse events, and surgical complications. To detect a hazard ratio of 0.70 with 80% power, 252 events are needed. The number of events is expected to be reached after the inclusion of 378 patients in 36 months, with analysis planned 18 months after the last patient has been randomized. Accrual started on September 7, 2021, and as of May 10, 2023, all centres are open for inclusion and 138 patients have been randomized.

Clinical trial identification: NCT04927780.

Legal entity responsible for the study: Erasmus MC.

Funding: Dutch Cancer Society and ZonMw.

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1686TiP Olaparib and durvalumab (MEDI4736) phase II study in patients with metastatic pancreatic cancer and DNA damage repair genes alterations

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Background: Patients with metastatic pancreatic cancer (mPC) and germline mutations in *BRCA1/2* genes benefit from PARP inhibitors. In addition, some studies have demonstrated that PDL-1 inhibitors therapeutically synergize with PARP inhibitors in tumours with DNA homologous repair deficiency. Our hypothesis is that patients with alterations in DNA damage repair genes (somatic or germline *BRCA1, BRCA2, PALB2, RAD51C, RAD51D* and other functional DDR genes) who have benefitted from platinum-based therapy might derive additional benefit from the combination of olaparib and durvalumab.

Trial design: This is an open-label, single-arm, phase II clinical trial opened to accrual in 15 Spanish hospitals attesting the combination of olaparib (300 mg (2x150 mg tablets) bid and durvalumab (1500 mg IV infusion Q4W) in patients with mPC. Patients are eligible for the study based on alterations in a panel of specific DDR genes including *BRCA1, BRCA2, PALB2, RAD51C, RAD51D* and other DDR genes, as determined by a local assay or by the central laboratory (if local assay is not available). Main inclusion criteria: age ≥18 years, alterations in DNA Damage Repair genes, up to 2 lines of prior chemotherapy for metastatic disease, have derived benefit from platinum-based chemotherapy and not presented progression to platinum-based chemotherapy, ECOG performance status 0-1 and adequate bone marrow, renal and liver function. Main exclusion criteria: other malignancies, unless curatively treated with no evidence of disease for ≥5 years. Patients with a history of uncontrolled clinically significant, symptomatic cardiovascular disease within 6 months before trial enrolment are excluded. Primary objective is to evaluate the efficacy of olaparib in combination with durvalumab in terms of overall response rate. Secondary objectives: progression-free survival, overall survival, duration of response, disease control rate and safety and tolerability. Exploratory objectives: impact of baseline and on treatment biomarkers predictive of the efficacy. The trial is in progress; 10 of up to 40 planned patients have been recruited at the end of April 2023 (first patient in November 2022).

Clinical trial identification: NCT05659914.

Legal entity responsible for the study: Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD).

Funding: AstraZeneca.

Disclosure: T. Macarulla: Financial Interests, Personal, Advisory Board: Ability Pharmaceutical, SL, AstraZeneca, Basilea Pharma, Batxer, BioLineRX Ltd, Celgene SLU, Eisai, Ipsen Pharma, Incyte; Financial Interests, Personal, Other, Direct research fund: Servier, Merck, Sharp and Dhome, Novocure, QED Therapeutics Inc., Roche, Sanofi-Aventis, Zymeworks; Financial Interests, Personal, Invited Speaker: Lilly, Janssen; Financial Interests, Institutional, Research Grant: Amc Medical Research, ARMO Biosciences, Basilea, BioKeralty Research Institute, Merck Sharp & Dohme, Oncomed Pharmaceuticals, QED Therapeutics, Vcn Biosciences, AbbVie Farmaceútica, Ability Pharmaceuticals, Agios, Amgen, Aslan, AstraZecena, Bayer, BeiGene, Biolinerx, Blueprint Medicines, Boston Biomedical, Bristol Myers Squibb (BMS), Cantargia, Celgene, Eisai, Erytech Pharma, F. Hoffmann-la Roche, FibroGen, Genentech, Hallozyme, Immunomedics, Incyte, Ipsen, Lab. Menarini, Lilly, Loxo Oncology, MedImmune, Merimarck, Novocure, Millenim, Nelum, Novartis, Zymeworks, Pfizer, Pharmacyclics, Roche; Non-Financial Interests, Member: American Society of Clinical Oncology - ASCO, "Sociedad Española de Oncología Médica" — SEOM, Sociedad Europea de Oncología Médica - ESMO. M. Lobo de Mena: Financial Interests, Personal, Invited Speaker: Leo Pharma, Servier. R. Garcia-Carbonero: Financial Interests, Personal, Advisory Board: AAA, Advanz Pharma, Amgen, Bayer, BMS, HMP, Ipsen, Merck, Midatech, MSD, Novartis, PharmaMar, Pierre Fabre, Servier; Financial Interests, Institutional, Research Grant: BMS, MSD, Pfizer; Non-Financial Interests, Leadership Role, Global PI of investigator-initiated clinical trials (AXINET, NICENEC, PEMBROLA): BMS, MSD, Pfizer; Other, Other, Honoraria received by spouse for advisory board or invited speaker roles: AbbieVie, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Genomica, Lilly, MSD, Merck, Novartis, Pfizer, PharmaMar, Roche, Sanofi, Servier, Takeda. R.A. Pazo Cid: Financial Interests, Personal, Advisory Board: Roche, BMS, Servier, Ipsen, Lilly, AstraZeneca; Financial Interests, Personal, Invited Speaker: Servier, BMS, Roche, Eisai; Financial Interests, Personal and Institutional, Local PI, Support for manuscript presentation (funding, provision of study materials, medical writing, article processing charges): Ipsen, Astellas. J. Gallego Plazas: Financial Interests, Personal, Advisory Board: AAA, Amgen, Bayer, BMS, Eisai, Ipsen, Lilly, Merck, MSD, Pierre-Fabre, Roche, Servier; Financial Interests, Personal, Invited Speaker: AAA, Amgen, Bayer, BMS, Ipsen, Lilly, Merck, MSD, Novartis, Servier; Financial Interests, Personal, Other, Educational: Amgen, Ipsen, Merck, Novartis, Pierre-Fabre, Roche; Financial Interests, Institutional, Funding: Astellas, AstraZeneca, BMS, Daiichi Sankyo, Lilly, Servier; Financial Interests, Member of Board of Directors: Spanish Society Medical Oncology, Spanish Group Of Neuroendocrine an Endocrine Tumours; Financial Interests, Project Lead: AGAMENON-SEOM Registry of Esophagohastric Cancer. I.C. Ales Diaz: Financial Interests, Personal, Advisory Board: Lilly, BMS, Merck, AstraZeneca. B. García Paredes: Financial Interests, Personal, Other, Travel and accommodation expenses: Servier, Novartis, Merck, Advanced Accelerator Applications. P. Espinosa Olarte: Financial Interests, Personal, Other, Travel and accommodation expenses: Roche. E. Aranda Aguilar: Financial Interests, Personal, Advisory Board: Amgen, Bayer, Bristol Myers Squibb, Merck, Roche, Sanofi, Servier. All other authors have declared no conflicts of interest.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

POLICY AND PREVENTIVE STRATEGIES

1687O PRIMCAT: A novel approach to informing health technology assessment decision making in Australia

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Background: Cancer is a major cause of mortality and high healthcare costs globally. Accurate and granular estimation of the number of patients requiring cancer care is crucial for healthcare planning and resource allocation. The PRIMCAT project provides evidence-based forecasts of the population health economic impact of new cancer treatments in Australia.

Methods: The PRIMCAT project takes a data-driven approach using real-world hospital and administrative data (RWD) for melanoma (MEL), non-small cell lung (NSCLC) and colorectal cancer (CRC). We analysed patterns of care for each cancer, refined using clinician-developed treatment algorithms. We estimated time-to-event analyses, treatment utilization, and progression rate based on retrospective data. We built a discrete event simulation (DES) model to forecast the number of individuals treated by line of treatment and stage of disease. To test the model, we identified the top 5 novel drugs through a systematic horizon scanning procedure and integrated scenario analyses to forecast the number of patients eligible for each drug.

Results: We included 90,522 patients with either MEL, NSCLC or CRC to populate the model with RWD. Treatment patterns provide an overview of how cancer care is managed in Victoria, and the DES estimates the number of patients currently treated. Scenario analyses estimate the numbers of patients likely to be treated with novel drugs for each cancer type based on forecasted incidence, stage distribution, and uptake of treatment. For example, the availability of pembrolizumab for deficient mismatch-repair in metastatic CRC as first line treatment from 2021 onwards would result in a range of 656-867 patients per year receiving this drug, depending on uptake.

Conclusions: Our simulation model estimates the impact of introducing new treatments at applicable points in treatment pathways, decreasing uncertainty associated with the eligible patient population for novel cancer therapies. We provide an invaluable tool for health technology assessment, allowing policymakers to plan and support decision-making for new drugs. Our model aims to ensure effective, affordable, and sustainable cancer care services with equitable access to high-quality care.

Legal entity responsible for the study: University of Melbourne.

Funding: Medical Research Future Fund grant.

Disclosure: M. Alexander: Financial Interests, Personal, Advisory Board: BMS/Pfizer. J. Desai: Financial Interests, Personal, Invited Speaker: Pierre Fabre, Merck KGaA, Novartis; Financial Interests, Personal, Advisory Board: Bayer, GSK, Boehringer Ingelheim, Roche/Genentech, Pfizer, Amgen, Pierre Fabre, BeiGene; Financial Interests, Coordinating PI: Roche/Genentech, BeiGene; Financial Interests, Local PI: Amgen, AstraZeneca, GSK, Novartis; Financial Interests, Steering Committee Member: Pfizer; Non-Financial Interests, Member: ASCO; Non-Financial Interests, Leadership Role: Australia New Zealand Sarcoma Association. B.J. Solomon: Financial Interests, Institutional, Advisory Board: AstraZeneca, Novartis, Merck, Bristol Myers Squibb; Financial Interests, Personal, Invited Speaker: Pfizer, AstraZeneca, Roche/Genentech; Financial Interests, Personal, Advisory Board: Amgen, Roche-Genentech, Eli Lilly, Takeda, Janssen; Financial Interests, Personal, Full or part-time Employment, Employed as a consultant Medical Oncologist at Peter MacCallum Cancer Centre: Peter MacCallum Cancer Centre; Financial Interests, Personal, Member of Board of Directors: Cancer Council of Victoria, Thoracic Oncology Group of Australasia; Financial Interests, Personal, Royalties: UpToDate; Financial Interests, Institutional, Steering Committee Member, Principal Investigator and Steering committee Chair: Roche/Genentech, Pfizer; Financial Interests, Institutional, Steering Committee Member: Novartis. P. Gibbs: Financial Interests, Personal, Advisory Board: Merck, Bayer, Amgen, Servier, Haystack Oncology; Financial Interests, Personal, Invited Speaker: MSD. G. McArthur: Financial Interests, Institutional, Coordinating PI, Financial interest is reimbursed costs for activities on clinical trials.: Genentech Roche; Financial Interests, Institutional, Coordinating PI, Financial interest is reimbursed costs for activities on clinical trials: Pfzier; Non-Financial Interests, Other, Advisory Board Member: Novartis, Bristol Myers Squibb, Canthera; Non-Financial Interests, Other, Director: Melanoma World Society. M. IJzerman: Financial Interests, Institutional, Advisory Board, Advisory Board about HTA of Genomic Sequencing in Blood Cancer (November 2022): Illumina; Financial Interests, Personal, Member of Board of Directors, Non-executive board member, compensated: Laboratory Microbiology Twente Achterhoek; Financial Interests, Institutional, Coordinating PI, Unrestricted research grant paid to my institution: Illumina; Non-Financial Interests, Leadership Role, Chair of the Health Sciences Policy Council: International Society for Pharmacoeconomics and Outcomes Research; Non-Financial Interests, Advisory Role, Member of technical assessment group (until June 2022): Medical Services Advisory Committee (MSAC) - Australian Government; Non-Financial Interests, Member of Board of Directors, Non-executive director, not-compensated: Rotterdam Global Health Institute. All other authors have declared no conflicts of interest.

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1688O Informative censoring of surrogate end-point data in FDA-approved cancer drugs

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Background: The use of surrogate endpoints in oncology is widespread and increasing, but their association with survival is often weak. Since informative censoring can affect survival analysis, we sought to investigate the patterns of censoring in oncology randomised controlled trials (RCTs) FDA-approved based on surrogate endpoints and examine their association with overall survival.

Methods: In this cross-sectional study we reconstructed K-M curves of RCTs leading to FDA drug approval based solely on surrogate endpoints between 2010 and 2020. The reverse K-M method (i.e., events and censoring are flipped) was used to examine differential censoring with the analogous reverse hazard ratio and restricted mean survival time. Sensitivity analysis was performed by restoring the balance in censoring between study arms.

Results: Of the 65 eligible studies, 22 (34%) reported significant overall survival benefit (concordant trials), and 43 (66%) did not (discordant trials). The proportion of studies with significant differential censoring in surrogates was 51% (22/43) and 45% (10/22) in discordant and concordant trials, respectively. Although censoring imbalance occurred in both groups, after sensitivity analysis, 74% (32/43) of the discordant trials lost their statistical significance, compared to 9% (2/22) of concordant trials (OR $= 29.09$ 95% CI 5.83 $-$ 145.08, $P = 0.0018$).

Conclusions: Drugs approved based on surrogate endpoints frequently exhibit uneven dropout rates between study arms. Our analysis indicates that studies without survival benefit often fail to demonstrate improvement in surrogates after accounting for excessive censoring.

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1689O Comprehensive mapping review of real-world evidence publications focusing on targeted therapies in solid tumors: A collaborative work from ESMO real-world data and Digital Health Working Group

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Background: A growing body of real-world evidence (RWE) aims to better reflect outcomes of cancer patients treated in real-world settings. We aimed to conduct a first comprehensive mapping review of the RWE produced over the past 3 years in terms of tumor type, treatment strategies, setting, and data sources, focusing on targeted therapies (TT) in solid tumors.

Methods: We conducted a systematic review in PubMed of RWE studies published between 01/2020 and 12/2022. We identified non-interventional studies using observational data, focusing on solid tumors exposure to targeted therapies, excluding immunotherapies. Abstract and full-text screening were performed by 11 independent reviewers.

Results: A total of 7,774 publications were retrieved with 1,251 considered eligible and extracted. The number of publications per year progressively increased during this period (328 in 2020; 421 in 2021; 502 in 2022). Most studies (50%) were performed in Asia, followed by Europe (25%) and North America (17%). Only 8% of studies had patients treated in more than one country. Treatment effectiveness and safety were assessed in 71% and 42% of studies respectively. Main data sources were medical records (60%), different types of registries (12%), and standardized data (9%). The majority were retrospective cohorts (87%), while 8% were prospective cohorts and 16% could be classified as population-based. Small molecules (62%) were the most frequently type of TT investigated. Most studies (30%) assessed gastrointestinal tract tumors, followed by lung (23%) and breast tumors (21%). In 17% of cases, study funding was industry-based.

Conclusions: RWE publications on TT for solid tumors are heterogeneous and mostly rely on retrospective data such as medical records. Population-based and international studies are rare. Collaborative efforts towards international representativeness and the use of routinely collected and/or standardized data sources must be encouraged to increase the relevance and future quality of publications and their potential impact on oncology practice.
Dr Perrat and Dr Grinda contributed equally to this study.

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1690O Impact of the SARS-CoV-2 outbreak on the initial clinical presentation of new solid cancer diagnoses: A systematic review and meta-analysis

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Background: Sars Cov-2-related disruptions to health services might have impaired the initial clinical presentation of new solid tumor patients. The aim of this systematic review was to compare the initial tumor stage of solid cancer diagnoses before and after the Sars Cov-2 outbreak.

Methods: Following PRISMA and MOOSE guidelines, we systematically reviewed articles in MEDLINE and EMBASE on the tumor stage of new solid cancer diagnoses before and after the initial Sars Cov-2 pandemic waves. A random-effects meta-analysis was conducted to compare the rate of metastatic tumors at initial presentation. Subgroup analyses were performed per primary tumor site, and per study country. Interstudy heterogeneity and subgroup differences were assessed with I^2 and X^2 tests, respectively.

Results: From 2,013 studies published between January 2020 and April 2022, we included 58 studies including 109,996 patients. The rate of metastatic tumors was higher after than before the pandemic (OR: 1.29 (95% confidence interval (95%CI), 1.06-1.57) with a I^2 of 89% (95%CI, 86%-91%). OR (95%CI) were 1,51 (1.07-2,12) for breast cancers, 1.51 (1.04-2.18) for gynecologic cancers, 0.79 (0.18-3.52) for lung cancers, 1.15 (0.89-1.49) for colorectal cancers, 1.45 (0.62-3.42) for other digestive cancer, 2.26 (0.51-10,05) for prostate cancer, 12.07 (0.57-253,68) for genitourinary cancers and 1.01 (0.59-1.75) for other types of cancer ($X^2 = 24,60$, $p<0.01$). Only 2 countries out of 17 studied showed a significantly higher rate of metastasis after the pandemic: Italy (OR (95%CI) = 1.55 (1.01-2.39)) and Spain (1.14 (1.02-1.29)) Conversely, Taiwan and Canada showed a significantly lower rate of metastasis after the pandemic: OR (95%CI): 0,51 (0,28-0,93) and 0,14 (0,07-0,29).

Conclusions: Despite inter-study heterogeneity, our meta-analysis showed a higher rate of metastatic tumors at initial presentation after the Sars Cov2 outbreak. The burden of social distancing policies might explain those results, as patients may have delayed seeking care.

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1691O Trends in new patient consultations during the COVID-19 pandemic at a comprehensive cancer centre in a public healthcare system

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Background: The impact of COVID-19 pandemic-related disruptions on cancer services is still emerging. We describe trends in new patient consultations in a comprehensive cancer centre before and during the pandemic.

Methods: New patient consultations were reviewed in the Princess Margaret Cancer Registry and grouped by Year=Y and quarter=Q1-Q4. Periods of interest were: baseline (Y2018-2019), pandemic declaration (Y2020Q1-Y2020Q2) and post-declaration period (PDP) (Y2020Q2-Y2021Q1). Logistic regression models were used to assess the effect of period before and during the COVID-19 pandemic on stage at presentation and adjusted for age, sex and diagnosis location (our hospital network vs. elsewhere).

Results: 53,759 new patient consultations took place from Jan 1, 2018-June 30, 2022. After pandemic declaration, new consultations decreased by 43.3% in Y2020Q2. During the PDP there were 2047 fewer overall, and 1618 new primary, consultations than expected which were not made up for at latest follow-up. The cancer sites with largest reduction in new primary assessments were neuroendocrine (84.6%), esophageal (62.1%) and colorectal (50.9%). Patients presenting with metastatic cancers were less likely to be diagnosed within our hospital network (aOR 0.70; CI 0.66-0.74, $p<0.001$), while patients with early-stage cancers were more likely (aOR 1.43; CI 1.34-1.52, $p<0.001$). After easing of pandemic restrictions in Y2020Q3, new patient assessments for metastatic cancers were higher than expected (aOR 1.23; CI 1.08-1.40, $p=0.002$). During the later periods of Y2021Q3-Y2022Q2 the odds of assessment for Stage 2/3 cancers were significantly lower than expected (aOR 0.81-0.90).

Conclusions: A large reduction in new patient consultations occurred during the COVID-19 pandemic; representing a gap in new cancer detection or change in care patterns with shift to other centres. The proportion of patients with stage 4 disease at consultation increased directly after the lockdown lifted, while the proportion of early-stage assessments remained below baseline during the later quarters, suggesting a protracted system recovery. Quantifying these changes are crucial for informing care delivery and recovery strategies.

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1692MO Is project Orbis successful? The Swiss perspective

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Background: An expedited market access for novel, effective & innovative drugs is warranted for patients. Swissmedic (SMC, Swiss Agency for Therapeutic Products) has participated since 2020 in Project Orbis, an US FDA launched collaborative parallel-review program where regulatory agencies remain decision-independent. We present the impact of the first 2 Project Orbis years from a SMC perspective.

Methods: We compared submission gaps (time between submission to FDA [1st] and SMC [2nd]), approval rates, consensus decision rates, and the approved indication labels between SMC and FDA for the 31 market authorization applications (MAA) in oncology submitted through Project Orbis (Orbis MAA) and the 41 oncology applications submitted in a conventional way to SMC (non-Orbis MAA) during 2020-2021. Assessment times at SMC were evaluated for Orbis and non-Orbis MAA with a decision until 6/2022.

Results: The median gap between submission to the FDA and SMC was 33.0 days (range: 7, 337) for Orbis MAA versus 168.0 days (range: -359, 1593) for non-Orbis MAA. The median assessment time at SMC was 235.5 days (range: 52, 476) for Orbis MAA and 314.0 days (range: 115, 542) for non-Orbis MAA. Approval rate at SMC was consistent with 76.9% for Orbis and 75.6% for non-Orbis MAA compared to 96.2% and 100% at the FDA, respectively. Consensus decision between SMC and FDA was with 80.8% numerically higher for Orbis as compared to 75.6% for non-Orbis MAA. Divergent decisions in Orbis MAA were due to different interpretations on trial design (uncontrolled), lack of benefit in subgroups (histology, race), and lack of overall survival (OS) benefit or immature OS data. Less labels with differences in indication wording between SMC and FDA was observed in Orbis than in non-Orbis MAA (60% vs 67.7%). Similarly, stricter label indications at SMC were reduced with Project Orbis from 61.3% to 50% with non-Orbis.

Conclusions: Project Orbis is successful for SMC because (1) Submission gaps and review times for oncology applications submitted to SMC are significantly reduced by Project Orbis, fostering a faster patient access. (2) Consensus decision rates are increased and indication differences and strictness between SMC and FDA are reduced with Project Orbis, potentially due to joint discussion amongst agencies.

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1693MO The high burden of long-term and late health-related problems among adolescent and young adult cancer survivors: Results of the SURVAYA study

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Background: Adolescents and young adults (AYAs), aged 18-39 years at primary cancer diagnosis, form a distinct population within the oncology community due to their spectrum of cancers, developmental life challenges, and care needs that differ from children and older adults. While the 5-year survival of AYAs is >80%, long-term and late effects can affect the quantity and quality of their life. We studied patient-reported long-term and late health-related problems among AYA cancer survivors.

Methods: Long-term AYA cancer survivors (5-20 years after primary cancer diagnosis) were identified by the population-based Netherlands Cancer Registry (NCR) and invited to participate in a questionnaire study. Participants reported their sociodemographic characteristics, and the occurrence and time of diagnosis of their long-term and late health-related problems. Clinical data were retrieved from the NCR.

Results: 3776 AYA cancer survivors (on average 31.6 years old at diagnosis; 12.4 years post-diagnosis) were included for analyses. Participants reported health-related problems with/of their digestive system (15.5%), vision (15.0%), back (14.6%), hormonal system (14.4%), cardiovascular system (12.6%), respiratory system (12.1%), urinary tract (11.0%), depression (8.6%), hearing (7.4%), osteoarthritis (6.9%), second primary cancer (6.4%), and anemia (5.1%). Of the 14 health-related problems that we examined, 35.1% of the participants reported none, 28.8% one and 36.1% reported two or more long-term and late health-related problems. Factors associated with an increased likelihood of long-term and late health-related problems include female sex, higher age at diagnosis, longer time since diagnosis, cancer of the colon/rectum, female genitalia, or thyroid, and treatment with stem cell therapy.

Conclusions: About two-thirds of the AYA cancer survivors experience at least one long-term or late health-related problem. If future research confirms that these problems are caused by cancer or its treatment, appropriate surveillance strategies to identify those at risk and interventions to mitigate those problems should be implemented preferably in AYA survivorship care programs.

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1694MO Socio-economic consequences among adolescent and young adult cancer patients: A European perspective

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Background: The effect of a cancer diagnosis is wide-ranging with potential negative impact on socioeconomic life such as high (in)direct treatment-related costs and income loss. These socioeconomic consequences differ per country, healthcare setting and patient population. Adolescents and young adults (AYAs), 18-39 years old at cancer diagnosis, are recognized as a distinct population within the oncology community with age-specific problems and needs. Insight into the socioeconomic consequences of cancer at this young age is of utmost importance to provide the best possible supportive care to this group. This study explores the socio-economic consequences among AYAs across 11 European countries.

Methods: This study presents a sub-analysis of the SEC-Study data, focusing on AYAs who were currently treated or treated before. Participants were included by hospitals of the Organization of European Cancer Institutes network and patient organizations in 11 countries (Belgium, Bulgaria, Cyprus, Denmark, Finland, France, Germany, Netherlands, Norway, Spain, Switzerland). Next to measuring financial distress through the Financial Index of Toxicity, our survey explored other socio-economic consequences like income loss, coping behaviour regarding treatment related expenses and access to financial services.

Results: 316 AYA cancer patients participated (median age: 35 years), of which 38% had to permanently quit their job due to their cancer (range: 19% (France, Norway); 71% (Spain)) and 70% suffered from income loss (range: 53% (Bulgaria); 89% (Belgium)). AYAs coped by using their savings (43%), spending less on luxury goods/leisure activities (37%), spending less on basic goods (29%), applying for financial assistance (26%), or borrowing money (20%), although differences exist between countries. Most AYAs (82%) were worried about their family's financial situation and 58% stated it's important to them to discuss the personal cost of treatment with their doctor.

Conclusions: This European study shows that many AYAs face serious socio-economic consequences, although differences exist between countries. Those AYA cancer patients at risk of impacted socio-economic outcomes require bespoke financial support.

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1695MO Cancer care during armed conflict: Factors associated with adult patient transfer for treatment abroad during the war in Ukraine

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Background: Because of Russian Federation's invasion of Ukraine, many patients with cancer are unable to receive treatment at home. We explored factors associated with transfer of cancer patients to the European Union (EU) for treatment through the joint program.

Methods: We conducted a retrospective review of data from the Ministry of Health (MOH) on patients who applied to be transferred abroad for cancer care from April 2022 to April 2023. Data was analyzed using descriptive statistics and standard tests of association.

Results: 336 (53.0%) of 634 patients were analyzed. We excluded children, patients without a cancer and with no available data. The mean age was 46.9 years (SD ± 13.5). 197 (58.6%) had ECOG 0-1, 94 (30%) ECOG 2, 14 (4.2%) ECOG 3-4, 31 (9.2%) ECOG unknown. The most common cancers were: 102 (30.4%) melanoma, 43 (12.8%) breast cancer, 31 (9.2%) chronic hematologic and 26 (7.8%) acute hematologic malignancies, 21 (6.3%) colorectal cancer, 20 (6.0%) lung cancer, 12 (3.6%) head and neck cancer. Of 336 patients, 280 (83.3%) were transferred for care abroad, 22 (6.5%) were pending, 28 (8.3%) transfers declined. Reasons for transfer were treatment not available, new diagnosis190 (56.5%), 105 (31.3%) for continuation of care, 19 (5.6%) cancer relapse, 32 (9.5%) bone marrow transplant, 15 (4.5%) radiotherapy, 13 (3.9%) surgery, 3 (0.9%) organ transplant. Factors independently associated with being transferred were breast cancer (OR 5.8, 95% CI: 2.7-5.7), melanoma (OR 2.6, 95% CI: 1.2-5.6), ECOG 3-4 (OR 0.1, 95% CI: 0.01-0.4). In univariate analysis, not having cancer treatment available in Ukraine (OR 2.5, 95% CI: 1.4-4.5), head and neck cancer (OR 0.2, 95% CI: 0.1- 0.6), and continuation of cancer care when drug was not available in Ukraine (OR 2.5, 95% CI: 1.4-4.5) were also associated with transfer.

Conclusions: The Ukraine-EU program for transferring cancer patients abroad is a strategy to mitigate issues with cancer care capacity during armed conflict, with almost all patients who applied currently receiving cancer treatment in the EU. Patient-related factors associated with transfer abroad for cancer care during war included patient condition, cancer type, and government treatment coverage.

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1696MO Partial orphan cancer drugs: FDA approval, clinical benefit, trials, epidemiology, price, beneficiaries, and spending

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Background: The Orphan Drug Act (ODA) incentivizes drug development for rare diseases with limited sales potential. Yet, orphan drugs frequently turn into multi-billion-dollar blockbusters, particularly those used to treat rare and common diseases: partial orphans. This study analyses the development, US Food and Drug Administration (FDA) approval, epidemiology, and economics of full, partial, and non-orphan cancer drugs.

Methods: 170 drugs with FDA approval for 455 cancer indications were identified between 2000-2022. Full, partial, and non-orphan drugs were compared regarding their regulatory approval, clinical benefit, trials, epidemiology, price, beneficiaries, and spending with data extracted from FDA documents, Global Burden of Disease study, and Medicare & Medicaid.

Results: We identified 110 full, 22 partial, and 38 non-orphan cancer drugs. Time from first to second FDA approval was shorter for partial than non-and full orphans (median 1.3 vs 1.6 vs 2.3 years). Full orphans, relative to partial and non-orphans, were more frequently third-line (17% vs 8 vs 7, $p=.025$) monotherapies (74% vs 58 vs 58, $p=.002$) for hematologic cancers (66% vs 4 vs 0, $p<.001$) supported by smaller (median 154 patients vs 416 vs 536, $p<.001$) open-label (56% vs 64 vs 87, $p<.001$) single-arm trials (19% vs 23 vs 50, $p<.001$). Disease incidence was lower and disease severity higher for full than partial and non-orphans. Full orphans offered a significantly greater overall survival (median: 4.0 vs 2.8 vs 2.8, $p<.001$) and progression-free survival (median: 5.1 vs 2.5 vs 3.6, $p<.001$). Monthly prices were higher for full and partial than non-orphans (median $17177 vs 13284 vs 12457, $p<.001$). Beneficiaries (8790 vs 4390 vs 1730) and spending ($570 vs 305 vs 156 million) per drug were greater for partial than non-and full orphans.

Conclusions: The benefit, trials, and epidemiology of partial orphan cancer drugs are more similar to non-orphans than full orphans. Yet, partial orphans receive all of the ODA's incentives and are swiftly extended to new indications, resulting in greater prices, beneficiaries, and spending. Establishing a maximum revenue threshold for the ODA's benefits alongside indication-specific pricing could reduce expenditure on partial orphans.

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1697MO Spending on and beneficiaries of orphan cancer drugs for ultra-rare, rare, and common diseases

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Background: The Orphan Drug Act of 1983 not only incentivizes drug development for rare (200,000-6,600 affected US citizens), but also for ultra-rare (<6,600 US citizens) and subsets of common diseases (>200,000 US citizens). This study estimates Medicare & Medicaid spending on and beneficiaries receiving ultra-rare, rare, and common orphan cancer drugs to understand their budget impact and usage.

Methods: We identified 153 cancer drugs with FDA approval in the Drugs@FDA database (2000-2022). Drugs were group into non-orphan, common orphan (>200,000 patients), rare orphan (6,600 to 200,000), and ultra-rare orphan (<6,600) according to the number of affected US citizens as published by the Global Burden of Disease study. Drug spending and the number of beneficiaries for Medicare Part D and B & Medicaid were obtained from public documents. We calculated and compared total and average spending on and the total number of beneficiaries receiving non-, common, and rare orphan cancer drugs.

Results: Medicare & Medicaid data were available for 118 on-patent drugs. Overall spending increased from $8.8 to $26.5 bn (2016-2020). In 2020, 2% ($0.5 bn) were spent on ultra-rare, 31% ($8.2 bn) on rare, 30% ($8.1 billion) on common, and 37% ($9.7 bn) on non-orphan drugs. In 2020, average spending was lower for ultra-rare and rare than common and non-orphan drugs ($70 vs 155 vs 323 vs 295 million, p=0.005). A total of 171,260 and 357,464 beneficiaries received novel cancer drugs under Medicare & Medicaid schemes in 2016 and 2020, respectively. Of these, 2% (6560) suffered from ultra-rare, 27% (97,319) from rare, 31% (111,125) from common, and 40% (142,460) from non-orphan diseases. The average number of beneficiaries per drug was lower for ultra-rare and rare than common or non-orphans (1093 vs 1098 vs 4445 vs 4452 beneficiaries, p=0.015) in 2020.

Conclusions: Significant resources are spent on orphan drugs for diseases affecting more than 200,000 US citizens, whilst shifting the FDA's and taxpayers' resources away from truly rare or ultra-rare diseases. Congress could either create three distinct special orphan designations (ultra-rare, rare, and common) or differentially tie the Orphan Drug Act's incentives to the treated disease's prevalence.

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1698MO E-cigarette use among us ever-smoking cancer survivors and its implications on lung cancer screening

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Background: E-cigarettes are increasingly used as a perceived safe alternative for smoking cessation, despite evidence of increased lung cancer risk. Young cancer survivors (<40 years old) use e-cigarettes 1.5 times more than their non-cancer survivor peers. Long-term cancer survivors have a higher risk of developing second primary lung cancer than the general population. However, lung cancer screening (LCS) guidelines that focus on cigarette smoking may overlook the cancer risk of using e-cigarettes. We aimed to study e-cigarette use in LCS-ineligible long-term cancer survivors.

Methods: Smokers aged 50-79 years were obtained from the 2017-2018 & 2020-2021 US Behavioral Risk Factor Surveillance System Ineligibility for LCS was defined using the US Preventive Service Task Force (USPSTF) 2021 criteria: smokers with <20 pack-year smoking history or former smokers quit >15 years. The prevalence of current e-cigarette use in LCS-ineligible smokers was calculated and compared between long-term cancer survivors (cancer diagnosed > 5 years ago) and non-cancer survivors. All calculations were weighted.

Results: Out of 11,431,095 smokers, 62.6% were ineligible for LCS. Ineligible cancer survivors had a significantly lower prevalence of e-cigarette use than their peers without a history of cancer (p<0.01) (Table). E-cigarette use was comparable between cancer survivors and non-cancer survivors who were current, heavy, or recently quit smokers (p>0.05).

Table: 1698MO

E-cigarette use prevalence % (95%CI)	LCS ineligible smokers (62.6%; N=7,159,703)		
	Non-cancer survivors (95.2%)	Long-term cancer survivors (4.8%)	p-value
Overall	9.7 (8.0-11.3)	4.2 (1.1-7.3)	<0.01
Gender			
Women	11.8 (9.4-14.2)	5.2 (0.1-10.3)	0.02
Men	7.3 (5.0-9.5)	3.0 (0.2-5.7)	0.03
Smoking status			
Current	15.4 (11.8-19.0)	14.7 (0.5-28.9)	0.93
Former	6.5 (4.9-8.1)	1.9 (0.1-3.6)	<0.001
Pack-years			
<20	10.6 (8.7-12.4)	5.0 (1.2-8.8)	0.01
≥20	4.2 (1.4-7.0)	1.3 (0.0-3.7)	0.14
Years since quitting (former smokers)			
>15	3.8 (2.3-5.3)	1.6 (0.0-3.2)	0.05
≤15	17.1 (12.1-22.1)	4.7 (0.0-13.7)	0.07

Conclusions: Nearly 0.8 million LCS-ineligible long-term cancer survivors currently use e-cigarettes in the US. While the overall prevalence of e-cigarette use among cancer survivors was relatively low, current/heavy smokers use e-cigarettes at rates comparable to non-cancer survivors. Given that cancer survivors already face an increased risk of lung cancer, the use of e-cigarettes may further heighten this risk. Future lung cancer risk assessment and screening studies may need to take e-cigarette use into consideration.

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1699MO Intervening factors for participation and non-participation in colorectal cancer screening in Spain

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Background: The Spanish Ministry of Health introduced a population-based colorectal screening program within its common services portfolio in 2014. The program targeted adults from 50 to 69 years. They receive a personal invitation letter asking them to perform the fecal occult blood test (FOBT). To achieve public health benefits on incidence, mortality, and cost-effectiveness from this screening program 65% participation in the program is needed[1]. Although participation rates have been improved since 2014, there is still room from improvement as only 56% of the Spanish regions reach the participation threshold[2]. In this study, we examined attitudinal and social factors impacting on participation in the target population.

Methods: A survey of the target population of the screening program was conducted using a national online panel representative of the Spanish population. A representative program's target population sample, with a size of 5131 valid responses, was obtained. The data collection was conducted from June to July 2022. The data was analyzed using a descriptive analysis for the entire sample as well as the logistic regression technique.

Results: We found that 62.5% of the target population in Spain has had the FOBT effectively carried out, 72.5% have received the information letter to participate in the screening program and 86.8% were familiar with the test. Furthermore, receipt of the information letter (OR 7.35, p<0.01) and knowledge of the FOBT (OR 6.32, p<0.01) are the main variables that increase the probability of the actual completion of the test. Other variables with a high contribution are the frequency with which one visits a doctor (OR 1.71, p<0.01) and the fact of belonging to higher age brackets (OR 1.52, p<0.01).

Conclusions: Alongside the universal implementation of the invitation to the program, researchers must work with attitudinal variables which act as barriers to the population's participation — such as prior knowledge of the test or the normalization of regular visits to a doctor — if we hope to achieve truly equal access to the screening program.

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1700MO Knowledge of cancer risk factors and risk-reduction in 20 high- and middle-income countries

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Background: The incidence of preventable cancers especially among adults younger than age 50 years in high-income countries (HIC) is increasing. This underscores the significance of disseminating prevention recommendations as it raises concerns about risk modification by individuals and individuals' knowledge of cancer risk factors that enable primary prevention. We explored relations between risk-reduction behavior and self-perceived knowledge of cancer risk factors in 20 countries using data from the International Public Opinion Survey on Cancer 2020.

Methods: We focused on selected risk factors in the survey which had a total sample of 15,427 adults and fit an ANCOVA model to evaluate the effect of knowledge, as well as its interaction with country and risk factor on risk reduction behavior engagement. Non-response options were graphically inspected.

Results: Every unit increase in the proportion of the population knowledgeable about a cancer risk factor, on average across risk factors and countries, significantly increases the proportion of people engaging in risk reduction by approximately 16.91% (95% CI 1.77 % to 32.05 %; $p=0.029$) in 10 HIC, and 32.94% (95% CI 16.22 to 49.66; $p<0.001$) in 10 middle-income countries (MIC), respectively. A significant interaction effect was found between knowledge and country, but not between knowledge and risk factor. France showed an estimated decreased engagement in overall risk-reduction activity of about 27.73% (95% CI -46.05, -9.42; $p<0.001$) compared to the overall average. Risk factors such as sugary drinks, and red and processed meat show a steeper positive linear relationship with risk reduction compared to alcohol and excess weight in HIC and MIC.

Conclusions: Knowledge of cancer risk factors is positively associated with risk reduction in HIC and MIC. Improved dissemination of cancer prevention recommendations including the European Code Against Cancer, World Cancer Research Fund and national clinical recommendations is crucial to address potential gaps in or inadequate knowledge of cancer risk factors in the population.

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1759MO Clinical breast examination for early diagnosis of breast cancer: An Egyptian nationwide study

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Background: Screening mammography is the standard approach for early detection of breast cancer (BC). Clinical breast examination (CBE) may serve as an alternative screening tool in limited resource countries where the late presentation of BC and young age at diagnosis prevail.

Methods: We designed a nationwide screening program with a multistep approach based on two-stage CBE. All Egyptian women $\geq$18 years (ys) were invited to participate in one of the 3538 primary health care (PHC) units across Egypt. Women who were 18-35 ys of age with predefined risk factors and all women $>$35 ys underwent CBE. Those with abnormal CBE were subsequently referred to one of 102 tertiary cancer clinics (TCC) for a confirmatory breast examination conducted by a BC oncologist/surgeon. Diagnostic imaging was requested for those with clinically suspicious findings in the confirmatory CBE. Here we report the outcomes of the first 2 ys of the program.

Results: From July 2019 to June 2021, 10,832,447 women participated in the program. Of those, 5,987,485 women met the criteria for CBE. Abnormal CBE was detected in 598,252 (10%) women. Of those, 390,633 (65.3%) presented to TCC for a confirmatory CBE with a median age of 43 ys. A total of 196,509 (50.3%) women had abnormal confirmatory CBE warranting breast imaging. The majority (162,898 (82.9%)) attended diagnostic imaging, with 14,794 cases reported as BIRADS 4 or 5 (9.1%). Among the 10,128 women who successfully performed a biopsy, 5,335 (52.6%) had malignant findings; of these, 5112 had mammary carcinoma. 270 women (5.1%) of the BC cases were $\leq$ 35 ys old. Stages 0-II were diagnosed in 80.5%, reflecting significant downstaging from prior historical cohorts. Risk factors for BC in Egyptian women were estimated for the first time on a nationwide scale (Table).

Table: 1759MO

Risk factor	Relative risk (95% CIs)	Cases/Controls (5,112/5,389,233)
Oral contraceptive pills use $\geq$ 5 ys	1.16 (1.10-1.22)	1,082/984,086
BMI $\geq$ 30 kg/m^2	1.59 (1.58-1.60)	4,860/3,217,506
Diabetes mellitus	1.82 (1.67-1.99)	460/266,495
Age of menopause $\geq$ 50 ys	2.12 (1.93-2.32)	422/209,822
Family history of breast/ovarian cancer	2.50 (2.36-2.64)	1,032/435,658
Prior breast biopsy	7.67 (6.80-8.65)	254/34,903

Conclusions: Personalized-risk CBE, as adopted in our program, is effective in downstaging BC. This is the largest study to report successful BC downstaging via CBE, meeting the WHO pillar 1 key performance indicator of $\geq$60% of stages 0-II.

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1701P Cancer premium: Explaining differences in prices for cancer vs non-cancer drugs with efficacy and epidemiological endpoints in the US, Germany, and Switzerland

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Background: High treatment prices of new cancer drugs are a global public health challenge to patients and healthcare systems. Policymakers in the US and Europe are debating reforms to drug pricing. The objective was to assess whether drug efficacy or epidemiological characteristics (prevalence, incidence, mortality) explain the gap in treatment prices between cancer and non-cancer drugs in the US, Germany, and Switzerland.

Methods: This cross-sectional study identified all new drugs approved in the US, Germany, and Switzerland between 2011 and 2020. Drug efficacy was extracted from the pivotal trials, drug prices from public and commercial databases, and epidemiological characteristics from the Global Burden of Disease (GBD) 2019 study. We used regression models to explain drug prices with drug efficacy and epidemiological characteristics (prevalence, incidence, mortality).

Results: The cohort included 181 drugs, including 68 (37.5%) drugs approved for treatment of cancer. A significant negative correlation was found between incidence/prevalence and treatment prices, and a significant positive correlation was observed between mortality and treatment prices for both, cancer and non-cancer drugs. A significant association between relative drug efficacy and treatment prices of drugs was observed, however, less pronounced for cancer drugs. Our regression estimates indicated that after adjusting for efficacy and epidemiological characteristics, cancer drugs were on average approximately three times more expensive compared to non-cancer drugs in all three countries, indicating a cancer premium. Our model explained 72% of the variance in observed prices (R2).

Conclusions: Drug pricing reforms should target the cancer premium to improve access of patients to cancer drugs as well as to achieve equity across the different therapeutic areas and sustainability in the health care systems.

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1702P Real-world evidence contributions to European medicines agency's safety and efficacy evaluations of oncology targeted therapies between 2018-2022

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Background: While Real-world Evidence (RWE) has documented value for safety monitoring and disease epidemiology, its objective contribution to safety and efficacy evaluations for regulatory purposes is still unclear. Here, we aim to describe the prevalence and type of RWE considered by European Medicines Agency (EMA) as contribution to efficacy and safety-related evidence generation among approved oncology targeted therapies.

Methods: On March 10, 2023, we screened the medicines listing of EMA to identify all anti-cancer targeted therapies for solid malignancies with a decision date (initial marketing authorizations and extension of indications) between 2018-2022. We screened the European public assessment reports (EPARs) using a standardized approach to collect data on RWE. When generated pre-authorization, the RWE contribution to the final regulatory decision was classified as definitive, supportive, or non-supportive. For published RWE studies, we collected their main characteristics.

Results: Out of a total of 1976 medicines, we identified 55 oncology targeted therapies, corresponding to 75 EPARs (indications), which are described in the table. The use of RWE in regulatory deliberations occurred in 24/75 (32%) EPARs, increasing from 30% in 2018-2020, to 34% in 2021-2022. Pre-authorization RWE was described in 20/24 (83%) EPARs, among which none were definitive, 8 RWE studies (in 7 EPARs) non-supportive, and 20 RWE studies (in 15 EPARs) were supportive of the decision. Published RWE (n=14) originated from data aggregators (n=5), patient registries (n=3), health records (n=3), standardized cohort data (n=2), or from combined sources (n=1).

Table: 1702P

Characteristic	Total EPARs (n=75)	EPARs w/ no RWE (n=51)	EPARs w/ RWE (n=24)
Year: n, %			
2018-2020	43	30 (70%)	13 (30%)
2021-2022	32	21 (66%)	11 (34%)
Targeted therapy type: n, %			
Small molecule	50	34 (68%)	16 (32%)
Monoclonal antibody	20	15 (75%)	5 (25%)
Antibody-drug conjugate	5	2 (40%)	3 (60%)
EPAR type: n, %			
Initial Marketing Authorization	42	27 (64%)	15 (36%)
Extended indication	33	24 (73%)	9 (27%)
First drug in class (Yes): n, %	19	11 (58%)	8 (42%)
Generic (Yes): n, %	3	3 (100%)	0 (0%)
Biosimilar (Yes): n, %	13	12 (92%)	1 (8%)
Accelerated assessment (Yes): n, %	9	4 (44%)	5 (56%)
Orphan medicine (Yes): n, %	4	3 (75%)	1 (25%)
Conditional approval (Yes): n, %	15	8 (53%)	7 (47%)
Additional monitoring (Yes): n, %	50	34 (68%)	16 (32%)

Conclusions: Over the past 5 years, RWE involvement in the approval of oncology targeted therapies in Europe tends to increase, with the majority being supportive for EMA regulatory decision making complementary to traditional clinical trials.

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Koopman: Financial Interests, Institutional, Advisory Board, advisory board and speaker: Pierre Fabre; Financial Interests, Institutional, Advisory Board: MSD, Bayer; Financial Interests, Institutional, Advisory Board, Advisory Board, speaker: Servier; Financial Interests, Institutional, Invited Speaker: Merck, BMS; Financial Interests, Institutional, Trial Chair: Servier; Financial Interests, Institutional, Research Grant: Servier, Roche, Bayer, Bristol Myers Squibb, Merck, Personal Genomics Diagnostics, Sirtex, Pierre Fabre; Financial Interests, Institutional, Funding: Pierre Fabre, Amgen, Nordic Pharma, Novartis, Merck, Servier, BMS; Non-Financial Interests, Leadership Role, vice-chair of DCCG: Dutch Colorectal Cancer Group; Non-Financial Interests, Advisory Role, Member of KWF scientific board: KWF; Non-Financial Interests, Other, ESMO faculty member for the Gastro-Intestinal Tumours — colorectal cancer: ESMO; Non-Financial Interests, Advisory Role, expert member of committee "regie op registers dure geneesmiddelen" ZINNL: ZiNNL; Non-Financial Interests, Advisory Role, CRC expert on Kanker.nl platform for answering online CRC questions of CRC (non) patients: Patient respresentative organisation (Kanker.nl); Non-Financial Interests, Leadership Role, chair of RWD & DH working group: ESMO; Other, Other, PI of the Dutch Prospective Colorectal Cancer Cohort study: PLCRC project. 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1703P Value of molecular targets and genome-targeted cancer therapies FDA-approved, 2015-2022

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Background: Genome-targeted cancer drug approvals have increased, offering personalized therapy at high cost. We assessed genome-targeted cancer drugs to determine the validity of the targets and clinical benefits identified in the pivotal clinical trials.

Methods: We identified trials FDA-designated as pivotal that supported genome-targeted cancer drug approvals between 2015-2022. From drug labeling and publications, we extracted characteristics of the trials. Strength of evidence supporting molecular targetability was assessed by the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT). Clinical benefit for approved indications was evaluated by the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) with substantial benefit defined as grade A or B for curative and 4 or 5 for noncurative intent. Molecular targets qualifying for ESCAT level I-A and I-B associated with substantial clinical benefit were rated as high benefit.

Results: Among 50 molecular-targeted drugs approved for 84 indications, 45 (54%) were based on phase I/II trials and 45 were supported by single-arm studies. The most common primary endpoint (46, 55%) was response rate (median 57%, median duration of response 11.1 months). Among the 84 pivotal trials, 38 (45%) had I-A and 32 (38%) had I-B ESCAT targetability score; 24 trials (29%) demonstrated substantial clinical benefit via ESMO-MCBS. Overall, 24 indications (29%) were high-benefit genomic-based cancer treatments.

Conclusions: Fewer than one-third recently approved molecularly-targeted cancer therapies demonstrated high patient benefits. Data often evolve after marketing, but when new cancer treatments are first approved based on exploratory analyses and anti-tumor activity alone, benefit frameworks like ESMO-MCBS and ESCAT can help identify the minority of therapies with the best clinical potential.

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1704P Clinical benefit of cancer drugs approved by the US food and drug administration based on appropriateness of control arm and its change over time

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Background: Value frameworks such as American Society of Clinical Oncology Value Framework (ASCO-VF) and European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) can be sensitive to control arms of randomized trials (RCTs). Standard of care changes over time. We explored clinical value based on appropriateness of control arm and its change over time.

Methods: We searched Drugs@FDA to identify new cancer drugs approved based on RCTs between January 2012 and December 2021, excluding trials with overlap between experimental and control arm. Appropriateness of control arm was based on published ESMO and NCCN guidelines both 1 year prior to start of accrual (as defined by ClinicalTrials.gov) and at time of drug approval. Control arm was defined as suboptimal if the strength of recommendation was 2B-3 for NCCN, III-V / C-E for ESMO guidelines and/or if prior RCT data showed that the control arm was inferior to an available alternative. Substantial clinical benefit was defined as ASCO-VF threshold score $\geq$45 and ESMO-MCBS grade A or B (curative intent) and 4 or 5 (palliative intent).

Results: We identified 55 RCTs supporting the approval of 32 drugs. Substantial benefit was observed in 65% and 55%, using ESMO-MCBS and ASCO-VF. Prior to accrual, appropriate control arm therapy was associated with non-significantly higher odds of clinical benefit using ESMO-MCBS with NCCN (OR 3.19, P=.23), but not ESMO guidelines (OR 1.29, P=.79). At the time of drug approvals associations were similar (OR 3.03, P=.06 and 1.17, P=.80). For ASCO-VF, appropriate control arm therapy was associated with non-significantly increased odds of clinical benefit (OR 5.52, P=.14) for both guidelines. These associations were not observed at the time of drug approval (OR 0.81, P=.69 for NCCN and 0.81, P=.72 for ESMO). Results were similar for RCTs performed exclusively in palliative intent.

Conclusions: ASCO-VF appears sensitive to change in appropriateness of control group therapy over time. ESMO-MCBS appears more consistent. Heterogeneity was observed based on scale, guideline and timepoint. Further exploration of impact of control group therapy on value frameworks is warranted.

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1705P Therapeutic value of first vs supplemental indications of drugs in the US and Europe (2011-2020): Retrospective cohort study

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Background: After first approval of a new drug, it may subsequently be approved for additional indications. The number of drugs approved for such supplemental indications has increased, however, their added therapeutic benefit is unclear. We analyzed the therapeutic value of supplemental indications compared to first indications for drugs approved in the US and Europe (2011-2020).

Methods: We identified first and supplemental indications that were approved by the FDA and EMA. Therapeutic value ratings were obtained from France and Germany. We used descriptive statistics to analyze the unadjusted proportion of first and supplemental indications rated highly by the French or German health authorities. To obtain adjusted estimates of the probability for supplemental indications to be rated highly, we used Poisson regression analyses.

Results: 124 first and 335 supplemental indications approved by the FDA, and 88 first and 215 supplemental indications by the EMA were included, the largest subset for cancer disorders. Therapeutic ratings were available for 107 (86%) first and 179 (53%) supplemental indications in the US, and 87 (99%) first and 184 (86%) supplemental indications in Europe. Among FDA-approved indications with available ratings, 41% (44/107) had high therapeutic value ratings for first, compared with 34% (61/179) for supplemental indications. In Europe, 47% (41/87) of first and 36% (67/184) of supplemental indications had high therapeutic value ratings. Among FDA approvals, when the sample was restricted to the first three approved indications, second indication approvals were 36% less likely to have a high value rating (RR=0.64, 95%CI, 0.43-0.96) and third indication approvals were 45% less likely (RR=0.55, 95%CI, 0.29-1.01) when compared to the first indication approval. Similar findings were observed for Europe and when weighting by the inverse number of indications for each drug.

Conclusions: The proportion of supplemental indications rated as having high therapeutic value was substantially lower compared to first indications. When indications do not offer added therapeutic value over other available treatments, that information should be clearly communicated to patients and physicians.

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1706P Time to full approval of novel anticancer medicines granted accelerated approval and implications for reform of the accelerated approval pathway

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Background: The Accelerated Approval (AA) pathway was established to speed development and approval of drugs for life-threatening conditions with limited treatment options. In December 2022, the US Congress enacted new policies to ensure that confirmatory studies for AA medicines are completed in a timely fashion. Here, we evaluate factors associated with conversion of AA to regular approval by the US FDA, including magnitude of clinical benefit as measured by European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).

Methods: We included all anticancer drugs that had received AA from the US FDA from 1992 to 2020, with follow up on approval status through January 2022. FDA drug labels and clinical trial reports were reviewed to apply ESMO-MCBS v1.1 grades to both initial and confirmatory studies. High clinical benefit was defined as a grade of A or B for trials of curative intent and 4 or 5 for those of palliative intent. Withdrawn AA indications, as determined by FDA, were considered as low benefit.

Results: From 1992 to 2020, the FDA granted AA to 46 anticancer solid drugs for 74 indications. The median time between AA and regular approval of oncology drugs was 3.7 years (range: 0.8-12.6 years). Of these 74 indications, 42 (57%) had clinical benefit confirmed in post-approval clinical trials and were converted to regular approval. Indications with high clinical benefit according to ESMO-MCBS were associated with shorter times to conversion to regular approval (median 2.5 vs 4.8 years; P=0.007). Similarly, indications with overall survival benefit were associated with shorter times to regular approval (median 2.6 vs 3.7 years; P=0.04).

Conclusions: Anticancer medicines with greater clinical benefit were associated with faster conversion to full FDA approval. New policy reforms to the AA pathway in the USA should prioritize further expediting market access of therapies with high clinical benefit as well as expedited completion of confirmatory studies.

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1707P Cancer drug prices in the US: Efficacy, innovation, clinical trial evidence, and epidemiology

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Background: Rising cancer drug prices pose a challenge for patients and healthcare systems in the US. Whilst prices are routinely assigned to a drug's original indication receiving US Food and Drug Administration (FDA) approval, the influence of supplemental indication approvals on prices remains uncertain. This study identifies and quantifies factors associated with cancer drug prices, distinctly analyzing original and supplemental indications.

Methods: Clinical trial evidence supporting each indication's FDA approval was collected from the Drugs@FDA database (2003-2022). Disease incidence and disability-adjusted life years (DALYs) were obtained from the Global Burden of Disease

study. Indication-specific monthly treatment costs were calculated for patients covered under Medicare Part B and D. The association between log-prices and collected variables was assessed in univariate regression analyses.

Results: We identified 145 drugs approved across 373 cancer indications. Drugs were priced at $24,444 per month on average (median $16,013; IQR 14,648 to 22,348). For original indications, prices were only weakly correlated to improvements in overall survival ($\hat{\beta}$=0.28, 95%CI 0.02 to 0.54, p=0.037) and progression-free survival ($\hat{\beta}$=0.16, 95%CI 0.07 to 0.25, p=0.001). Original indications' prices were: (1) negatively associated with disease incidence ($\hat{\beta}$=-0.21, 95%CI -0.28 to -0.13, p<0.001) and prevalence; (2) positively correlated for first-in-class drugs (26%, 95%CI -1 to 60, p=0.057), gene & cell therapies (176%, 95%CI 79 to 324, p<0.001), hematologic cancers (52%, 95%CI 28 to 106, p<0.001), and severe diseases with substantial unmet needs (6% per DALY, 95%CI 3 to 8, p<0.001); and (3) negatively correlated to indications with randomized controlled phase III trials. Prices were only poorly associated with supplemental indications' efficacy, clinical evidence, and epidemiology.

Conclusions: Cancer drug prices are set based on the original indication's characteristics, thereby omitting the value of supplemental indications. *Indication-specific* pricing, coverage, and reimbursement policies considering each indication's safety, efficacy, innovativeness, and unmet needs are necessary to align a drug's value and price.

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1708P The registration pathways in China for globally developed novel anticancer drugs

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Background: Since China implemented the regulations on adjusting the approval process of imported drugs in 2017, the integration of China into the global development of novel anticancer drugs has accelerated. The changing registration pathways for these products inspire us to present this data analysis.

Methods: Based on the review reports of approved global anticancer drugs from the database of the Center of Drug Evaluation of China, the cancer type, scope and timeline of pivotal supporting trials for each indication were extracted by the end of 2022. The distribution of registration pathways was explored using the number of indications as the key indicator.

Results: A total of 83 approved indications were retrieved. Participating in synchronous global studies (39, 47.0%) was the most common registration pathway, which was divided into dose expansion/phase II (4, 4.8%) and confirmatory studies (35, 42.2%). Launching China-dominant studies was another main pathway (35, 42.2%), including bridging (26, 31.3%) and confirmatory studies (10, 12.0%). Clinical studies in China were exempted in 15 (18.1%) indications. Multiple pathways were used to support 7 (8.4%) indications. The number of indications supported by China-dominant studies decreased from 19 (2017-2019) to 15 (2020-2022), while that of synchronous global studies increased from 15 (2017-2019) to 23 (2020-2022). Among the 9 indications for esophageal, gastric and hepatocellular cancer, eight (88.9%) were approved by global studies. The median days between China and the first global approval was 371 in indications supported by global studies, compared with 1326 in that supported by China-dominant studies.

Conclusions: Participating in synchronous global studies is the most common and time-saving registration pathway in China for globally developed novel anticancer drugs in recent years, especially for Chinese high-prevalent cancers. Efforts should be made to help China join more global early-phase studies in the future.

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1709P Influence of censoring on conclusions of FDA-approved cancer drugs using the modified time to treatment failure

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Background: Time-to-treatment failure (TTF), in which both disease progression and treatment interruption are regarded as events, is a common measure in clinical trials that can be used as a sensitivity analysis for informative censoring. However, TTF is inappropriate for excessive censoring in the control group as it exaggerates the effect size instead of penalizing the bias. We propose a novel measure, the modified TTF (mTTF), that considers censoring as events only for excessive censoring in the intervention group. Here we examine whether excessive censoring in the intervention could affect the results of randomized controlled trials (RCTs) leading to FDA-approved drugs using mTFF.

Methods: We conducted a cross-sectional study collecting data from phase II and phase III RCTs of FDA drugs approved based on surrogate endpoints between 2010 and 2020. We reconstructed individual patient data from the published Kaplan-Meier curves of the primary surrogate endpoint. The reverse Kaplan-Meier method (i.e., events and censoring are flipped) was used to quantify excess censoring between study groups. The mTTF sensitivity analysis was conducted and statistical significance was calculated using the log-rank test.

Results: One hundred and one RCTs comprising 60,697 patients were included. The most common surrogate endpoint was progression-free survival with 86 (85.1%) of the studies. The median HR for surrogate endpoints was 0.54 (IQR [interquartile range], 0.41 to 0.63) and the median p-value was $3.0*10^{-5}$ (IQR, $2.8*10^{-8}$ to $1.5*10^{-3}$). Following adjustment for excess censoring using the mTTF the median HR was 0.68 (IQR, 0.52 to 0.84) and the median p-value was $4.2*10^{-3}$ (IQR, $2.5*10^{-6}$ to 0.12). Across all trials, 35 (34.6%) lost statistical significance using the mTTF.

Conclusions: We introduce mTFF as a practical clinical endpoint that is less conservative than the TTF and is sensitive to excessive censoring in the intervention group. Our findings suggest that some studies are associated with an excessive drop-out rate favouring the intervention group that may lead to a false conclusion regarding the efficacy of FDA-approved treatments. Meaningful shared decision-making requires careful consideration of informative censoring.

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Table: 1708P

Year	No. of indications							
	Dose-expansion/ phase II	Global confirmatory studies	Synchronous global studies	Bridging studies	China-dominant confirmatory studies	China-dominant studies	Exemption of clinical studies in China	Total
2015	0	1	1	1	0	1	0	1
2017	1	2	3	3	2	5	1	7
2018	0	5	5	5	2	6	0	10
2019	2	5	7	5	3	8	4	18
2020	0	9	9	4	1	5	5	19
2021	0	8	8	4	2	6	4	17
2022	1	5	6	4	0	4	1	11
Total (%)	4(4.8%)	35(42.2%)	39(47.0%)	26(31.3%)	10(12.0%)	35(42.2%)	15(18.1%)	83(100.0%)
Median days between China and global approval	1399	365	371	1230	2082	1326	2064	1045

1710P Protocol waivers and consequences on treatment safety and efficacy in the Drug Rediscovery Protocol (DRUP)

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Background: Although eligibility criteria are an essential component of clinical trial design, overly restrictive criteria contribute to low accrual and poor generalizability of study results. To make trials more inclusive, there has been an increasing interest in broadening eligibility criteria, but how this affects patient safety remains unclear. In the Drug Rediscovery Protocol (DRUP, NCT02925234), protocol exceptions that were granted by the study team, taking into account the balance of potential benefits and risks, were analyzed. Here we describe the impact of these protocol waivers on patient safety and treatment efficacy.

Methods: DRUP is a Dutch multicentred, non-randomized, pan-cancer platform trial in which treatment-refractory patients are treated with targeted- and immunotherapies outside their registered indications, based on their tumor molecular profile. We collected data of all included patients for whom a waiver was granted and analyzed them in terms of treatment safety and efficacy. Also, safety and efficacy outcomes of these patients were compared to those of patients that did not need a waiver to participate.

Results: Between September 1, 2016, and September 1, 2021, 1019 patients were included in DRUP. In total, 88 protocol waivers were granted for 82 patients (8%). Most waivers were granted for general- or drug-related eligibility criteria (44%). For 32 of 82 patients that received a waiver (39%), 49 SAEs regardless of relationship to study treatment, were reported. For the included patients without a waiver (n=937), 666 SAEs were reported in 385 patients (41%, $p = 0.81$). The clinical benefit rate (CBR; either objective response or stable disease (SD) $\geq$ 16 weeks) of patients for whom a waiver was granted was 40% (14 patients (17%) with a partial response and 19 (23%) with SD $\geq$ 16 weeks), compared to a CBR of 33% in the non-waiver population ($p = 0.43$).

Conclusions: Safety and clinical benefit were preserved in patients for whom a waiver was granted in DRUP. Our data advocate omittance of 'old' unnecessarily strict safety criteria when setting up molecularly driven trials and support a more personalized approach in assessing eligibility criteria, especially in trials with therapeutic intent for patients without other treatment options.

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1711P The DRUP-like clinical trials family: A distributed European trial network for equitable access to precision medicine

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Background: While the promise of personalised cancer medicine (PCM) is clear, implementation remains challenging. In the European Union (EU), healthcare systems fall under national responsibility and differ greatly in structure, financing and capacity. Furthermore, EU countries are predominantly small, limiting generated evidence from national trials. The family of DRUP-like clinical trials (DLCTs) addresses this challenge: as a bottom—up, clinician-initiated initiative, DLCTs share the pragmatic core clinical trial design of the original Drug Rediscovery Protocol (DRUP), anchored into national context and financed independently. The result is a distributed DLCT network that addresses local priorities while collaborating internationally for scale and impact.

Methods: In 2022, the DLCT community successfully applied for two projects funded by the EU that will expand the network by supporting investigators to establish national DLCTs in additional countries. At the same time, the projects will build shared cross-DLCT capacity in molecular diagnostics and education (PCM4EU) as well as cross-trial data analytics, initiate shared cohorts and provide Health Technology Assessments (HTA) (based on the EUnetHTA core model) and Health Economic Evaluations (PRIME-ROSE). To ensure successful implementation, the projects involve various national and European decision-makers as well as the cancer patient community.

Results: Our approach demonstrates the feasibility of a novel type of pragmatic clinical trial networks that rely on distributed rather than centralized leadership. This way ensures wide and equitable patient inclusion and building national capacity in PCM diagnostics and treatments. Further, the set-up of a shared core, but variable side modules, allows for parallel experimentation and fast implementation of successful findings by adding these to the common DRUP core model.

Conclusions: This Europe-wide PCM deployment will address key scientific and methodological questions to accelerate broad and equitable access to new and effective cancer treatments. The ongoing effort is leading to standardization and pragmatic consensus, thereby anticipating the benefits of the upcoming European Health Data Space.

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Helland: Financial Interests, Institutional, Advisory Board, Advisory boards: Jansen, Takeda, AstraZeneca, AbbVie, Roche, BMS, Pfizer, MSD, Bayer, Lilly,; Financial Interests, Institutional, Invited Speaker, talks at meetings: AstraZeneca, Roche, AbbVie, Pfizer; Financial Interests, Institutional, Coordinating PI, BMS provides drug to patients in an investigator initiated clinical trial: BMS; Financial Interests, Institutional, Coordinating PI, Ultimovacs provides drug and funds for investigator initiated clinical trial: Ultimovacs; Financial Interests, Institutional, Coordinating PI, AstraZeneca provides drug and funds for investigator initiated clinical trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, Roche provides drug and funds for investigator initiated clinical trial: Roche; Financial Interests, Institutional, Coordinating PI, Novartis provides drug and funds for clinical trial: Novartis; Financial Interests, Institutional, Coordinating PI, Eli Lilly provides drug and funds for clinical study: Eli Lilly; Financial Interests, Institutional, Coordinating PI, Incyte provides drug and funds for clinical study: Incyte; Financial Interests, Institutional, Coordinating PI, Illumina provides assays for patients in a clinical trial: Illumina; Non-Financial Interests, Other, Board member in the patient organisation until 2022. 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1712P Implementation of a molecular pre-screening program (MPP) in a network of public cancer centres for phase I clinical trial (Ph1-CT) candidates: The PREICO program

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Background: Next-generation sequencing (NGS) and molecular tumor boards (MTB) might optimize patient (pt) selection for Ph1-CT. Here we report the first-year results of the PREICO Program, a coordinated and histology-independent NGS MPP in a network of public cancer centres in Catalonia, Spain.

Methods: Multicentre retrospective study of adult pt with advanced solid tumors candidates for Ph1-CT but ineligible for standard practice NGS. Pt underwent a centralised in-house tumor NGS panel (Illumina TruSight Oncology 500) at 3 different Catalan Institute of Oncology (ICO) centres: Hospitalet, Badalona, Girona. Molecular results were weekly reviewed by an MTB and pt were offered treatment accordingly within Ph1-CT or Special Medication Situation (SMS) program if available. The aim of the study was to analyze clinical outcomes and MPP utility for access to molecularly targeted agents (MTA).

Results: From Feb2022 to Mar2023, 120 pt were included: NGS results were available in 112 (93.3%) pt, 5 (4.2%) pt had no quality sample and 3 (2.5%) pt died before the analysis. Median age was 62 y (34-78), 60 (53.5%) pt were female and 101 (90.2%) pt had ECOG $\leq$1. Most common tumor sites were central nervous system (14.3%), colorectal (CRC) (12.5%) and pancreatobiliary (9.8%). Sixty-four (57.1%) pt had received $\geq$2 prior lines and 57 (50.9%) pt had no alternative standard of care. On average, 13 MTA Ph1-CT were recruiting per month during study period. After NGS results, 73 (65.2%) pt were not eligible for any Ph1-CT, while 12 (10.7%) pt harbored alterations eligible for at least one MT Ph1-CT. Nine (8%) pt received MTA based on actionable alterations: 7 within Ph1-CT (3 RAS/RAFwt, 2 KRAS G12Cmut, 1 ARID1A-mut, 1 METmut) and 2 within SMS program (MSI-H glioblastoma, HER2-amplified CRC). ORR and median PFS/OS for these pt were 33.3% and 2.8 (.7-5.4)/5.1 (1.9-7.9) months, respectively. According to prior therapy ($\leq$2 vs $\geq$3 prior lines), 3 and 6 pt received MTA, respectively.

Conclusions: Our results suggest that implementation of a coordinated MPP within a public network of cancer centres helps to identify potentially actionable alterations and increases the chances of receiving personalised therapies in a wide range of cancer types.

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1713P Non-inferiority oncology clinical trials in major journals: Purposes, methods and results

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Background: Non-inferiority (N-I) trials in oncology aim to prove that an experimental intervention is not significantly worse than a reference treatment, while offering other advantages. Clear explanation of the trial design and chosen margins is crucial.

Methods: We searched in leading oncology and general medical journals (Annals of Oncology, Journal of Clinical Oncology, JAMA, JAMA Oncology, Lancet, Lancet Oncology and New England Journal of Medicine) for N-I randomized clinical trials on solid tumours. We included phase II/III trials published in the last five years (since April/2018) and analyzed the primary N-I endpoint, margin of N-I, reasons for the margin, results and funding.

Results: The search yielded 637 articles, 367 were excluded after title/abstract screening, 190 after full-text screening, resulting in 80 analyzed articles (44 on cancer drugs, 19 radiotherapy, 11 surgery, 5 diagnostics, 1 follow-up). N-I design reasons: less intense drug treatment (22), less intense or hypofractionated radiotherapy (n17), less aggressive or no surgery (16) and less toxic/more convenient drug schedules (16). The primary sites were breast cancer (28), head/neck and gastric cancers (9 each) and

colon (7). Main scenarios: neo/adjuvant protocols (32) curative (20) and first-line (17). Most common primary endpoints: recurrence/disease free survival (25), progression free survival (21) and overall survival (17). 25 received support from for-profit organizations, mainly drug trials from pharmaceutical industries (18/25). Most primary outcomes were within the non-inferiority margin (60), however 27 (33%) did not explicitly state the reasons for choosing such margin. Median N-I margin for time-to-event outcomes was 1.27 (95% CI 1.2−1.32; hazard ratio), while for binary outcomes, it was 8% (95% CI 5.4%−10%). No significant differences were observed between the results (positive or negative) or the chosen margin according to funding or type of trial (drug or not).

Conclusions: Most oncology N-I clinical trials reported in major medical journals are about less intense, less toxic or more convenient drug schedules and are positive. A considerable part is funded by pharmaceutical industries and another sizable part lacks reporting the reasons for the chosen margin.

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1714P Geographical disparities in access to cancer clinical trials in Korea

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Background: Ensuring equal opportunity to participate in clinical trials is important. We analyzed the effectiveness of efforts to ensure geographically equal access to cancer clinical trials in Korea.

Methods: Clinical trials registered between 2012 and 2023 in Korea were captured from the Ministry of Food and Drug Safety database. To measure geographic disparity, we calculated the ratio of clinical trials conducted in local areas compared to those conducted in metropolitan areas and called it the trial geographical disparity index (TGDI). Regression analysis was used to analyze the annual trend of the TGDI.

Results: From 191 hospitals, 9424 cancer clinical trials were identified. The mean TGDI was 46%, indicating that cancer patients living in local areas can only access 46% of cancer clinical trials available to patients living in metropolitan areas. The disparities did not increase or decrease over 12 years. The situation varies among cancer sites, however. There was an improvement in the geographical disparity in lung cancer ($p = 0.019$), whereas a deterioration existed in pancreatic and prostate cancer ($p = 0.035$ and 0.016, respectively). Additionally, TGDI has worsened in clinical trials for domestically developed drugs (R-squared 0.58). In contrast, it has significantly improved for trials initiated by global pharmaceutical companies (R-squared 0.61), especially in lung and breast cancer ($p = 0.016$ and 0.005).

Conclusions: Although geographical disparities in access to cancer clinical trials seem to have been fixed in Korea, our data suggest that sponsor-initiated phase II/III trials conducted by global pharmaceutical companies may have a significant role in lowering the geographical barrier and ensuring equal access.

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1715P Analysis of the adequacy of control arms in oncology randomized clinical trials published between 2017 and 2021: A meta-research study

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Background: Randomized controlled trials (RCTs) are usually considered the highest level of evidence for clinical practice. Patients assigned to control arm in RCTs should always receive the best available treatments to protect participants while also allowing for proper interpretation and applicability of study results. Here we analyzed RCTs published in oncology between 2017 and 2021, to describe the frequency of suboptimal control arms.

Methods: We identified phase III studies testing active treatments in patients with solid tumors among 11 major oncology journals. Each control arm was analyzed, and the standard of care was determined according to international guidelines and scientific evidence at accrual beginning and until accrual completion. We identified studies with suboptimal control arm from the beginning (type 1) and studies with an initially optimal control arm which became outdated during the accrual period (type 2).

Results: This analysis included 387 studies. 43 (11.1%) control arms were judged as suboptimal: 24 (6.2%) type 1 and 19 (4.9%) type 2. Suboptimality rates were higher in industry-sponsored compared to academic trials: 9.3% vs 1.9% for type 1 ($p=0.003$); 7.9% vs 0.6% for type 2 ($p= 0.001$). Suboptimality rates were higher in studies with positive results: 8.1% vs 4.0% for type 1 ($p=0.09$); 7.6% vs 1.7% for type 2 ($p=0.007$).

Conclusions: A non-negligible percentage of control arms, even in journals with high impact factor, was suboptimal according to our criteria. Many patients were treated with suboptimal control treatments in those trials, and the interpretation and applicability of study results can be challenging.

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1716P Addressing clinical trial disparities in Spain: A digital solution

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Background: In Spain, many eligible patients do not participate in clinical trials (CT) due to the lack of reliable information about trial availability. Trialing, created in 2021, is an artificial intelligence-based CT search engine that enables oncologists to directly refer their patients to available trial sites.

Methods: We analyzed aggregate data in Trialing, including information from public registries of CT (clinicaltrials.gov, reec.aemps.es), public data from the Spanish Ministry of Health, and data from the Trialing platform itself.

Results: Of the 561 Spanish oncology centers, 23% (131) offer CT. Of these, 69% centers offer <20 CT (small), 21% between 21 and 75 CT (medium), 8% between 76 and 150 CT (large), and 2% >150 CT (giant). Through Trialing: (i) all large and giant centers receive referral requests, 75% of medium centers and 27% of small centers; (ii) oncologists from 55% of small centers, 80% of medium centers, 83% of large centers and 60% of giant centers request referrals. We found that only two of the 17 administrative regions in Spain account for more than 50% of available CT, while most communities have no more than 10% of the CT available in Spain. The pathology for which there are most CT is non-small cell lung cancer, followed by breast cancer and colorectal cancer (28%, 16% and 12% of the total number of clinical trials,

respectively). More than 2,500 CT searches are performed each month on the Trialing platform, and the pathology for which most referrals are requested through Trialing is lung cancer, followed by breast and colorectal cancer.

Conclusions: Our findings show that the distribution of CT in Spain is highly concentrated, with only certain regions offering a significant number of trials. Trialing provides real-time information on CT availability, referral patterns, and potential solutions to increase patient access to CT and improve treatment equity. The acceptance of Trialing in the Spanish oncology community suggests that it can be replicated in other countries with similar challenges.

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1717P Management of patients during a digital healthcare record system transition: A phase I unit experience

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Background: Digitalisation of healthcare delivery enhances security, efficiency, and cost-effectiveness. The challenges of transitioning to a modern electronic healthcare system with multiple workflows remain poorly described, especially for early phase trial units. We present our recommendations for digital healthcare transition based on our experiences and outcomes. The Royal Marsden (RM) and Institute of Cancer Research (ICR) Drug Development Unit (DDU) is one of the largest early phase centres in Europe, enrolling ∼300 patients across >60 trials per year, with a dedicated ward, day unit and outpatient clinic.

Methods: In March 2023, RM transitioned to a new healthcare system. DDU adopted a patient centric approach, as per table, with emphasis on safe treatment delivery for patients within the dose-limiting toxicity (DLT) period.

Results: All planned trial activities were completed during weeks 1-4; though late IMP dosing up to 21:00 were experienced. Over these weeks, 36 patients were treated within the DLT period, and no safety issues raised. Adaptation pace among staff varied, with reports of fatigue from learning new workflows, improving from Week 4. From Week 5, the number of attendances returned to pre-transition levels.

Table: 1717P Planning aims

a) Virtual walk-through trial pathways from referral to discharge b) Patient visits planning and forecast for first 4 weeks. For Week 1, targeted reduction in planned patient attendance by 10% with no patients starting on trial and on-site attendance is prioritised for those within DLT period. c) Staff training < 8 weeks in advance and absences minimised during the transition period d) Managing expectations of patients, staff, and partners e) Daily team meetings to feedback and escalate issues

Conclusions: Major digital transformation projects can be undertaken safely within a phase I trial setting whilst maintaining service delivery, with investments in implementation beyond the technology itself. Staff digital literacy assessments, training, pathway walkthrough, interface familiarisation, managing staff morale are critical for managing such transitions. Extensive planning and focus on the end users are vital in ensuring both short-term delivery and long-term benefits of digital transformation.

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1718P Impact of the economic status of the patient's country of residence on the outcome of oncology clinical trials

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Background: Prolongation of overall survival (OS) is commonly evaluated as a primary endpoint in confirmative oncology clinical trials; however, it is potentially affected by the healthcare environment, which often varies from country to country. We compared progression-free survival (PFS) and OS between the Organisation for Economic Co-operation and Development (OECD) and non-OECD countries. We also investigated the causes of the survival difference.

Methods: Individual patient data from industry-sponsored multi-regional phase III oncology trials were obtained from the Project Data Sphere. Cox regression analysis was conducted to estimate the hazard ratio (HR) for PFS and OS between the different subgroups such as race and country in each trial, and summary HR was estimated. Patients' demographic data such as performance status (PS) and ratio of the elderly were compared between the subgroups by calculating the odds ratio. The incidence of serious adverse events (SAEs) was calculated by the subgroups, and median survival time in patients with SAEs was estimated using the Kaplan-Meier method. The rate of post treatment in each subgroup was calculated.

Results: Eleven arms from 10 clinical trials were eligible for the analysis. No statistically significant difference was observed in PFS and OS between races. A prolongation of OS was observed in patients enrolled in the OECD, while no statistically significant difference was observed in PFS. Patients enrolled in the OECD were older and showed favorable PS. Although incidence of SAEs was higher in the OECD, the median PFS and OS in patients with SAEs were longer in the OECD. The rate of post treatment was higher in the OECD.

Conclusions: The economic status and healthcare environment of countries where patients were enrolled had an impact on the outcome of OS. Differences were observed in patients' demographic data such as PS and age as well as in the management of SAEs depending on the patients' country of residence. Clinical trial sponsors are recommended to consider carefully how to design and conduct oncology clinical trials including the selection of countries, provision of appropriate AE management guidelines and related training, and data management of subsequent treatments.

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1719P Decentralized clinical trials: Is there a space in Italy?

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Background: The need to identify appropriate formulae to decentralize the clinical trials (DCTs) and enabling their implementation outside hospitals became a dramatic priority during COVID-19 pandemic. However, many obscure points remain concerning DCTs, starting from the regulatory definition.

Methods: In June 22, Life Science Innovation shared an anonymous online survey with the Italian Group of Data Manager to investigate how DCTs' elements were widespread in Italian clinical research centers. The final survey was structured with 14 questions and remained open for 15 days.

Results: The survey was completed by 35 study coordinators, mostly (54.3%, n=19) from public hospitals, with a median work experience of 8 years. Just over half (48.6%, n=17) declared they could count on Electronic Medical Records, while Electronic Case Report Forms were widely (74.2%, n=26) used. Only in 2 cases (5.7%) these tools are integrated. Over 60% of respondents (n=22) declared no experience in conducting DCTs but the vast majority (72.7%, n=16) expressed interest for the future. The lack of interest is mainly (50%) due to the need of specific skills. Analyzing the answers on the specific digital solutions (n=24, multiple answers option), the most used ones, regardless of the pandemic emergency, are devices (eg sensors) for remote parameter collection (60%), tools for collecting patients' data like apps for monitoring the therapeutic adherence (60%) and for delivering Electronic Patient Reported Outcomes (60%). More than half of the respondents (60%) declare a future interest in the remote informed consent process. On a 1-10 scale (strongly disagree - strongly agree), DCTs are considered not fully useful to increase patient adherence (mean score 6.6) or to reduce research time (5.8) and costs (5.9). Even lower (5.5) the suggestion that DCTs could increase patient involvement. There is a convergent thinking that DCTs can increase the amount of Real-world data collected (7.5) and that they require very specific skills (8) as well as address key data privacy and security (8) issues.

Conclusions: Despite the pandemic experience, the interest in a greater diffusion of studies with a partial or total digital component remains limited and crucial aspects should be addressed regarding Italy's ability to implement DCTs in short run.

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1720P Experience in the provision of oncology services immediately after a major disaster

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Background: On February 6, 2023, an earthquake occurred in Turkey that affected 11 provinces, many hospitals and millions of people. In Hatay, one of the provinces most affected by the earthquake, all 4 oncology centers in were partially or completely destroyed. So, a new unit was established in Dörtyol District Hospital, one of the few standing hospitals. On February 27, 2023, the first oncologist was assigned to the new oncology unit in Dörtyol Hospital. On 01 March 2023, the oncology outpatient clinic started to work and with the arrival of drugs, the first intravenous systemic anticancer treatment was administered on 03 March 2023. The aim of this abstract is to share our experience on how oncology services continue in the event of a major disaster.

Methods: In this abstract, the attempts made to provide oncology services after the earthquake in Hatay and the results of the first 100 patients followed in the new facility are summarized. The patients followed at the oncology outpatient clinic had their age, gender, primary diagnosis, and causes for admission retrospectively analysed.

Results: Between 01 and 10 March 2023, 100 patients applied to the oncology unit. A total of 62 of the patients were women. The median age of the group was 54. The most common diagnosis was breast cancer (N=46), followed by GIS (N=17) and lung (N=14) malignancies. The numbers of local, locoregional and metastatic diseases were 20, 33 and 47, respectively. Most common admission purpose was routine follow up (N=38), followed by scheduled systemic therapy (N=34). A total of 38 patients received systemic therapy while 9 had hormonotherapy and 3 had palliative treatment. Respectively, 5 patients were referred to different cities for PET scan, 3 patients for radiotherapy, and 7 patients due to the absence of drugs in the hospital.

Conclusions: Oncology is not a suitable field to delay or cancel active or palliative treatments. For this reason, it is inevitable to continue oncological services under all conditions, as has been seen in the recent COVID pandemic. On the other hand, due to the treatments applied, oncology centers have to meet some basic requirements in terms of infrastructure and work force. As in the Hatay experience, it is vital to take quick actions and ensure coordination after a disaster.

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1721P Self-assessment tool and best-practice sharing to support hospitals in improving the quality of multi-disciplinary teams in lung cancer care

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Background: Regular meetings of multi-disciplinary teams (MDTs) constitute a key moment in the care pathway in lung cancer, where physicians discuss patient cases and decide on treatment plans. MDTs increase the volume of patients treated, improve diagnosis, and positively impact survival. However, the way MDTs are organized is variable across hospitals and countries. These variations may lead to suboptimal outcomes, reflected by inconsistencies on the numbers of patients treated with curative intent and variable 5-year survival rates. The importance of MDTs keeps increasing, as the therapeutical landscape becomes more complex and evolves towards personalization.

Methods: Here we share a self-developed MDT maturity model and support hospitals to self-assess the performance of their MDTs in six dimensions: access to the MDT, processes, technology, quality, culture and capabilities. Once performance is self-assessed, gaps in hospitals' current MDT practices are identified. The maturity model is accompanied by 40+ best practices covering each of the six key dimensions. This way identified gaps are matched to actionable best practices which can be implemented by hospitals.

Results: We have supported various hospitals to identify gaps in their current MDTs by leveraging this MDT maturity model and have used our identified best practices to address those gaps. Hospitals across Europe and Canada have this way been able to improve their MDTs along the model's six identified dimensions in a measurable way. This process has been led by a network of 20 hospitals where the 40+ best practices were identified and is resulting in improved MDTs across other hospitals in Europe and Canada.

Conclusions: As MDTs become a standard part of patient care, inter-hospital collaboration should become standard to provide a platform for improvement. This work shows that self-assessment tools, best-practice sharing, support from leading hospitals, and change management can help hospitals improve the way their MDTs are organized and managed, which ultimately benefits patients' lives. Optimization of MDTs should be a key part of a continuous improvement cycle for every hospital, and this work ultimately facilitates this process.

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1722P Factors contributing to differences in evidence compliance rate in cancer treatment among second opinion cases

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Background: Adherence to guidelines is linked to favorable prognosis in various cancer types. Nevertheless, the increasing complexity and sophistication of cancer drug therapy have posed challenges in identifying evidence-based treatment options. Thus, patients with cancer and local physicians are increasingly resorting to the cancer center's second opinion (SO) system for advice on treatment strategies. Integrating academic opinions from multiple physicians via SOs is expected to improve the evidence compliance rate (ECR). However, it remains unclear which cases would benefit from SOs to enhance the ECR. This study aimed to identify the factors contributing to the differences in ECR in patients with cancer.

Methods: A single-center retrospective study was conducted at the Department of Medical Oncology, National Cancer Center Hospital (Tokyo, Japan), analyzing electronic medical records of 305 patients with cancer who received SOs between January and June 2022. Two medical oncologists evaluated ECR according to the latest international standard guidelines for each cancer and classified them into two levels (Compliance: ECR is ≧50%, Non-compliance: ECR is <50%).

Results: Of 305 cases referred from 130 hospitals, 247 (81%) were female; the median age was 56 years (range: 15—85). Among them, 150 (49.2%)/152 (49.8%) were common/rare cancers, with 95 (31%) having gynecological cancers, 84 (28%) having breast cancers, and 66 (22%) having mesothelial and soft tissue cancers as major groups. After excluding cancer types for which no guidelines existed, 214 cases were eventually analyzed. Japan had a significantly higher ECR with designated core or designated hospitals for cancer genomic medicine (p=0.036). No significant relationship was found between ECR and hospital types, such as oncology, university, or urban hospitals. Moreover, no significant relationship was found between ECR and cancer types and who requested the SO.

Conclusions: This study highlights differences in ECR based on referral hospital type. The findings may aid in the appropriate allocation of medical resources between cancer centers and local hospitals as online medical care networks become more prevalent in the future.

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1723P Improving access to molecular tumour boards for complex genomic profiles: A healthcare policy from the Netherlands

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Background: The role of Molecular Tumour Boards (MTBs) is becoming increasingly important in the interpretation of complex genomic profiles; for instance, in pinpointing the most optimal (targetable) therapy for rare or uncommon variants or in situations when more than one actionable aberration is detected, in rejecting suboptimal treatment strategies and in finding matched clinical trials based on genomic insights. In general, only academic hospitals and large cancer research institutes can facilitate an in-house MTB, as expertise in medical oncology, pathology, molecular biology, genetics and bioinformatics is required. As a result, patients treated in general hospitals may have limited or delayed access to expert interpretation of complex molecular diagnostics and relevant therapeutic guidance. One of the major barriers is the absence of reimbursement for such remote consultations.

Methods: In the Netherlands, health insurance companies have created a specific payment code for MTBs to be able to reimburse the consultations directly and monitor access.

Results: Empowering MTBs enhances their potential to gain and disseminate knowledge in the highly dynamic field of precision medicine due to an increased number of consultations. Moreover, it stimulates development and maintenance of guidelines and further standardisation of the recommendations for more frequent aberrations based on the evidence and the outcomes.

Conclusions: From a national health perspective, it is essential to ensure access to MTB's recommendations, thereby providing equal treatment opportunities (including enrolment in clinical trials) but also reducing the unjustified costs and clinical burden of ineffective treatment strategies. Eventually, a national data infrastructure and an umbrella organisation of the MTBs will facilitate better and equal options for patients and creates a true learning health system for precision oncology.

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1724P Improving access to breast cancer diagnosis and treatment through navigation: Evaluation of a one-year pilot project in Botswana

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Background: In Botswana, 65% of breast cancers present at an advanced stage due to multifactorial delays. The WHO Global Breast Cancer Initiative recommends a maximum of 60 days of lead time in diagnostic workup and strongly advocates for the use of patient Navigation. A Patient Navigation Project was created to improve the timely diagnosis and treatment of breast cancer patients around Gaborone, the capital.

Methods: A 2-day theoretical and practical course was delivered in March 2022 to 15 clinical navigators (nurses from 6 district Hospitals and from the Referral Hospital) and 7 non-clinical navigators (advocacy groups). A navigation coordinator served as the point of contact, reported on program outcomes and provided smartphone airtime.

Different virtual communication groups were created with navigators to accelerate patient flow and facilitate problem solving.

Results: Between April 2022 and July 2023, 75 patients were included in the navigation program: 21 were in early stages (stages I and II) (28%) and 53 in advanced stages (stages 3 and 4) (71%). From those patients, 46% received neoadjuvant chemotherapy, 17% adjuvant chemotherapy and 25% palliative therapy. Navigation enabled faster access to CT-scan staging, unveiling more stage IV disease (23%), thus avoiding inappropriate curative treatments.

Table: 1724P Key navigation challenges and improvements

Key persistent challenges	Key improvements
Delays in biopsy (needle shortages)	Biopsies and staging done locally, avoiding referral delays for diagnostic workup
Delays in obtaining biopsy and IHC results (pathology backlogs, loss of sample, reagent shortages)	Fast referral pathway for patients in need of urgent consultation
Patient transport issues	Closer tracking of patients and tests results
Treatment delays: Stock-outs of drugs (hormone therapy, chemotherapy) and radiation therapy delays	Facilitated access to counselling and transport services
Time constraints: Limited time allocated to navigation	Increased multidisciplinary collaboration

Conclusions: The Botswana Breast Cancer Navigation project succeeded in implementing Cancer Navigation in accordance with international guidelines. It improved management of breast cancer patients through a smoother access to diagnosis and treatment, and it addressed barriers to care for specific situations. Many navigation sites referred patients with upfront biopsy diagnosis and minimal staging, and this reduced the time from first consultation in breast clinic to treatment (median delay 22 days). Dr Migeotte and Dr Soares de Pinho contributed equally to this work.

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1725P Genetic counselling for cancer in EU member states: Review and foundation for consensus recommendations

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Background: Somatic and germline genetic alterations are significant drivers of cancer development, with new technologies to profile these alterations a major asset for personalized diagnosis, prognosis, and therapy, as well as prevention. Effective integration of genomic medicine into cancer care requires high-quality genetic counselling to facilitate informed decision-making by patients and their families. However, timely delivery of genetic counselling is complex, with rapidly increasing usage of clinical genetic services necessitating alternative delivery and reimbursement strategies. Further, common standards are needed to ensure consistent quality across the EU. This project aims to survey genetic counselling legislation and practice across EU Member States to provide a foundation for consensus genetic counselling recommendations.

Methods: National legislation databases of all 27 Member States were searched using terms relevant to genetic counselling, translated as appropriate. Interviews with relevant experts (*medical geneticists/counsellors, oncologists*) from each EU Member State are being conducted to validate legislation search results and provide detailed insights into genetic counselling practice in each country.

Results: Genetic counselling is included in legislation as a mandatory component of clinical genetic services in 22/27 (81%) Member States. Legislation in 9/27 (33%) Member States prescribes the personnel, content, and timing of genetic counselling; legislation in 13/27 (48%) Member States generally mandates the inclusion of genetic counselling. Interviews reveal that current clinical workflows consistently lead to suboptimal patient waiting times across Member States, driven by limited availability of genetics expertise. Specialized genetic counsellors and cooperative interdisciplinary approaches are sparsely utilized.

Conclusions: The inclusion of genetic counselling in legislation of most EU Member States underscores its importance. Forthcoming consensus recommendations will aim to propose strategies to ensure this importance is reflected by sustainable EU-wide integration of high-quality genetic counselling into cancer care.

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1726P Optimizing oncology drug spending in a cancer centre in Ireland

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Background: The rising costs of innovative oncology agents is a global challenge. In Ireland, despite rising per capita spending, access to new agents is delayed compared to other European states. A strategy to optimise existing drug spending nationally in not in place. We aimed to review how existing prescribing in a cancer centre could be optimised to accelerate access to new agents.

Methods: We performed a retrospective review of expanded access programmes (EAPs, 2011-21, 3 hospitals) and biosimilar use (2020-22, 4 hospitals) within the southwest of Ireland, and a review of clinical trial availability nationally (2022). We surveyed oncology patients receiving treatment in 3 centres, and healthcare professionals (HPCs) nationally on their view on barriers to biosimilar integration (survey 1, 2020-22) and other potential mechanisms of cost optimisation (survey 2, 2023).

Results: Our review found 193 patients accessed EAPs over 10 years (33 agents, 50 indications & 189 programmes). No national database to ensure equity of access was in place; an increasing trend of availability over time was noted. Immune checkpoint inhibitors (55%); targeted therapies (35%) and antibody drug conjugates (6%) were available through EAPs, treating lung (28%), breast (17%) and ovarian (9%) cancers. Of the 287 patients accrued to clinical trials in 2022, 48% participated in immunotherapy trials. Biosimilar use of trastuzumab and rituximab ranged from 39-100%, and 0-89% respectively among 4 hospitals. Cost savings by using biosimilars compared with reference products ranged from 28% to 73%.

Table: 1726P Results of surveys on (1) barriers to biosimilar use & (2) other methods of optimisation

Survey 1	Patients (n=16)	Pharmacists (n=205) & students (n=33)	Doctors (n=11) & students (n=64)
Biosimilar awareness	37% (n=61) †	97% (n=231) †	45% (n=34) †
Agreeableness to biosimilar switching	85% (n=141)	N/A	N/A
Support pharmacist-led biosimilar substitution	N/A	37% (n=87) †	9% (n=7) †
Support consistent nomenclature of biosimilars	N/A	84% (n=200)	80% (n=60)
Survey 2	Patients (n=53)	HPCs (n=60)	
Support split fill dispensing initially	82% (n=42)	75% (n=45)	
Support split fill dispensing long term	60% (n=28)†	30% (n=18)†	
Support redispensing unused oral agents	29% (n=14)*	22% (n=13)*	

*$p<0.05$, † $p<0.01$

Conclusions: Multiple disparate mechanisms are in place to optimise drug costs. We found biosimilar use and split fill dispensing was acceptable to both patients and HCPs but the majority of HCPs do not approve of pill sharing. Additional optimisation could occur through prioritisation of biosimilar substitution and education of prescribers on their benefits, a national registry of EAPs, expansion of clinical trial portfolios, and modified drug dispensing.

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1727P Barriers and facilitators of physician involvement in clinical oncology database management in Ukraine

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Background: Oncology databases/cancer registries can help facilitate quality cancer care and novel research. Their maintenance remains challenging in low and middle-income countries (LMICs). We explored barriers and facilitators of oncology database maintenance in Ukraine.

Methods: We conducted semi-structured interviews with a purposeful sample of oncology physicians at the Ukraine National Cancer Institute (NCI) to explore barriers and facilitators of oncology database data entry and use. Interviews were audio-recorded, transcribed, and analyzed via hybrid analysis.

Results: 13 physicians were interviewed, including 6 (46%) junior and 7 (54%) senior NCI faculty. All were aware of local or international oncology databases. 10 (77%) entered patient data into them, including 7 (54%) to international and 8 (62%) to local databases. 6 (69%) thought that most of their oncology colleagues in Ukraine are not aware of the existence or value of cancer databases. The following themes have been identified: perceived benefits of cancer databases included improving patient care, research, standardizing clinical practice, care monitoring, and quality improvement. Obstacles of data entry included: time required, low quality of medical documentation, complex online interface. Some thought that physicians should be responsible for data entry, while others thought it should be done by nonmedical providers. Facilitators of data entry included appointing a physician leader to oversee quality and engagement, direct direction from supervisor, use for research publication or as part of a project of personal interest, monetary compensation, collaborating with colleagues abroad, data entry training.

Conclusions: Factors affecting data entry into and use of local and international cancer databases by oncology physicians in Ukraine included perceived benefits for career and patient care, required time, requirements from leadership, database technology characteristics. Given limited resources for local and population-based cancer registry maintenance in Ukraine and other LMICs, novel low-cost strategies for this are urgently needed.

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1728P Implementation of a comprehensive oncology unit: Needs detected in cancer survivors during follow-up

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Background: The prevalence of oncology survivors is increasing exponentially. More than half of them experience difficulty in returning to their pre-disease socio-familial role. Comprehensive Oncology Units are infrequent in our environment. In our center we have implemented this novel Unit in order to improve the quality of life of our cancer survivors during follow-up.

Methods: Prospective quasi-experimental study. From March 2022 to March 2023. A total of 232 patients were included in the Comprehensive Oncology Unit of the Juan Ramón Jiménez Hospital in Huelva. The aim of our study is to describe the psycho-social, nutritional and physical needs of cancer survivors during follow-up and the impact of the intervention on their quality of life.

Results: The median age of the patients was 53 years (33 - 78). Ninety-six percent were women. Ninety percent had been diagnosed with breast cancer, followed by 6 % CRC, 2 % other digestive tumors and 2 % gynecological tumors. 67.1% required assessment for nutrition, 62.9% for rehabilitation, 59.28% for psycho-oncology and 4.8% for social intervention. Of the patients who were evaluated by psycho-oncology, 50% improved their fear of recurrence with only 3 sessions. Regarding nutrition assessment, the median BMI in the population with BMI $>$ 25kg/m2 was 30.7 Kg/m2 at baseline and 29.71 Kg/m2 (22.7 - 40) 6 months after nutrition intervention ($p<0.001$).

Conclusions: The results of our study reveal that there is a high demand of needs to be covered in cancer survivors beyond the purely clinical aspects that impact on their quality of life. Implementing a Comprehensive Oncology Unit could help to detect these needs and improve their healthy lifestyle habits as well as improve their quality of life.

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1729P Targeted interventions in registration and reporting of multidisciplinary team meetings (MDT) in oncology help to improve tumor board decisions

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Background: MDTs are a central institution of decision making in oncological centres. Good recommendations are comprehensible, follow guidelines, are consistent to following treatment and responsibility for this case must be made explicit. In order to constantly improve our performance, we examined key factors influencing MDT recommendations. After this analysis, structural intervention was performed to exclude the main factors influencing our performance negatively. Here we report the outcomes and results of this intervention.

Methods: After examining our MDT performance retrospectively in 488 tumor board decisions, we changed the registration process, including definition of required input for aspects of patient history and the protocol of our MDT for GI cancers. We also made sure that personal responsibility was provided for case presentation as well as for further action. Analysis of MDT recommendation after this intervention was performed using the same questionnaire as in the first analysis prospectively in 488 tumor board presentations and decisions of the complete following year. We correlated input-factors of MDT registration to output-factors defining reasonable MDT recommendations. Simple comparison was performed using chi-square testing between individual factors, group of factors and outcome variables.

Results: Following our intervention, we measured significant increase of all factors considered to be most influential for good recommendations (Table).

Table: 1729P

Input factor	Before (%)	After (%)	p-value
Presence of core team members	54,7	62,8	$<$ .0001
Clear indications of patient wishes	85,96	96,93	$<$ .0001
Complete case information	80,12	89,55	$<$ .0001
Information of thorough discussion	5,7	17,2	.095
Good recommendations	65,16	84,63	$<$ .0001

Conclusions: Oncological treatment is often based on MDT recommendations. Therefore, high quality of MDT must be ensured, transparency and understandability of the protocol must be clear and responsibility for further action needs to be addressed. We hereby demonstrate that changing infrastructural factors in registration and protocol of recommendations lead to improved tumor board decisions.

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1730P Dealing with digital paralysis: Surviving a cyberattack in a cancer centre

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Background: A constellation of a large attack surface of interconnected devices and cyberimmaturity renders healthcare ripe to cybercrime. These vulnerabilities and their consequences will be magnified by the exponential growth in artificial intelligence. We assess the impact and implications of a cyberattack on a national cancer centre.

Methods: On 14 May 2021 (day 0), the first national healthcare ransomware attack occurred within which all hospitals including Cork University Hospital (CUH) Cancer Centre was implicated. Contingency plans were only present in laboratory services who had previously experience information technology (IT) failures. Departmental handwritten logs of activity and responses for 700 days after the attack were reviewed.

Results: Following the attack, all IT systems were shut down. No hospital cyberattack emergency plan was in place. Within CUH, on day 0, all radiotherapy (RT) treatment stopped, outpatient activity fell by 50%, and elective surgery stopped. Haematology, biochemistry and radiology capacity fell by 90% (daily sample deficit (DSD) 2700 samples), 75% (DSD 2,250 samples), and 90% (100% mammography/PETscan) respectively. Histopathology reporting times doubled (7 to 15 days). or paused IT links. Outsourcing of radiology and radiotherapy (RT) commenced, alternative communication networks (e.g., proton mail; Siilo) were utilised and national conference calls for RT and clinical trials were established. 136 patients had interrupted RT: median gap day 6 days category 1, 10 days for remaining patients. By day 28, e-mail communication was restored. By day 210, reporting and data storage backlogs were cleared and over 2000 computers were checked/replaced by the Irish Army. Notification of patients and staff whose data was compromised is ongoing (day 720).

Conclusions: Cyberattacks have rapid, profound and protracted impacts. While laboratory and diagnostic deficits were readily quantified, the impact of disrupted/delayed care on patient outcomes is less readily quantifiable but likely to be much greater. As criminals and nation states weaponize the internet, cyberawareness and cyberattack plans need to be embedded in healthcare.

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1731P Providing access to anticancer drugs within an armed conflict: The experience of Mission Kharkiv (MK) and Medecins Sans Frontieres (MSF) in Ukraine

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Background: Since the outbreak of the Russian Federation invasion, the border city of Kharkiv has come under bombardments leading to disruptions of the medical supply chain. Mission Kharkiv (MK) is a non-governmental organization (NGO) created in 2022 by Ukrainian volunteers to organize a consistent supply of chronic medications, especially anticancer drugs, in the area of Kharkiv.

Methods: A partnership was created between MK and MSF in June 2022. MSF decided a donation of 12 anticancer drugs, all registered on the World Health Organization list of essential medicines. The supplies were dispensed to MK by MSF teams in Ukraine. MK was in charge of the storage and the distribution of the drugs to patients meeting eligibility criteria determined with Ukrainian oncologists. Digital database was created to allow traceability of every medication from its donation to its dispensation.

Results: From October 2022 to April 2023, platinum compounds, taxanes, fluorouracil, trastuzumab, doxorubicin and hormone therapies were given to MK. Drugs were stocked in a warehouse unit equipped with cold chain facilities. 749 patients met eligibility criteria and were registered on the database to receive a whole course of treatment prescribed by Ukrainian oncologists. >99% of patients were ECOG 0-2. The largest types of cancers were digestive cancers (200 patients with gastrointestinal cancer, 21 with pancreatic cancer and 2 with biliary tract cancer representing 29.7% of all patients), breast cancers (206 women — 27.5%), gynaecologic cancers (151 women — 20.2%) followed by lung cancers (49 patients — 6.5%), hematologic malignancies (44 patients — 5.7%) and head and neck cancers (44 patients — 5.4%). Disease stage was reported in 723 patients. 32% were diagnosed with stage I-II, 33% with stage III and 35% with stage IV. Included patients received an average of 4.5 cycles of chemotherapy.

Conclusions: This model of humanitarian cancer medication release, coupled with cooperation between NGOs and a high level of digital traceability, has proven to be efficient. This approach could be scaled up in the future, enabling more cancer patients suffering from the consequences of war to benefit from this humanitarian program.

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1732P War and the fragility of anticancer drug supply networks in Ukraine

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Background: Systemic therapy availability in Ukraine is fluid due to the war. This information is key to optimizing cancer care.

Methods: Online surveys assessing cancer treatment capacity were distributed to physicians in Ukraine through cancer-focused social media in April 2023. Results were analyzed with descriptive statistics and Fisher's exact test.

Results: 15 oncologists from 14 oncology centers and 12 hematologists from 9 hematology centers completed surveys, including 3 (25%) and 4 (27%), respectively, from the more war-affected Northern, Southern, and Eastern Ukraine. Of the 36 drugs used for solid tumors, limited availability (half of the time, rarely available, or unavailable) was reported for 11 (31%) drugs by 2-4 (14-29%) respondents: cisplatin, cyclophosphamide, doxorubicin, etoposide, fluorouracil, ifosfamide, methotrexate, vincristine, filgrastim, dexamethasone, tamoxifen. 7 (19%) had limited availability per 5-6 (36-42%): capecitabine, irinotecan, mesna, anastrozole, leuprolide, zoledronic acid, erlotinib. 12 (33%) drugs were limited per 7-8 (50-57%): abiraterone, bleomycin, carboplatin, docetaxel, gemcitabine, oxaliplatin, paclitaxel, vinblastine, vinorelbine, folinic acid, bicalutamide, trastuzumab. 7 (19%) were limited per 8-13 (57%-93%): nivolumab, diethylstilbestrol, bevacizumab, palbociclib, trastuzumab emtansine, sorafenib. Of 31 drugs used for hematologic malignancies, 4 (21%) were limited in availability per 2-4 respondents: vincristine, bortezomib, imatinib, azacitidine. 5 (16%) were limited per 5-6: bendamustine, filgrastim, doxorubicin, lenalidomide, hydroxycarbamide. 10 (32%) were reported to be limited by 7-8: rituximab, thalidomide, vinblastine, chlorambucil, bleomycin, methotrexate, daunorubicin, nilotinib. 10 (32%) were limited per 9-12: ibrutinib, mercaptopurine, eltrombopag, erythropoietin, thrombopoietin, ruxolitinib, venetoclax, brentuximab, gemtuzumab, obinutuzumab. Drug availability did not differ by country region ($p > 0.05$).

Conclusions: Shortages of essential anticancer drugs are a continued challenge in Ukraine during the war. Results are limited by small sample size and limited sampling from regions affected by active hostilities.

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1733P Two wars at time: Fight against cancer during war time - experience of Ukraine

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Background: On 24th of February 2022 reality in Ukraine changed. Ukraine became a victim of unfair attack of the neighbouring county. It influenced civilian population hugely, including the most vulnerable - children, elderly and patients. Since then, cancer patients became fighters of two fights - malignant disease and external aggressor. After more than a year of this reality Ukrainian oncologists would like to remind international society that the problem is not solved, and Ukrainians desperately need support.

Methods: It is generalized description of situation in the sphere of oncology in Ukraine since 24th of February 2022.

Results: According to Ukraine's Minister of Health, Victor Lyashko, during the first year of the war in Ukraine 1218 hospitals were damaged, 540 - partially destroyed and 173 destroyed completely. Among them - oncological hospitals. More than a million (∼1.2) Ukrainians currently stay on temporary occupied territories of the country and do not have access to qualified medical care. Around 7 million people had to move to safer areas of the country to stay safe and thousands of cancer patients had to move abroad for further treatment. It influenced the oncological landscape significantly. Oncological centers currently have to deal with 70% more patients than before the war. Moreover, the quantity of advanced stage disease has risen dramatically because a lot of people just couldn't get medical help in time. Therefore, it caused bigger pressure on the medical system, requiring even more resources when they are so limited. At the same time, all clinical trials were put on pause leaving patients with advanced and rare diseases with no options for further treatment. Luckily, international society is extremely friendly to Ukraine providing Ukrainians with shelters and supplies, both material and intellectual. It helped and is helping a lot. But unfortunately, war is not over, and help is still needed.

Conclusions: The aim of the work is to show how things were going during this year of war and how they are actually going now for word to realize that even during the hardest time there is a place for high quality medical care. That only became possible thanks to huge support of international society, but there is still a lot to do to rebuild and improve reality that was destroyed on 24th of February.

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1734P Early impact of a personalized lung cancer interception program for heavy smokers

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Background: Screening for lung cancer (LC) with Low-Dose Chest Computed Tomography (LDCT) reduces LC specific mortality. Interception-Lung is a French, soon to be nationally deployed, community-hospital and digital-physical personalized pilot LC screening and prevention program with an ultimate objective of reducing the incidence of advanced LC.

Methods: After physician (or self-) referral, men and women aged $\geq$ 50, active or former smokers (quit $\leq$ 10 years), are invited to attend a dedicated "One Stop Shop" that includes personalized prevention consultations, counselling on smoking cessation, lung cancer screening with LDCT on the basis of a shared medical decision in addition to educational group workshops on smoking, LC, nutrition and physical activity. As per the European position statement on LC screening recommendations, screening outcome is either positive, negative or indeterminate. A shared personalized prevention plan is handed to the participants and sent to their physicians. A follow-up visit is scheduled after each screening round.

Results: Between May 2021 and 2023, 276 persons (187 females, median age 57) attended the One Stop Shop. Fifty-four percent had post high school training or college education, 37% had a previous history of another cancer (mainly breast). Two hundred and two (73%) were active smokers, 15% had a regular cannabis consumption and 16% reported any use of vape. Median 6-year lung cancer risk as per the PLCOm2012noRace prediction model was 1.4% (0.7-2.9). Results of the first screening round were negative, indeterminate and positive in 65%, 31% and 4% of the participants, respectively. Five participants had surgery; 3 had lung cancer (stage 1 adenocarcinoma) and 2 a benign histology. The proportion of indeterminate screenings decreased from 31% to 8% at the second round. Out of 56 initially active smokers with already available extended follow-up data, 12 (21%) were abstinent at one year from the One Stop Shop.

Conclusions: A combined intervention mixing LC screening and prevention is feasible and could increase the benefit of LDCT screening and long-term smoking cessation rates. Reducing false-positives and improving risk-based identification and referral for screening is a major challenge.

Legal entity responsible for the study: Gustave Roussy.

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1735P Impact of revised US Preventive Services Task Force (USPSTF) 2021 lung cancer screening guideline on long-term cancer survivors in the United States

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Background: Among long-term cancer survivors (i.e., survived $>$ 5 years since most recent cancer diagnosis) with a non-lung primary cancer, second primary lung cancer (SPLC) has the highest incidence (19%) and mortality (32%) rate among all secondary primary cancers. There are currently no separate screening guidelines for SPLC, though most providers have adopted the general USPSTF recommendation for lung cancer screening (LCS) in cancer survivors. We aimed to assess the differences in LCS eligibility rates among long-term cancer survivors under the USPSTF 2013 vs revised 2021 guidelines.

Methods: Smokers aged 50-79 years were selected from the 2017-2021 US Behavioral Risk Factor Surveillance System data. We assessed the eligibility of LCS using USPSTF 2013 criteria: current or former smokers (quit $\leq$ 15 years), 55-80 years of age and $\geq$ 30 pack-year smoking history, and the revised 2021 criteria (expanding age to 50-80 and pack-year to 20) in long-term cancer survivors. Weighted chi-square tests were used with SAS (9.4).

Results: A weighted total of 17,544,768 smokers were selected (2.7% were cancer survivors). The LCS eligibility rate of long-term cancer survivors using the 2013 criteria was similar to the non-cancer survivors (21.1% vs 22.4%; p=0.62) but lower when using the 2021 criteria (31.5% vs 38.0%; p=0.03). The 2021 criteria increased eligibility for long-term cancer survivors across all groups (Table). However, the degree of increase in eligibility rate in cancer survivors was lower than in non-cancer survivors.

Table: 1735P

Weighted eligibility rate % (95%CI)	Long-term cancer survivors (CS)		Δ % in CS	Δ % in non-CS	p-value*
	2013 USPSTF	2021 USPSTF			
Overall	21.1 (16.0-26.2)	31.5 (26.0-37.1)	10.4	15.6	<0.01
Gender					
Women	20.5 (13.9-27.1)	34.3 (27.3-41.5)	13.8	15.8	0.43
Men	21.6 (14.0-29.2)	29.1 (20.9-37.4)	7.5	15.4	<0.001
Race					
Non-Hispanic White	23.2 (17.4-29.0)	34.0 (27.8-40.1)	10.8	16.1	<0.01
Non-Hispanic Black	9.9 (0.2-19.6)	16.6 (4.3-29.9)	6.7	14.2	0.08
Other races	9.0 (0.0-19.0)	21.5 (2.4-40.5)	12.5	13.5	0.90

*P-value compares non-cancer survivors vs cancer survivors in the change of eligibility rate from 2013 to 2021 USPSTF criteria.

Conclusions: The increase in eligibility from the revised 2021 USPSTF appears to be less in long-term cancer survivors than in non-cancer survivors. Cancer survivors are facing a significant burden from SPLC due to their prior diagnostic tests and treatments (e.g., chest irradiation), genetic susceptibility, and shared risk factors. Tailored LCS eligibility criteria are urgently needed in the growing cancer survivor population.

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1736P Young adult lung cancer demands more attention in a low-resource area: Bangladesh perspective

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Background: Young adult lung cancer's socioeconomic and clinical implications make it a unique disease. However, in Bangladesh, the status and features of early-onset lung cancer are not well understood. This study aimed to investigate the socio-demographic status and clinical characteristics of lung cancer in young adults in Bangladesh.

Methods: A retrospective review of patients with lung cancer was performed in our institute from January 2018 and December 2022. Young adults were defined as individuals between 18 and 45 years old. Demographic, clinicopathological and prognostic data were systematically analysed.

Results: Of the 6310 patients, 819 (12.98%) were young adults, and 780 were included in this study. The average age of young adult lung cancer patients was 38.92 years, and the average BMI was 20.46. Of all adult lung cancer patients, 29.49% were female, 58.97% were illiterate, and 87.56% had poor or below-average economic status. Among young adults, 23.08% did not use tobacco, while 41.41% had more than one tobacco-related habit. 33.52% of young patients with right-sided dominant lung cancer had a previous respiratory disease. At the time of presentation, 43.85% of patients had a score of $\geq$2 on the ECOG scale, and 33.52% had comorbidities, with hypertension being the most frequent (37.36%) and DM (33%) being the second most common. Adenocarcinoma was the most prevalent subtype (58.97%), followed by squamous (24.74%), small cell varieties with undifferentiated (14.74%), and others like sarcoma and mesothelioma. Stage 4 was diagnosed in 28.46% of patients, and the most frequent metastatic site was the lung (14.42%), followed by the pleura (12.5%) and the liver (11.06%). Young lung cancer patients in Bangladesh significantly differed from older adults regarding higher BMI, lower education, more female patients, fewer tobacco users, adenocarcinoma, and different metastatic sites (p 0.05).

Conclusions: The high prevalence of young adult lung cancer in Bangladesh necessitates specialized attention to this vulnerable group during treatment. These patients face unique challenges, making the management of their cancer complex and resulting in poor outcomes. A personalized and comprehensive approach is essential to manage young lung cancer effectively.

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1737P Use of the predictive risk model LungFlagTM for lung cancer screening in screening in a Spanish reference center: A cost-effectiveness analysis

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Background: Lung cancer screening programs using low dose computed tomography (LDCT) reduce mortality by early detection. LungFlag is an artificial intelligence-based predictive model of non-small cell lung cancer (NSCLC) risk, evaluating routine clinical and laboratory data to improve selection of individuals at-risk for enrollment in screening programs. The aim of this analysis was to assess the cost-effectiveness of LungFlag in the area of a Spanish reference center.

Methods: A combination of a decision tree and a Markov model was adapted to the Spanish setting. A multidisciplinary group of experts validated all the parameters and assumptions used in the model. Demographic characteristics were in line with those reported by Gould et al. (2021) . We defined 2 hypothetical cohorts, a broader cohort of 3000 ever-smokers aged 55-80 years, and another cohort of 1000 individuals meeting 2013 USPSTF criteria. A lifetime horizon was used, and only direct medical costs were considered. Sensitivity and specificity values were obtained from Gould et al. (2021) , and unit costs were obtained from local databases (€ 2023). Results were expressed in life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER). Sensitivity analyses were performed to assess the consistency of the model results.

Results: LungFlag provides a higher number of LYs and QALYs with a lower cost (dominant) compared to non-screening, as shown in the table. Sensitivity analyses confirmed the robustness of base case results.

Table: 1737P Results for the hypothetical cohorts

	LungFlag		Non-screening		LungFlag vs non- screening	
	EvSm (n=3.000)	USPSTF (n=1.000)	EvSm (n=3.000)	USPSTF (n=1.000)	EvSm (n=3.000)	USPSTF (n=1.000)
LYs	67.402	62.321	66.702	61.552	+700	+769
QALYs	59.244	53.753	58.875	53.316	+369	+437
Total cost	5.752.233€	7.584.866€	9.291.237€	12.154.655€	-3.539.015€	-4.569.799€
ICER (€ / QALY gained)					dominant	dominant

Conclusions: The implementation of LungFlag as a risk model for NSCLC screening in a Spanish reference center would be cost-effective compared to no screening for the 2 hypothetical cohorts analyzed, providing savings and a higher clinical benefit.

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1738P Impact of digital platforms on exposure to tobacco and new smoking devices: A survey approach

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Background: Tobacco remains the leading preventable risk factor for cancer in the world. Although the prevalence of tobacco use has a decreasing trend in most European countries, the availability of new smoking devices is causing an increase in smokers, especially among the younger population. Several studies have confirmed the relationship between this increase and indirect or covert advertising, carried out on social media and VOD platforms, through product placement, etc. This study aims to measure the impact of tobacco and new smoking devices in these digital spaces on the young Spanish population; and how this impact is related to increased consumption.

Methods: A survey has been conducted on the young Spanish population (aged between 16 to 21 years old) using a representative online panel of this population. The final sample obtained was 1730 interviews, and the data collection was conducted in December 2022. A questionnaire with an average duration of 10 minutes was administered, in which questions related to tobacco and new smoking devices use, and the recall of having seen content related to traditional tobacco and new smoking devices were collected. Descriptive and logistic regression analyses have been performed, taking the habitual consumption (last month) of tobacco and new smoking device as dependent variables.

Results: 82.5% of young people remember having had some impact related to traditional tobacco, and 83% with new smoking forms. Among young people who have had this impact, there are twice as many smokers (53.1%) as among those who have not (24.5%). Having seen someone smoking cigarettes on these platforms (AOR 1.56), cigarette product placement (AOR 1.71), or recalling e-cigarette brands (AOR 1.58) are the variables that most increase the risk of regularly consuming traditional cigarettes. The same happens in the risk of habitual consumption of new devices, with the recall of having seen specific brands or logos taking special relevance (AOR 2.47).

Conclusions: There is a correlation between the recall of these types of consumption and the regular consumption of tobacco or new forms of smoking. It is necessary to continue researching this avenue of normalization of consumption and to ensure the protection of young people from the promotion of new devices.

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1739P Lung cancer mortality patterns of tobacco users in the United States: A 21-year analysis (1999-2020)

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Background: According to the American Cancer Society, lung cancer is the leading cause of cancer-related deaths globally, and tobacco use is the 1ry cause of the disease. The association between tobacco use and lung cancer is well recognized, with smoking cigarettes accounting for approximately 85% of all lung cancer cases. Despite significant public health efforts to reduce tobacco use, it remains a prevalent issue, with an estimated 14% of the U.S. adult population being current smokers. Therefore, there is a continued need to investigate the relationship between tobacco use and lung cancer to better establish public health interventions and policies that can reduce the burden of this deadly disease.

Methods: Using the CDC multiple causes of death database (ICD-10 revision codes), we identified all patients with history of tobacco use who died of lung cancer (C34.x registered as the underlying cause of death) in Caucasian, African American, Asian, American Indian races, between 1999 and 2020 in the United States. Age-adjusted mortality rates were calculated per 1,000,000 persons (PMP), standardized to the U.S. census data from 1999, and stratified by gender.

Results: Between 1999 and 2020, 1,084,140 deaths were due to lung cancer in persons with history of tobacco use (age-adjusted mortality= 144.6 PMP). We identified a total of 970,370 Caucasian, 96,001 African American, 11,279 Asian, and 6,490 American Indian deaths in each population (total age-adjusted mortality was 151.5 PMP, 129.5 PMP, 38.3 PMP, and 117.7, respectively). Over 21 years, age-adjusted mortality increased by 782% in Caucasians (19.5 PMP in 1999 to 152.4 PMP in 2020), 575% in African Americans (21.2 PMP in 1999 to 121.9 PMP in 2020), 724% in Asians (5 PMP in 1999 to 36.2 PMP in 2020), and 351% in American Indians (27.2 PMP in 1999 to 95.5 PMP in 2020).

Conclusions: The study's results show a significant and consistent rise in the mortality rates of tobacco-related lung cancer among all ethnicities, ranging from 351% in American Indians to 782% in Caucasians. These findings emphasize the urgent need for effective public health interventions and policies that can address the destructive impact of tobacco use on lung cancer mortality across all racial groups in the U.S.

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1740P Geolocation of respiratory tract cancer and its relationship with chronic exposure to PM2.5 pollutants

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Background: About 55% of the population worldwide lives in urban areas, and agreeing to WHO (World Health Organization), 91% of people in cities do not breathe safe air. There is evidence of a positive correlation between PM2.5 and lung cancer mortality. The Metropolitan Area of Monterrey, México, is the country's third most significant and most polluted, with an annual average of 23 $\mu g/m^3$ PM2.5, equivalent to 2.3 times the value established by the WHO. Objective. This study aimed to identify if spatial exposure patterns to PM2.5 correlate to respiratory tract cancer incidence.

Methods: Daily concentrations of PM2.5 were estimated considering the PM10/PM2.5 ratio in local stations that measured both fractions. Subsequently, the available fraction per station was calculated, considering the fractions of all available station data. Finally, the general fraction of the entire study period was calculated. The morbidity data for this study came from an individual-level database that contained the geographical coordinates of the residences of the airway cancer cases (bronchi, lung, larynx, and paranasal sinuses).

Results: The average concentration of PM2.5 was 32.4 $\mu g/m^3$, 3.24 times the limit established by the WHO. We identified that the increase in PM levels was associated with the number of cancer cases. The mean age of the cases was 70 years. There were 76.77% ($n = 476$) patients with a lung cancer diagnosis, followed by laryngeal cancer at 21.77% ($n = 135$). Interestingly, we detect that 44.35% ($n = 275$) has never smoked. On the other hand, there were 44.67% ($n=277$) heavy smokers in the cancer cases.

Conclusions: Implementing preventive measures to reduce emissions and exposure to PM2.5 and other air pollutants in polluted cities is necessary. High concentrations of PM2.5 are related to cancer cases, and it is essential to implement preventive cancer detection measures in polluted areas, not only in smokers' cases. In addition, spatial analyses are valuable to describe, quantify and explain the geographical variations of diseases associated with particulate matter exposure.

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1741P Are physicians aware of lung cancer screening benefits and the importance of implementing this? Data from two public hospitals in Buenos Aires province, Argentina

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Background: Lung cancer is the third most common cancer in Argentina in both sexes and the leading cause of cancer death, being smoking the most significant risk factor. Despite the effectiveness of a low dose computed tomography (LDCT) as a screening method, more than 70% of cases are still diagnosed at advanced stages, limiting patients' survival chances.

Methods: Observational, descriptive, and cross-sectional study. An anonymous online survey with closed-ended questions was conducted among physicians from San Roque and San Juan de Dios hospital, to assess their knowledge of lung cancer screening, its implementation, and possible barriers related to accessibility.

Results: The final sample of the study consisted of 102 physicians, with a median age of 33 years-old and a median of 6 years of practice. 70% of physicians knew about lung cancer screening methods, but 40% considered the risk-benefit balance to be

negative. Only 8 physicians knew the criteria for selecting the high-risk population, and 78 were not familiar with the NLST and NELSON trials. Although 61.8% knew about LDCT, 82.4% did not use it as a screening test, and 69.6% were unaware of its availability at their hospital. 31.4% were not confident in using LDCT as a screening tool, and 12.7% would not use it at all.

Conclusions: The results indicate that most physicians surveyed are not familiar with the criteria for selecting the high-risk population and do not routinely recommend lung cancer screening. Additionally, there was a significant lack of knowledge about the NLST and NELSON trials and the availability of LDCT at their hospitals. Urgent training, updates on the application of a lung cancer screening program and the dissemination of current scientific information on the topic are of paramount importance for local healthcare professionals in order to Improve patient outcomes.

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1742P Gender differences in incidence trends of early-onset GI cancer: The European perspective

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Background: The US Surveillance, Epidemiology and End Result (SEER) data indicate an increasing incidence of early-onset cancer across the GI tract. A female predominance has been shown for early-onset pancreatic cancer (EOPC) in the US. Due to environmental factors which may underlie the pathogenesis of early-onset cancer, incidence across the globe may differ. However, data regarding the incidence of gastrointestinal cancers in young patients in Europe is scarce. Therefore, we aimed to investigate patterns of GI cancers in young patients across various European countries.

Methods: National cancer registries of seven European countries - Germany, Netherlands, Spain, Slovenia, Norway, Czech Republic and Israel - were approached for absolute number of cancer incidences per age group (15-50 years in 5-year intervals) and the size of the population for each age group yearly from 2008-2018. Data was analyzed to calculate year-by-year the Average Annual Incidence Rate Change (AARC) and Average Annual Percent Change (AAPC).

Results: We observed heterogeneous patterns in different GI cancers across countries. An increase was noted in oesophageal cancer in females in the Czech Republic and Germany (AAPC 11.65% and 1.11% respectively) and slightly in males in the Netherlands (AAPC 0.88%) and Slovenia (AAPC 0.40%). Gastric cancer increased in females in Norway (AAPC 15.00%) and Slovenia (AAPC 11.90%). An increase in incidence of EOPC in men and women was noted in Germany, Norway and Netherlands and in females in Israel and Slovenia (AAPC 6.0%, 4.30% respectively). Early-Onset Colorectal cancer (EOCRC) is on the rise in men and women in Israel, Netherlands and Norway, while increasing only in males in the Czech Republic (AAPC 1.50%) and only in females in Slovenia (AAPC 5.40%). In Spain, only EOCRC showed an increased incidence.

Conclusions: The incidence of early-onset cancer along the GI tract displays differential patterns across countries, which differs from the trends observed in SEER data. In some GI cancers the incidence is stable between 2008-2018 and some are increasing mainly in women. Due to the environmental role in the pathogenesis of early-onset GI cancer, future studies should unravel potential etiologies especially with regard to gender-related factors.

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1743P Bridging the gender gap in oncology: GEORGiNA'S quest for equality in academic research

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Background: Gender disparities in academic research in oncology remain a persistent global challenge. There is a significant lack of research on gender inequity in Africa. GEORGiNA ("Gender Equity in Oncology Research" Group of North Africa) is a gender focusing bibliometric study that reviewed cancer research of North-African countries intending to build policy, recommendations, and gender equality actions in the field of cancer research.

Methods: A Pubmed-based bibliometric analysis was conducted over 2018-2022 period. Eligible articles had at least one author from a North-African country in the first or last position. Cancer researchers reviewed articles with authors from their own country to determine their gender accurately. A manual data extraction guide was developed and shared with collaborators to ensure consistent and accurate reporting. Factors associated with gender distribution were studied as appropriate.

Results: A total of 7,109 articles (2018-2022) published by North-African oncologists were included in the bibliometric analysis. Females represented 51% of first authors, with a notable women's presence in Tunisia (71.9%). Morocco, Algeria, and Egypt demonstrated a fair distribution of female first authors with ratios close to 0.5, while Sudan and Libya exhibited male dominance with percentages of 62% and 70%, respectively. Among 37,019 of co-authors, 44.13 % (n=16,333) were females. Male oncologists were found to have significantly higher representation as principal investigators (PIs) in all countries ($p < 0.001$). Notably, there has been a remarkable increase in women taking lead authorship roles in recent years, including during the period of the COVID-19 pandemic. Male researchers dominated original articles as PIs ($p < 0.001$). Indeed, male had received more funding than females and published more open access science ($p<0.01$). There was a significant difference observed in the involvement of male authors (both first and last positions) in international collaboration compared to females in equivalent positions.

Conclusions: While women in cancer research appear to achieve a fair position, there are still barriers such as insufficient funding and limited international collaboration to drive progress towards gender equity.

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1744P Socioeconomic inequalities in the diagnosis and treatment of colon cancer: A population-based English cancer registry study

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Background: Patients with colon cancer from more deprived areas may face barriers to accessing timely, quality healthcare. These barriers may contribute to socioeconomic inequalities in survival. We examined differences in treatment and time to diagnosis and treatment between socioeconomic groups.

Methods: The English Cancer Registry identified a retrospective cohort of patients diagnosed with colon cancer in England between 2016-2017. Cancer Registry data were linked to Hospital Episode Statistics, Cancer Pathway, Systematic Anti-Cancer Dataset and Diagnostic Imaging Datasets. Lasso logistic regression identified predictors of colon cancer treatment. The secondary care diagnostic interval (SCDI) was used to calculate the time to diagnosis and treatment, analysed using quantile regression. All analyses were conducted using STATA. The study was registered on ClinicalTrials.gov (NCT05185388).

Results: A total of 35,248 patients were included in the analyses. Area deprivation was a significant predictor of receipt of surgery and chemotherapy. The adjusted odds of treatment were reduced for patients from the most deprived quintile: surgery (OR 0.78), chemotherapy in stage IV (OR 0.88), and chemotherapy in stage II-III (OR 0.79). The median SCDI was 20 days for patients from the most and least deprived areas. However, patients from the most deprived area had a significantly longer time to diagnosis after adjusting for other factors (median difference 0.73 days [95% CI 0.09-1.36]). Meanwhile, the median treatment interval was 55 and 57 days for patients from the least and most deprived areas, respectively. The treatment interval was significantly longer for patients from the most, compared with the least deprived areas after adjusting for important factors (median difference 2.29 days [95% CI 1.28-3.31]).

Conclusions: In this large cohort of patients with colon cancer in England, we demonstrated that patients from more deprived areas are less likely to receive surgery or chemotherapy and wait longer to commence treatment. Further research is needed to understand why and what evidence-based actions can reduce these inequalities in treatment and timeliness.

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1745P Why do adult patients with cancer abandon treatment in India? A nationwide qualitative study to understand the perspectives of healthcare workers

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Background: Treatment abandonment (TA) is a major challenge in cancer care leading to poor outcomes and wastage of resources. Reasons for TA are multi-factorial and country specific. Understanding these complexities is the first step toward developing effective strategies for the prevention of TA. Insights and experiences of healthcare workers (HCWs) can provide valuable information about the factors contributing to TA; hence we conducted a qualitative study to understand the issues.

Methods: The participants were purposively selected, experienced HCWs (N=30) treating cancer patients from high-volume cancer centres nationwide. In-depth interviews (semi-structured, open-ended) were conducted by a person trained and experienced in qualitative interviews to understand the perspectives of HCWs on TA among adult cancer patients. We used the grounded theory approach to thematically analyze the data using inductive analysis.

Results: The HCWs (oncologists=17, nurses=6, psycho-oncologists=3, counselors=4) were selected from 9 states of India representing all geographical regions and working in both private (paid services, N= 14) and government (free services, N=16) sectors. The average duration of the interview was 30 minutes, and the reasons for TA perceived by the HCWs were classified under 6 themes: 1) Socio-demographic, 2) Patient-specific, 3) Clinical, 4) Psychological, 5) Health system related, and 6) Economic factors. Catastrophic health expenditure, direct medical and/or non-medical costs, indirect medical costs, poor socio-economic status, lack of specific knowledge about disease and treatment, poor patient-provider communication, accessibility, psychological distress, and toxicities of treatment were the common reasons for TA cited by the HCWs.

Conclusions: The study is one of the first studies reporting on HCWs' perspective on TA among cancer patients in India. In addition to well-known socio-economic factors, this study identified important themes such as lacunae in communication and psychological issues (e.g., distress) causing TA. The results of this study will help plan quantitative research into the complex issues of TA and interventions to counter the problem.

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1746P Unintended consequences: Working time directives and oncology staff implications

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Background: On-call work is an inherent component of Oncology care. Managerial models focus on length of stay in calculating efficiency within hospitals. Ensuring compliance with the European Working Time Directives (EWTD) for doctors is a legal requirement for Hospitals. Calculations of required physician staff to provide overnight care is not necessarily based on numbers of patients to be cared for, nor the complexity of care. The acute oncology service (AOS) after-hours has to date been provided by the day-time medical team in whole. To improve safety and quality of the AOS for patients being seen after hours, as well as to comply with the EWTD, a change to shift-work for the 1st-on-call oncology doctor is planned in 7/23. We sought to quantify the impact on the service.

Methods: The numbers of non-consultant hospital doctors (NCHDs), with allowances for full staff and also allowing for annual and educational leave entitlements were gathered for 1) pre-shift work implementation and 2) post-implementation of shift work. The number of NCHDs multiplied by the hours available to the ambulatory services (day unit and outpatient clinics) were calculated per week for both service structures to produce the "available NCHD hours".

Results: Assuming the normal working day is 8am to 5pm, this change would result in the reduction of available NCHDs to the ambulatory oncology service from 270 available NCHD hours per week to 171 available NCHD hours once vacation and study leave are factored into the equation, despite the addition of one NCHD to the medical oncology team. This represents a 36% reduction in available staff yet with a likely continued increase in patient activity.

Conclusions: While modifying the after-hours service to shift-work augments availability of medical staff for the acutely unwell patient with cancer and achieves compliance with EWTD, it reduces the numbers of doctors available for a significant part of the day, placing more strain on those doctors trying to manage a similar number of patients in a safe and patient-focused manner. Changes to the after-hours service inadvertently has knock-on effects on the "Oncology Ecosystem" and may impact on future service quality. Adjustments to NCHD numbers to cover the predicted significant staff fall short of those required.

Legal entity responsible for the study: Beaumont RCSI Cancer Centre.

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1747P The need for a better discussion between doctors and patients with regards to fertility preservation and vaginal rehab after anti cervical cancer treatments

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Background: Cervical cancer patients' age is relatively young (considering only 35-39 and not 60-64). At this young age, patients might consider birth planning and other sexual health considerations such as vaginal rehabilitation.

Methods: A call for answers to a survey was published and patients and verified survivors were invited to respond voluntarily and anonymously through a coded and encrypted web form.

Results: 116 women responded to the survey (age 21-72, median=42, age range at diagnosis 18-65). 8% were diagnosed with CIN1-2, 43% with CIN3, 20% with stage 1, 7% with stage 2, 10% with stages 3-4, 12% did not know how to answer. Past treatments were recorded. 84% of those required to use a vaginal dilator did not do so (results were modified in accordance to guidelines). At childbearing age [67 women, ages 21-45, median=37; 55.22% CIN3, 19.4% stage 1, 5.97% stage 2, 5.97% stages 3-4, 13.43% did not know how to answer; 77.61% were sexually active with a single known partner], only 58.2% recall having a discussion with their physician regarding fertility preservation, before beginning treatments. 32.83% recall such a discussion afterwards. 11.94% give birth after illness or had a child thanks to a surrogate mother.

Conclusions: This study underscores the need for greater attention to patients' sexual health and fertility aspects before and after completion of treatments. There is a need in coordinate patients' expectations regarding birth planning and in making the information regarding vaginal dilator accessible. Research involving a larger sample size may help to better support the information needs of survivors.

Legal entity responsible for the study: HaBait Shel Bar — Israel's Women's Cancer Association (RA).

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1748P Tackling childhood obesity epidemic on southern Europe through soft drink advertisement policies: Should oncology societies have a say?

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Background: Obesity has been recognised as one of the main risk factors for non-communicable diseases including cancer. WHO European report suggests that obesity affects 30% of children in Europe. Unhealthy diet is one of the most important determinants of childhood obesity, a condition that has become very prevalent in the south of Europe. Consumption of sugar-sweetened beverages (SSBs) influence childhood obesity and food advertisement is one of the strongest determinants of SSB consumption.

Methods: A multidisciplinary panel of clinicians from the South of Europe (Cyprus, Greece, Italy, Malta, Spain and Portugal) critically reviewed the available legislation and recommendations on SSB advertisements, in native language. The website of relevant national societies (Cardiovascular, Diabetic, Oncology, Paediatric and Stroke) was reviewed. Herein we present the recommendations from Oncology national societies.

Results: The countries in study have national legislations on SSB advertisements following EU directives with Spain having the most comprehensive regulatory framework. None of the oncology societies had recommendations on SSB consumption from children. The Spanish oncology society (SEOM) recognised obesity as risk factor for developing cancer and a close collaboration with the Spanish Association for the study of obesity is suggested. The Portuguese Society of Oncology (SPO) provides general guidance on the role of food and nutrition in cancer development. In Greece and Cyprus sporadic publications from the oncology society (HeSMO) on the preventive role of diet was noticed with no concrete guidance. Italian Oncology society (AIOM) has published on the role of nutritional support for cancer patients but the preventive role of healthy diet on childhood obesity is not available. European society of Medical Oncology links to IARC prevention strategies in the society website.

Conclusions: Recommendations on healthy diet to tackle childhood obesity, including SSB advertisement, from national medical societies in South Europe is fragmented. Oncology societies should join forces with other medical societies to increase awareness of childhood obesity and implement measures to address the phenomenon.

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1749P Prevention of modifiable cancer risks in informal family caregivers of cancer patients: Implementation and evaluation of a personalised primary prevention intervention (PREV-AIDANT)

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Background: The situation of caregiving can lead the informal family caregiver to neglect his or her own health, develop "risky" behaviours (smoking, alcohol consumption), adopt an unbalanced diet, encourage a sedentary lifestyle, and thus increase the risk of cancer. The sharing of the same lifestyle, including the same risk factors, within the informal family caregivers-patients dyad can also increase this risk. In addition, compared to the general population, informal family caregivers have a better perception of their risks and a greater motivation to change their behaviour. The objectives of the present study are to evaluate the feasibility and acceptability of a personalised primary prevention intervention for modifiable cancer risk factors in informal family caregivers of cancer patients.

Methods: The study is being conducted at the Léon Bérard Cancer Centre (Lyon, France), since April 2022, among informal family caregivers (first-degree relative or partner/spouse) who are adults and cancer-free. The personalised intervention was co-constructed with the representatives of informal family caregivers. It targets 6 risks factors (tobacco, alcohol, diet, physical activity, overweight/obesity, ultraviolet exposure) and screening. The intervention consists of an initial consultation (quantification of exposure, information on recommendations, drafting of a personalised primary prevention programme), support for the implementation and a four-month follow-up consultation (assessment of the actions taken, readjustment of the programme, exchanges to perpetuate the changes).

Results: To date, out of the 50 informal family caregivers expected, 26 have been seen at the initial consultation and 7 at the follow-up consultation. Inclusion will end in August 2023, the study looks feasible and acceptable, more results will be presented at the Congress.

Conclusions: The PREV-CARE transferability study of this intervention at the Institut Gustave Roussy (Paris, France) began in December 2022. Its objectives are to analyse the transferability of the intervention, to meet the challenges of territorial diversity, before considering evaluation on a larger scale.

Clinical trial identification: NCT05310045.

Legal entity responsible for the study: Centre Léon Bérard.

Funding: Institut National du Cancer.

Disclosure: All authors have declared no conflicts of interest.

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1750P Knowledge and awareness of hepatitis B and C virus reactivation among oncologists in Dutch-speaking Belgium: The CHOICe trial (Chronic Hepatitis B/C screening in patients on immunosuppressive therapy and chemotherapy)

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Background: Hepatitis B and C virus (HBV, HCV) reactivations are an emerging problem. Several societies have composed screening guidelines, but HBV reactivation still occurs in daily practice. This survey aims to assess knowledge and awareness of HBV/HCV reactivation in oncologists.

Methods: A questionnaire was designed to assess descriptive variables (i.e., subdiscipline, years of experience, working in an academic center, and having witnessed an HBV reactivation in clinical practice) and nine content questions (four background and five clinically oriented). The survey was disseminated in spring 2022 in 11 hospitals in Belgium (3 university, 8 non-university).

Results:

Table: 1750P Characteristics of responding oncologists

		N = 64	%
Subdiscipline	Solid tumours	33	52.4
	Haematological malignancies	21	33.3
	Gastrointestinal tumours	9	14.3
Years of experience	<5 years	20	31.2
	>5 years	44	68.8
Working in an academic center	Yes	26	40.6
	No	38	59.4
Already witnessed a HBV reactivation in clinical practice	Yes	24	37.5
	No	40	62.5

The table provides an overview of characteristics of responding oncologists. Mean overall scores were 33.7%, and mean scores for background and clinical questions were 20.3% and 44.4%, respectively. Less than half of participating oncologists was aware of universal HBV screening prior to initiation of chemotherapy (48.4%) and immunosuppression (37.5%). Only 7.8% of them was aware of the high reactivation risk that comes with administration of anthracyclines. Moreover, oncologists that have already witnessed a hepatitis B reactivation in clinical practice, are better aware of hepatitis B screening guidelines prior to administration of chemotherapy ($p=0.005$) and immunosuppression ($p=0.033$).

Conclusions: Knowledge of HBV/HCV reactivation is insufficient in oncologists. In addition, HBV screening guidelines prior to initiation of chemotherapy and immunosuppression are poorly implemented, given that over one third of responding oncologists already witnessed an HBV reactivation in clinical practice. Encouragingly, these respondents are also better aware of HBV screening guidelines. Oncology organisations play an important role in raising awareness and providing clear guidance.

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1751P Re-ranking cancer mortality using years of life lost

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Background: Standardized incidence and mortality rates are the default measures to describe cancer trends while survival assesses advances in cancer detection and treatment. Mortality compounds both incidence and survival but does not fully address age at death or long-term survival, both essential to quantify the cancer burden on society.

Methods: Using Swedish National Cancer and Cause of Death Register data together with publicly accessible projections of life expectancy, we calculated *years of life lost* (YLL) as the difference between age at cancer death and expected age at death for an individual of the corresponding age, sex, and birth year in the general population. All adults (18-95 years) with death reported as caused by one of the 10 solid tumors causing most deaths (lung, colorectal, prostate, pancreatic, breast, hepatobiliary, urinary, central nervous system, gastric cancer, or melanoma) in Sweden from 2010-2019, were included.

Results: When YLL were related and compared to mortality estimates in 2019 (Table), lung cancer (43,152 YLL) and colorectal cancer (32,340 YLL) remained at the top. Pancreatic cancer was up-ranked from 4th to 3rd place (22,592 YLL) and breast cancer from 5th to 4th place (21,810 YLL), while prostate cancer was down-ranked from 3rd to 5th place (17,380 YLL). In the table, a traditional approach ranking the 10 most common causes of cancer death in number of deaths and mortality rate (A), and new ranking using years of life lost approach (B), Sweden 2019.

Table: 1751P

	A. Traditional approach			B. Years of life lost approach	
Cancer site	Deaths	Mortality rate	Rank	Years of life lost	New rank
Lung	3144	38.7	1	43152	1
Colorectal	2543	31.3	2	32340	2
Prostate	2063	25.4	3	17380	5
Pancreatic	1600	19.7	4	22592	3
Breast	1335	16.5	5	21810	4
Hepatobiliary	998	12.3	6	14568	6
Urinary	740	9.1	7	7435	8
Central nervous system	548	6.7	8	11628	7
Gastric	510	5.8	9	7159	9
Melanoma skin	472	6.3	10	6973	10

Assessing YLL trends over the period from 2010-2019, women consistently lost more life years due to lung and pancreatic cancer than men. A downward trend in colorectal cancer mortality was reflected as a YLL decline only among women but not men.

Conclusions: Although all vital statistics have inborn advantages and disadvantages, this study demonstrates that YLL is simple to calculate, intuitive to interpret, and is as a meaningful measure to be added to the statistical toolbox box when presenting and comparing cancer trends within and between populations.

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1752P Clinical benefit of immunotherapies in advanced cancer in France: A population-based estimate from 2014 to 2021

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Background: In France, new treatments' benefit is evaluated by the *Haute Autorité de Santé* (HAS) to inform on reimbursement and pricing, but they are rarely evaluated afterwards. Although immunotherapies (ITs) considerably improved patients' survival, few data are available on their clinical benefit at the population-treated level. The objective of this study was to retrospectively quantify the clinical benefit of ITs compared to previous standard of care (SoC) in France from 2014 to 2021.

Methods: Analysis covers all ITs marketed in early access and/or reimbursed in France between 2014 and 2021, regardless of indication, with a cost-effectiveness (CE) model validated by HAS. For year between 2014 and 2021, the number of patients having initiated an IT, per drug and per indication, was retrieved from the French Hospital Reimbursement database. The clinical benefit was expressed as the number of deaths prevented (DP), life years gained (LYG) and quality-adjusted life years (QALYs) of ITs versus their comparators until 2021. DP and LYG were calculated thanks to extrapolated overall survival curves from randomized clinical trials, validated by the HAS. The number of additional QALYs was calculated using utility scores from the HAS CE opinion. Sensitivity analyses were performed according to the population size, survival, utility values and the period of availability.

Results: From 2014 to 2021, 5 ITs (atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab) were available in monotherapy or in combination in France corresponding to 8 tumor types and 21 indications. Overall, 132,924 patients initiated an IT, mainly in non-small cell lung cancer (66.5%) and melanoma (12.3%). By Dec 31st of 2021, 16,173 [13,803 − 17,141] deaths were prevented compared to previous SoC, representing 12.2% of patients initiating an IT. Compared to previous treatments, ITs allowed 37,318 [33,583 − 41,053] LYG and 27,710 [23,785 − 30,451] QALYs. Nivolumab contributed in 64.6% of LYG and 63.1% of QALYs. Early access of ITs participated in 14.7% of DP, 6.1% LYG and 6.0% QALYs.

Conclusions: Immunotherapies allowed significant clinical benefits for French cancer population in term of DP, LYG and QALYs. This type of analysis should be replicate in other countries.

Legal entity responsible for the study: Bristol Myers Squibb.

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1753P Universal DPYD genotyping in patients with gastrointestinal malignancies: Real-world data from a single institution in Italy

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Background: In up to 30% of gastrointestinal (GI) malignancies, fluoropyrimidines (FP) are associated with severe adverse drug reactions (ADRs). Dihydropyrimidine dehydrogenase (DPYD), is a polymorphic gene involved in FP catabolism. The identification of deleterious variants associated with increased toxicity is recommended before treatment initiation [c.1905+1G>A (*2A); c.1679T>G (*13); c.1129-5923C>G (*IVS10); c.2846A>T (*949) or during treatment in case of ADR [c.2194G>A (*6)]. The estimated prevalence of DPYD deficient genotypes in the European population is <8%. This study aimed to determine the prevalence and implication of systematic DPYD testing in an unselected population with GI tumours.

Methods: The germline DPYD test was conducted on a consecutive series of 1000 pts diagnosed with GI malignancies at our Department between June 2020 and December 2022, candidates for FP for colorectal (CRC 69%), gastroesophageal (GEC 15%), biliopancreatic (BPC 12%), other GI tumours (4%) or double GI malignancy (<1%).

Results: Overall, 819 pts (82%) were DPYD wild type (WT) and 181 (18%) had a deleterious DPYD variant. Among DPYD mutated pts, 134 had CRC (74%), 23 GEC (13%), 17 BPC (9%), 5 other GI tumours (2%) and 1 had CRC and GEC (1%). 184 deleterious variants were observed in 181 pts, the most prevalent was DPYD *6 (*N*=146 15%) (Table). In 4 pts *6 coexisted with other variants, requiring dose personalization. Of 133 pts enrolled in interventional trials including FP treatment, 24 (18%) reported a deleterious variant: *2A N=1,* IVS10 *N*=2, *6 *N*=21.

Table: 1753P

DPYD status	N= 1000	%	FP dose[a]
DPYD WT	819	82%	100%
DPYD6_c2194G>A homozygosis heterozygosis	146 * 5 141	15%	70% 85%
IVS10_1129_5923c>G	20	2%	50-70%
DPYD2A_1905+1G>A	12	1%	50%
DPYD949_c2846A>T	5	<1%	50%
DPYD13_c1679T>G	2	<1%	50%

[a] recommended dose based on SIF and CPIC guidelines *4 patients presented a double heterozygosis DPYD6 and *2A (*N*=1), FP dose <50% DPYD6 and c*949 (*N*=1), FP dose <50% DPYD6 and *IVS10 (*N*=2), FP dose 50%
FP= fluoropyrimidines, WT=wild type

Conclusions: Our large cohort of GI pts revealed a higher prevalence of deleterious DPYD variants compared to previous reports. DPYD*6 was the most frequent genotype and, at a low rate, occurred with other variants requiring major dose adjustments. To prevent severe ADR and to adequately report toxicity and changes in pts' quality of life, our data suggest that DPYD assessment should be mandatory and included in all FP-based clinical trials.

Legal entity responsible for the study: Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale.

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1754P Towards a next-generation sequencing/comprehensive genomic profiling value framework: Systematic review for identifying new domains and adapting a diagnostic test value framework in Europe

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Background: Next Generation Sequencing / Comprehensive Genomic Profiling (NGS/CGP) have recently expanded, mainly in oncology. To guide healthcare decision-making, it is key to have a value framework (VF), which allows a transparent assessment of value criteria. In 2020, IECS published a VF for diagnostic tests in Latin America (Augustovski et al, VIH 2021). This study aims to enrich, update, and adapt the previous VF to develop an NGS/CGP VF targeted to oncology in Europe. The aim of this study is to identify value criteria/sub criteria from published VFs, map them to the current VF, and report an updated and evidence-based list of non-overlapping criteria for subsequent assessment of their relevance for an NGS/CGP VF in Europe.

Methods: A systematic review (SR) of VFs aimed at any type of health technology. A mapping was then performed to determine similarities and differences with the IECS VF criteria.

Results: A total of 43 VFs were identified from 2067 unduplicated records and grey literature. The vast majority (n=38, 88%) were developed in high-income countries, 30% (n=13) were oriented towards genetic testing and only 16% (n=7) targeted oncology. A total of 223 criteria (C) and sub criteria (SC) were retrieved (93% of them fully or partially included in IECS VF). The two most common criteria related to clinical benefit and economic aspects. VFs oriented to oncology had higher overlap with the IECS VF, as well as those VFs oriented to genetic testing. A total of 18 criteria (C) and 35 non-overlapping sub-criteria (SC) were listed (15C and 21SC from IECS VF and 3C and 14SC from the SR). Some examples of new potential criteria included quality assurance/improvement; and public health/population benefit.

Conclusions: Our study provides an evidence-based, user-oriented update of criteria and sub criteria for healthcare decision-making tailored for NGS/CGP genetic testing in oncology, which may be a helpful list of criteria for health technologies in general. This list will serve as the basis to adapt the existing VF with the assistance of key European experts and stakeholders in order to co-create a European NGS/CGP VF in oncology.

Legal entity responsible for the study: Institute for Clinical Effectiveness and Health Policy (IECS).

Funding: Precision Cancer Consortium (PCC).

Disclosure: All authors have declared no conflicts of interest.

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1755P Carbohydrate quality index and incidence of obesity-related cancers: The Seguimiento Universidad de Navarra (SUN) project

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Background: Obesity is a strong risk factor for cancer, with more than 40,000 diagnosed cancers every year attributed to obesity. The role of nutrition in obesity-related cancers (ORC) needs to be better understood to develop tailored prevention strategies. The quality, rather than the quantity, of carbohydrate intake, seems to play a significant role. We investigated the relationship between dietary carbohydrate quality and risk of developing ORC in the "Seguimiento Universidad de Navarra" (SUN) Mediterranean cohort.

Methods: A total of 18,446 Spanish university graduates [mean age 38 years (SD 12), 61% women, mean BMI 23.5 kg/m2 (SD 3.5 kg/m2)], with no personal history of cancer, were followed-up for a median of 13.7 years. Baseline carbohydrate quality index (CQI) was assessed using 4 previously defined criteria: high dietary fibre intake, low glycemic index, high whole-grain: total-grain ratio and high solid carbohydrate: total carbohydrate ratio. Subjects were classified into tertiles according to their CQI score. Obesity-related incident cases were confirmed by an oncologist using medical records and by querying the National Death Index blindly to dietary exposures.

Results: During follow-up, 269 incident cases of obesity-related cancer were confirmed. A higher quality of carbohydrate intake, as measured by the baseline CQI, was associated with a lower risk of ORC with multivariable-adjusted hazard ratio (HR) for the upper (T3) versus the lowest tertile (T1) of 0.68 (95% confidence interval: 0.48, 0.97). Particularly, a higher dietary fibre intake was inversely associated with ORC, HR T3 vs. T1 = 0.58 (0.38, 0.89).

Conclusions: In this Mediterranean cohort, we observed a significant inverse association between a better global quality of carbohydrate intake and the risk of obesity-related cancers. This finding suggests that strategies for cancer prevention should emphasize the quality of carbohydrate intake, and particularly the dietary fibre intake.

Legal entity responsible for the study: University of Navarra.

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1756P Vizcan: A Swedish population-based study to address cancer outcomes using an interactive platform

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Background: Cancer is a severe disease, where many of the patients are diagnosed late in their disease course. A detailed understanding of cancer burden at a population level is important to control efforts aimed at reducing the incidence and mortality of cancer. The aim of the present project, which is still in progress, is to build an interactive platform to address and visualize cancer outcomes in Sweden by malignancies, geographical regions, and calendar time for different subgroups such as gender, age groups, level of education and stage at diagnosis.

Methods: In the first step, an interactive visualization platform using the statistical software R and the R Shiny application was developed. In the second step, a registry-based secondary data collection study where subjects will be identified using ICD codes from the Swedish Cancer Registry (SCR) from 2014 and onwards will be conducted. The SCR is held by the National Board of Health and Welfare and is mandatory to report into. Additional information will be retrieved from the Cause of Death Registry, and a social database (LISA) at Statistics Sweden via record-linkage utilizing the Swedish unique personal number. Outcomes will include incidence rates, mortality rates, overall survival and the proportion diagnosed with late-stage disease. Once populated with study data, the interactive platform will be available on a dedicated homepage.

Results: The present study will capture virtually all patients diagnosed with cancer in Sweden from 2014 and onwards. The results from the study will be included in interactive maps, tables and figures so that the user (e.g., health care professionals, patients, and researchers) can explore the outcomes of interest on their own. The data sources together with the interactive tool will increase the understanding of potential socio-economic inequalities and differences in cancer outcomes by geographical regions, gender, and age groups.

Conclusions: The use of population-based information available in the present study in combination with an interactive platform provides a unique opportunity to address a wide range of issues of importance not only for an improved general understanding of cancer, but also for quality assurance and improvement of cancer care.

Legal entity responsible for the study: The authors.

Funding: This study was undertaken by Epistat AB sponsored by AstraZeneca.

Disclosure: E. Fernholm, A. Juhlin, D. Eek: Financial Interests, Institutional, Affiliate, Employee: AstraZeneca AB. All other authors have declared no conflicts of interest.

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1757P A real-world evaluation of the effectiveness of thermogram along with clinical breast examination in community-based breast cancer screening program

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Background: Breast cancer is a crucially prevailing cancer among women. Early detection and diagnosis of breast cancer are very important for patient survival. This study was conducted to devise a cost-effective and robust community-based breast cancer screening programme for LMIC.

Methods: All enrolled participants will undergo breast thermogram (BT) using an AI-based Thermalytix test along with clinical breast examination (CBE) by trained health workers. Women found suspicious in either CBE/BT or both will undergo confirmatory tests using Sonomammography (US) and/or Mammography; biopsy, where warranted, will be done to confirm the diagnosis. All symptomatic and asymptomatic women aged above 35 years of age, willing to give written informed consent for study participation were included. Those who are pregnant or lactating, treated for any cancers of breast/thorax, active inflammatory disorders on the skin of the breast, breast implants that can hamper testing using a BT or CBE were excluded from this study. The primary study endpoint is to evaluate the effectiveness of combined modality testing for breast cancer detection in healthy women. The benefit of a combined modality of Thermogram and clinical breast examination (CBE) for cancer detection rate were evaluated.

Results: A total of 3030 (both symptomatic and asymptomatic women) were screened for breast cancers over a period of 6months (Oct 2022 to April 2023). Women residing within a 120square kilometre radius were screened. Patients who were detected with screen abnormality on a thermogram B- Score 4 and above were 561 (18.51%). Six hundred and forty-six subjects (21.3%) who had an abnormality on both thermogram and CBE were recalled for further investigations. Out of which 5 subjects were detected with biopsy-proven breast malignancy (3 were early-stage breast cancer and 2 had locally advanced breast cancer).

Conclusions: Dual modality screening tool improves cancer detection rates, and this demonstrates the efficacy of these tools for breast cancer screening. Thermalytix with its artificial intelligence-based scoring system can assist the health care worker in the detection of breast cancer at a community level.

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1758P Body composition meets precision medicine: The prognostic value of sarcopenia in patients (pt) treated with Molecularly Targeted Agents (MTA)

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Background: Sarcopenia is associated with worse prognosis in pt treated with chemo (CT) or immunotherapy, yet there is scarce information with MTA. Some gene mutations (mut) have been involved in muscle wasting pathogenesis but remains unclear which molecular mediators can alter body composition. Our study aimed to analyze the association between sarcopenia and clinical outcomes in MTA-treated pt and to explore the tumor genomic landscape.

Methods: Retrospective analysis of metastatic solid tumors treated with MTA within the spEcial Medication (ME) program at the Catalan Institute of Oncology (off-label or expanded access use) between Jan'11-Dec'19. Skeletal mass index (SMI) was assessed at L3 landmark in computed tomography scans performed one month before first MTA dose. SMI was dichotomized according to the median [high (H) vs low (L) SMI]. Histology-oriented single analysis assays were performed according to the prevalence of actionable findings (IHC, FISH or PCR).

Results: We included 167 cases: 56% female, 86% <75 years, 84% ECOG <2 and 79% received <3 lines of treatment. Locations were thoracic (33%), breast (15%), sarcoma (15%), gastrointestinal (14%), gynae (9%), genitourinary (7%) and others (7%). Oncogenic drivers that guided matched MTA were found in 97 tumors: 75% received MTA monotherapy and 25% combinations (CT or other MTA). Globally there were 28% cases with HER2 overexpression (ove), ALK (23%)/MET (1%)/ROS1 (1%) fusions and EGFR (19%)/BRAF (11%)/BRCA1/2 (7%)/KRAS (4%) mut. Overall survival (OS) was 21.8 months (m) in H-SMI/driver, 13.9 m in H-SMI/no-driver, 10.8 m in L-SMI/driver and 9 m in L-SMI/no-driver groups (p=0.0037). Of note, OS rate at 12 m was 65% (CI 95%; 53-81) in H-SMI/driver group compared to 38% (CI 95%; 24-59) in L-SMI/no-driver group. Interestingly, 81% HER2ove cases had L-SMI (p=0.005).

Conclusions: Our exploratory study shows that pt with H-SMI and presence of an oncogenic driver have better survival outcomes, hence highlights the relevance of guaranteeing early access to MTA through ME programs. L-SMI in HER2ove pt warrants further confirmation and investigation of the underlying mechanism in muscle wasting.

Legal entity responsible for the study: The authors.

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1760P Systematic review of quality of life (QoL) inclusion among endpoints, reporting and impact of QoL results in phase III non-inferiority trials of systemic treatments in oncology

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Background: Quality of life (QoL) is an increasingly important endpoint in oncology clinical trials. In the non-inferiority (NI) setting, the experimental treatment should confirm to be preferable, and patient-reported outcomes should have a relevant role. Aim of this study was to assess the inclusion of QoL among endpoints in phase III NI trials, the presence of QoL results in the publications and the impact of QoL results on the interpretation of the study.

Methods: We performed a PubMed search for phase III NI trials published between 2012 and 2021, testing systemic treatments in adult patients with solid tumours. Trials were divided according to 4 NI strategies: (1) different treatments; (2) different route of administration of the same drug; (3) shorter duration of treatment; (4) omission of one or more drugs. Trials were analysed according to three endpoints: (1) proportion of publications including QoL among endpoints; (2) proportion of publications reporting QoL results; (3) proportion of publications with demonstration of NI, in which QoL results actually favour the experimental treatment.

Results: 106 publications were eligible. In 47 studies (44.3%), QoL was not included among endpoints, and QoL results were not available in 66 (62.3%) primary publications. Out of 74 trials with demonstration of NI, QoL was not assessed in 36 (48.64%) and QoL results were not available in 43 primary publications (58.1%); QoL results actually favoured the experimental treatment in 19 trials (25.7%). Considering only the subgroup of 73 trials testing the NI of different treatments, 30 (41.1%) did not include QoL and QoL results were not available in 42 (57.5%) publications; within this subgroup, focusing on 55 trials with demonstration of NI, 25 (45.5%) did not include QoL; QoL results were not available in 29 (52.7%) primary publications; QoL results actually favoured the experimental treatment in 15 trials (27.3%).

Conclusions: Quality of life is not assessed and/or reported in many non-inferiority trials testing cancer treatments. Among trials formally demonstrating the non-inferiority, only a minority can claim quality of life results actually favouring the experimental treatment.

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1761P Incidence of herpes zoster in cancer patients in Europe: A systematic review

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Background: Immunocompromised (IC) patients e.g., due to cancer or immunosuppressive therapy, are at increased risk for herpes zoster (HZ) with severe complications, recurrence and mortality. HZ affects up to one in three adults over 50 years, with post-herpetic neuralgia in up to one in ten HZ cases. The objective was to document HZ incidence in a broad range of IC populations, including cancer, in Europe.

Methods: A systematic literature review (2002-2022) identified observational studies reporting HZ incidence in IC populations in the European Union/European Economic Area, Switzerland and the United Kingdom.

Results: 26 studies were included: five in cancer patients reported HZ incidence rates per 1,000 person-years. In mixed hematologic malignancy (HM) patient studies, overall HZ incidence was 12.0-15.2 vs 4.6-6.2 in non-IC controls, increasing with age (Table). Chronic lymphocytic leukemia (CLL) patients had an 11.3 times greater risk of HZ (incidence 2.94 vs controls 0.26). In myelofibrosis (MF) patients, ruxolitinib use increased HZ risk (incidence in long-term, short-term, new and switch users vs non-ruxolitinib users). In mixed solid organ malignancy (SOM) patient studies, overall HZ incidence was 8.8-11.0 vs 4.6-6.2 in non-IC controls, increasing with age (Table), and was higher for women vs men (10.8 vs. 9.0).

Table: 1761P

	Age group	Non-IC	HM	SOM
Spain (2009-2014)	18-29y	2.26 [2.21; 2.31]	4.96 [4.1; 5.94]	3.87 [2.59; 5.56]
	50-59y	5.52 [5.44; 5.61]	13.95 [12.5; 15.52]	10.24 [9.66; 10.85]
	≥80y	9.54 [9.36; 9.71]	18.44 [16.46; 20.6]	12.00 [11.43;12.59]
England (2000-2012)	18-49y	2.12 [2.03; 2.22]	8.46 [7.29; 9.77]	4.32 [3.96; 4.70]
	50-59y	4.90 [4.72; 5.08]	15.41 [13.61; 17.37]	6.79 [6.36; 7.25]
	≥80y	11.02 [10.64; 11.41]	17.53 [15.47; 19.79]	11.63 [11.08; 12.20]

y: year

Conclusions: This systematic review reported a higher HZ risk for HM and SOM patients, varying across countries and cancer type. Stratified data showed risk differed by age, sex and treatment. These real-world studies highlight the increased HZ risk and burden in cancer patients, which may be prevented with the adjuvanted recombinant HZ vaccine approved for multiple IC populations.

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1762P Are published data up-to-date? Analysis of time to publication in major oncological journals

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Background: Dissemination of research results, including data from clinical trials, is one of the essential responsibilities of all scientists. Moreover, whole community of researchers, patients, and general public, should have access to research data at earliest possible moment. However, significant delay between completion of the study and publication of its results has been observed; thus, we aimed to analyze the time from database lockdown to publication and factors that might be associated with it.

Methods: We analyzed all original publications reporting any clinical data published in 2020 and 2021 in 2 leading oncological journal — *Journal of Clinical Oncology* (JCO) and *Annals of Oncology* (AoO). Information of cut-off (database lock) date, publication date, type of the study and its sponsor has been extracted. Descriptive statistics, t-test and chi-square tests were used for statistical analyses.

Results: Overall, 652 articles (482 from JCO, 170 from AoO) has been identified - 63% (411) reported results of clinical trials, 47% (193) of them reporting data from clinical trials. Only 52.3% (341) of trials reported the cut-off date. Reports from clinical trials reported cut-off date more often than other studies (65.5% vs 29.9%, $p<0.001$). Median time from data cut-off to publication (PT) was 15.4 months (range 1.2-130.8), with PT of 12-24 months and >24 months being 45.2% (154) and 22.6% (77), respectively. Reports of studies other than clinical trials had PT>24m more often than clinical trials (36.1% vs 19%; $p=0.003$). Commercially sponsored studies reported cut-off date more often than academic studies (79.2% vs 41.4%; $p<0.001$) but there was no difference in PT depending on type of sponsor ($p=0.170$).

Conclusions: Despite presence of reporting guidelines, significant proportion of scientific publications do not report exact date of data cut-off or last follow-up what make difficult to assess topicality and maturity of data. Moreover, nearly one-quarter of publications report results that are older than 2 years. Causes leading to such disproportion and publication of outdated results may lead on the authors', editors' or publishers' side and need to be studied in more depth to ensure timely publication of relevant research data.

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1763P The challenge for Cancer Trials Ireland (CTI) to sponsor NCI and non-EU sponsored trials in the EU

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Background: The environment for academic clinical trials has become more challenging in the EU and beyond. There are a number of factors contributing, in particular the regulatory challenges. While Ireland and Northern Ireland governments signed an MOU with the US NCI Director in March 2021, solidifying a 25-year arrangement where Ireland and Northern Ireland is considered an NCI site and Irish hospitals are registered and Irish investigators are registered with CTEP, the practicalities of groups like CTI sponsoring NCI trials outside of the US are onerous.

Methods: Gathering experiences from our international partners (EORTC (EU), ANZUP (Australia) and BIG) where significant issues are reported in setting up NCI or other US-sponsored trials. The common thread is the lack of "regulatory harmony" in running international academic clinical trials in the EU with a non-EU sponsor.

Results: Approaches to GDPR in clinical trials are not aligned between the EU and non-EU. The experience of the Groups interviewed is that Standard Contractual Clause with regard to data transfer is a stumbling block. When working with the NCI, the OHRP are also involved and there are clear standards to follow as NCI trials are federally sponsored and funded. The Federalwide Assurance (FWA) is the only type of assurance currently accepted and approved by OHRP. Cancer Trials Ireland and other collaborative groups must have this in place in order to sponsor NCI trials outside of the US.

Conclusions: Public funding is not utilized to its optimal level in multinational academic trials. Propose greater collaboration at government level and mutual recognition agreements with regard to GDPR in clinical trials.

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1764O Timing of radiotherapy (RT) after radical prostatectomy (RP): Final results of RADICALS RT randomised controlled trial

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Background: The optimal timing of RT after RP for prostate cancer is uncertain. RADICALS-RT compared the efficacy and safety of adjuvant RT (aRT) versus an observation policy with salvage RT for early PSA failure (Obs+sRT). We previously reported an early outcome measure (OM): bPFS, and now have enough events to report on the primary OM, freedom from distant metastases (FFDM).

Methods: Patients with post-op PSA≤0.2ng/ml and ≥1 risk factor (pT3/4, Gleason 7-10, positive margins, or pre-op PSA≥10ng/ml) were randomised ≤22wk after RP to aRT or Obs+sRT for PSA failure: PSA ≥0.1ng/ml or 3 consecutive rises. Stratification factors were Gleason score, margin status, planned RT volume (prostate bed only, prostate bed + pelvis), RT schedule (52.5Gy/20f, 66Gy/33f) and centre. The primary OM was FFDM with >1200 pts needed for 80% power to detect an improvement from 90% to 95% at 10yr with aRT. Secondary OMs include overall survival, safety & patient reported OMs (1, 5, 10yr). Standard survival analysis methods were used.

Results: 1396 pts were randomised (697 aRT, 699 Obs+sRT) from Oct-2007 to Dec-2016 (82% UK, 13% Denmark, 4% Canada, 1% Ireland). Median age was 65yrs and 37% (517/1396) had a CAPRA-S score of 6+. Data were frozen May 2022 and median follow-up was 8yrs. 93% (650/697) aRT started RT within 5mo; 39% (270/699) Obs+sRT started RT. Median PSA at time of sRT was 0.2ng/ml. 24% (156/650) aRT and 27% (72/270) Obs+sRT reported HT with their RT. With 80 events, FFDM at 10 yrs was 93% for aRT v 90% for Obs+sRT (HR= 0.68 (95%CI 0·43-1·07, p=0·095). Overall survival at 10-yrs was 88% vs 87% (HR=0.98 (95%CI 0.67 to 1.44, p=0.92). Self-reported urinary incontinence and faecal incontinence were worse at 1yr for aRT (p<0.001).

Conclusions: RADICALS-RT is the largest study ever conducted addressing the value of adjuvant RT in prostate cancer. Final results from RADICALS-RT show no evidence of a meaningful benefit for aRT after RP in this patient group. Adjuvant RT increases risk of urinary & bowel morbidity. An observation policy with salvage RT for PSA failure should be the current standard after RP.

Clinical trial identification: NCT00541047.

Legal entity responsible for the study: UCL.

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1765O Interim results from a phase I study of AMG 509 (xaluritamig), a STEAP1 x CD3 XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)

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Background: Xaluritamig is a novel bispecific XmAb® 2+1 T-cell engager with two STEAP1 binding sites designed to facilitate T-cell—mediated lysis of STEAP1-expressing cells. We report results from the dose exploration of xaluritamig monotherapy in a first-in-human study for patients (pts) with mCRPC.

Methods: Eligible pts had mCRPC refractory to prior novel hormonal therapy and 1—2 taxane regimens, ECOG 0—1, and adequate organ function. Xaluritamig was administered as an IV weekly (QW) or Q2W with various dose levels/schedules (DLs). Study objectives were to evaluate safety, tolerability, antitumor activity, PK, and determine the MTD and RP2D.

Results: As of 23 March 2023, 97 pts in 15 DLs received ≥1 dose of xaluritamig. Median (range) age was 67 (40—86) years; 67 pts (69.1%) had received > 3 prior lines of therapy. Treatment emergent adverse events (TEAEs) were reported in 100% of pts (grade ≥3, 74.2%); 95.9% reported treatment-related AEs (TRAEs) (grade ≥3, 52.6%). The most common AEs were cytokine release syndrome (CRS; 72.2%), fatigue (52.6%), anemia (45.4%), pyrexia (40.2%), and myalgia (39.2%). CRS was primarily grade 1 or 2, one event being grade 3 (no grade 4/5 CRS; cycle 1). In the DL15 QW cohort, 3 of 6 DLT evaluable subjects experienced DLTs, defining DL14 QW as the MTD. TRAEs leading to discontinuation occurred in 17.5% of pts. PSA50 (≥ 50% PSA decline) responses occurred in 42 pts (47.2%); PSA90, in 24 pts (27.0%) (Table). PSA responses were more frequent at higher DLs (DL8—15) than in lower DLs (DL1—7). Overall, RECIST responses included 15 (22.7%) confirmed PR and 30 (45.5%) SD. At higher DLs, 14 pts (38.9%) had confirmed PR and 12 (33.3%) SD. Preliminary PK showed dose-proportional increase in exposure with a mean terminal half-life of approximately 3-4 days.

Table: 1765O

	Lower DLs (DL 1−7)	Higher DLs (DL8−15)	Overall
PSA evaluable	N = 43	N = 46	N = 89
PSA ≥ 50%, n (%)	17 (39.5)	25 (54.3)	42 (47.2)
PSA ≥ 90%, n (%)	8 (18.6)	16 (34.8)	24 (27.0)
RECIST evaluable	N = 30	N = 36	N = 66
PR, n (%)	1 (3.3)	14 (38.9)	15 (22.7)
SD, n (%)	18 (60.0)	12 (33.3)	30 (45.5)

Conclusions: Xaluritamig was tolerable with low-grade CRS (occurring primarily cycle 1) with encouraging preliminary efficacy in heavily pretreated pts with mCRPC.

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1770O Refining risk stratification in patients undergoing radiotherapy (RT) and long-term (lt) ADT for high-risk/locally advanced prostate cancer (HR/LA-PC): An individual patient data (IPD) analysis of randomized controlled trials (RCTs) from the ICECaP consortium

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Background: RT + ltADT (18-36 months) is a standard-of-care in the treatment of HR/LA-PC. Efforts are ongoing to evaluate intensification of systemic therapy beyond ADT to further improve outcomes. We evaluated 5-year metastasis-free survival (MFS) rates in subgroups of patients (pts) with HR/LA-PC to define patients more likely to benefit from treatment intensification, and guide design and interpretation of adjuvant trials in HR/LA-PC.

Methods: IPD from patients with HR/LA-PC (as defined by any of the following 3 risk factors [RFs]: Gleason ≥8, ≥cT3, PSA >20; or cN1) treated with RT+ltADT in RCTs collated by ICECaP were pooled. 5-year MFS was calculated by Kaplan-Meier method in various risk-groups and by number of RFs. Multivariable Cox regression estimated hazard ratios (HR) for the 3 RFs and cN1 disease, stratified by trials and years of enrolment. MFS was defined as distant metastasis on conventional imaging or death from any cause.

Results: 3604 pts with HR/LA-PC treated with RT+ltADT on 10 randomized trials between 1987-2016 were eligible. Median age was 68 and median PSA was 24 (IQR 12-48). 2602 (72%) were cT3/4, 1942 (54%) had Gleason 8-10 and 422 pts (12%) had cN1 disease. The HR for MFS was 1.5 (95% CI 1.4-1.7) for Gleason ≥8, 1.2 (1.1-1.4) for PSA>20, 1.2 (1.1-1.4) for cT3/T4, and 1.8 (1.5-2.1) for cN1. 5-year MFS (%, 95% CI) rate was 83 (81-85), 78 (75-80) and 77 (73-80) for pts with 1, 2 and 3 RFs respectively, and 68 (63-72) for cN1 disease. Table shows 5-yr MFS rates in various subgroups.

Table: 1770O

5-yr MFS (%, 95% CI)	Gleason 7		Gleason 8-10	
	Tx1-2	T3-4	Tx1-2	Tx3-4
PSA <10	-	87 (82-91)	82 (76-87)	75 (69-80)
PSA 10-20	-	81 (75-85)	84 (77-89)	79 (73-83)
PSA >20	84 (79-87)	80 (76-83)	74 (67-79)	77 (73-80)
cN1	76 (67-82)		64 (58-69)	

Conclusions: Pts with HR/LA-PC treated with RT+ltADT who had ≥2 RFs or cN1 disease had 5-yr MFS rates <80% and are the ones most likely to benefit from treatment intensification. This will guide patient counselling and the design and interpretation of adjuvant trials in HR/LA-PC.

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1766MO Health-related quality of life (HRQoL) in nonmetastatic hormone-sensitive prostate cancer (nmHSPC) patients (pts) with high-risk biochemical recurrence (BCR) from the EMBARK study

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Background: Enzalutamide (ENZ) + leuprolide acetate (L) and ENZ alone delayed metastasis-free survival (MFS) vs placebo (P) + L in high-risk BCR nmHSPC in the phase 3 EMBARK (NCT02319837) trial. Pt-reported outcomes (PROs) provide a pt perspective on disease/treatment (Tx) experience not captured by clinical assessment.

Methods: nmHSPC pts with high-risk BCR (prostate-specific antigen [PSA] doubling time $\leq$9 months, screening PSA $\geq$2 ng/mL above nadir post radiotherapy or $\geq$1 ng/mL post radical prostatectomy) were randomized (1:1:1) to ENZ + L, ENZ alone, and P + L. PROs were assessed at baseline (BL) and every 12 weeks until development of metastasis or death. The main objectives were to assess Tx effects in time to first and confirmed (at next visit) clinically meaningful deterioration (TTFD/TTFCD) as measured with the Brief Pain Inventory Short Form (BPI-SF) worst pain and Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score using predefined thresholds. Other objectives were: Tx effects in TTFD and TTFCD measured by the European Organisation for Research and Tx of Cancer QoL Questionnaire-Prostate 25 (QLQ-PR25) and European QoL 5-Dimensions 5-Levels (EQ-5D-5L) visual analogue scale (VAS). Comparisons were made for ENZ + L vs P + L and ENZ alone vs P + L. Intent-to-treat population was analysed.

Results: At BL, 327—332 pts per group completed the PRO questionnaire; completion rates were 85—95%. No significant differences in TTFD or TTFCD were seen among Tx groups vs P + L in FACT-P total score, BPI-SF worst pain, or EQ-5D-5L VAS. In QLQ-PR25, TTFCD for sexual activity was significantly longer with ENZ alone vs P + L; TTFCD for hormone Tx-related symptoms was significantly shorter with ENZ + L vs P + L (Table).

Table: 1766MO

PRO	Months, median			HR (95% CI)	
	ENZ + L	ENZ	P + L	ENZ + L vs P + L	ENZ vs P + L
BPI-SF					
Worst pain					
TTFD	13.9	16.6	19.4	1.08 (0.89—1.30)	1.09 (0.90—1.31)
TTFCD	80.0	60.9	66.3	0.82 (0.65—1.04)	1.02 (0.82—1.28)
FACT-P					
FACT-P total score					
TTFD	8.3	8.4	11.1	1.14 (0.95—1.36)	1.17 (0.98—1.39)
TTFCD	38.8	30.6	36.5	1.04 (0.85—1.28)	1.16 (0.95—1.41)
QLQ-PR25					
Sexual activity					
TTFD	2.9	2.9	2.9	1.12 (0.93—1.35)	0.92 (0.76—1.11)
TTFCD	3.0	5.6	3.0	1.09 (0.89—1.32)	0.76* (0.62—0.94)
Hormonal Tx					
TTFD	2.8	2.9	2.8	1.09 (0.93—1.28)	0.95 (0.81—1.12)
TTFCD	2.9	3.0	2.9	1.19* (1.01—1.40)	1.06 (0.90—1.25)
EQ-5D-5L					
VAS					
TTFD	8.3	8.4	11.1	1.09 (0.91—1.30)	1.15 (0.97—1.38)
TTFCD	44.6	38.9	52.4	1.02 (0.82—1.26)	1.16 (0.94—1.43)

*$p<0.05$

Conclusions: ENZ + L or ENZ alone improved MFS without negatively impacting global HRQoL or clinical pain progression, vs P + L in nmHSPC pts. Sexual activity may be better preserved with ENZ alone vs P + L.

Clinical trial identification: NCT02319837.

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1767MO External validation of a digital pathology-based multimodal artificial intelligence (MMAI)-derived model in high-risk localized (M0)/metastatic (M1) prostate cancer (PCa) starting androgen deprivation therapy (ADT) in the docetaxel (Doc) or abiraterone (AAP) phase III STAMPEDE trials

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Background: Effective prognostication will allow better targeting of treatment (Rx) combinations for advanced PCa. A MMAI prognostic test (ArteraAI Prostate) was recently developed in localized PCa. We aimed to validate ArteraAI in advanced PCausing final data from 3 STAMPEDE trials (NCT00268476).

Methods: The MMAI model used digitized whole scan images from new H&E core prostate biopsies (PB), local Gleason score (GS), tumor stage (T), age and pre-ADT serum PSA. Fine-Gray/Cox regression adjusted for Rx allocation and cumulative incidence analyses were performed to evaluate associations with endpoints, as defined in STAMPEDE, for both continuous score (per standard deviation increase) and categorical (quartile,Q). PCa-specific mortality (PCSM) was the endpoint of primary interest. Death not from PCa was treated as a competing risk. HR, 95% CI, and $p<0.001$ (denoted by *) are reported.

Results: Of 3879 patients recruited Oct 2005 — Jan 2014 to ADT +/- radiotherapy (RT) alone or + Doc +/-zoledronic acid or + AAP, 3725 consented to tissue analysis, 2079 had H&E with sufficient tumor of which 1964 had all of GS, T, pre-ADT PSA (918 M0, 1046 M1, median follow-up: 7.8 years, yr). ArteraAI was strongly associated with PCSM (HR 1.67, 1.5-1.84*), overall survival (1.51,1.4-1.63*), failure-free survival (1.48, 1.38-1.59*), and metastatic progression-free survival (1.59, 1.46-1.73*). ArteraAI Q4 v Q1-3 showed similar results for all endpoints, including PCSM (2.27, 1.95-2.65*). Of component clinical variables, p* for PCSM were PSA Q4 v Q1-3 (1.8, 1.54-2.11), Gleason 8-10 v <=7 (1.64, 1.36-1.98), and T4 v T1-2 (1.77, 1.36-2.32). ArteraAI Q4 v Q1-3 had more PCSM events at 5 yr: 16% (11-21) v 6% (4-8) in M0, 58% (52-64) v 40% (36-43) in M1 and notably for M0 treated with ADT +/- RT+ AAP: 18% (9-28) v 2% (0-4%).

Conclusions: ArteraAI successfully validated in STAMPEDE with stronger prognostic associations than individual clinical variables. The MMAI model identified poor prognostic features in PB from high-risk M0 and M1 PCa.

Clinical trial identification: NCT00268476.

Legal entity responsible for the study: University College London (UCL) - Professor Gerhardt Attard.

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1768MO Incidence of fracture related hospitalisations in men with de novo high risk localised and metastatic hormone sensitive prostate cancer: Analysis of routinely collected healthcare data from the STAMPEDE docetaxel and zoledronic acid comparisons

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Background: Androgen deprivation therapy (ADT) is the mainstay medical treatment for men with locally advanced (M0) and metastatic hormone sensitive prostate cancer (M1 mHSPC): bone loss and increased fracture risk are recognised complications. The STAMPEDE trial compared patients (pts) treated with ADT ± docetaxel (Doc) ± zoledronic acid (ZA). No survival benefit was demonstrated with the addition of ZA however, long term effects on bone health and fracture risk were not formally collected within the trial. Health systems data through Hospital Episode Statistics (HES) for pts in England provides data with demonstrated integrity and provenance beyond standard trial follow up permitting evaluation of fracture risk.

Methods: HES data were obtained (up to Mar 2021) for pts randomised to ADT (Arm A), ADT+ZA (Arm B), ADT+Doc (Arm C) and ADT+Doc+ZA (Arm E). ZA (4mg) was given as six 3 weekly cycles, then 4 weekly for 2 years. Fracture related hospitalisations (FRH) were identified using a prespecified coding framework of ICD10 diagnosis and OPCS procedure codes. Flexible parametric competing risks models were used to estimate 5- and 10yr cumulative incidence of FRH and subdistribution hazard ratios (SDHR).

Results: Linked data were available for 2,042 (734 M0, 1,308 M1) out of 2,140 eligible pts (95%). The 5-year cumulative incidence of FRH for M1 and M0 pts treated with ADT were 23% (95% CI 19-28%) and 11% (95% CI 8-15%) respectively. The 10-year cumulative incidence with ADT in M0 pts was 26% (95% CI 20-33%). Addition of ZA significantly reduced the incidence of FRH in M1 pts (SDHR 0.73, 95% CI 0.55-0.97; $p=0.015$). Data were inconclusive in M0 pts (SDHR 0.88, 95% CI 0.59-1.32, $p=0.549$). Doc had no significant effect on FRH in both M1 ($p=0.264$) and M0 ($p=0.570$), with no evidence of interaction between ZA and Doc in both M1 ($p=0.526$) and M0 ($p=0.805$).

Conclusions: High incidence of 10yr fracture related hospitalisations was observed in STAMPEDE trial participants with either M0 or M1 prostate cancer. Addition of ZA reduced risk of FRH in people with M1 disease but not with M0 disease. These data support the use of bone protection agents to reduce fracture risk in men with mHSPC.

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Legal entity responsible for the study: MRC Clinical Trials Unit UCL.

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1771MO Pembrolizumab (pembro) plus enzalutamide (enza) for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Randomized double-blind phase III KEYNOTE-641 study

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Background: Pts with mCRPC with progressive disease (PD) during 2nd generation hormonal agent therapy typically receive chemo next. Additional therapies are needed in this setting. Pembro + enza had antitumor activity in pretreated mCRPC in early phase studies. KEYNOTE-641 (NCT03834493) evaluated pembro + enza vs placebo (pbo) + enza in pts with chemo-naïve mCRPC with/without prior abiraterone (abi).

Methods: Eligible pts were male, aged ≥18 years, had ECOG PS ≤1, had confirmed mCRPC with no prior chemo except docetaxel in the hormone-sensitive setting, and had intolerance to or PD during prior abi or no prior abi. Pts were randomized 1:1 to pembro 200 mg or pbo IV Q3W for ≤35 cycles + enza 160 mg orally daily. Dual primary endpoints were overall survival (OS) and radiographic progression-free survival (rPFS) per PCWG-modified RECIST 1.1 by blinded independent central review. Time to initiation of first subsequent anticancer therapy (TFST) was a key secondary endpoint. Safety/tolerability was a secondary endpoint.

Results: 1244 pts were enrolled between Aug 21, 2019, and Jun 10, 2022 (n=621 to pembro + enza; n=623 to pbo + enza). As of Dec 12, 2022, the median (range) follow-up time at first prespecified interim analysis was 27.6 mo (6.1−39.8). 60.9% of all pts had prior abi and 29.1% had prior docetaxel, balanced between arms. The dual primary endpoints of rPFS (median 10.4 mo with pembro + enza vs 9.0 mo with pbo + enza; HR 0.98, 95% CI 0.84−1.14; P=0.41) and OS (median 24.7 mo vs 27.3 mo; HR 1.04, 95% CI 0.88−1.22; P=0.66) were not met. The prespecified boundary for futility for OS was crossed and the study was stopped. Median TFST was 13.2 mo vs 12.6 mo, respectively (HR 0.95, 95% CI 0.83−1.09). Any-grade and grade ≥3 treatment-related AEs occurred in 77.9% and 31.2% of 615 pts with ≥1 dose pembro + enza and 61.6% and 10.8% of 620 pts with ≥1 dose pbo + enza. 3 treatment-related deaths occurred with pembro + enza and none with pbo + enza.

Conclusions: Pembro + enza did not significantly improve efficacy outcomes vs pbo + enza in pts with mCRPC with/without prior abi. Pembro + enza was associated with more treatment-related AEs vs pbo + enza; no new safety signals were observed.

Clinical trial identification: NCT03834493.

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1772MO Pembrolizumab (pembro) plus enzalutamide (enza) and androgen deprivation therapy (ADT) for patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC): Randomized double-blind phase III KEYNOTE-991 study

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Background: New therapeutic options are needed to delay disease progression for pts with mHSPC. The combination of pembro + enza has shown antitumor activity in pts with metastatic prostate cancer. The phase 3 KEYNOTE-991 study (NCT04191096) investigated pembro or placebo (pbo) + enza + ADT in pts with next-generation hormonal agent (NHA)-naïve mHSPC.

Methods: Eligible pts (aged ≥18 yrs, ECOG PS ≤1) had confirmed mHSPC (≥2 bone lesions and/or visceral disease, verified centrally), no prior NHA, and had completed any prior docetaxel (≤6 cycles) ≤2 mo from randomization. Pts were randomized 1:1

to receive pembro 200 mg or pbo IV Q3W for ≤35 cycles + enza 160 mg orally daily + continuous ADT (if no history of bilateral orchiectomy). Dual primary endpoints were radiographic progression-free survival (rPFS) per PCWG-modified RECIST 1.1 by blinded independent central review and overall survival (OS). Key secondary endpoints included time to initiation of first subsequent anticancer therapy (TFST) and time to first symptomatic skeletal-related event (TTSSRE). Safety was a secondary endpoint.

Results: Between Mar 2, 2020, and Aug 9, 2021, 626 pts were randomized to pembro + enza and 625 to pbo + enza. As of Oct 31, 2022, the median (range) follow-up time at first prespecified interim analysis was 21.1 mo (14.8−32.0). Baseline characteristics were generally balanced between arms; ∼10% of pts received prior docetaxel in each arm. The primary endpoint of rPFS for pembro + enza vs pbo + enza was not met (median not reached [NR] vs NR, HR 1.20, 95% CI 0.96−1.49, P=0.95). Median OS was NR vs NR (HR 1.16, 95% CI 0.88−1.53). Median TFST was NR in both arms (HR 1.24, 95% CI 1.01−1.54). Median TTSSRE was NR in both arms (HR 0.89, 95% CI 0.61−1.30). Serious AEs occurred in 40.3% vs 23.2% of pts with pembro + enza vs pbo + enza. Any-grade and grade ≥3 treatment-related AEs occurred in 88.0% vs 67.0% and 41.8% vs 13.9% of pts, respectively.

Conclusions: The study was stopped for futility. The addition of pembro to enza plus ADT did not improve rPFS or OS in pts with NHA-naïve mHSPC and was associated with more serious and treatment-related AEs vs enza plus ADT.

Clinical trial identification: NCT04191096.

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1773P ICECaP-2: Validation of metastasis-free survival (MFS) as a surrogate for overall survival (OS) in localized prostate cancer (LPC) in a more contemporary era

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Background: Prior work from ICECaP (Xie et al, JCO 2017; ICECaP-1) showed that MFS is a valid surrogate for OS for patients (pts) with LPC treated predominantly before 2004, when docetaxel became available for metastatic castrate-resistant prostate cancer (mCRPC). We sought to validate this finding in a more contemporary era (ICECaP-2) with greater availability of docetaxel and AR-pathway inhibitors (ARPIs) for mCRPC.

Methods: Eligible trials for ICECaP-2 were those providing individual patient data (IPD) after publication of ICECaP-1 and evaluating adjuvant/salvage therapy for LPC, and which collected MFS and OS data. MFS was defined as distant metastases or death from any cause, and OS defined as death from any cause. Surrogacy was evaluated using a meta-analytic two-stage validation model, with an R^2 ≥0.7 defined *a priori* as clinically relevant.

Results: 15,164 IPD from 14 trials were included in ICECaP-2. For surrogacy condition 1, Kendall's tau was 0.92 for MFS with OS at the patient-level, and R^2 from weighted linear regression (WLR) of 8-yr OS on 5-yr MFS was 0.73 (95% CI 0.53-0.82) at the trial level. For condition 2, R^2 was 0.83 (0.64-0.89) from WLR of log (HR)-OS on log (HR)-MFS. The surrogate threshold effect on OS was an HR(MFS) of 0.81. Comparisons between ICECaP-1 and ICECaP-2 are shown in the table.

Table: 1773P

	ICECAP-1	ICECAP-2
N	12,712 pts (19 trials)	15,164 pts (14 trials)
Years of enrolment (%)		
1987-2004	11539 (91)	4716 (31)
2005-2009	1111 (9)	6059 (40)
2010-2016	62 (1)	4389 (29)
Median follow-up, yrs	9.9	8.3
Median time from metastasis to death (yrs)	1.9	3.1
No. of OS events (%)	5350 (42)	3168 (21)
No. of MFS events (%)	5733 (45)	3953 (26)
Individual-level surrogacy measures		
Kendall's tau	0.91	0.92
R^2 WLR 8-year-OS on 5-year MFS	0.83	0.73
Trial-level surrogacy measures		
R^2 WLR log(HR)-OS on log(HR)-MFS	0.92	0.83
Surrogate threshold effect	0.88	0.81

Conclusions: MFS remains a valid surrogate for OS in pts with LPC treated in a contemporary era with greater access to docetaxel and ARPIs for mCRPC. Surrogacy

effects were similar to those observed in ICECaP-1. This supports the use of MFS as the primary outcome measure for ongoing trials in LPC.

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1774P PC-PEP, a comprehensive daily six-month home-based prostate cancer: Patient empowerment program improves quality of life, physical fitness, and urinary function outcomes among prostate cancer patients with localized disease - Secondary analyses of a randomized clinical trial

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Background: In a recently published manuscript we demonstrated significant decreases in mental distress, anxiety and depression compared to standard of care following a 6m daily comprehensive program developed with patient engagement. Here we conduct secondary analyses examining the effects of this Prostate Cancer-Patient Empowerment Program (PC-PEP) on patient-reported urinary, bowel, sexual, hormonal and physical function among men scheduled for curative prostate cancer (PC) treatment.

Methods: This crossover randomized clinical trial evaluated 128 men aged 50−82 yr scheduled for curative prostate cancer surgery or radiotherapy (± hormone), 66 received the 6-mo PC-PEP intervention and 62 were randomized to standard of care for 6m and received PC-PEP to the end of the year. PC-PEP comprises regular physical strength and PFMT training, daily dietary advice, bio-feedback stress reduction, and social networking. Weekly online compliance surveys, the International Prostate Symptom Score (IPSS), Expanded Prostate Cancer Index Composite (EPIC), and SF-12 at baseline, 6 and 12m were completed. MLM analyses were used to evaluate the results.

Results: Baseline patient characteristics and outcomes between the two groups were comparable, and weekly compliance for PC-PEP was high among both groups (early v. late intervention). At six months, the PC-PEP group had improved IPSS bother score, EPIC Urinary Incontinence, EPIC Irritative/Obstructive score, physical fitness (lower weight and BMI), SF-12 physical, and mental health function when compared to the control group ($p=0.004$, $p=0.001$, $p=0.008$, $p=0.001$, $p=0.002$, and $p=0.003$ respectively). Analyses revealed that providing the intervention early or late was equally beneficial to patients. No other significant results emerged.

Conclusions: PC-PEP significantly improves lower urinary tract symptoms, physical function and overall quality of life among men scheduled for curative PC treatment compared to standard of care. The program is being currently tested in an international phase 4 trial.

Clinical trial identification: NCT03660085.

Legal entity responsible for the study: Nova Scotia Health Authority, Canada.

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1775P A newly-developed deep-learning algorithm: NAFNet outperforms ResNet50 for predicting adverse pathology events and biochemical recurrence time using MRI from prostate cancer patients

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Background: Although deep learning algorithms have shown promising results in medical imaging, their application in predicting adverse pathology events (AP) and biochemical recurrence-free survival (bRFS) in prostate cancer patients is relatively lagging. Here we aimed to evaluate the performance of a novel deep learning network, NAFNet, in predicting AP and bRFS based on pre-treatment multiparametric MRI imaging.

Methods: This multicentre study enrolled 514 prostate cancer patients from six tertiary hospitals throughout China from 2017 and 2021. A total of 367 patients from Fudan University Shanghai Cancer Centre with whole-mount histopathology of radical prostatectomy specimens were assigned to the internal set, and cancer lesions were delineated with whole-mount pathology as the reference. The external test set included 147 patients with BCR data from five other institutes. The prediction model (NAFNet-classifier) and integrated nomogram (DL-nomogram) were constructed based on NAFNet. To evaluate the predictive ability of DL-nomogram for AP, we compared DL-nomogram with radiology score (PI-RADS), and clinical score (Cancer of the Prostate Risk Assessment score (CAPRA)). ROC curves and DCA analyses were performed to assess the AP prediction ability of various models, and survival analyses were also made for bRFS.

Results: After training and validation in the internal set, ROC curves in the external test set showed that NAFNet-classifier alone outperformed ResNet50 in predicting AP (AUC:0.799, 95%CI:0.724-0.873 vs. AUC:0.703, 95%CI:0.618-0.787, $P=0.013$). The DL-nomogram, including the NAFNet-classifier, clinical T stage and biopsy results, showed the highest AUC (0.915, 95% CI: 0.871-0.959) and accuracy (0.850) compared with the

PI-RADS and CAPRA scores. Additionally, the DL-nomogram outperformed the CAPRA score with a higher C-index (0.732, P<0.001) in predicting bRFS.

Conclusions: Our newly-developed deep learning network, NAFNet, combined with clinical factors, accurately predicted AP and poor prognosis in prostate cancer patients from preoperative MRI imaging, providing a potential AI tools in medical imaging risk stratification.

Legal entity responsible for the study: B. Dai.

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1776P Body composition in adult life and prostate cancer (PCa) incidence and mortality: The PROCA-life study

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Background: The global increase in obesity parallels the increase in PCa incidence, but the role of excess weight and weight change throughout adult life and their implications for PCa risk and prognosis are still under debate. We studied whether pre-diagnostic body mass index (BMI) and weight change is linked to PCa risk and prognosis.

Methods: A total of 16 879 healthy men were included to study PCa risk and prognosis in the Prostate Cancer Study throughout life (PROCA-*life),* based on those who participated in the prospective cohort Tromsø Study (1994-2016). Pre-diagnostic BMI and weight change (relative weight change in percent of baseline weight between two waves of the Tromsø study) during follow-up were measured. Detailed information from histopathological and clinical medical records for PCa cases were obtained. Cox proportional hazard and logistic regression models were used to estimate hazard ratios (HRs) and odds ratios (ORs) for the associations between pre-diagnostic measurements of BMI and weight change during follow-up, and PCa risk and overall and PCa specific mortality. Regression models were used to evaluate incidence rate ratios (IRR).

Results: Overall, the participants had a median age at study entry of 44 years, 46.0% were overweight and 13.8% were obese. In total 904 men developed PCa during follow-up, with a median age at diagnosis of 68 years. The incidence rates for PCa increased from 1995 to 2019 (overall IRR 2.27, 95% CI 1.82-2.83). We observed that men with a pre-diagnostic BMI $\geq$ 30kg/m^2 at study entry, and who had a weight gain $\geq$ 5% during follow-up, had a three-fold increased risk for incident PCa (HR 2.94, 95% CI 1.36-6.36). Overweight was associated with lower Gleason grade (OR 0.64, 95% CI 0.43-0.96) and lower Prostate Specific Antigen (OR 0.69, 95% CI 0.48-0.99). Overall, 311 PCa cases died, of whom 154 was PCa related deaths (17%). Pre-diagnostic obesity was associated with PCa-specific death (HR 1.73, 95% CI 1.03-2.91).

Conclusions: Our observation that weight gain in adult pre-diagnostic obese men was associated with increased risk for incident PCa, and that pre-diagnostic obesity increased the risk of PCa-mortality, support the importance to combat excess weight gain in the general population.

Legal entity responsible for the study: Data protection office at University Hospital of North-Norway (UNN).

Funding: University of Tromsø.

Disclosure: All authors have declared no conflicts of interest.

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1777P Enzalutamide (enza) monotherapy for the treatment (tx) of prostate cancer with high-risk biochemical recurrence (BCR): EMBARK secondary endpoints

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Background: The primary analysis of EMBARK demonstrated that after a median follow-up of 60.7 months metastasis-free survival for enza + leuprolide acetate (LA; HR 0.42; 95% CI, 0.30–0.61; p<0.0001) and enza monotherapy (HR 0.63; 95% CI, 0.46–0.87; p=0.0049) was clinically meaningful and statistically superior to placebo + LA. Here, we present other non-key secondary efficacy endpoints for enza monotherapy vs placebo + LA.

Methods: EMBARK (NCT02319837) is a phase 3 study of patients (pts) with high-risk BCR: prostate-specific antigen (PSA) doubling time $\leq$9 months and PSA $\geq$2 ng/mL above nadir post-radiotherapy (RT) or $\geq$1 ng/mL after radical prostatectomy (RP) $\pm$ postoperative RT. Pts were randomized (1:1) to 160 mg/day enza monotherapy (open-label) or placebo + LA (LA alone). LA 22.5 mg was administered every 12 weeks. If the PSA was <0.2 ng/mL at Week 36, tx was suspended at Week 37 and restarted when PSA was $\geq$2 ng/mL for pts with primary RP, and $\geq$5 ng/mL for pts without RP. Secondary endpoints included time to: distant metastasis, symptomatic progression, first symptomatic skeletal event, and resumption of any hormonal therapy following tx suspension.

Results: 713 pts were eligible and randomized (enza monotherapy, n=355; LA alone, n=358). Median (range) tx duration excluding tx suspension was 45.9 (0.4–88.9) months for enza monotherapy and 35.4 (0.7–85.7) months for LA alone. Time to: distant metastasis (HR 0.61; 95% CI, 0.41–0.92; p=0.0171), symptomatic progression (HR 0.62; 95% CI, 0.49–0.79; p<0.0001), and first symptomatic skeletal event (HR 0.42; 95% CI, 0.23–0.79; p=0.0057) all favored enza monotherapy vs. LA alone. Time to resumption of any hormonal therapy after tx suspension favored LA alone vs enza monotherapy (HR 1.66; 95% CI, 1.38–1.98; p<0.0001). All p-values are nominal.

Conclusions: In pts with high-risk BCR, enza monotherapy showed clinically meaningful delays in time to distant metastasis, symptomatic progression, and time to first symptomatic skeletal event vs LA alone. After tx suspension, enza monotherapy shortened time to resumption of any hormonal therapy vs LA alone. Further work is needed to understand the risks and benefits of enza monotherapy vs other options for high-risk BCR.

Clinical trial identification: NCT02319837.

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1778P Treatment (tx) of high-risk biochemically recurrent prostate cancer with enzalutamide (enza) in combination with leuprolide acetate (LA): Secondary endpoints from EMBARK

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Background: In the phase 3 EMBARK trial, after a median follow-up of 60.7 months, enza + LA (HR 0.42; 95% CI, 0.30–0.61; p<0.0001) and enza monotherapy (HR 0.63; 95% CI, 0.46–0.87; p=0.0049) demonstrated statistically superior and clinically meaningful improvements in metastasis-free survival vs placebo (pbo) + LA. Here, we present other non-key secondary efficacy endpoints for enza + LA vs pbo + LA.

Methods: EMBARK (NCT02319837) is a study of patients (pts) with high-risk biochemical recurrence (BCR): prostate-specific antigen (PSA) doubling time ≤9 months and PSA ≥2 ng/mL above nadir post-radiotherapy (RT) or ≥1 ng/mL after radical prostatectomy ± postoperative RT. Pts were double-blinded and randomized (1:1) to enza 160 mg/day + LA or pbo + LA (LA alone). LA 22.5 mg was administered every 12 weeks. If the PSA at Week 36 was <0.2 ng/mL, tx was suspended at Week 37 and restarted when PSA was ≥2 ng/mL for pts with primary RP, and ≥5 ng/mL for pts without RP. Secondary endpoints included time to: distant metastasis, resumption of any hormonal therapy after tx suspension, castration resistance, symptomatic progression, and first symptomatic skeletal event.

Results: 713 pts were eligible and randomized into the study (enza + LA, n=355; LA alone, n=358). Median (range) tx duration excluding tx suspension was 32.4 (0.1–83.4) months for enza + LA and 35.4 (0.7–85.7) months for LA alone. Time to: distant metastasis (HR 0.44; 95% CI, 0.28–0.69; p=0.0002), resumption of any hormonal therapy after tx suspension (HR 0.69; 95% CI, 0.58–0.83; p<0.0001), castration resistance (HR 0.09; 95% CI, 0.05–0.16; p<0.0001), symptomatic progression (HR 0.55; 95% CI, 0.43–0.70; p<0.0001), and first symptomatic skeletal event (HR 0.26; 95% CI, 0.13–0.55; p=0.0001) favored enza + LA vs LA alone. All p-values are nominal.

Conclusions: In pts with high-risk BCR, enza + LA vs LA alone demonstrated clinically meaningful delays in time to: distant metastasis, resumption of any hormonal therapy after tx suspension, castration resistance, symptomatic progression, and first symptomatic skeletal event. If approved, enza combination may represent a new standard of care for pts with high-risk BCR.

Clinical trial identification: NCT02319837.

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Disclosure: S.J. Freedland: Financial Interests, Institutional, Speaker, Consultant, Advisor: Astellas Pharma Inc., Pfizer, Janssen, Bayer, Sanofi, Dendreon, Myovant, AstraZeneca, Merck. M.E. Gleave: Financial Interests, Institutional, Stocks or ownership: OncoGenex Technologies, Sustained Therapeutics, Sitka Pharmaceuticals; Financial Interests, Institutional, Speaker, Consultant, Advisor: Astellas Pharma Inc., AstraZeneca, Bayer, GDx, Janssen, Sanofi, Pfizer, TerSera, Roche; Financial Interests, Institutional, Other, Holds patents for OGX-011: OGX-011; Financial Interests, Institutional, Other, Holds patents for OGX-427: OGX-427; Financial Interests, Institutional, Other, Holds patents for ST-CP: ST-CP; Financial Interests, Institutional, Other, Holds patents for ST-POP: ST-POP. U.F.F. De Giorgi: Financial Interests, Institutional, Speaker, Consultant, Advisor: Astellas Pharma Inc., Bayer, BMS, Ipsen, Janssen, Novartis, Pfizer, Sanofi, PharmaMar; Financial Interests, Institutional, Research Funding: AstraZeneca, Roche, Sanofi; Financial Interests, Personal, Funding, Travel funds: BMS, Ipsen, Janssen, Pfizer, Roche. A. Rannikko: Financial Interests, Institutional, Advisory Board: Bayer, Janssen, Orion Pharma; Financial Interests, Institutional, Leadership Role, Board chair: Orion Research Foundation; Financial Interests, Institutional, Member of Board of Directors: Ida Montin Research Foundation. C. Pieczonka: Financial Interests, Institutional, Speaker, Consultant, Advisor: AstraZeneca, Bayer, Blue Earth, CellVax, Dendreon, Eli Lilly, Janssen, Merck, Myovant Sciences, Pfizer, Daiichi Sankyo, Sun; Financial Interests, Institutional, Other, Honoraria: AstraZeneca, Bayer, Dendreon, Janssen, Merck, Myovant Sciences, Sun; Financial Interests, Institutional, Other, Honoraria; received equipment, materials, drugs, medical writing, gifts or other services: Astellas Pharma Inc., Pfizer. K. Brasso: Financial Interests, Institutional, Speaker, Consultant, Advisor: Astellas Pharma Inc., Bayer, Janssen, Merck Sharp & Dohme, Novartis. H. Woo: Financial Interests, Institutional, Speaker, Consultant, Advisor, Consultant and shareholder: Prospection Party Ltd; Financial Interests, Institutional, Advisory Board, Advisory board member and has received honoraria: Astellas Pharma Inc.; Financial Interests, Institutional, Other: Bayer, Boston Scientific, Cipla, Janssen; Financial Interests, Institutional, Member of Board of Directors: Australian and New Zealand Urogenital and Prostate Cancer Trials Group, Australasian Urological Foundation, Australasian College of Surgeons, Urological Society of Australia and New Zealand. A. Gomez Caamaño: Financial Interests, Institutional, Speaker, Consultant, Advisor: Astellas Pharma Inc., Bayer, Janssen; Financial Interests, Institutional, Funding, Institutional funding: Astellas Pharma Inc.; Financial Interests, Institutional, Other, Honoraria: Astellas Pharma Inc., AstraZeneca, Bayer, Janssen; Financial Interests, Personal, Other, Travel expenses: Astellas Pharma Inc., Bayer, Janssen. Y. Tang, B. Rosbrook, F. Zohren: Financial Interests, Personal, Full or part-time Employment: Pfizer; Financial Interests, Personal, Stocks/Shares: Pfizer. G.P. Haas, M. Rosales: Financial Interests, Personal, Full or part-time Employment: Astellas Pharma, Inc.; Financial Interests, Personal, Stocks/Shares: Astellas Pharma, Inc.. N.D. Shore: Financial Interests, Institutional, Research Funding: AbbVie, Amgen, Astellas Pharma Inc., AstraZeneca, Bayer, BMS, Dendreon, Exact Sciences, Ferring, FerGene, Janssen, MDx Health, Merck, Myovant, Nymox, Pfizer, Sanofi, Tolmar. All other authors have declared no conflicts of interest.

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1779P PSMA guided approach for bIoCHEmical relapse after prostatectomy-PSICHE trial

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Background: Salvage radiotherapy (SRT) is one of the cornerstone for treatment of biochemical relapse (BR) after radical prostatectomy (RP). One randomized controlled trial suggested that next generation imaging (NGI) may have a significant impact on patients management in this scenario. Nonetheless, how to best manage oligometastatic patients identified by PSMA PET imaging requires additional investigation. PSICHE (NCT05022914) is a prospective multicentric trial aimed to test a [68Ga]Ga-PSMA-11 PET/CT imaging tailored strategy.

Methods: Patients affected by biochemical relapse post RP (defined as PSA >0.2 ng/ml, <1 ng/ml) underwent [68Ga]Ga-PSMA-11 PET/CT imaging. After staging, management was performed according to a pre-defined algorithm. Observation and re-staging at further PSA progression were proposed to patients with negative PSMA and previous postoperative RT. Prostate bed SRT was proposed to all patients with a negative staging or positive imaging within prostate bed. Stereotactic body radiotherapy (SBRT) to all sites of disease was used for all patients with pelvic nodal recurrence (nodal disease < 2 cm under aortic bifurcation) or oligometastatic disease. Androgen deprivation therapy +/- androgen receptor targeted agent was provided in case of widespread metastatic disease. In the present analysis, we report early biochemical analysis focusing on complete biochemical response (PSA ≤0.2 ng/ml) and biochemical response (PSA ≤50% if compared to baseline value before treatment). Gastrointestinal (GI) or genitourinary (GU) toxicity was assessed according to CTCAE v 4.0.

Results: Overall, 110 patients were included in the current analysis. At 3 months after treatment, complete biochemical response and biochemical response were detected in 45.4% and 53.6% of patients, respectively. Seven patients had G1 GI toxicity, GU toxicity was reported in 30 patients (only 3 G2 adverse events, overall). No G>2 toxicity was reported.

Conclusions: A PSMA targeted treatment strategy led to promising results and was well tolerated within a prospective multicentric trial.

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1780P The health inequality impact of darolutamide for non-metastatic castration-resistant prostate cancer: A distributional cost-effectiveness analysis

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Background: In the backdrop of keener scrutiny of health equity issues, the impact of a new intervention on inequality in health outcomes is increasingly viewed as an element in health technology assessment. Non-Hispanic (NH) Black patients are disproportionally affected by non-metastatic castration-resistant prostate cancer (nmCRPC). Darolutamide is an approved treatment for nmCRPC and was shown to be effective and safe among NH-Black patients in the ARAMIS trial. The objective of this study was to quantify the health inequality impact of darolutamide+ androgen-deprivation therapy (ADT) relative to ADT for nmCRPC in the U.S. by means of a distributional cost-effectiveness analysis.

Methods: With a decision model, the quality-adjusted life years (QALYs) and costs were estimated for NH-White, NH-Black, Asian, and Hispanic patients. The degree of differences in QALYs among these subgroups was expressed with Atkinson relative inequality indices (0 = equal outcomes and 1 = maximum inequality between subgroups) for both strategies. Their difference was defined as the inequality impact of darolutamide among treated patients. Subtracting equally distributed health opportunity costs from the QALY gains with darolutamide facilitated calculation of the overall health inequality impact across population subgroups.

Results: Darolutamide+ADT resulted in an additional 1.04 (95% confidence interval 0.57; 1.49) QALYs per treated patient relative to ADT, with the greatest gain observed among NH-Black patients (1.48 QALYs (0.49; 2.72)). The relative inequality in QALYs among patients reduced by 66%, from an inequality score of 0.032 (0.004; 0.080) with ADT to 0.011 (0.000; 0.049) with darolutamide+ADT. Factoring in health opportunity costs, treatment of eligible nmCRPC patients with darolutamide resulted in the largest net gain in QALYs among the NH-Black population, thereby having a favorable impact on inequalities in quality adjusted life expectancy.

Conclusions: Darolutamide+ADT for the treatment of nmCRPC results in greater health outcomes than ADT, and reduces inequality in health outcomes across subgroups according to race and ethnicity in the U.S.

Legal entity responsible for the study: The authors.

Funding: Bayer Pharmaceuticals.

Disclosure: J. Janssen, T. Flottemesch, I. Brewer, P. Sullivan: Financial Interests, Institutional, Full or part-time Employment, Precision heor was hired by Bayer to perform the research: PRECISIONheor. J. Partridge: Financial Interests, Personal, Full or part-time Employment, Full time employee of Bayer: Bayer Pharmaceuticals.

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1781P Health-related quality of life (HRQoL) deterioration-free survival (DetFS) by prostate-specific antigen (PSA) decline in darolutamide (DARO)-treated patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) from ARAMIS

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Background: In ARAMIS (NCT02200614), DARO plus androgen-deprivation therapy (ADT) significantly increased metastasis-free survival by nearly 2 years and reduced the risk of death by 31% in patients (pts) with nmCRPC. DARO also significantly delayed time to deterioration of HRQoL and had a positive impact on local disease recurrence and symptom control. We report the effect of DARO on HRQoL DetFS by PSA decline in ARAMIS.

Methods: Pts with nmCRPC were randomized 2:1 to DARO or placebo, both with ADT. Using the primary analysis data cutoff (Sept 3, 2018), DARO-treated pts were grouped by PSA decline from baseline at wk 16 of ≥90% (PSA90), ≥50% to <90% (PSA50-90), and <50% (PSA50). DetFS was defined as the time from randomization until the earliest event of deterioration in HRQoL (EORTC Quality of Life Questionnaire Prostate Cancer Module urinary and bowel symptoms subscales and Functional Assessment of Cancer Therapy-Prostate [FACT-P] prostate cancer subscale [PCS] and Total), metastasis, death, or treatment discontinuation. Median (95% CIs) DetFS was calculated using Kaplan-Meier estimates.

Results: Of 955 DARO pts, 899 had PSA values at wk 16 and 403 (44.8%) achieved PSA90. Pts achieving PSA90 decline had longer median DetFS of HRQoL for urinary and bowel symptoms and for FACT-P Total and PCS vs those with PSA50-90 and <50% PSA decline (Table). For pts with PSA90, PSA50-90, and <50% PSA decline, 3-year DetFS rates were 38.0%, 31.2%, and 14.6% for urinary symptoms and 33.8%, 17.4%, and 13.3% for bowel symptoms.

Table: 1781P HRQoL DetFS in DARO-treated pts by PSA decline from baseline at wk 16

DetFS, median (95% CI), months	PSA ≥90% decline (n=403)	PSA ≥50% to <90% decline (n=379)	PSA <50% decline (n=117)
EORTC urinary symptoms subscale	22.3 (18.6–30.8)	18.5 (14.8–22.2)	11.6 (7.6–15.0)
EORTC bowel symptoms subscale	25.6 (18.4–26.0)	14.7 (11.2–15.0)	11.5 (7.6–15.0)
FACT-P PCS	22.3 (18.4–NR)	15.0 (11.1–18.5)	11.1 (7.6–18.3)
FACT-P Total	NR (NR–NR)	32.9 (26.0–40.5)	16.1 (11.1–25.8)

NR, not reached.

Conclusions: In ARAMIS, a high proportion of DARO pts achieved PSA90. DARO demonstrated local symptom control for urinary and bowel measures and better HRQoL in pts who achieved PSA90. These findings confirm the cancer control and HRQoL benefits of early DARO treatment for pts with nmCRPC.

Clinical trial identification: NCT02200614.

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1782P Prostate radiotherapy reduces long-term risk of obstructive uropathy in metastatic hormone sensitive prostate cancer (mHSPC): Results from the STAMPEDE M1|RT comparison

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Background: Men with advanced prostate cancer are at risk of upper urinary tract obstruction (UUTO) due to local progression leading to increased morbidity. Primary site radiotherapy (RT) improves overall survival in patients with low volume metastatic hormone sensitive prostate cancer (mHSPC), with limited data available to demonstrate its impact on local progression. Accessible, high quality healthcare systems data (HSD) provides accurate event data beyond standard trial follow up, permitting evaluation of the impact of primary RT on need for UUTO interventions.

Methods: Linked HSD from Hospital Episode Statistics (HES) with follow-up to March 2021 were available for patients randomised 1:1 in England between arms A (standard of care [SOC]) and H (SOC+RT). Radiotherapy was delivered either daily: 55 Gy in 20 fractions over 4 weeks or weekly: 36 Gy in six fractions over 6 weeks. Interventions for UUTO (including percutaneous nephrostomy and or ureteric stent insertion) were identified using a comprehensive coding framework using International Classification of Diseases (ICD 10) diagnosis and Classification of Interventions and Procedures (OPCS 4) codes Multivariate flexible parametric survival models adjusted for randomisation stratification factors were used to estimate the treatment effect of primary RT on the cumulative incidence of UUTO and sub distribution hazard ratios (SDHR).

Results: 1791/2061 (88%) were followed up by English hospitals; connected HSD were available for 1724/1791 (96%). After excluding 19 patients who had a UUTO intervention in the 90 days leading to randomisation, model-based 5-year incidence of UUTO requiring intervention was 5% [4; 7%] in patients randomised to SOC, and 3% [2; 4%] in patients randomised to SOC + RT (SDHR 0.568, 95% CI 0.353-0.912; p=0.017). Treatment effects were comparable in high- and low-volume metastasis subgroups.

Conclusions: UUTO interventions are performed in a modest proportion of mHSPC patients. Prostate radiotherapy significantly reduced the use of UUTO interventions. These data support the use of prostate radiotherapy in men with mHSPC at risk of UUTO.

Clinical trial identification: NCT00268476.

Legal entity responsible for the study: MRC Clinical Trials Unit and UCL.

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1783P PROSTRATEGY: A SOGUG randomized trial of androgen deprivation therapy (ADT) plus docetaxel (dct) +/- nivolumab (nivo) or ipilimumab-nivolumab (ipi-nivo) in high-volume metastatic hormone-sensitive prostate cancer (hvHSPCa) - Efficacy results from the pilot phase

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Background: ADT+ dct has been a standard of care first-line for hvHSPC patients (pt). We hypothesized that early addition of ipi and/or nivo could improve outcomes.

Methods: PROSTRATEGY was designed as a seamless randomized (2/1/1) multi-arm multi-stage trial, to compare ADT+dct (75 mg/m^2 x6 cycles) vs ADT+dct→nivo (3 mg/Kg/2w x 12 mo), or ADT+ipi+dct→nivo (ADT + ipi 1 mg/Kg/3w x 2 cycles → dct x3 cycles → ipi 3mg/Kg/3w x2 cycles → dct x3 cycles → nivo x 12 mo) in hvHSPCa pt in 30 academic centers in Spain. The aims of the pilot phase were to check ffeasibility, safety and efficacy outcomes in terms of radiographic and PSA response, radiographic and clinical progression-free survival or death (rPFS, cPFS), time to castration-resistant prostate cancer or death (TCRPC), time to symptomatic skeletal-related event (TSSRE) and overall survival (OS) from the first dose of ADT, based on both RECIST1.1 + PCWG3 and iRECIST (Seymour, Lancet Oncol 2017) + PCWG3 criteria.

Results: 150 pt were randomized to dct (75 pt), dct-nivo (37 pt) or dct+ipi-nivo (38 pt). Mean age was 66.4 y (39% >70 y), 98% were Caucasian, 99.3% had ECOG 0-1, 88% were metastatic at diagnosis, mean PSA was 157 ng/ml, 88% had Gleason ≥ 8, 31% visceral involvement, and 17% received local therapy to the prostate, with no differences among arms. With a median follow-up of 32.5 mo from ADT, 60% of pt have progressed and 41.3% have died. Safety is described separately. Efficacy results are summarized in the table.

Conclusions: The addition of ipi and/or nivo to ADT + Dct in pt with hvHSPCa is feasible. So far, we have found no statistical or clinically meaningful differences between arms that justify the continuation of the study. Results seem to be similar regardless of using PCWG3 plus either RECIST or iRECIST criteria although some differences between both methods may appear with longer follow-up.

Clinical trial identification: EudraCT 2017-004377-13.

Legal entity responsible for the study: SOGUG (Spanish Genitourynary Oncology Group).

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Table: 1783P

	RECIST 1.1 + PCWG3			iRECIST 1.1 + PCWG3	
	Dct	Dct→nivo	Dct+ipi→nivo	Dct→nivo	Dct+ipi→nivo
PSA < 50% PSA nadir <0.2 Median PSAPFS (mo)	88% 21.3% 15.0	97.3% 27% 17.4	76.3% 36.8% 14.2	-	-
CR+PR CR+PR+SD	34.7% 88.0%	43.2% 81.1%	44.7% 73.7%	43.2% 81.1%	44.7% 73.7%
Median rPFS (mo) (95%CI)	29.2 (23-31)	25.9 (14.2-30)	23.7 (14.3-39)	24.8 (18-33)	27.8 (15.8-39)
Median cPFS (mo) (95%CI)	16.2 (12-23)	14.2 (10-29)	14.3 (8.4-22)	23.3 (13.7-30)	18.6 (8.4-32)
Median TCRPC (mo) (95%CI)	10.4 (8.5-12)	13.7 (8-27)	12.5 (5-16)	13.8 (9-26)	12.5 (45-17)
Median TSSRE (mo)	25.8	NR	NR	-	-
Median OS (mo) (95%CI) 18-mo OS HR vs Dx (95%CI)	32.1 (28-39) 88.4% -	29.5 (19-NR) 76.2% 1.3 (0.7-2.4)	30.4 (25-38) 76.5% 1.2 (0.7-2.2)	-	-

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1784P Prostate-specific antigen (PSA) outcomes with darolutamide (DARO): Androgen-deprivation therapy (ADT) and docetaxel (DOC) in patients (pts) with high- and low-volume metastatic hormone-sensitive prostate cancer (mHSPC) in ARASENS

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Background: In ARASENS (NCT02799602), DARO + ADT + DOC significantly reduced risk of death by 32.5% (HR 0.68; 95% CI 0.57—0.80; $P<0.0001$) vs ADT + DOC in pts with mHSPC. In post hoc analyses, HRs for overall survival (OS) were similar for pts with high-volume (HV HR 0.69; 95%CI 0.57—0.82) and low-volume (LV HR 0.68; 95% CI 0.41—1.13) disease. We report PSA outcomes in these pt subgroups.

Methods: Pts with mHSPC were randomized to DARO 600 mg twice daily or placebo (PBO), both with ADT + DOC. PSA was measured at screening and every 12 weeks. Analyses included the proportion of patients achieving undetectable PSA (<0.2 ng/mL) and time to PSA progression. The association between undetectable PSA at any time with time to PSA progression and OS was evaluated using Kaplan-Meier estimates with HRs (95% CI) based on a stratified Cox regression model.

Results: Of 1305 pts, 1005 (77%) had HV disease and 300 (23%) had LV disease. Rapid undetectable PSA response as early as 12 weeks was achieved in nearly twice as many patients receiving DARO vs PBO and continued to increase for both HV and LV subgroups over time (at 24 weeks: HV 43.1% vs 21.7%, LV 66.9% vs 31.5%; at 52 weeks, HV 54.7% vs 23.6%, LV 77.9% vs 34.9%; and at any time, HV 62.2% vs 25.8%, LV 83.8% vs 38.4%). Time to PSA progression was prolonged in pts receiving DARO vs PBO in HV (HR 0.30; 95% CI 0.24—0.37) and LV (HR 0.09; 95% CI 0.05—0.18) pts (4-yr PSA progression-free rates: HV 65.8% vs 27.0%; LV 91.7% vs 36.3%). Pts receiving DARO who achieved undetectable PSA had improved time to PSA progression (HV HR 0.11, 95% CI 0.07—0.16; LV HR 0.02, 95% CI 0.004—0.10) and improved OS (HV HR 0.20; 95% CI 0.15—0.27; LV HR 0.34; 95% CI 0.14—0.79) vs those who did not.

Conclusions: Early treatment intensification with DARO + ADT + DOC allows pts with HV and LV mHSPC to achieve rapid, deep, and durable PSA responses that are associated with improved time to PSA progression and OS.

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1785P Changes in bone mineral density, trabecular bone score and body composition in metastatic hormone-sensitive prostate cancer (mHSPC) patients randomized to receive androgen deprivation + enzalutamide plus/minus zoledronic acid: The BonEnza study

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Background: Androgen deprivation therapy (ADT) is associated with increased fracture risk, due to bone loss and bone quality impairment, as well as with profound alterations in body composition favoring the transition to sarcopenic obesity. Additional metabolic effects of next generation hormonal agents (NGHA) in combination with ADT have been poorly studied.

Methods: BonEnza (NCT03336983) is a prospective phase II trial in which mHSPC patients were randomized to receive either ADT plus enzalutamide (E arm) or the same combination with the addition of zoledronic acid (EZ arm). Bone mineral density (BMD), trabecular bone score (TBS), fat body mass (FBM) and lean body mass (LBM) were assessed at baseline and after 18 months using dual energy x-ray absorptiometry (DEXA) scan.

Results: From February 2018 to December 2022, a total of 89 patients (46 from EZ arm and 43 from E arm), had paired DEXA evaluation at both timepoints. Femoral BMD and TBS significantly reduced in E arm (-9.1%, $p<0.001$; -3.1%, $p=0.001$, respectively), while they increased in EZ arm (5.3%, $p<0.001$; 2.8%, $p=0.008$, respectively). FBM increased by 22.7% ($p<0.001$) and LBM decreased by 6.3% ($p<0.001$) after 18 months of therapy, irrespective of study arm.

Conclusions: The addition of enzalutamide to ADT is associated with a marked reduction in BMD and impaired bone quality as measured by TBS. Both effects are prevented by zoledronic acid administration. The reduction in LBM and increase in FBM were doubled compared to previous observations with ADT alone, putting patients at an elevated risk of sarcopenic obesity.

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1786P Effect of rapid ultra-low prostate-specific antigen decline (UL PSA) in TITAN patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) who received apalutamide (APA) plus androgen deprivation therapy (ADT)

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Background: In TITAN mCSPC pts, 3 mos' APA + ADT produced rapid and deep $\leq$0.2 ng/mL PSA decline that was associated with improved overall survival (OS) (Chowdhury et al, Ann Oncol. 2023). Here we evaluate the effect of UL PSA on outcomes.

Methods: 525 and 527 pts receiving 240 mg/d APA or placebo (PBO) + ADT were analyzed. Two groups of UL PSA, >0.02 to $\leq$0.2 ng/mL (UL1) and $\leq$0.02 ng/mL (UL2), were assessed for association with OS, radiographic progression-free survival, time to castration resistance, and time to PSA progression using landmark analysis, Kaplan-Meier method, and Cox proportional hazards model.

Results: Of 515 APA and 520 PBO pts with evaluable UL PSA values, 49% and 17%, respectively, achieved UL2 PSA during the study. By 3 mos, UL1 and UL2 were achieved in 38% and 23% of APA and 15% and 5% of PBO pts. By 6 mos, these values were 29% and 36% (APA), and 17% and 6% (PBO). APA pts with UL1/UL2 at 3 mos had lower baseline PSA and higher % of low-volume disease vs PSA>0.2 ng/mL. Pts with UL1/UL2 at 3 or 6 mos had improved long-term outcomes irrespective of volume. Volume-adjusted outcomes were significantly improved in pts with UL1/UL2 achieved at 3 mos (Table) or at 6 mos. At 42 mos' follow-up post landmark, survival rate (% [95% CI]) was 89 (81-94), 81 (75-85), and 34 (26-43) when UL2 was achieved at 3 mos, after 3 mos, or never after 3 mos and was 89 (83-93), 77 (70-83), and 34 (26-43) when UL2 was achieved at 6 mos, after 6 mos, or never after 6 mos. Survival rate at 42 mos with UL1, UL2, or none achieved at any time was 59 (48-68), 92 (88-95), and 33 (26-41). APA safety profile across subgroups was consistent with previous reports.

Table: 1786P

HR (95% CI)	PSA values achieved at landmark 3 mos vs PSA >0.2 ng/mL (ref) in APA group[a]	
	UL1 (>0.02 to $\leq$0.2 ng/mL)	UL2 ($\leq$0.02 ng/mL)
OS[b]	0.46 (0.31-0.67)	0.24 (0.13-0.43)
Radiographic progression-free survival[c]	0.54 (0.35-0.83)	0.28 (0.14-0.54)
Time to castration resistance[b]	0.56 (0.39-0.8)	0.2 (0.11-0.38)
Time to PSA progression[b]	0.51 (0.34-0.76)	0.11 (0.04-0.27)

[a]Stratified by disease volume at baseline. [b]44.0 mos follow-up. [c]22.7 mos follow-up.

Conclusions: More TITAN mCSPC pts achieved UL PSA with APA vs PBO. Rapid and deep UL PSA was associated with significantly improved survival outcomes regardless of disease volume, most notably UL2. Data may guide design of future treatment escalation/de-escalation trials in mCSPC.

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1787P Prostate specific membrane antigen positron emission tomography (PSMA PET)-directed clinical outcomes in metastatic hormone-sensitive prostate cancer (mHSPC): Implications for the STAMPEDE2 trial design

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Background: The potential for PSMA PET-directed treatment decisions to improve outcomes in mHSPC remains unknown. We explored first response and progression/relapse patterns in newly diagnosed PSMA PET-detected mHSPC and correlated PET-directed staging with clinical outcomes.

Methods: 184 patients with baseline PSMA PET were retrospectively reviewed. Patients were sub-grouped into oligometastatic disease (OMD) and polymetastatic disease (PMD) utilising the STAMPEDE2 trial definition. Data on patient demographics, treatment, and imaging findings were collected. Treatment response was assessed using PSA nadir and radiological imaging at six months from PSA nadir. Disease progression/relapse was assessed using PCWG3, RECIST 1.1 and PERCIST 1.0 criteria. Kaplan Meier method estimated median time to radiographic progression-free survival (rPFS).

Results: Median age was 69 years. All patients had androgen deprivation therapy. 161/184 (88%) had additional systemic therapies. 99/184 (54%) had OMD and 85/184 (46%) had PMD. Prostate radiotherapy was given in 76/99 (77%) OMD patients and 47/85 (55%) PMD patients. Median time to PSA nadir in OMD and PMD was 10 months (range 1 to 29) and 8 months (range 1 to 36), respectively. Response images were available in 35/99 (35%) OMD patients and 39/85 (46%) PMD patients. Median time to radiological response in OMD and PMD was 10 months (range 2 to 58) and 9 months (range 2 to 36), respectively. Radiological progression in OMD most frequently occurred with new sites of disease (73%). Median rPFS was 53 months (95% CI 40, undefined) in OMD patients and 35 months (95% CI 22, 43) in PMD patients.

Table: 1787P Radiological response and progression/relapse in OMD and PMD

	OMD (N= 99)	PMD (N= 85)
Radiological response	**n= 35 (35%)**	**n= 39 (46%)**
Complete Response	12 (34%)	7 (18%)
Partial Response	21 (60%)	29 (74%)
Stable Disease	1 (3%)	2 (5%)
Not evaluable	1 (3%)	1 (3%)
Site of Radiological progression/relapse compared with baseline disease	**n= 22 (22%)**	**n= 37 (43%)**
Same sites	5 (23%)	18 (49%)
Different sites	10 (45%)	9 (24%)
Mixed sites	6 (27%)	10 (27%)
Not evaluable	1 (5%)	0 (0%)

Conclusions: PSMA PET-guided outcomes were similar to series with conventional staging, suggesting PET-directed therapy choices might not significantly influence time to progression. This will be further investigated in the forthcoming STAMPEDE2 trial.

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1788P Association between deep prostate-specific antigen decline and survival in patients with high-volume metastatic hormone-sensitive prostate cancer treated with rezvilutamide in the CHART trial

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Background: CHART trial has demonstrated the survival benefit of rezvilutamide plus androgen deprivation therapy (ADT) over bicalutamide plus ADT in treating patients with high-volume, metastatic hormone-sensitive prostate cancer (mHSPC). This post-hoc analysis aimed to evaluate the association between achievement of deep PSA decline with survival outcomes in patients with high-volume mHSPC in the CHART trial.

Methods: Patients with high-volume mHSPC were randomly assigned (1:1) to receive ADT plus either rezvilutamide or bicalutamide. PSA kinetics and the association between deep PSA decline ($\leq$0.2 ng/ml) and radiographic progression-free survival (rPFS) and overall survival (OS) in two groups were evaluated.

Results: A total of 654 patients were included in the analysis, with 326 patients in the rezvilutamide plus ADT group, and 328 patients in the bicalutamide plus ADT group. The median PSA nadir levels were 0.02 ng/ml, and 0.68 ng/ml in two groups, respectively. At 6-month, 170 (52.15%) and 90 (27.44%) patients achieved a deep PSA decline, respectively. With a median follow-up of 29.3 months, patients who achieved a deep PSA decline at 6-month had longer rPFS (HR=0.359, 95%CI 0.238, 0.543, P<0.001) and OS (HR=0.339, 95%CI 0.212, 0.540, P<0.001) than those who did not achieve it in the rezvilutamide plus ADT group. Significantly, rezvilutamide plus ADT was found to significantly prolong rPFS compared to bicalutamide plus ADT, regardless of whether patients achieved deep PSA decline at 6-month (HR=0.462, 95%CI 0.283, 0.754, P=0.002) or not (HR=0.587, 95%CI 0.428, 0.804, P<0.001).

Table: 1788P PSA kinetics in CHART trial

Variables	Rezvilutamide plus ADT (n=326)	Bicalutamide plus ADT (n=328)
PSA baseline (ng/ml), median (Q1, Q3)	78.79 (12.82, 314.80)	51.32 (8.08, 236.63)
PSA nadir (ng/ml), median (Q1, Q3)	0.02 (0.00, 0.41)	0.68 (0.08, 3.16)
Time to PSA nadir, day, median (Q1, Q3)	308.0 (169.0, 634.8)	167.0 (85.0, 281.0)
PSA nadir $\leq$0.2 ng/ml, n (%)	224 (68.7)	109 (33.2)
Time to PSA $\leq$0.2 ng/ml, day, median (Q1, Q3)	392.0 (222.3, 671.0)	238.0 (141.0, 393.0)
PSA $\leq$0.2 ng/ml at 3-month, n (%)	125 (38.34)	58 (17.68)
PSA $\leq$0.2 ng/ml at 6-month, n (%)	170 (52.15)	90 (27.44)
PSA $\leq$0.2 ng/ml at 12-month, n (%)	201 (61.66)	108 (32.93)

Conclusions: Rezvilutamide plus ADT resulted in a deep PSA decline, which was associated with improved long-term survival in patients with high-volume mHSPC.

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1789P Low- and high-volume disease in mHSPC: From CHAARTED to PSMA PET

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Background: The volume of disease (high-volume disease (HVD) / low-volume disease (LVD)) as defined by the CHAARTED criteria based on conventional imaging, is associated with overall survival and used for treatment decisions in mHSPC patients. It remains unknown how the definition of HVD and LVD can be transferred to PSMA-PET imaging.

Methods: In this retrospective study that included 4 international sites, mHSPC patients who underwent a ^{68}Ga-PSMA-11 PET/CT or PET/MRI and a BS (CI) (within a maximum time interval of 100 days) were included. Treatment in between both scans was excluded. HVD and LVD was determined on the BS and on the CT or MRI component. CHAARTED stratification into HVD and LVD was also applied to PSMA-PET. HVD was defined by the presence of visceral metastases and / or > 4 bone metastases (with > 1 beyond spine and pelvis). EXINIbone™ 3.4 (EXINI Diagnostics) was used for the number / localization of bone metastases on BS. The whole-body (WB) PSMA-PET positive tumor volume (PSMA-TV) was obtained using a semi-automatic thresholding method on Affinity 3.0.2 (Hermes Medical Solutions).

Results: Paired PSMA-PET+BS of 50 mHSPC patients were included (median PSA 43.8 (0.2 — 2840.0) ng/ml). 13/50 patients had disease detected in the prostate fossa, 25/50 in lymph nodes, 34/50 in bones and 2/50 in visceral organs by CI and 31/50, 28/50, 29/50 and 2/50 by PSMA-PET, respectively. Based on CI, 14/50 patients had CI-HVD (28%) and 36/50 CI-LVD (72%). Based on PSMA-PET, 21/50 patients had PSMA-HVD (42%) and 22/50 PSMA-LVD (44%). 7/50 (14%) patients had no PSMA-positive lesion or only in the prostate fossa while CI was at least CI-LVD. Overall, mean WB-PSMA-TV was 248.1 ml (0 — 3734.0 ml). In CI-HVD, mean WB PSMA-TV was 713.7 (0.3 — 3734.0) ml, in CI-LVD, 46.4 (0-228.0) ml. In PSMA-HVD, 518.1 (0 — 3734.0) ml and in PSMA-LVD, 59.7 (0 — 228.0) ml. Downstaging from CI to PSMA-PET occurred in in 7/50 patients (14.0%), upstaging (LVD to HVD) in 8/50 patients (16.0%).

Conclusions: Stage migration between LVD and HVD from CI to PSMA PET occurs both by up- and downstaging. Correlation with outcome will lead to new definitions of HVD/LVD based on PSMA PET/CT.

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1790P Utilisation rates of treatment intensification for metastatic hormone sensitive prostate cancer (mHSPC) in England, UK

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Background: Following several practice changing clinical trials regarding management of mHSPC, international guidelines now recommend 'treatment intensification' of ADT in combination with either docetaxel and/or novel hormonal therapy (NHT). The national utilisation of these treatments in England, UK and the determinants of variation are yet to be explored.

Methods: This national population based study using data from the National Prostate Cancer Audit (NPCA) identified all patients newly diagnosed with mHSPC in the English National Health Service (NHS) between 2018 and 2021. Patients receiving docetaxel, enzalutamide, abiraterone or apalutamide within 6 months of diagnosis were identified in the Systemic Anti-Cancer Dataset (SACT). Treatment patterns were studied in the overall population and also by age, ethnicity, deprivation and co-morbidity.

Results: Of the 13,820 men diagnosed with mHSPC in England between 2018 and 2021, 5,346 (38.7%) received 'treatment intensification' with either docetaxel, enzalutamide, abiraterone or apalutamide. Of these, 3,386 (24.5%) received docetaxel, 1,736 (12.6%) enzalutamide, 167 (1.2%) Abiraterone and 57 (0.4%) apalutamide. Utilisation of docetaxel peaked in 2018 and utilisation of enzalutamide has steadily increased (0.2% 2018 to 28.3% 2020). Abiraterone and Apalutamide utilisation have also increased during the study period (Table). Patients who were younger or who lived in least deprived areas or who had fewer co-morbidities were more likely to receive treatment intensification. There was no evidence of variation in utilisation according to patient ethnicity.

Table: 1790P Percentage utilisation of treatment intensification for mHSPC over time

	2018	2019	2020	2021
Any treatment intensification	38.1%	38.3%	42.0%	36.7%
Docetaxel	37.6%	37.3%	11.6%	11.2%
Enzalutamide	0.2%	0.7%	28.3%	21.8%
Abiraterone	0.3%	0.3%	2.1%	2.1%
Apalutamide	0%	0%	0%	1.6%

Conclusions: This study identifies the underutilisation of treatment intensification for mHSPC in England, particularly amongst certain patient groups. Further studies are needed to understand the reasons for underutilisation of intensified treatments in this setting.

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1791P Molecular profiling and prognostic relevance of low PTEN expression in metastatic hormone-sensitive prostate cancer patients

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Background: Alterations in *PTEN* are associated with aggressive behavior and treatment resistance in patients (pts) with castration-resistant prostate cancer (PC). The aim of this study is to characterize the molecular alterations related to *PTEN* low mRNA expression and its prognostic value in metastatic hormone-sensitive PC (mHSPC) pts.

Methods: This is a multicenter retrospective study enrolling mHSPC pts. Alterations in *PTEN* were assessed by mRNA expression by nCounter platform, targeted sequencing, and protein by IHC in FFPE tumor samples. RNA-seq analysis was performed to assess differences in gene expression between low vs. high/medium *PTEN* expression tumors. *PTEN* expression was correlated with castration resistance-free survival (CRPC-FS) and overall survival (OS) by Kaplan Meier and multivariate Cox analysis.

Results: 218 pts were included: 125 treated with ADT + docetaxel (D) and 93 with ADT, with a median follow-up of 46 months (7-223). Median age was 66 years, 76% of pts presented *de novo* stage IV and 68% had high-volume disease. 54 pts were tested for *PTEN* expression and targeted sequencing. Pts with low *PTEN* expression (*PTEN*-low) had higher frequency of *PTEN* mutations ($p<0.02$) and lower IHC expression ($p<0.01$). RNAseq (n=66) differential expression analysis found 13 genes differentially expressed (padj<0.05) in *PTEN*-low vs the rest. In the functional analysis *PTEN*-low tumors had overexpression of several pathways including cell cycle, DNA repair, metabolism and immune reponse, and infraexpression of the androgen-response hallmark. In the whole cohort, *PTEN*-low (31%) was independently associated with lower CRPC-FS (13 vs. 20.5 m, HR 1.8 (95% CI, 1.3 − 2.5), $p<0.001$) and OS (40.1 vs 57.9 m, HR 1.7 (95% CI, 1.2 − 2.3) p=0.003). Moreover, *PTEN*-low pts treated with ADT+D or ADT presented similar CRPC-FS (12.1 and 14.6 m, respectively) or OS (38.8 and 41 m), while *PTEN*-high/mid treated with ADT+D had the largest CRPC-FS (21.9 m, p=0.01) and OS (60.1 m, p=0.032), suggesting that *PTEN*-low pts may not benefit from chemotherapy.

Conclusions: Lower expression of *PTEN* correlates with a distinct molecular profile and a more aggressive disease in pts with mHSPC, supporting the development of new therapeutic strategies for these pts.

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1792P Effects of enzalutamide on overall survival +/- early docetaxel in participants aged less than 70 yrs versus greater than or equal to 70 yrs in ENZAMET (ANZUP 1304)

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Background: Enzalutamide (ENZA) and abiraterone are standard of care for people with metastatic hormone-sensitive prostate cancer (mHSPC). It is important to understand the benefits of these agents in older patients, who may be more frail and have more co-morbidities. In this post-hoc analysis, we assessed the efficacy of ENZA in patients with mHSPC ≥70yrs vs <70yrs of age.

Methods: ENZAMET randomly assigned participants (pts) with mHSPC to treatment with testosterone suppression (TS) plus either a non-steroidal anti-androgen (NSAA) or enzalutamide (ENZA). Stratification factors included age, volume of disease (high vs low), and planned use of concurrent docetaxel (DTX) as agreed by the participant and the treating physician. The same methods were used for overall survival (OS) analysis as in the full trial. Quality of Life (QoL) and safety analyses by age ≥70yrs vs <70yrs are ongoing.

Results: Of 1125 pts randomised, 514/1125 (46%) were aged ≥70yrs. The rate of DTX usage was lower in pts aged ≥70yrs (35% vs 52%). The beneficial effects of ENZA on OS seen in the whole cohort are maintained in pts aged ≥70yrs, regardless of planned use of early DTX (Table). Pts aged ≥70yrs treated with ENZA had a significant improvement in OS (Table) in line with younger pts.

Table: 1792P Hazard ratios (HR) and confidence intervals (CI) for effects of ENZA vs NSAA on OS in subgroups according to age and planned DTX

Characteristic	N	Deaths	HR	95% CI
Full cohort	1125	476	0.70	0.58-0.84
Age alone				
<70yrs All	611	239	0.75	0.58-0.97
≥70yrs All	514	237	0.64	0.50-0.83
Age and DTX				
<70yrs and DTX	322	147	0.87	0.63-1.20
≥70yrs and DTX	181	84	0.73	0.47-1.12
<70yrs and No DTX	289	92	0.62	0.41-0.94
≥70 and No DTX	333	153	0.60	0.44-0.83

Conclusions: This post-hoc analysis demonstrates that pts aged ≥70 yrs treated with ENZA/TS +/- DTX have similar benefical treatment effects to the overall cohort. These data suggest ENZA is a suitable option for older men with mHSPC fit for enzalutamide.

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1793P PPROSTRATEGY: A SOGUG randomized trial of androgen deprivation therapy (ADT) plus docetaxel (dct) +/- nivolumab (nivo) or ipilimumab-nivolumab (ipi-nivo) in high-volume metastatic hormone-sensitive prostate cancer (hvHSPCa) - Safety and toxicity profiles from the pilot phase

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Background: ADT+ dct has been a standard of care first-line for hvHSPC patients (pt). We hypothesized that early addition of ipi and/or nivo could improve outcomes.

Methods: PROSTRATEGY was designed as a seamless randomized (2/1/1) multi-arm multi-stage trial, to compare ADT+dct (75 mg/m^2 x6 cycles) vs ADT+dct→nivo (3 mg/Kg/2w x 12 mo), or ADT+ipi+dct→nivo (ADT + ipi 1 mg/Kg/3w x 2 cycles → dct x3 cycles → ipi 3mg/Kg/3w x2 cycles → dct x3 cycles → nivo x 12 mo) in hvHSPCa pt in 30 academic centers in Spain. The aims of the pilot phase were to check feasibility and safety (presented in this abstract) as well as to estimate efficacy outcomes. Dose reductions were only planned for dct. Primary prophylaxis with GCSF during dct was recommended, and secondary prophylaxis was mandatory.

Results: 150 pt were randomized to dct (75 pt), dct-nivo (37 pt) or dct+ipi-nivo (38 pt). Mean age was 66.4 y (39% >70 y), 98% were Caucasian, 99.3% had ECOG 0-1, 88% were metastatic at diagnosis, mean PSA was 157 ng/ml, 88% had Gleason ≥ 8, 31% visceral involvement, and 17% received local therapy to the prostate, with no differences among arms. With a median follow-up of 32.5 mo from ADT, 60% of pt have progressed and 41.3% have died. Efficacy is described separately. Main adverse events (AEs) are summarized in the table. Two pt in the Dx+Ipi-Nivo arm died due to toxicity (1 pt febrile neutropenia and sepsis, 1 pt immune-related encephalitis).

Table: 1793P

	Dct	Dct → Nivo	Dct +Ipi → Nivo
Any AE Any serious AE	97.3% 18.7%	97.3% 62.2%	100% 39.5%
Treatment-related G3-4 AEs Any Infusional reactions Anemia Neutropenia Febrile neutropenia Thrombocytopenia ALT/AST Diarrhea/colitis Mucositis Rash/dermatitis Arthomialgias Peripheral neuropathy Myasthenic sd Hypophysitis Myocarditis Nephritis Encephalitis	34.7% 0% 0% 4.0% 6.7% 0% 0% 1.3% 0% 0% 0% 2.7% 0% 0% 0% 0% 0%	67.6% 0% 2.7% 8.1% 5.4% 0% 2.7% 5.4% 2.7% 0% 0% 2.7% 0% 0% 0% 0%	60.5% 2.6% 2.6% 2.6% 2.6% 0% 2.6% 5.3% 0% 2.6% 2.6% 0% 0% 2.6% 2.6% 2.6% 2.6%
Dct dose reduction	22.7% 2.6% - -	27% 2.7% 5.4% -	7.9% 7.9% 5.4% 2.7%
Discontinuation due to AEs docetaxel nivolumab ipilimumab			
Treatment-related dead	0%	0%	5.4%

Conclusions: The addition of ipi and/or nivo to ADT + Dct in pt with hvHSPCa is feasible. No unexpected or more frequent toxicities were observed in this trial with the addition of checkpoint inhibitors to ADT+ Dx. As expected, the addition of ipi + nivo to ADT+dct is associated with a slightly increase of immune-related AEs.

Clinical trial identification: EudraCT 2017-004377-13.

Legal entity responsible for the study: SOGUG (Spanish Genitourinary Oncologic Group).

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1794P Prognostic role of metastatic site in patients with de novo metastatic prostate cancer: A population-based analysis in new hormonal agents era

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Background: Recently, triplet therapies have improved outcomes in patients with metastatic castration-sensitive prostate cancer (mCSPC). Triplet therapies might be reasonable, especially in de novo metastatic disease. Bones are the most common site of distant metastases, but visceral metastasis also occurs in about 10%. It is still largely unknown how the site of de novo metastasis impacts survival in patients treated with new hormonal agents.

Methods: We identified patients from the Surveillance, Epidemiology, and End Results (SEER) database (17 reg, Nov 2022). We used the following criteria for inclusion: microscopically confirmed de novo metastatic, prostate adenocarcinoma, diagnosed between 2016 and 2020; and exclusion: unknown metastatic site and metastasis only to distant lymph nodes. The primary endpoint was overall survival (OS). We used Cox's proportional hazards regression models for multivariable analysis.

Results: We included 20,100 patients. Metastatic sites were classified as bone only, bone + distant lymph node metastasis, lung without liver metastasis, liver metastasis, and other sites (i.e., except for bone, lung, liver, and distant lymph node). Bone was the most common metastatic site (95.4%), followed by lung (10%), other sites (6.3%), and liver (4.7%). The median OS was 33.0 (95% Confidence Interval (CI): 31.9-34.1), 29.0 (95% CI: 21.1-30.8), 28.0 (95% CI: 25.1-30.8), 23.0 (95% CI: 20.5-25.4), and 12.0 (95% CI: 10.5-13.4) months in bone only, bone + distant lymph node, lung without liver, other sites, and liver metastatic groups. Liver metastasis was an independent prognostic factor for worse OS (Hazard Ratio: 8.14, 95% CI:3.06-21.62, $p<0.001$) after adjusting for confounding factors, such as age, race, PSA, and Gleason. However, bone + distant lymph node metastasis, lung metastasis, and metastasis to other sites were not associated with significantly increased mortality compared to bone only metastasis.

Conclusions: Distinguishing by the site of visceral metastasis could add more granularity to the classification of metastatic hormone-sensitive disease and thus may help to select those who would benefit most from the triplet therapies.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Other, Employee at DFCI. Please see https://www.danafarber.org/ for mission statement (non-profit hospital). I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Other, Professor at HMS, please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, Other, No financial interest. Institutional.Filed patents related to biomarkers of immune checkpoint blockers and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. Y. Urun: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Janssen Oncology, Pfizer, BMS, Roche, MSD; Financial Interests, Personal, Invited Speaker: Astellas, Janssen Oncology, Pfizer, BMS, Roche, Amgen; Financial Interests, Personal and Institutional, Invited Speaker: BMS, AstraZeneca, MSD, Janssen, Roche. All other authors have declared no conflicts of interest.

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1795P China ARCHES: A multicenter phase III randomized double-blind placebo (PBO)-controlled efficacy and safety trial of enzalutamide (ENZA) + androgen deprivation therapy (ADT) vs PBO + ADT in Chinese patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC)

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Background: In the global ARCHES trial (NCT02677896), ENZA + ADT improved overall survival and radiographic progression-free survival (rPFS) vs PBO + ADT in pts with mHSPC. The China ARCHES trial evaluated the efficacy and safety of ENZA + ADT vs PBO + ADT in Chinese pts with mHSPC.

Methods: Chinese men with mHSPC (positive bone scan or CT scan) were randomized 2:1 to ENZA (160 mg/day) + ADT or PBO + ADT, stratified by disease volume and prior docetaxel therapy. Treatment continued until intolerability or confirmed radiographic progression. The primary endpoint was time to prostate-specific antigen (PSA) progression (TTPP; PSA progression defined as ≥25% increase and absolute increase of ≥2 ng/mL above the nadir, confirmed after ≥3 weeks), based on central laboratory test. Selected secondary endpoints included rPFS, time to castration resistance (TTCR), PSA undetectable (<0.2 ng/mL) rate in patients with detectable PSA at baseline, and safety. We report the results of a prespecified interim analysis (63 TTPP events accrued).

Results: At data cut-off (November 18, 2022), 180 pts (ENZA + ADT, n=120; PBO + ADT, n=60) had been randomized from 27 centers in China (median age, 68.5 years). Baseline characteristics were balanced between treatment arms. Median treatment duration with ENZA + ADT vs PBO + ADT was 25.66 vs 15.11 months. Based on 63 centrally confirmed PSA progressions (ENZA + ADT, 23; PBO + ADT, 40), ENZA + ADT significantly reduced the risk of PSA progression by 87% vs PBO + ADT (Table). rPFS, TTCR, and PSA undetectable rate were among the secondary endpoints improved with ENZA + ADT vs PBO + ADT. Safety outcomes in pts from China were consistent with those in the global ARCHES population.

Table: 1795P

Endpoint	ENZA + ADT N=120	PBO + ADT N=60	Hazard ratio[a] (95% CI)	p value
TTPP[b] (95% CI)[c]	NR (NR, NR)	9.2 (6.54, 17.48)	0.13 (0.076, 0.222)	<0.0001[d]
rPFS[b] (95% CI)[c]	NR (28.25, NR)	19.4 (13.63, NR)	0.33 (0.196, 0.556)	<0.0001[d,e]
TTCR[b] (95% CI)[c]	NR (31.18, NR)	8.3 (6.41, 14.69)	0.172 (0.107, 0.276)	<0.0001[d,e]
PSA undetectable, % (95% CI)[f]	76.3 (67.4, 83.8)	22.8 (12.7, 35.8)		<0.0001[e,g]

[a]Cox proportional hazards model[h] [b]Median months: Kaplan-Meier method [c]Brookmeyer and Crowley method [d]Log-rank test[h] [e]Nominal p value [f]Clopper-Pearson method based on exact binomial distribution [g]Cochran-Mantel-Haenszel score test[h] [h]Stratified model/test CI=confidence interval; N=no. of randomized pts; NR=not reached.

Conclusions: Efficacy and safety results in China ARCHES were generally consistent with those in the global ARCHES trial.

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1796P Real-world analysis of metastatic hormone-sensitive prostate cancer: Are randomized clinical trials more trustworthy? Insights from PIONEER, the European network of excellence for big data in prostate cancer

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Background: Androgen deprivation therapy (ADT) was the standard of care (SOC) for patients with metastatic Hormone Sensitive Prostate Cancer (mHSPC); recently, emerging therapies associated with ADT have proven to be more effective than ADT alone, however there is an unmet need of standardization of randomized control trials (RCTs) comparing the various combinations of available drugs. Real Word Data (RWD) may be used to identify relevant outcomes with unmet clinical needs with a greater likelihood of benefiting from new therapies. We aim to describe demographics, clinical characteristics, treatment patterns and clinical outcomes of a large multicenter cohort of patients with mHSPC in RWD under the PIONEER project.

Methods: Data of patients with mHSPC across a distributed network of observational databases were collected. Male patients without prior orchiectomy with mHSPC were enrolled in Cohort 1, while Cohort 2 was defined as the start of ADT as a surrogate definition of mHSPC disease, both in metachronous and synchronous disease settings.

Results: Overall, 94,261 mHSPC patients were included among which 77,123 patients received treatment. 28% of mHSPC diagnosed were not on ADT monotherapy. More than half of the patients were over 70 years old (54%), older than the average age on the available RCT. In cohort 2, 2,819 patients were metachronous and 55,502 patients were synchronous. Most of the patients are treated with ADT only; after a Median follow-up (ranged from 398-699 days) in the metachronous setting 22% of them discontinued the treatment. Regarding the clinical outcomes, time to admission to hospital or emergency Department, adverse events and death increase with time, but noticeably events are more common in synchronous disease.

Conclusions: This is the largest study in Europe with RWD in the mHSPC setting. Landscape of prostate cancer treatment is constantly evolving, so it is important to understand the behavior of the disease in real-world setting, so we are able to fill gaps or create new questions to create evidence. In RWD that patients are older, with more co-mobilities and 1/3 of them do not undergo a SCO treatment when compared to RCT.

Legal entity responsible for the study: PIONEER consortium.

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1797P Application of novel machine learning model in [68Ga] Ga-PSMA-11 PET/CT: Predicting survival in oligometastatic prostate cancer patients

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Background: Biochemical recurrence is estimated to occur in $\geq$ 25% of patients with prostate cancer (PC) following primary curative therapy. Machine learning models are being developed for lesion detection and tracking to provide a comprehensive view of disease burden, allowing clinicians to quantify and predict effectiveness of treatment for individual lesions. This study applied novel AI-assisted technology to automatically extract features from [^{68}Ga] Ga-PSMA-11 (PSMA) PET/CT images that correlate with treatment intervention and survival data to create a scoring system.

Methods: Between 2015 and 2016, 185 men with oligometastatic PC had a baseline and follow-up PSMA PET/CT scan (at ~6-months) whilst treated per standard clinical care. Lesions were quantified and matched between timepoints using AIQ Solutions technology. Imaging features were extracted from each patient, including change in basic features (SUV_{max}, SUV_{mean}, and number of lesions at baseline), and heterogeneity features (intrapatient heterogeneity of disease and response). Univariate predictive power of overall survival (OS) prediction of each measure was determined using Cox regression models. An AI approach was evaluated to predict OS using 5-fold cross-validation of a random survival forest. Model performance was evaluated using the c-index.

Results: The top univariate predictors of survival were all heterogeneity features, proportion of lesions increasing (c-index=0.62), number of stable lesions (0.62), number of decreasing lesions (0.60), and number of new lesions (0.59). In an individual scan, the proportion of increasing lesions >29% correlated with poorer progression. The AI model was able to predict responders vs suboptimal responders based on whether they had a treatment intervention or observation alone (35%) (c-index=0.83 in both cases).

Conclusions: This study demonstrates that an AI-assisted lesional response analysis can help predict response and prognosis of oligometastatic PC patients. These results support further studies to validate these findings in a prospective cohort.

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1799P Real-world (RW) treatment (tx) patterns of metastatic prostate cancer (mPCa) with enhanced access to homologous recombination repair (HRR) genomic testing and poly ADP ribose polymerase inhibitor (PARPi)

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Background: Metastatic castration resistant prostate cancer (mCRPC) patients (pts) with HRR alterations (HRR^+) benefit from PARPi. We aimed to elucidate the RW outcomes and impact of streamlined access to a biomarker driven tx approach.

Methods: In a multicentre prospective mPCa cohort study, cell free DNA next generation sequencing (cfDNA NGS) was performed using accredited assays (BC Cancer, Foundation Medicine, Alberta panel). Time to CRPC was compared between HRR^+ and negative/unknown status (HRR^0) using log rank test. In olaparib tx pts, $\geq$50% PSA decline, radiographic progression free survival (rPFS), serious adverse events (SAE), and overall survival (OS) were examined.

Results: Of 119 pts, 41 (35%) were HRR^+ (23 *BRCA2*, 14 *ATM*, 5 *CDK12*, 3 *CHEK2*, 2 *PPP2R2A*, 1 *BRCA1*, 1 *PALB2*). Median age at diagnosis was 64 yrs, 45% had Gleason $\geq$ 8, and 13% were non-caucasian. HRR^+ pts had a shorter time to CRPC than HRR^0 pts (13.7 vs 31.3 months; HR: 2.2; p=0.001). 28 HRR^+ pts (19 BRCA2, 8 ATM, 1 BRCA1) received olaparib, demonstrating a trend towards improved OS from mCRPC compared to HRR^+ pts without PARPi (38.1 vs 17.4 mo, p=0.20). In 9 HRR^+ pts without PARPi, 7 had androgen receptor pathway inhibitor (ARPi) tx and taxane, 1 had ARPi, and 1 had docetaxel. 50% of pts received olaparib after $\geq$2 systemic tx lines. A longer OS trend was observed in pts receiving 1st line mCRPC olaparib tx than pts receiving olaparib in later tx lines (17.2 vs 11.1 mo, p=0.07). OS from mCRPC was similar in HRR^0 and olaparib tx HRR^+ pts (37.4 vs 38.1 mo, p=0.70). In olaparib tx pts, median OS post initiation was 11.7 mo, rPFS was 5.4 mo, 36% had $\geq$50% PSA decline, and 29% had $\geq$30 days tx beyond PSA progression (PCWG3 criteria). SAE occurred in 39%; 4 pts required transfusion for anemia. Of 8 pts receiving additional systemic tx, 6 had taxane- and 2 had platinum-based chemotherapy.

Conclusions: In this study of heavily pre-treated mPCa pts, RW rPFS and OS on olaparib were reduced compared to clinical trials. Similar OS was seen in olaparib tx HRR^+ and HRR^0 pts, despite historically poorer prognosis in HRR^+ pts. These results demonstrate that a biomarker driven tx approach and earlier access to PARPi may improve outcomes in HRR^+ pts.

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1800P Differential tumor gene-expression profiling of patients (pts) with de-novo metastatic castration-sensitive prostate cancer (dn-mCSPC) versus (vs.) mCSPC relapsing after prior localized therapy (PLT-mCSPC)

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Background: Dn-mCSPC is markedly aggressive, with shorter time to castration resistance and poorer overall survival than PLT-mCSPC (PMID: 28899723). We interrogate and validate differences in tumor gene expression profiles of dn-mCSPC vs. PLT-mCSPC.

Methods: In this IRB-approved retrospective study, eligibility criteria included histologically confirmed prostate adenocarcinoma (PC) and available RNA sequencing results from treatment naïve primary prostate tissue from a CLIA-certified lab [either Tempus (T) or Caris (C)]. T cohort was used for interrogation and C for validation. Pts in each cohort were categorized into two groups: dn-mCSPC vs. PLT-mCSPC. The DEseq2 pipeline was used to analyze differentially expressed genes between the groups. The data included the Log2 fold change, Wald-Test p-values, and Benjamini-Hochberg adjusted p-values for each differentially expressed gene. Results were subjected to Gene Set Enrichment Analysis (GSEA) to identify pathways enriched in each cohort. Bioinformatic analysis was performed using R v4.2.

Results: 128 pts were eligible. T cohort: n=78 (dn-mCSPC=37, PLT-mCSPC=41); C cohort: n=50 (dn-mCSPC=30, PLT-mCSPC=20). Both T and C showed that dn-mCSPC had an increased expression of the TNFα signaling, hypoxia signaling, and inflammatory response pathway (PTW). PLT-mCSPC had higher expression of E2F target,

G2M checkpoint, and MYC target PTW. Normalized enrichment scores (NES) are reported in the table.

Table: 1800P Differential GSEA in dn-mCSPC vs. PLT-mCSPC (q value for each pathway <0.01)

T		C	
PTW	NES	PTW	NES
TNFα signaling	3.1	TNFα signaling	3.0
Hypoxia	2.3	Hypoxia	2.3
Inflammatory response	2.2	Inflammatory response	2.3
MYC target	-1.9	MYC target	-1.5
G2M checkpoint	-2.0	G2M checkpoint	-1.3
E2F target	-2.3	E2F target	-1.5

Positive NES = upregulation in dn-mCSPC, negative NES = downregulation in dn-mCSPC

Conclusions: Pts with dn-mCSPC had PTW associated with tumor aggressiveness such as TNFα signaling, hypoxia, and inflammatory response. After external validation, these hypothesis-generating data may provide rationale for personalized therapy in men with PC.

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1801P Impact of intensified androgen deprivation therapy (ADTi) in the metastatic castration-sensitive prostate cancer (mCSPC) setting on metastatic castration-resistant prostate cancer (mCRPC) disease characteristics and survival outcomes

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Background: ADTi is the standard of care treatment (Rx) for mCSPC. We hypothesized that pts who received ADTi in mCSPC and progressed to mCRPC would have different disease characteristics and survival than those treated with ADT monotherapy (ADTm) in the mCSPC setting.

Methods: After IRB approval, patient (pt)-level data were collected retrospectively. Eligibility: confirmed diagnosis of mCRPC, treated with 1L approved Rx with follow up data available. Pts were stratified based on whether they received ADTi (docetaxel or novel hormonal therapies) or ADTm in the mCSPC setting. Study endpoints: Progression-free survival (PFS) as and overall survival (OS) from time of mCRPC diagnosis. A multivariate analysis using the Cox proportional hazards model was used adjusting for potential confounders.

Results: 519 consecutive pts (368 ADTm and 151 ADTi) seen at our institution between 2009 to 2022 were eligible. mCRPC pts who received ADTi compared to ADTm had lower PSA (10.3 vs. 21.5 ng/ml, $P = 0.002$), more visceral metastases (20.5 vs. 11.1%, $P = 0.005$), higher alkaline phosphatase (110.5 vs. 96 U/L, $P = 0.034$); and had worse median PFS (5.3 vs. 8.6 months, $P < 0.001$) and OS (21.2 vs. 31.7 months, $P < 0.001$) compared to those with ADTm in both univariate and multivariate analysis (Table).

Table: 1801P

	PFS HR (95% CI, *P*-value)	OS HR (95% CI, *P*-value)
ADT vs. ADTi (univariate)	0.7 (0.57-0.86, $P < 0.001$)	0.63 (0.49-0.8, $P < 0.001$)
ADT vs. ADTi (multivariate)	0.7 (0.53 − 0.91, $P = 0.009$)	0.69 (0.50 − 0.97, $P = 0.03$)
Visceral Metastasis	0.73 (0.52 − 1.02, $P = 0.062$)	0.62 (0.43 − 0.90, $P = 0.012$)
Log PSA	1.12 (1.06 − 1.18, $P < 0.001$)	1.13 (1.06 − 1.21, $P < 0.001$)
Hemoglobin	0.86 (0.80 − 0.92, $P < 0.001$)	0.87 (0.81 − 0.94, $P < 0.001$)
Alkaline Phosphatase	1.00 (1.00 − 1.00, $P = 0.081$)	1 (1.00 − 1.00, $P = 0.086$)
Gleason Score > 8	0.77 (0.58 − 1.01, $P = 0.062$)	0.79 (0.57 − 1.09, $P = 0.14$)

Conclusions: In the era of ADTi for mCSPC, the survival outcomes in the mCRPC is poorer compared to those in the era of ADTm for mCSPC. These hypothesis-generating data may aid patient counseling, prognostication, and clinical trial design in mCRPC in the current era.

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1803P Phase I/II study of bavdegalutamide, a PROTAC androgen receptor (AR) degrader in metastatic castration-resistant prostate cancer (mCRPC): Radiographic progression-free survival (rPFS) in patients (pts) with *AR* ligand-binding domain (LBD) mutations

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Background: Pts with mCRPC and mutations in *AR* LBD (amino acids 671-920) have poor prognosis. The oral PROteolysis TArgeting Chimera (PROTAC) AR degrader bavdegalutamide (bavdeg; ARV-110) showed clinical activity in previously treated pts with mCRPC in a phase 1/2 study (NCT03888612), with enhanced activity seen in pts with the *AR* LBD mutations T878 and/or H875.

Methods: In phase 1, pts with mCRPC and ≥2 prior therapies (including a novel hormonal agent [NHA]) received bavdeg 35–700 mg once daily (QD) or 210–420 mg twice daily. In phase 2, pts with mCRPC and 1–2 prior NHAs ± prior chemotherapy were assigned to biomarker-defined subgroups; pts who had 1 prior NHA and no prior chemotherapy were enrolled in a clinically defined subgroup. All phase 2 pts received 420 mg bavdeg QD. In exploratory analyses across the phase 1/2 population treated with 420 mg bavdeg QD, efficacy was assessed in pts with *AR* 878/875 mutation(s) without an *AR* L702 mutation (*AR* 878/875 pts) and in those with any *AR* LBD missense mutation except *AR* L702H alone (*AR* LBD pts).

Results: As of Dec 20, 2022, median rPFS (95% CI) per PCWG3 was 11.1 months (7.10–not reached) in 25 *AR* 878/875 pts (10 events; 4 pts still on treatment) and 8.1 months (3.81–10.97) in 44 *AR* LBD pts (20 events; 5 pts still on treatment). Best prostate-specific antigen (PSA) declines of ≥50% after ≥1 month of PSA follow-up were seen in 56.0% of *AR* 878/875 pts (n=25) and 37.2% of *AR* LBD pts (n=43). In response-evaluable pts with measurable disease at baseline, overall response rate was 9.1% in *AR* 878/875 pts (n=11) and 10.0% in *AR* LBD (n=20) pts; 55% and 50%, respectively, had stable disease. There were no grade ≥4 treatment-related adverse events (TRAEs) with 420 mg bavdeg (n=158 across phase 1/2); any grade TRAEs reported in ≥20% of pts were nausea (54%; 1% grade 3), fatigue (35%; 1% grade 3), vomiting (31%; 1% grade 3), diarrhea (25%; 2% grade 3) and decreased appetite (23%; 0 grade 3).

Conclusions: Bavdeg had encouraging efficacy in post-NHA pts with mCRPC and *AR* 878/875 or any *AR* missense LBD mutation (excluding *AR* L702H alone) and was tolerable; these pt populations will be analyzed in a phase 3 study of bavdeg.

Clinical trial identification: NCT03888612.

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Applicant/Proprietor Exelexis, Inc. Application No/Patent No. 11764665.4- 1464 Application No/Patent No. 11764656.2-1464 Applicatio. E. 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1804P APEX-01: First-in-human phase I/II study of ARX517 an anti-prostate-specific membrane antigen (PSMA) antibody-drug conjugate (ADC) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

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Background: ARX517 is a novel ADC composed of a fully humanized anti-PSMA mAb conjugated to amberstatin-269, a potent tubulin inhibitor. ARX517 was designed to reduce off-target ADC instability-related toxicity issues observed in earlier anti-PSMA ADCs by using site-specific synthetic amino acids and stable oxime conjugation chemistry to minimize premature payload release in the human circulation.

Methods: An i3+3 dose escalation design was used. Eligible pts had ≥ 2 FDA-approved treatments for mCRPC with progression by Prostate Cancer Working Group criteria. Key objectives include safety, PK and clinical efficacy. Baseline PSMA PET expression was not required for eligibility but was evaluated as a biomarker.

Results: 24 pts received ARX517 q3w at escalating doses (Table). Pts had a median of 4 prior lines of therapy; 100% received ≥ 1 androgen pathway inhibitor, 50% received taxane, and 12.5% received PSMA-targeted radionuclide. Grade (Gr) 1/2 treatment-related adverse events (TRAEs) were dry mouth (41.7%), fatigue (33.3%), diarrhea and platelet count decrease (20.8% each). Four Gr3 TRAEs were reported at 1.7, 2.4, and 2.88 mg/kg (two lymphopenia, two platelet count decrease). No DLTs, treatment-related serious AEs (SAEs), or ≥ Gr 4 AEs were reported. At higher doses (Cohorts 4-8), median duration on-treatment was 6.3 months (range 0.7+, 11.8+). Additionally, > 50% PSA and ctDNA decline were observed (Table); 2/7 pts had confirmed RECIST v1.1 responses. PK profiles for total antibody and ADC were similar, suggesting strong stability of ARX517 with minimal premature payload release.

Table: 1804P PSA and ctDNA decline, confirmed responses, DLTs, and Grade 3/4/5 TRAEs by dose level

	Cohort 1 0.32 mg/kg	Cohort 2 0.64 mg/kg	Cohort 3 1.07 mg/kg	Cohort 4 1.4 mg/kg	Cohort 5 1.7 mg/kg	Cohort 6 2.0 mg/kg	Cohort 7 2.4 mg/kg	Cohort 8 2.88 mg/kg
Best % change from baseline*								
PSA > 30%	0/1	1/3	1/3	2/3	2/5	3/3	2/3	2/3
PSA > 50%	0/1	0/3	0/3	1/3	0/5	3/3	2/3	2/3
PSA > 90%	0/1	0/3	0/3	0/3	0/5	2/3	0/3	0/3
ctDNA > 50%	0/1	1/2	2/3	1/3	3/5	3/3	2/2	n/d
Confirmed RECIST v1.1 response	0/1	0/1	0/0	1/2	0/3	1/1	0/1	n/d
DLT	0/3	0/3	0/3	0/3	0/5	0/3	0/3	0/3
Gr3 TRAE	0/3	0/3	0/3	0/3	1/5	0/3	1/3	2/3
Gr4/5 TRAE	0/3	0/3	0/3	0/3	0/5	0/3	0/3	0/3

*Data cut-off 03May23; n/d = no data available

Conclusions: ARX517 treatment resulted in PSA declines and RECIST v1.1 responses without treatment-related SAEs. Dose expansion has begun, additional safety, PD, efficacy, and PSMA PET data will be presented.

Clinical trial identification: NCT04662580.

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1805P Efficacy of olaparib (ola) + abiraterone (abi) vs placebo (pbo) + abi in the non-BRCA mutation (non-BRCAm) subgroup of patients (pts) with metastatic castration-resistant prostate cancer (mCPRC) in the PROpel trial

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Background: PROpel (NCT03732820) met its primary endpoint with a significant investigator-assessed radiographic progression-free survival (IA rPFS) benefit with ola + abi vs pbo + abi in the intention-to-treat (ITT) population in first-line mCRPC (hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54–0.81; $P<0.001$). At final prespecified analysis there was a trend to improved overall survival (OS) with ola + abi vs pbo + abi (median 42.1 vs 34.7 months [m]; HR 0.81, 95% CI 0.67–1.00; $P=0.0544$). The greatest magnitude of benefits was seen in the BRCAm subgroup. *Post hoc* exploratory analyses were conducted to further investigate outcomes in non-BRCAm pts.

Methods: PROpel was a phase 3 double-blind trial. Pts were enrolled irrespective of biomarker status and randomized 1:1 to receive ola (300 mg twice daily [bid]) or pbo, and abi (1000 mg once daily) + prednisone/prednisolone (5 mg bid). Treatment continued until radiographic disease progression, unacceptable toxicity or withdrawal of consent. Aggregated tumour tissue (FoundationOne®CDx) and ctDNA (FoundationOne®Liquid CDx) test results, performed after randomization and before primary analysis, were used to classify pt mutation status. Non-BRCAm pts had no positive BRCAm test result and at least 1 negative BRCAm tissue or ctDNA result.

Results: In the non-BRCAm subgroup (n=693), there was a meaningful clinical benefit across endpoints for pts treated with ola + abi (Table). Safety profile of the combination was consistent with the ITT population. Within the non-BRCAm subgroup, analyses by baseline clinical characteristics showed consistent effect and will be presented.

Table: 1805P

	Non-BRCAm		
	Ola + abi (n=343)	Pbo + abi (n=350)	HR (95% CI)
Median (m):			
IA rPFS*	24.1	19.0	0.76 (0.61–0.94)
BICR rPFS*	27.6	16.6	0.72 (0.58–0.90)
OS†	39.6	38.0	0.91 (0.73–1.13)
Median time to (m):			
PSA progression*	22.1	13.1	0.63 (0.50–0.79)
First subsequent therapy†	24.0	19.9	0.84 (0.70–1.01)
First cytotoxic chemotherapy†	30.1	22.7	0.80 (0.66–0.97)
Second progression or death†	NC	NC	0.86 (0.65–1.14)
PSA 50 response,* %	78.6	71.4	
ORR,* %	51.1	45.4	
FACT-P change from baseline†	-6.3	-5.3	
Any AE of CTCAE Grade ≥3,† %	57.0	43.7	
Any AE with outcome of death, † %	7.0	4.9	

*DCO1; 30/7/21 †DCO3; 12/10/22 AE, adverse event; DCO, data cutoff; NC, not calculable; ORR, objective response rate; PSA, prostate-specific antigen

Conclusions: Exploratory analyses across multiple endpoints support a clinically meaningful benefit with ola + abi vs pbo + abi in non-BRCAm pts and a safety profile consistent with the overall ITT population.

Clinical trial identification: NCT03732820.

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1806P Efficacy of niraparib and abiraterone acetate plus prednisone (NIRA+AAP) in homologous recombination repair gene-altered (HRR+) metastatic castration-resistant prostate cancer (mCRPC) by tissue and/or plasma assays in the MAGNITUDE trial

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Background: The randomized, double-blind, phase 3 MAGNITUDE study evaluated NIRA+AAP vs placebo and AAP (PBO+AAP) as 1st line therapy for mCRPC that was HRR+ based on targeted next-generation sequencing of tumor tissue and/or plasma-based assays.[1] Here we aimed to assess treatment efficacy by assay.

Methods: Tumor tissue and/or plasma was collected from mCRPC patients (pts) who consented to the pre-screening protocol and tested using local tissue assays or centrally using the Foundation Medicine FoundationOne®CDx (F1CDX®) tissue assay or Agilent-Resolution Bioscience Resolution HRD™ Plasma assay. Pts HRR+ (BRCA1, BRCA2, FANCA, PALB2, CHEK2, BRIP1, HDAC2, ATM, CDK12) were randomized 1:1 to receive NIRA+AAP or PBO+AAP (NCT03748641). Primary (radiographic progression-free survival, rPFS) and secondary end-points (time to cytotoxic chemotherapy, TCC; time to symptomatic progression, TSP; and overall survival, OS) are reported for interim analysis 2 for each subgroup (events [NIRA+AAP/PBO+AAP], Hazard ratio and 95% CI).

Results: Overall, 423 pts were HRR+ with 225 BRCA+. Pts, 159 (96), were HRR+ (BRCA+) with both assays, the remaining pts were positive with either tissue/plasma (Table). Pts, 124 (62) HRR+ (BRCA+), were tissue positive but plasma negative, and 38 (17) HRR+ (BRCA+) pts were positive with plasma, but tissue negative. Hazard ratios for end-points, except OS, had $p<0.05$ for pts BRCA positive by either assay, with similar results for HRR+ pts.

Table: 1806P

	Population, n (NIRA+APP / PBO+APP)	rPFS	TCC	TSP	OS
BRCA+	**Overall** 113/112	57/78 0.55 (0.39-0.78)	28/44 0.56 (0.35-0.90)	31/51 0.54 (0.35-0.85)	43/49 0.88 (0.58-1.34)
	Plasma 71/79	0.63 (0.42-0.96)	0.49 (0.28-0.87)	0.51 (0.30-0.89)	0.88 (0.53-1.46)
	Tissue 76/86	0.51 (0.33-0.77)	0.44 (0.24-0.82)	0.50 (0.28-0.89)	0.83 (0.49-1.40)
All HRR	**Overall** 212/211	124/140 0.76 (0.60-0.97)	57/77 0.67 (0.47-0.94)	54/83 0.60 (0.42, 0.84)	90/89 1.01 (0.75-1.36)
	Plasma 129/148	0.77 (0.57-1.04)	0.60 (0.39-0.92)	0.58 (0.38-0.88)	1.04 (0.73-1.49)
	Tissue 144/147	0.80 (0.59-1.08)	0.62 (0.40-0.96)	0.56 (0.36-0.86)	0.97 (0.67-1.42)

Conclusions: Clinically meaningful benefit from NIRA+AAP are similar for BRCA+ pts detected by either tissue or plasma-based assays. Positivity by either test is sufficient to guide treatment decisions. 1. Efstathiou E, et al. *J Clin Oncol*. 2023;41(suppl 6):170.

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1807P Talazoparib (TALA) plus enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC): Subgroup analyses of the all-comers cohort from TALAPRO-2 by homologous recombination repair (HRR) status

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Background: The randomized, Phase 3, placebo (PBO)-controlled TALAPRO-2 study demonstrated statistically significant improvements in radiographic progression-free survival (rPFS) for 1st-line TALA + ENZA vs PBO + ENZA in patients (pts) with mCRPC in all-comers and in HRR subgroups (HRR-deficient [HRR+] and HRR-non-deficient [HRR-] or unknown). Here, we report baseline characteristics and secondary efficacy and safety endpoints for all-comers by HRR status.

Methods: Pts randomized 1:1 to TALA 0.5 mg or PBO, + ENZA 160 mg/day, were stratified by prior abiraterone or docetaxel for castration-sensitive PC (yes vs no) and by HRR status (HRR+ vs HRR-/unknown). The primary endpoint was rPFS by BICR per RECIST 1.1/PCWG3. Secondary endpoints included overall survival (OS), objective response rate (ORR), time to PSA progression, time to initiation of cytotoxic chemotherapy, time to progression on first subsequent antineoplastic therapy or death (PFS2), and safety.

Results: Of 805 enrolled pts, all had prospective tumor tissue HRR test results. Overall, baseline characteristics were relatively well-balanced between treatment groups and by HRR status; however, in the younger group (age <65 y), there were more HRR+ (29.6%) than HRR-/unknown (19.3%) pts, and HRR+ pts had evidence of more aggressive disease (Table). Treatment with TALA + ENZA improved ORR, and

Table: 1807P

		HRR+	HRR+	HRR-/unknown	HRR-/unknown
		TALA + ENZA (N=85)	PBO + ENZA (N=84)	TALA + ENZA (N=317)	PBO + ENZA (N=319)
Gleason score ≥8	**N (%)**	69 (81.2)	65 (77.4)	212 (66.9)	218 (68.3)
Time since initial diagnosis	**Median, mo**	24.3	26.0	33.1	41.0
ORR	**N**	33	26	87	106
	% (95% CI)	78.8 (61.1–91.0)	46.2 (26.6–66.6)	55.2 (44.1–65.9)	43.4 (33.8–53.4)
	P	0.010		0.10	
Time to PSA progression	**N**	38	42	126	135
	Median, mo	26.7	11.1	26.6	19.2
	HR (95% CI)	0.53 (0.34–0.82)		0.78 (0.62-1.00)	
	P	0.0040		0.050	
Time to cytotoxic chemotherapy	**N**	24	24	59	115
	Median, mo	NR	NR	NR	NR
	HR (95% CI)	0.71 (0.40–1.26)		0.44 (0.32–0.61)	
	P	0.24		<0.0001	
PFS2	**N**	21	34	105	109
	Median, mo	36.4	30.8	NR	35.3
	HR (95% CI)	0.47 (0.27–0.81)		0.88 (0.67–1.14)	
	P	0.0059		0.33	

P values 2-sided

prolonged time to PSA progression; time to initiation of cytotoxic chemotherapy; and PFS2 vs PBO + ENZA, with benefit seen in both HRR+ and HRR-/unknown subgroups (Table). OS remains immature. Further data will be presented on baseline characteristics, efficacy, and TEAEs by treatment group for HRR+ and HRR-/unknown subgroups.

Conclusions: TALA + ENZA demonstrated improvements in secondary efficacy endpoints over PBO + ENZA as 1st-line treatment in pts with mCRPC in both HRR+ and HRR-/unknown subgroups.

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There are multiple research projects sponsored by these companies which pay money to my institution: Arnivas, Astellas, AstraZeneca, Bavarian Nordic, Bayer, BMS, Calithera, Celldex, Crispr, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, GSK, Immunomedics, Janssen, Lava, Medivation, Merck, Nektar, Neoleukin, New Link Genetics, Novartis, Oric, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon.; Financial Interests, Steering Committee Member, I am involved in the steering committee of the trials sponsored by these pharmas with no personal honorarium: AstraZeneca, Calithera, Clovis, Crispr, Eisai, Eli Lilly, Exelixis, Immunomedics, Janssen; Financial Interests, Steering Committee Member, I am involved in the steering committee of the trials sponsored by these pharma companies with no personal honorarium: Merck, Nektar, New Link Genetics, Oric, Pfizer, Prometheus, Rexahn, Takeda, and Tracon. 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1808P Pain response and health-related quality of life (HRQL) analysis in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel every 2 weeks (16 mg/m^2) versus every 3 weeks (25 mg/m^2) in the CABASTY phase III trial

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Background: In CABASTY trial (NCT02961257), CBZ 16 mg/m^2 q2w + G-CSF significantly reduced grade $\geq$3 neutropenia and/or neutropenic complications vs CBZ 25 mg/m^2 q3w + G-CSF with comparable overall survival (OS) benefit in older and heavily pretreated patients (pts) with mCRPC *(Oudard et al. ESMO 2022)*. Here, we report changes in HRQL in both arms during therapy.

Methods: The Functional Assessment Cancer Therapy-Prostate (FACT-P) questionnaire was collected at each visit and analyzed in all pts exposed to CBZ with evaluable HRQL at baseline and post-baseline. Higher values indicated better HRQL. Changes of $\geq$10 points in FACT-P total score and $\geq$2 points in Prostate Cancer Subscale (PCS)-pain score, confirmed by 2 consecutive evaluations were judged clinically meaningful.

Results: 196 pts (median age, 74.6 yrs; $\geq$75 yrs, 49%; G8 $<$14, 20%; vulnerable or frail per SIOG guidelines, 30.1%; moderate to severe pain, 18%) previously treated with docetaxel and novel hormonal therapies (median 3 lines) were randomized to CBZ q3w (n=97) or q2w (n=99) + G-CSF. Median treatment duration was 19.0 and 20.1 weeks with CBZ q3w and q2w, respectively. HRQL was evaluable in 88 (90.7%) and 96 (97.0%) pts with CBZ q3w and q2w. PCS-pain improved in 35.2% vs 38.5% (CBZ q3w vs q2w). The probability of not having PCS-pain deterioration during treatment was 81.8% vs 75.0% with CBZ q3w vs q2w (HR=1.5 [95% CI, 0.80-2.9], p=0.2). Total FACT-P score improved from baseline in 17.0% vs 13.5% of pts with CBZ q3w vs q2w, respectively. FACT-P score was either stable or improved from baseline in 75.0% vs 74.0% of pts with CBZ q3w vs q2w. At 75% percentile, time to deterioration was 4.9 vs 3.3 months (HR: 1.2; p =0.57) with CBZ q3w vs q2w.

Conclusions: In this older and heavily pretreated mCRPC pts population, CBZ q3w and q2w + G-CSF similarly relieved pain and maintained or improved HRQL in 3 out of 4 pts with a comparable OS benefit. Since bi-weekly dosing induces less grade $\geq$3 neutropenia and/or neutropenic complications, it should be offered to pts unfit to receive the standard CBZ regimen.

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Legal entity responsible for the study: ARTIC.

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1809P Dynamics of plasma tumour DNA and copy number alterations in advanced metastatic castration-resistant prostate cancer (mCRPC) patients treated with cabazitaxel: A prospective biomarker trial

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Background: Liquid biopsies enable non-invasive detection of circulating biomarkers for disease monitoring and treatment resistance interrogation. We aimed to study circulating tumour DNA (ctDNA) to identify biomarkers of response from cabazitaxel in mCRPC patients (pts).

Methods: mCRPC pts (N=104) candidate for cabazitaxel treatment were enrolled in a prospective biomarker multi-centre trial (NCT03381326). Plasma was collected at baseline (BL), prior to cycle 3/4 (C3) and at progression (PD) and analyzed using a bespoke prostate cancer capture panel (PCF_SELECT, Orlando et al, NAR Cancer 2022). ctDNA fraction was calculated using allelic imbalance-based quantitation of the most abundant hemi-deletions. Primary outcome measures were overall survival (OS) and progression-free survival (PFS). Medians and [IQR] or 95% CI are reported.

Results: 97 pts were evaluable. ctDNA fraction was significantly lower at C3 (0.05 [0.04-0.38]) versus (vs) BL (0.40 [0.25-0.51]) and PD (0.41 [0.27-0.59] p=0.003). ctDNA dynamics strongly associated with outcome: pts with any increase in ctDNA fraction at C3 vs BL (N=20/65) had the worst outcome (PFS 2.6 months (mo), 95% CI 2.2-3.1; OS 7.5 mo, 95% CI 5.2-9.9) whilst pts who had a decrease at C3 (N=27/65) had a similar PFS (6.7 mo, 95% CI (5.1-8.2) but worse OS (15.7 mo, 95% CI 11.4-21.4) compared to undetectable ctDNA at both BL and C3 (N=18/65; PFS 8.2 mo, 95% CI 4.9-11.2; OS 29.9 mo, 95% CI 22.5-39.6). Median ctDNA fraction was significantly higher (0.50 [0.38-0.64]) in early progressors (at or before C3) vs late (after 4 cycles; 0.32 [0.17-0.55] p=0.03). In samples with detectable ctDNA, there was overall a consistent prevalence of gene copy number alterations at BL and PD; however, a significantly higher prevalence of gains of *PIK3CB* (chr3q22; 55 vs 29%, p=0.01) and *AKT1* (chr14q32; 31 vs 14%, p=0.048) was observed in PD samples compared to BL.

Conclusions: ctDNA dynamics associated with cabazitaxel outcomes and identified pts progressing early. An enrichment in *PIK3CB* and *AKT1* gains was observed upon cabazitaxel progression.

Clinical trial identification: NCT03381326.

Legal entity responsible for the study: The authors.

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1810P Association of health-related quality of life with efficacy outcomes in the VISION study of patients with metastatic castration-resistant prostate cancer

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Background: This *post hoc* analysis of the phase 3 VISION study of [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) plus standard of care (SoC) vs SoC alone in adults with progressive, prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC), assessed associations of PSA decline, radiographic progression-free survival (rPFS) and overall survival (OS) with time to worsening (TTW) of health-related quality of life (HRQoL).

Methods: Associations of PSA decline with TTW of HRQoL ($n = 385$) were assessed in the ^{177}Lu-PSMA-617 arm. Patients were grouped by PSA decline (unconfirmed) overall or up to 12 weeks of treatment: no decline, $\leq 50\%$, > 50 to $\leq 90\%$ and $> 90\%$. Worsening of HRQoL was defined as a decrease of ≥ 10 (total) or ≥ 3 (subdomain) points in FACT-P, an increase of ≥ 2 points in BPI-SF or any decrease in EQ-5D-5L. Associations of rPFS or OS with TTW of HRQoL were carried out in the full analysis set (FAS; $N = 831$) using three Spearman's rank methods (restricted, highest rank, iterative multiple imputation), with and without imputation for missing OS and rPFS data.

Results: In the ^{177}Lu-PSMA-617 arm, greater PSA decline overall and up to 12 weeks of treatment was associated with longer median TTW in FACT-P total and subdomain scores (Table). Correlations of rPFS and OS with and without imputation with TTW of HRQoL were positive and significantly different to zero in both arms, but mainly weak/moderate. In the total FAS without imputation, rPFS correlations were 0.27—0.51 (FACT-P total), 0.19—0.34 (EQ-5D-5L) and 0.26—0.47 (BPI-SF severity); OS correlations were 0.41—0.55 (FACT-P total), 0.13—0.31 (EQ-5D-5L) and 0.20—0.55 (BPI-SF severity).

Table: 1810P HRQoL outcomes by magnitude of PSA decline

	Median[a] TTW in FACT-P score, months (95% CI)				
	Total	Physical wellbeing	Emotional wellbeing	Social/family wellbeing	Functional wellbeing
PSA decline up to week 12[b], %					
0 (n = 104)	3.3 (2.5, 3.9)	2.3 (2.0, 3.3)	3.3 (3.0, 4.5)	3.5 (3.2, 4.4)	3.2 (2.3, 3.9)
≤ 50 (n = 62)	6.2 (4.6, 7.9)	4.7 (3.3, 7.8)	7.1 (4.6, 9.1)	6.7 (5.1, 9.1)	4.6 (1.9, 5.7)
> 50 to ≤ 90 (n = 113)	8.0 (6.4, 10.7)	8.8 (6.2, 10.6)	8.4 (6.7, 10.7)	8.0 (6.3, 10.6)	7.0 (4.6, 8.6)
> 90 (n = 61)	11.3 (6.9, 15.6)	10.2 (4.6, 14.6)	15.6 (9.3, 18.4)	8.8 (5.3, 15.1)	7.8 (2.6, 11.5)

[a]Kaplan–Meier estimates; [b]^{177}Lu-PSMA-617 + SoC group.

Conclusions: Greater PSA decline and increased rPFS and OS were associated with longer TTW of HRQoL. Ongoing analyses will assess associations of other HRQoL measures with PSA decline and overall response rate.

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1811P Patient-reported outcomes (PROs) in men with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) mutations receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA: Results from a phase III (TALAPRO-2) study

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Background: TALAPRO-2 (NCT03395197) showed statistically significant improvement in imaging-based progression-free survival with TALA + ENZA (n=200) vs PBO + ENZA (n=199) (HR=0.45; 95% CI 0.33–0.61; P<0.0001) in men with HRR mutations receiving first-line treatment for mCRPC. Here we report PRO data for this HRR mutation cohort.

Methods: PROs were assessed at day 1 and scheduled visits (every 4 weeks until week 53, then every 8 weeks) until radiographic progression using the EORTC QLQ-C30 and its prostate cancer module, QLQ-PR25. Prespecified PRO endpoints included

overall mean change from baseline (per longitudinal repeated measures mixed-effects model) and time to definitive deterioration (TTD) with a clinically meaningful change of ≥10-points. Stratified log-rank test and Cox proportional hazards model were used to make TTD between-arm comparisons.

Results: Of the 399 men in the HRR mutation cohort, 394 (n=197 both arms) had at least a baseline plus 1 post-baseline PRO score. No statistically significant difference in treatment effect on the global health status (GHS)/quality of life (QoL) scale was observed between arms. The treatment effect on the physical, emotional, and cognitive functioning scales favored TALA + ENZA, but did not meet the clinical meaningful threshold (Table). A longer TTD for TALA + ENZA vs PBO + ENZA was observed in GHS/QoL (HR=0.69; 95% CI 0.49–0.97; *P*=0.032; median 27.1 vs 19.3 months) and urinary symptoms (HR=0.56; 95% CI 0.34–0.93; *P*=0.022; median not reached vs 30.2 months).

Table: 1811P Overall change from baseline in PROs

Scale	TALA + ENZA estimated mean (95% CI)	PBO + ENZA estimated mean (95% CI)	Estimated mean difference (95% CI)	P value
GHS/QoL	−3.6 (−5.9, −1.4)	−4.9 (−7.3, −2.6)	1.3 (−2.0, 4.5)	0.447
Physical	−3.5 (−5.5, −1.5)	−7.3 (−9.4, −-5.2)	3.8 (0.9, 6.7)	0.010*
Role	−4.5 (−7.1, −1.9)	−6.6 (−9.3, −3.9)	2.1 (−1.7, 5.8)	0.276
Emotional	−0.3 (−2.4, 1.8)	−3.5 (−5.7, −1.3)	3.2 (0.2, 6.2)	0.038*
Cognitive	−5.6 (−7.9, −3.4)	−9.1 (−11.5, −6.8)	3.5 (0.3, 6.7)	0.034*
Social	−5.6 (−7.9, −3.4)	−6.2 (−8.6, −3.8)	0.6 (−2.7, 3.9)	0.730

Positive scores indicate better GHS/QoL and functioning
*Did not meet the predefined threshold of clinical meaningfulness

Conclusions: TTD in GHS/QoL and urinary symptoms were significantly longer with TALA + ENZA vs PBO + ENZA. Modest treatment differences favoring TALA + ENZA vs PBO + ENZA were observed for some functioning scales. These data complement the benefit–risk assessment of TALAPRO-2 for men with mCRPC who have HRR mutations.

Clinical trial identification: NCT03395197.

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1812P Exploration of germline (g) vs somatic (s) origin of homologous recombination repair (HRR) gene alterations and potential associations with antitumor activity in the HRR-deficient population from TALAPRO-2

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Background: TALAPRO-2 evaluated the PARP inhibitor talazoparib (TALA) combined with the androgen receptor pathway inhibitor enzalutamide (ENZA) as 1st-line treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). The primary endpoint was radiographic PFS (rPFS) assessed centrally. Exploratory biomarker analyses assessed g vs s origin of HRR gene alterations and potential associations with efficacy in the HRR-deficient population from TALAPRO-2.

Methods: Alterations were defined as known/likely pathogenic variants. The frequency of gHRR alterations (gHRRm) was assessed in pts evaluable for saliva sequencing using the Ambry CustomNext-Cancer panel (sequenced 9/12 genes from

the HRR12 tumor panel). Association of g vs s tumor HRRm and efficacy was assessed in the ITT population using saliva data (or solid tumor s-g-zygosity prediction when adequate saliva results unavailable) to annotate tumor alteration origin (limited to short variants). Associations with rPFS were evaluated using a stratified log-rank test. Data cutoff: October 3, 2022.

Results: 91/302 pts (30.1%) evaluable for gHRR exhibited $\geq$1 HRR alteration in their saliva: *BRCA2* (14.9%); *CHEK2* (7.3%); *ATM* (4.0%); *PALB2* (2.3%); *BRCA1* (1.0%); *NBN* (1.0%); *MRE11A* (0.7%); *MLH1* (0.3%). Where evaluable, solid tumor and prospectively tested baseline ctDNA HRR alterations were typically of s origin (eg *BRCA2* [44 g vs 50 s], *CDK12* [1 g vs 27 s], *ATM* [14 g vs 49 s]) with some exceptions (eg *BRCA1* [7 g vs 4 s], *CHEK2* [24 g vs 2 s], *NBN* [5 g vs 2 s]). rPFS was comparable for pts with g and s alterations in the TALA + ENZA arm (HR 0.74, 95% CI, 0.35−1.58; 2-sided *P* value = 0.44), but relatively shorter for gHRRm pts in the placebo (PBO) + ENZA arm (HR 1.87, 95% CI, 1.06−3.30; $P = 0.03$).

Conclusions: GHRRm incidence in mCRPC pts with tumor HRRm was 30.1%. No association with differential antitumor activity for TALA + ENZA was observed in tumors bearing HRRm of g vs s origin. Though the analyses were exploratory, a shorter rPFS in PBO + ENZA-treated gHRRm pts may reflect an intrinsically poor prognosis subgroup that could be prioritized for TALA + ENZA treatment. Further study is warranted.

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There are multiple research projects sponsored by these companies which pay money to my institution: Arnivas, Astellas, AstraZeneca, Bavarian Nordic, Bayer, BMS, Calithera, Celldex, Crispr, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, GSK, Immunomedics, Janssen, Lava, Medivation, Merck, Nektar, Neoleukin, New Link Genetics, Novartis, Oric, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon.; Financial Interests, Steering Committee Member, I am involved in the steering committee of the trials sponsored by these pharmas with no personal honorarium: AstraZeneca, Calithera, Clovis, Crispr, Eisai, Eli Lilly, Exelixis, Immunomedics, Janssen; Financial Interests, Steering Committee Member, I am involved in the steering committee of the trials sponsored by these pharma companies with no personal honorarium: Merck, Nektar, New Link Genetics, Oric, Pfizer, Prometheus, Rexahn, Takeda, and Tracon. 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1813P Phase I/II trial of oral EPI-7386 in combination with enzalutamide (enz) compared to enz alone in metastatic castration-resistant prostate cancer (mCRPC) subjects: Current phase I (PI) results

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Background: EPI-7386 is a next generation aniten designed to inhibit androgen receptor (AR) activity by binding the N-terminal domain and blocking transcription despite resistance driven by point mutations and splice variants in the ligand-binding domain. In preclinical models, the combination of EPI-7386 with Enz results in a deeper blockade of the AR pathway and greater antitumor activity, prompting this trial.

Methods: This phase I/II multicenter, open-label clinical trial (NCT05075577) is enrolling mCRPC patients on androgen deprivation therapy and naïve to second-generation antiandrogens (1 line of prior chemotherapy in the metastatic hormone sensitive setting allowed). PI examines escalating doses of EPI-7386 with Enz. Primary and secondary endpoints of PI evaluate the safety and pharmacokinetics (PK) of EPI-7386 and Enz when co-administered to establish recommended phase II combination doses (RP2CDs) and address possible drug-drug interactions (DDIs). Once RP2CDs are established, phase II (PII) will commence as a two arm, 2:1 randomized trial evaluating antitumor activity of EPI-7386 in combination with Enz versus Enz alone.

Results: To date, 11 patients have been enrolled in cohorts 1-3 (cohort 4 is currently enrolling). Safety is consistent with second-generation antiandrogens (e.g., Grade 1 or 2 AEs of fatigue and hot flashes). PK results demonstrate Enz exposure is minimally impacted by EPI-7386, allowing testing of the full dose of Enz (160 mg) in the current cohort 4. EPI-7386 exposure is strongly reduced by Enz (CYP3A4 inducer that metabolizes EPI-7386) but remains in the clinically relevant range seen in xenograft studies. EPI-7386 BID dosing shows an increase in EPI-7386 exposure and mitigates DDI caused by Enz. Data from the first 10 evaluable patients show 9/10 achieve a PSA90, and 7/10 patients reach PSA $<$0.2 ng/mL.

Conclusions: With no safety concerns from cohorts 1-3, cohort 4 is currently enrolling at EPI-7386 BID + 160 mg QD Enz to evaluate optimal RP2Ds before the P2 component of the trial. Updated results, including cohort 4, will be presented.

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1814P First real-life data on [177Lu]Lu-PSMA-617: Descriptive analysis on the largest metastatic castration-resistant prostate cancer (mCRPC) cohort treated in early access in France

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Background: VISION study showed that [^{177}Lu]Lu-PSMA-617 added to BSoC prolonged imaging based progression-free survival and overall survival in patients (pts) with PSMA-positive mCRPC. French Health Authorities has granted a "cohort" early access for [^{177}Lu]Lu-PSMA-617 in this indication.

Methods: PSMA positive pts with mCRPC pretreated with 1-2 taxane chemotherapy and $\geq$1 androgen receptor pathway inhibitor (ARPI) were included. Treatment administration planned 6 IV of [^{177}Lu]Lu-PSMA-617 (7.4 GBQ) every 6 weeks. Pts' characteristics, efficacy and safety data were collected during the 6 follow-up visits (average: 17,1 $\pm$ 11,2 weeks). AE grading was not evaluated.

Results: From 12/1/2021 to 1/31/2023, 664 pts were exposed to treatment. At data closure, 428 were still under treatment, and 236 stopped treatment due to disease progression (50.2%), adverse events (AE) (14.0%) or death (11.0%; 1 death suspected to be due to the treatment). 42 pts (17.6%) completed all 6 injections. Pts baseline characteristics: median age 72.9 years; ECOG status 0-1: 85.4%; median PSA level 81.94 ng/ml; metastases: bone 94.1%, lymph node 63.0%, liver 11.3%; prior taxane regimen: 97.4% of which 65.5% received 2 taxane; prior ARPI treatment: 100% of which 67.9% received 2-5 previous ARPI treatments. For pts who received all injections, disease control was estimated by radiological (2.7% CR, 40.5% PR, 27.0% SD), clinical (11.9% clinical improvement and 78.9% stabilization), and PSA evaluation (34.2% decreased PSA level and 34.2% stabilization). 11.9% of pts experienced $>$1 treatment-related AE, including 63 pts with $\geq$1 serious AE. 3 fatal cases and 3 life-threatening cases related to treatment have been reported. The most reported AEs were thrombocytopenia (5.7% of pts) and anemia (4.5% of pts).

Conclusions: We observed a higher incidence of prior 2 taxane regimen and lymph nodes metastases at baseline compared to VISION study but the safety profile of [^{177}Lu]Lu-PSMA-617 remains safe and well tolerated. Since the study is still ongoing, updated efficacy results will be further analyzed and presented at ESMO congress, including longer follow-up period and higher number of pts who completed treatment.

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1815P Emergent circulating tumor DNA (ctDNA) variants and ctDNA burden dynamics with potential associations with talazoparib antitumor activity in TALAPRO-1

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Background: TALAPRO-1 evaluated talazoparib in patients (pts) with mCRPC and homologous recombination repair (HRR) alterations (11-gene panel, including *BRCA1/2, PALB2,* and *ATM*), who had received at least a taxane-based chemotherapy regimen and progressed on $\geq$1 novel hormonal therapy. Primary endpoint was objective response rate (RECIST 1.1) by blinded independent central review. Exploratory biomarker analyses assessed ctDNA and its associations with antitumor activity.

Methods: Serial ctDNA samples from Weeks (Wks) 1, 9, and 25, and Safety follow-up visit (SFUV) were assessed using FoundationOne Liquid CDx. Plasma tumor fraction (TF) was calculated based on tumor aneuploidy as described by Husain et al (JCO Precis Oncol 2022; 6:e2200261). Data cut-off was September 4, 2020 (primary completion date).

Results: *BRCA2* mutational complexity (variants/*BRCA2*m pts) was 18/16 (1.1), 12/10 (1.2), 62/11 (5.6), and 57/14 (4.1) at Wks 1, 9, and 25, and SFUV, respectively. At Wk 25, the median number of *BRCA2* variants was 2 (range 1−18; 3 pts had $\geq$15 variants). Mutational complexity increased for *BRCA1* and *PALB2* by Wk 25 but remained unchanged for *ATM*. Of 26 evaluable pts, 7 cases of emergent variants in PARP1, PARP2, or PARP3 at Wk 25 and/or SFUV were detected. These included 5 cases of PARP1 variants predicted to truncate PARP1 and/or inhibit talazoparib binding, including 3 cases of A898T. 15/27 pts had TF quantifiable at Wk 1 (range 10−68%). Of these 15 pts, 10 had TF below limit of quantitation (BLQ; 10%), 1 had TF reduction $\geq$50%, and 4 had TF unchanged (change $<$50%) at Wk 9. Reductions to BLQ were seen in 4/4 with partial response, 2/2 with non-complete response/non-progressive disease, 3/5 with stable disease (an additional patient reduced $\geq$50%), and 1/4 with progressive disease.

Conclusions: Increased mutational complexity of genes in the *BRCA1-PALB2-BRCA2* axis and emergent PARP variants likely reflects selective pressure to escape talazoparib-mediated synthetic lethality and/or PARP trapping. Early reductions in TF were evident and numerically more common in pts with antitumor responses. Further exploration of emergent variants in HRR and PARP genes and of ctDNA burden are warranted.

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1816P Combination treatment with radium-223 (223Ra) and enzalutamide (enza) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) in the REASSURE study

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Background: ^{223}Ra and enza both prolong overall survival (OS) in pts with mCRPC. Their different mechanisms of action and non-overlapping safety profiles make them attractive combination partners. Here, we present clinical outcomes of pts who received combined or layered treatment with ^{223}Ra and enza in REASSURE (NCT02141438), a global, prospective, observational study of ^{223}Ra use in pts with mCRPC.

Methods: Data from 1,465 pts (All pts) were analysed. Pt subgroups included "combined" (pts started ^{223}Ra and enza within 30 days of each other, n=46) and "layered" (pts started ^{223}Ra >30 days after starting enza or vice versa, n=205). Statistics were descriptive in nature.

Results: The proportions of pts who had completed ≥1 life-prolonging therapy for mCRPC prior to ^{223}Ra were 43%, 52% and 61% in the combined, layered and All pts groups, respectively (30%, 27% and 33% had received prior abiraterone and 17%, 29% and 36% had received prior docetaxel, respectively). More pts in the combined group (74%) completed 6 cycles of ^{223}Ra than in the layered (61%) or All pts (59%). Median duration of observation from start of ^{223}Ra for combined, layered and All pts was 17.3, 11.1 and 11.5 months (mo), respectively. The proportions of pts with a ≥30% decline in alkaline phosphatase at week-12 were 58%, 41% and 47% in the combined, layered and All pts groups, respectively; corresponding values for a ≥30% decline in prostate specific antigen were 54%, 17% and 20%. Median OS was 22.2 mo (95% CI 13.7—26.8) in the combined group, 16.5 mo (95% CI 13.9—19.5) in the layered group and 15.6 mo (95% CI 14.6—16.5) in All pts.

Table: 1816P Summary of safety

	Combined group n=46	Layered group n=205	All Pts n=1,465
Drug-related any-grade TEAE, n (%)	17 (37)	58 (28)	510 (35)
Drug-related grade ≥3 TEAE, n (%)	6 (13)	17 (8)	155 (11)
Drug-related serious adverse events, n (%)	5 (11)	15 (7)	80 (5)
Concomitant bone health agent (BHA), n (%)	25 (54)	95 (46)	566 (39)
Fractures in pts with concomitant BHA, n (%)	2 (8)	2 (2)	19 (3)
Without concomitant BHA, n (%)	21 (46)	110 (54)	899 (61)
Fractures in pts without concomitant BHA, n (%)	1 (5)	4 (4)	51 (6)

Conclusions: When combined or layered with enzalutamide, treatment with ^{223}Ra was not associated with new safety signals and did not appear to increase fracture risk. Median OS was numerically longer in the combined vs the layered group or All pts. A phase 3 trial (PEACE III, NCT02194842) investigating the combination of enza with ^{223}Ra is ongoing.

Clinical trial identification: NCT02141438.

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1817P A phase I/II efficacy and safety study of LAE001/prednisone and afuresertib in patients with metastatic castration-resistant prostate cancer (mCRPC) following 1-3 lines of standard of care

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Background: New therapy for mCRPC patients refractory to the second-generation anti-androgen or androgen receptor hormonal therapy and/or chemotherapy is a definite unmet medical need. The ORR and median rPFS of refractory mCRPC patients are 7% to 17% and 2 to 4 months in second to fourth line settings, respectively. Studies have reported that AKT inhibitor plus an anti-androgen inhibitor is a potential treatment for refractory mCRPC with a longer rPFS and a better ORR compared to standard of care (SOC).

Methods: This is a multicenter, open-label, global phase I/II study to assess the efficacy and safety of combination therapy of LAE001 (a dual inhibitor of CYP17A1 and CYP11B2)/prednisone plus afuresertib (an AKT inhibitor) in refractory mCRPC patients who failed 1-3 lines of SOC. The patients in phase I and phase II received the combination therapy of LAE001 75 mg BID/prednisone 5 mg BID plus afuresertib 125 mg QD were included in analysis.

Results: The study enrollment was completed on 01Mar2023. At the data cut-off date on 25Apr2023, 40 patients (6 from phase I and 34 from phase II) were treated and followed-up between 1.8 to 31.3 months. The median prior lines of therapy were 2 and median Gleason score was 9. Seven rPFS events were observed and 26 patients are still in the study without radiographic tumor progression. The rPFS data is expected to be mature and will be reported at the meeting. Partial response per RECIST 1.1 were observed in 3 of 10 patients who had measurable lesions at baseline and at least one post-baseline tumor assessment. The most commonly reported AEs ($\geq$ Grade 3) were thrombocytopenia (7.5%), anaemia (5.0%), hyperglycaemia (5.0%), hyponatraemia (5.0%), and hypertension (5.0%). SAEs were reported in 9 patients (22.5%), 5 (12.5%) were assessed as related to study treatment. No related G5 AE occured.

Conclusions: The combination therapy demonstrated clinical benefit and a tolerable safety profile in mCRPC patients who failed multiple lines of SOC. The preliminary results warrant further evaluation in a phase III pivotal trial.

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1818P Final results from a randomized phase II study of cabazitaxel (CBZ) versus an androgen receptor targeted agent (ARTA) in patients with poor-prognosis castration-resistant prostate cancer (mCRPC)

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Background: In the multicenter, phase IIb OSTRICH trial, poor-prognosis mCRPC patients were randomized between CBZ and ARTA, directly following progression on docetaxel (DOC) treatment.

Methods: mCRPC patients with poor-prognosis ($\geq$1 factor: visceral metastases, CRPC within 1 year, progression $\leq$6 months after DOC completion) were randomized 1:1 between CBZ and ARTA (Abiraterone OR Enzalutamide). Primary endpoint was to establish the Clinical Benefit Rate (no radiotherapy, no ECOG PS increase $\geq$2, no therapy switch and no radiological progression) at 12 weeks (CBR) in both study arms, while comparison of the CBR was a secondary endpoint. A Fisher Exact test was used to assess differences in rates and a log rank test to assess differences in time to event endpoints.

Results: A total of 106 patients were randomized, 53 in each arm. Baseline median age was 70 and PSA 76 ng/ml. DOC was received in the HSPC stage in 36 patients (34%), while 40 patients (38%) received ARTA prior to DOC. CBR was 60.8% (95% CI: 46.1 − 74.2%) in the CBZ arm and 67.3% (95% CI: 52.9 − 79.7%) in ARTA arm (p=0.54)). At 12 weeks, PSA responses were 17% (95% CI: 8.1−29.8%) and 5.3% (95% CI:31.6−59.6%) in the CBZ and ARTA arms, respectively (p = 0.003). After a median follow-up of 30.9 (95% CI: 25 − NA) months, median Time to Symptomatic Progression was 4.2 (95% CI: 3.7 − 5.9) vs 5.8 (95% CI: 4.6 − 6.5) months in the CBZ vs ARTA arm (p=0.07). Time to Radiological progression was 7.1 (95% CI: 5.3 − 13.8) and 5.8 (95% CI: 5.4 − 11.4) months in CBZ and ARTA (p=0.77), Time to PSA progression was 3.6 (95% CI: 2.6 − 7.8) and 4.1 (95% CI: 3.3 − 8.9) months in the CBZ and ARTA arm (p=0.95), respectively. Progression free survival 2.5 (95% CI: 2.2 − 3.4) in the CBZ arm and 3 (95% CI: 2.6 − 3.6) months ARTA arm (p=0.24). Overall Survival was 14.9 (95% CI: 9.7 − 19.5) months in CBZ and 13.9 (95% CI: 11.7 − 16.5) months in the ARTA arm (p=0.53). Grade $\geq$3 adverse events (AEs) occurred in 62% and 26% patients in CBZ and ARTA arm.

Conclusions: No significant difference in CBR and time to event endpoints was established between CBZ and ARTA treated patients. Further studies will concentrate on prespecified subgroups.

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1819P PSMA-BAT: Prospective biomarker trial of patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) undergoing bipolar androgen therapy (BAT)

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Background: BAT has shown clinical activity and capacity of tumor resensitization to androgen receptor targeted therapy in mCRPC. We aimed to explore imaging and genomic biomarkers of response to BAT.

Methods: This is a single-arm study of pts with mCRPC and progressive disease on at least one novel AR-targeted therapy. Pts were treated with BAT (testosterone cypionate 400 mg intramuscular) every 4 weeks. All pts underwent PSMA-PET/CT (PSMA-PET) and FDG-PET/CT (FDG-PET) at baseline and week 12. Molecular tumor volume (mTV), total lesion expression (TL), standardized uptake value (SUV) max and mean were evaluated in PSMA-PET scans; total lesion glycolisys (TLG), metabolic tumor volume (MTV), SUVmax and SUVmean in FDG-PET scans. AR-V7 expression in circulating tumors cells (CTCs) was analyzed in each cycle and at week 12. Variables were correlated with PSA response, 6-month progression-free survival (PFS) and overall survival (OS).

Results: A total of 20 pts were included from Oct 2020 to Mar, 2022. Median age was 66y, and median number of prior systemic therapies was 3.5 (2-5). Any PSA and PSA50 responses were achieved in 45% and 30% of pts. Median PFS was 5.6 months (mos) (95% CI 3.4 - 7.8 mos), and 40% reached a PFS >6 mos. PFS or OS were not associated with baseline PSA or demographic characteristics. Higher interim PSMA mTV, variation (Δ) mTV week 12-baseline mTV > -17%, Δ TL-PSMA week 12-baseline >39% and higher week 12 PSA/PSMA SUVmax were associated with PFS < 6 mos (p=0.01; p=0.009; p=0.009, p=0.01). Median OS was 23.1 mos. Higher baseline PSMA mTV, TL-PSMA, FDG MTV and TLG were associated with worse OS (p=0.009; p=0.02; p=0.006; p=0.02). At baseline, 14/20 pts were positive (+) for CTCs. Of those, 8 were AR-V7+. At week 12, 6 pts became negative (-) for CTCs and 6 became - for AR-V7; only 2 pts became + for CTCs and none became + for AR-V7. The difference between baseline and week 12 AR-V7 + pts was statistically significant (p=0.03). Positive AR-V7 was associated with worse OS (p<0.05).

Conclusions: Higher PSMA-PET mTV and TL-PSMA may predict worse PFS in pts treated with BAT. Positive AR-V7 was associated with worse OS. Responses to BAT can influence AR-V7 dynamics. Larger trials are necessary to confirm our findings.

Clinical trial identification: NCT04424654.

Legal entity responsible for the study: Hospital Sírio-Libanês.

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Disclosure: A.B. Lara Gongora: Financial Interests, Invited Speaker, Travel, Accommodations, Expenses: Bayer, Astellas, Janssen, MSD, AstraZeneca. D.L.F. Jardim: Financial Interests, Invited Speaker, Speaker/scientific support for events: Astellas; Financial Interests, Invited Speaker, Speaker/Scientific support for events: Janssen, BMS; Financial Interests, Advisory Board: Janssen, Libbs; Financial Interests, Sponsor/Funding, Scientific support for events: Roche; Financial Interests, Invited Speaker: Libbs, MSD; Financial Interests, Writing Engagements: Libbs; Financial Interests, Funding, Research Funding: Recepta. G.B. Grossman: Financial Interests, Invited Speaker, Speaker/Consultant: Pfizer, Siemens. D.A. Bastos: Financial Interests, Personal, Invited Speaker: MSD; Financial Interests, Invited Speaker: BMS, Janssen, Astellas, AstraZeneca, Bayer. All other authors have declared no conflicts of interest.

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1820P Cardiovascular effects of androgen receptor signalling inhibitors in the treatment of advanced and metastatic prostate cancer: A systematic review and meta-analysis of randomised controlled trials

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Background: Cardiovascular (CV) events remain a significant cause of mortality amongst men with advanced and metastatic prostate cancer (PCa). The introduction of novel androgen receptor signalling inhibitors (ARSI) has transformed the treatment landscape of PCa in recent years, however their impact on CV toxicity remains unclear. We aimed to assess the CV effects of ARSI treatment in combination with standard of care (SOC) in advanced and metastatic PCa.

Methods: Systematic search of PubMed, SCOPUS, Web of Science, EMBASE and Clinicaltrials.gov were performed to identify randomized controlled trials (RCTs) comparing the addition of ARSI agents (Enzalutamide, Abiraterone, Apalutamide and Darolutamide) with SOC in treatment of non-metastatic and metastatic PCa, across both hormone-sensitive and castrate resistant settings. Outcomes of interest included: CV events defined by CV event grade (primary outcome), hypertension, acute coronary syndrome (ACS), cardiac dysrhythmia, CV death, cerebrovascular event, and venous thromboembolism (secondary outcomes).

Results: A total of 22 studies (n=22,967) were eligible for inclusion. ARSI therapy increased risk of any grade CV event (RR 1.72, 1.49-2.00, p<0.0001) and grade $\geq$ 3 CV events (RR 1.98 [1.58-2.48] p<0.0001). ARSI therapy also resulted in an increase in grade $\geq$ 3 hypertension (RR 2.02 [1.62-2.53] p<0.0001), ACS (RR 2.00 [1.46-2.74] p<0.0001), grade $\geq$3 cardiac dysrhythmia (RR 1.64 [1.23-2.19] p=0.0007), CV related death (RR 1.88 [1.22-2.89] p=0.004) and cerebrovascular events (RR 1.76[1.33-2.34] p<0.0001) across all PCa settings. Subgroup analysis demonstrated increased risk of all CV events and grade $\geq$3 across the disease spectrum (RR for all CV events: non-metastatic hormone sensitive PCa 2.20 [1.4-3.47], p<0.0007; metastatic hormone sensitive PCa 1.69 [1.39-2.06], p<0.0001; metastatic castrate resistant PCa 1.53 [1.36-1.71], p<0.0001).

Conclusions: There is compelling evidence indicating a significantly increased risk of all and high-grade CV events in men treated with ARSIs.

Legal entity responsible for the study: Genitourinary Cancer Research Group, University of Manchester, Manchester, United Kingdom.

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Disclosure: N.W. Clarke: Non-Financial Interests, Institutional, Other, Investigator on PRONOUNCE Trial. All other authors have declared no conflicts of interest.

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1821P High serum FSH/T ratio as a marker for the development of cardiovascular disease in ADT recipients

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Background: Cardiovascular disease (CVD) is a leading cause of death in men with prostate cancer (PC). Androgen deprivation therapy (ADT) may increase this risk. GnRH agonists or antagonists induce equivalent castration but have a distinctive effect on follicle-stimulating hormone (FSH). We hypothesize that FSH mediates the atherogenic and cardiovascular effects associated with testosterone (T) deficiency.

Methods: We investigated mouse models of atherosclerosis using gain and loss of FSH and two clinical studies with primary CVD endpoints. Low-density lipoprotein receptor-deficient (LDLR-/-) and FSHβ-/-;LDLR-/- mice were treated with different modes of ADT for 14 weeks and aortic atherosclerotic plaque, its necrotic and inflammatory content and serum hormones were determined. In a prospective cohort of PC patients commencing on ADT, serum FSH and T were determined after three and six months and related to the development of cardiovascular events. In a prospective nested case-control study of 848 men undergoing surgery, serum FSH and T were related to the development of cardiovascular event.

Results: Compared to LDLR-/- mice, FSHβ-/-;LDLR-/- mice, untreated or castrated, demonstrated significantly less atherosclerosis, but not following delivery of FSH. The significant differences in necrotic core and total atherosclerotic plaque in mice treated with GnRH-agonists vs. antagonists were nullified by loss of FSH in the FSHβ-/-;LDLR-/- mice. Atherosclerotic plaque, its necrotic and inflammatory content, correlated significantly with the serum FSH/T ratio. In PC patients commencing on ADT, serum FSH/T after three and six months significantly predicted the development of cardiovascular event. In men undergoing surgery, high FSH/T ratio increased odds of a postoperative cardiovascular event by 39% (95% CI 3-87%).

Conclusions: FSH facilitates CVD in men with low or castrated T. Serum FSH/T ratio associates with the risk of developing a cardiovascular event following a stressful cardiovascular trigger such as ADT or surgery. Accordingly, GnRH-antagonists associated with lower necrotic and atherosclerotic plaque burden in mice and clinically, with significantly lower serum FSH/T levels and fewer cardiovascular events compared to GnRH-agonists.

Legal entity responsible for the study: J. H. Pinthus.

Funding: Ferring.

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1822P PSMA-alpha targeted radionuclide therapy (TRT) with or without prior PSMA-beta TRT

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Background: PSMA-TRT has included either beta-emitters (Lutetium-177) or alpha-emitters (Actinium-225). Responses have been observed in patients treated with 225Ac after 177Lu, supporting sequential administration. There are no known data-driven normal organ dose limits for radionuclide therapy, with putative limits extrapolated from EBRT. Here, we evaluate baseline demographics and prior exposures for association with outcome following treatment with 225Ac-J591.

Methods: Patients treated on prospective clinical trials of 225Ac-J591 were retrospectively analyzed with focus on efficacy and adverse events (AEs) with prior therapies (Table). Kaplan-Meier method was used for time to event endpoints (overall survival/OS, progression-free survival/PFS). Fisher's exact test for analysis of associations between categorical variables.

Results: No significant difference in efficacy of 225Ac-J591 with/without prior 177Lu-PSMA: PSA50 (52 vs 58%), PFS (4.03 vs 5.07 mo), or OS (16.4 vs 17.3 mo); no efficacy differences based upon prior Ra223. Gr 4 myelosuppression may be more common in those with prior 177Lu, though numbers are small (n=1 for ANC and Hb; 14 vs 7.8% Gr 4 plts, p=0.4). No differences in frequency of nausea, xerostomia, or pain were seen with/without prior 177Lu, but Gr 2 fatigue was more common in those with prior 177Lu (48 vs 17%, p=0.023). No treatment-related renal failure observed with short-term follow up +/- prior 177Lu. Similar AE trends were seen for Gr 4 heme AE with prior Ra223 exposure, but no trend for non-heme AEs. Those with ≥2 lines chemo may be more likely to have Gr 4 heme AE. Within limits of small sample size, higher exposure of sequential 177Lu, Ra223, EBRT, and 225Ac-J591 associated with higher rate of Gr 4 plts (p=0.031).

Table: 1822P

225Ac-J591 n=86	
Median PSA	50.9 (range 2.43-9614)
Median age	71.5 (range 51-91)
Bone metastases	74 (86%)
Nodal metastases	49 (57%)
Lung metastases	10 (12%)
Liver metastases	10 (12%)
CALGB high risk	47 (55%)
CALGB intermediate risk	29 (34%)
CALGB low risk	10 (12%)
Prior 177Lu-PSMA TRT	22 (26%)
Prior Radium-223 (Ra223)	15 (17%)
>1 androgen-receptor pathway inhibitor	51 (59%)
Taxane chemotherapy	50 (58%)
Median # External Beam Radiation Therapy (EBRT)	1 (range 0-6)

Conclusions: Alpha-TRT with 225Ac-J591 retains efficacy following beta-TRT and Ra223. Risk of Gr 4 plts appears highest in those with prior 177Lu and Ra223 and EBRT, but high-grade events are rare. New examination of organ dose-limits with TRT is warranted.

Legal entity responsible for the study: Weill Cornell Medical Center.

Funding: Weill Cornell Medicine, Department of Defense, NIH.

Disclosure: J. Nauseef: Financial Interests, Advisory Board: AIQ Solutions. A.M. Molina: Financial Interests, Advisory Board: Eisai, Exelixis, Janssen. C.N. Sternberg: Financial Interests, Personal, Advisory Board, AD board and speaker at ESMO: Pfizer; Financial Interests, Personal, Advisory Board: MSD, AstraZeneca, Astellas, Sanofi-Genzyme, Roche-Genentech, Foundation Medicine, Immunomedics, Janssen; Financial Interests, Personal, Invited Speaker: Merck; Financial Interests, Personal, Advisory Board, Was the head if the oversignt committee, of Phase III trial but last meeting over 1 year ago: Seattle Genetics; Financial Interests, Personal, Other, AD board: BMS; Financial Interests, Personal, Other, Speaker, owned by Prostate Cancer Foundation: Uro Today; Financial Interests, Personal, Other, Speaker, CME activities: Medscape. D.M. Nanus: Financial Interests, Advisory Board: AstraZeneca. N.H. Bander: Financial Interests, Personal, Leadership Role, Leadership and Equity: Convergent Therapeutics, Xenimmune Therapeutics; Financial Interests, Personal, Stocks or ownership: Telix Pharmaceuticals. S.T. Tagawa: Financial Interests, Personal, Advisory Board: Convergent Therapeutics, Alkido Pharma; Financial Interests, Personal, Other, Consultant: EMD Serono, Telix Pharma, Blue Earth Diagnostics, POINT Biopharma, Myovant, Bayer, 4D Pharma, Gilead, Pfizer, Janssen, Astellas, AbbVie, Novartis, Seagen, Clarity, Merck, Myovant, EMD Serono; Financial Interests, Personal, Stocks/Shares: Alkido Pharma; Financial Interests, Personal, Other, Patent co-inventor: Gilead; Financial Interests, Institutional, Local PI: Medivation, Astellas, Janssen, Amgen, BMS, AstraZeneca, Bayer, Merck, Clovis, Seagen; Financial Interests, Institutional, Steering Committee Member: Gilead, Novartis, POINT Biopharma, Clarity, Ambrx, Promontory. All other authors have declared no conflicts of interest.

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1823P The impact of baseline PSMA PET/CT vs. CT on outcomes of Radium-223 therapy in mCRPC patients

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Background: Imaging prior to Radium-223 therapy (Ra-223) is crucial for selecting metastatic castration-resistant prostate cancer (mCRPC) patients with bone-only disease. The purpose of this study was to evaluate if baseline PSMA PET/CT versus CT is associated with biochemical response during Ra-223.

Methods: A secondary analysis of the data of a prospective observational study (NCT04995614) was performed. Patients received a maximum of six cycles of Ra-223 and were retrospectively divided into the PSMA PET/CT (bPSMA) or CT (bCT) group based on baseline imaging technique. All patients received baseline bone scintigraphy. Primary endpoints were alkaline phosphatase (ALP) and prostate specific antigen (PSA) response, defined as ≥ 30% decline from baseline. Secondary endpoints were overall survival (OS) and radiological response.

Results: Between 2017 and 2020, 122 mCRPC patients were included: 18 (14.8%) in the bPSMA and 104 (85.2%) in the bCT group. All baseline characteristics were comparable. No significant differences in ALP or PSA response were found between the groups. The bCT group showed a significant shorter OS compared to the bPSMA group (12.4 vs.19.9 months, $p < 0.01$, table). Post-therapy soft tissue involvement (STI) was detected in 29/76 patients (38.2%) that received bCT and post-therapy CT (bCT/pCT), compared to 0/18 bPSMA patients. No significant difference in OS was found between bCT/pCT patients without STI and bPSMA patients.

Table: 1823P OS (months) among subgroups

Baseline imaging	Post-therapy imaging	N	Median OS (IQR)	P-value
PSMA	Total PSMA A. STI B. W/o STI CT C. STI D. W/o STI No imaging	18 11/18 0/11 11/ 11 4/18 0/4 4/4 3/18	19.9 (12.7 — 29.0) - - 21.2 (14.7 — 40.8) - - 20.3 (15.2 — 36.8) 4.9 (3.1 - NR)	**0.038** vs. bCT - - - - - - -
CT	Total PSMA A. STI B. W/o STI CT C. STI D. W/o STI E. Unknown STI No imaging	104 7/104 6/7 1/7 76/104 29/76 44/76 3/76 21/104	12.4 (7.9 — 18.2) - 14.6 (11.5 — 24.9) 21.5 (NR) - 10.6 (6.0 — 14.2) 14.8 (9.3 — 26.0) - 9.2 (4.0 — 12.9)	**0.038** vs. bPSMA - - - - **<0.01** vs. bCT/pCT w/o STI 0.457 vs. bPSMA - -

Abbreviations: W/o, without; NR, not reached.

Conclusions: bPSMA versus bCT does not seem to predict biochemical response during Ra-223. Nevertheless, patients in the bCT group had a significantly shorter OS, most likely due to underdetection of STI in this group. Therefore, replacing baseline CT with PSMA PET/CT appears to be a valuable screening method to ensure in-label use of Ra-223.

Clinical trial identification: NCT04995614.

Legal entity responsible for the study: The authors.

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Personal, Advisory Board: Bayer; Financial Interests, Personal, Other, Personal fees and travel expenses: Bayer. N. Mehra: Financial Interests, Personal and Institutional, Advisory Board, And personal fees and research funding: Bayer; Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal and Institutional, Advisory Board, And research grants and personal fees: Roche, Merck Sharp and Dohme; Financial Interests, Personal and Institutional, Advisory Board, And research grants, research funding and personal fees: Astellas, Janssen Pharmaceuticals; Financial Interests, Personal and Institutional, Other, Research grants and personal fees: AstraZeneca, Sanofi; Financial Interests, Institutional, Research Grant: Pfizer, Genzyme. W.R. Gerritsen: Financial Interests, Personal, Advisory Board: BMS, Sanofi Gemzyme, Amgen, Morphosys and CureVac; Financial Interests, Personal and Institutional, Advisory Board, Plus research funding: Astellas, Janssen Pharmaceuticals; Financial Interests, Personal and Institutional, Advisory Board, Plus research funding and speaker fees: Bayer; Financial Interests, Personal, Invited Speaker: MSD. M.J. van der Doelen: Financial Interests, Institutional, Research Grant: Bayer, Janssen Pharmaceuticals; Financial Interests, Personal, Other, Speaker fees: Astellas. I.M. van Oort: Financial Interests, Personal and Institutional, Advisory Board, Plus research funding: MSD/AstraZeneca; Financial Interests, Personal and Institutional, Research Grant, Plus research funding and personal fees: Astellas, Bayer; Financial Interests, Personal and Institutional, Research Grant, Plus personal fees: Janssen Pharmaceuticals; Financial Interests, Personal and Institutional, Research Funding: Pfizer; Financial Interests, Institutional, Research Funding: AAA Novartis. All other authors have declared no conflicts of interest.

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1824P Treatment patterns among novel hormonal therapy-experienced patients with metastatic castration-resistant prostate cancer

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Background: Patients with advanced prostate cancer are commonly treated with novel hormonal therapy (NHT). However, treatment patterns following NHT remained unclear. This study evaluated treatment patterns among metastatic castration-resistant prostate cancer (mCRPC) patients with prior NHT.

Methods: This study used the Flatiron Health electronic health records data between 1/1/2013-7/31/2022. NHT-experienced mCRPC patients with $\geq$ 1 line of therapy (LOT) in the mCRPC setting and without chemotherapy in the last 365 days were included. The first LOT in the post-NHT mCRPC setting was defined as index line. Treatment patterns in the post-NHT mCRPC setting were summarized.

Results: A total of 804 patients (median follow-up: 10.6 months) were included. Of these, 239 (30%) patients used enzalutamide as index LOT, 191 (24%) patients used abiraterone, 171 (21%) used docetaxel, and 203 (25%) used other treatment (Table). Patients receiving prior NHT in the non-metastatic castration-resistant or metastatic castration-sensitive settings were more likely to cycle to NHTs than those receiving prior NHT in the mCRPC setting. The median time on treatment for index LOT was 4.1 months. A total of 126 (16%) patients died within 90 days after index LOT while 494 (61%) patients received a 2nd post-NHT LOT. Subsequently, 104 (13%) patients died within 90 days after the 2nd post-NHT LOT while 265 (33%) patients received a 3rd post-NHT LOT. Most patients received chemotherapy while fewer patients received NHTs in the 2nd and 3rd post-NHT LOTs. Commonly observed treatment sequences included index enzalutamide followed by docetaxel (N=62, 8%), index docetaxel followed by other chemotherapy (N=54, 7%), and index abiraterone followed by docetaxel (N=48, 6%).

Table: 1824P Treatment patterns in the post-NHT mCRPC setting

	NHT-experienced patients with mCRPC (N = 804)
Index line (the 1st post-NHT LOT)	804 (100%)
Enzalutamide	239 (30%)
Abiraterone	191 (24%)
Docetaxel	171 (21%)
Other NHTs	29 (4%)
Radium-223	22 (3%)
Other chemotherapy	21 (3%)
Poly adenosine diphosphate ribose polymerase inhibitors (PARPi)	8 (1%)
Other	123 (15%)
The 2nd post-NHT LOT	494 (61%)
Docetaxel	145 (18%)
Other chemotherapy	90 (11%)
Enzalutamide	58 (7%)
Abiraterone	39 (5%)
Radium-223	29 (4%)
Other NHTs	21 (3%)
PARPi	15 (2%)
Other	97 (12%)
The 3rd post-NHT LOT	265 (33%)
Other chemotherapy	96 (12%)
Docetaxel	58 (7%)
Enzalutamide	17 (2%)
Radium-223	16 (2%)
PARPi	10 (1%)
Other NHTs	9 (1%)
Abiraterone	7 (1%)
Other	52 (6%)

Conclusions: The real-world treatment patterns in the post-NHT mCRPC setting are heterogeneous, but the majority of patients attempted additional NHT followed by chemotherapy.

Legal entity responsible for the study: The authors.

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1825P Molecular features of circulating tumour cells (CTCs) associate with response to 177Lu-PSMA-617 plus pembrolizumab for metastatic castration resistant prostate cancer (mCRPC)

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Background: The phase I PRINCE trial (NCT03658447) is evaluating efficacy of ^{177}Lu-PSMA-617 plus pembrolizumab for mCRPC. Genomic and clinical features at baseline of patients who respond best to this combination are not yet known.

Objective: Evaluate associations of PET imaging and CTC features at baseline with Department of prostate specific antigen (PSA) response.

Methods: A total of 37 patients were enrolled. PSA levels were assessed 3 weekly. CTCs (CK+, CD45-, and DAPI+) were enumerated from 3ml of blood, immunoassayed for Prostate Specific Membrane Antigen (PSMA) expression, and single CTCs profiled with low-pass whole-genome sequencing (Epic Sciences). Baseline PSMA-PET metabolic tumour volume (MTV) and PSMA expression (SUV) were measured. Patients were split into response groups based on the best percentage change in PSA from baseline: Good (drop in PSA >90%, n=17), Intermediate (drop in PSA <90%, n=16) and Poor (no decrease in PSA, n=4). Wilcoxon and Kruskal-Wallis tests were used for pairwise and multi-group comparisons, respectively.

Results: MTV (mls) was lower in the Good (median: 218) than in both Intermediate (median: 328) and Poor (median: 538) response groups, but pairwise comparison of Good versus Intermediate-Poor responders combined was not significant (Wilcoxon p=0.286). The strongest image-based association was mean PSMA-PET SUV, which increased from Poor (median: 7.8), to Intermediate (median: 8.5) and Good (median: 11) responders, achieving a Wilcoxon p-value of 0.079 for the Good versus the Intermediate-Poor groups. In contrast, stronger associations with PSA response were based on features of baseline CTCs. Baseline PSMA+ CTC counts were higher in Good (mean: 23.7) than Intermediate (mean: 4.3) and Poor (mean: 6) responders (p=0.022). Number of Large-scale State Transitions, a measure of genome instability was lowest for CTCs in Good (mean: 10.2), higher in Intermediate (mean: 15.1), and highest in Poor responders group (mean: 24.4), a highly significant trend (Kruskal-Wallis p=0.0004).

Conclusions: In the PRINCE cohort, CTCs data were more strongly associated with extent of drop in PSA than PET metrics.

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Legal entity responsible for the study: Peter MacCallum Cancer Centre.

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1826P Lutetium-177-PSMA in pre- and post-taxane mCRPC setting: Results from a phase II clinical trial

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Background: Lutetium-177(177Lu)-PSMA-617 prolonged progression-free survival (PFS) and overall survival (OS) versus standard of care in metastatic castration-resistant prostate cancer (mCRPC) patients, as shown in the phase III VISION trial; in this trial, patients already received taxane-based chemotherapy. Here we report the analysis from a phase II trial of 177Lu-PSMA617 administered in pre- and post-taxane mCRPC settings.

Methods: In the IRST-185.03 study, which is an open-label, single-center, phase 2 prospective trial, 145 mCRPC patients were enrolled between April 2017 and October 2022. 142 patients received up to 6 cycles of 177Lu-PSMA617 - radiolabelled by IRST Radiopharmacy - every 6 weeks, with a mean dose of 17.5 GBq (up to 33 GBq of total dose). Best biochemical response (BBR), defined as ≥50% PSA reduction from baseline, is the main clinical endpoint of the trial, whilst PFS, OS, and safety are the main secondary endpoints.

Results: Among 142 evaluable patients, 100 patients received at least one cycle of taxane-based chemotherapy for castration-sensitive and castration-resistant disease (post-taxane group), whilst 42 were taxane-naïve (pre-taxane group). Baseline clinical characteristics of the two groups were balanced in terms of age, Gleason score, and previous ARSI, except for a higher proportion of ECOG PS 1-2 patients in the post- versus pre-taxane group (42 and 16.7%, respectively). At the first interim analysis, after a median follow-up of 28.8 months, BBR was obtained in 23 (54.8%) and 35 (35%) patients in the pre- and post-taxane groups, respectively. Median PFS was 8.5 and 6.0 months while median OS was 35.1 and 12.6 months in the pre- and post-taxane groups, respectively. Concerning safety, anemia was the most common adverse event (G1: 71.4 and 69%, G2: 9.6 and 11%. G3: 0 and 5%, in the pre- and post-taxane groups, respectively). No G3 adverse events were recorded in the pre-taxane group.

Conclusions: 177Lu-PSMA617 could be a valid therapeutic choice in taxane-naïve mCRPC patients, especially in those who are deemed frail and unfit for chemotherapy.

Clinical trial identification: EudraCT/RSO 2016-002732-32, Start date: 2017-02-15.

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1827P Real-world (RW) overall survival (OS) with enzalutamide (ENZ) and abiraterone acetate (ABI) in patients (pts) with chemotherapy (cx)-naïve metastatic castration-resistant prostate cancer (mCRPC)

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Background: There are no head-to-head phase 3 clinical trials comparing OS between ENZ and ABI. A French National Database (SNDS) study reported improved RW OS with ENZ vs ABI.[1] We compared OS in US Medicare pts with cx-naïve mCRPC who initiated ENZ or ABI.

Methods: This retrospective analysis of Medicare fee-for-service claims data (2009—2020) included adult men with ≥1 claim for prostate cancer and a metastatic diagnosis who were cx-naïve and initiated ENZ or ABI (index date) between September 10, 2014, and May 31, 2017. OS overall and by subgroups defined by baseline characteristics was evaluated using Kaplan—Meier analysis with inverse probability treatment weighting (IPTW) to adjust for potential baseline confounders.

Results: Overall, 2911 pts who initiated ABI and 2595 pts who initiated ENZ were included. Baseline characteristics were generally comparable between cohorts. Median follow-up was 19.1 months for ABI and 20.3 months for ENZ. The IPTW-adjusted median OS (95% CI) was 20.6 months (19.7, 21.4) for ABI and 22.5 months (21.2, 23.8) for ENZ, with an IPTW-adjusted hazard ratio (HR) of 1.10 (95% CI 1.04, 1.16; P<0.001). Median OS was significantly shorter for ABI vs ENZ in subgroups of pts who were ≥75 years old, White, low or middle/high (not shown) socioeconomic status (SES), and with baseline comorbidities (cardiovascular disease [CVD], diabetes, and renal disease; table).

Table: 1827P IPTW-adjusted OS

	n	Median OS (IPTW-adjusted), months (95% CI)			P-value
		ABI	ENZA	HR	
Age, years					
≥75	3609	17.4 (16.5, 18.4)	19.5 (18.7, 20.5)	1.16	<0.001
<75	1897	28.0 (26.0, 30.1)	27.9 (26.2, 29.5)	1.00	0.928
Black	700	20.1 (17.0, 23.9)	21.9 (19.0, 24.2)	1.05	0.495
White	4285	20.0 (19.1, 21.0)	22.0 (20.6, 23.7)	1.11	0.002
Low SES	1240	17.6 (16.3, 20.1)	21.7 (19.4, 23.8)	1.14	0.040
With baseline					
CVD	4155	18.0 (17.2, 19.2)	20.6 (19.5, 22.0)	1.15	<0.001
Diabetes	1873	18.9 (17.2, 20.7)	21.8 (20.3, 23.8)	1.14	0.009
CVD or diabetes	4432	19.0 (17.9, 20.0)	21.6 (20.1, 23.0)	1.15	<0.001
CVD and diabetes	1556	16.6 (15.2, 18.0)	20.2 (18.3, 21.8)	1.15	0.008
Renal disease	1332	14.5 (13.1, 15.9)	16.8 (15.6, 17.8)	1.15	0.018

Conclusions: In the large, representative US Medicare dataset, pts with cx-naïve mCRPC treated with ABI had significantly shorter OS than those treated with ENZ. This study with >5500 pts validates previous RW studies reporting improved OS with ENZ vs ABI, including a prior French SNDS study with >10000 pts,[1] and shows that results are robust across different health systems. These findings may be particularly important in older pts and those with comorbidities. 1. Scailteux, et al. *Am J Epidemiol*. 2021;190:413—22.

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1828P ARX517: A next generation anti-PSMA antibody drug conjugate (ADC) demonstrates notable stability and pharmacokinetic (PK) profile in the ARX517 phase I clinical trial (APEX-01)

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Background: ARX517 is a next-generation, anti-PSMA, ADC conjugated to AS269 (pAF-269; a potent tubulin inhibitor), at a drug-to-antibody ratio (DAR) of two. ARX517 was designed to address the instability issues encountered by previous PSMA-targeted ADCs with three key components: a non-cleavable PEG linker, a non-cell permeable payload, and stable oxime conjugation chemistry. The site-specific conjugation of AS269 to the mAb is enabled using proprietary synthetic amino acid incorporation. This ADC design minimizes premature payload release and off-target toxicity.

Methods: 21 patients received ARX517 at doses ranging from 0.32 to 2.4 mg/kg across 7 cohorts. ARX517 was administered by intravenous infusion q3w. Patient serum samples were collected at fixed time points and evaluated in validated Total Antibody (TA; sum of deconjugated antibody and conjugated antibody), ADC (conjugated antibody with a DAR of 1 or 2), and payload pAF-AS269 assays. The lower limit of quantitation for the TA, ADC, and pAF-AS269 assays were 62.5 ng/mL, 7.8 ng/mL, and 0.02 ng/mL, respectively. PK parameters were determined using non-compartmental analysis based on serum concentrations of TA, ADC, and pAF-AS269.

Results: ARX517 exhibited virtually overlapping TA and ADC PK concentration-time curves at all dose levels tested, indicating strong stability of the ADC with minimal premature payload release. A long ADC terminal half-life of ~6—10 days was observed at doses $\geq$ 1.4 mg/kg, thereby maximizing drug exposure over a dosing cycle of 3 weeks. Low concentrations of pAF-AS269 (approximately 0.02—0.2 ng/mL) were observed at all dose levels and appeared slowly in the circulation, with Cmax observed approximately 7 days after administration. This is in contrast to other ADCs that typically exhibit payload Cmax hours to days after dosing.

Conclusions: ARX517 is the first anti-PSMA ADC tested in the clinic to demonstrate notable stability and a long terminal half-life. These attributes enable continuous drug delivery throughout the dosing cycle to potentially improve efficacy and minimize toxicity due to premature payload release, indicating a clear and favorable therapeutic index.

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1829P Exposure-safety analyses of talazoparib in combination of enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) in TALAPRO-2 trial

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Background: The TALAPRO-2 trial (NCT03395197) showed that the addition of talazoparib (tala), a potent PARP inhibitor, to enzalutamide (enza) significantly improved radiographic progression-free survival in patients with mCRPC. Approximately 75% and 56% of patients (pts) in TALAPRO-2 experienced dose interruption and dose reduction of tala, respectively, due to an adverse event (AE). We investigated the relationship between tala exposure as well as other factors and Grade 3 or higher Anemia, Thrombocytopenia, and Neutropenia, the most common AEs leading to dose interruptions or reductions.

Methods: Safety and PK data from 412 pts in the tala (starting dose of 0.5 mg QD) + enza (160 mg QD) arm were available. To account for the changes in tala exposure over time due to dose modifications and effect of enza and its n-desmethyl metabolite on tala exposure, time-varying average tala concentrations ($C_{avg,t}$) were used in the analysis. $C_{avg,t}$ was calculated as posthoc estimated AUC_t/t based on population PK model. The relationship between $C_{avg,t}$/potential predictive factors and the selected safety events was evaluated using Cox proportional hazard (PH) univariate and multivariate models with p value cutoff of 0.05.

Results: Visual examination suggested a higher $C_{avg,t}$ in pts with Anemia, Thrombocytopenia, and Neutropenia events versus pts without events. Cox PH models indicated that a higher $C_{avg,t}$ was associated with a higher risk of Grade 3 or higher Anemia, Thrombocytopenia, and Neutropenia. The HR (95% CI) for $C_{avg,t}$ was 1.433 (1.32, 1.555) for Anemia, 1.609 (1.35, 1.917) for Thrombocytopenia, and 6.942 (3.337, 14.44) for Neutropenia. Higher risk of all tested safety endpoints was associated with lower baseline hemoglobin. Higher risk of Anemia was associated with lower baseline body weight (BWT) and higher baseline lactate dehydrogenase. Higher risk of Neutropenia was associated with lower absolute neutrophil count and lower BWT.

Conclusions: A higher risk of Anemia, Thrombocytopenia, and Neutropenia was associated with higher tala exposure. These findings support the proposed dose modification algorithm as an effective approach for management of AEs.

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1830P CBP-1018, a bi-ligand-drug conjugate treated in patients with advanced solid tumors: A phase I, multi-center, open-label, dose-escalation and dose expansion study

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Background: Prostate-specific membrane antigen (PSMA) is highly expressed on prostate cancer and folate receptor α (FRα) overexpressed in various malignant tissues which both related to tumor invasiveness. CBP-1018 is a first-in-class bi-ligand-drug conjugate targeting both PSMA and FRα with monomethyl auristatin E (MMAE) as payload.

Methods: This phase 1 study included both a dose-escalation and expansion stage. In the dose-escalation stage, an accelerated titration was conducted in single patient at 0.03mg/kg followed by an i3+3 design for dose levels (DLs) $\geq$ 0.06 mg/kg, Q2W (IV.) in a 4-week cycle. This stage mainly enrolled patients (pts) with metastatic castration resistant prostate cancer (mCRPC) which had experienced standard treatment failure or intolerance before. The primary objectives were to evaluate the safety and tolerability, determine dose limiting toxicity (DLT) and maximum tolerated dose (MTD). Additionally, pharmacokinetics (PK) and preliminary efficacy will also be evaluated.

Results: As of 27 April 2023, 20 pts (18 mCRPC, 1 bladder cancer and 1 ureteral carcinoma) were enrolled at 6 dose levels (DLs). No DLTs or drug-related deaths were observed. For 15 pts (75%) experienced treatment-related adverse events (TRAEs) $\geq$ grade 3, most common were neutrophil decrease (50%), WBC decrease (40%), hypokalemia (10%) and hypertriglyceridaemia (10%). Among 17 evaluable mCRPC pts, 5 SD and 7 Non-PD were observed with 9 pts delayed administration and 6 pts dropped for COVID-19. Prostate-specific antigen (PSA) 50% decrease was detected in 2 pts. The median PFS was 9.2 months (95%CI, 1.7-9.2) in mCRPC pts. For PK profile of CBP-1018 and free MMAE, $t_{1/2z}$ was ranged 0.54-1.15 h and 38.27-57.27 h, respectively, no accumulation of both substances after multiple doses.

Conclusions: CBP-1018 was well-tolerated at DLs of 0.03-0.14 mg/kg Q2W. Multiple SD and PSA decrease were observed at DLs of 0.08-0.14 mg/kg, conferred a promising preliminary antitumor activity in pts with mCRPC despite of COVID-19's impacts. MTD was not reached and dose-escalation to establish the RP2D is continuing.

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1831P Dissecting the meaning of obesity in metastatic castration resistant prostate cancer: Size or metabolism?

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Background: Obesity is associated with longer survival in patients with metastatic castration resistant prostate cancer (mCRPC). Our group has also established that elevated circulating sphingolipids are associated with a poorer prognosis in patients with mCRPC. Additionally, we have validated a CLIA-compliant circulating lipid biomarker, PCPro, which identifies patients with the poor prognostic lipid profile. This study aimed to define the metabolic characteristics underlying the obesity phenotype in mCRPC.

Methods: Six Australian Centres enrolled 72 patients with mCRPC (45% taxanes, 55% abiraterone or enzalutamide). DEXA scans assessed the distribution of lean muscle, fat, water and bone in the body. The PCPro biomarker status at baseline was assessed by mass spectrometry. Cox proportional hazards modelling assessed the association between DEXA parameters, PCPro and overall survival (OS).

Results: According to standard Body Mass Index (BMI) criteria, 32% of patients were obese, 38% overweight and 30% healthy weight range. Increasing BMI was associated with longer OS (HR=0.92, 95% CI=0.85-0.99, p=0.027). Increasing total weight (p=0.019), fat weight (p=0.014) and fat mass index (p=0.021) were all associated with improved OS. Changes in lean weight, android/gynoid weight patterns and visceral fat distribution were unrelated to OS (p>0.1). PCPro positive patients (21%, 14/66) had a shorter OS (HR=3.17, 95% CI=1.50-6.70, p=0.001). PCPro expression was an independent prognostic variable when modelled against BMI, fat weight or fat mass index.

Conclusions: Obesity and a higher amount of body fat are associated with longer OS in mCRPC. However, a PCPro positive plasma lipid profile is associated with shorter OS after adjusting for these variables. This supports the concept that clinical outcomes are driven by metabolic aspects, rather than BMI or measures of body fat alone. Future therapeutic interventions should target lipid metabolic aberrations.

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1832P Centralized screening for homologous recombination repair (HRR) genes in metastatic castration-resistant prostate cancer (mCRPC): A feasibility study from a multicenter Spanish cohort

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Background: The presence of pathogenic variants (PV) in BRCA1-2 in mCRPC patients has been associated with improved response to PARP inhibitors (PARPi) and better survival outcomes. Thus, tumor testing for somatic alterations in HRR genes in mCRPC patients has been recently incorporated to the main clinical guidelines. However, its implementation in daily practice could represent a challenge due to lack of access to testing. Moreover, there is scarce data about PV prevalence and distribution in Spain.

This study aims to characterize the feasibility of centralized genetic testing for HRR mutations in mCRPC samples and to describe the PV prevalence and distribution from a large multicenter Spanish cohort.

Methods: From January-22 to April-23, formalin-fixed paraffin-embedded (FFPE) samples from patients with mCRPC pre-treated with ≥1 novel hormonal agent and who were eligible for a successive line of treatment (ECOG 0-1 and hemoglobin >10 mg/dl) were collected. Samples older than 5 years were excluded in order to guarantee the quality of the genetic material. The molecular analysis and the interpretation of the results were centralized at Hospital Marqués de Valdecilla, where an HRR panel which included BRCA1, BRCA2, CHEK2, ATM, and CDK12 genes was used. Bioinformatics analysis was performed on DataGenomics platform.

Results: 633 samples from 70 centers from 14 Spanish regions were analyzed. 49 (8%) samples were rejected, 67% due to poor DNA quality and 33% due to insufficient material. In total, 74 variants of uncertain significance and 111 PV were detected. The global prevalence of HRR PV was 19%. The PV detected in order of frequency were: BRCA2 (39%), ATM (28%), CDK12 (17%), BRCA1 (10%), and CHEK2 (6%).

Conclusions: Centralization of HRR genetic screening in reference centers is a feasible option to provide HRR mutation to practice physicians. Aspects such as FFPE conservation and processing are vital for the success of the technique and one of the points that could potentially be improved. A better understanding of the distribution of PV can help to detect those patients that could benefit from PARPi treatment, as well as guide the indication of family genetic studies.

Legal entity responsible for the study: AstraZeneca Spain.

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1833P Concurrent high-dose IV Vitamin C (IVC) and docetaxel for metastatic castrate-resistant prostate cancer (mCRPC): A randomized, placebo-controlled, double-blind phase II trial

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Background: Integrative medicine practitioners offer high-dose IVC for cancer treatment, but its incorporation into clinical practice has sparked controversy and remains an active area of investigation. While preclinical studies have shown that IVC may have anti-cancer effects in prostate cancer models, evidence from clinical research is limited. While several clinical trials showed that IVC is well tolerated, can reduce toxicities, and may improve quality of life (QoL), uncertainties remain. Here we investigated if combining IVC with docetaxel could improve the prostate-specific antigen (PSA) response rate in patients with mCRPC and could mitigate docetaxel toxicities.

Methods: We randomized (2:1) patients with mCRPC who progressed despite androgen receptor-targeted therapy to receive docetaxel (75mg/m^2 IV every 3 weeks) with IVC (1g/kg) (n=32) or placebo twice/week (n=15). Primary endpoints were PSA50 response by 24 weeks and adverse events (AEs) of fatigue, nausea, bone pain, and anorexia. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and QoL measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P).

Results: PSA response rate was 41% in the vitamin C and 33% in the placebo group, with no statistically significant difference (p=0.44). Grade 1-2 and grade 3-4 AEs occurred in 69% and 6% vs 60% and 0% of patients, respectively (one-sided Cochran Armitage test, p=0.90). FACT-P was not significantly different at any timepoints. Median rPFS was 10.1 months (95% CI, 5.85, 14.7) vs 10.0 months (95% CI: 5.32, NA), HR 1.35 (95% CI, 0.66-2.75, p=0.40). Median OS was 15.2 months (95% CI, 13.2-25.3) vs 29.5 months (95% CI, 18.1-NA; HR 1.98 [95% CI 0.85-4.58], p=0.11). The median PFS (modified PCWG2 definition) was 5.5 months vs 8.4 months (HR 1.19 [95% CI 0.60-2.38], p=0.62).

Conclusions: Concurrent high-dose IV vitamin C did not improve PSA response, toxicity, or clinical outcomes in mCRPC patients receiving docetaxel.

Clinical trial identification: NCT02516670.

Legal entity responsible for the study: C. J. Paller.

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1834P Exposure-efficacy analyses of talazoparib in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) in the TALAPRO-2 trial

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Background: The TALAPRO-2 trial (NCT03395197) showed that the addition of talazoparib (TALA), a potent PARP inhibitor, to enzalutamide (ENZA) significantly improved radiographic progression-free survival (rPFS) in mCRPC unselected for DNA damage repair deficiencies. The objective of the analysis was to evaluate the relationship between TALA exposure and rPFS to support the recommended TALA dosing regimen in combination with ENZA and identify potential prognostic factors for rPFS

Methods: Efficacy and pharmacokinetics (PK) data from 391 patients in Part 2 Cohort 1 (All-comers group) who received TALA starting dose of 0.5 mg QD plus 160 mg QD ENZA were included in the analyses. To account for the changes in TALA exposure over time due to dose modifications and effect of ENZA and its n-desmethyl metabolite on TALA exposure over time, time-varying average TALA concentrations ($C_{avg,t}$) were used in the analysis. $C_{avg,t}$ was calculated as post-hoc estimate AUC_t/t based on population PK model. The relationship between $C_{avg,t}$ as well as potential prognostic factors and rPFS was evaluated using Cox proportional hazard univariate and multivariate models with p value cutoff of 0.05.

Results: Visual examination suggested higher $C_{avg,t}$ in patients with longer rPFS than in those with shorter rPFS. Multivariate analysis showed that higher exposure was associated with longer rPFS. Lower baseline lactate dehydrogenase, lower baseline alkaline phosphatase, absence of measurable disease and bone only metastatic disease were associated with longer rPFS, while lower baseline lymphocyte was associated with shorter rPFS.

Conclusions: Longer rPFS was found to be associated with higher $C_{avg,t}$, This supports using 0.5 mg QD (in combination with ENZA) which provides similar exposure as 1 mg QD, the maximum tolerable dose of TALA monotherapy, for the treatment of mCRPC. These data also support treating grade 1-2 AEs with symptomatic management without TALA dose reduction to maximize efficacy.

Clinical trial identification: NCT03395197.

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1835P A prospective study to determine the prevalence of DNA repair defects in patients (pts) with advanced prostate cancer (PC)

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Background: Up to 30% of pts with advanced PC have homologous recombination repair (HRR) gene alterations. Pts with HRR gene alterations (HRR+), particularly those with BRCA gene alterations, have poor outcomes with standard of care therapies and may benefit from PARP inhibitor treatment. PREVALENCE (NCT03871816) prospectively evaluated the frequency of HRR+ in metastatic castration sensitive and castration resistant prostate cancer (mCSPC/mCRPC) pts.

Methods: In this multicenter, international study across 319 sites in 25 countries, mCSPC and mCRPC pts aged ≥18 consented to specimen collection (eg, saliva, blood, archival tumor) for germline, tumor tissue, and/or ctDNA testing. HRR genes of interest included ATM, BRCA1, BRCA2, CHEK2, CDK12, BRIP1, FANCA, HDAC2, PALB2, RAD51B, and RAD54L. PREVALENCE test results were also used to assess biomarker eligibility for niraparib interventional studies: MAGNITUDE (NCT03748641) and AMPLITUDE (NCT04497844).

Results: 14598 pts enrolled between April 2019 and October 2022. Of 14073 pts who had at least one result by any assay, 1972 (14.0%) pts had at least 1 mutation in the HRR genes of interest; BRCA gene alterations were the most common, occurring in 756 pts (5.4%). 7%, 22%, and 11.5% of pts who had a test result by germline, tumor tissue and ctDNA, respectively, had at least 1 HRR gene alteration. The frequency of HRR+ was similar in mCSPC and mCRPC. Of the pts who did not have at least one result by any assay, 143 pts (1%) had no specimens submitted and 382 pts (2.6%) failed testing by all assays. Test failure rate was highest in tumor tissue (24.1%), followed by germline (3.2%) and ctDNA (2.4%).

Conclusions: In a study of over 14000 pts with advanced PC, 14% had at least 1 HRR gene alteration; BRCA gene alteration was most common. The frequency of HRR+ was highest in pts tested by tumor tissue. PREVALENCE demonstrates the feasibility of prospective genetic testing to identify PC pts who benefit most from a precision oncology approach.

Table: 1835P

	All n=14073[#]	mCSPC n=7949	mCRPC n=5595
HRR+, n (%) BRCA[*] ATM CHEK2 Other[+]	1972 (14.0%) 756 (5.4%) 409 (2.9%) 309 (2.2%) 498 (3.5%)	1094 (13.8%) 429 (5.4%) 220 (2.8%) 157 (2.0%) 288 (3.6%)	817 (14.6%) 307 (5.6%) 175 (3.1%) 138 (2.5%) 197 (3.5%)
By Assay Germline, n HRR+, n (%) BRCA+, n (%) Tumor, n HRR+, n (%) BRCA+, n (%) ctDNA, n HRR+, n (%) BRCA+, n (%)	11365 793 (7.0%) 337 (3.0%) 5020 1103 (22.0%) 416 (8.3%) 4247 488 (11.5%) 200 (4.7%)	6538 447 (6.8%) 190 (2.9%) 3417 723 (21.2%) 278 (8.1%) 1737 150 (8.6%) 64 (3.7%)	4372 311 (7.1%) 136 (3.1%) 1467 352 (24.0%) 128 (8.7%) 2359 322 (13.6%) 128 (5.4%)

[#]Unknown mCSPC/mCRPC: n=529 [*]Includes BRCA1/2 and BRCA co-occurring with other HRR genes [+]Includes non-BRCA co-occurring

Clinical trial identification: NCT03871816.

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The contracts for my role as an advisor are set up with the institution and the funds go to a research fund at Peter MacCallum Cancer Centre: Novartis; Financial Interests, Institutional, Advisory Board, I have served on an advisory board for Merck Serono. 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1836P Blood based biomarkers identify metastatic castration-resistant prostate cancer (mCRPC) with the greatest benefit from continuing enzalutamide (ENZ) beyond progression in combination with docetaxel (Doc): A pre-specified biomarker study of the phase IIIb PRESIDE trial

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Background: PRESIDE (NCT02288247) was a randomised, international trial that met its primary endpoint of prolonged progression-free survival (PFS) with continued ENZ beyond progression in patients (pt) starting Doc. A pre-specified aim of PRESIDE was to test for androgen receptor (AR) blood-based biomarkers to test for differential benefit.

Methods: Pt who participated in PRESIDE, consented to the biomarker sub-study and donated blood at randomization (Period 2 baseline, P2BL) were included. Blood was also collected on treatment (P2 Week [W] 4 and 13), progression and follow up. Pre-specified primary objectives were to evaluate PFS for 1) ENZ versus (v) Placebo (P) in pt split by +/- plasma *AR* gain or AR-V7 in circulating tumor cells (CTC) at P2BL and 2) PFS for all pt split by +/- tumor in plasma DNA (ptDNA) at P2W4. Custom targeted next-generation sequencing on plasma DNA was performed using a bespoke panel (PCF SELECT). Identification of CTC +/- AR-V7 in whole blood samples was performed by Epic Sciences (San Diego, California).

Results: Of 271 pt randomised to ENZ / P, 157 (57.9%, 79 on ENZ + Doc, 78 on P + Doc) donated blood. 100 (64%) were plasma *AR* wild type (wt), 56 (36%) had *AR* gain. 126 (80%) were AR-V7 negative (-), 17 (11%) AR-V7 positive (+). AR status not available for plasma DNA (1 pt) and CTC (14 pt, 9%). Pt who were AR wt and AR-V7- (N=87, 55%) had significantly prolonged PFS from continuing ENZ (11.2 months (m) v 8.7 m P, HR: 0.49; 95% CI: 0.29-0.82, p=0.006), whilst pt with *AR* gain or AR-V7+ (N=62) did not (6.2 m ENZ v 7.9 m P; HR: 1.29; p=0.44). Restricted mean survival times at 18 m for *AR* wt and AR-V7- was 11.5 m ENZ v 8.9 m P, p=0.0046, for *AR* gain or AR-V7 + was 7.9 m ENZ vs 7.1 m P, p=0.5023. Compared with negative ptDNA at P2W4 (99, 74% of 134 pt included), pt with positive ptDNA (35, 26%) had significantly shorter PFS (5.4 m vs 10.8 m, HR: 1.92; 95% CI: 1.14-3.23, p=0.0145).

Conclusions: The benefit of continuing ENZ beyond progression with Doc vs Doc alone is greatest in patient with no evidence of plasma *AR* gain or AR-V7+ CTC. Plasma tumor DNA detection after 3 weeks Doc +/- ENZ identifies patients with shorter PFS.

Clinical trial identification: NCT02288247.

Legal entity responsible for the study: Prof. Gerhardt Attard (Principal Investigator), Head of Treatment Resistance Group, University College London.

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1837P Assessing PSA

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Background: Prior data have shown that prostate specific antigen (PSA) $\leq$ 0.2 ng/dL with androgen deprivation therapy (ADT) is prognostic for OS. We explored whether PSA $\leq$ 0.2 ng/dL at 4-7 months post randomization is a valid surrogate for OS in men with mHSPC. If so, it could be used to expedite phase 3 clinical trials. This hypothesis was investigated by the STOPCAP M1 Collaboration.

Methods: Individual patient data (IPD) from 13 eligible randomized trials comparing treatment regimens (ADT or docetaxel in the control or research arms in mHSPC) were utilized. We considered PSA measurements collected post randomization and evaluated the surrogacy of PSA $\leq$ 0.2 ng/dL at 4-7 months at the patient and trial levels. We utilized the proportional hazards model and estimated the hazard ratios (HR) for PSA $\leq$ 0.2 ng/dL predicting OS. We also fitted weighted linear regression, stratified by trial and treatment arm, and computed R^2 to quantify the proportion of variance that was explained by the regressions. We defined *a priori* clinically relevant surrogacy of R^2 value greater than 0.75. Lastly, we computed the surrogate threshold effect (STE), which is the minimum PSA treatment effect necessary to estimate a non-zero effect on OS.

Results: IPD from 5513 pts randomized from 1994-2012 from 13 trials were pooled for a stratified analysis. There were 3324 deaths, of which 70.5% were due to prostate cancer. The median follow-up was 74 months. At 4-7 months, the proportion of patients who had PSA $\leq$0.2 was 25.8%. At the individual level, PSA $\leq$0.2 ng/dL was a strong predictor of OS. Median OS in patients who experienced PSA$\leq$0.2 and the results for the surrogacy analysis are presented in the table.

Table: 1837P

	PSA<=0.2 ng/dL (n=1425)	PSA>0.2 ng/dL (n=4088)
Median OS months (95%CI)	91.6 (85.1-98.2)	40.9 (39.3-42.7)
Hazard Ratio (95% CI)	2.5 (2.3-2.7)	
Condition 2	0.93 (0.78-0.99)	
STE	0.75	

Conclusions: PSA$\leq$0.2 ng/dL at 4-7 months met the surrogacy criteria and appears to be a valid surrogate endpoint for OS in men with mHSPC treated with ADT as backbone hormonal therapy. Validation of this endpoint in trials with drugs having other mechanisms of action is planned.

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1838P Prognostic value of neutrophil-to-lymphocyte ratio and lymphopenia in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with [177Lu]Lu-PSMA-617: VISION post hoc analysis

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Background: The prognostic value of neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) in patients with mCRPC treated with prostate-specific membrane antigen (PSMA)-targeted radioligand therapy has not been studied. Here, we assessed the association of NLR and ALC with [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) treatment outcomes in patients from the VISION study.

Methods: Adults with PSMA-positive mCRPC received ^{177}Lu-PSMA-617 (7.4 GBq every 6 weeks, $\leq$ 6 cycles) + standard of care (SoC), or SoC alone. In this *post hoc* analysis, patients were categorized by NLR $<$ 3 vs $\geq$ 3 and ALC $<$ 1.0 $\times$ 10^3/μl vs $\geq$ 1.0 $\times$ 10^3/μl at baseline. Associations with overall survival (OS) and radiographic progression-free survival (rPFS) were assessed using the Kaplan−Meier method. Hazard ratios (HR) were estimated using Cox proportional hazards models.

Results: NLR and ALC data were available for a subset of patients (Table). Baseline characteristics were well balanced across subgroups. At baseline, median NLR was 3.8 vs 4.0 and median ALC was 1.06 $\times$ 10^3/μl and 1.0 $\times$ 10^3/μl, for ^{177}Lu-PSMA-617 + SoC vs SoC alone, respectively. Shorter OS and rPFS were observed with higher NLR and lower ALC in each treatment arm (Table). ^{177}Lu-PSMA-617 + SoC prolonged OS and rPFS vs SoC alone in all subgroups (Table). More patients with baseline NLR $\geq$ 3 reported serious adverse events (^{177}Lu-PSMA-617 + SoC, 41.0%; SoC, 28.7%) than those with NLR $<$ 3 (30.7%; 24.1%).

Conclusions: NLR $\geq$ 3 and ALC $<$ 1.0 $\times$ 10^3/μl at baseline are prognostic for poor efficacy outcomes in patients with mCRPC in VISION. Treatment with ^{177}Lu-PSMA-617 improved OS and rPFS vs SoC alone regardless of baseline NLR/ALC. Additional analyses including change in NLR and ALC during treatment, associations with prostate-specific antigen and biochemical and objective response rates will be presented.

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Table: 1838P OS and rPFS by baseline NLR and ALC

		NLR < 3		NLR ≥ 3		ALC < 1.0 K/μL		ALC ≥ 1.0 K/μL	
		^{177}Lu-PSMA-617 + SoC	SoC	^{177}Lu-PSMA-617 + SoC	SoC	^{177}Lu-PSMA-617 + SoC	SoC	^{177}Lu-PSMA-617 + SoC	SoC
OS	Available data, n (%),	189 (34.3)	58 (20.7)	324 (58.8)	143 (51.1)	224 (40.7)	92 (32.9)	289 (52.5)	109 (38.9)
	Median, months	19.2	14.8	14.2	10.6	13.5	10.4	17.8	13.3
	HR (95% CI)	0.73 (0.49, 1.08)		0.68 (0.54, 0.85)		0.69 (0.52, 0.92)		0.65 (0.49, 0.86)	
rPFS	**Available data, n (%)**	136 (35.3)	50 (25.5)	232 (60.3)	114 (58.2)	160 (41.6)	77 (39.3)	208 (54.0)	87 (44.4)
	Median, months	10.8	6.0	8.7	2.7	8.0	3.5	10.8	3.6
	HR (95% CI)	**0.66** (0.39, 1.09)		**0.38** (0.28, 0.51)		**0.46** (0.32, 0.66)		**0.43** (0.30, 0.61)	

CI, confidence interval

Pharmaceuticals, Menarini Silicon Biosystems, ImCheck Therapeutics, Crescendo; Financial Interests, Institutional, Advisory Board: Harpoon; Financial Interests, Institutional, Research Grant: Astellas, AstraZeneca, Bayer, Cellcentric, Daiichi Sankyo, Genentech Roche, Genmab, GSK, Harpoon, Janssen, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Sanofi Aventis, Sierra Oncology, Taiho, Vertex Pharmaceuticals, Crescendo Biologics, Menarini Silicon Biosystems; Non-Financial Interests, Principal Investigator: Amgen, Astellas, AstraZeneca, Bayer, Bioxcel Therapeutics, Boehringer Ingelheim, Cellcentric, Daiichi Sankyo, Eisai, Genentech Roche, Genmab, GSK, Harpoon, Janssen, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, Vertex Pharmaceuticals, Crescendo, ImCheck Therapeutics; Non-Financial Interests, Institutional, Product Samples: Daiichi Sankyo, Bayer, Merck Serono, AstraZeneca, Harpoon, Pfizer, Sierra Oncology, Genentech/Roche, Sanofi Aventis, GSK. 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1839P Circulating tumor DNA (ctDNA) low pass whole genome sequencing (lpWGS) studies identify genomic alterations associating with taxane outcomes in prospective phase III taxane trials for metastatic castration resistant prostate cancer (mCRPC) sufferers

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Background: Taxanes are a standard of care for mCRPC and no clinically qualified biomarker has as yet been identified for these. lpWGS of ctDNA identifies copy-number alterations (CNAs) common in advanced PC and may identify mCRPC subtypes most responsive to taxane therapy. ctDNA lpWGS identified genomic aberrations associating with treatment outcomes for participants of three prospective Phase III taxane trials (CARD, FIRSTANA and PROSELICA).

Methods: Genomic alterations in ctDNA were assessed for correlations with overall survival (OS), radiologic progression-free survival (rPFS), and PSA or radiological response rate (RR) using univariable and multivariable mixed-effect regression models to study CNAs significantly associated with differential outcomes of prognostic and predictive significance.

Results: Genome-wide analysis identified several genomic alterations that were significantly associated with worse OS in these taxane-treated individuals including chromosome 2p, 9p and 13 deletions. Several CNAs remained independently significant (Chr2p HR 2.89, $p<0.01$; Chr9p HR 2.9, $p<0.01$, Chr12q HR 2.06, $p<0.01$) following multivariable analyses incorporating PSA, LDH, haemoglobin, the presence of visceral metastases and tumour fraction estimate. Conversely, several loci including 20q and X gain, and 15q loss associated with worse rPFS and OS on the CARD control arm (abiraterone post enzalutamide or vice versa) but exhibited no difference in rPFS and OS on the cabazitaxel-treated arm. To confirm these results, we explored the association of CNAs with response rate in the FIRSTANA and PROSELICA study cohorts and found that several loci were associated with higher taxane-response rates in biomarker-positive individuals.

Conclusions: These ctDNA lpWGS studies in mCRPC patients have identified genomic alterations in ctDNA of prognostic and predictive significance in men suffering from mCRPC receiving taxane treatment. Prospective validation will facilitate treatment selection and identify potential clinical biomarkers associated with outcome.

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1840P RNASEH2B loss and PARP inhibition (parpi) in metastatic castration resistant prostate cancer (mCRPC)

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Background: mCRPC is molecularly heterogenous and PARPi is the only precision medicine for these diseases. PARPi improves outcomes in DNA repair defective (DRD; 20-30%) mCRPC but may also impact other mCRPC molecular subsets not currently encompassed in the FDA approved companion biomarker suite for PARPi. The *RNASEH2B* gene is located on chromosome 13, flanking *RB1*, with this locus being commonly lost in mCRPC at treatment resistance, associating with lineage plasticity and genomic instability. *RNASEH2B* may be co-deleted with *RB1*, with loss of the former but not the latter sensitising to PARPi. We have hypothesised that *RNASEH2B* loss in mCRPC is subclonal and that PARPi can clear these *RNASEH2B* deleted subclones.

Methods: Immunohistochemistry (IHC) for RNASEH2B and RB1, utilising validated assays, was performed on matched (same patient) hormone-sensitive (HSPC) and mCRPC patient biopsies, together with whole-exome sequencing (WES), targeted next-generation sequencing (NGS), and RNA sequencing. Low-pass whole genome sequencing (LP-WGS) was performed on a distinct mCRPC cohort for copy number analysis. RNASEH2B expression was correlated with clinical outcome, DRD and DNA damage signatures.

Results: Subclonal deletions on chromosome 13 encompassing *RB1* and *RNASEH2B* are frequent in HSPC and mCRPC biopsies, although deep deletions are rare, and co-loss of RB1 and RNASEH2B protein is surprisingly uncommon. Heterogeneous and subclonal RNASEH2B protein loss was detected by IHC in mCRPC biopsies, with 54/124 (44%) samples having RNASEH2B loss in 50% cells, although complete RNASEH2B loss is uncommon (8.8%). Interestingly, RNASEH2B loss is not an independent prognostic variable, perhaps related to increasing PARPi and platinum use (50/125 (40%) patients in this study), but did not associate with established DRD or DDR signatures. Studies of the impact of PARPi on RNASEH2B subclone clearance in human mCRPC are ongoing.

Conclusions: RNASEH2B protein is frequently lost in mCRPC subclones, with RB1 loss being less common, and may be of critical importance as this discordant loss is most likely to sensitise to PARPi. This needs further exploration in clinical trials of PARPi.

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1841TiP Darolutamide plus androgen-deprivation therapy (ADT) in patients with high-risk biochemical recurrence (BCR) of prostate cancer: A phase III, randomized, double-blind, placebo-controlled study (ARASTEP)

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Background: Patients (pts) with prostate cancer treated with radiotherapy (RT) or radical prostatectomy (RP) as primary therapy may develop BCR, defined as a prostate-specific antigen (PSA) increase without evidence of metastases on conventional imaging. Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT), a more effective and precise imaging method, may detect small lesions in patients with BCR. Patients with BCR at high risk of metastatic progression and who have lesions identified by PSMA PET/CT need effective treatment to delay this progression. Darolutamide (DARO) is a structurally distinct and highly potent androgen receptor inhibitor, which significantly improved metastasis-free survival (MFS) and overall survival (OS) in pts with nonmetastatic castration-resistant prostate cancer (CRPC). The ARASTEP study (NCT05794906) is designed to evaluate whether DARO plus ADT improves radiological progression-free survival (rPFS) by PSMA PET/CT vs placebo (PBO) plus ADT in pts with BCR following primary therapy and PSMA PET/CT-positive lesions.

Trial design: Eligible pts have prostate cancer treated by primary RT or RP followed by adjuvant RT (ART) or salvage RT (SRT), or RP alone if ART/SRT was not appropriate, with BCR (defined as PSA doubling time [PSADT] <12 months and PSA ≥0.2 ng/mL after primary RP [± ART/SRT] or PSA ≥2 ng/mL above nadir after primary RT only), ≥1 PSMA PET/CT-positive lesion without visible lesions on conventional imaging, and serum testosterone >150 ng/dL. Approximately 750 pts from 184 sites worldwide will be randomized to oral DARO 600 mg twice daily or PBO, both with ADT, for 24 months. Image-guided radiotherapy or surgery is allowed within 12 weeks from randomization. Randomization is stratified by PSADT <6 vs ≥6–<12 months, prior RP vs primary RT, and distant ± locoregional vs locoregional-only metastases. The primary endpoint is rPFS by PSMA PET/CT, assessed by blinded independent central review (BICR). Secondary endpoints include MFS by BICR, time to CRPC, OS, quality of life, and safety. Enrollment began in April 2023.

Clinical trial identification: NCT05794906.

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1842TiP Phase II randomized trial of two dose levels of vobramitamab duocarmazine in participants with metastatic castration resistant prostate cancer (mCRPC; TAMARACK)

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Background:: B7-homolog 3 (B7-H3) is highly expressed in multiple solid tumors including mCRPC (Guo, PMID 36114082) with limited expression in normal tissue, may play an immune suppressive role, and favors cancer growth. Vobramitamab duocarmazine (vobra duo, or MGC018) is an investigational anti–B7-H3 IgG1 antibody-drug conjugate with a duocarmycin-based DNA-alkylating payload that can damage DNA in both dividing and nondividing cells, causing cell death (Scribner, PMID 32967924). Phase 1 testing of vobra duo (NCT03729596) demonstrated acceptable safety at doses up to 4.0 mg/kg IV every 3 weeks (Q3W) in patients with solid tumors (Jang, ASCO 2021, Abstract 2631). In an mCRPC cohort, 4/16 (25%) evaluable patients had an objective response and 21/39 (53.8%) had reduction in PSA from baseline of > 50% (PSA50) (Shenderov, ESMO 2021, Abstract 620P). In this cohort, which received vobra duo at 3.0 mg/kg Q3W, adverse events resulted in discontinuation, dose reduction, or interruption of drug in 10%, 30%, and 55% of participants respectively, and the median number of doses received was 3.5 (range 1.0-8.0) (Shenderov, ESMO 2021, Abstract 620P). Lowering the starting dose may improve tolerability, extend treatment duration, and enhance effectiveness.

Trial design: TAMARACK is a randomized, open-label, Phase 2 dose selection (Simon, PMID 4075313) study assessing the efficacy, safety, and tolerability of two dose levels of vobra duo (2.0 mg/kg and 2.7 mg/kg IV Q4W). The study will enroll participants with mCRPC previously treated with one prior ARAT (abiraterone, enzalutamide, or apalutamide) for prostate cancer. Approximately 100 participants will be randomized 1:1 between the two study treatment arms. The primary endpoint of the study is radiographic progression-free survival by investigator assessment using Prostate Cancer Working Group 3 criteria. Secondary endpoints include frequency and severity of adverse events, PSA50 response rate, objective response rate, and occurrence of symptomatic skeletal events. One futility analysis based on PSA50 response rate will be performed for each arm after 20 evaluable patients are enrolled. Enrollment is ongoing.

Clinical trial identification: NCT05551117.

Legal entity responsible for the study: MacroGenics, Inc.

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Fizazi: Financial Interests, Institutional, Advisory Board: Astellas, Bayer, Janssen, AAA, MSD, AstraZeneca, Novartis/AAA, Pfizer, Daiichi Sankyo; Financial Interests, Institutional, Invited Speaker: Astellas, Bayer, Janssen, Sanofi, MSD, AstraZeneca, Novartis, Pfizer; Financial Interests, Personal, Advisory Board: Curevac, Orion; Financial Interests, Personal, Advisory Board, February 2022: Arvinas; Financial Interests, Personal, Advisory Board, April 2022: Macrogenics; Financial Interests, Institutional, Research Grant, Trial chair: Pfizer, Bayer, AstraZeneca, Orion, MSD, BMS, Janssen; Non-Financial Interests, Principal Investigator, Chair of the 7DX phase 3 trial: BMS; Non-Financial Interests, Principal Investigator, Chair of the Docetaxel-pembrolizumab phase 3 trial: Merck; Non-Financial Interests, Principal Investigator, Chair of the Darolutamide BCR phase 3 trial: Bayer; Non-Financial Interests, Principal Investigator, Chair of the PSMAfore phase 3 trial: AAA/Novartis; Non-Financial Interests, Principal Investigator, Chair of the CYPIDES ODM-208 Phase I-II trial: Orion; Non-Financial Interests, Principal Investigator, Chair of the STESIDES ODM-209 Phase I-II trial: Orion; Non-Financial Interests, Principal Investigator, Chair of the CAPITELLO 281 phase 3 trial: AstraZeneca; Non-Financial Interests, Principal Investigator, Chair of the TALAPRO-2 and TALAPRO-3 phase 3 trials: Pfizer; Non-Financial Interests, Principal Investigator, Chair of the RADIANT phase 3 trial: Bayer; Non-Financial Interests, Principal Investigator, Chair of the TRITON-3 phase 3 trial: Clovis. J. Sun, A. Ward: Financial Interests, Personal, Full or part-time Employment: MacroGenics; Financial Interests, Personal, Stocks/Shares: MacroGenics. E.S. Antonarakis: Financial Interests, Personal, Speaker, Consultant, Advisor: Janssen, Astellas, Sanofi, Dendreon, Pfizer, Amgen, Eli Lilly, Bayer, AstraZeneca, BMS, ESSA, Clovis, Merck, Curium, Blue Earth Diagnostics, Foundation Medicine, Exact Sciences, Invitae; Financial Interests, Institutional, Research Funding: Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Tokai, BMS, MacroGenics, Constellation, Bayer, AstraZeneca, Clovis, Merck.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

PSYCHO-ONCOLOGY

1843MO The effect of chronic psychological stress on the efficacy of first-line therapy of ICIs in advanced NSCLC (STRESS-LUNG-1 trial)

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Background: Immune checkpoint inhibitors (ICIs) achieved breakthroughs in advanced non-small cell lung cancer (NSCLC). Chronic psychosocial stress manifests as depression and anxiety symptoms and is common among NSCLC patients. It activates the HPA axis and sympathetic nervous system, which impairs organic immunity and induces an immunosuppressive tumor microenvironment. We aim to investigate the role of chronic psychosocial stress on the efficacy of ICIs.

Methods: The STRESS-LUNG-1 study is a multicenter prospective observational trial (NCT05477979). Stage IIIB-IV NSCLC treated with first-line therapy of ICIs were enrolled. The patients' stress status was assessed using PHQ-9 and GAD-7 scales. The last follow-up date was March 1, 2023. Prediction models integrating psycho-biological factors to predict efficacy was established.

Results: A total of 166 NSCLC patients were enrolled with 53.6% of patients classified as stressed. The baseline characteristics between stressed and non-stressed groups were well-balanced. With the median follow-up of 11.5 months, the stressed group had a lower ORR (38.8% vs 68.4%, $p<0.001$) and a worse median PFS (7.9 vs 15.5 months; $p=0.028$). The stress group had a lower 1-year (69.0% vs 91.9%; p=0.001) and 2-year survival rate (50.6% vs 71.8%; $p=0.092$). Patients in the stress group demonstrated multidimensional detriments of quality of life (QoL). Chronic psychological stress was the independent prognostic factor for ORR (HR=3.93; $p<0.001$), PFS (HR=1.59; $p=0.038$), and OS (HR=3.16; $p=0.005$). A negative correlation was observed between the degree of stress and the efficacy. The stressed group had higher plasma epinephrine (160.97 vs 122.94 pg/ml, $p=0.029$) and serum cortisol levels (445.05 vs 382.10 nmol/L, $p=0.037$). Notably, an integrated model including stress status, stage, and PD-L1 expression demonstrated superior efficiency in predicting PFS (AUC=0.810) and OS (AUC=0.865) than using psychological and biological factors alone.

Conclusions: Chronic psychological stress was associated with poor efficacy of ICIs and QoL in advanced NSCLC. Combining psychological with biological factors may represent a useful psycho-biomarker able to predict the clinical response to ICIs.

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Legal entity responsible for the study: The authors.

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1844MO Association of peripheral blood leukocyte DNA methylation profiles with the development of depressive symptoms in lung cancer patients undergoing systemic therapy

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Background: Depression is a serious comorbidity in cancer patients and is associated with increased morbidity and mortality. We investigated blood DNA methylation profiling as a potential biomarker for monitoring the likelihood of developing depressive symptoms during systemic anticancer treatment in order to early detect vulnerable patient populations.

Methods: Lung cancer patients receiving systemic anticancer therapy at the Medical University of Vienna were included in this analysis. Leukocyte DNA methylation profiling from whole blood samples at timepoint of inclusion was performed with Infinium Methylation EPIC microarrays. Patients completed the EORTC QLQ-C30 questionnaire at inclusion and at every re-staging. The development of clinically relevant depressive symptoms was defined by an emotional functioning (EF) subscore below 80. The lowest EF score during the observation period per patient was used for the analyses.

Results: Seventy-three lung cancer patients (29/73 female, 39.7%; 44/73 male, 60.3%; median age 65 years, range 36-83 years) were included in this analysis. Six of 73 patients received chemotherapy, 34/73 immunotherapy and 33/73 chemo-immunotherapy. At least one EF score was available from each patient (median of 3 available scores, range 1-12 available scores). Fifty-seven of 73 (78.1%) patients developed relevant depressive symptoms during anticancer treatment while 16/73 (21.9%) patients maintained EF scores $\geq$80. DNA methylation differences defined by statistical tests as well as effect size were calculated between patients with EF scores $<$80 and patients with EF scores $\geq$80. Both patient groups formed well-separated clusters based on the methylation patterns of the top 500 differentially methylated CpG sites, independent of gender, the type of received systemic therapy or histologic subtype.

Conclusions: DNA methylation profiling from peripheral blood leukocytes may identify lung cancer patients at risk for the development of depressive symptoms during systemic cancer therapy. Larger studies and biological interrogations are needed to substantiate our finding.

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1845P Exclusion of patients with psychiatric disorders from early phase oncology trials: A limited access to innovation?

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Background: Psychiatric disorders (PD) are highly prevalent in patients with cancer and associated with poorer outcomes. This may be partly explained by a limited access to innovation since patients with PD are often underrepresented in oncology

clinical trials. This study examines the frequency and the nature of exclusion criteria for patients with PD in a large sample of early phase oncology clinical trials (EPCT).

Methods: All protocols of EPCT opened to inclusion at the Drug Development Department at Gustave Roussy Cancer Centre in November 2022 were independently reviewed by 2 authors to identify exclusion criteria related to PD and classify them according to a 4-cluster classification (A: any PD, not specified; B: specific PD; C: pharmacology criteria and D: exclusion based on the clinician's judgment). The type of investigational drug, the route of administration and the type of cancer included in each trial were also collected.

Results: We analyzed a total of 117 protocols. The drugs most commonly studied included immune checkpoint blockers (44%), tyrosine kinase inhibitors (30%) and bispecific antibodies (15%). The most frequent route of administration was the intravenous route. A vast majority of ongoing studies (n=114, 97.4%) featured at least one criterion that could exclude patients with PD. Cluster D was the most prevalent (96.6%), followed by cluster C (14.5%), A (12.0%) and B (4.3%). Within cluster B, substance use disorder was the most frequently mentioned PD. In cluster C, all criteria concerned QT-prolonging drugs.

Conclusions: Nearly all the examined EPCT contained at least one criterion that could potentially result in the exclusion of patients with PD, most commonly based on subjective clinical judgment. Enhancing subjective clinical judgement with validated tools for evaluating consent capacity and future compliance may help in making more informed decisions and in reducing the impact of personal biases on the decision to exclude a patient with PD. Additionally, improved communication between psychiatry and oncology units engaged in clinical trials is also warranted.

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1846P The impact of newly diagnosed early breast cancer on distress, perception of health and psychologic resilience

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Background: Confronting breast cancer diagnosis, alongside with complex and challenging treatment procedures comprise an extremely stressful experience. Psychological resilience (PR) is the ability to maintain or restore normal functioning while facing the adversity, leading to better quality of life and preventing stress-related health conditions in cancer patients. We aimed to investigate the impact of early breast cancer (EBC) diagnosis on PR, distress and perception of health.

Methods: Case-controlled study included 50 newly diagnosed EBC patients and 67 women without breast cancer whose screening mammography was graded by Breast imaging-reporting and data system 1 and 2. The level of distress, perception of health and PR were assessed using the Depression Anxiety and Stress Scale 21, SF 36-Item Health Survey 1.0 and Connor-Davidson RISC-25 scale. EBC patients were questioned after confronting EBC diagnosis and before starting the treatment.

Results: The EBC patients reported deterioration of health, compared to previous year (t *(df)* 3,835, $p<0.01$), while there were no differences between groups related to general and emotional health. There was no significant statistical difference between groups regarding the levels of depression, anxiety and stress. Majority of the EBC patients and controls, 66% and 82%, had no symptoms of depression, while severe depression was noted in 10% and 3%, respectively. Around 78% EBC patients and 89% controls didn't show any anxiety. Still, 8% EBC patients and 4.5% controls were severely anxious, and 10% EBC and 4% controls were severely stressed. And finally, regarding resilience, EBC patients showed significantly higher levels of PR than healthy control (t*(df)* 2,530, $p<0.05$).

Conclusions: Confronting EBC diagnosis, possibly leads to activation of intra-individual coping mechanisms and dynamic processes of effective adaptation leading to higher PR levels of EBC patients compared with healthy controls. Further research of PR should be encouraged, by investigating the mechanisms that protect individuals and prevent stress-related health conditions, resilience research shifts a paradigm from a disease-oriented to health-oriented and focuses on mechanisms that prevent stress-related disorders.

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1847P Monitoring of psychological state and quality of life during Simonton-training for oncologic patients

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Background: With the increasing number of oncologic patients, consultation time per patient shortens, which negatively affects the doctor — patient relationship. Participation in psychotherapeutic groups can help patients gain trust in their treatment. The aim of this study is to quantify the effects of Simonton-training on the psychological state, quality of life and compliance in oncologic patients.

Methods: This survey was carried out at the University of Debrecen in the course of a 12-occasion-long Simonton training. A total of 27 patients in the psychotherapeutic

group, and 63 patients in the control group were included in this study. Patients filled out an online questionnaire three times, before the training (t0), right after the training (t1), and again 3 months later (t2). The online questionnaire contained: The Hospital Anxiety and Depression Scale (HADS), WHO Quality of Life 5-item questionnaire (WHO QOL5), Morisky Medication Adherence Scale (MMAS-8) and five questions (5Q) about the general attitude towards their treatment and the trust in their oncologist. The distribution of continuous variables was statistically analysed with the Shapiro-Wilk test, and Wilcoxon test was used for comparisons between the case and control groups due to the non-normal distribution of the majority of variables.

Results: From t0 to t1, the Simonton group's quality of life significantly increased (p=0,016), meanwhile the control group's QoL didn't change significantly (p=0,575). According to HADS scale, the Simonton group's anxiety significantly decreased from t0 to t1 (p=0,0005), and the change of the control wasn't significant (p=0,247). Depression values also showed a significant decrease for the Simonton group from t0 to t1 (p=0,003), whereas the control's depression values didn't change significantly (p=0,122). After psychotherapy, the Simonton group evaluated their therapy-related attitude better with the 5Q, than at t0 (p=0,026). During this time, the control's value didn't change significantly (p=0,532).

Conclusions: On the basis of this study the Simonton training had a positive impact on the patients' psychological state and their quality of life increased.

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1849P Use of antipsychotic drugs during radiotherapy in adult cancer patients in Korea: The nationwide retrospective cohort study based on the health insurance review and assessment service database

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Background: Antipsychotic drugs (APDs) are used in cancer patients for mental illness. There have been attempts to repurpose APD for cancer treatment based on suggestions that APD may have anti-cancer effects. However, reports on the use of APDs in cancer patients have been absent in Korea. Therefore, we conducted a nationwide study to assess the use of APDs during radiotherapy (RT) in adult cancer patients in South Korea.

Methods: We utilized the Health Insurance Review and Assessment Service database of all Koreans. We conducted an analysis on cancer patients identified by the International Classification of Diseases, aged ≥18, from 2010 to 2020, who underwent RT or chemotherapy (cisplatin or 5-Fluorouracil). Data including sex, age, diagnosis code, and prescription details of APDs were collected. The APDs included in the analysis were aripiprazole, quetiapine, olanzapine, risperidone, haloperidol, and chlorpromazine.

Results: A total of 558,318 patients received RT, and 100,810 patients received concomitant chemo-radiotherapy (CCRT). Among the patients who received RT, 78,785 were prescribed APD, and 19,689 (4%) took APD during RT. Among the patients who received CCRT, 21,689 were prescribed APD, and 4,612 (4.7%) took APD during CCRT. The number of patients who took ADP during RT was 3.598 (78.01%) in men. The age distribution was as follows: 0.67%, 2.23%, 8.54%, 23.87%, 34.35%, 26.24%, and 4.10% were in <30s, 40s, 50s, 60s, 70s, and ≥80, respectively. When classifying patients who took ADP during RT by diagnosis, lung cancer accounted for 18.53% (12,355 out of 66,669), and breast cancer accounted for 2.21% (2,896 out of 130,700). The most frequently used ADPs during RT were quetiapine (62.11%), chlorpromazine (14.21%), risperidone (12.64%), olanzapine (11.03%), aripiprazole (0.01%), and haloperidol (0.002%). Survival of patients prescribed APD during RT was worse compared to those without APD (HR 2.84).

Conclusions: Only 4% of patients who received RT took ADP simultaneously during RT and took quetiapine the most. The survival rate of patients who took ADP during RT was worse than those who did not. Further studies are needed on the effects of ADP in cancer patients.

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1850P The effectiveness of a CBT-based mobile application for the mental state of women with breast cancer

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Background: Anxiety and depression are the most common psychopathological problems encountered in psycho-oncological care. It is estimated that among cancer patients, the prevalence rates of these disorders range between 17% and 49% in the case of anxiety disorders and between 4% and 60% in the case of depression. Access to psycho-oncological assistance is still significantly difficult, and many cancer patients do not receive adequate help. The digital form of psychological intervention can be the answer to these problems. The study's objective was to investigate the effect of mobile application-based cognitive-behavioural therapy (LivingWell app) in addition to usual psycho-oncological care on the anxiety and depression in women with breast cancer undergoing primary oncological treatment, compared with the usual psycho-oncological standard of care alone.

Methods: The participants (n=78) were recruited via two cancer breast units up to two weeks after breast cancer diagnosis. The mobile-app intervention group consists of 44 women (app group). The control group with a standard of care included 34 women (SoC group). The app group was asked to use the mobile application at least three times a week. There were 4 measurements conducted at baseline and 6th, 12th and 18th week to assess levels of experienced depression and anxiety (Hospital Anxiety and Depression Scale).

Results: Within all measurements, only in the app group was observed a significant anxiety decrease. Additionally, the app group had an overall level of anxiety in the norm since the sixth week, while the level of this emotion in the SoC group stayed high. Within all measurements, was observed a significant decrease in depression in both groups, although average values in the app group remained constantly lower.

Conclusions: Mobile application-based CBT is an effective digital intervention for improving the mental state and functioning of women with cancer during oncological treatment. Mobile application-based CBT can be a valuable psycho-oncological support tool.

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1851P Psychological well-being of patients with colorectal cancer during the third wave of the COVID-19 pandemic: Results from cohort II of the PICO-SM study

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Background: We have previously reported on the initial results of the prospective longitudinal PICO-SM study (Lim *et al.* 2023), highlighting the impact of the COVID-19 pandemic on the lives of patients with colorectal cancer. Herein, we present the psychological impact of the third wave of the pandemic to patients, when the Omicron variant became prevalent (December 2021 to early 2022).

Methods: Patients were invited to participate in cohort II of the PICO-SM study by completing a questionnaire, including screening psychometric tools. Multivariate analysis was performed using logistic regression for binary outcomes: anxiety (GAD-7 score ≥ 5), depression (PHQ-9 score ≥ 10), and poor well-being (WHO-5 < 50); and odds ratios (OR) with 95% confidence interval (CI) were calculated.

Results: In total, 96 participants were included: mean age 64 years, 64% (n = 61) males. 33% (n = 32/96) reported poor well-being (WHO-5 < 50), 27% (n = 26/96) anxiety (GAD-7 ≥ 5), 11% (n = 11/96) depressive symptoms (PHQ-9 ≥ 10) and 3% (n = 3/96) probable post-traumatic stress disorder (PC-PTSD-5 ≥ 4). The results compare

with distress levels in the second pandemic wave: 31%, 24%, 15% and 3%, respectively. Multivariate analysis showed that patients who had investigations cancelled (OR 9.22, 95% CI 1.09-77.85; p = 0.041) or felt that the pandemic would affect their mental health (OR 3.82, 95% CI 1.96-7.44; p < 0.001) had increased risk of anxiety. Similarly, concern that the pandemic would affect their cancer treatment (OR 4.59, 95% CI 1.03-20.56; p = 0.046) or would affect their mental health (OR 3.90, 95% CI 1.38-11.03; p = 0.010) were found independent predictors of poor wellbeing.

Conclusions: The psychological distress experienced by patients, particularly anxiety, remained persistently high during the third wave of the COVID-19 pandemic. These updated results align with our initial findings, emphasizing the critical importance of continuing cancer treatment amidst the ongoing humanitarian emergency. It is crucial for healthcare services to prioritize ongoing psychological support for cancer patients, with a particular focus on those who are more vulnerable.

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1852P Mental health among Tunisian oncologists

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Background: Oncology is a satisfying career. Helping patients through their cancer diagnosis and treatment can offer a sense of self fulfilment. But on the other hand, it can take its emotional toll on doctors. Long hours, dealing with life and death can affect oncologist's mental health. It can cause depression, anxiety and PTSD. Our aim is to identify individuals who are at risk for burnout and facilitate interventions to prevent it.

Methods: This study used a descriptive design to identify individuals at risk for burnout among oncologists. It included 100 clinicians, working in various hospitals in Tunisia, recruited via email invitations. Inclusion criteria included being a practicing oncologist with at least one year of experience. Participants anonymously completed the Maslach Burnout Inventory (MBI) questionnaire, a tool used to detect burnout. The MBI consists of 22 items that assess emotional exhaustion, depersonalization, and personal accomplishment.

Results: The population is made of 77% females and 23% males. With an average age of 33 years, medical oncologists represented 80%, radiotherapists 12% and surgical oncologists 8%. The majority had professional experience ranging from 1 to 5 years. Gender difference was seen on the emotional exhaustion subscale where women scored higher. No significant differences were observed in the scores based on professional experience or field of practice. Emotional Exhaustion: Participants had a mean score of 29. Meaning the participants experienced high levels of emotional exhaustion. Only 20% of the population had low score, 20% scored moderately and 60% had high scores. Depersonalization: Results showed a mean score of 10. Participants are experiencing moderate levels of depersonalization, with 28% scoring low, 32% scoring moderate and 40% scoring high. Personal Accomplishment: the average score was 35. Participants are experiencing moderate levels of personal accomplishment, with 32% at low risk of burnout, 20% at moderate risk and 48% at high risk of burnout.

Conclusions: Our study provides valuable information about the levels of burnout experienced by oncologists. It should inform interventions and strategies to mitigate burnout and promote wellbeing in this population. It should also ring alarm bells to oncologists' suffering mental health.

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1853P Effect of logotherapy on anxiety in patients with cancer: A systematic review and meta-analysis

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Background: Frankl's Logotherapy is a psychotherapeutic approach aimed at finding meaning in life. Although the incidence of death anxiety, existential loneliness, and depression in cancer patients is high, the efficacy of Logotherapy in this population is not well established.

Methods: Two independent investigators searched PubMed, Embase, and Cochrane Library databases up to March 2023. We systematically reviewed, according to PRISMA guidelines, controlled clinical trials evaluating the use of Logotherapy in cancer anxiety symptoms. We performed a pooled analysis on anxiety scores of patients that underwent group Logotherapy sessions vs. non-exposed control groups.

Results: We included seven studies, four randomized controlled trials (RCTs), and three quasi-experimental, comprising 280 patients, published between 1977 and 2023. A total of 139 patients (49.6%) had sessions of Logotherapy, and ages ranged from 18 to more than 68 years. Total treatment duration ranged between 360 and 1200 minutes. The Standard Mean Difference (SMD) for anxiety symptoms was -1.63 (95% CI = [-2.65, -0.61]; z = 3.12; P = 0.002; I^2 = 92%) in patients who underwent Logotherapy compared to non-exposed control groups. In a subgroup analysis including only RCTs, a similar effect was observed with an SMD of -0.64 (95% CI = [-1.72, 0.44]; z = 1.16; P = 0.25; I^2 = 91%).

Conclusions: Despite limited evidence, Logotherapy group sessions were associated with a reduction in anxiety scores of adult patients with cancer when compared to inactive control groups.

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1854P The role of "1 minute" time perception in evaluating depression and anxiety in cancer patients receiving chemotherapy

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Background: Impaired perception of time has been associated with many psychiatric and neurological diseases. Time perception has been studied with different validated scales in the literature. However, the length of these scales limits its feasibility. The aim of our study was to evaluate the relationship of "1 minute" time perception with depression and anxiety in cancer patients receiving chemotherapy.

Methods: The cancer patients receiving active systemic therapy were included in the study. Time perception assessment was performed by testing how they perceived the 1-minute period. The patients were asked to guess the length of 1 minute by using a chronometer. Time perception duration (TPD) were recorded. The median 39 seconds was used to categorize patients as fast and slow time perception. Depression and anxiety were evaluated using the Hospital Anxiety and Depression Scale (HADS).

Results: In the study; 242 patients with a median age of 61 (33-88 years) were evaluated. In the TPD evaluation, the median estimation time was 39s (7-135sec) and 50.4% was found to be rapid time perception (<39sec). Anxiety and depression scores were recorded as high in 12% of the patients. There was no significant correlation between TPD and anxiety (r=0.027, p=0.68) and depression scores (r= 0.017, p= 0.79). TPD was similar between the groups with high and normal anxiety scores (39 vs 39 sec, p= 0.90) and those with short perception patients were similar in both groups (51.7% vs 50.2%, p=0.51). TPD was shorter in those with high depression scores (34 vs 40s, p= 0.37). Those with rapid TDP were more common in these patients, but this did not reach statistical significance (58.6% vs 49.3%, p= 0.22). In the multivariate analysis. Female gender and low income were found to be risk factors for high anxiety scores.

Conclusions: The 1-minute time perception assessment could not be shown to be effective in predicting depression and anxiety scores. In our study, in which the group with high depression/anxiety scores was low, the small sample size may be the reason for the insignificant result. Testing the efficacy of 1 minute time perception in larger groups can provide important data to the literature.

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1855P Assessment of depression and anxiety among adult patients with solid tumours admitted in national institute of cancer research & hospital

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Background: Cancer is one of the most common causes of mortality & morbidity globally, and the diagnosis of cancer is a stressful event causing significant psychological distresses, most commonly depression and anxiety, directly interfering with disease outcome and quality of life.

Methods: This cross-sectional type of descriptive study was conducted at the National Institute of Cancer Research & Hospital (NICRH), Dhaka for a period of 12 months. Sample size was 405 using purposive sampling. Data were collected from the patients through face-to-face interviews using a semi-structured questionnaire and Bangla version of the DASS-21 scale.

Results: In this study, the mean age of the respondents was 47.4 ± 16.5 years, predominantly male. Gastrointestinal cancers (27.4%) were most prevalent, followed by lung cancer (19.5%). The prevalence of depressive and anxious symptomatology was 38.02% and 42.96%, respectively. More than half (53.3%) of the patients were suffering from either of depression and/or anxiety.

Table: 1855P

Severity	Depression	Anxiety
Mild	19.7%	17.3%
Moderate	13.6%	11.6%
Severe	3.7%	9.4%
Extremely Severe	1%	4.7%

In inpatient setting, depressive disorders were significantly higher in females than males ($p<0.01$) and among the lung cancer patients; in contrast, gastrointestinal cancer and the presence of co-morbidities predisposed more to anxiety ($p<0.05$). Although mode of treatment and severity of disease showed no significant relationship with the prevalence of depression or anxiety, ECOG performance status was found to have significant impact on both of the disorders. On analysis of the socio-demographic variables, illiterate and low-income people were seen to suffer more with a severe and extremely severe level of depression, on the other hand, homemakers and lower socio-economic class had higher levels of anxiety.

Conclusions: The study findings showed a higher prevalence of depression and anxiety in the inpatient setting; therefore, counseling, screening, and timely evaluation of mental health should be a part of the standard protocol of oncology care.

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1857P Psychological distress in Georgian cancer patients undergoing chemotherapy: Before and after the COVID-19 pandemic

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Background: The COVID-19 pandemic has been closely associated with a decline in mental health. The goal of this study was to identify the degree of distress of cancer patients before and after the pandemic and to find out if COVID-19 worsened the mental health of cancer patients.

Methods: A self-rated survey was conducted for 2 groups of patients at The Todua Clinic, Tbilisi, Georgia twice: at the peak of pandemic and again 6 months after the pandemic. Study included adult cancer patients, with solid tumors, over 18 years of age, receiving chemotherapy, being able to understand and answer the questions in written English. Event Scale-Revised (IES-R) test was implemented to measure Post-Traumatic Stress Disorder (PTSD). Total IES-R score of 33 or over signifies the likely presence of PTSD.

Results: Study enrolled total of 195 patients, 103 patients - during and 92 - after the pandemic. 3 independent and 5 dependent variables were created. Independent variables were: 1. IES-R score ≥24 (y=1 if score ≥ 24, y=0 if score ≤ 24); 2. IES-R score≥ 33 (y=1 if score ≥ 33, y=0 if score ≤ 33); 3. IES-R score 37 (y= 1 if score ≤ 37, y=0 f score ≤ 37). Five dependent variables were: time, type of disease, stage, sex, and marital status. We created 3 regression models with independent and dependent variables (model 1: independent variable was IES-R score ≥24, model 2 independent variable was - IES-R score ≥ 33, model 3 IES-R score ≥ 33). We observed improvement in IES-R scores in the post-pandemic period: In model 1 - results improved by 20%, In model 2 - 16%, and in model 3 — 14%. Female and married individuals had better results in both periods. We calculated the data and observed that all dependent variables other than the disease type and the disease stage had a significant impact on IES-R scores.

Conclusions: Our findings showed a significant difference in IES-R scores in patients before and after the COVID-19 pandemic, with notable improvement in the post-COVID period. We also observed that sex, disease stage, marital status, and disease stage affected IES-R scores. We conclude that COVID-19 worsened the mental health of cancer patients. Our study highlighted the need for efforts to better integrate psychosocial support into cancer treatment.

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1858P Discrepancies between psychological stress and emotional care in cancer patients revealed in a social listening analysis

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Background: Identifying the patient's discomfort and unmet needs is crucial for providing effective care. However, accurately understanding the patient's discomfort can be challenging due to various limitations in the medical field, and in some cases, their discomfort may be underestimated. To better understand the difficulties faced by cancer patients, we implemented Social Listening to identify areas where improved treatment may be provided.

Methods: From October 1, 2021 to September 30, 2022, we gathered online data related to cancer and anti-cancer treatments. Using NetBase as our social listening platform, we filtered out irrelevant and commercial content from the collected data.

Results: A total of 169,575 social mentions related to cancer and anticancer treatment were collected. Among them, 12% (n=20,899) addressed the challenges experienced by patients following a cancer diagnosis. These challenges were further categorized based on the content of social media posts, with 52% focusing on physical difficulties, 42% on emotional challenges, and 6% on difficulties related to daily life. Emotional difficulties such as worry, denial, depression, fear, and anxiety were prevalent among cancer patients, with variations in priority depending on the time of diagnosis, treatment, and post-treatment stages. Of the 16,743 social media discussions related to cancer care, only 9% were related to managing emotional stress. A majority (84%) of discussions related to mental health management involved receiving psychiatric treatment, with the remaining 16% focusing on self-help groups, communication with others, meditation, hobbies, and religious practices.

Conclusions: Emotional burdens, along with physical difficulties, were frequently discussed on social media. However, there appeared to be a relative lack of focus on the management of emotional burdens. Considering the known association between emotional management and cancer treatment outcomes, it is imperative for physicians to prioritize their patients' emotional well-being and offer appropriate support.

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1859P Digital goal management training as treatment for cognitive impairment in cervical cancer survivors: A feasibility study

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Background: Cognitive impairment (CI) is a common late effect after cancer treatment, for which effective treatment is lacking. Goal Management Training (GMT) is a validated cognitive remediation protocol reported to improve cognition including perceived daily life executive functioning, in neurological conditions. However, GMT has never been examined in cancer survivors, nor been presented in a digital format. This study examined the feasibility and acceptability of digital GMT in cervical cancer survivors (CCS) with subjective and/or objective CI.

Methods: We invited 65 CCS with CI to participate. Participants were randomized in a 1:1 ratio between digital GMT and a computerized cognitive training (CCT) program (BrainHQ). GMT consists of six weekly group-based modules encompassing discussion of participants' real-life cognitive deficits, practice on tasks of attention and self-monitoring, as well as homework assignments. BrainHQ is a web-based training platform with exercises targeting several cognitive domains. For six weeks, participants joined digital training sessions of one hour twice a week. The primary endpoint was attendance, and participants attending $\geq$80% of the sessions were categorized as completers. Acceptability was evaluated 1 week post-intervention using the Client Satisfaction Questionnaire-8 (CSQ-8). A total CSQ-8 score $\geq$ 26 was defined as "very satisfied", scores 20-25 as "satisfied", and scores $<$20 as "not satisfied".

Results: 33 CCS with a median age of 50.0 years (range 35-67) were randomized to either GMT ($N = 16$) or CCT ($N = 17$). In the GMT group, all participants completed the intervention (100%), compared to 15 (88%) in the CCT group. Median CSQ-8 in the GMT and CCT group was 25 (*SD* 3.7, range 18-31) and 24 (*SD* 3.1, range 19-30) respectively. Participants in both groups reported a high level of satisfaction as 40% reported being "very satisfied" and 53% "satisfied".

Conclusions: A digital cognitive training program such as GMT is feasible with a high level of compliance and satisfaction in CCS and is suitable to be tested in a larger study. Exploratory analyses of neuropsychological assessments in our study will provide important preliminary data on the efficacy of improving cognitive function in CCS.

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1860P Objective and subjective neurocognitive functioning (NCF) in advanced cancer survivors treated with immune checkpoint blockade (ICB)

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Background: Limited knowledge currently exists on NCF in advanced cancer survivors treated with ICB. Here, we present the baseline data of an ongoing prospective trial regarding objective and subjective NCF.

Methods: Patients (pts) followed-up at a single center, diagnosed with stage III/IV cancer of any type, who initiated ICB at least one year prior to and were in complete remission (CR) at time of inclusion, were invited to participate. Objective NCF was assessed using the test battery COGBAT®. Neurocognitive impairment (NCI) was defined by the International Cancer and Cognition Taskforce guidelines and deficits per subtest as 1.5 standard deviation below the normative mean. Subjective NCF, anxiety, depression and fatigue were assessed respectively through the Cognitive Failures Questionnaire, Hospital Anxiety and Depression Scale, and Fatigue Severity Scale.

Results: From July 2022 to April 2023, 58 pts were enrolled (48 melanoma, 6 non-small cell lung carcinoma, 2 colon cancer, 1 renal cell carcinoma, 1 bladder cancer), median age was 64 y [34-92]); 34 male; 55 pts (95%) had stage IV disease; 12 pts (21%) had a history of brain metastasis. Median time since CR was 3.0 y [0.1-14.1]; median time since last ICB administration was 3.6 y [0.0-11.4]. We found objective NCI in 34 pts (59%), with deficits predominantly in memory (33%) and attention (31%) and in a lesser amount in executive functioning (16%). Moderate to severe subjective cognitive complaints were found in 12 pts (21%). Objective NCF only correlated significantly with age (r = -.782, $p < .001$) but not with subjective NCF, fatigue, anxiety, depression or a history of brain metastasis. Subjective NCF correlated significantly with anxiety, depression and fatigue (respectively $r = .694$, $r = .454$, $r = .447$, all p-values $< .001$).

Conclusions: A majority of the advanced cancer survivors treated with ICB had objective NCI. A noteworthy lesser proportion had subjective cognitive complaints, indicating the need of neuropsychological assessment. Moderate to strong associations exist between subjective NCF and psychological distress, indicating the value of an integrative approach, including NCF remediation and psychosocial support when treating cognitive complaints.

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1861P A randomized controlled trial on the efficacy and safety of the Untire app for moderate-to-severe cancer-related fatigue in German patients

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Background: This RCT examined the clinical efficacy and safety of the German version of the self-management Untire app for reducing fatigue and improving quality of life in cancer patients and survivors, with the hypothesis that app access as an add-on to care as usual will lead to superior clinical outcomes in patients with moderate-to-severe fatigue as compared to care as usual only, over 12-weeks.

Methods: Patients with cancer-related fatigue (CRF) were recruited from across Germany through newspaper advertisements, and randomized (1:1) to receive either care-as-usual alone (control; n=111) or care-as-usual plus access to the Untire app (intervention; n=104). The primary outcome measure was fatigue, and secondary outcomes included quality of life, stress, depression, and anxiety, all assessed at baseline, 4, 8, and 12 weeks. Linear mixed models, ANCOVAs were employed for all outcomes to evaluate the treatment effects over 12 weeks while adjusting for baseline values and adhering to the intention-to-treat principle.

Results: The intervention group experienced a significantly larger improvement at week 12, with an average fatigue score of 4.8 (SE=0.18) compared to 5.6 (SE=0.17) in the control group (p=0.0016, 95% CI: -1.29 to -0.30). This difference of -0.79 is statistically significant and also clinically relevant as it is larger than the MCID of -0.57, with 58.7% of patients in the intervention group experiencing an improvement of more than 0.57 points compared to 43.2% in the control group. For the secondary outcomes, disease-related quality-of-life scores were also significantly higher in the intervention group at week 12 (p=0.0178, 95% CI: 0.16 to 1.64), and improved to a clinically relevant degree. No significant interactions were found between the treatment groups and the subgroup variables. Sensitivity analyses (per-protocol and reference-based) indicated the robustness of the findings. The degree of app usage did not affect the treatment effect over 12 weeks. Adverse events occurred with no discernible patterns between groups, and no deaths occurred during the trial.

Conclusions: The German version of Untire can be an effective and safe digital health application for patients with moderate to severe CRF.

Clinical trial identification: DRKS00027477.

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1862P Measuring the prevalence of fatigue in children with cancer: Evidence from Egypt

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Background: Cancer related fatigue (CRF) is a common side effect of cancer and cancer treatment that impacts every aspect of quality of life. To our knowledge, the statistics for prevalence in pediatrics are lacking in Egypt. The aim of this study is to record the prevalence of fatigue and its significant predicting factors in pediatric oncology patients.

Methods: We interviewed children aged 8-18 years with cancer, prescribed chemotherapy and not in severe distress. After the consent of the guardian is taken, the children personally filled 2 fatigue-related questionnaires (PROMIS Pediatric Short Forms of Fatigue (PROMIS fatigue), pedsQL multidimensional fatigue (PedsQL fatigue)) and 3 symptoms related questionnaires.

Results: 42 children (47.6% female) (mean age 12.1 years (SD 3.3 years)) participated. Half of the children were in primary school (n=21, 50%) and most of them had their parents accompanying them (n=35, 83.3%). Most children suffered from a hematological tumor (n=35, 83.3%) and didn't suffer from other chronic health conditions (n=39, 92.8%). Reported moderate to severe fatigue in children is between half to third of the children depending on the measurement tool used. The mean T-score for PROMIS fatigue was 53.76 (SD 12.5), the mean score for PedsQL fatigue was 74.27 (SD 21.79). Stepwise standardized multivariant linear regression showed that fatigue following PROMIS fatigue could be predicted by depressive symptoms.

Conclusions: CRF is multifactorial and prevalent among children and adolescents with cancer. Moreover, predicting factors differed between different tools as they measure fatigue from different dimensions. PedsQL fatigue was predicted by more factors. There is a need to include fatigue screening for pediatric oncology patients and incorporate its management in the medical care plan.

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Disclosure: The author has declared no conflicts of interest.

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1863P Compassion fatigue among the staff involved in medical carcinology services

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Background: A descriptive, cross-sectional, multicenter study was carried out among the nursing staff working in several departments caring for cancer patients (Carcinology Sousse, Monastir, Sfax, Institut Salah Azaiez and Ariana).

Methods: The instrument used to measure CE was the "Professional quality of life" (PRO-QOL version5), which is composed of 3 subscales: 10 items to measure compassion satisfaction (SC), 10 items to measure professional exhaustion (PE) and 10 items to measure secondary traumatic stress (STS).

Results: A total of 120 health personnel responded to the questionnaire. The average age of the participants was 36.13±8.06 with a clear female predominance (sex ratio=0.29). Most respondents were physicians (55.9%). The mean CS score was 33.57±6.24, which is consistent with an average level of CS. However, 13.3% of the staff had a high SC score. The mean PE score was 29.88±5.12, which corresponds to an average level of PE. Only 10.9% had a low PE score. The mean STS score was 33.16±7.56, which corresponds to an average level of STS. However, 17.5% had a high STS score.

Conclusions: Compassion fatigue can lead to real burnout. Its prevention, detection and implementation of solutions to stem the process is essential.

Legal entity responsible for the study: 1-Service of carcinological medicine CHU FarhatHached Sousse 2- Hospital hygiene service CHU FarhatHached Sousse 1-Service of carcinological medicine CHU FarhatHached Sousse 2- Hospital hygiene service CHU FarhatHached Sousse Service of carcinological medicine CHU FarhatHached Sousse and Hospital hygiene service CHU FarhatHached Sousse.

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1864P To what extent do nulliparous, female adolescents and young adults diagnosed with cancer have children after cancer treatment?

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Background: Globally, more than 1.3 mio adolescents and young adults (AYAs) are diagnosed with cancer each year. Long-term survival has increased due to improved cancer therapy; however, a potential side effect is reduced fertility. Despite development in fertility preservation uncertainty regarding future fertility is still of major concern to the AYAs. The aim of this study was to identify to what extent nulliparous, female AYAs with cancer have children after cancer treatment compared to nulliparous female AYAs without cancer.

Methods: This is a national register study based on the Danish National Assisted Reproductive Technology-Couple cohort including female AYAs diagnosed with cancer when aged 18-39 from 1978—2016. According to diagnosis onset, the female AYAs with cancer were randomly age-matched with 60 female AYAs without cancer (comparison group: CG). Study participants were followed until end of study, death, or migration (31/12-2017). Death was incorporated as a competing risk in all analyses. Hazard Ratio (HR) were calculated, comparing the female AYAs with cancer with the CG. HR was adjusted for time of diagnosis, immigration status, marital status, and educational level.

Results: 33.3% of AYAs with cancer had at least one child after cancer treatment vs. 40% in the CG. Female AYAs with malignant melanoma had solely a higher HR of having children after cancer treatment compared to the CG. Female AYAs with leukaemia, breast and CNS cancer had the lowest HR of having children after cancer treatment, especially in the age interval 32-39 years.

Table: 1864P

	N (%)	≥ 1 child after cancer N (%)	Adjusted HR (95% CI)*		
			18-25 y	26-31 y	32-39 y
All	7519 (100)	2505 (33.3)	0.77 (0.72-0.82)	0.65 (0.61-0.69)	0.59 (0.52-0.67)
Gyn cancer	1773 (23.6)	435 (24.5)	0.49 (0.42-0.58)	0.44 (0.38-0.50)	0.39 (0.29-0.52)
Breast cancer	1115 (14.8)	179 (16.1)	0.63 (0.42-0.95)	0.46 (0.37-0.56)	0.35 (0.26-0.48)
Mal melanoma	1960 (26.1)	1071 (54.6)	1.02 (0.93-1.12)	1.03 (0.93-1.13)	1.13 (0.92-1.39)
CNS cancer	303 (4.0)	65 (21.5)	0.70 (0.51-0.97)	0.40 (0.26-0.61)	0.25 (0.06-0.97)
Leukaemia	258 (3.4)	37 (14.3)	0.39 (0.26-0.57)	0.25 (0.09-0.65)	0.41 (0.13-1.26)
Lymphoma	278 (3.7)	78 (28.1)	0.63 (0.47-0.85)	0.48 (0.30-0.75)	0.76 (0.32-1.84)
CG	499,616	199,861 (40.0)	1	1	1

*Adjusted analysis is based on complete case sample, N=6275. Approximately 16% (6275/7519) is excluded in the adjusted analysis due to missing data.

Conclusions: A third of nulliparous, female AYAs with cancer had at least one child after cancer which is lower than for female AYAs without cancer. The HR for having children after cancer decrease with increased age being lowest in female AYAs with leukaemia, breast- and CNS cancer.

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1865P Women with elderly early-stage breast cancer with type A personality may have decreased self-esteem after chemotherapy: A pilot study (POSEIDON Study)

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Background: This study aimed to determine how the chemotherapy process can lead to a change in self-esteem in elderly patients with early-stage breast cancer according to personality type.

Methods: The research was completed as a pilot study between 2019-2022. Female patients aged 65 and over who were planned for adjuvant treatment were included in

the study. Personality type and self-esteem were determined in all patients before and after adjuvant chemotherapy. Bortner Rating Scale was used to determine personality type, and Rosenberg Self-Esteem Scale was used to determine self-confidence. Paired t-test was performed for recurrent variables in pre-treatment and post-treatment measures. Multivariate logistic (binary) regression analysis was performed to determine the independent factors affecting low self-esteem from the study variables with the model created as a result of correlation and univariate analysis. Statistical analysis was performed using the SPSS v19 program and a p value of <0.05 was considered statistically significant.

Results: A total of 69 Her2-negative elderly female patients were included in this pilot study. The mean age of the patients was 68 years (65-72). 54% had radical mastectomy. 69% received paclitaxel for 12 weeks, 21% received 6x DC, and 10% received 3x CEF followed by 3x docetaxel for adjuvant setting. 56% of them had personality type A. Before treatment, 62% had high self-esteem and this was significantly higher in type A personality than in type B (84% vs 48%, respectively; p=0.037). While the rate of high self-esteem decreased in type A personality after treatment (p=0.009), there was no change in type B personality (p=0.379). It was determined that type A personality structure was independent affecting low self-esteem after treatment (OR 5.37 95%CI 1.489-9.396; p=0.006).

Conclusions: In this study, it was concluded that elderly women with type A personality structure may be more sensitive and may have low self-esteem after the treatment is completed. It was concluded that the personality type should be guided by the patient's treatment compliance, need for psychosocial support, and coping methods after the completion of the treatment, supported by the physician.

Legal entity responsible for the study: Ethics committee approval could not be obtained because it was a pilot study. In the follow-up research, the results of the pilot study will be declared and consent will be obtained.

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1866P Unmasking the extent of hidden sexual distress in young breast cancer survivors

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Background: The aim of this study was to compare sexual health between young breast cancer survivors and healthy young women without history of cancer, to better analyse the impact of breast cancer diagnosis and treatment on sexual health.

Methods: We conducted a cross-sectional study including all young breast cancer patients ($\leq$40 year-old) referred for radiotherapy between 2017 and 2021. Patients were asked to fill in the Female Sexual Function Index (FSFI) in its validated Arabic translated version. A comparable cohort of young healthy women was recruited to fill in the same questionnaire. Sexual scores were calculated for both groups and statistically compared.

Results: A total of 102 young breast cancer patients (BC group) and 53 young healthy women (control group) were included in this study. Only 39.2% of breast cancer patients answered the questionnaire. Ninety-seven percent of patients underwent chemotherapy. Adjuvant endocrine therapy was prescribed for 77% of patients, of whom 97% underwent ovarian function suppression. All patients received adjuvant hypofractionated radiotherapy. Mean FSFI score was 24.01 (2.4-33) in the BC group versus 28.88 (23.8-34.4) in the control group (p=0.000). Two patients declared having unpleasurable sexual activities before their diagnosis. Sexual dysfunction (FSFI score $<$ 26,55) was reported in 55% and 20%, respectively in the BC and control group (p=0.001). Mean desire score was 3.58 vs 4.08 (p=0.016), respectively in the BC group and the control group. Ninety-two percent of breast cancer patients suffered from hypoactive sexual desire disorder (desire score $<$5), versus 87% in the control group (p=0.35).

Table: 1866P Female Sexual Function Index questionnaire scores

Domain	Breast cancer group	Control group	P value
Desire	3.58	4.08	0.016
Arousal	3.71	4.56	0.001
Lubrification	4.15	5.16	0.00
Orgasm	4.23	4.97	0.007
Satisfaction	4.44	5.49	0.00
Pain	3.85	4.62	0.008

Conclusions: This study showed a significant alteration of sexual function in young breast cancer survivors when compared with a control group. Assessment and management of sexual dysfunction should become a standard practice, in order to improve quality of life and sexual health in young breast cancer survivors.

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1867P A cross-sectional examination of information disclosure and health literacy amongst patients with lymphoma

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Background: Health literacy of patients is a requirement for shared decision making. However, little is known about the experiences of patients with lymphoma with regard to health literacy and information disclosure from their treating physicians. We sought to explore health literacy through a survey deployed across a large and diverse group of patients with lymphoma.

Methods: The 2022 Lymphoma Coalition (LC) Global Patient Survey (GPS) was completed by 7113 patients from 84 countries. We sought to understand how patients initially understood their disease. Responses to the question: "To what extent, if at all, were diagnostic tests and results explained to you?" were stratified across core demographics and tabulated. Tests for significant differences across strata were computed with JMP Pro v17.

Results: Of the 6684 respondents who indicated a level of satisfaction or dissatisfaction with regard to the comprehension of diagnostic and laboratory tests, 58% and 42% were males and females respectively with a median age of 60 and range of 18 - 97 years. Overall, 36% of respondents reported poor comprehension. Increasing age was a significant positive predictor of health literacy with a Range OR = 6.9 [5.4 - 8.9]. Likewise, male biological sex was a significant predictor of improved comprehension OR = 1.5 [1.3 - 1.6]. Regional disparities were identified that indicated North America and Europe had the highest rates of satisfactory comprehension with 72% and 68% respectively. This was contrasted with the Asia-Pacific region at 53% ($p<0.0001$).

Conclusions: One of the goals of precision medicine is to deliver the right therapeutics to the right patient at the right time. [LW1] Shared decision making has the ability for patients to provide valuable feedback to their treating physicians. However, a lack of health literacy essentially excludes patients from participating in the decision making process. All three demographics examined above indicated highly significant disparities that can have adverse ramifications on healthcare equity. We feel that patients should understand their disease and the available treatment options which will yield increased participation in their care.

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1868P Challenges for shared decision making in incurable cancer, with a focus on health literacy

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Background: Patients with incurable cancer often face difficult decisions about their care. Shared decision making (SDM) can help people make the decisions that are right for them, by supporting understanding and ensuring their priorities are considered. Essential for this is health literacy (HL) - the personal competencies and situational resources needed for people to process information to make decisions. This study sought to understand the barriers to SDM in the context of HL from the perspective of patients and clinicians, and consider how they may be overcome.

Methods: This mixed methods study comprised: 1) semi-structured interviews with patients with incurable cancer and suspected HL difficulties, identified by clinicians from 2 district hospitals; and 2) an online survey of NHS healthcare professionals caring for patients with incurable cancer. Interview data were analysed using the Framework Approach to identify important and recurrent themes. For the survey, a descriptive analysis was carried out for the quantitative data, and thematic analysis for the qualitative data.

Results: Twenty-one interviews were conducted. Patients had a range of diagnoses and had received various treatments. Themes related to experiences (supportive staff in an imperfect system, additional pressure from COVID-19, in the expert's hands, treatment not so bad) and barriers to SDM (emotional hurdles, accessing and understanding information, wanting to be a good patient). Survey participants (N=70)

included doctors, nurses, and a pharmacist. Views towards SDM ranged from those who aim to 'always' use it, to those who feel its use should be limited. Patient, clinician, and situational barriers were identified. Key challenges for SDM include the persistence of paternalistic clinician-patient roles, dealing with emotional hurdles, and practical issues.

Conclusions: There are socio-cultural, emotional and system barriers to SDM in incurable cancer for those with HL difficulties. Addressing this combination of issues will be important to fully embed its use in practice. Recommendations to improve SDM range from large scale policy changes to provision of easily accessible and understandable patient information and decision aids in a variety of formats.

Legal entity responsible for the study: University of Southampton.

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1869P First impressions: A prospective evaluation of patient comprehension and satisfaction in the communication of diagnosis, treatment, and prognosis following the initial medical oncology consultation

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Background: Despite the plethora of patient (pt) communication studies in the past decade, many of them include a diverse and heterogeneous pt and physician cohort. Thus, this single-centre prospective study aimed to measure gastrointestinal (GI) cancer pts' understanding of the information discussed during their *first* medical oncology visit and their satisfaction with the communication from subspecialized GI medical oncologists.

Methods: Between January and August 2021, chemotherapy-naïve pts in the gastrointestinal clinic at the Princess Margaret Cancer Centre (PMCC), Toronto, Canada, were consecutively approached within 24 hours of their initial consultation to complete a paper-based questionnaire about their understanding of their cancer (diagnosis, treatment plan/intent, prognosis) and satisfaction with the communication. GI medical oncologists concurrently completed a similar questionnaire. Pt and physician responses were compared to assess the degree of concordance. Uni/multivariable analyses were performed to identify pt/physician-based factors associated with concordance levels and pt satisfaction.

Results: A total of 184 matched pt-physician surveys were completed. The concordance rates for understanding of diagnosis, treatment plan, treatment intent, and prognosis were 92.9%, 59.2%, 66.8%, and 59.8%, respectively. Pts who reported treatment intent to be unclear at the time of the consultation were independently associated with lower satisfaction scores compared to those who reported their treatment intent to be curative (p=0.014). There was no statistical significance between patient satisfaction and whether prognosis was disclosed (p=0.08).

Table: 1869P

N=184	Fully concordant, n (%)	Partially concordant, n (%)	Fully discordant, n (%)	Missing, n (%)
Diagnosis	171 (92.9)	N/A	10 (5.4)	3 (1.6)
Treatment Plan	109 (59.2)	75 (40.8)	0 (0.0)	0 (0.0)
Treatment Intent	123 (66.8)	N/A	55 (29.9)	6 (3.3)
Prognosis	110 (59.8)	N/A	65 (35.3)	9 (4.9)

Conclusions: Pt understanding of treatment intent and prognosis after the first medical oncology consultation remain low. Further studies on the effectiveness of consultation aids in this setting are needed.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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1871P The PainRELife ecosystem: A new aid for improving clinical care and shared decision-making in breast cancer patients with chronic pain

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Background: Evidence suggests that introducing *e*Health ecosystems improves the clinical management of chronic pain (CP) in breast cancer patients (BCPs). These tools contribute to overcoming established contextual, social, and individual barriers by monitoring patients' physical health and psychological well-being and early recognizing high-risk patients. Moreover, *e*Health ecosystems increase patient participation in treatment decisions through specific *decision aids* modules, thus enabling shared decisions.

Methods: This pilot study is nested in *PainRELife Project* (ID:1173269). The primary endpoint was investigating patients' usability experience using an *e*Health ecosystem constituted by *Nu Platform* joined with the *PainRELife mobile application*. Twenty-five female BCPs (M_{age}=47, SD=8.41) were enrolled and utilized the mobile application for three months. A set of self-report measures were administered at scheduled time points evaluating the following constructs: physical and mental characteristics; pain experience and intensity; pain self-efficacy; and patients' preferences for participating in clinical decision-making and shared decision-making. The usability was evaluated by means of the Mobile Application Rating Scale (MARS).

Results: A reduction in pain intensity was observed from baseline (M=5) to 3 months (M=3.72), p<.04. The BCPs reported high values in all subscales of the MARS: *engagement* (M=3.31); *functionality* (M=4.14); *aesthetics* (M= 3.98); *quality of the information* (M=4.18); *subjective quality* (M=3.5); *influence to change patient behaviors* (M=4.05). A positive correlation was found between shared decision-making and engagement (r=.445*), quality of the information (r=.427*), and subjective quality attributed to the mobile application (r=.548**).

Conclusions: The *e*Health ecosystems could be valuable *aids* in supporting clinicians and patients to accomplish the physical, social, and psychological challenges associated with the *disease's trajectory*, also improving patients' participation in treatment decisions allowing the implementation into clinical practice of shared decision-making models.

Legal entity responsible for the study: Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology, IRCCS.

Funding: This work is supported by a grant from Regione Lombardia - "PainRELife, Sustainable and integrat-ed big data ecosystem for continuity of care and decision support for patients with pain" (ID: 1173269). The European Institute of Oncology (Istituto Europeo di Oncologia - IEO, Italy) monitors the scientific, legal, and ethical aspects of the study. Participants are recruited at IEO.

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1872P Financial distress of a cancer disease in Germany: A new patient reported outcome measure (PROM) and first results from a bi-centered cross-sectional analysis

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Background: Individual financial distress (FD) of a cancer disease impacts patient's health-related quality of life. FD also occurs in countries with universal healthcare coverage, but comprehensive data about the extent is lacking. We have developed a new standardized PROM for FD in Germany based on qualitative pre-studies (patients/social services representatives) and a literature review. The validity of the

PROM is tested in two survey waves including at least n=400 cancer patients. This study aims to determine the degree of FD in cancer patients using the PROM.

Methods: A bi-centered cross-sectional study was performed including n=112 cancer patients; the PROM was administered between June/ July 2022 in outpatient units, ambulances or oncological wards of two university hospitals in Germany. Patients were eligible if they had confirmed solid cancer (ECOG-Status <2) and had undergone >2 months of therapy. A MANOVA was performed to analyze the dimensions of FD.

Results: 88.3 percent of patients reported higher (non-)medical costs due to cancer disease in the last six month, spending on average 400€ per month. 65.1 percent of patients experienced a loss of income (p<.001), so that the average monthly income changed from 2000-2499€ (M: 4.39; SD: 2.82) to 1500-1999€ (M: 3.17; SD: 2.19). Most patients cope with changes by gaining an overview of their financial situation, being frugal or adopting a relaxed attitude to their financial situation. Perceived FD is mainly attributed to difficulties in maintaining a healthy lifestyle and housing. Female gender, living alone and a low income are significantly associated with higher FD. There are no significant differences in age, education level, occupational status, type of insurance and time since cancer diagnosis.

Conclusions: FD is a common phenomenon that also occurs in countries like Germany. It is driven by rising direct (non-) medical costs and income losses due to diagnosis and treatment. In the next step, we validate the PROM in a second larger sample with n=400 participants and verify our initial findings of FD. There is a need to comprehensively measure FD using a validated PROM to determine the effects on health outcomes and to derive targeted support.

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1873P Patients with myeloproliferative neoplasms and self-care behaviours: Preliminary data of a cross-sectional study

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Background: Patients living with myeloproliferative neoplasms (MPN), including myelofibrosis (MF), polycythaemia vera (PV) and essential thrombocythemia (ET), should engage in self-care behaviours to improve their health. This study aims to preliminary assess self-care behaviours in MPN patients.

Methods: A descriptive cross-sectional study has been conducted in 9 haematology centres in Italy since November 2021. The Italian Association of MPN Patients (AIPAMM) promoted this study. The Self-Care in MyeloProliferative Neoplasms Inventory (SC-MPNI), a 31-item questionnaire measuring self-care behaviours according to the Middle-Range Theory of Self-Care of Chronic Illness, was developed and tested for its content validity. MPN patients were asked to complete a paper-and-pencil questionnaire during their outpatient visit or at home.

Results: Preliminary data from 171 patients (54% male; mean age=58, SD=19) and 5 centres were analysed (45.6% of the expected sample). Participants were living with overt MF (n=51), prefibrotic MF (n=24), PV (n=48) or ET (n=44). Concerning self-care maintenance, the most frequent behaviour was attending all scheduled clinical appointments (M=5.9, SD=0.6), and the least used one was performing activities that improve mental and physical well-being (M=3.1, SD=1.7). Concerning self-care monitoring, the most frequent behaviour was getting blood tests as prescribed by the haematologist (M=5.9, SD=0.5), and the least used one was checking any measurement the healthcare providers recommend (M=4.7, SD=1.4). Concerning self-care management, the most frequent behaviour was accurately reporting symptoms to the healthcare providers during visits to get a comprehensive response (M=5.5, SD=0.9), and the least used one was asking for psychological support to overcome emotional problems (M=2.6, SD=1.5).

Conclusions: This study will contribute to assessing self-care behaviours in patients with MPN. Health professionals should support innovative interventions to promote self-care, which is crucial for MPN patients to reduce cardiovascular events and be medically fit to undergo hematopoietic stem cell transplantation.

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1874P Beliefs about chemotherapy in Tunisian patients newly diagnosed with cancer

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Background: Patients may hold opinions about chemotherapy and cancer that may influence their decisions. We aimed to examine beliefs regarding chemotherapy (CT) and explore associated factors.

Methods: This is a cross-sectional study, conducted between January –April 2023 including 156 patients receiving chemotherapy in a day hospital. A questionnaire adapted from the BMQ (beliefs about medicines questionnaires) was delivered to patients regardless of gender, cancer site or stage, and how are under ongoing CT. We reported demographic and clinical features and beliefs about CT and evaluated correlated factors.

Results: The mean age was 53 years, 79% were female and 60% were treated for breast cancer. Forty-three per cent of patients believed that CT leads automatically to weight loss and 34% to cognitive impairment. The 3 main symptoms that patients feared were alopecia (65%), vomiting (50%) and asthenia (48%) and 40% associated the intensity of side effects to higher levels of efficacy. Patients considered that their life depended on CT in 89%, that without it they will be very sick in 53%, and that it protected their health in 55%. However, 35% were uncertain if CT was addictive, 20% thought there is no drug for CT-induced vomiting, 7% thought it is contagious and 28% believed that some plants may be more effective on cancer. After receiving CT, 60% changed their negative beliefs about it and 89% endorsed the necessity of chemotherapy. Women who were satisfied with the information given by their physicians and those who had a close relative treated with CT had stronger beliefs about the necessity of chemotherapy (p=0,01). However, the advanced-stage, questionnaire before chemotherapy initiation, gender and socioeconomic level did not impact patients' beliefs about CT.

Conclusions: Providing better interpersonal communication with patients may increase patients' belief in chemotherapy. Oncology nurses could help advocate for tailored educational programs to support informed decision-making regarding chemotherapy acceptance.

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1875P Behind the use of ChatGPT for oncological purposes: Fears and challenges

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Background: Technological innovations made rapid progress in the last years and are expected to play a growing role in the decision-making process. ChatGPT, a new chatbot that uses deep learning to mimic human language processing, has increased. In the health domain, ChatGPT could support healthcare delivery thanks to its language models and ability to simulate human conversational manner. Even if the advantages are multiple, there are some psycho-social and ethical aspects related to the implementation of these technologies that remain open.

Methods: This study examines psychological challenges associated with using ChatGPT to clarify its role in screening decisions. Forty-one participants (aged M=29.8) were provided with a scenario describing a hypothetical conversation between ChatGPT and a user who has received an oncological breast or prostate diagnosis report. Successively, each participant answered questions about concerns related to the chatbot, intention to use, decision-making process, and emotional activation.

Results: Descriptive analysis highlighted that 58.5% (n= 24) of participants have already used ChatGPT, but only 0.05% (n= 2) use the chatbot for healthcare purposes. 31.7% (n= 13) of participants reported the absence of fears about using the chatbot for oncological purposes, whereas the remaining 68.3% (n= 28) confirmed the presence of several concerns. Specifically, participants reported concerns about the risks related to data privacy and possible conflict of interest related to developers (n= 2). Other participants described the ChatGPT elaboration processes as a "black box" and highlighted doubts about the correct use of the results (n= 13). Additionally, some participants (n= 8) highlighted the risk that ChatGPT could generate hypochondriacal symptoms and inappropriate healthcare practices. Lastly, participants showed a fear that ChatGPT could replace human doctors in healthcare practice (n=6).

Conclusions: Current results will contribute to understanding the general population's attitude towards ChatGPT and its possible uses in the health domain.

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1876P Cancer stigma: How Tunisian patients perceive their cancer

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Background: Societal beliefs about cancer can impact how patients perceive their disease generating cancer stigma (CS) with risk of emotional distress especially in Arab countries where cancer remains a taboo. This study aimed to evaluate aspects of CS according to Tunisian cancer patients, explore risk factors and describe the impact on mental health.

Methods: The study was a cross-sectional questionnaire-based study, conducted between February and April 2023, including 100 patients treated for cancer regardless of gender, type or stage. We developed the questionnaire by adapting items from the "Cancer stigma scale" using questions grouped in three domains: impossibility of recovery, stereotypes of cancer patients and experience of social discrimination. Depression and anxiety were evaluated by using the "Hospital Anxiety and Depression Scale".

Results: Median age was 50 years old, 75% of patients were women. On average, patients were surveyed 20.48 months after diagnosis. Patients reported at least one form of CS in 57% of cases. They believed in the impossibility of recovery after cancer experience in 47% of cases. Forty percent of patients held stereotypical views of themselves: 48% endorsed that cancer patients would have a difficult time having sexual intimacy which was the item with the highest mean (2.45) among all questions. Thirty four percent of patients reported social discrimination on grounds of cancer: by family/spouse in 31%, at the workplace in 15% and by friends/neighbors in 13% of cases. Cancer stigma was significantly more perceived by patients with low socio-economic status (OR= 3.74 [1.42-9.82]), living in rural areas (OR=26 [3.38-205] and with advanced stage disease (OR=4.2 [1.67-10.5]). Forty percent of patients reported significant depressive symptoms and 47% significant anxiety symptoms. Patients who experienced CS were 4.27 times more likely to have depression ($p < 0.001$) and 3.57 times more probably to be anxious ($p < 0.001$) than patients with positive attitudes.

Conclusions: Despite increased awareness, cancer patients had high levels of CS with negative impact on mental health. These results ring the alarm bell to change societal beliefs and to help patients perceive "better" their disease.

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1877P Meaning-making in the re-entry phase: A qualitative focus group study with patients with breast cancer and melanoma

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Background: After completion of curative cancer treatment patients enter the re-entry phase, which is characterized by the difficult task to pick up life again. In the re-entry patients face existential concerns, besides physical and psychosocial concerns. Finding meaning and purpose in this new situation may help in dealing with existential concerns. More insight is needed in the existential concerns and the meaning-making process in order to support patients in the re-entry phase.

Methods: We conducted 6 focus groups with 16 patients (5 patients with melanoma and 11 with breast cancer) during the re-entry phase, defined as the point from completion of treatment (after surgical treatment and adjuvant systemic treatment, except for hormonal therapy) up to 18 months in remission. A thematic content analysis was performed by two researchers.

Results: In general, patients experienced existential concerns regarding their world-view, inner posture, values and the future. In addition, patients with melanoma struggled with trust and responsibility for their health; patients with breast cancer struggled with relationships and identity. Outcomes of the meaning-making process identified were: meaning is affected and gives distress, existing sources of meaning are helpful, search for meaning or new meaning has been found. These outcomes were found at the beginning as well as further into the re-entry, however during the re-entry the focus of the meaning-making process shifted from the disease to (picking up) life.

Conclusions: The transition from being a patient to picking up daily life in the re-entry phase involves dealing with existential concerns causing distress. Patients use existing sources of meaning, search for new meaning or have found new meaning in order to deal with these existential concerns and distress. A meaning-centered intervention increasing patients awareness of their personal sources of meaning might strengthen their meaning-making process and can help in dealing with existential concerns.

Legal entity responsible for the study: A. Visser and L. Post.

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Disclosure: All authors have declared no conflicts of interest.

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1878P Prevalence of burnout in GU oncologists in central Asia: BUCARE survey

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Background: The growing number of patients with genitourinary cancers (GU) could create an increasing burden on GU oncologists. Bureau for Cancer Research (BUCARE) describes the prevalence of burnout in GU oncologists in Central Asia region.

Methods: This is a cross-sectional survey study conducted among practicing cancer care physicians (surgical, medical, radiation) at the ASCO / Asian American GU Symposium (Almaty, April 2023). The primary outcome was burnout experience assessed through the Maslach Burnout Inventory.

Results: A total of 101 oncologists completed the questionnaire. Table summarizes physician's characteristics. Despite the fact that 100% of responders are interested in their work, 66% (67 of 101) had symptoms of burnout (high emotional exhaustion and/or depersonalization scores). Fifty percent of oncologists are ready to turn to a psychologist for help. Significant drivers of burnout identified in multivariable regression modeling included $^{3}20$ patients per day (odds ratio [OR] = 14.8; $P<0.001$) and $^{3}10$ working hours per day (OR=8.6; $P<0.001$). Male gender (OR=0.14; $P<0.001$) and specialization in radiation therapy (OR=0.20; $P<0.01$) were associated with lower odds of burnout.

Conclusions: More than half of participants met predefined standardized criteria for burnout. Expanding the staff of GU oncologists and reducing the daily workload may improve the emotional state of physicians.

Table: 1878P

Characteristics	N=101
Gender, N (%)	
Female	68 (67.3)
Male	33 (37.7)
Region, N (%)	
Kazakhstan	85 (84.2)
Other countries	17 (16.8)
Specialty, N (%)	
Surgery	39 (38.6)
Medical Oncology	44 (43.6)
Radiation Oncology	18 (17.8)
Department, N (%)	
In-patient	79 (78.2)
Out-patient	22 (21.8)

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Disclosure: All authors have declared no conflicts of interest.

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1879P Investigating the effect of family support on the mental health of patients with breast cancer

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Background: Cancer affects many aspects of life and can have negative consequences such as reduced: health and quality of life and mental disorders. Cancer patients face most of the stressors associated with diagnosis and treatment. The aim of this study is

investigating the effect of family support on the mental health of patients with breast Cancer.

Methods: This cross-sectional study examined 70 breast cancer patients who were referred within 6 months to Imam Khomeini and Shohadah Ha* Tir Hospitals for radiotherapy, chemotherapy or follow- up treatment. In terms of mental health, these patients were assessed using the criteria of hospital anxiety and depression and distress thermometer, and the level of family support using the McMaster Family Assessment Device and attachment style criteria. The psychiatric interview with the patients was conducted by the psychiatric resident and all questionnaires were completed by her in face-to-face interviews or video calls with the patient. Before the start of the study, all patients gave written informed consent. The Family Support Questionnaire contains 60 questions that identify the structural, professional, and interactive characteristics of the family. This questionnaire has 7 subscales.

Results: The mean (standard deviation) of the total score on the Family Support Questionnaire for the subjects studied was 15.7 (2.96) with a range of 9.87 to 21.06. the mean (standard deviation) of anxiety and depression scores were 9.68 (5.34) and 8.34 (4.41), respectively. the results show that increasing the score on anxiety and depression significantly increases family support and its sub-comparisons.

Conclusions: The study revealed that the mean scores of the depression and anxiety in breast cancer patients is more than normal limitation. The results showed that decreasing family support and its sub- comparisons (an increase in the score indicates an unhealthy situation) significantly increases anxiety and depression in these individuals.

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1880P Cancer care: Psychoeducational intervention for first-year residents of a general hospital in northeastern Mexico

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Background: Physicians must help patients to maintain motivation and resolve barriers to adherence to treatment, but this does not happen in many cases. The impact of cancer in the coming years will have devastating consequences for the health system since it is the third cause of mortality in the country. Therefore, a substantial change in medical education, health policies is imperative. They are future specialists, the attitudinal barriers could limit their skills and abilities in the task for general surgeons, gynecologists, otolaryngologists, and anesthetists. To detect and change barriers, implement a strategy of 180 minutes in a reflexive focus group.

Methods: Descriptive, non-blind study approved by the Research Ethics Committee (ON23-00003), informed consent was requested from 51 medical residents of the surgical areas of a general hospital who attended a psychoeducational focus group in 2 frequencies, they answered the survey about their beliefs and attitudes regarding the care of cancer patients. 3 key questions were analyzed to ensure knowledge together with reflection, reinforcing empathic attitudes and team collaboration of the participants.

Results: The subjects correctly considered the definition of oncology pre and post-intervention (84 vs 91%), that the treating physician had to give the diagnosis (55 vs 92%) that there is no correct answer for how long a patient would live (89 vs 96%), The term used by the patient to name the cancer doesn't matter as long as they understand the disease (32 vs 42%), That they should not join the conspiracy of silence proposed by the patient or family (77 vs 91%) If they believed that there is treatment in any stage of cancer (55 vs 87%), if they should care for patients with cancer with a CPR indication vs other chronic patients with hypertensive crisis and DM (64 vs 81%), if they considered palliative care and psycho-oncology for diagnostic phases (63 vs 85%). In the qualitative aspect they left satisfied and mostly looking forward to new sessions that would allow them to carry out their work and education.

Conclusions: There was a percentage impact in generating substantive changes in the opinion of the subjects; this first step should be followed up with more studies and is of relevance to medical educators.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

RENAL CANCER

1881O Safety and efficacy of two doses of belzutifan in patients (pts) with advanced RCC: Results of the randomized phase II LITESPARK-013 study

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Background: In the phase 1 LITESPARK-001 study of the HIF-2α inhibitor belzutifan for ccRCC, the MTD was not reached for dosages up to 240 mg per day, and the RP2D was 120 mg QD based on PD, PK, and safety. The phase 2 LITESPARK-013 study (NCT04489771) examined if a higher belzutifan dose could improve efficacy while maintaining an acceptable safety profile.

Methods: Pts with advanced ccRCC, measurable disease per RECIST v1.1, ≤3 prior systemic regimens for advanced ccRCC including an anti—PD-1/L1 agent, and disease progression during or after an anti—PD-1/L1 agent were randomly assigned 1:1 to belzutifan 120 mg or 200 mg QD. Pts were stratified by IMDC risk score (0 vs 1-2 vs 3-6) and number of prior TKI therapies for advanced ccRCC (0 vs 1 vs 2-3). Primary end point was ORR per RECIST v1.1 by blinded independent central review. Secondary end points included DOR, PFS, OS, safety, and PK. Database cutoff was February 10, 2023.

Results: 154 pts were enrolled (120 mg: n=76; 200 mg: n=78). Baseline characteristics were well balanced between arms. Median follow-up was 20.1 months (range 14.8-28.4). ORR was 23.7% (18 PR) vs 23.1% (4 CR; 14 PR) for the 120 mg and 200 mg arms, respectively (P=0.5312; −0.5% [95% CI, −14.0 to 12.9] using the Miettinen-Nurminen method stratified by IMDC risk). PFS (median 7.3 vs 9.1 months; HR 0.94 [95% CI 0.63-1.40]) and OS (medians not reached; HR 1.11 [95% CI, 0.65-1.90]) did not differ between arms. Median DOR was not reached for the 120 mg arm (range 2.6+ to 16.1+) and was 16.1 mo (2.1+ to 23.5+) for the 200 mg arm; 64.7% and 51.3% of pts had ongoing responses ≥15 mo, respectively. 142 pts had a treatment-related AE (TRAE; 70 [92.1%] with 120 mg; 72 [92.3%] with 200 mg]. 2 pts (2.6%) in the 120 mg arm and 7 (9.0%) in the 200 mg arm discontinued treatment due to a TRAE. Treatment-related anemia (81.6% with 120 mg and 83.3% with 200 mg) and hypoxia (23.7% with 120 mg and 26.9% with 200 mg) was similar between arms.

Conclusions: The efficacy of belzutifan was similar between the RP2D of 120-mg dose and the 200-mg dose and was consistent with prior reports of antitumor activity in ccRCC. Safety at both doses was consistent with the known safety profile of belzutifan. These results further support 120 mg QD as the preferred dose for belzutifan.

Clinical trial identification: NCT04489771.

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1882O RENOTORCH: Toripalimab combined with axitinib versus sunitinib in first-line treatment of advanced renal-cell carcinoma (RCC) - A randomized, open-label, phase III study

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Background: Anti-PD-1 antibody plus antiangiogenic therapy can play a synergistic antitumor role in the treatment of advanced renal cancer. Toripalimab is a humanized monoclonal antibody against PD-1. Here, we report the results of a randomized, open label, phase 3 trial (NCT04394975) comparing toripalimab plus axitinib with sunitinib as first-line treatment for advanced RCC patients (pts).

Methods: Eligible pts had untreated unresectable or metastatic clear cell RCC and were intermediate or poor risk per International Metastatic Renal Cell Carcinoma Database Consortium criteria. Pts were randomized in a 1:1 ratio to receive toripalimab (240mg) intravenously once every 3 weeks plus axitinib (5mg) orally twice daily or sunitinib (50mg) orally once daily for 4 weeks (6-week cycle) or 2 weeks (3-week cycle). The primary endpoint was progression-free survival (PFS) assessed by the blinded independent central review per RECIST version 1.1.

Results: A total of 421 pts were randomized: 210 to the toripalimab plus axitinib arm and 211 to the sunitinib arm. After a median follow-up of 14.6 months, a significant

improvement in median PFS was detected for the toripalimab plus axitinib arm compared to the sunitinib arm (18.0 vs. 9.8 months, HR = 0.66 [95% CI: 0.49-0.87], P = 0.0034). The 1-year PFS rates were 62.5% and 45.4%, respectively. The objective response rate (ORR) was 56.7% (95% CI: 49.7-63.5) for the toripalimab plus axitinib arm versus 30.8% (95% CI: 24.6-37.5) for the sunitinib arm (P < 0.0001). The median overall survival was not reached in the toripalimab plus axitinib arm and 26.8 months in the sunitinib arm (HR = 0.61 [95% CI: 0.40-0.92], P = 0.0186). The incidence of Grade ≥ 3 adverse events (AEs) (71.2% vs 67.1%), AEs leading to discontinuation of treatment (14.4% vs 8.1%), and fatal AEs (1.0% vs 1.0%) were similar between two arms.

Conclusions: Among patients with previously untreated advanced RCC, treatment with toripalimab plus axitinib resulted in significantly longer PFS, as well as a higher ORR, than treatment with sunitinib. These results support the use of toripalimab with axitinib as a first-line treatment for advanced RCC.

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1883MO MEDI5752 (volrustomig), a novel PD-1/CTLA-4 bispecific antibody, in the first-line (1L) treatment of 65 patients (pts) with advanced clear cell renal cell carcinoma (aRCC)

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Background: PD-1/CTLA-4 inhibition has improved survival in aRCC but maximizing the potential benefit of CTLA-4 inhibition is limited by toxicity. MEDI5752 (volrustomig) is designed to fully inhibit PD-1 while preferentially inhibiting CTLA-4 on activated PD-1+ T cells. This first-time-in-human trial showed encouraging activity with volrustomig 1500 mg in 1L aRCC. We present data from the 750 mg and 500 mg cohorts (M750 and M500).

Methods: Treatment-naïve pts with aRCC received M750 mg or M500 mg every 3 weeks until disease progression or unacceptable toxicity. The primary objective was objective response rate (ORR).

Results: In M750 (n=32)/M500 (n=33), 75.0/63.6% had IMDC I/P risk. Median duration of follow-up in M750/M500 was 15.9 (range, 2.2-20.4)/8.6 (1.6-14.7) months. ORR was similar in M750/M500 (46.9%/45.5%), with higher CR rate/DCR and longer mPFS in M750 (Table). The median duration of response (DOR) was 13.2/8.4 months; mDOR in pts who discontinued due to AE was not reached in M750. Grade 3-4 immune-related adverse events (irAEs) were higher at M750 (46.9% vs 24.2%), although nearly half of events did not require steroids and nearly all non-endocrine irAEs resolved. There was increased T cell proliferation at both doses and greater T cell activation in M750 vs M500.

Conclusions: Volrustomig is a novel bispecific antibody with high degree of efficacy in 1L aRCC and across IMDC risk groups, with a low rate of upfront treatment failure. The safety profile is consistent with dual checkpoint inhibition. Volrustomig with lenvatinib is also being evaluated in 1L aRCC (NCT04522323).

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Table: 1883MO

Efficacy DCO 25Jan2023	M750			M500		
	Total	IMDC		Total	IMDC	
		F	I/P		F	I/P
Response-evaluable, N	32	8	24	33	12	21
ORR, n (%)	15 (46.9)	2 (25)	13 (54.2)	15 (45.5)	7 (58.3)	8 (38.1)
CR, n (%)	3 (9.4)	1 (12.5)	2 (8.3)	2 (6.1)	2 (16.7)	0 (0)
DCR, n (%)	28 (87.5)	6 (75)	22 (91.7)	23 (69.7)	11 (91.7)	12 (57.1)
Progressive disease, n (%)	4 (12.5)	–	–	8 (24.2)	–	–
mPFS (95% CI), months	11.1 (4.5–NE)	–	–	9.9 (3.9–NE)	–	–

Per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. CI, confidence interval; CR, complete response; DCR, disease control rate; F, favorable; IMDC, International Metastatic RCC Database Consortium; I/P, intermediate/poor; mPFS, median progression free survival; NE, not estimable.

1884MO Phase II study of avelumab (Ave) plus intermittent axitinib (Axi) in previously untreated patients (pts) with metastatic renal cell carcinoma (mRCC): The TIDE-A study

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Background: Combinations (combos) of VEGFR-TKI plus anti-PD1/L1 immunotherapy (IO) are the standard of care for first-line therapy of mRCC pts due to increased response rate, prolonged progression-free (PFS) and overall (OS) survivals compared to TKI alone. It is well recognized that the majority of toxicities of the combos are due to the TKI.

Methods: mRCC pts with prior nephrectomy, and with no symptomatic/bulky disease nor liver mets, were treated with Ave 800 mg flat dose IV Q2W + Axi 5 mg PO BID for 36 weeks (W). At W36, pts who achieved RECIST partial response (PR) discontinued Axi and continued Ave until disease progression (PD) or unacceptable toxicity. In case of PD, they re-started Axi for 24W and discontinued it again in case of new PR while continuing Ave. Pts with stable disease at 36W continued the combo until PD or unacceptable toxicity. Primary endpoint: rate of pts free of progression (FoP) after 8W from Axi discontinuation ($\geq$48%). Secondary endpoints: median PFS, objective response rate (ORR) and safety. 75 pts have been planned to be enrolled.

Results: 79 pts were enrolled and 75 evaluated for efficacy (IMDC risk: 40.0% favorable, 57.3% intermediate, 2.7% poor). A total of 29 (38.2%) pts discontinued Axi at 36W; the rate of pts FoP after 8W was 72.4%. With a median follow-up of 19.3 mos, the mPFS was 23.8 mos (95%CI, NR-NR) with 70% of pts FoP at 18 mos; mOS was not reached. The ORR was 76.0% (12.0% CR, 64.0% PR); 18.7% had SD and 4.0% had PD. The median duration of first Axi discontinuation was 16.0 weeks (95%CI, 10.9 − 21.1). Among the 29 pts who discontinued Axi, 9 were still ongoing, 20 had PD and 19 restarted Axi (9 ongoing, 6 had further PD, 4 discontinued Axi again). Safety: 96.2% of pts had at least one adverse event (AE) and 40.5% had G3-G4 AEs with no treatment-related death. All-grades and G3-G4 axitinib-related AEs were reported in 34.2% and 11.4% of overall pts, respectively, and in 10.3% and 0% of those who discontinued Axi.

Conclusions: The TIDE-A study shows that TKI discontinuation is safe for selected mRCC pts with evidence of response to TKI+IO combos in first line. Axi discontinuation allows decreasing of toxicity, while maintaining the possibility of Axi benefit in case of its reintroduction.

Clinical trial identification: NCT04698213.

Legal entity responsible for the study: Consorzio Oncotech (info@oncotech.org).

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1885P Pexa-vec (thymidine kinase-deactivated vaccinia virus plus GM-CSF) in combination with cemiplimab (REGN2810; ANTI-PD-1) for metastatic or unresectable renal cell carcinoma REN026: Results from a phase II study

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Background: Pexa-vec (PV) is an oncolytic and immunotherapeutic vaccinia virus engineered to express GM-CSF. The REN026 study assessed the antitumor activity and safety of intravenous (IV) or intratumoral(IT) PV in combination with cemiplimab (REGN2810, anti-PD-1 inhibitor) in patients with metastatic or unresectable renal cell carcinoma (RCC).

Methods: The study enrolled 89 patients with measurable histologically or cytologically confirmed metastatic or unresectable RCC, randomly assigned to one of four study arms. Patients who were treatment-naive to immune check point inhibitors (ICIs) with accessible tumors were randomized into Arm A (IT PV and cemiplimab) or Arm B (cemiplimab monotherapy, upon disease progression PV (IT) was added. Patients who were treatment-naïve to ICIs with non-accessible tumors were assigned to Arm C with IV PV, and those with prior treatment with ICIs were assigned to Arm D with IV PV. PV was given IT (Arms A and B) administered every 2 weeks or IV (Arms C and D) weekly for 3 or 4 treatments as 1×10^9 pfu. Cemiplimab IV infusion (all arms) was administered every 3 weeks, at a dose of 350 mg.

Results: Between June 2018 and October 2022, 89 patients were assigned to the study arms as follows: 15 in Arm A, 16 in Arm B, 30 in Arm C, and 28 in Arm D. The median number of prior systemic regimens in the metastatic setting was 1 (0-4) in Arms A, B, and C and 3 (1-5) in Arm D. With the median follow-up of 22.2 months, efficacy outcomes are shown in table. The most common treatment-related adverse event was pyrexia, with a Grade $\geq$ 3 of 13.3% in Arm A, 0% in Arm B,0% in Arm C, and 3.6% in Arm D. No Grade 5 events occurred in any of the study arms.

Table: 1885P Summary of efficacy results

	A (n=15)	B (n=16)	C (n=30)	D (n=28)
	IT		IV	
ORR (95% CI)-%	13.3 (1.7-40.5)	12.5 (1.6-38.4)	23.3 (9.9-42.3)	17.9 (6.1-36.9)
DCR (95% CI)-%	60.0 (32.3-83.7)	56.2 (29.9-80.3)	60.0 (40.6-77.3)	67.9 (47.7-84.1)
PFS median (mo) (80% CI)	4.3 (3.3-6.3)	5.6 (2.1-NA)	4.8 (4.4-8.3)	6.4 (3.6-12.3)
OS median (mo) (80% CI)	22.0 (22.0-NE)	20.8 (19.5-NE)	25.1 (22.7-NE)	18.5 (14.8-NE)
Median duration of response (range,months)	6.1 (3.7-8.5)	7.7 (4.1-11.3)	10.4 (5.5-24.1)	8.5 (1.1-11.3)

Conclusions: The combination immunotherapy of IV PV and cemiplimab demonstrated an acceptable safety profile and encouraging efficacy of ORR and survival with durable responses in patients with metastatic or unresectable RCC, regardless of previous ICI treatment.

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1886P Pembrolizumab and denosumab in clear cell renal cell carcinoma (ccRCC): A phase II trial (KeyPAD, ANZUP1601)

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Background: Anti-PD1 immune checkpoint inhibitors (ICI) are effective in some people with ccRCC. Preliminary data suggest inhibition of Receptor Activator of Nuclear Factor κB Ligand (RANKL) signaling may potentiate ICI. We evaluated the activity and safety of the RANKL-inhibitor denosumab (D) with pembrolizumab (P) in people with pretreated advanced ccRCC.

Methods: This single arm, multi-centre, phase 2 trial recruited participants (pts) with metastatic or unresectable ccRCC, progressing on or after vascular endothelial growth factor receptor inhibitors (VEGFi), and no prior treatment with an ICI or D. Study treatment was P 200mg IV q3w plus D 120mg SC on days 1, 8 and 22, then q3w until disease progression, unacceptable toxicity, or a maximum of 24 months. The primary endpoint was objective tumour response (OTR) per RECIST 1.1. Secondary objectives included median progression free survival (PFS), PFS at 6 months (PFS6), duration of response (DOR), and adverse events (AE). Biospecimens were collected for future correlative studies of immune and RANKL signaling.

Results: We recruited 59 of a planned 70 pts from Dec 2017 — Jul 2022; accrual was impacted by COVID-19. Pts were typical of this population; mostly male (81%), 48% International Metastatic Database Consortium favorable risk, one prior VEGFI in all pts, two or more prior agents in 16%. With median follow-up of 40 months in 58 evaluable pts, an OTR was documented in 31% (all partial; 95%CI 20-45%). Median DOR was 17 months. 53% of pts experienced PFS6 (95%CI, 39-65%), with mPFS 7.5 months. Immune related grade 3+ AE were reported in 20% of pts; study treatment discontinued for toxicity in 22%. One pt suffered G3 osteonecrosis of the jaw, one G3 hypocalcaemia. One pt died of myositis attributed to study treatment.

Conclusions: Compared to studies of anti-PD1 ICI in ccRCC progressing after VEGFi (Table), KeyPAD shows encouraging activity without overlapping toxicity, warranting further studies combining RANKL inhibitors like D with ICI like P.

Table: 1886P

Prior clinical trial	OTRR (%)	mPFS (months)	PFS6 (%)
KeyPAD	31	7.5	53
Checkmate-025	25	4.6	38
NIVOREN	21	3.7	35
TITAN	17	3.7	38
NORA	20	5.3	46
NCT01354431 0.3mg/kg	20	2.7	30
NCT01354431 2mg/kg	22	4.0	30
NCT01354431 10mg/kg	20	4.2	40
NIVES	17	5.6	42
MEDI0680	24	3.6	36
WITNESS	28	5.3	44

Clinical trial identification: NCT03280667.

Legal entity responsible for the study: ANZUP Cancer Trials Group.

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1887P Adjuvant everolimus (EVE) in patients (pts) with completely resected very high-risk renal cell cancer (RCC) and clear cell histology: Results from the phase III SWOG S0931 (EVEREST) trial

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Background: EVEREST is a ph3 trial of pts with either clear or non-clear cell RCC at intermediate-high or very-high risk for recurrence after nephrectomy, randomized to receive adjuvant EVE 10 mg QD or placebo x 54 wks. Longer recurrence free survival (RFS) for EVE [HR 0.85; 95%CI, 0.72-1.0; P= 0.051] was seen but the nominal significance level (p=0.044) was narrowly missed (Ryan, ASCO22). Placebo-controlled ph3 trials of sunitinib (STRAC) & pembrolizumab (KN546) limited entry to clear cell subtype and reported modest benefits in disease-free survival (DFS) despite other trials of in-class agents reporting no such benefit. Differences in pt recurrence risk have been suggested as a possible factor for the conflicting results. Here we report the results of an analysis of a very high-risk cohort of pts with clear cell in EVEREST.

Methods: Post-nephrectomy RCC pts w/ any clear cell component & very high-risk disease, defined as pT3a (gr 3-4), or pT3b-c (any gr), or T4 (any gr), or node-positive (N+), were identified. Pt characteristics, treatment, and adverse event (AE) data were summarized. A Cox regression model stratified by performance status was used to evaluate RFS & OS.

Results: Of 1,499 pts, 717 had both clear cell & very high-risk disease. 699 were eligible: 348 EVE; 351 placebo. Only 163/348 (47%) of EVE pts completed all treatment as planned while more pts completed planned treatment with placebo [225/351 (64%)]. Grade 3+ AEs were more frequent with EVE (42%) vs placebo (8%). Adjuvant EVE resulted in significant RFS improvement in ITT and per-protocol cohorts.

Table: 1887P

Outcome	Hazard Ratio for EVE vs Placebo (95% CI)	5-year Kaplan-Meier estimates: EVE vs Placebo	2-sided p-value
RFS, Intent to Treat (n=699)	0.80 (0.65, 0.99)	57 vs. 50%	0.040
RPS, Per Protocol* (n=685)	0.80 (0.65, 0.99)	57 vs. 50%	0.040
OS, Intent to Treat (n=699)	0.85 (0.64, 1.14)	85 vs. 81%	0.28

*per-protocol: all pts who received any of their protocol-assigned treatment

Conclusions: EVEREST remains the only phase III adjuvant RCC trial of an mTOR inhibitor. In pts with clear cell RCC at very high-risk for recurrence, adjuvant EVE was associated with significantly improved RFS vs. placebo in a subset of pts comparable to those in STRAC and KN546. These results can inform the design & development of future adjuvant trials in high-risk RCC.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Other, Employee at DFCI. Please see https://www.dana-farber.org/ for mission statement (non-profit hospital). I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Other, Professor at HMS, please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, Other, No financial interest. Institutional. Filed patents related to biomarkers of immune checkpoint blockers and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. N. Agarwal: Financial Interests, Personal, Advisory Board, In the last two calendar years, I participated in the scientific advisory board of these pharma companies between February 2021 to April 2021. None after that: Merck, Aveo, Gilead, Lilly, Exelixis, Foundation Medicine; Financial Interests, Invited Speaker, I am involved in the following phase 3 trials as the trial co-chair: TALAPRO-2, TALAPRO-3 (both Pfizer), and CONTACT-2 (Exelxis): Pfizer, Exelixis; Financial Interests, Institutional, Other, I serve in the leadership of my cancer center (Huntsman Cancer Institute, University of Utah. Salt Lake City, UT, USA). There are multiple research projects sponsored by these companies which pay money to my institution: Arnivas, Astellas, AstraZeneca, Bavarian Nordic, Bayer, BMS, Calithera, Celldex, Crispr, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, GSK, Immunomedics, Janssen, Lava, Medivation, Merck, Nektar, Neoleukin, New Link Genetics, Novartis, Oric, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon.; Financial Interests, Invited Speaker, I am involved in the steering committee of the trials sponsored by these pharmas with no personal honorarium: AstraZeneca, Calithera, Clovis, Crispr, Eisai, Eli Lilly, Exelixis, Immunomedics, Janssen; Financial Interests, Invited Speaker, I am involved in the steering committee of the trials sponsored by these pharma companies with no personal honorarium: Merck, Nektar, New Link Genetics, Oric, Pfizer, Prometheus, Rexahn, Takeda, and Tracon. R. Uzzo: Financial Interests, Personal and Institutional, Advisory Role: Merck, Pfizer. U.N. Vaishampayan: Financial Interests, Personal and Institutional, Research Grant: BMS, Merck; Financial Interests, Personal, Advisory Role: Alkermes, Bayer, Gilead, Exelixis, Sanofi, Merck, Pfizer; Financial Interests, Personal, Invited Speaker: Bayer, Exelixis, Sanofi. All other authors have declared no conflicts of interest.

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1888P 24-month follow up of durvalumab and savolitinib combination in MET-driven clear cell and non-clear cell renal cancer

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Background: The CALYPSO trial (NCT02819596) showed promising response rates (RR) for the combination of durvalumab (D) (PD-L1 inhibitor) and savolitinib (S) (MET inhibitor) in MET-driven tumours in papillary renal cancer (PRC). Response data for the combination in other settings such as clear cell (ccRCC) and non-MET driven tumours was less impressive (Suárez et al, JCO, 2023). Here we give the updated 24-month efficacy analysis.

Methods: This study included a ccRCC and PRC cohort, both of which have been presented previously with shorter follow up. The ccRCC cohort was a randomised phase II study comparing DS combination with D alone, in previously treated ccRCC. The PRC cohort was a single arm study of DS in treatment naïve or pre-treated patients. RR (confirmed, RECIST 1.1), progression-free survival (PFS) and overall survival (OS) were the efficacy endpoints. DNA alterations were measured using Foundation One analysis.

Results: At 24 months follow-up, the RR in the ITT PRC population (n=41) was 29% (95% CI, 16-46) and 53% (95% CI, 28-77) in MET-driven patients (n=17). The median PFS was 5.8 months (95% CI, 2.9 -12.3) in the ITT population and 15.7 months (95% CI, 3.0 - 27.4) in MET-driven patients. The median OS was 14.1 months (95% CI, 7.3 - 30.7) in the ITT population and 27.4 months (95% CI, 9.3 — 34.7) in MET-driven patients. The hazard ratio (HR) for PFS in MET-driven vs non MET-driven in PRC cohort is 0.43 (95% CI, 0.20-0.93, p=0.03). In the ccRCC cohort, 39 patients received DS combination and 39 D alone. RR for DS was 13% vs 10% for D alone. The HR for PFS was 1.38 (95% CI, 0.5-1.2, p= 0.2) and HR for OS was 1.5 (95% CI, 0.9-2.6, p= 0.1). Median OS was 21.9 months (95% CI, 18.0-26.7) for all ccRCC patients and 8.2 months (3.7- 26.7) for MET-driven patients (n=17). No new safety signals were seen.

Conclusions: Durvalumab and savolitinib combination has activity in MET-driven PRC, supporting the ongoing SAMETA trial (NCT05043090). Savolitinib does not appear to improve efficacy of durvalumab in clear cell tumours.

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Legal entity responsible for the study: Queen Mary University of London.

Funding: AstraZeneca.

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1889P Phase Ib/II study of batiraxcept (BT, AVB-S6-500, an AXL pathway inhibitor) in combination with cabozantinib (cabo) in patients with advanced clear cell renal cell carcinoma (ccRCC) who failed first-line (1L) therapy

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Background: BT is a recombinant fusion protein containing an extracellular region of AXL combined with human immunoglobulin G1 heavy chain (Fc), demonstrating potent and specific AXL inhibition through competitive binding of its ligand GAS6. In a prior phase (P)1 study, BT RP2D was identified as 15 mg/kg IV every 2 weeks (q2w) in combination with cabo 60 mg oral daily (QD).

Methods: P1b and P2 data was analyzed for BT 15 mg/kg (n=41), 20 mg/kg (n=10), q2w + cabo 60 mg QD in advanced ccRCC pts who received at least 1 prior systemic therapy. Primary endpoint was investigator-assessed objective response rate (ORR) by RECIST v1.1; key secondary endpoints were safety, progression free survival (PFS), and overall survival.

Results: As of April 21, 2023, 51 pts received at least one dose of BT with cabo with median (m) follow-up of 11.4 months (mo) (range 3.7-23.7). All pts had received prior immune-oncology therapy (IO). 51% of pts had prior VEGF-tyrosine kinase inhibitor (TKI). The ORR for the entire cohort and prior-VEGF-TKI pts was 43.1% and 53.8%, receptively. The mPFS for the entire cohort and prior-VEFG-TKI pts was 9.2 and 11.4 mo, respectively. Table presents results.

Table: 1889P

	Batiraxcept + Cabo N=51 (%)	Prior VEGF-TKI	
		Yes N=26 (%)	No N=25 (%)
Median age (range)	62 (40-81)	61 (40-76)	62 (42-81)
Sex (male)	36 (71)	18 (69)	18 (72)
IMDC Intermediate/poor risk	40 (79)	20 (77)	20 (80)
1, 2, 3+ Prior lines of therapy	27 (53), 12 (24), 12 (24)	6 (23), 8 (31), 12 (46)	21 (84), 4 (16), 0
ORR (CR + PR), n [95% CI]	22 (43.1) [29.3, 57.8]	14 (53.8) [33.4, 73.4]	8 (32.0) [14.9, 53.5]
mPFS mo [95% CI] Censor (n), Events (n)	9.2 [7.29, 11.4] 21, 30	11.4 [7.16, 16.76] 12, 14	9.2 [6.44, 9.33] 9, 16
BT related AEs, n*	43 (84)	23 (89)	20 (80)
Grade ≥ 3 BT related AEs, n	13 (26)	8 (31)	5 (20)

*BT related AE in ≥ 20%: diarrhea (31%), fatigue (31%), and infusion-related reactions (IRR) (24%) with 10% discontinuing BT. Cabo dose reduced in 45% and discontinued in 16% pts.

Conclusions: BT + cabo demonstrated acceptable tolerability and promising efficacy in treatment-refractory ccRCC pts. BT + cabo will be further studied in a P3 trial of 2L+ ccRCC patients whose disease has progressed following IO and VEGF-TKI therapies.

Clinical trial identification: NCT04300140.

Legal entity responsible for the study: Aravive, Inc.

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1890P Switch-maintenance therapy with nivolumab in TKI-sensitive patients with metastatic renal cell carcinoma (mRCC): Subgroup analysis for PD-L1 status of a randomized phase II study (NIVOSWITCH)

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Background: In mRCC patients combinations of tyrosine kinase inhibitors (TKI) and checkpoint inhibitors (CPI) are standards of care. We previously reported on our switch-maintenance approach (CPI after TKI) in mRCC. Today, we report on exploratory analyses that investigated predictive value of the PD-L1 status.

Methods: Pts. with measurable clear cell mRCC, ECOG 0-2, adequate organ function and partial remission or stable disease to TKI therapy were eligible. 49 patients were randomized to early study termination between 12/2016 and 08/2018. After 12 weeks, 1:1 randomization to TKI continuation (24 pts.) or nivolumab (NIVO; 25 pts.; 240 or 480 mg IV q2-4wk) was performed. PD-L1 expression was determined by immunohistochemistry using the SP163 antibody clone and defined as combined positivity score (CPS) with setting 1 as cut-point for positivity (n=41). Objective response rate (ORR) was assessed according to RECIST 1.1. KM and log-Rank analyses were used for survival analyses.

Results: Median age was 65 years (range 35 - 79), 82% were male and 4% had ECOG PS 2. With metastases predominantly in lung (47%), lymph nodes (27%) and liver (24%). 55% received sunitinib. ORR for NIVO vs. TKI differed when assessed from randomization (16 vs. 48%; P=0.03). Accordingly, progression free survival (PFS) from randomization was 3.0 vs. 11.9 mo. (HR = 2.57 [95% CI: 1.36 − 4.89]) in favor for TKI continuation. With a 2-year OS of 64% for NIVO vs. 66% for TKI (HR = 1.12 [95% CI: 0.43 − 2.89]; P=0.82). ORR in CPS<1 vs >1 RCC was 13.3% and 40.0% for NIVO and 37.5% and 75.0% in TKI cases. Tumors with a CPS<1 most frequently showed PD as the best response in both arms. However, a greater proportion of patients reported PD for NIVO (n=9, 60.0%) compared to TKI (n=1, 12.5%).

Conclusions: Continuation of TKI is more efficacious than early switch to NIVO, despite PD-L1 positivity. The major limitation of our trial is the premature closure and its limited sample size. Authoring Group Name: IAG-N of the German Cancer Society Sponsor, funding source: AIO-Studien-gGmbH, financial support BMS

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1891P Determinants of exceptional response to immune checkpoint inhibition in metastatic clear cell renal cell carcinoma

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Background: In a subset of patients (pts), immune checkpoint inhibitors (ICIs) hold the potential to achieve lasting and sustainable responses, or even complete recoveries in pts with clear cell renal cell carcinoma (ccRCC). We sought to understand the immunogenomic determinants of these exceptional responses to ICIs.

Methods: We analyzed pre-therapy genomic and transcriptomic data in treatment-naive metastatic ccRCC pts treated with standard-of-care immunotherapies: (1) combination of PD-1/PDL1 and CTLA-4 (IO/IO), or (2) PD-1/PD-L1 inhibitor and VEGF-receptor (IO/VEGF) combination. We also compared baseline characteristics and outcomes between these cohorts and the International Metastatic RCC Database Consortium (IMDC) dataset. We defined 3 groups of pts in each cohort: (a) extreme responders (ER): pts with complete response (CR) and progression free survival (PFS) $\geq$ 12 months or partial response (PR) with tumor shrinkage 50% and PFS $\geq$ 24 months or PR with PFS $\geq$ 36 months; (b) intermediate responders, pts with CR and PR who were not exceptional responders (IR); (c) pts with progressive disease (PD).

Results: 550 pts on IO/IO had available whole exome sequencing (WES) data while 434 pts in the IO/VEGF cohort had available WES and RNA-sequencing data. A greater proportion of pts from clinical trials had ER (25%) when compared to real-world data (6%) in the IO/IO cohort. Neither tumor mutation burden, mean HLA-I evolutionary divergence, whole genome integrity index, tumor purity nor tumor ploidy were associated with ER in the trial cohorts. In the IO/IO cohort, clonal neoantigen load (CNL) was significantly higher in ER pts (vs. IR: p=0.043; vs. PD: p=0.017). In a multivariate Cox regression, only CNL remained associated with improved PFS (p = 0.007). In the IO/VEGF cohort, ER pts had high expression of signatures for plasma cells, memory B-cell inside, and tertiary lymphoid structures (TLS). Pts with ER had higher TLS signature score compared to IR and PD using 3 different gene expression signatures.

Conclusions: Our results suggest that ER is partly mediated by clonal neoantigen-driven cytotoxic T-cell responses and TLS formation in the tumor microenvironment.

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1892P A pooled meta-analysis of salvage nivolumab/ipilimumab (N+I) after nivolumab (N) in patients with advanced renal cell carcinoma (RCC)

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Background: N+I has demonstrated improved survival for patients with treatment-naïve advanced clear cell RCC. A series of phase 2 trials (OMNIVORE NCT03203473; HCRN GU16-260 NCT03117309; TITAN-RCC NCT02917772) evaluated N+I in patients lacking an objective response to N. We performed a pooled meta-analysis of these studies to better inform the activity of N+I after N.

Methods: Key baseline characteristics and outcomes were collected and analyzed centrally. The primary endpoint was confirmed objective response rate (ORR) to N+I as defined by investigator assessed RECIST v.1. Secondary endpoints included ORR to N, progression-free survival (PFS) rate from N+I start (only for OMNIVORE and HCRN GU-16-260), and overall survival (OS) rate from N start.

Results: The analysis included 448 patients of whom 410 (91.5%) had clear cell RCC, 369 (82.3%) had IMDC intermediate/poor risk disease, and 139 (31.0%) had prior treatment. The 16-18-week ORR to N prior to N+I was 21.9% (n=98) and best ORR to N was 24.1% (n=108). 249 (55.6%) patients treated with N received N+I at a median of 16 weeks (9-21 IQR) after initiation of N [26.1% (n=65) with stable disease (SD) to N and 73.9% (n=184) with progressive disease (PD) to N]. The ORR to N+I was 12.9% (n=32) (Table). Median follow-up was 34.2 months. 6-month PFS on N+I was 39% (95% CI 30-49). 3-year OS was 57% (95% CI 52-62) from N start.

Table: 1892P ORR to N+I

Subgroup	N	ORR (%)
Overall	249	12.9
Treatment naïve	145	12.4
Prior therapy	104	13.5
IMDC Favorable	39	15.4
IMDC Intermediate	169	14.2
IMDC Poor	41	4.9
Clear cell RCC	230	12.6
Non-clear cell RCC	19	15.8
Response to N at N+I Start — SD	65	9.2
Response to N at N+I Start — PD	184	14.1
Best response to N — CR/PR	24	25.0
Best response to N — Non-response	225	11.6

Conclusions: A small subset of patients lacking a response to N monotherapy derive benefit from salvage N+I. Additional correlative studies are warranted to investigate markers associated with benefit to N+I post N.

Clinical trial identification: NCT03203473, NCT03117309, NCT02917772.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Other, Employee at DFCI. Please see https://www.dana-farber.org/ for mission statement (non-profit hospital). I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Other, Professor at HMS, please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, Other, No financial interest. Institutional. Filed patents related to biomarkers of immune checkpoint blockers and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. All other authors have declared no conflicts of interest.

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1893P Immune-related adverse events from contemporary first-line combination therapies in metastatic renal cell carcinoma: Results from the IMDC

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Background: A favourable relationship between immune related adverse events (irAEs) and survival has been established across tumours. However, for patients with metastatic renal cell carcinoma (mRCC) treated with Immuno-oncology (IO) based combination first-line therapies, the prognostic impact of irAEs remains uncertain.

Methods: To examine the association between irAEs and survival among first-line ipilimumab-nivolumab (IOIO) or anti-PD-1/PD-L1 + vascular endothelial growth factor receptor inhibitors (IOVE), we used an IMDC dataset, a large multicenter international cohort study. Only clinically impactful irAEs (requiring systemic steroids or IO treatment delay), were included. To minimize immortal time bias, only patients surviving longer than 3 months were included in the survival analysis.

Results: 328/1448 (22.7%) patients developed an irAE. As per table, patients that developed an irAE had a similar median age and BMI, were more likely to have pre-existing auto-immune co-morbidities, improved IMDC risk and clear cell histology. Frequency of irAEs were similar in patients treated with IOIO and IOVE (23.2% vs 21.2% respectively p=0.40). Cytoreductive nephrectomy (OR 1.69 95% CI 1.16 — 2.47 p=0.006) and non-sarcomatoid histology (OR 1.98 95% CI 1.26 — 3.12 p=0.003) were more likely to be associated with an increased odds of developing irAEs. Development of an irAE was associated with a longer overall survival, median not estimable [95% CI 44.5 — not estimable] vs 47.2 months [95% CI 40.7 — 53.4] logrank p = 0.005). A favourable independent association of irAEs with overall survival was found in multivariable analysis, after IMDC risk factor adjustment (HR 0.68 [95% CI 0.52 — 0.89] p=0.006).

Table: 1893P

Characteristic	IRAE		*P*
	No	Yes	
Median Age (IQR)	63.0 (55.8 - 70.0)	64.4 (58.6 - 69.8)	
Median BMI (IQR)	27.1 (23.8 - 31.0)	28.1 (24.3 - 31.5)	
ECOG			*0.002*
0	553/748 (73.9%)	195/748 (26.1%)	
1	405/494 (82.0%)	89/494 (18.0%)	
2	51/75 (68%)	24/75 (32%)	
3	13/16 (81.3%)	3/16 (18.8%)	
Autoimmune Condition			*0.01*
Yes	14/25 (56%)	11/25 (44%)	
No	1106/1423 (77.7%)	317/1423 (22.3%)	
IMDC			*0.03*
Fav	152/200 (76%)	48/200 (24.0%)	
Int	493/671 (73.5%)	178/671 (26.5%)	
Poor	295/365 (80.8%)	70/365 (19.2%)	
Sarcomatoid			0.004
Yes	156/192 (81.3%)	36/192 (18.9%)	
No	534/572 (71.0%)	218/572 (29.0%)	
1L IO Combination			0.4
IOIO	786/1024 (76.8%)	238/1024 (23.2%)	
IOVE	334/424 (77.8%)	90/424 (21.2%)	

Conclusions: Development of an irAE is a potential treatment biomarker of improved outcome for patients treated with first-line IO combination therapy in mRCC. Patients with pre-existing auto-immune co-morbidities at baseline have a high incidence of irAEs.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Other, Employee at DFCI. Please see https://www.dana-farber.org/ for mission statement (non-profit hospital). I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Other, Professor at HMS, please see https://hms.harvard.edu/ for mission statement (non-profit school): Harvard Medical School (HMS); Other, Other, No financial interest. Institutional.Filed patents related to biomarkers of immune checkpoint blockers and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. All other authors have declared no conflicts of interest.

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1894P Termination of renal cell carcinoma clinical trials: Reasons and future recommendations

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Late withdrawal

1895P Time to treatment failure (TTF) and treatment beyond progression (TBP) in pretreated metastatic renal cell carcinoma (mRCC) patients (pts) receiving nivolumab: A survival outcome and a therapeutic strategy of clinical benefit (meet-uro 15)

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Background: Immunotherapy is associated with different response patterns compared with chemotherapy and targeted therapy, including delayed response and stabilization after disease progression. In clinical practice, immunotherapy can be continued after radiological progression when clinical benefit is observed. Therefore, progression-free survival (PFS), calculated with the first disease progression, may not express the real benefit derived from immunotherapy.

Methods: The Meet-URO 15 study was a multicentric retrospective analysis on 571 pretreated mRCC pts receiving nivolumab. TTF was defined as the time from start of therapy to the definitive disease progression which changed the therapeutic line or death. The comparison between TTF and PFS and the prognostic performance of the Meet-URO score versus (vs) the IMDC score according to TTF and PFS were assessed. Moreover, response and survival outcomes between TBP pts and non-TBP pts were evaluated.

Results: 571 pts were included in the analyses (PMID: 34046089). Median TTF was 8.9 months (range: 7.2-10.2) and mPFS was 7.2 months (range: 5.8-8.6). The Meet-URO score performed better than the IMDC score in both TTF (c index: 0.63 vs 0.59) and PFS (0.62 vs 0.59). TBP pts were associated with higher overall response rate (34.4% vs 23.6%; $p = 0.035$) and disease control rate (61.3% vs 54.8%; $p = 0.30$). Moreover, TBP pts interestingly correlated with longer TTF (25.0 vs 10.7 months; $p<0.001$) and OS (42.5 vs 26.7 months; $p<0.001$), but had similar PFS compared with non-TBP pts. In TBP pts, a mean delay of 13.2 months (range: 6-20.4) from first to definitive disease progression was observed (25 vs 11.8 months), while non-TBP pts had overlapped TTF and PFS (10.8 months).

Conclusions: In pretreated mRCC pts receiving nivolumab, a small difference between mTTF and mPFS (∼2 months) was observed in the overall population. However, TBP pts were associated with significantly better ORR (+10%), TTF (+13 months) and OS (+ 15.8 months). Moreover, the Meet-URO score prognostically performed better with TTF than with PFS and compared with the IMDC score in both survival outcomes.

Clinical trial identification: Regional Ethical Committee of Liguria - registration number 068/2019.

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1896P Clinical management and outcomes of patients with advanced renal cell carcinoma (aRCC) treated with nivolumab+ipilimumab (N+I): A real-world study

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Background: N+I is approved for the first-line (1L) treatment of adult patients with intermediate/poor-risk aRCC, with efficacy demonstrated in CheckMate 214. Real-world effectiveness (RWE) data are limited; we assessed clinical characteristics and outcomes for aRCC patients who received N+I in England.

Methods: This retrospective, observational chart review examined patient demographics, clinical characteristics, treatment patterns, safety and outcomes (objective response [OR], progression-free survival [PFS], overall survival [OS]) of patients with aRCC treated with N+I at five sites in England. Eligible patients-initiated N+I at any line of therapy from 5-Apr-19 to 1-Apr-22 (including during COVID lockdown periods) and were followed until death or study end.

Results: 128 patients met eligibility criteria (mean age 60.7 yr, 71.1% male); 85.2% had clear cell histology; most had intermediate or poor IMDC classification at index (49.2% and 39.1%, respectively). Median follow-up (min-max) was 13.6 (0.8-37.9) mo. 95.3% (n=122) received 1L N+I. Median time on treatment from 1L initiation was 2.8 (0.03-34.4) mo and 54.1% (n=66) advanced to 2L therapy, mostly (n=56, 77.8%) to cabozantinib. Overall, 82% discontinued 1L therapy; most frequently for disease progression (n=23; 50.5%) or AEs (n=40; 38.1%). In patients receiving 1L N+I, OR was 29.7%, with a complete response rate of 1.1%; median PFS from 1L initiation was 7.6 mo; 1-yr PFS was 40.3% and 1-yr OS was 71.4%.

Conclusions: This study provided RWE on the characteristics and outcomes of patients with aRCC who received N+I. OR, PFS and OS were slightly inferior to those observed in CheckMate 214 but comprised a real-world population with a higher proportion of poor risk patients, those with CNS metastases, non-clear cell histology and treatment during the COVID pandemic.

Legal entity responsible for the study: BMS.

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1897P Geographical differences in the management of metastatic de novo renal cell carcinoma in the era of immune-combinations

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Background: The upfront treatment of metastatic renal cell carcinoma (mRCC) has been revolutionized by the introduction of immune-based combinations. The role of cytoreductive nephrectomy (CN) in these patients is still debated. The ARON-1 study (NCT05287464) was designed to globally analyze real-world data of mRCC patients receiving first-line immuno-oncology combinations. This sub-analysis is focused on the role of upfront or delayed partial or radical CN in three geographical areas (Western Europe, Eastern Europe, America/Asia).

Methods: We conducted a multicenter retrospective observational study in mRCC patients treated with first-line immune combinations from 55 centers in 19 countries. From 1152 patients in the ARON-1 dataset, we selected 651 patients with *de novo* mRCC. 255 patients (39%) had undergone CN, partial in 14% and radical in 86% of cases; 396 patients (61%) received first-line immune-combinations without previous nephrectomy. Primary endpoint was overall survival (OS) while progression-free survival (PFS) and tumor response rate were secondary endpoints.

Results: Median OS from the diagnosis of *de novo* mRCC was 41.6 months and not reached (NR) in the CN subgroup and 24.0 months in the no CN subgroup, respectively ($p<0.001$). Median OS from the start of first-line therapy was NR in patients who underwent CN and 22.4 months in the no CN subgroup ($p<0.001$). Patients who underwent CN reported longer OS compared to no CN in all the three geographical areas (Western Europe: NR vs 23.7 months, $p<0.001$; Eastern Europe: NR vs 29.8 months, $p=0.005$; America/Asia: 57.3 months vs 25.5 months, $p<0.001$).

Conclusions: No significant differences in terms of patients' outcome seem to clearly emerge in our analysis, even if the rate CN and the choice of the type of first-line immune-based combination varies across the different Cancer Centers participating in the ARON-1 project.

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1898P Comparative real-world effectiveness of PD-1/L1 inhibitor (PD-1i) plus cabozantinib (cabo) vs cabo after progression with prior immune checkpoint inhibitor (ICI) treatment (Rx) in metastatic clear cell renal cell carcinoma (mccRCC)

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Background: ICI rechallenge in solid tumors (including in mccRCC) after discontinuation or disease progression following a prior ICI is often practiced in the clinic and is an area of active investigation. Two ph 3 trials (NCT04338269/Contact-3 and NCT04987203/*TiNivo*-2) are evaluating this Rx paradigm in mccRCC. Cabo is the most common 2L Rx in mccRCC.

Methods: This study used the de-identified nationwide (US based) Flatiron Health EHR-derived database. Inclusion: diagnosis of mccRCC, receipt of 1L Rx with any ICI based Rx (between 3/2016 to 7/2022) followed by receipt of 2L Rx with cabo or cabo + PD-1i (between 6/2018 to 9/2022). Exclusion: 1L Rx with cabo, or pts with no evidence of contact for 90 days from diagnosis of mccRCC at treating institution to ensure pts were actively engaged in care. TTNT (time to next therapy; measured from 2L to 3L) and overall survival (OS; measured from 2L) were summarized via Kaplan-Meier survival estimates with 95% confidence interval (CI) and compared in the context of propensity score (PS) matching weighted analysis and Cox proportional hazard model (PSM- CoxHzM). PS model included 1L baseline covariates: age, race, smoking status, practice type, insurance, year of 1L, six IMDC risk factors, and missingness of covariates. Missing data were multiply imputed using predictive mean matching on 50 chained equations. All analysis done using R version 4.2.3.

Results: Of 12,285 mccRCC pts in the dataset, 314 pts met eligibilty. Results summarized in table.

Table: 1898P 2L cabo vs cabo-PD-1i in pts with PD-1i based therapy in 1L

	Median TTNT (95% CI) mos	Median OS (95% CI) mos
Cabo (n=251)	7.6 (6.9 — 8.9)	29 (25 - 33)
Cabo + PD-1i (n=63)	15 (10, not reached)	31 (25- not reached)
PSM- CoxHzM Hazard ratio (95% CI, p-value)	0.69 (0.45 - 1.06, 0.087)	1.08 (0.69 - 1.68, 0.74)

Conclusions: No benefit of adding PD-1i therapy to cabo vs cabo alone in 2 L was observed on PSM — CoxHzM. These results from a real world mccRCC pts are similar to those in a recent press-release on CONTACT-03 trial and question the practice of ICI rechallenge in mccRCC and other solid tumors.

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1899P Comparative effectiveness of second-line (2L) treatment (Rx) with cabozantinib (cabo) in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC) after first-line (1L) Rx with ipilimumab + nivolumab (ipi+nivo) vs. PD-1/L1 inhibitor (PDI) + tyrosine kinase inhibitor (TKI)

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Background: The preferred 1L Rx for pts with mccRCC is either ipi+nivo or PDi + TKI (NCCN Guidelines V4.2023). Cabo was approved based on Ph3 METEOR trial results from pts after prior mccRCC progression on 1-2 TKIs but not PDi Rx. In real world, cabo is the most used 2L therapy but its effectiveness after prior PDi based combination is unknown.

Methods: De-identified nationwide (US based) Flatiron Health EHR-derived database was used. Inclusion: diagnosis of mccRCC, 1L Rx with ipi+nivo or PDi+TKI (from 10/2017 to 7/2022) followed by 2L Rx with single-agent cabo. Exclusion: 1L Rx with cabo, pts with no documentation of 1L Rx or pts with no evidence of contact for 90 days from diagnosis of mccRCC at treating institution to ensure pts were actively engaged in care at the data providing institution. TTNT (time to next therapy; measured from 2L to 3L) and overall survival (OS; measured from 2L) were summarized via Kaplan-Meier survival estimates with 95% confidence interval (CI) and compared in the context of propensity score (PS) matching weighted analysis and Cox proportional hazard model (PSM- CoxHzM). PS model included baseline covariates: age, race, smoking status, practice type, insurance, year of 1L, IMDC risk factors (all six), and missingness of covariates. Missing data were multiply imputed using predictive mean matching on 50 chained equations. All analysis done using R version 4.2.3.

Results: Of 12,285 mccRCC pts in the dataset, 237 pts met eligibility, and all received ipi+nivo or PDi+TKI followed by cabo. Results summarized in table.

Table: 1899P

	Median TTNT (95% CI) mos	Median OS (95% CI) mos
Ipi+nivo (n=145)	8.0 (6.9 - 11)	26 (21 - 32)
PDi+TKI (n=92)	7.5 (6.3 - 16)	34 (27- NR)
PSM-CoxHzM Hazard ratio (95% CI, p-value)	1.43 (0.98 - 2.11, 0.07)	1.16 (0.73 - 1.83, 0.88)

Conclusions: Cabo retained similar effectiveness in 2L regardless of prior ipi+nivo or PDi+TKI. These results may aid with counseling of pts, prognostication, treatment decision in clinic and design of future clinical trials.

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1900P Role of cytoreductive nephrectomy (CN) in metastatic clear cell renal cell carcinoma (mccRCC) in the era of immunotherapy (IO): An analysis of the national cancer database (2004-2020)

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Background: The effectiveness of CN is still uncertain despite two significant trials, SURTIME and CARMENA, which aimed to demonstrate its benefits for mccRCC. These trials, conducted with Sunitinib as the standard treatment, did not provide evidence supporting the use of CN.

Methods: We identified stage IV mccRCC only patients (pts) who received IO with or without surgery in the NCDB 2004-2020. Overall survival (OS) was calculated among three groups of IO alone (group (gr)1), IO followed by CN (gr2), CN followed by IO (gr3). Cox models compared OS by treatment group after adjusting for sociodemographic, health, and facility variables.

Results: From 1,549,101 renal cancer cases, 7,367 met our criteria. 2.8% of ccRCC had sarcomatoid histology. Pts in the gr 2 and gr 3 had 63%, 95% CI [0.304 - 0.460] and 47%, 95% CI [0.492-0.571] (P= 0.001) risk reduction in mortality compared to gr 1.Black race compared to white race, Medicare pts compared to privately insured, and pts treated at a comprehensive community cancer center compared to academic center had an increased mortality risk by 15%, 95% CI [1.025-1.290] (P= 0.017), 12%, 95% CI [1.017-1.242] (P= 0.021), 17%, 95% CI [1.092-1.260] (P= 0.001) respectively. Median income quartiles ranging > 63k, had 22% reduction in mortality over income quartiles < 40k, 95% CI [0.696-0.888] (P= 0.044). Regardless of the sequence of CN, partial nephrectomy was minimally used. Pts in gr 3 had a 40% increased mortality risk compared to pts in gr 3, 95% CI [1.126-1.735] (P= 0.002).

Conclusions: Pts receiving CN regardless of sequence with IO did better than IO alone in this national registry-based adjusted analysis for mccRCC. Over the past few decades, the understanding of the role of CN has undergone changes, and while we await additional trial outcomes, the current evidence supports the notion that select mRCC patients can benefit from CN.

Table: 1900P

	IO (%) 95% CI	IO◇CN (%) 95% CI	CN◇IO (%) 95% CI
2 YRS FOLLOW UP	35.82 [34.44-37.20]	73.87 [68.48-78.49]	58.78 [56.75-60.74]
5 YRS FOLLOW UP	13.01 [11.32-14.82]	43.17 [33.94-52.05]	34 [31.32-36.39]

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1901P Specific dynamic changes of peripheral blood immune profile (PBIP) associate with clinical response to nivolumab (NIVO) in patients (pts) with metastatic renal cell carcinoma (mRCC): The I-RENE trial (meet-URO 8)

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Background: Here, we describe the potential of measuring dynamic changes occurring in peripheral blood as indicators of response to NIVO in mRCC pts.

Methods: After failure to antiangiogenics, mRCC pts (n=60) received NIVO within the I-RENE trial (NCT04891055). Blood samples were collected during NIVO at baseline, 2, 4, 12 weeks (wks) and at PD. Therapy induced dynamic changes were evaluated in PBMCs and plasma, by high resolution flow cytometry (n=144 lymphoid and myeloid

cell subsets) and multiplex analysis, respectively. A panel of very good (n=17, R) and very poor (n=16, NR) responders were selected for correlations. Tumor transcriptomics and immune infiltrate assessment were performed on baseline biopsy to gain insight into the immunomodulation occurring at tumor site.

Results: Dynamic changes were detected in multiple PBMC subsets and plasma cyto/chemokines since 2 wks from NIVO and at subsequent time points in all pts. However, R pts showed at 2 wks a statistically significant decrease of monocytic MDSCs (M-MDSC, $CD14^{+}HLA\text{-}DR^{neg}$) cells, followed at 4 wks by a boost of $CD8^{+}$ and central memory T cells, and reduction of $CD38^{+}$ T cells. At 12 wks $CD14^{+}HLA\text{-}DR^{neg}$ MDSCs reached the lowest peripheral blood level without further changes in the lymphoid cell subsets. At opposite, NR pts showed a progressive increase of M-MDSCs and inflammatory/immunosuppressive monocytes ($CD14^{+}PD\text{-}L1^{+}$), associated at 12 wks with a significant upregulation of senescent ($KLRG1^{+}CD28^{-}CD57^{+}$) $CD8^{+}$ T cells and $CD38^{+}$ T cells. Nivo induced a decrease of plasma IL-8, Pentraxin 3, PCSIK9 and miR-125b, and an increase of VEGFR2, all of which were associated with good response at 12 wks. Integration of PBIP with tumor tissue results will pair systemic immunomodulations with tumor microenvironment.

Conclusions: Specific kinetics of immunosuppressive myeloid cell subsets versus memory/effector T cells early during NIVO associate with outcome. Combining dynamic peripheral blood variables with clinical information may give rise to novel biomarkers for tailored therapeutic decision-making in mRCC pts.

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1902P Comparison of cabozantinib (CABO) versus sunitinib (SUN) following first-line (1L) nivolumab plus ipilimumab (NIVO+IPI) for metastatic renal cell carcinoma (mRCC): A target trial emulation using real-world data from the International mRCC Database Consortium (IMDC)

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Background: While the benefit of CABO in mRCC is well established post-tyrosine kinase inhibitor, its comparative effectiveness vs SUN after 1L NIVO+IPI is uncertain.

Methods: A target trial emulation was designed using data from the IMDC to estimate the effect of second-line (2L) CABO versus SUN within one year of discontinuing 1L NIVO+IPI on overall survival (OS). Patients (pts) diagnosed after January 1, 2017, were followed from initiation of 2L until death or last known contact. Inverse-probability of treatment weighting was used to adjust for hemoglobin, calcium, platelets, and neutrophils at 2L, Karnofsky performance score (KPS) at 2L, time from diagnosis to initiation of 2L, and response to 1L NIVO+IPI. Treatments were compared using adjusted Kaplan-Meier curves and adjusted hazard ratios (HR) from a Cox regression model. Missing data were addressed with multiple imputation by chained equations. E-values were used to assess the likelihood findings could be explained by residual confounding.

Results: 121 and 123 pts who received CABO and SUN after 1L NIVO+IPI were included. Among the baseline characteristics, only the proportion with a KPS < 80% differed significantly between CABO (21%) and SUN (45%) (p = 0.002) (Table). The objective response was 27% (21/79) for CABO vs 20% (18/89) for SUN with a median time to treatment failure of 8.5 (95% CI: 6.9-12.9) and 4.5 (95% CI 3.7-5.8) months. Median OS was 21.4 (95% CI 17.9—NA) months from initiation of CABO and 10.1 (95% CI 7.6—17.7) months for SUN (Adjusted HR 0.44 (95% CI: 0.23-0.85)). This corresponds to an E-value of 2.91 suggesting a low likelihood of findings being due to residual confounding alone.

Conclusions: This investigation provides real-world evidence supporting CABO as a 2L treatment option for mRCC following NIVO+ IPI .

Table: 1902P Characteristics of pts receiving 2L CABO and SUN

	CABO (n = 121)	SUN (n = 123)	P-value
Mean age (SD)	61.6 (11.03)	60.6 (9.27)	0.16
Male	90/121 (74.4)	94/123 (76.4)	0.82
Non-clear cell histology	14/110 (12.7)	10/63 (15.9)	0.73
Sarcomatoid	15/86 (17.4)	16/61 (26.2)	0.28
KPS < 80%*	18/86 (20.9)	35/78 (44.9)	0.002
Time from diagnosis to treatment < 1 year	100/121 (82.6)	96/121 (79.3)	0.62
Hemoglobin < LLN*	69/106 (65.1)	74/109 (67.9)	0.77
Neutrophils > ULN*	23/103 (22.3)	23/108 (21.3)	0.99
Platelets > ULN*	16/107 (15.0)	24/109 (22.0)	0.25
Calcium > ULN*	6/99 (6.1)	9/97 (9.3)	0.56

LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal. *: At 2L.

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1903P Tumor response by baseline metastases in patients (pts) with renal cell carcinoma (RCC) treated with lenvatinib (L) plus pembrolizumab (P) vs sunitinib (S): Post hoc analysis of the CLEAR trial

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Background: L+P is a standard of care (SoC) in 1L RCC based on significantly improved efficacy versus S in the CLEAR study [Motzer 2021]. We report tumor response by baseline metastases at the final prespecified overall survival analysis timepoint (cutoff date: 31 Jul 22).

Methods: Treatment-naive adults with RCC were randomized to L (20 mg orally QD in 21-day cycles) plus P (200 mg IV Q3W) or L (18 mg orally QD in 21-day cycles) plus everolimus (5 mg orally QD in 21-day cycles) or S (50 mg orally QD; 4 wks on/2 wks off). This post hoc analysis examined response by baseline metastases in L+P (n=355) vs S (n=357) arms. Objective response rate (ORR), complete response (CR) rate, partial response (PR) rate, and progression-free survival (PFS) via independent imaging review (IIR) per RECIST v1.1 by baseline metastatic characteristics (site of metastasis [lung, lymph node, bone, liver, brain], number of metastatic sites [1 vs ≥2] and sums of diameters of target lesions [≥60 mm vs <60 mm]) are analyzed. Odds ratios (ORs) for ORR and hazard ratios (HRs) for PFS with 95% CIs are reported.

Results: The most common metastatic site by IIR at baseline was lung (L+P: 71.0%; S: 63.9%); 22.5% and 24.9% of pts, respectively, had bone metastases. 65.1% Of pts randomized to L+P and 66.1% of pts randomized to S had metastases at ≥2 sites. ORR favored L+P irrespective of metastatic site (Table). ORR favored L+P in pts with 1 (OR, 2.98 [95% CI 1.71, 5.21]) or ≥2 metastatic sites (OR, 5.06 [95% CI 3.40, 7.53]), and in pts with target lesion diameter sums ≥60 mm (OR, 10.50 [95% CI 6.08, 18.13]) or <60 mm (OR 3.14 [95% CI 1.94, 5.07]). PFS favored L+P vs S across subgroups (Table). CR and PR rates were higher in L+P vs S across subgroups (to be reported).

Conclusions: Tumor response favored L+P in all subgroups of interest, particularly in patients with increased burden of disease. Data further support L+P as a SoC in pts with 1L RCC.

Table: 1903P

	L+P vs S	
	ORR[a,b] OR (95% CI)	PFS[a,b] HR (95% CI)
Metastatic Site[a]		
Lung		
Y	5.19 (3.48, 7.72)	0.41 (0.32, 0.52)
N	3.02 (1.75, 5.20)	0.51 (0.34, 0.75)
Lymph Node		
Y	3.66 (2.28, 5.88)	0.49 (0.37, 0.66)
N	4.83 (3.14, 7.43)	0.45 (0.34, 0.60)
Bone		
Y	4.09 (2.11, 7.94)	0.50 (0.33, 0.77)
N	4.30 (2.97, 6.20)	0.45 (0.36, 0.57)
Liver		
Y	3.51 (1.68, 7.30)	0.48 (0.31, 0.77)
N	4.53 (3.17, 6.47)	0.46 (0.36, 0.57)
Brain		
Y[c]	3.00 (0.43, 20.72)	0.32 (0.07, 1.59)
N	4.29 (3.11, 5.92)	0.47 (0.38, 0.57)
No. Metastatic Sites[a]		
1	2.98 (1.71, 5.21)	0.60 (0.41, 0.87)
≥2	5.06 (3.40, 7.53)	0.40 (0.31, 0.50)
Target Lesion Diameter Sums[a]		
≥60 mm	10.50 (6.08, 18.13)	0.39 (0.29, 0.53)
<60 mm	3.14 (1.94, 5.07)	0.53 (0.40, 0.71)

[a]IIR; [b]RECIST v1.1; [c]L+P n=6; S n=10.

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1904P Treatment options and outcome of metastatic renal cell carcinoma patients with brain or bone metastases: A real-world evidence from a German retrospective multi-center analysis

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Background: Brain (BM) and bone metastases (BOM) in renal cell carcinoma (RCC) are associated with poor outcome. We evaluated real-world treatment paradigms of RCC patients with BM and BOM.

Methods: We retrospectively analyzed RCC patients with BM and BOM treated at 9 German tertiary cancer centres from 2003 to 2023. Adverse events (AE) were reported according to CTCAE 5.0, objective response rate (ORR) according to local standard. Progression free survival (PFS) and overall survival (OS) were calculated from start of treatment to progression or death.

Results: We included 349 patients with a median age of 64 years (IQR 55-71). 93% of all patients had BOM, 15% BM and 8% both. Most patients (86%) had clear cell RCC, 5% of all patients had sarcomatoid differentiation. 82% of patients had an ECOG PS of 0/1. IMDC risk was favorable/intermediate/poor in 19/58/23%. 76% received prior nephrectomy. Patients with BOM received first-line IO-combinations in 64% (IO-IO: 39%, TKI-IO: 61%), TKI-monotherapy in 36%, while patients with BM received IO-combinations in 73% (IO-IO: 42%, TKI-IO: 58%) and TKI in 27%. IO-based first-line therapy increased from 2003 to 2023. AE of all grades occurred in 87% and 50% during IO-based therapy or TKI monotherapy, and CTCAE grade $\geq$ 3 in 44% or 21%. ORR and survival outcomes with median follow-up of 33 months (IQR 14-78) are described in table. 49% and 50% of all patients with BOM and BM received second-line treatment, with Cabozantinib (34%; 31%) and Nivolumab (19%, 27%) being the most common treatment options.

Table: 1904P

Parameter	Total (%; n=270)			BOM (%; n=250)			BM (%; n=45)		
	TKI n=95	IO-IO n=69	IO-TKI n=106	TKI n=89	IO-IO n=62	IO-TKI n=99	TKI n=12	IO-IO n=19	IO-TKI n=14
ORR; %	40	29	57	38	27	58	58	41	42
SD; %	36	29	31	37	31	32	25	28	21
PD; %	24	42	12	25	42	10	17	21	37
ORR vs. SD vs. PD	p<0.001			p<0.001			p=0.750		
mPFS; months, 95% CI	7 (5.2-8.8)			7 (5.2-8.2)			6 (3.1-8.9)		
mOS; months, 95% CI	39 (29.5-48.5)			39 (29.8-48.2)			39 (19.1-58.9)		

Conclusions: RCC patients with BOM and BM are increasingly treated with IO-combinations but lead to higher rates of AE grade $\geq$ 3. In patients with BOM, IO-TKI revealed higher ORR compared to IO-IO combination, but not in patients with BM. Small sample size and retrospective design are major limitations of our analysis. Prospective studies evaluating treatment options for BOM and BM in patients with RCC is critical.

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1905P Heterogeneity in tertiary lymphoid structures predicts the distinct prognosis and immune microenvironment of clear cell renal cell carcinoma

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Background: Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that form postnatally in non-lymphoid tissues and arise under physiological conditions. However, the clinical and immunological implications of heterogeneous subpopulations of TLS in clear cell renal cell carcinoma (ccRCC) remain to be elucidated.

Methods: H&E, immunohistochemistry and 12-marker multispectral fluorescent were used to evaluate the spatial location and maturation status of TLS with TME cell-infiltrating characterizations. We comprehensively assessed the prognostic value of TLS heterogeneity in 395 patients with ccRCC from two independent cohorts using log-rank tests, Cox hazards models, and scoring nomograms. Associations between TLS heterogeneity and immunologic activity of TME were assessed using quantified lymphocytes infiltration fraction.

Results: By pathological review, TLS were identified in 34.2% of the ccRCC samples. For ccRCC patients, the presence of intratumoral TLS markedly correlated with both superior progression-free survival (PFS) and overall survival (OS), while the peritumoral TLS exerted the opposite predictive trend of clinical outcomes. Multivariate Cox analysis revealed that the presence of intratumoral TLS was prominently correlated with better outcomes. Additionally, the novel nomograms incorporating the presence of intratumoral TLS prominently predicted the probability of 8-year PFS and OS of ccRCC (AUC >0.80). Moreover, a higher proportion of early TLS was found in peritumoral TLS (P=0.016), while intratumoral TLS were mainly composed of secondary follicle-like TLS (P=0.004). Interestingly, in ccRCC samples with the presence of peritumoral TLS enriched with primary follicle-like TLS, the proportion of PD-L1$^+$ tumor-associated macrophages and Treg infiltration in the stroma were prominently increased, showing a typical suppressive tumor immune microenvironment.

Conclusions: In conclusion, this study revealed the predictive value of TLS heterogeneity on the progression and immunological responses of ccRCC for the first time. The intratumoral TLS could be used to assess both the prognostic patterns and the unique TME characteristics of each patient.

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1906P Metastasized non-clear cell renal cell carcinoma: Which entities are dangerous? Results learned from reference pathology of the SuniForecast study

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Background: In the 2022 WHO classification more than 20 entities of renal cell carcinomas (RCC) were defined. Several molecularly defined RCC were separated. There is urgent need for studies investigating well defined patients with these specific entities. One prerequisite is an exact classification of non-clear cell RCC (nccRCC) including histopathological and molecular diagnostics.

Methods: The SUNNIFORECAST study (NCT03075423) is a phase 2 randomised investigator-initiated trial of nivolumab with ipilimumab vs. standard of care in patients with previously untreated and advanced nccRCC. For study inclusion a reference pathology to confirm diagnosis of nccRCC was mandatory.

Results: 350 cases were submitted for reference pathology as paraffin blocks or unstained slides. Diagnoses was done by HE staining, immunohistochemistry and molecular testing. Reference pathology confirmed the diagnoses of nccRCC in 334 of 350 cases. Only few cases were diagnosed in reevaluation as ccRCC, liposarcoma or epithelioid angiomyolipoma. Histopathological diagnoses included papillary RCC (n=138-41%), chromophobe RCC (n=58-17%), RCC, NOS, mostly with sarcomatoid pattern (n=46-14%) TFE3 or TFEB altered RCC (n=25 and n=1,8%), FH-deficient RCC (n=33-10%), SDHB-deficient RCC (n=4-1%), SMARCB1-deficient renal medullary carcinoma (n=9-3%), collecting duct carcinoma (n=14-4%) and tubulocystic RCC (n=1). Interestingly no tumors out of the group of other oncocytic tumous or clear cell papillary renal cell tumors were detected. Compared to primary pathology diagnosis changed in 116/350 cases. There was no correct primary diagnosis in 28/33 cases of FH-deficient RCC, 3/4 cases of SDHB deficient RCC and 17/26 cases of translocation RCC. All chromophobe RCC showed sarcomatoid dedifferentiation or coagulative tumor necrosis. In papillary renal cell carcinoma, micropapillary and microcystic architecture was very frequently detected in G1/G2 tumors.

Conclusions: Reference pathology is a prerequisite for clinical studies investigating ncc RCC. The diagnosis of molecular defined RCC is still problematic in daily diagnosis. The study was supported by a grant of BMS (BMS).

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1907P Multi-omics mapping positions antigenic myeloid-T cell crosstalk at the core of advanced renal cell carcinoma (aRCC) response to immune checkpoint blockade (ICB)

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Background: ICB can achieve durable benefit in aRCC, but reliable biomarkers are lacking. Despite ongoing research, current aRCC biomarkers fail across trials.

Methods: We performed a comprehensive biomarker discovery in our in house, real world aRCC transcriptomic dataset of ICB treated patients (anti-CTLA4+anti-PD1 and anti-PD1) with corresponding human leukocyte antigen (HLA) genotypes to characterize antigen presenting features. Using machine learning (ML) as a wrapper, a transcriptomic biomarker set reflecting HLA promiscuity (HLA*pr*) was developed. We studied its impact on outcome in our ICB treated cohort, in external ICB treated aRCC cohorts (IMmotion150/Miao *et al*/Choueiri *et al*, Javelin101) and post-nephrectomy patients (TCGA KIRC).

Results: Increased tumor-relevant antigen binding specificity of HLAs over other antigens (low HLA*pr*) correlated with improved overall survival (OS) after ICB (hazard ratio (HR) 0,4; 95% CI 0,21-0,75, p=0,004, n=98), independent of IMDC risk groups on multivariable analysis, and with a trend towards longer progression free survival (PFS) (HR 0,69, 95%CI 0,38-1,27, p=0,2). Analysis of immunopeptidome-derived and experimentally-validated HLA allele-antigen pairs confirmed that HLA alleles with lower HLA*pr* and correlated with OS upon ICB preferentially bound neo-antigens. A ML based signature was developed that cross-linked transcriptomic footprints with low HLA*pr*, which correlated with OS in our ICB treated cohort (HR 0,56, 95%CI 0,34-0,94, p=0,03), and trended towards correlation with PFS (HR 0,66, 95%CI 0,42-1,03, p=0,07). The signature correlated with PFS in external ICB treated cohorts Javelin101 (HR 0,73, 95%CI 0,54-0,99, p=0,04, n=354) and IMmotion150/Miao *et al*/Choueiri *et al* (HR 0,47, 95%CI 0,26-0,86, p=0,015, n=207) and with OS in TCGA KIRC (HR 0,52, 95%CI 0,38-0,71, p<0,001, n=511). In Departmenth tumor immune analyses identified antigen presentation, interferon signalling and myeloid-T cell crosstalk as determinants of ICB responders.

Conclusions: In Departmenth multi-omics analysis revealed critical importance of antigenic myeloid-T cell crosstalk, driven by high neo-antigenicity, to ensure adequate ICB response in aRCC.

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1908P Utility of circulating tumor (ct)DNA testing for molecular residual disease (MRD) detection and treatment response monitoring in patients (pts) with renal cell carcinoma (RCC)

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Background: Increased heterogeneity in outcomes has been observed post nephrectomy in pts with RCC with standard clinical parameters being primarily used for risk assessment. Currently, no blood-based biomarkers are available that can predict recurrence or response to therapy. Herein, we demonstrate the utility of ctDNA in identifying MRD and assessing concordance with radiographic imaging in this pt population.

Methods: This real-world evidence-based multi-institutional study included a cohort of 82 pts with stages I-IV RCC who underwent nephrectomy (+/- metastasectomy), with 41 pts receiving adjuvant therapy (AT) (Table). Longitudinal ctDNA testing on post nephrectomy plasma samples (n=256) was performed using a tumor-informed ctDNA assay (Signatera™). ctDNA results were analyzed and association with clinical outcomes was assessed.

Results: In this cohort, the majority of the pts (75.6%; 62/82) were serially ctDNA negative and 91.9% (57/62; negative predictive value) of these showed no evidence of disease (NED) or non-progressive disease (partial response or stable disease) on imaging at the end of the follow-up. Longitudinal ctDNA detection was 24.3% (20/82; any time positivity) and 65% (13/20) of these demonstrated concordance between ctDNA status/dynamics and imaging. Among the 13 concordant pts, 53.8% (7/13) were ctDNA positive and relapsed, and among the remaining 7, 5 had insufficient imaging/ctDNA testing and 2 were discordant with positive ctDNA and NED on imaging.

Table: 1908P Patient demographics and clinical features (N=82)

Median Age (years)	66 (range: 21-88)
Median follow-up from time of surgery (weeks)	35.7 (range: 7.3 - 476)
Number of Relapse Cases	13 (16%)
Postsurgical clinical NED status	
Yes	74 (90.2%)
No	8 (9.8%)*
Subtype	
Clear cell	55 (67.1%)
Non-clear cell	10 (12.2%)
Unclassified	17 (20.7%)
Stages	
I	1 (1.2%)
II	9 (10.9%)
III	57 (69.5%)
IV	13 (15.9%)
Unknown	2 (2.4%)

*all 8 were stage IV patients

Conclusions: Overall, we demonstrate the utility of ctDNA testing for MRD detection. Future prospective studies in RCC would be needed to validate the utility of ctDNA in informing clinical decision-making.

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1909P Baseline cytokine levels according to the line of treatment in patients with metastatic clear cell renal cell carcinoma treated with nivolumab: NIVOREN GETUG-AFU 26 translational study

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Background: The translational study NIVOREN GETUG-AFU 26 explored baseline cytokine correlation with outcomes under nivolumab in patients with metastatic renal cell carcinoma. We previously identified five cytokines (IL-6/IL-8/IL-7/VEGF/4-1BB) as potential serum-derived biomarkers of immune checkpoint inhibitors outcomes (N=80), subsequently validated (N=233), we confirmed a significant negative association between IL-6/IL-8/VEGF/BAFF/CXCL13 and worse OS (Carril-Ajuria et al. 2022). In this report, we present the baseline cytokine concentrations according to the line of treatment and investigate their additional prognostic value.

Methods: During the trial, blood samples were collected prospectively. Using the MSD-assay, we measured a panel of eight cytokines (VEGF, VCAM-1, IL-6, IL-7, IL-8, BAFF, 4-1BB, and CXCL13) at baseline. We evaluated the median cytokine levels using the Kruskal-Wallis test. The patients were categorized based on whether they underwent a single line of treatment or multiple lines of treatment.

Results: Overall, 353 patients were included in our analysis among 720 patients treated with nivolumab in the trial. Of these patients, 205 had received only one line of prior treatment, while 148 had received two or more lines of prior treatment. We found that patients who had undergone multiple lines of treatment had significantly higher levels of two cytokines, IL-6 and BAFF. IL-6 is known to be associated with protumoral inflammation and neutrophil activation, while BAFF regulates the trafficking and maturation of B cells.

Table: 1909P

Cytokines Median (pg/ml)	1 line of prior systemic therapy N=205	≥ 2 lines of prior systemic therapy N=148	Kruskal-Wallis test
IL-6	2.8 (0,4 - 276,1)	3,9 (0,5 - 802,7)	P=0.014
IL-7	6,8 (1,4- 29,3)	6.7 (1,9 — 29,7)	P=0.372
IL-8	13,5 (4,3 - 2599,9)	16 (4,3 — 2793,3)	P=0.177
VEGF	46,3 (2,6 - 681,6)	57,7 (7,9 — 798,4)	P=0.262
4-1BB	48,1 (0,1 - 344,2)	46,7 (0,3 — 59,5)	P=0.455
CXCL13	72,7 (20,2 - 705,7)	74,9 (16,6 — 800,4)	P=0.803
BAFF	1159,2 (346,7 - 9788,4)	1356,6 (342,5 — 10555,7)	P=0.004

Conclusions: Patients demonstrated a gradual enrichment of IL-6 and BAFF the number of prior lines of systemic therapy: patients more heavily pretreated presented higher baseline levels of those two cytokines. Our findings highlight the potential of baseline cytokine levels as a prognostic tool for metastatic clear cell renal cell carcinoma.

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1910P Evaluation of a genome-wide methylome enrichment platform for circulating tumor DNA quantification and prognostic performance in renal cell carcinoma (RCC)

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Background: Circulating tumor DNA (ctDNA) can be utilized to identify the presence of cancer as well as minimal residual disease. Quantification of ctDNA using plasma-based tests can be a useful cancer management tool to assess prognosis; however, some methodologies also require tumor tissue for analysis or are limited to tumor types that tend to have higher amounts of associated ctDNA. Here we demonstrate the feasibility of using a tumor-uninformed genome-wide methylome enrichment platform to quantify ctDNA in plasma and predict prognosis in RCC.

Methods: Biobanked pre-treatment samples from individuals with newly diagnosed stage I-IV RCC (University Health Network, Ontario Tumor Biobank) were analyzed with a bisulfite-free, non-degradative genome-wide DNA methylation enrichment platform using 5-10 ng of cell-free DNA isolated from plasma. ctDNA was quantified from average normalized counts across informative regions. Events were defined as cancer recurrence or progression. A ctDNA quantity threshold was set such that 95% of samples without an event fell below the threshold (i.e., 95% specificity). Time to event was compared for samples with ctDNA quantities above the threshold to those below the threshold.

Results: The cohort included 151 samples [64 stage I, 2 stage II, 23 stage III, 15 stage IV, 47 with unknown or incomplete stage information]. There was a median follow-up of 15.4 months and a total of 21 events. Samples with ctDNA quantities above the threshold were significantly more likely to recur or progress than those below the threshold [hazard ratio 13.28 (95% CI 5.47, 32.26), log-rank $P<0.001$].

Conclusions: This analysis demonstrates the feasibility of using a blood-based, tumor-uninformed genome-wide methylome enrichment platform for ctDNA quantification and prognostic prediction in renal cancer. This is a promising demonstration of prognostic performance in a cancer type that is typically difficult to detect due to low amounts of ctDNA. Additional evaluation in post-treatment and longitudinal samples will further test the performance of this platform.

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1911P Effect of VHL mutations on efficacy of immune checkpoint inhibitors in renal cell carcinoma

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Background: Mutations of the von Hippel-Lindau (VHL) tumor suppressor gene occur in the majority of sporadic renal-cell carcinomas (RCC). Certain VHL mutations correlate with low expression of classical HLA-I molecules and HLA-E expression that determine higher NK susceptibility. Therefore, VHL mutation maybe a predictor of responses to immune checkpoint inhibitors (ICIs). Our research aims to elucidate its mutation association with ICI efficacy.

Methods: In order to investigate the correlation between VHL mutation and ICI efficacy in the RCC, we used cBioportal to collect clinical and mutation data of 151 ICI-treated RCCs from MSKCC cohort. Gene expression and WES data of 313 samples were obtained from the TCGA database for further analysis of potential biological mechanisms between VHL-mutant and VHL-wildtype tumors. Tumor mutation burden (TMB) was calculated as the total number of somatic non-synonymous mutations per megabase in both MSKCC and TCGA cohorts. CIBERSORT algorithm was applied to infer 22 human immune cell type proportions in TCGA RCCs.

Results: In the MSKCC immunotherapy cohort, we observed 70.2% (106/151) patients harbored VHL mutation, while TCGA had lower mutation frequency with 50.5% (158/313). As indicated by Kaplan-Meier analysis, the patients with VHL mutation had significantly better OS in the MSKCC cohort ($P < 0.001$, median OS: 50 months vs 26 months). This link was still existing when controlling for age, sex, ICI types, TMB and metastasis in the multivariate Cox regression analysis ($P = 0.005$, $HR = 0.45$, 95%CI = 0.26-0.78). As expected, the VHL-mutant group had higher TMB than that of the VHL-wildtype group in both the MSKCC cohort ($P < 0.001$) and TCGA cohort ($P = 0.047$). Immune cell analysis showed that CD8+ T cells, CD4 naïve T cells, T follicular helper cells and Macrophage M1 cells were abundant in the VHL-mutant group (both $P < 0.05$). These results indicated VHL-mutant tumors had an activated antitumor immune microenvironment.

Conclusions: VHL mutations might be a potential biomarker to predict the efficacy of immunotherapy for RCC. Considering the heterogeneity among the patients and other confounding factors, further prospective validation cohorts are warranted.

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Disclosure: All authors have declared no conflicts of interest.

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1912TiP STELLAR-304: A randomized phase III study of zanzalintinib (XL092) and nivolumab in non-clear cell renal cell carcinoma (nccRCC)

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Background: nccRCCs are a heterogenous group of rare histologic subtypes, each with distinct biology and response to treatment. There have been few dedicated randomized phase 3 studies in nccRCC, highlighting an urgent unmet need for effective therapies. Sunitinib is the only TKI to have shown a clinical benefit (vs everolimus) in a broad range of histologic subtypes of metastatic nccRCC (Armstrong et al. *Lancet Oncol* 2016). To date, no single agent or combination has shown a significant overall survival (OS) benefit over sunitinib in any nccRCC subtype. Zanzalintinib (XL092), a novel TKI of VEGFR2, MET, AXL, and MER, has shown antitumor and immunomodulatory activity alone, and synergistic antitumor effect with PD1 inhibition, in animal models (Hsu et al. *Mol Cancer Ther* 2023). In a phase 1 study of metastatic solid

tumors including RCC, zanzalintinib showed promising clinical activity and a manageable toxicity profile, alone and with an immune checkpoint inhibitor (ICI) (Sharma et al. *ESMO* 2022 Abs 481P). STELLAR-304 was designed to assess the efficacy and safety of zanzalintinib + nivolumab versus sunitinib in first-line nccRCC (NCT05678673).

Trial design: STELLAR-304 is a global, randomized, open-label study of adults with unresectable/advanced/metastatic nccRCC that is measurable per RECIST v1.1. The trial includes papillary, unclassified, and translocation-associated histologies (sarcomatoid features are allowed); chromophobe, renal medullary carcinoma, or pure collecting duct histology are excluded. Histologies are confirmed by central pathology review. Prior systemic anticancer therapy for advanced or metastatic nccRCC is not permitted; however, 1 prior systemic adjuvant therapy, including ICI and excluding sunitinib, is allowed for completely resected RCC if recurrence occurred $\geq$6 months after the last adjuvant therapy dose. Patients (N=291) are randomized 2:1 to zanzalintinib + nivolumab or sunitinib alone. The primary endpoints are PFS and ORR per RECIST v1.1 by blinded independent radiology committee. The secondary endpoint is OS; safety will also be assessed. STELLAR-304 is currently recruiting patients in 29 countries in Europe, North and South America, and the Asia-Pacific region.

Clinical trial identification: NCT05678673.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SARCOMA

1913O A randomised, multicenter phase-III study comparing doxorubicin (dox) alone versus dox with trabectedin (trab) followed by trab in non-progressive patients (pts) as first-line therapy, in pts with metastatic or unresectable leiomyosarcoma (LMS): Final results of the LMS-04 study

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Background: In the LMS-04 study primary analysis (NCT02997358), the combination of dox + trab demonstrated a significant progression-free survival (PFS) benefit (12·2 months *versus* 6·2 months], adjusted hazard ratio (HR) 0·41 [95% CI 0·29—0·58]; p<0·0001) in 1st-line treatment of patients with advanced LMS (Pautier; Lancet Oncol 2022). Herein, we report the updated PFS (uPFS) and final results of overall survival (OS) analyses (planned when all pts had at least 3 years of follow-up).

Methods: Pts received either dox alone 75 mg/m^2 (arm A) or dox 60 mg/m^2 followed by trab 1.1 mg/m^2 as a 3-hour infusion (arm B), repeated every 3 weeks for up to 6 cycles (cy) followed in arm B by trab in non-progressive pts up to 17 cy. Surgery for residual disease was permitted. Randomisation was stratified by tumour location (uterine *versus* soft tissue) and disease (locally advanced *versus* metastatic). The analysis of PFS and OS was adjusted for stratification factors.

Results: Overall, 150 pts with LMS (67 with uterine LMS and 83 with soft-tissue LMS), and mostly with metastatic disease (90%), were enrolled. The median duration of follow-up was 54.9 months [95% CI = 51.25-60.48] with 107 deaths (60 in arm A and 47 in arm B). Median uPFS was significantly longer with dox + trab *versus* dox alone (12.19 mo [95% CI = 10.09-15.57] *versus* 6.21 mo [95% CI = 4.07-7.06] with adjusted HR: 0.37 [95%CI = 0.26-0.53] and p<0.0001). Median OS was also significantly longer with the association (33.08 [95% CI = 26.22-47.54] *versus* 23.78 months with dox alone [95% CI = 18.86-30.68], adjusted HR=0.65 [95% CI = 0.44-0.95] p=0.0253). No new safety signal was observed.

Conclusions: dox + trab combination can be considered as first -line treatment for metastatic/advanced uterine and soft-tissue LMS.

Clinical trial identification: NCT02997358.

Legal entity responsible for the study: Gustave Roussy Cancer Campus.

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1914MO The clinico-radiological outcome of desmoid type-fibromatosis after discontinuing the sorafenib treatment in responders: Single-arm phase II clinical trial

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Background: The treatment duration of sorafenib in desmoid-type fibromatosis is not established. Finding the optimal duration to improve the quality of life of patients with DTF remains important.

Methods: This is a single arm, Simon's phase 2 study started in July 2021 and is still ongoing. Patients with extremity DTF on sorafenib were screened for inclusion and sorafenib was discontinued. After discontinuation, patients were examined clinically every 3 months and MRI every 6 months. The EORTC QLQ C30 questionnaire was administered every 3 months for 1 year. RECIST 1.1 criteria were used for radiological assessment. The primary endpoint was progression-free survival (PFS) at 1 year.

Results: There were 33 patients with a median age of 28.5 years and the female-to-male ratio was 1.3. Sorafenib at a dose of 200 mg/day was used in 55% of the patients. The median duration of sorafenib was 25 months. At enrolment, one patient was in CR, 21 (61.7%) in PR, and 12 (35.3%) patients had SD. The median duration of follow-up after enrolment was 13 months. 20 patients completed 1 year of follow-up. Of 20 patients, who completed a 1-year follow-up, 19 patients had SD. The change in tumor size at 1 year ranged between a decrease of 21% to an increase of 32% (median change of 2%). Of 33 patients, 3 were restarted on sorafenib, 2 because of worsening pain (radiologically SD), and 1 because of radiological PD. There was significantly more pain at the end of 1 year of stopping sorafenib measured on the EORTC scale but the difference in the global health status (GHS) and other parameters was not significant (Table).

Table: 1914MO Demographic details and results

Variable	Values (N = 33)
Age (Median ± SD) in years	28.5 ± 9.4
Gender n (%) Male Female	15 (44.1%) 19 (55.9%)
The duration of sorafenib treatment before enrollment Median ± SD in months	25.4 ± 11.8 months
Disease status at 1 year of stopping sorafenib SD PD	N = 20 19 (95%) 1 (1%)
PFS rate at 1 year	95%
The difference in the mean EORTC scores (Compared between the time of stopping sorafenib and at 1-year completion) GHS Pain	82.69 ± 21.9 vs 79.48 ± 20.58, p = 0.529 21.1 ± 29.1 vs 29.4 ± 7.6, p = 0.013

Conclusions: Sorafenib can be stopped safely after 1 year of treatment for extremity fibromatosis without compromising the quality of life of patients. However, clinical follow-up at regular intervals is required to assess for the symptoms and disease progression.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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1915MO Fear, anxiety and depression in gastrointestinal stromal tumor (GIST) patients in the Netherlands: Data from a cross-sectional multicenter study

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Background: The introduction of tyrosine kinase inhibitors (TKIs) has led to a phenomenal progress in the treatment of gastrointestinal stromal tumors (GIST). Prolonging the survival of GIST patients may also entail more psychological and emotional distress. This study aims to investigate (1) the prevalence of anxiety, depression and fear of cancer recurrence or progression (FCR) in GIST patients on TKI treatment or not on TKI treatment, (2) factors associated with anxiety, depression and severe FCR, and (3) the relationship between anxiety, depression, severe FCR and global quality of life.

Methods: In a cross-sectional population-based survey study, Dutch GIST patients completed self-report questionnaires including the Hospital Anxiety and Depression Scale (HADS), Cancer Worry Scale (CWS) and the EORTC QLQ-C30.

Results: A total of 328 (response rate 63%) patients responded, 108 (32.9%) of whom received TKI treatment at time of the questionnaire. Patients on TKI treatment had a significantly higher prevalence of symptoms of depression (21.5% vs 8.7%, p=0.001) and severe FCR (59.3% vs 35.4%, p=<0.001) compared to those not on TKI treatment, while anxiety did not differ between the groups (18.7% vs 13.0%). Patients on TKI treatment had 2.3 (95% CI 1.1-4.9; p=0.025) and 2.7 (95% CI 1.6-4.5; p=<0.001) higher odds of experiencing symptoms of depression and severe FCR, respectively, than those not on TKI. Other factors associated with symptoms of depression and severe FCR were younger age at diagnosis and having more than two comorbidities. Global quality of life was significantly lower in patients who experienced symptoms of anxiety (64.9 vs 82.8, p=<0.001), depression (59.8 vs 83.2, p=<0.001) or severe FCR (73.2 vs 85.0, p=<0.001) as compared to patients who were not anxious, depressed or experienced severe FCR.

Conclusions: GIST patients on TKI treatment are more prone to experience symptoms of depression and severe FCR than those not on TKI treatment, which can significantly impair their global quality of life. Given the high prevalence of FCR and symptoms of depression, this deserves more attention in clinical practice and appropriate interventions should be provided.

Legal entity responsible for the study: The authors.

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1916MO A first-in-human phase I trial of NB003, a potent and selective KIT/PDGFRa inhibitor, in patients with advanced gastrointestinal stromal tumors (GIST)

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Background: NB003 is a potent and selective small-molecule tyrosine kinase inhibitor (TKI) of KIT and PDGFRα, designed to inhibit a broad range of primary and acquired imatinib-resistant mutations in KIT/PDGFRα in GIST. This study is aimed to determine the safety and tolerability, the MTD, and the RP2D of NB003 in patients (pts) with advanced GIST.

Methods: This is a phase 1, multicenter, open-label, dose-escalation study of adult pts with confirmed GIST who progressed on or intolerant to imatinib and other standard of care treatments. A BOIN dose-escalation design was used; pts received oral NB003 in 7 dose levels (DL), ranging from 3mg to 40mg twice daily (BID). The primary endpoint was safety and tolerability. Other endpoints were PK, PD, and early efficacy signal by mRECIST.

Results: As of 19 April 2023, 23 pts (median age, 56.0) were enrolled; 60.9% were male and 78.3% had ECOG PS 1. 78.3% received at least 4 lines of prior TKIs. The most frequent treatment-related adverse events (TRAEs) were CPK increased (95.7%), AST increased (87.0%), face oedema (82.6%), periorbital oedema (82.6%), WBC decreased (78.3%), anaemia (73.9%), neutrophil count decreased (69.6%), amylase increased (65.2%), platelet count decreased (47.8%), lipase increased (43.5%), ALT increased (34.8%), fatigue (34.8%) and oedema peripheral (34.8%). 2 pts from 40 mg BID DL (Grade 3 fatigue, Grade 3 face oedema) and 1 pt from 30mg BID DL (Grade 3 febrile neutropenia, Grade 3 rash maculo-papular) experienced DLTs. TRAE (face oedema) leading to permanent discontinuation in 1 patient at 40mg BID. 3 of the 19 evaluable pts had confirmed and 2 pts had unconfirmed RECIST partial responses (PRs). The confirmed ORR was 15.8% (3/19), disease control rate (DCR: PR + stable disease [SD]) was 78.9% (15/19). The increase of drug exposure was approximately dose proportional at steady state.

Conclusions: NB003 has a manageable toxicity profile and promising clinical activity in heavily pretreated pts with advanced GIST harboring a broad spectrum of acquired imatinib-resistant mutations. The 20mg and 30mg BID doses are selected for further investigation in the phase I RP2D confirmation cohort.

Clinical trial identification: NCT04936178.

Legal entity responsible for the study: Ningbo Newbay Technology Development Co., Ltd.

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Disclosure: K. Hu, L. Zhang, Y. Xu: Financial Interests, Institutional, Member: Ningbo Newbay Technology Development Co. Ltd. All other authors have declared no conflicts of interest.

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1917MO CHAPTER-GIST-101: A phase I study of pimitespib combined with imatinib in patients with imatinib-refractory gastrointestinal stromal tumor

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Background: Pimitespib (PIMI), a novel heat shock protein 90 inhibitor, was approved in Japan for patients (pts) with advanced gastrointestinal stromal tumor (GIST) after chemotherapies based on the results of the phase 3 study (CHAPTER-GIST-301). PIMI showed anti-tumor activity in an imatinib (IMA)-resistant GIST xenograft model and enhanced the activity when combined with IMA. Thus, PIMI + IMA could be effective in pts resistant to IMA. Here, we will present the results from dose-escalation part of the study (NCT05245968), of PIMI + IMA in pts with IMA-refractory GIST.

Methods: Pts with histologically confirmed, IMA-refractory GIST in second-line setting were eligible. Once daily dose of 120 mg (DL1) or 160 mg (DL2) PIMI was administered orally on a 5-day on/2-day off schedule, and 400 mg of IMA was administered once daily on a standard 3+3 dose escalation. The primary endpoint was to determine dose-limiting toxicity (DLT) and maximum tolerable dose (MTD) of PIMI + IMA. The secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: Twelve pts (DL1 [n=6] and DL2 [n=6]) who were treated with IMA in first-line setting for median 21.7 months (mos) were enrolled in Japan. No DLTs were

observed at both doses and the MTD was at DL2. The common (≥ 60%) treatment-related adverse events (TRAEs) in DL1 and DL2 were diarrhea (83.3%/ 100%), nausea (50%/ 83.3%), night blindness (16.7%/ 83.3%), blood creatinine increased (33.3%/ 66.7%), dysgeusia (16.7%/ 66.7%) and decreased appetite (0%/ 66.7%), respectively. No serious TRAEs, TRAEs leading to study discontinuation or death were observed. The ORR was 8.3% (one confirmed partial response) and the DCR was 91.7%. 66.7% showed tumor shrinkage and 58.3% were stable for more than 6 mos. Median PFS was 12.9 mos (95% CI, 2.8 — not calculated).

Conclusions: PIMI + IMA combination was well tolerated with no new concerns at DL1 and DL2. It was effective despite pts being refractory to IMA, even when compared to those reported in previous studies on second-line setting with sunitinib. The expansion part of this study to evaluate safety and efficacy is currently recruiting pts globally at DL1, that has a better safety profile.

Clinical trial identification: NCT05245968.

Legal entity responsible for the study: Taiho.

Funding: Taiho.

Disclosure: Y. Naito: Financial Interests, Personal, Invited Speaker, Speakers Bureau: Chugai, Pfizer, Eli Lilly, Eisai, AstraZeneca, PDR pharma, Novartis, Gardant, Ono, Takeda, Taiho, Bayer, Nihon Kayaku, Daiichi Sankyo, BMS, MSD; Financial Interests, Personal, Funding: Roche; Financial Interests, Personal, Local PI: AbbVie, Boehringer Ingelheim, Ono, Chugai, Taiho, Pfizer, AstraZeneca, Gilead, Takeda; Financial Interests, Personal, Steering Committee Member: Daiichi Sankyo; Non-Financial Interests, Principal Investigator, JCOG: Natera. Y. Komatsu: Financial Interests, Personal, Invited Speaker: Ono Pharmaceutical Co., Ltd., Daiichi Sankyo, Taiho, Chugai, Lilly, Merck, MSD, BMS, Takeda, Bayer Yakuhin, Moroo Co., Asahi Kasei, Pfizer, Nippon Zoki Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Incyte Corporation, Zeria Pharmaceutical Co., Ltd., Yakult Honsha, Nipro Corporation, Sanofi/Aventis, Astellas Pharma Inc., Nippon Kayaku Co., Ltd.; Financial Interests, Personal, Writing Engagement: Eli Lilly and Company, Yakult Honsha Co.,Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Ono Pharmaceutical CO., Ltd.,Taiho Phamaceutical Co., Ltd.; Financial Interests, Institutional, Research Grant: Ono Pharmaceutical Co., Ltd., Taiho, Chugai, Sanofi, Nipro, Daiichi Sankyo, BMS, Sysmex Corporation, EPS Holdings, Inc., Asahi Kasei Pharma Corporation, Nippon Zoki Pharmaceutical Co., Ltd., Nippon Kayaku Co. Ltd.; Non-Financial Interests, Member: JSCO, JSMO, ASCO. Y. Kurokawa: Financial Interests, Institutional, Local PI: Taiho; Financial Interests, Institutional, Research Grant: Taiho; Financial Interests, Personal, Invited Speaker: Taiho. H. Hirano: Financial Interests, Personal, Invited Speaker: Taiho Pharmaceutical, Ono Pharmaceutical, Teijin Phama, Novartis; Financial Interests, Personal, Writing Engagement: Nichi-Iko; Financial Interests, Institutional, Research Grant: Chugai Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Ono Pharmaceutical, Janssen Pharmaceutical, Merck Biopharma, BMS, Pfizer, Eisai, AMGEN, Astellas, Seagen, MSD, Insyte, BeiGene, Novartis. T. Nishida: Financial Interests, Institutional, Invited Speaker, Speaker's Bureau: Taiho; Financial Interests, Institutional, Invited Speaker: Pfizer, Eisai. T. Doi: Financial Interests, Personal, Other, Advisory Role: Noil-Immune Biotech, Oncolys BioPharma, Boehringer Ingelheim, A2 Healthcare, Nano Carrier, PRA Health Sciences, Kaken Pharma, Chugai Pharma, Sumitomo Pharma, Shionogi, Otsuka Pharma, Takeda, Kyowa Kirin, Rakuten Medical, Giliad; Financial Interests, Personal, Invited Speaker: Daiichi Sankyo; Financial Interests, Institutional, Research Grant: Taiho, MSD, AbbVie, Eisai, Pfizer, BMS, Janssen Pharma, Daiichi Sankyo, Chugai Pharma, Boehringer Ingelheim, PRA Health Sciences, Amgen, GSK, Shionogi, RIN Institute, Ono Pharma.

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1918MO Circulating tumor DNA in relation to tumor volume in gastro-intestinal stromal tumors

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Background: Locally advanced/metastatic gastro-intestinal stromal tumors (GIST) are followed with 3-6 monthly CT-scans to evaluate treatment response with tyrosine kinase inhibitors (TKIs). As a result, patients are exposed to accumulative levels of radiation. Therefore, a growing interest on the use of circulating tumor DNA (ctDNA) to monitor treatment response has arisen. Previous research reported the correlation of ctDNA with tumor volume as new tool for monitoring treatment response. The aim of this exploratory study was to evaluate the use of ctDNA testing in GIST patients treated with TKIs, and to compare changes in the levels of ctDNA with tumor volume (3D) with CT-scan results assessed according to RECIST 1.1.

Methods: 147 plasma samples from 7 GIST patients with a KIT exon 11 mutation were prospectively collected before or during treatment and follow-up between 2014-2021. Plasma ctDNA levels were determined using a validated KIT exon 11 digital droplet PCR (ddPCR) drop-off assay. RECIST outcome was extracted from routine imaging reports of follow-up CT scans. Clinical relevant samples were selected based on RECIST outcome (response to treatment or progressive disease) or start of a new treatment line. Total tumor volume measurements with a semi-automated manner, allowing for manual correction, were performed by an independent radiologist.

Results: 101 clinically relevant plasma samples were analyzed. In all baseline samples the primary tumor KIT exon 11 mutation could be detected in ctDNA, ranging from 1.54 to 2287.81 copies per mL plasma. Upon response to treatment, ctDNA completely disappeared in all patients. At progressive disease, ctDNA could be, at least once, detected in 6 of 7 patients. Higher tumor volumes (from 450 mL) correlated with higher levels of ctDNA. In each individual patient with progressive disease on imaging, undetectable ctDNA was consistent with lower tumor volumes than detectable ctDNA.

Conclusions: Total tumor volume measurement is the most accurate indicator of GIST disease activity. No absolute cut-off value of tumor volume in which ctDNA could be detected could (yet) be determined to indicate active (progressive) disease. CtDNA can be a promising and cost-effective additional follow-up tool to monitor treatment response.

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Legal entity responsible for the study: The authors.

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1919MO Efficacy and safety of botensilimab (BOT) plus balstilimab (BAL) in patients (pts) with refractory metastatic sarcoma

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Background: BOT, a multifunctional Fc-enhanced anti-CTLA-4 antibody, enhances T cell priming, activation, and memory formation, depletes intratumoral Tregs and minimizes complement fixation. BOT±BAL has shown effectiveness across a wide variety of 'cold'/ I-O—resistant solid tumors. We report results from an expanded phase Ib study in refractory metastatic sarcoma treated with BOT+BAL (NCT03860272).

Methods: Pts received BOT 1 or 2 mg/kg every 6 wks (or fixed-dose equivalent) + BAL 3 mg/kg every 2 wks. Endpoints include overall response rate (ORR), disease control rate (DCR; best response of stable disease [SD], complete [CR] or partial response [PR]), progression free survival (PFS), overall survival (OS), and safety.

Results: We report on 22 evaluable pts who started treatment by Dec 5, 2022 with at least one 6-wk scan and ≥18 wks follow-up (data cutoff: May 3, 2023). Median age was 62 (range 40—80). Most common histologies were leiomyosarcoma, angiosarcoma (including 5 visceral) and liposarcoma. Median number of prior lines was 3, 18% had failed immunotherapy and median follow-up was 6.5 mos (range 1.4—26.1). ORR by RECIST1.1 was 27% (6/22; 95% CI 11—50) and median duration of response (DOR) was not reached across multiple subtypes. Six additional pts had meaningful clinical benefit: 1 with minor early progression (followed by a deep, durable ongoing response of 108+wks; 98%); 1 with an unconfirmed CR; and 4 with SD at 24 wks (3 ongoing). DCR was 68%, 6mo PFS was 50% (95% CI 26—70), and 12-mo OS was 82% (95% CI 52—94). More than 20 additional pts have been treated, and mature efficacy and safety data along with preliminary biomarker analyses will be presented. Safety profile (N=22) remains favorable and consistent with previously reported data. Any grade treatment-related adverse events (TRAEs) occurred in 91% of pts, grade 1-2 TRAEs 77%, grade 3 TRAEs 14% and no grade 4/5 TRAEs. The only grade 3 TRAEs occurring in >1 pt was diarrhea/colitis (9%). No treatment-related deaths occurred.

Conclusions: BOT+BAL exhibits significant efficacy with durable responses in pts with poorly immunogenic, refractory sarcomas, with a manageable safety profile. The expanded phase Ib study is ongoing.

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Legal entity responsible for the study: Agenus Inc.

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1920MO Regomune: A phase II study of regorafenib + avelumab in solid tumors - Results of the advanced or metastatic gastrointestinal stromal tumors (mGIST) cohort

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Background: Regorafenib (R) has been approved as 3d line in mGIST patients (pts), with a median progression-free survival (mPFS) of 4.9 months (GRID study). R can alleviate the immunosuppressive GIST tumor micro environment by several mechanisms such as modifying the polarization of tumor-associated macrophages, reducing T regs infiltration. Thus, combining anti-PD1/PDL1 agents with anti-angiogenics appears promising in this population.

Methods: This is a single-arm open-label multicentric phase II trial assessing the efficacy and safety of R (160 mg QD 3weeks/4) + Avelumab (A) (10 mg/kg every 2 weeks) combination in pts with mGIST. The primary endpoint was the 6-month progression-free rate (6-month PFR) based on RECIST 1.1 criteria after central review. Secondary endpoints included: 6-month objective response, 1-year PFS, 1-year overall survival (OS), and safety using NCI-CTCAE v5.0. Correlative studies were planned from pts tumor samples obtained at baseline.

Results: Between November 2018 to July 2022, 50 pts were enrolled in 6 centers. Median age was 64 (range: 26-82). Median follow-up was 28.6 months (95% CI: 15.5 − 35.2). Median number of previous treatment lines was: 2 (range: 1-4). 42 (84%) pts experienced at least 1 dose modification or treatment interruption due to R and/or A. The most common grade 3/4 adverse events were: Palma-plantar erythrodysesthesia syndrome (18% of pts), hypertension (14%), diarrhea and maculopapular rash (12% each). No death was related to the treatment. Among the 46 assessable pts, 6-month PFR is 37% (N=17): 3 (6.5%) had partial response, 14 (30.4%) a stable disease, 23 (50%) a progressive disease, 6 were not evaluable. 24 (52.2%) had tumor shrinkage. Median PFS and OS are 5.5 months (95% CI: 3.6 − 7.5) and 19.5 months (95% CI: 13.7-33.5) respectively. 22% of pts are progression-free at one year. 6-month and 1-year OS rates are 93.5% (95% CI: 81.1-97.8) and 70.8% (95%CI: 55-81.9) respectively.

Conclusions: Regomune is the largest prospective study evaluating an approved TKI in combination with an IO agent in pts with advanced GIST. A subset of pts derived long term clinical benefit. Correlative studies will be presented at the meeting.

Clinical trial identification: NCT03475953.

Legal entity responsible for the study: S. Cousin.

Funding: Bayer and Merck Serono S.A.S.

Disclosure: S. Cousin: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, BMS, MSD, Novartis; Financial Interests, Personal, Advisory Board: Sanofi, AbbVie; Non-Financial Interests, Institutional, Principal Investigator: MSD, BMS, GSK, Sanofi, AbbVie, Roche. T. Valentin: Financial Interests, Personal, Advisory Board: Boehringer Ingelheim, GSK, Blueprint. B. Verret: Financial Interests, Personal, Other, travel expenses: Lilly, Novartis, Pfizer, accord healthcare, Amgen, AstraZeneca, Daiichi Sankyo; Financial Interests, Institutional, Speaker, Consultant, Advisor: Lilly, Daiichi Sankyo, Novartis, MSD, AstraZeneca, Owkins; Financial Interests, Personal, Speaker, Consultant, Advisor: Pfizer, Netcancer, Pierre Fabre, Seagen, Gilead. A. Adenis: Financial Interests, Personal, Advisory Board: Bayer, BMS, MSD; Financial Interests, Personal, Invited Speaker: Novartis, BMS; Financial Interests, Personal, Other, Travel: Servier, BMS, MSD; Financial Interests, Institutional, Research Grant: Bayer; Financial Interests, Institutional, Coordinating PI: Roche, BMS, MSD, Sanofi; Financial Interests, Institutional, Local PI: BeiGene, AstraZeneca. P. Cassier: Financial Interests, Personal, Invited Speaker: Amgen; Financial Interests, Personal, Advisory Board: Roche, Amgen, Boehringer Ingelheim; Financial Interests, Personal, Other, Advisor: OSE immunotherapeutics; Financial Interests, Institutional, Local PI: AbbVie, Blueprint, Boehringer Ingelheim, BMS, Exelixis, GSK, Incyte, Janssen, Loxo/Eli Lilly, Novartis, Roche, Taiho, Toray Industries; Financial Interests, Institutional, Coordinating PI: Amgen, Transgene; Non-Financial Interests, Institutional, Product Samples: Plexxikon, Novartis, MSD, AstraZeneca, GSK. A. Hollebecque: Financial Interests, Personal, Invited Speaker: Servier, Incyte, Eisai; Financial Interests, Personal, Advisory Board: Basilea, Taiho, Relay Theraeutics, QED Therapeutics, Debiopharm, MSD, Boehringer Ingelheim; Financial Interests, Institutional, Funding: Incyte; Financial Interests, Institutional, Research Grant: AstraZeneca; Non-Financial Interests, Principal Investigator, M19-345: AbbVie; Non-Financial Interests, Principal Investigator, CO42216; WP42627; CO40939: Roche; Non-Financial Interests, Principal Investigator, MCLA-158: Merus; Non-Financial Interests, Principal Investigator, SGNB6A: Seatle Genetics; Non-Financial Interests, Principal Investigator, TAS-120-202: Taiho; Non-Financial Interests, Principal Investigator, Krystal-10: Mirati; Non-Financial Interests, Principal Investigator, ADP-0033: Adaptimmune; Non-Financial Interests, Principal Investigator, ACT16902: Sanofi; Non-Financial Interests, Principal Investigator, C4201002: Pfizer; Non-Financial Interests, Principal Investigator, RLY-4008: Relay Therapeutics; Non-Financial Interests, Principal Investigator, CC-90011: Celgene/BMS; Non-Financial Interests, Principal Investigator, Loxo-IDH: Loxo/Lilly; Non-Financial Interests, Principal Investigator: AstraZeneca; Non-Financial Interests, Principal Investigator, SN-201 study: Sotio; Non-Financial Interests, Principal Investigator, Tropics-03: Gilead; Non-Financial Interests, Principal Investigator, BI1403: Boehringer Ingelheim. A. Italiano: Financial Interests, Personal, Advisory Board: Bayer, Roche, Philips, Chugai, GSK; Financial Interests, Institutional, Coordinating PI: Bayer, AstraZeneca, Roche, MSD, Ipsen, Merck. All other authors have declared no conflicts of interest.

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1921MO Patterns of care, outcome and molecular landscape of PATZ1-rearranged sarcomas identifies two prognostic profiles: A cohort study from the French Sarcoma Group (FSG)

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Background: PATZ1 rearranged sarcomas (PRS) belong to the "round cell sarcomas with EWSR1—non-ETS fusions" group in 2020's WHO classifications. With only small case series (<10 cases) reporting deep clinical and histological heterogeneity, uncertain prognosis and absence of standard of care, PRS imperatively require further clinico-molecular characterization.

Methods: Pediatric and adult patients from 13 French centers with a diagnosis of PRS from 2011 to March 2023 were included. All PRS diagnosis were histologically and molecularly reviewed by 4 expert pathologists. Patients and tumors characteristics were collected from the national NETSARC+ database (netsarc.sarcomabcb.org) and whole exome-RNAseq was performed with FFPE material.

Results: Seventeen patients were included with a mean follow up of 44 months including 16 with EWSR1::PATZ1 and one with MN1::PATZ1 fusions. Clinical data were heterogeneous in term of baseline clinical characteristics, histopathology, management and outcome. In univariate analyses, age, tumor size, FNCLCC-grade, adjuvant systemic therapy for non-metastatic disease did not correlate to overall survival (OS) whereas stage, Ki67 and some transcriptomic signatures -relative to cell cycle- did. A group of patients with metastasis or Ki67>30% had aggressive clinical course and poor responses to treatment (whether Ewing-like regimen or other). A distinct group of patients had indolent profiles and were long-term free of recurrence (>5years) after surgery alone without adjuvant chemo/radiotherapy.

Table: 1921MO Univariate analysis of OS using the Cox model: Median OS is 33.5 months (range 5 :120)

Parameter	Variable	N=	HR	CI95%	P-Value	P level[1]
Age	Continuous	17	1.01	(0.98;1.05)	0.378	ns
Sex	M vs F	11 vs 6	2.02	(0.279;7.24)	0.279	ns
Tumor size (mm)	Continuous	17	1.02	(0.99;1.04)	0.053	ns
Primary site	Trunk vs others	7 vs 10	1.4	(0.43;4.70)	0.55	ns
Stage (initial)	Localized/ loc.Adv. vs Metastatic	10 vs 7	21.1	(2.942;2.94)	2.942	**
Ki67% (adult)	Continuous	9	1.02	(1.02;)	0.0274	*
Grade (FNCLCC)	Grade 2 vs 3	8 vs 7	0.59	(0.16;2.15)	0.427	ns
RNAseq cell cycle G2_M score	Continuous	15	4.1243	(1.33;12.76)	0.0139	*
Adjuvant systemic treatment	Systemic treatment vs Surveillance	7 vs 3 all no metastasis	0.46	(0.04;4.9)	0.52	ns

1 level of significance: p>0.05:ns; p<0.05:,p<0.01:**;p<0.001:***

Conclusions: Our study suggests that the natural history pf PRS differs from Ewing sarcomas. We reveal that some good prognosis PRS are cured with surgery alone while others are aggressive. Stage and ki67 should help to identify those patients while further molecular analyzes are pending.

Legal entity responsible for the study: The authors.

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1922P Immunosarc II master trial: phase II of sunitinib and nivolumab in vascular sarcomas cohort - A GEIS, ISG and UCL study

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Background: Advanced angiosarcoma comprises an aggressive sarcoma subset that exhibits poor prognosis and short-term duration of responses. Series treated with anthracyclines or taxanes reported an mPFS that ranged from 2.7 to 3.7 m. A trial with sorafenib reported a mPFS of 1.8 and 3.8 m, 6-m-PFSr of 25% and 31% (9m-PFSr of 0 and 3.8%), ORR of 15 and 13% and mOS of 9 and 12 m, for superficial and visceral cohorts respectively. As IMMUNOSARC I master-trial exploring sunitinib (S) plus nivolumab (N) in sarcoma detected signal of activity in angiosarcoma patients, a specific cohort of vascular sarcomas was designed as phase II trial in IMMUNOSARC II (NCT03277924).

Methods: Advanced, recently progressing, measurable and centrally reviewed vascular sarcomas (angiosarcoma, intimal sarcoma and epithelioid hemangioendothelioma) were enrolled and treated with S: 37.5 mg/d in first 14 days, then continued with 25 mg/d, along with N 240 mg every 2 weeks up to progression or intolerance. Imaging tests were assessed every 8 weeks. The main endpoint was 6m-PFSr, and the statistical assumptions were obtaining a 6m-PFSr in at least 11 patients out of 23 patients, with H_0=30% and H_1=60% (α 0.05; β 0.10).

Results: Patients with angiosarcoma (17), EHE (6) and intimal sarcomas (3) were accrued from Oct. 2019 to Apr. 2023 in 8 centers from Spain, Italy and UK. Patients had a median age of 60 y (25-82), F=20/M=6 distribution and a median of previous lines of 2 (0-5). Median follow-up was 24 m (5.9-42.1). The 6m-PFSr was 45% (23-66) for 23 evaluable patients. Considering angiosarcoma patients, there were 5 (33%) PR, 7 (47%) SD and 3 (20%) PD out of 15 evaluable patients. The mPFS was 3.93 m and the 6m-PFSr was 36% (11-61). The mOS was 15.73 m (1.83-29.64). End-of-treatment reasons were PD 71%, toxicity 22% and doctor decision 7%. Most common grade 3-4 TREAEs were neutropenia (11.8%) and asthenia (11.8%).

Conclusions: S and N combination has demonstrated to be active in advanced vascular sarcomas. This activity favorably compares with that previously reported for sorafenib activity. Even though the outcome did not reach the H1, antiangiogenics and PD1 inhibitors deserve to be explored, maybe with other combinations, in vascular sarcomas.

Clinical trial identification: NCT03277924.

Legal entity responsible for the study: Spanish Group for Research on Sarcoma (GEIS).

Funding: Pfizer and BMS.

Disclosure: J. Martinez Trufero: Financial Interests, Personal, Advisory Board, Advisory Board meeting: PharmaMar, Eisai; Financial Interests, Personal, Invited Speaker: Roche, Eisai, Merck, Medicamenta, MSD, Ipsen; Financial Interests, Personal, Advisory Board, Advisory Board Meeting: GSK, Deciphera, Boehringer Ingelheim, Eisai; Financial Interests, Institutional, Local PI, Clinical trial: RAIN Therapeutics, Blueprint, Lilly, Kariopharm Therapeutics, Syneos Health, Boehringer Ingelheim, Ayala Pharmaceuticals, SynOx Therapeutics; Non-Financial Interests, Member of Board of Directors, Spanish group of Sarcoma Research: GEIS Group; Non-Financial Interests, Member of Board of Directors, Spanish Group of Head and Neck cancer Research: TTCC Group. S. Strauss: Financial Interests, Personal, Advisory Board: GSK; Financial Interests, Personal, Advisory Board, medical advisor: Ceridwen Oncology. S. Stacchiotti: Financial Interests, Personal, Advisory Board: Bayer, Bavarian Nordic, Daiichi Sankyo, Novartis, Ikena, Astex Pharmaceuticals, Rain Therapeutics; Financial Interests, Personal, Invited Speaker: GSK, PharmaMar, Aadi; Financial Interests, Personal, Advisory Board, Advisory board meeting: Agenus; Financial Interests, Personal, Advisory Board, Advisory board meetings: Boehringer Ingelheim; Financial Interests, Personal, Invited Speaker, Lectures: Gentili; Financial Interests, Personal, Advisory Board, Advisory board: Servier; Financial Interests, Institutional, Local PI: Advenchen, Deciphera, Epizyme, Daiichi Sankyo, GSK, Karyopharm, PharmaMar, SpringWorks, Hutchison MediPharma International Inc, Inhibrix; Financial Interests, Institutional, Coordinating PI: Bayer; Financial Interests, Institutional, Funding: Blueprint, Novartis; Non-Financial Interests, Member of Board of Directors, Secretary: Connective Tissue Oncology; Non-Financial Interests, Advisory Role: Chordoma Foundation, Epithelioid Haemangioendothelioma Foundation , Desmoid Foundation , Epithelioid Hemangioendothelioma (EHE) Rare Cancer Charity (UK); Non-Financial Interests, Other, Secretary: EORTC soft tissue and bone sarcoma group; Non-Financial Interests, Leadership Role, President: Italian Sarcoma Group. D. Da Silva Moura: Financial Interests, Personal, Other, Travel: Pfizer. J. Martin-Broto: Financial Interests, Personal, Advisory Board, Honoraria: Lilly, PharmaMar, Eisai, Bayer, Roche, Boehringer Ingelheim, Amgen; Financial Interests, Personal, Invited Speaker: PharmaMar; Financial Interests, Personal, Advisory Board, Speaker: Tecnofarma, Asofarma; Financial Interests, Institutional, Coordinating PI: PharmaMar, Eisai, Novartis, IMMIX Biopharma, Lixte, Karyopharm, Bayer, Celgene, Pfizer, BMS, Lilly; Financial Interests, Institutional, Local PI: Blueprint, Deciphera, Nektar, Forma, Amgen, Daiichi Sankyo, Arog, Adaptimmune, GSK, Ran Therapeutics, Inhibrx, Ayala Pharmaceuticals, Philogen, Cebiotex, PTC Therapeutics, Inc. and SpringWorks therapeutics. All other authors have declared no conflicts of interest.

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1923P Combined analysis of phase III ANNOUNCE study and phase II study exploring olaratumab in advanced soft tissue sarcoma

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Background: Doxorubicin remains the standard of care for most of advanced soft tissue sarcoma. However, survival for patients with advanced soft tissue sarcoma is unsatisfactory. Consequently, there is an urgent need for new treatments. Olaratumab is a monoclonal antibody directed against the platelet-derived growth factor receptor and has been studied in soft tissue sarcoma. In a phase II study, olaratumab in combination with doxorubicin showed an overall survival benefit over doxorubicin alone. However, a confirmatory phase III ANNOUNCE study failed to demonstrate the benefit of olaratumab. One possible explanation of the contradictory results is that the dose of doxorubicin used in each trial is significantly different. Therefore, we examined the effect of doxorubicin dose on survival using individual data from the phase II and phase III studies.

Methods: Individual patient data were retrieved from the Vivli platform (https://vivli.org/) after study proposal approval. Patient characteristics including clinicopathologic findings, progression-free and overall survival (OS) data, and doxorubicin dose were analyzed. Cox proportional hazard model was used to estimate the effect of doxorubicin dose on survival.

Results: A total of 632 patients (128 from phase II and 504 from phase III study) were included in the current study. Median age was 58 years, 267 (42.2%) were male, 375 (59.3%) were performance status 0, and 282 (44.6%) had leiomyosarcoma. Median cumulative doxorubicin dose was 449 mg/m^2 in all patients, 426 mg/m^2 (488 in phase II and 409 in phase III) for doxorubicin with olaratumab arm and 451 mg/m^2 (300 in phase II and 483 in phase III) for doxorubicin alone arm. In the combined analysis olaratumab showed marginal OS benefit (HR: 0.83, 95%CI: 0.69-1.01, p-value: 0.061). Cumulative doxorubicin dose had statistically significant impact on OS (HR for difference in dose of 75mg/m^2: 0.80, 95%CI: 0.77-0.83, p-value: $<$0.001).

Conclusions: Cumulative doxorubicin dose had a significant impact on OS, with a HR of 0.80 for the difference by doxorubicin dose per cycle, which may explain the discrepancy between the phase II and phase III results. Our investigation reaffirms the importance of doxorubicin in advanced soft tissue sarcoma.

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Disclosure: Y. Naito: Financial Interests, Personal, Invited Speaker, Speakers Bureau: Chugai, Pfizer, Eli Lilly, Eisai, AstraZeneca, PDR pharma, Novartis, Gardant, Ono, Takeda, Taiho, Bayer, Nihon Kayaku, Daiichi Sankyo, BMS, MSD; Financial Interests, Personal, Funding: Roche; Financial Interests, Personal, Invited Speaker: AbbVie, Boehringer Ingelheim, Daiichi Sankyo, Ono, Chugai, Taiho, Pfizer, AstraZeneca, Gilead, Takeda; Non-Financial Interests, Principal Investigator, JCOG: Natera. T. Mukohara: Financial Interests, Personal and Institutional, Invited Speaker: Daiichi Sankyo, Eisai, MSD, Pfizer, Novartis, Sanofi, Chugai, AstraZeneca, Ono; Financial Interests, Personal and Institutional,

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1924P Targeting microenvironment and cellular immunity in sarcomas with trabectedin combined with metronomic cyclophosphamide: The TARMIC study

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Background: Recent pre-clinical data have suggested that the antitumor activity of trabectedin is not only related to their effects on tumor cells, but also on its ability to affect the tumor microenvironment (TME), in particular tumor associated macrophages and their pro-tumoral functions. We report results of the phase II part of the first study evaluating trabectedin in combination with metronomic chemotherapy on the TME of patients (pts) with advanced sarcomas.

Methods: TARMIC is an open-label multicenter phase I/II study of trabectedin in combination with low-dose cyclophosphamide in pts with advanced STS. The RP2D was of 0.5 mg/m^2. Primary endpoint was 6-month non progression rate. Secondary endpoints included efficacy and evaluation of impact on TME through mandatary tumor biopsies at baseline and after one cycle of treatment.

Results: 30 patients (17 males, 13 females) have been included. Median age was 67 years (23 − 80). The two most frequent histologies were undifferentiated pleiomorphic liposarcoma (n=9) and leiomyosarcoma (n=7). The median number of previous lines of treatment was 2 (range 1-5). The most frequent adverse events were: grade 1/2 fatigue (86.7%), nausea (66.7%) and anemia (66.7%). 24 pts were eligible and assessable for efficacy. Best objective response as per RECIST based on central review was: partial response for 2 (8.3%), stable disease for 9 (37.5%) and progressive disease for 13 pts (54.2%) respectively. 3 pts (12.5% IC95% [2.7%; 32.4%]) were progression-free at 6 months indicating that the first endpoint was not reached. Median progression-free survival and overall survival were 1.9 months (95% CI: [1.7; 4.4]) and 12.0 months (95% CI: [5.8; -]), respectively. RNA sequencing of paired biopsies indicated that patients with activation immune response and Th17 differentiation had a better outcome. Increase in CD8 T cell density was significantly associated with improved PFS. No impact of trabectedin on macrophage infiltration was observed.

Conclusions: We report the first clinical study investigating the immunological activity of trabectedin in patients with advanced STS. Modulation of TME under trabectedin appear to be correlated with outcome.

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Legal entity responsible for the study: Institut Bergonie.

Funding: PharmaMar.

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1925P Results of SOC-2082 phase II study using metronomic gemcitabine, doxorubicin, and docetaxel plus nivolumab as second/third-line therapy for advanced leiomyosarcoma

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Background: Metronomic dosing of gemcitabine, doxorubicin and docetaxel causes less severe side effects than standard chemotherapy for advanced leiomyosarcoma.

Methods: Primary objective: To assess progression-free survival (PFS); Secondary objectives: (1) To evaluate the best overall response, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 12 months, and (4) Incidence of treatment-related adverse events (TRAEs). Inclusion criteria: Previously treated male and female subjects, ≥ 18 years of age, pathologically confirmed diagnosis of locally advanced, unresectable, or metastatic leiomyosarcoma, measurable disease by RECIST v1.1, and acceptable hematologic and organ functions. Exclusion Criteria: History of autoimmune disorder. Treatment schedule: Metronomic doses of gemcitabine (600 mg/m^2 max:1000 mg), doxorubicin (18 mg/m^2; max: 32 mg), docetaxel (25 mg/m^2; max:42 mg) on Day 1 and Day 8, and nivolumab (240 mg) on Day 1 only. Repeat treatment cycles may be given every three weeks if the toxicity grade is ≤1.

Results: Efficacy (n=17). This population completed at least one treatment cycle and had a follow-up CT or MRI scan at week 6. Confirmed best overall response = 4 PR, 11 SD, 2 PD. The overall response rate was 23.5%, disease control rate (CR+PR+SD) was 88.2%. The median PFS was 6.3 (95% CI: 2.837-7.363) months; 6-month PFS rate 53%. As of data cut-off date, the median OS was >14.6 months. Safety (n=18): This population had at least one dose of study drugs. Grade 3/4 TRAEs include thrombocytopenia (50%), neutropenia (44%), white blood cell count decreased (38.9%), anemia (22.2%), nausea (16.7%), anorexia (5.6%), diarrhea (5.6%), fatigue (5.6%), rectal bleeding (5.6%), transaminitis (5.6%). There were no unexpected adverse events reported. As of data cut-off date, the median OS was >14.3 months.

Conclusions: Taken together, the data suggest that nivolumab plus metronomic doses of gemcitabine, doxorubicin, and docetaxel (1) may have synergistic activity, and (2) is an effective second/third -line therapy for advanced leiomyosarcoma with manageable toxicity.

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1926P Trabectedin plus radiotherapy on symptomatic advanced sarcoma patients: Results from the SYNERGIAS study - A Spanish group for research in sarcoma (GEIS) phase II study

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Background: Pain relief and improvement of quality of life (QoL) is a critical objective in the therapy of patients (pts) with symptomatic advanced soft-tissue sarcoma (STS). The combination of trabectedin (T) and low-dose radiotherapy (RT) showed unprecedent activity in a previous study showing an overall response rate (ORR) of 60% by central review. This study further explores this combination, with the aim of analyzing the QoL improvement in sarcoma patients.

Methods: Pts with pretreated advanced/unresectable STS and symptomatic lesions were eligible to receive T 1,5mg/m^2 every 24h and RT 30Gy in 10 fractions (or 45 Gy in 25 fractions if the lesion was in limbs) on the symptomatic lesion/s, then T up to progression or unacceptable toxicity. Primary end-point was ORR by RECIST on the irradiated lesion. Secondary endpoints included QoL assessments (Brief pain inventory (BPI), EORTC QLQ C30), progression-free survival (PFS) and overall survival (OS). With H0 (10%), H1 (35%), (α 0.05 and β error 0.1), 27 evaluable pts were necessary.

Results: From June/2021 to March/2023, 33 pts were included (18M/15F, median age 53y (22-75), median previous lines 1 (0-4), ECOG 0/1 in 15/18 pts) and 26 pts were evaluable for response (efficacy population). Among the 26 evaluable pts, ORR in the irradiated lesions according to local assessment was 42.3% (1 CR, 10 PR, 13 SD, 2 PD). With a median FU of 7 months (mos) (95% CI 1-13), 18 pts have progressed, with a median PFS of 5.2 mos (95% CI 3.77-6.62) and 6m-PFS 44% (95% CI 23-64). During therapy, 17/33 (55%) of pts experienced a decrease of at least 2 points in the worst pain assessment of the BPI, with a median reduction of 2 points (range 0-8). 20/33 (64%) pts and 16/33 (52%) of pts reported an improvement of at least 1 point (on a scale 1-7) in their global health assessment and in their own QoL evaluation respectively. The main treatment-related G3-4 toxicities were neutropenia (18.2%), febrile neutropenia (9.1%), and ALT increased (9.1%). No toxic deaths have occurred.

Conclusions: Trabectedin plus palliative RT is a safe and active therapeutic regimen, able to induce clinical improvement in more than half of symptomatic sarcoma patients, and with a manageable toxicity profile.

Clinical trial identification: NCT05131386.

Legal entity responsible for the study: Grupo Español de Investigación en Sarcomas (GEIS).

Funding: PharmaMar.

Disclosure: J. Martin-Broto: Financial Interests, Personal, Advisory Board, Honoraria: Lilly, PharmaMar, Eisai, Bayer, Roche, Boehringer Ingelheim, Amgen; Financial Interests, Personal, Invited Speaker: PharmaMar; Financial Interests, Personal, Advisory Board, Speaker: Tecnofarma, Asofarma; Financial Interests, Institutional, Coordinating PI: PharmaMar, Eisai, Novartis, IMMIX Biopharma, Lixte, Karyopharm, Bayer, Celgene, Pfizer, BMS, Lilly; Financial Interests, Institutional, Local PI: Blueprint, Deciphera, Nektar, Forma, Amgen, Daiichi Sankyo, Arog, Adaptimmune, GSK, Ran Therapeutics, Inhibrx, Ayala Pharmaceuticals, Philogen, Cebiotex, PTC Therapeutics, Inc. and SpringWorks therapeutics. J. Cruz Jurado: Financial Interests, Personal, Advisory Board: PharmaMar, Roche, Lilly, Pfyzer, Novartis, Gilead, AstraZeneca, Daiichi Sankyo, Seagen, GSK, Bayer; Financial Interests, Personal, Invited Speaker: PharmaMar, Roche, Lilly, Pfizer, Novartis, Eisai, Gilead, AstraZeneca, Daiichi Sankyo, Seagen, Esteve; Financial Interests, Personal, Steering Committee Member: Roche. R.M. Alvarez: Financial Interests, Personal, Invited Speaker: PharmaMar; Financial Interests, Personal, Advisory Board: Boehringer Ingelheim, Novartis, Roche; Financial Interests, Personal, Other, conference registration: MSD Oncology; Financial Interests, Institutional, Coordinating PI: Roche; Financial Interests, Personal and Institutional, Coordinating PI: Janssen Oncology, Rain Therapeutics, Boehringer Ingelheim, Cebiotex, Novartis. C.M. Valverde Morales: Financial Interests, Personal, Advisory Board: PharmaMar, Bayer, GSK, Mundipharma, Lilly, Boehringer Ingelheim; Financial Interests, Personal, Invited Speaker: Roche; Financial Interests, Institutional, Local PI, Clinical Trial: Adaptimmune, Karyopharm, Lilly, Foghorn Therapeutics, Ayala therapeutics, Inhibrx; Financial Interests, Institutional, Coordinating PI, Clinical Proyect: Bayer; Non-Financial Interests, Member of Board of Directors, President 2018-ongoing: GEIS- Spanish Sarcoma Group for Research. A. Redondo Sanchez: Financial Interests, Personal, Invited Speaker: PharmaMar; Financial Interests, Institutional, Advisory Board: PharmaMar. D. Da Silva Moura: Financial Interests, Institutional, Research Funding: PharmaMar; Financial Interests, Personal, Invited Speaker: Tecnofarma. N. Hindi Muñiz: Financial Interests, Personal, Advisory Board: PharmaMar; Financial Interests, Personal, Invited Speaker: PharmaMar, Tecnofarma; Financial Interests, Institutional, Research Funding: PharmaMar, Lixte, ImmixBio, Boehringer Ingelheim, Ayala, Deciphera, Inbrx, Phillogen, Lilly; Financial Interests, Personal, Advisory Role: GSK. All other authors have declared no conflicts of interest.

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1927P Epithelioid hemangio-endothelioma (EHE) in NETSARC: The nationwide series of 267 patients over 12 years

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Background: Epithelioid hemangioendothelioma (EHE) is an ultrarare sarcoma whose natural history and treatment are not well defined. We report on the presentation and outcome of the nationwide exhaustive series of 267 patients with EHE in the NETSARC+ network since 2010 in France.

Methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized multidisciplinary tumor boards (MDTB), funded by the French NCI (INCA). Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients. Patients' characteristics are collected in a nationwide database regularly monitored. Exhaustivity in the collection of cases was reached since 2013. The characteristics of patients with EHE at diagnosis are presented as well as progression-free survival (PFS), overall survival (OS), and outcome under treatment.

Results: 267 patients with EHE were included in the NETSARC+ database since 2010. Median age in the series was 51 (range 10-90) years, 58% were women. Median tumor size was 37mm (4-220). 48%, 42%, and 10% were visceral, soft parts, or bone primaries. The most frequent sites were liver (28%), lung (13%). 40% were reported as metastatic at diagnosis. With a median follow-up of 20 months, OS and PFS rates at 24 months were 82% and 67%, with 10-years projected OS and PFS of 62% and 21% respectively. Male and M+ patients at diagnosis had a significantly worse OS, but not PFS. Local treatment was associated with a favorable survival in localized but not in advanced stage. For 23 patients receiving medical treatment, PFS and OS were 50.2% and 33.2% at 60 months were respectively.

Conclusions: EHE is a frequently metastatic sarcoma at diagnosis with a unique natural history. This study shows in an exhaustive nationwide series over 12 years that most patients progressed but are still alive at 10 years, both in localized and metastatic stages.

Legal entity responsible for the study: Centre Leon Bérard for NETSARC+ network.

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1928P Differential presentation and outcome of sclerosing epithelioid fibrosarcoma (SEF) vs low grade fibromyxoid sarcoma (LGFMS): The nationwide series of 330 patients in NETSARC since 2010

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Background: Sclerosing Epithelioid Fibrosarcoma (SEF) and Low Grade Fibromyxoid Sarcoma (LGFMS) are ultrarare sarcomas (incidence 0.15 and $0.51/10^6$/year respectively, PMID: 33630918) with close/similar translocations whose natural history and optimal treatment are not well known. We report on the nationwide exhaustive series of 330 patients with SEF or LGFMS in NETSARC+ since 2010.

Methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized multidisciplinary tumor boards (MDTB). Since 2010, pathological review is mandatory for sarcoma patients and patients' characteristics are collected in the NETSARC+ nationwide database. The characteristics of patients with SEF and LGFMS and their outcome are presented and compared.

Results: 35/73 (47.9%) and 125/257(48,8%) of patients with SEF and LGFMS were female. More primary visceral, bone and trunk primary sites were observed in SEF ($p<0.001$). 30.1% of SEF vs 4.3% of LGFMS were metastatic at diagnosis ($p<0.0001$). Median size of the primary tumor was 51mm (range 10-90). For LGFMS vs 80mm (20-320) for SEF ($p<0.001$). Median age of LGFMS was 12 years younger than that of SEF (43 [range 4-98] vs 55 [range 10-91], $p<0.001$). Neoadjuvant treatment was more often given to SEF (16.4% vs 8.6%, $p=0.05$). More patients with LGFMS were operated first in reference centers (51% vs 26%, $p<0.001$).The R0 rate was 41% in LGFMS vs 16% in SEF ($p<0.001$). Median PFS of SEF and LGFMS were 32 and 136 months ($p<0.0001$) respectively. The median OS was not reached. 50-months OS was 92.6% vs 81% fr SEF ($p=0.05$). Median survival was 77 months after first relapse, similar for SEF and LGFMS. In multivariate analysis for PFS, SEF histotype, size of the tumor, met at diagnosis were independently correlated to survival. In multivariate analysis for OS, age, size of the tumor, met at diagnosis, but not SEF, independently correlated to survival.

Conclusions: Although sharing close molecular alterations, SEF and LGFMS have a very different natural history, clinical presentation and outcome with a higher risk of metastatic relapse in SEF. Survival after relapse is longer than with other sarcomas, and similar for SEF and LGFMS.

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1929P phase II results from the RINGSIDE phase II/III trial of AL102 for treatment of desmoid tumors

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Background: There is an unmet need for more effective and well tolerated systemic therapy for desmoid tumors (DT, aggressive fibromatosis). Gamma secretase inhibitors (GSIs) have shown antitumor activity against DT. AL102 is a potent, oral, selective GSI under investigation for treatment of DT.

Methods: RINGSIDE is a phase 2/3 study for pts with progressing DT. In the open-label phase 2 study, adults with progressing DT ($\geq$10% unidimensional growth $\leq$18 mo or DT-related pain requiring non-opioid medication) were randomized to 3 dose regimens: 1.2 mg QD (once daily), 2 mg intermittent BIW (2 days on 5 days off), or 4 mg intermittent BIW. RINGSIDE phase 3 is a double-blind, placebo-controlled study evaluating the chosen dose regimen from phase 2 (1.2 mg QD). We report updated efficacy and safety results from RINGSIDE phase 2.

Results: All 42 phase 2 pts enrolled as of Mar 2022. As of Jan 3, 2023, median time on study was 10.5 mo (range 0.8 – 14.7) and 30 pts (71%) were still on study, 10 (24%) of whom rolled over to an open-label extension. Mean age was 40 yrs, 74% were women, and 69% had received prior DT therapy. The best response in the evaluable population by blinded independent central review (BICR) was partial response in 6/12 pts (50%) for 1.2 mg QD, 3/13 pts (23%) for 4 mg BIW, and 5/11 pts (46%) for 2 mg BIW. Disease control rate was 100%, 91%, and 97%, respectively. Deeper, more rapid and maintained response was observed with 1.2 mg QD. Median volume change (BICR) from baseline was -52% for 1.2 mg QD, -10% for 4 mg BIW, and -15% for 2 mg BIW at Week 16 and -76%, -36%, and -52%, respectively, at Week 28, with similar patterns for T2 signal intensity (reduced tumor cellularity). The 5 most common Grade 1-2 treatment-emergent adverse events (TEAE) were diarrhea, nausea, fatigue, alopecia, and dry skin. Grade 3 drug-related TEAE were reported in 10/42 (24%) pts. There were no Grade 4-5 or serious drug-related TEAE and no new safety signals. Final phase 2 data will be reported.

Conclusions: AL102 was well tolerated with a safety profile consistent with other GSIs. Tumor response, volume reduction and T2 signal reduction were observed earlier with 1.2 mg QD, with deeper and maintained treatment responses. This dose was selected for RINGSIDE phase 3 (currently enrolling).

Clinical trial identification: NCT04871282.

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1930P phase II trial of avelumab in combination with gemcitabine in advanced leiomyosarcoma as a second-line treatment (KCSG UN18-06)

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Background: Combined chemotherapy and anti-PD-1/PD-L1 antibody has shown a synergistic antitumor effect in several types of cancers. This study evaluated the efficacy and safety of avelumab plus gemcitabine in patients with leiomyosarcoma (LMS) who failed first-line chemotherapy.

Methods: This is a phase II, multicenter, open-label, single-arm study (NCT03536780). Patients with unresectable, locally advanced, or metastatic LMS received avelumab 10 mg/kg on days 1 and 15 (up to 24 months), plus gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 of a 28 day cycle until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). The secondary endpoints included duration of response (DOR), progression free-survival (PFS), overall survival (OS), and safety.

Results: Thirty-eight patients were enrolled between October 2018 and May 2022. Responses were observed in 7 out of 35 evaluable patients (ORR, 20%; 95% confidence interval [CI], 8–37%): 1 complete response and 6 partial responses. Disease control rate was 71.4%. Median DOR was 21.0 months (range, 7.6–32.7+ months). With median follow-up of 22.3 months, median PFS was 5.6 months (95% CI, 2.9–8.3 months) and median OS was 24.4 months (95% CI, 18.5–30.3 months). There was no grade 5 adverse event (AE). In safety analysis set (n=37), grade 3–4 AE occurred in 25 (67.6%) patients; neutropenia (n = 19, 51.4%) was the most common. Immune-mediated AEs occurred in 4 (10.8%) patients (hepatitis, n = 2; hypothyroidism, n = 2). There was no significant difference in ORR between PD-L1 -positive (SP263 tumor proportion score $\geq$1%) and PD-L1 -negative groups (25.0% [3/12] vs. 21.1% [4/19]; P=1.000).

Conclusions: Avelumab plus gemcitabine showed favorable toxicity profiles in patients with LMS. Although the primary endpoint for ORR (35% for P1) was not reached, the DOR, PFS, and OS observed are encouraging. Next-generation sequencing and immune phenotype analyses will be presented.

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1931P Ultra-rare sarcomas have worse survival compared to non-ultra-rare sarcomas: A national cancer registry study

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Background: Our understanding of the clinical characteristics, survival rate, and prognostic factors of ultra-rare sarcomas (URSs) is limited due to the low incidence. The aim of this study is to understand the clinical differences among URS, non-URS (NURS), and other non-sarcoma solid tumors (NSST).

Methods: Clinical demographics and survival of solid tumor patients(pts) of Taiwan Cancer Registry diagnosed between January 1, 2002, and December 31, 2019, were retrieved. URS included sarcoma histologies with an incidence $<$ 1/1,000,000 persons. The annual percent change (APC) was computed to summarize the change in incidence for the recent years. Overall survival (OS) was estimated from the time of diagnosis to death or the last follow-up. The impact of gender, age, diagnosis period (2002-2010 vs. 2011-2019), and histology type on OS were estimated by Cox proportional hazard method.

Results: A total of 1,578,049 pts were included (URS [n=2,154], NURS [n=32,454], and NSST [n=1,543,441]). Among all sarcoma pts, 6.2% were URS; the top three most common histologies of URS were endometrial stromal sarcoma (n=292), pleomorphic liposarcoma (n=212), and epithelioid sarcoma (n=209). The APC of URS continued a surging trend from 2002 to 2019 (APC 3.81, $p < 0.05$) while the APC of NURS and NSST decelerated after 2010. URS pts are younger ($p < 0.001$) and more likely to be female ($p < 0.001$). In the multivariate analysis adjusted for gender, age, and diagnosis period, URS pts had worse OS than NURS pts (HR 1.70, 95% CI 1.59-1.81, $p < 0.001$). When all pts were divided into four age groups (0-18, 18-40, 40-70, and $>$70), the negative impact of URS on OS was most significant in adolescents and young adults (AYA, age 18-40) (HR:2.23; 95% CI, 1.94-2.55; $p < 0.001$). Unlike NSST, where the OS improved in the past decade (HR:0.84, 95% CI, 0.83-0.84, $p < 0.001$), OS of URS and NURS both worsened (URS: HR:1.14, 95% CI, 1.01-1.30; $p < 0.05$; NURS: HR:1.05, 95% CI, 1.02-1.09, $p < 0.005$) in the period 2011 to 2019 compared to 2002 to 2010.

Conclusions: Our findings showed that the incidence of URS is increasing but the OS worsened. Among different age groups, the detrimental effect of URS was most prominent in the AYA pts. Awareness of URS and precision medicine-based therapies for URS are desperately needed.

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1932P First in human trial of CEB-01 for retroperitoneal soft tissue sarcoma

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Background: Local recurrence after radical surgery for retroperitoneal soft tissue sarcoma (RPS) occurs in 41—50% of patients and constitutes a major cause of death. CEB-01 is a biocompatible and biodegradable membrane implant with PLGA nanofibers entangled with SN-38 for a steady delivery. When placed in the surgical bed after RPS resection, it may increase local control rates and survival.

Methods: This is a multicentre, first in human trial (EudraCT: 2018-001026-25) following a 3+3 dose escalation design, and an expansion cohort at the recommended phase II dose (RP2D). Efficacy is evaluated using RECIST 1.1. Primary objective is RP2D. Safety, pharmacokinetics (PK) are secondary objectives.

Results: At present, 10 patients (pts) have been enrolled: 3 female / 7 male; mean age 62.1 years (40 - 77) with dedifferentiated liposarcoma (LPS) (5 cases), well differentiated LPS (3), LPS (1), and leiomyosarcoma (1). 7 pts had unresected primary lesions, and 3 were locoregional relapses. Post-surgery margins were R0 (7), R1 (2) and unknown (1). CEB-01 was implanted in 3 dose-increasing cohorts: 1st) 2 membranes of 180 cm^2 each, 25 mcg/cm^2, total 9 mg; 2nd) 2 x 180 cm^2, 50 mcg/cm^2, total 18 mg and 3rd) 4 x 180 cm^2, 50 mcg/cm^2, total 36 mg. No dose limiting toxicity (DLT) has been observed in any of the cohorts. The expansion phase is ongoing. Adverse events are similar to those post-surgery of RPS. Death (3 pts), after abdominal infection, bleeding (both unrelated) or retroperitoneal haemorrhage (related). After a median follow-up of 16.3 months (2.1 to 24.9), 2 (with the lower dose) local recurrences in the area of the implant have been observed after 5.5- and 8.6-months post-surgery. 2 pts completed 24 months of follow-up. In 5 ongoing pts no recurrences have been observed after 2.1 to 17.8 months of follow-up (median 16.2 months). SN-38's PK shows dose linearity, half-life ranging from 287 - 372 hours, Cmax: 0.76 - 3.58 ng/ml and AUC 0-t: 118 - 321 ng/ml*h. Blood levels of SN-38 were detectable 28 days after surgery.

Conclusions: With CEB-01 no DLT has been observed. Local recurrence occurred in 2 out of 10 pts at 5.5- and 8.6-months post-surgery. CEB-01 provides a local steady and prolonged release of SN-38, with a much lower Cmax than when SN-38 is administered as irinotecan.

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1933P Perioperative chemotherapy could reduce the risk of recurrence in resected leiomyosarcoma of the vena cava (LMS-VC): A retrospective bi-centric series on 41 patients

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Background: Leiomyosarcoma of the vena cava (LMS-VC) is a rare sarcoma with poor oncological outcome. The role of perioperative chemotherapy (CT) and/or radiotherapy (RT) remains unclear.

Methods: All consecutives cases of pathologically confirmed LMS-VC resected between 2003 and 2022 in two tertiary referral centers were retrospectively collected. Perioperative treatments were discussed in a multidisciplinary tumor board for large tumors with/without organ involvement. CT were based on adriamycin regimens. The surgical strategy aimed to obtain a complete en-bloc resection of the LMS-VC. We evaluated disease-free survival (DFS) and overall survival (OS) using Kaplan-Meier estimates with a Cox model.

Results: Forty-one patients were identified, with a median age of 57.5 years. LMS-VC median size was 9.5 cm (interquartile range [6.8-12.5] cm) with 67.5% of complete obstruction (no outflow at CT scan). The Kieffer levels (K) were K1, K2 and K3 in 9(22%), 23(56%) and 9(22%) patients respectively. At surgery, 55% had a nephrectomy and 20% a minor hepatic resection. Vena cava was replaced by prosthetic graft in 40% of patients and 32.5% had no reconstruction. Severe complications (Clavien-Dindo$\geq$3) occurred in 12(30%) cases. No postoperative mortality was reported. R0 was obtained

in 29(71%) patients, R1 in 11(27%) and one patient had a R2 resection. FNCLCC grades were 1, 2 and 3 in 5(12%), 26(63%) and 10(24%) cases respectively. Twelve (30%) patients received CT with 10 and 2 in pre and postoperative setting respectively, only in FNCLCC grade 2 or 3. Five (12%) patients received adjuvant RT. After a median follow-up of 70 months, median DFS was 22 months and median OS was 55 months. Among the 27 recurrences, 24 were distant. The multivariate analysis identified FNCLCC grade (Hazard Ratio (HR), 20; 95% confidence interval [CI], 2.29 to 175 for grade 2 vs 1 and 65.6; 95% CI, 6.30 to 683 for grade 3 vs 1; $p<0.001$) and pre and/or postoperative chemotherapy (HR, 0.38; 95% CI, 0.16 to 0.92; $p=0.026$) as main prognostic factors.

Conclusions: LMS-VCs have high risk of distant recurrence, evaluated as 58% in this cohort. Pre and/or postoperative chemotherapy and FNCLCC tumor grade were associated with improved DFS.

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1934P Pharmacokinetics of unesbulin in a phase Ib study of patients with advanced leiomyosarcoma

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Background: Patients with metastatic or unresectable leiomyosarcoma (LMS) have a poor prognosis and a high risk of relapse with limited therapeutic options. In a phase 1b dose escalation study, unesbulin, an oral microtubule polymerization inhibitor, plus dacarbazine (DTIC), showed promising efficacy and tolerability in patients with advanced LMS. Here we report the results of drug-drug interactions (DDI) and the impact of food on the PK of unesbulin (NCT03761095).

Methods: This analysis evaluated the PK of unesbulin 300 mg in patients with advanced LMS. The DDI was investigated by staggering or coadministering unesbulin with DTIC. For the food effect assessment (FEA), patients received DTIC 1000 mg/m^2 on Day 1 and unesbulin 300 mg twice weekly starting Day 2 of every cycle (21 day/cycle schedule). Unesbulin was administered under fasted conditions on Day 2 and under fed conditions (low-fat diet) on Day 5. Blood samples for the FEA were collected at predose and up to 72 hours postdose.

Results: When DTIC was coadministered with unesbulin, the C_{max}, and $AUC_{0\text{-}24h}$ of 5-aminoimidazole-4-carboxamide (an inactive metabolite of DTIC) were reduced by 77.4% and 61.7%, respectively. No apparent difference was observed in mean unesbulin exposure when administered with or without food, but the inter-subject variability (CV%) reduced significantly from 42% - 59% under fasted condition to 19% - 29% with a low-fat diet.

Table: 1934P

	T_{max}* (h)	$T_{1/2}$† (h)	C_{max}† (ng/mL)	$AUC_{0\text{-}48}$† (h*ng/mL)	$AUC_{0\text{-}inf}$† (h*ng/mL)
Fed	4.0 (3.0-6.0)	13 (18.0%)	1240 (28.6%)	18400 (19.0%)	20000 (21.5%)
Fasted	4.0 (3.0-6.0)	15 (45.0%)	1090 (42.3%)	21800 (52.8%)	22400 (59.1%)
Ratio (Fed/Fasted)			1.186	0.939	1.009

*Reported as median (minimum-maximum); †Reported as mean (CV%).

Conclusions: The DDI evaluation showed that CYP1A2-mediated inhibition of DTIC metabolism can be mitigated by staggering unesbulin and DTIC doses by one day. Results showed no clinically meaningful difference in mean unesbulin exposures when administered with or without food. However, administering unesbulin with a low-fat diet is recommended as it reduces the inter-subject variability. Unesbulin is being evaluated in an ongoing randomized, placebo-controlled, phase 2/3 trial, SUNRISELMS (NCT05269355).

Clinical trial identification: NCT03761095.

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They evaluating a new investigational drug to license into Ayala for the treatment of TGCT and wish to talk to a KOL about the current treatment options, to better understand if there is an unmet need for another drug on the market (in addition to pexidartinib): Ayala Pharmaceuticals; Financial Interests, Personal, Advisory Role, Consulting/Advisor (2020) exp. 7/23: Cytokinetics Inc; Financial Interests, Personal, Other, Consulting and Ad Board: Bayer; Financial Interests, Personal, Advisory Board, Attended an Advisory Board Meeting (2021) : Deciphera Pharmaceuticals; Financial Interests, Personal, Other, Extended the consulting relationship 9/2022. 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1935P Exploration of tertiary lymphatic structure in soft tissue sarcoma for the prognostic and immunotherapy response

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Background: The tertiary lymphoid structure (TLS) is an important part of the tumor microenvironment. It generates circulating immune cells and inhibits tumor growth and progression, which is closely related to the efficacy of immunotherapy.

Methods: This study collected the transcriptome information and clinical data of 10327 tumor samples and 730 normal samples of 33 cancer types from the TCGA database. Based on previous literature, three sets of TLS-related gene sets were selected and merged into the total TLS gene set. The TLS enrichment scores were calculated by the GSVA algorithm. Further, utilize TIMER 2.0 and CIBERSORTNE algorithms to analyze the distribution of tumor-infiltrating immune cells. Based on the enrichment score of TLS, sarcoma patients were divided into three TLS subtypes via the "hclust" R package. TLS-related prognostic core genes were screened via Lasso Cox

and multivariate Cox regression and further used to establish the TLS-related prognostic signature. The public immunotherapy cohorts and our center immunotherapy patients were used to validate the efficacy of immunotherapy.

Results: The TLS gene set enrichment score established in this study is significantly positively correlated with immune cell infiltration such as T cells, B cells, and DC cells, which can reflect the TLS status in tumor tissue. Kaplan Meier survival analysis showed that patients with high TLS had better overall survival and progression-free survival compared to patients with low TLS. Through Lasso Cox and multivariate Cox regression, two TLS-related prognostic core genes (TNFRSF14 and DUSP9) were ultimately screened, and a TLS-related prognostic signature was established. Immunohistochemistry showed that the expression of TNFRSF14 was increased and the expression of DUSP9 was reduced in patients with soft tissue sarcoma who achieved optimal immunotherapy.

Conclusions: The TLS-Total gene set, TLS-related prognostic signature, TNFRSF14, and DUSP9 selected in this study can predict the prognosis of patients with soft tissue sarcoma. TNFRSF14 and DUSP9 are associated with immune cell infiltration, which can indicate the efficacy of immunotherapy and may become new predictive markers of immunotherapy efficacy.

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1936P Targeted therapy of desmoplastic small round cell tumor guided by multilayered molecular profiling

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Background: Desmoplastic small round cell tumor (DSRCT) is an ultra-rare soft-tissue sarcoma characterized by an *EWSR1::WT1* gene fusion that affects predominantly male adolescents and young adults. Despite intensive multi-modality treatment outcomes remain dismal, with only 25% of patients being alive after five years. Beyond conventional therapies, novel, molecular mechanism-aware therapies are urgently needed.

Methods: Patients with advanced DSRCT underwent multilayered molecular profiling as part of NCT/DKFZ/DKTK MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a prospective, multicenter observational study that applies whole-genome/exome, transcriptome, methylome, and — more recently — mass spectrometry-based (phospho-)proteome analysis in young adults with advanced malignancies and patients with rare cancers to inform clinical decision-making and the design of molecularly stratified clinical trials.

Results: Between 2013 and 2022, 29 patients with DSRCT were analyzed with a median follow-up of 17 months (range, 0—48). The median age at the time of molecular analysis was 30 years (range, 18—56). The median time between diagnosis and molecular analysis was 12 months (range, 1—216). The median survival and the 4-year survival rate from registration were 2.4 years (95% confidence interval [CI], 1.4—3 years) and 7.4% (95% CI, 1.2—45.2%), respectively. In 8 of 9 samples with available proteomics data, we observed pronounced activation of ERBB (also called HER) signaling and high *ERBB2* mRNA expression levels, providing a rationale for personalized therapy with ERBB2-specific antibody-drug conjugates. In addition, selected somatostatin receptor family members, i.e., SSTR3 and 5, were highly expressed in all patients with available transcriptome data, providing the basis for treatment with pasireotide, a novel multireceptor-targeted somatostatin receptor ligand, within an academic clinical trial, which is currently being prepared.

Conclusions: We describe the molecular profiles of patients with DSRCT enrolled in MASTER and demonstrate the utility of broad molecular profiling for the clinical management of this disease, including the application of targeted treatment strategies.

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1937P KM-subtraction meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma

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Background: The role of adjuvant chemotherapy for patients with a resected extremity soft tissue sarcoma (STS) is controversial. Prior individual patient data meta-analyses are limited by omission of certain randomized controlled trials. The objective of this systematic review was to reassess the efficacy of adjuvant chemotherapy in resected STS, harnessing the ability of a new method termed Kaplan Meier (KM) subtraction to obtain patient level information.

Methods: A comprehensive literature search was performed to identify RCTs of adjuvant chemotherapy for adult patients diagnosed with localized resectable soft-tissue sarcoma. We searched PubMed, Web of Science, Cochrane Controlled Trials Register, UKCCCR Register of Cancer Trials, Physicians Data Query, EMBASE, MEDLINE and CancerLit (until December 2022). Data on the following endpoints were evaluated: disease free survival (DFS) and overall survival (OS). Data were summarized as hazard ratios (HR) with 95% confidence intervals (CI). Two reviewers independently assessed eligibility and quality of the studies using a modified version of the Detsky Quality Scale. The outcome measures were disease free survival (DFS) and overall survival (OS) calculated through the fixed effect or random effect model. We applied KM subtraction in R to obtain individual patient level data from the trials for subsequent metanalysis.

Results: A total of 24 trials representing 5936 patients were be included in the final analysis. The disease-free survival hazard ratio was 1.76 (95% CI 1.38-2.24) in favour of adjuvant chemotherapy. The overall survival hazard ratio was 1.30 (95% CI 1.11-1.53) favouring adjuvant chemotherapy. For adjuvant chemotherapy with doxorubicin alone, the hazard ratio of DFS and OS were 1.78 (95% CI 1.10-2.88) and 1.47 (95% 1.01-2.13).

Conclusions: This is the largest individual patient meta-analysis to-date of adjuvant doxorubicin and ifosfamide based chemotherapy in localized resectable soft-tissue sarcoma, and confirms a survival benefit (particularly for single-agent doxorubicin) with respect to disease free survival and overall survival.

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1938P Assessment of clinical benefit of cancer drugs recommended in National Comprehensive Cancer Network (NCCN) guidelines for advanced soft tissue sarcomas (STS) and bone sarcomas (BS)

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Background: Magnitude of clinical benefit from drugs used in tumours must be evaluated using validated and reproducible tools. European Society for Medical Oncology-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS) and American Society for Medical Oncology (ASCO) Value Framework (ASCO-VF) are the most important. Here, we evaluate characteristics and outcomes of clinical trials supporting drugs used in STS and BS, and their association with ESMO-MCBS and ASCO-VF.

Methods: We reviewed publications between January 1988 and December 2022 that support the recommendations of NCCN guidelines version 1.2023 for STS and 3.2023 for BS (gastrointestinal stromal tumours were excluded). We collected data regarding trial characteristics, efficacy, toxicity and quality of life (QoL). ESMO-MCBS and ASCO-VF were applied. Substantial clinical benefit was defined as a grade 4 or 5 (in a scale from 1 to 5) for ESMO-MCBS and a $\geq$45 for ASCO-VF.

Results: We identified 119 studies (71 for STS and 48 for BS) that support the use of 49 drugs or combinations. ESMO-MCBS could be applied in 58 trials (48.7%). Of them, 37 (64%) were single arm and 21 (36%) randomized clinical trials (RCT; 13 phase III and 8 phase II). ASCO-VF could only be applied in 10 of the previously described (6 phase III and 4 phase II RCT). QoL was reported in 17.2% (10/58), all published beyond 2011. Among these, only 1 (10%) showed improvement in QoL. Only 33.3% of RCT (7/21) demonstrated improvement in overall survival. Ten (17.2%) trials, all of them RCT, met the ESMO-MCBS substantial benefit threshold (7 involving STS and 3 BS). Only 4 of these met the ASCO-VF criteria (all for STS). Spearman's correlation coefficient between scales was 0.65.

Conclusions: Less than half of the studies supporting the NCCN recommendations for the prescription of drugs in advanced sarcomas can be evaluated using validated scales to assess the magnitude of their clinical benefit. Substantial clinical benefit was only achieved in a minority of those. QoL analysis should be incorporated in further studies to better evaluate their actual clinical benefit. Correlation among ESMO-MCBS and ASCO-VF was noteworthy.

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1939P phase I clinical results of SQ3370, a doxorubicin-based click chemistry therapeutic in advanced solid tumor patients

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Background: Shasqi is a clinical stage biotech that uses click chemistry, a Nobel Prize winning technology, to selectively activate cancer treatments at the tumor. The Click Activated Protodrugs Against Cancer (CAPAC®) platform comprises of 1) tumor targeting agents, which carry an activator, and 2) attenuated cancer drugs, which are selectively activated at the tumor by the targeting agent through click chemistry, maximizing therapeutic index and minimizing toxicities. We have demonstrated clinical proof of concept with SQ3370, which uses an intratumorally injected biopolymer (bp) with a doxorubicin (Dox) protodrug injected systemically (NCT04106492).

Methods: Patients (pts) received 10/20 mL bp and protodrug IV QDx5. Key eligibility: locally advanced or metastatic solid tumors, $\leq$ 300 mg/m^2 prior Dox exposure and no limit to prior systemic therapies. Objectives: safety, determining recommended phase 2 dose (RP2D), pharmacokinetics (PK), and immune profiling.

Results: 38 pts were treated: 30 with 10 mL bp and 8 with 20 mL bp at 9 escalating protodrug dose levels up to 15x of clinical Dox dose/cycle. Most pts had sarcoma (63% at 10 mL; 88% at 20 mL) and metastases (83% at 10 mL; 63% at 20 mL). 93% (10 mL) and 88% (20 mL) pts received prior systemic therapies including prior Dox in 40% (10 mL) and 88% (20 mL) pts. Median age was 62 (26-92; 10 mL) and 58 (23-84; 20 mL). Frequent AEs in bp group: 10 mL - nausea (17; 57%) and fatigue (15; 50%); 20 mL - anemia (4; 50%) and nausea (4; 50%). Best response was SD in 58% (10 mL) and 71% (20 mL). Disease control rate (CR+ PR+ SD $\geq$ 60 days) was 58% (10 mL) and 71% (20 mL). MTD was not reached in either bp cohort; myelosuppression was not dose-limiting. Based on systemic Dox exposure, 12x was selected as the RP2D. PK and immune profiling support safety findings and will be presented. SQ3370 induced a shift towards a T-cell permissive tumor immune microenvironment.

Conclusions: SQ3370 is the first clinical click chemistry-based cancer therapy. The results show the following: the biopolymer activates protodrug in patients; that the Dox protodrug is not a vesicant; PK data demonstrates activation of protodrug; reaction achieves liberation of Dox; click chemistry favorably alters PK and safety of the payload.

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1940P Deep molecular profiling of advanced synovial sarcoma as a basis for interventional clinical trials

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Background: Synovial sarcoma (SySa) is a rare soft-tissue malignancy occurring predominantly in the lower extremities of young adults. It is driven by a unique SS18::SSX fusion gene. In locally advanced/metastatic SySa, treatment options are limited, and it is of high interest to identify targetable molecular alterations.

Methods: Within the MASTER precision oncology program of DKFZ, NCT Heidelberg/Dresden, and DKTK (ClinicalTrials.gov Identifier: NCT05852522), patients with advanced SySa were analyzed by whole-genome/exome (WGS/WES) and RNA sequencing to inform the care of individual patients and provide starting points for interventional clinical trials in adolescents and young adults. Median age at the time of molecular analysis was 37 years (range, 22—65 years), and 45% of patients were female. Median time between diagnosis and molecular analysis was 29 months (range, 2—288 months). Median follow-up for survival was 89 months.

Results: Between 2013 and 2022, 69 patients were studied. Median survival and 3-year survival rate after molecular analysis were 14 months (95% confidence interval [CI], 12—19 months) and 8% (95% CI, 3—22%), respectively. Molecular profiling included WES (n=33) or WGS (n=32) as well as RNA sequencing (n=56). Beyond SS18::SSX fusions, the most common somatic and germline single-nucleotide variants and small insertions/deletions affected TTN (17%), NIPBL (9%), CTNNB1 (8%), ATM, TAF1L, TP53, MADD, and COL7A1 (each 6%). Based on the presence of a significant single-base substitution signature 3 (SBS3), two patient groups could be distinguished (group 1, SBS3 present, 28 patients; group 2, SBS3 absent, 37 patients). The most frequent genomic gains involved chromosomes 8 and 12; the most frequent deletions involved chromosomes 3 and 11. Comparative analysis of SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5 expression between the SySa cases (n=56) and the entire MASTER cohort (n=3,023) revealed significant differences for SSTR2, SSTR4, and SSTR5, with top 10% expression in 13, 31, and 22 patients, respectively.

Conclusions: Our study demonstrates the utility of broad molecular profiling in patients with advanced SySa for identifying subgroups of patients, whose molecular profiles may inform the design of future clinical trials.

Legal entity responsible for the study: National Center for Tumor Diseases, German Cancer Research Center and Heidelberg University Hospital.

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1941P Preliminary efficacy and safety of SHR-2554 in advanced epithelioid sarcoma: A phase II trial

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Background: Epithelioid sarcoma (ES) is a rare and aggressive subtype of soft-tissue sarcoma. The loss of INI1 expression which leads to oncogenic dependence on the transcriptional repressor EZH2 has been observed in over 90% of ES. There remains a need for effective and safe treatment options for patients (pts) with advanced ES. We investigated the efficacy and safety of SHR-2554, an oral selective EZH2 inhibitor, in pts with refractory ES.

Methods: Pts were eligible if they were aged 12 years or older with histologically confirmed advanced or metastatic ES. Other key inclusion criteria: the presence of measurable disease according to RECIST 1.1; an ECOG performance status of 0-1; progressive disease after at least one line of adriamycin containing chemotherapy; documented loss of SMARCB1 (INI1) alterations or the upregulated mRNA level of EZH2. Pts received SHR2554 (350 mg, bid, po) until disease progression or unacceptable toxicity. The primary endpoint was progression-free rate at 12 weeks. A Simon two-stage design was applied. Success at stage 1, which would enroll 9 pts, required ≥3 pts remaining progression-free at 12 weeks.

Results: Between Jul 2021 and Dec 2022, a total of 9 pts were enrolled and received SHR-2554. The median age was 44 years and 33.3% were males. 5 (55.6%) pts had received previous immunotherapy targeting PD-1/L1 and 4 (44.4%) pts had received previous antiangiogenesis therapy. The median line of previous treatment was 2 (range 1-4). Loss of INI1 was confirmed in 6 (66.7%) pts. 5 (55.6%) pts remained progression-free at 12 weeks, which allowing to move on to stage 2. Based on investigator assessments, one (11.1%) of 9 pts had a confirmed partial response at data cutoff. The median progression-free survival was 3.8 months (95% CI: 1.2—NA). Adverse events (AEs) were generally mild. The most common treatment-related AEs were anaemia (3, 33.3%). No serious treatment-related AEs were observed.

Conclusions: SHR-2554 showed promising efficacy and an acceptable safety profile in pts with refractory ES, warranting further investigation.

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1942P Non-metastatic malignant phyllodes tumors of the breast (B-MPT): A retrospective analysis from a referral center

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Background: B-MPT accounts for <1% of breast neoplasms. The standard treatment for non-metastatic disease consists of wide local excision. Type of excision and adjuvant treatments are still matter of debate. Because of its rarity, only few case series with less than 100 B-MPT patients (pts) are available.

Methods: We conducted a retrospective single-centre observational study to describe outcomes and possible prognostic factors of pts with B-MPT. Data of consecutive patients aged ^{3}18 years old, with a histologically confirmed diagnosis of non-metastatic B-MPT, who underwent surgery from January 2000 to December 2021, were collected. The primary endpoint was recurrence-free survival (RFS). Survival was calculated using Kaplan—Meier method. Multivariable analysis was performed with Cox proportional hazards model (significance at p-value<0.05).

Results: 131 pts were included. Patient characteristics are reported in table. All patients received a surgery, 5 adjuvant anthracycline-based chemotherapy and 15 radiation therapy. After a median follow-up of 6.8 years, 36 (28%) pts experienced a disease recurrence: 19 (15%) a distant and 23 (18%) a loco-regional relapse. The median RFS, distant RFS (DRFS) and local RFS (LRFS) were not reached. The 5-year RFS, DRFS and LRFS rates were of 72%, 85% and 82%. At univariate analysis DRFS significantly correlated with the presence of at least one negative pathological prognostic factor (i.e., Size >5 cm, Multifocal disease or Heterologous differentiation [SMH]) (p=.03). If adjusted for type of breast surgery, SMH was associated also with

LRFS (HR 3.3; 95%CI, 1.4-7.8; p=.008). The type of surgery was not prognostic for RFS, DRFS and LRFS.

Table: 1942P Patient characteristics

	N=131
Age at diagnosis, mean (DS)	46.7 (12.7)
Negative pathological prognostic factors	
Size >5 cm - %	43%
Multifocal disease - %	11%
Heterologous differentiation - %	20%
At least one negative prognostic factor - %	62%
Surgery strategy	
Upfront wide local excision with attention to margins - %	45%
Re-excision after previous inadequate resection - %	46%
Inadequate resection without re-excision - %	9%
Type of last breast surgery	
Excisional biopsy (no attempt at margins) - %	9%
Lumpectomy (wide local excision with attention to margins) - %	34%
Mastectomy - %	57%
pR1 - %	14%
Adjuvant chemotherapy - %	4%
Adjuvant radiotherapy - %	11%

Conclusions: Natural history of B-MPT is burdened by local and distant recurrences. Pathological features more than the type of wide local excision seem to represent the most significant prognostic factor for recurrences.

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1943P Efficacy and safety of eribulin plus anlotinib and camrelizumab in advanced or metastatic retroperitoneal liposarcoma (RLPS) or leiomyosarcoma (RLMS): A single-center retrospective cohort study

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Background: RLPS and RLMS are not sensitive to conventional chemotherapy. We evaluated the efficacy and safety of eribulin plus anlotinib and camrelizumab for RLMS and RLPS.

Methods: Patients (pts) with advanced/metastatic RLPS or RLMS treated with eribulin plus anlotinib and camrelizumab (Q3W) at Peking University Cancer Hospital Sarcoma Center were included in this retrospective analysis. Response (RECIST v1.1) was evaluated every 3 treatment cycles. Adverse event severity was graded per CTCAE v5.0.

Results: From December 17, 2020 to November 18, 2022, 60 pts (27 male; 33 female) were included. 22 pts had RLMS; RLPS subtypes were well-differentiated (n=9), de-differentiated (n=24), and myxoid (MLPS; n=5). Eribulin was given to 21 pts (35%) at 0.7—1.1 mg/m^2, and 39 (65%) at 1.1—1.4 mg/m^2.5 pts (RLMS, n=2; RLPS, n=3) were excluded from efficacy analyses due to drug intolerance and the COVID-19 pandemic. After a median of 5 cycles (range, 2—21), a partial response was observed in 15 pts (27.3%), stable disease in 27 (49.1%) and progressive disease in 13 (23.6%). The objective response rate (ORR) and disease control rate (DCR) were 27.3% and 76.4%, respectively. ORR and DCR in pts with RLMS were 42.1% and 84.2%, respectively; in pts with RLPS, they were 19.4% and 72.2%, respectively. After a median follow up of 11.3 months (mo), 10 pts had complete resection, 2 of whom had pathological complete response (1 with RLMS and 1 with MLPS); 3 other pts had locoregional recurrence after surgery. Median progression-free survival (mPFS) for the remaining 45 pts was 5.8 mo; mPFS for RLPS and RLMS subgroups were 5.5 and 6.2 mo, respectively. Any-grade treatment-related AEs (TRAEs) occurred in 51/60 pts (85.0%), with 22 (36.7%) experiencing grade ≥3 TRAEs. The most common TRAEs were neutropenia (58.3%), proteinuria (23.3%) and anorexia (23.3%). Due to AEs, 15 pts (25.0%) discontinued treatment and 6 (16.7%) reduced their eribulin dose.

Conclusions: Eribulin plus anlotinib and camrelizumab demonstrated clinically meaningful efficacy and a manageable safety profile in pts with advanced or metastatic RLPS or RLMS, especially in those with RLMS.

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1944P MAGE-A4 and NY-ESO-1 expression analysed in a synovial sarcoma tissue micro-array

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Background: T-cell based therapies are currently explored in clinical trials (NCT04044768, NCT01343043) in patients with synovial sarcoma (SySa). These therapies are targeting cancer testis antigens like Melanoma-Associated Antigen 4 (MAGE-A4) or New York Esophageal Squamous Cell Carcinoma-1 (NY-ESO-1). We explored the molecular epidemiology of these targets using a tissue micro-array (TMA) from clinical SySa samples.

Methods: We created a TMA consisting of 323 cores from 108 clinical samples (≥2 cores/sample) from archival, paraffin-embedded material originating from 91 individual donors. A sarcoma reference pathologist verified the diagnosis of SySa in the donor sample. Most samples (62%) were collected from the primary tumour, 22% and 16% originated from a metastasis or local recurrence. Slides were stained with MAGE-A4 antibody (#82491, dilution 1:100, Cell Signaling) and NY-ESO-1 antibody (clone E978, dilution 1:200, Sigma), during an overnight incubation. Normal human testis tissue was used as a positive control. Expression of each core was scored as an H-score, defined as: (% stained cells at 0 intensity) × 0 + (% stained cells at 1+ intensity) × 1 + (% stained cells at 2+ intensity) × 2 + (% stained cells at 3+ intensity) × 3. The average of the H-scores from the cores corresponding to the same tumour sample was used for subsequent analyses. Expression of the target was defined as an average H-score ≥ 1 and high expression was defined as an average H-score > 100. Kruskal-Wallis test was used for the statistical analyses.

Results: Expression of NY-ESO-1 and MAGE-A4 was found in 50.9% (55/108) and 68.5% (74/108) of TMA samples. High expression was noticed in 20/108 samples (18.5%) for NY-ESO-1 and in 25/108 samples (23.1%) for MAGE-A4. In 77.8% of the samples there is at least one of these cancer testis antigens expressed. There was no correlation between the expression level and disease status at the sampling moment, nor with clinical outcome of the patient. Additionally, there was no correlation between the expression level and the size of the original tumour.

Conclusions: MAGE-A4 and NY-ESO-1 are expressed in a clinically relevant proportion of SySa cases represented in our TMA, this supports the utility of these antigens as targets for novel cell-based therapies in this disease.

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1945P Diagnostic and therapeutic impact of liquid biopsy in soft tissue sarcomas: A case series

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Background: Soft tissue sarcomas (STS) are a group of rare heterogeneous mesenchymal tumours with distinct clinical and molecular features. Current therapeutic approaches in advanced STS are limited to conventional chemotherapy and targeted therapy without significant impact on survival. Liquid biopsy (LB) or cell-free DNA is an innovative tool in cancer practice that detects particular molecular alterations (MA) with diagnostic and therapeutic implications. In this case series, we report the outcomes of LB in a cohort of international STS patients.

Methods: In this prospective cohort, all STS patients from the international department treated in Gustave Roussy Cancer Campus that underwent a LB during their disease course between 01/2022 and 03/2023 were included. Demographic data were gathered with various significant MA.

Results: 18 STS patients were included in this series with a median age of 49 yrs. 9 were men (50%) and all patients had inoperable or metastatic disease at the time of LB. They had a median of 1 prior line of therapy. Three patients had a high TMB (tumour mutational burden) (16.6%) with more than 10 mut/mb. Four patients (22.2%) had targetable MA: Three pts had MSI-high tumors (microsatellite instability, two uterine leiomyosarcoma and 1 with GIST) with high sensitivity to immune checkpoint inhibitors and 1 angiosarcoma patient had BRAF mutation in which a BRAF and MEK inhibitors were introduced. On the other hand, four patients had confirmed STS diagnosis with the detection of fusion transcripts: two had Ewing sarcoma, one had desmoplastic round cell tumour and one patient had the EWSR1-ATF1 fusion transcript which helped changing the diagnosis from suspected melanoma to clear cell sarcoma. Also four patients had genetic counselling after detecting germline mutations (2 NF1 in GIST and MPNST, 1 APC in desmoid tumor and 1 POLD1 in chondrosarcoma). Two patients benefited from haematology referral after confirmed JAK2 mutations.

Conclusions: LB proved to be an attractive technique to detect significant MA in advanced STS, a group of malignant tumors with a challenging diagnosis and therapeutic approach. This tool can be implemented as an adjunct tool to offer novel therapeutic options to patients as well as fine-tuning of the diagnostic process.

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1946P Bladder primary sarcomas (BSar): A genomic landscape and clinical outcomes study

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Background: BSar are rare and often present at advanced stage with poor prognosis. Limited data on genomic alterations (GA) exist; we evaluated GA and outcomes in separate cohorts.

Methods: 18 (0.2%) pts with Bsar were identified from 11,193 bladder cancers and underwent hybrid capture-based comprehensive genomic profiling (CGP) using DNA only (6 pts) or DNA and RNA seq (12 pts) to assess GA and other biomarkers. Predominant genetic ancestry was assessed using a SNP-based approach and classified as: African (AFR), European (EUR), Central and South American (AMR), South Asian (SAS), or East Asian (EAS). Assessments of tumor mutational burden (TMB), MSI status, genomic signature (GS), gLOH and prediction of germline status were performed. PD-L1 was determined in 2 pts by IHC (1 DAKO 22C3; 1 Ventana SP142). A separate analysis of 317 patients (pts) with stage I-III BSar using NCBD data (2004-2019) was done.

Results: 18 Bsar (11 male, median age 66) were included: 12 leiomyosarcomas (LMS), 3 rhabdomyosarcomas (RMS),3 high grade undifferentiated sarcomas (HGS). 16 pts of EUR ancestry, 1 AMR, 1EAS. Mean driver GA frequency was 4.8 (1-10); mean TMB 2.9 mutations/Mb (0-9.6), all MS stable; 1 tumor was PD-L1 negative, the other had 1-49% TPS. Mean gLOH 10.4% (1.7-16.9%). APOBEC GS was noted in 1/12 (8.3%) with 11/12 (91.7%) with no dominant GS. Relevant germline mutations were predicted in RB1 (pt with prior retinoblastoma), VHL (pt with radiation-treated prostate cancer), PTEN (pt with Cowden Syndrome) and MUTYH (pt with intestinal polyposis); 1 pt with prior Wilms tumor had somatic GA only. Most frequently identified GA:TP53 (78%), ATRX (22%), RB1 (22%), PTEN (22%), CDKN2A (17%) and RICTOR, MLL2, DNMT3A, MTAP, KDM6A, TERT, HGF, NF1 (each 11%). In the BSar NCDB cohort (LMS only, overall survival was shorter in pts treated with surgery (S) and chemotherapy (CM), S and radiotherapy (RT) vs with S alone, HR 2.73 (95%CI 1.28-5.80), HR 2.24 (95%CI 1.03-4.88) respectively, after adjusting for sociodemographic and health factors. Age and tumor size had prognostic role.

Conclusions: CGP of Bsar revealed several GA relevant for clinical trial design and germline mutations requiring dedicated germline testing. Limitations: retrospective nature and confounding.

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1947P Predictors and outcomes of recurrent retroperitoneal liposarcoma: New insights into its recurrence patterns

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Background: The clinical profiles of recurrent retroperitoneal liposarcoma (RLS) need to be explored. The recurrence patterns of RLS are controversial and ambiguous.

Methods: A total of 138 patients with recurrent RLS were finally recruited in the study. The analysis of overall survival (OS) and recurrence-free survival (RFS) was performed by Kaplan−Meier analysis. The nomogram model was built to predict the survival status of patients. Univariate and multivariate analysis were performed for the selection of independent prognostic factors that were correlated with OS or RFS.

Results: Among patients, the 1-, 3-, and 5-year OS rates were 70.7%, 35.9% and 30.9%, respectively. The 1-, 3- and 5-year RFS rates of the 55 patients who underwent R0 resection were 76.1%, 50.8% and 34.4%, respectively. The multivariate analysis revealed that resection method, tumor size, status of pathological differentiation, pathological subtypes and recurrence pattern were independent risk factors for OS or RFS. Patients with distant recurrence (DR) pattern usually had multifocal tumors (90.5% vs. 74.7%, $P < 0.05$); they were prone to experience changes of pathological differentiation (69.9% vs. 33.3%, $P < 0.05$) and had a better prognosis than those with local recurrence (LR) pattern. R0 resection and combined organ resection favored the survival of patients with DR pattern in some cases.

Conclusions: Patients with DR pattern have a better prognosis, and they may benefit more from aggressive combined resection than those with LR. Classifying the recurrence patterns of RLS provides guidance for individualized clinical management of recurrent RLS.

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1948P Concordance of the pathological diagnosis between local institutional and central judgment in high-grade non-round-cell sarcomas: A supplementary analysis of JCOG1306

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Background: JCOG1306 was a multicenter randomized phase II/III trial comparing perioperative chemotherapy with adriamycin plus ifosfamide (AI) and gemcitabine plus docetaxel (GD) for high-grade non-round-cell sarcomas of FNCLCC classification ≥G2. After the histopathological diagnosis was confirmed by each local institution, specialized sarcoma pathologists reviewed each pathological diagnosis. In this study, we examined the concordance proportion of pathological diagnoses between the local institutional judgment (LIJ) and central judgment (CJ) and its impact on the study.

Methods: A total of 142 patients with proven high-grade non-round-cell sarcoma based on an incisional biopsy were included. We evaluated the concordance between the LIJ and CJ for pathological types and FNCLCC classification.

Results: The concordance proportion for pathological types between the LIJ and CJ was 63.4%. Compared to the LIJ (G1: 0%, G2: 59.9%, G3: 40.1%), the CJ (G1: 15.5%, G2: 61.3%, G3: 23.2%) showed more patients diagnosed with G1, and the concordance proportion for the FNCLCC classification was 62.7%. Histological types diagnosed as G1 were myxofibrosarcoma in 15 patients, myxoid liposarcoma in 6 patients, and fibrosarcoma in 1 patient. The proportion of patients in which the LIJ agreed with the CJ for each histological type was higher for synovial sarcoma (100%) and myxofibrosarcoma (88.2%) and lower for undifferentiated/unclassifiable sarcoma (17.6%). The 3-year survival proportions for 120 patients excluding G1 cases (AI: 59, GD: 61) were 89.8% and 74.9%, respectively, and those for all 143 patients (AI: 70, GD: 73) were 91.4% and 79.2%, respectively.

Conclusions: The present analysis included 15% of G1 patients who were not originally eligible for this trial. However, this did not significantly affect the results, as the AI and GD groups contained similar numbers of G1 patients. Patients with a background of myxoid components tended to be judged as G1 by the CJ. Although the limitations of assigning a grade using an incisional biopsy should be considered, the CJ is still useful for ensuring the accuracy of the clinical trial for such rare cancers.

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1949P Pegylated liposomal doxorubicin (PLD) combined with trabectedin as a treatment option in uterine sarcomas

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Background: Conventional use of doxorubicin as a single-agent or in combinations with other drugs in the treatment of uterine sarcomas is associated with dose-limiting toxicities. Doxorubicin plus trabectedin was shown to increase progression-free survival (PFS) at the price of higher toxicity. PLD plus trabectedin revealed to be feasible in larger phase 2 and 3 randomised studies in ovarian cancer. We hypothesise that the therapeutic index of trabectedin plus PLD could be superior to the combination with doxorubicin because of a more favourable toxicity profile.

Methods: In this retrospective single-arm study the clinical outcome was analysed in 21 patients with uterine sarcomas treated with PLD 30 mg/m^2 plus trabectedin 1.1 mg/m^2 every three weeks between January 2000 and April 2023 at the University Hospital in Innsbruck. Response evaluation was done every 3 cycles and every 3 months during the post-treatment follow-up. Toxicity was evaluated according to the National Cancer Institute-Common Terminology criteria, on a total of 148 administered cycles in 33 patients.

Results: In 66% of patients PLD plus trabectedin was given as first-line treatment, in 19% and 14% as second and third-line treatment, respectively. After 6 months one patient (4.8%) achieved complete remission (CR), four others (19%) showed a partial remission (PR), resulting in an objective response rate (ORR) of 24%. Four patients (19%) showing stable disease (SD), resulting in a clinical benefit rate (= ORR + SD) of 43%; progression was recorded in 12 patients (57%). Median PFS was 6.0 months (SD: ±21 months), while median overall survival was 26 months (SD: ±32 months). A median of 4 (range: 1-11) cycles per patient were given. Regarding ≥ grade 3 toxicity, thrombocytopenia was recorded in 9%, anaemia in 12% and neutropenia in 36% of patients. Febrile neutropenia was present in 7 patients (21%). Haematologic toxicity was the most frequent reason for dose delays (25 events) and dose reductions in eight cases.

Conclusions: Compared to conventional doxorubicin plus trabectedin, the herein investigated combination shows limited but similar anti-tumor efficacy in metastatic uterine sarcomas, but exhibits a more favourable toxicity profile.

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1950P A single-arm, phase II clinical trial of neoadjuvant pegylated liposomal doxorubicin plus anlotinib in locally advanced soft tissue sarcoma

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Background: Neoadjuvant therapy might improve excision and limb salvage rates in locally advanced soft tissue sarcomas (STS). This phase II trial aimed to investigate the safety and activity of neoadjuvant pegylated liposomal doxorubicin (PLD) plus anlotinib in local advanced STS.

Methods: In this prospective, single-center, single-arm phase II study, major eligible criteria were locally advanced, non-metastasis, treatment-naive STS, age at 14-75 years old, pathological stage IIb/III, ECOG PS 0-2. Patients received PLD (50mg/m^2, IV, D1, Q3W) and anlotinib (12mg/d, PO, D8-21, Q3W) for 2～4 cycles. The primary endpoint was objective response rate (ORR). Secondary endpoints included overall survival (OS), progression-free survival (PFS), pathological complete response (ypT0/is ypN0, pCR) and safety.

Results: From November 2020 to November 2022, 45 patients were recruited. The median age was 47 years (range, 15-75) and 19 were female. The predominant histologies included Spindle cell sarcoma 7 (15.56%), Myxofibrosarcoma 5 (11.11%), Myxoid liposarcoma 5 (11.11%), Malignant peripheral nerve sheath tumor 4 (8.89%), Synovial sarcoma 4 (8.89%), Leiomyosarcoma 3 (6.67%). Median treatment cycles of neoadjuvant therapy were 2 (range, 1-4). The ORR and DCR of 29 patients with at least one assessment as Choi criteria was 62.1% and 100%, respectively. Of 39 (86.67%) patients underwent radical resection, 33 (84.62%) patients had an R0 resection. With a median follow-up time of 11.47 months, the median OS were not reached. Median PFS was 14.19 months, and the 1-year OS rate was 84.23%. The limb salvage rates was observed in 39 (100%) patients. The most common adverse events (AEs) of all grade were mucositis oral 19 (42.22%), proteinuria 13 (28.89%), neutropenia 12 (26.67%), and leucopenia 11 (24.44%). Grade 3/4 AEs were 13 (28.89%). PLD plus Anlotinib was well tolerated without significant unexpected toxic effects.

Conclusions: PLD combined with Anlotinib showed a promising efficacy and acceptable toxicity for patients with locally advanced soft tissue sarcomas, suggesting a potential therapeutic option for this population.

Clinical trial identification: NCT04765228.

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1951P Propranolol monotherapy in angiosarcoma: A window-of-opportunity study (PropAngio)

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Background: Angiosarcoma is a rare and aggressive cancer of the endothelial cells. It has been shown that β-adrenergic signaling through the β-adrenoceptors (ADRB) 1 and 2, that are overexpressed in angiosarcoma, promotes tumor growth. Propranolol, a non-selective β-blocker, was able to initiate apoptosis in angiosarcoma cell lines and its anti-tumor activity has been demonstrated in several case reports. The aim of this window-of opportunity trial was to prospectively evaluate the anti-tumor activity of propranolol in patients with angiosarcoma.

Methods: Patients with angiosarcoma with a waiting time of 3 to 6 weeks until start of standard treatment were eligible. Propranolol was dosed 80 mg to 240 mg/day according to a dose titration schedule. The primary endpoint was clinical response rate. Clinical response was defined as either complete response (CR), partial response (PR) (according to RECIST 1.1) or stable disease (SD) with improvement of erythema, edema and thickness. Exploratory objectives included histologic response, PET response and assessment of potential biomarkers for response in tumor tissue by IHC (e.g., ADBR 1/2, PD-L1).

Results: To date, 13 patients with a median age of 67 years (range 52-86) are enrolled and have initiated treatment. The median duration of treatment was 28 days (range 21-42 days). The median dose was 160 mg/day. Three patients showed exceptional good tolerance (blood pressure/heart rate) and could be escalated to the highest dose (240 mg/day). Two patients showed clinical response. The most common adverse event was grade 1/2 bradycardia (85%). There were no grade $\geq$3 adverse events. Preliminary IHC results showed ADBR2 overexpression in the majority of the tumors (12 out of 17 tumor samples, both in responders and non-responders). None of the tumors showed ADBR1 overexpression.

Conclusions: This window-of-opportunity trial did not demonstrate clinical efficacy of propranolol monotherapy in patients with angiosarcoma. Two out of 13 patients did however show clinical benefit. ADBR1 or 2 expression did not correlate with response. Translational research to better comprehend the anti-tumor activity of propranolol for adequate selection of patients in future studies is ongoing (e.g., immune system-based biomarkers).

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1952P Efficacy and safety of utidelone in previously treated patients with advanced or metastatic soft tissue sarcomas (HX-SARC02): A prospective, single-arm, phase II study

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Background: Treatment options are limited for patients with advanced or metastatic soft tissue sarcomas (STSs) after failure of anthracycline-based chemotherapy and large-spectrum tyrosine kinase inhibitor. Utidelone, a genetically engineered epothilone analogue, has demonstrated high activity in preclinical and clinical studies against a broad range of tumors. This study aimed to evaluate the efficacy and safety of utidelone in refractory STSs.

Methods: This prospective, single-arm, phase II trial included patients aged 18 years or older with histologically proven advanced and inoperable STSs who had at least received anthracycline-based chemotherapy and large-spectrum tyrosine kinase inhibitor. Patients were treated with intravenously transfused utidelone (30 mg/m^2, day 1-5, every 21 days) until disease progression or intolerable toxicity. The primary endpoint was the median progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results: Between August 19, 2022 and March 1, 2023, a total of 10 patients were enrolled. As of April 16, 2023, all patients could be analyzed. There were 7 patients with leiomyosarcoma, one patient with synovial sarcoma, one patient with dedifferentiated liposarcoma, one patient with myofibroblastic sarcoma. 10 patients are evaluable for response with median cylces of 4 (1-7), 7 of whom are still under treatment. The median number of previous systemic therapies was two. The median PFS has not been reached. The ORR was 10% and DCR was 80%. Most of the common adverse events (AEs) were grade 1 or 2 and were considered manageable and reversible. Grade $\geq$3 AEs included peripheral neuropathy (1 [10%]), AST increase (1 [10%]) and diarrhoea (1 [10%]). Doses of utidelone were reduced (24 mg/m^2, on day 1-5) in two patients and discontinued in one patient. No treatment-related deaths occurred.

Conclusions: The present study demonstrated a promising anti-tumour activity of utidelone in patients with advanced or metastatic STSs who were previously treated with and refractory to both anthracycline-based chemotherapy and large-spectrum tyrosine kinase inhibitor.

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1953P Prognostic value of pretreatment inflammatory markers and other clinicopathological factors for early recurrence in soft tissue sarcoma

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Background: The diversity of clinical and pathological characteristics of soft tissue sarcoma (STS) presents a challenge for the prediction of prognosis. Recently, pretreatment inflammatory markers have gained interest as predictive factors for survival in cancer patients. The aim of this study is to evaluate inflammatory markers as a predictive biomarker for early recurrence in STS.

Methods: 118 patients with primary, localized soft tissue sarcoma were retrospectively reviewed for early recurrence. Early recurrence was defined as a disease relapse (local or distant) within the first year after diagnosis. Pretreatment inflammatory markers including leukocytes, interleukin-6 (IL-6), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and other variables including tumor grade, tumor Departmenth, location, size, and the presence of tumor necrosis on imaging were analyzed for their association with early recurrence. Survival data was analyzed using Log-rank test and Cox regression to identify prognostic factors for early recurrence.

Results: Pretreatment IL-6 elevation was associated with higher tumor grade, increased size, and necrosis on imaging. Elevated CRP was associated with higher tumor grade, NLR and PLR with tumor Departmenth, and PLR with tumor location. Early recurrences were found in 23 of 118 patients (19.5%): 7 local, 15 distant recurrences and 1 with both manifestations. Univariate analysis revealed that tumor grade (low vs high, $p = 0.008$), tumor Departmenth (superficial vs deep, $p = 0.005$), and IL-6 level (< 7 vs ≥ 7 ng/L, $p = 0.012$) were significantly associated with early recurrence; other inflammatory markers including leukocytes, CRP, NLR and PLR were not. Multivariate analysis did not reveal independent risk factors associated with the development of early recurrences in STS, although the number of cases were low.

Conclusions: Early recurrences in STS are not only associated with higher grade and deeper tumors, but also with increased plasma levels of IL-6.

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Biotherapeutics, Luszana, Merck, Merck Sharp & Dohme, Merus, Molecular Partners, Navire Pharma, Novartis, Numab Therapeutics, Pfizer, Relay Pharmaceuticals, Revolution Medicin, Roche, Sanofi, Seattle Genetics, Taiho, Takeda; Financial Interests, Institutional, Research Grant: AstraZeneca, Bayer, Deciphera, GSK, Lixte, Merck, Novartis, Pfizer, Roche. W. Van Houdt: Financial Interests, Institutional, Invited Speaker: Amgen; Financial Interests, Institutional, Advisory Board: Belpharma, Sanofi, MSD; Financial Interests, Personal, Other, travel grant: Novartis; Financial Interests, Institutional, Local PI: BMS. All other authors have declared no conflicts of interest.

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1954P The risk of second primary gastrointestinal tract GIT malignancy after primary retroperitoneal liposarcoma

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Background: Gastrointestinal tract (GIT) retroperitoneal sarcomas are rare tumors representing 1-2% of all solid malignancies and 20% of sarcomas and the most common subtype is liposarcoma. As reported in the literature, the occurrence of multiple primary tumors in a different site than the first primary site is a rare event in the literature, and there are very limited data about retroperitoneal liposarcoma (RPLS) with only a few case reports and case series, so this study aimed to assess the risk of multiple GIT malignancies after primary RPLS.

Methods: Data of RPLS patients was extracted from Surveillance, Epidemiology, and End-Results (SEER) database diagnosed in 2000-2020. We used an MP-SIR session to calculate the standardized Incidence Ratio (SIR) as Observed/Expected (O/E) with 95% Confidence Intervals (CI) showed significance at $P<0.05$ and the Excessive Absolute Risk (EAR) per 10,000.

Results: In 2257 patients, we observed an increased risk of synchronous and metachronous retroperitoneal malignancy after primary RPLS with EAR of 56.34 (O/E=213.24, 95%CI: 271.30-164.92, $P<0.05$). There was an increased risk for small intestinal cancer in the 0-11 months after primary RPLS with O/E of 31.76 (95%CI: 81.32-8.65; $P<0.05$, EAR=5.31) and appendicular cancer (O/E=45.14, 95%CI: 163.05-5.47; $P<0.05$, EAR=9.86). The overall risk to develop 2nd primary gastric carcinoma (O/E= 1.49, 95%CI: 3.81-0.41; $P>0.05$, EAR =1.13), colorectal cancer (O/E=1,44, 95% CI: 2.30-0.84; $P>0.05$, EAR=4.44), hepatocellular carcinoma (O/E=2.08, 95%CI: 4.52-0.76; $P>0.05$, EAR=2.67), and pancreatic cancer (O/E=1.61, 95%CI: 3.17-0.69; $P>0.05$, EAR=2.60). While there was slightly decreased risk in esophageal carcinoma (O/E=0.56; $P>0.05$, EAR= -0.68) and gall bladder cancer (O/E= 0.00; $P>0.05$, EAR= -0.37).

Conclusions: These results show a significantly increased risk of synchronous and metachronous retroperitoneal cancer by 213-fold through ten years while the peak increase of small intestinal cancer and appendicular cancer as 2nd primary malignancies is during the first-year interval. This highlights the importance of regular screening for tumors of the retroperitoneum, small intestine, and appendix after RPLS diagnosis for early detection and better management plan.

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1955P Distinguishing lipomas from atypical lipomatous tumors/ well differentiated liposarcomas in histology slides using deep learning

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Background: Liposarcomas are fat tissue tumors with an incidence rate of 1 case per 100,000 population per year. Atypical Lipomatous Tumors / Well Differentiated Liposarcomas (ALT/WDLPS) are malignant tumors accounting for around 40-45% of liposarcomas and are particularly challenging to diagnose as they can be easily confused with lipomas, another tumor of mesenchymal origin which is benign. The current diagnosis protocol consists in producing a histology slide from a tumor sample (either obtained by resection or biopsy) so that pathologists can determine the type of tumor. If the visual inspection remains uncertain, or the clinical suspicion of ALT/WDLPS is high, a FISH test is ordered in order to analyze the status of MDM2 gene.

Methods: This is a study on the ability of modern deep learning based AI technologies to automatically classify a whole slide image (WSI) containing fat tissue tumor into lipoma or ALT/WDLPS. Two cohorts were provided by Institut Bergonié (IB), Bordeaux, France and Centre Léon Bérard (CLB), Lyon, France. The IB cohort contains 1103 slides (536 Lipomas / 567 ALT/WDLPS) while the CLB cohort contains 956 slides (668 Lipomas / 288 WDLPS). We propose to use a deep learning pipeline relying on (i) a process mapping a WSI into 4000 (112x112 micrometers) small areas randomly sampled from regions containing matter, (ii) a transformer network that maps image areas into a 768 dimensional vectors and (iii) a multiple instance learning (MIL) head for the computation of a probability of WDLPS at the slide level.

Results: We trained our deep learning model using a 4-fold cross-validation (CV) with 5 repeats. Evaluation is reported in terms of accuracy (ACC), i.e., correct prediction rate. In the IB cohort, the model achieves 84.7% of ACC (std 2.5%). In the CLB cohort, it achieves 90.5% of ACC (std 2.1%).

Conclusions: The trained model exhibits excellent performances on (held-out) test samples in both cohorts. Many improvements can be made to the model by either adding clinical data in the pipeline or learning a multi-cohort model through federated learning.

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1956P Neoadjuvant chemoradiotherapy in locally advanced soft tissue sarcoma: NASAR prospective study

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Background: Patients with locally advanced soft tissue sarcomas (ASTS) have a poor prognosis. Several studies attempt to analyze the role of neoadjuvant chemotherapy (NACT) and radiotherapy (NART).

Methods: Prospective unicentric study in ASTS with neoadjuvant treatment based on epirubicin (60 mg/m^2 day 1 and 2) and ifosfamide (1800 mg/m^2 d1-5), every 3 weeks for 3 cycles, concurrently with NART (46-50 Gy) starting on day 22th. Adjuvant boost of NART may be administered after surgery. ASTS greater than 5 cm, high grade and deep localization, and those initially considered as unresectable were included. Patients were evaluated by radiology before and after of neoadjuvant treatment.

Results: From 2017 until 2022, 22 patients with a median age of 43 years (range, 15-78) were enrolled in the study. 17 were men and 5 women. 13 of them were diagnosed of undifferentiated pleomorphic sarcoma, 2 angiosarcoma, 3 liposarcoma, 2 leiomyosarcoma and 2 other. 17 tumours were located in the extremities, 2 in the scapula and the other in the pelvis. The median size was 10 cm (4- 20 cm). The dose of ASTS and NART was completed in all patients. 13 patients received RT boost after surgery. The response was: 31,8% (7/22) obtained clinical response; 13,6% (3/22) partial response according to RECIST criteria; 76% (13/17) achieved a response by PERCIST criteria; and 73,3% (11/15) achieved a response by DIFUSSION criteria. The surgery was an en bloc complete resection in 95,5% patients (21/22). The histological response was $\geq$ than 90% of necrosis in 63,6% (14/22), with 36,4% complete response (8/22). The most frequent toxicity was delay in wound healing and 59,1% patients with skin toxicity grade 2. With median follow up of 50,1 months (range, 18-96), 10 patients remain without disease (45,5%) and 12 have had pulmonary relapses (54,5%) and only 3 local relapse (13,6%). 7 deaths were registered. Median of progression free survival is 26,1 months (95%IC 8,2 − 44,0) and median overall survival not reached.

Conclusions: Neoadjuvant treatment with ASTS concurrent with NART achieves a very high rate of pathological responses and local control. Nonetheless, systemic relapses remain. PERCIST and DIFUSSION criteria have better correlation with necrosis than the RECIST criteria.

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1957P Results from a phase I/II trial of tinostamustine monotherapy in advanced solid tumours (NCT03345485): Safety and efficacy in a subset of patients (pts) with soft tissue sarcoma (STS)

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Background: Tinostamustine, a novel alkylating deacetylase inhibitor, improves drug access to cancer cell DNA strands, breaks them and counteracts damage repair. Here we report safety and efficacy of tinostamustine in a subset of pts with STS from an open-label Ph I/II trial.

Methods: Pts ≥18 years with advanced solid tumours, life expectancy >3 mo, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 were enrolled. Ph I dose escalation (standard 3+3 design 60−100mg/m^2) defined the maximum tolerated dose and recommended Ph II dose (RP2D). In Ph II, the objective response rate (complete response + partial response [PR]), together with pts with stable disease (SD) ≥4 mo duration, following the RP2D (80mg/m^2 over 60 min on D1 & 15 of each 4-wk treatment cycle) were determined, and are summarised here using descriptive statistics. Two substudies characterised the effects of tinostamustine (60−80mg/m^2) on cardiac repolarisation.

Results: Forty-nine pts with advanced solid tumours (13 with STS) were enrolled (Table). In Ph II, tinostamustine-related treatment-emergent adverse events (TEAEs) included thrombocytopenia, anaemia, nausea and fatigue. Serious tinostamustine-related AEs were mainly haematological; 1 tinostamustine-related fatal AE (intra-abdominal haemorrhage; ovarian cancer pt) occurred. In the STS subset, a greater proportion of patients experienced tinostamustine-related and serious tinostamustine-related TEAEs compared with the overall Ph II pt population; there were no tinostamustine-related fatal TEAEs. One pt with STS achieved PR as best response, and 3 had SD ≥4 mo duration; 5 pts with STS discontinued treatment due to progressive disease.

Conclusions: Tinostamustine demonstrated modest signals of efficacy with manageable tolerability in pts with STS.

Table: 1957P Demographic & safety data: Pts with advanced solid tumours receiving tinostamustine & the STS pt subset

	Ph II pt population	STS pt subset
N	49	13*
Age (mean ± std dev), yrs	57.0 ± 12.5	51.9 ± 12.1
Female, n (%)	39 (79.6)	9 (69.2)
ECOG PS 0 1	20 (40.8) 29 (59.2)	3 (23.1) 10 (76.9)
# prior therapies, median (range)	3 (1,9)	5 (2, 8)
N	49	12†
≥1 drug-related TEAE, n (%)	44 (89.8)	9 (75.0)
Serious drug-related AEs, n (%)	12 (24.5)	3 (25.0)
Study discontinuation due to drug-related TEAEs, n (%)	3 (6.1)	0

*Ph I, II & substudies safety analysis set. †Ph II & substudies safety analysis set. AE, adverse event; ECOG-PS, Eastern Cooperative Oncology Group performance status; Ph, Phase; STS, soft tissue sarcoma; TEAE, treatment-emergent adverse event

Clinical trial identification: NCT03345485.

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1958P Head and neck soft tissue sarcoma: Evaluation of the 8th AJCC as a prognostic tool for patients treated with curative intent in a multidisciplinary cancer center

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Background: HN-STS is a challenging disease due to its diverse clinical presentation. In an attempt to refine the prognostication of these pts, the AJCC in its 8th edition proposed a new dedicated T staging group based on cutoffs of 2 and 4 cm for classifying T1, T2 and T3, and surrounding tissue invasion as T4, as opposed to the dichotomic T1-T2 5cm cutoff adopted by the 7th AJCC.

Methods: This is a retrospective study of pts diagnosed with nonmetastatic HN-STS treated with curative intent in a single tertiary hospital, approved by the institutional ethical review committee. The aim was to compare the 8th AJCC T staging to the previous classification as a prognostic tool for HN-STS, added to other variables such as age, histological subtype, grade and regional lymph node metastasis (LNM). AJCC 7th and 8th have been compared regarding T staging with Cohen's kappa coefficient (KC) using inter-rater agreement analysis. The Kaplan-Meier estimator was used to calculate median survival time and differences in time-to-event outcomes were assessed using the log-rank test. Cox proportional hazard model was used to assess the effect of features in overall survival (OS).

Results: From 1997 to 2000, 135 pts were identified in institutional archives. Sarcoma NOS (N=50) and Leiomyosarcoma (N=17) were the most common histologic subtypes, as well as high-grade tumors (N=85). KC of inter-rater agreement was 0.46, statistically significant (p=0.03), indicating poor agreement between both T staging systems. Regarding OS, AJCC 7th (T1 and T2) and 8th (T1, T2, T3 and T4) T size stratification was not statistically different (P=0.42 and P=0.27, respectively). High-grade (71.4% vs 93.6%, P=0.005) and regional LNM (31.3% vs 81.4%, P=0.008) had worse 5-year OS in Cox multivariate analysis. Pts with tumor size>4cm or local invasion, high grade and LNM had 2.30, 7.11 and 4.37-fold increased risk of death respectively.

Conclusions: In our series, neither 7th nor 8th AJCC T size classifications adequately stratified prognostic groups or correlated survival for HN-STS pts. The 8th AJCC T4, the high-grade tumors and regional LNM demonstrated significant worse prognostic impact in pts harboring HN-STS.

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1959P Clinicopathological features and survival analysis of orbital rhabdomyosarcoma

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Background: Orbital rhabdomyosarcoma is a very rare childhood malignancy and the most common primary orbital malignancy in children, with incidence of 250 new cases per year. Due to its scarcity, there is not enough data available in the literature regarding its etiology and risk factors. The aim of this study is to explore the clinicopathological features of the disease and to evaluate the overall survival to add new updated evidence to the literature.

Methods: Data of 152 patients was extracted from The Surveillance, Epidemiology and End Results (SEER) database from 17 registries and diagnosed from 2000 to 2020. The following International Classification of Diseases for Oncology was adopted, Third Edition (ICD-O-3), histology code: 8,900, 8,901, 8,902, 8,910, 8,912, and 8,920; and the ICD-O-3/ WHO 2008 site code (eye and orbit). SPSS version 23 was used for data analysis, Kaplan-Meier Curve and Log rank test for survival analysis.

Results: the 1-year and 5-year relative survival for orbital rhabdomyosarcoma was 98.8% and 90.0%. performing COX-regression model for age, race, gender, year of diagnosis and stage showed age (HR=1.031, 95% CI: 1.062- 1.001; P=0.04) and stage (HR=0.03, 95% CI: 0.290- 0.005; P=0.02) were significantly associated with survival

outcome while gender (HR= 2.487, 95% CI: 12.370- 0.500; P= 0.226) and race (HR= 0.902, 95% CI= 6.465-0.126; -P= 0.919) had no statistical significance. However, 93.7% of the sample were white and only 3.1% had distant metastasis. Regarding histological types; we found 114 patients (70.8%) had embryonal rhabdomyosarcoma, 18 patients (11.8%) had the alveolar type and four patients (2.5%) had the spindle type.

Conclusions: The results of this study showed promising survival outcome for orbital rhabdomyosarcoma with increased incidence in the white race and increased risk with age and stage. The most common histological subtype was embryonal rhabdomyosarcoma. These results give clear updated data about orbital rhabdomyosarcoma to understand the nature of this disease better which help in designing a plan of management putting into consideration the age and stage for better outcome.

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1960P Clinical outcomes of the patients with alveolar soft part sarcoma developed brain metastasis

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Background: Bone and soft tissue sarcomas are uncommon neoplasms that rarely metastasize to the brain. Alveolar soft tissue sarcomas (ASPS) have been reported to have a higher propensity to develop brain metastasis (BM) than other sarcomas. Our study aimed to retrospectively scrutinize the clinical outcome of BM in ASPS.

Methods: 35 patients diagnosed with ASPS between 2006 and 2021 were identified from our database. We evaluated the presence or absence of BM, age at diagnosis, gender, primary lesion site, tumor size, other distant metastases at diagnosis, and prognosis. We compared these clinical characteristics between patients with BM and those without BM (nBM). In the BM group, we also assessed symptoms, duration between diagnosis and BM, treatment for BM, and outcomes.

Results: Fifteen patients (43%) exhibited BM. We observed no significant difference in age at diagnosis, gender, primary lesion site, tumor size, or other distant metastases at diagnosis or median overall survival, compared to the nBM group. Seven cases were asymptomatic when BM was diagnosed. Most symptoms were headache and visual disturbance. The mean duration between diagnosis and BM was 46 months (range: 0-189). BM treatment consisted of gamma-knife radiosurgery in 10 cases, multi-targeted kinase inhibitors (TKI) (pazopanib and/or sunitinib) in eight cases, surgery in three cases, and whole-brain irradiation in three cases. After receiving sunitinib treatment, two patients developed brain hemorrhages. The survival after BM was 33 months (range: 0.5-104).

Conclusions: Approximately half of the ASPS cases included in our study developed BM, with 47% of ASPS patients being asymptomatic at the time of BM detection. Periodic imaging, including the head region, may be advisable. Our analysis did not identify specific clinical features that predict BM in ASPS patients. Selective irradiation and chemotherapy have recently emerged as potential therapeutic options for treating BM in ASPS. These advances may contribute to improved prognosis after BM. However, potential serious adverse events associated with these treatments should be carefully considered. In particular, patients receiving TKI therapy may be at risk for brain hemorrhages and should be closely monitored and managed.

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1961P Prevalence of diagnostic discrepancies in soft tissue and bone tumors from initial diagnosis to referral center

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Background: Sarcomas are rare malignant tumors and represent a heterogeneous group of tumors. An accurate diagnosis of histology is important for treatment strategies. We assessed the pathological review of all patients diagnosed with sarcoma at Siriraj Hospital over a 5-year period to identify the number of first diagnoses compared to the central expert review.

Methods: Histological data from patients diagnosed with sarcoma at Siriraj Hospital were collected over a 5-year period. The initial diagnoses were compared with a certified soft tissue and bone tumor pathologist.

Results: Of the 185 selected patients, 107 (57%) met the inclusion criteria and were analyzed. Full concordance between primary diagnosis and second opinion (the first pathologist and expert reached identical conclusions) was observed in 35 (32.7%) cases, partial concordance (identical diagnosis of connective tumor but different grade or histological type) in 12 (11.2%) cases, and complete discordance (benign versus malignant, different histological type, or invalidation of the diagnosis of sarcoma) in 60 (56.1%) cases. The rate of discordance was higher in incomplete initial IHC ($p = 0.003$), private laboratory, grade 2 and 3, tumor size $\geq$ 100 mm ($p = 0.01$) and age >18. The most common 'full concordance' histology is osteosarcoma (100%, 4 of 4). The main discrepancies were related to histological type ($n = 60$, 56.1%), subtype ($n = 8$, 7.5%), and grade plus subtype ($n = 4$, 3.7%). The mean duration from diagnosis to treatment was 96 days. Only the complete initial report appeared different in the subgroup <97 days group 39 (73.6%) and 97 days group 14 (26.4%) (p=0.03).

Conclusions: More than 65% of the first histological diagnoses were modified in the second reading, possibly resulting in different treatment decisions. The second opinion of the expert improves the quality of diagnosis and possibly the treatment of patients.

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1962P phase II study for nonmetastatic extremity high-grade osteosarcoma in pediatric and AYA patients with a risk-adapted strategy based on P-glycoprotein expression by the ISG (ISG/OS-2): A correlative study on tumor microenvironment

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Background: According to retrospective osteosarcoma series, P-glycoprotein (Pgp) overexpression predicts for poor outcome. Mifamurtide, a modulator of innate immunity, which activates macrophages, was approved for localized osteosarcoma. A risk-adapted treatment strategy, with mifamurtide in Pgp- positive patients, was prospectively assessed in the ISG/OS-2 study (NCT01459484). Here we present a correlative study on tumor microenvironment (TME).

Methods: RNA was extracted in pre-treatment FFPE and non-decalcified tissue of 62 localized osteosarcoma patients and 730 immune genes were investigated (Pancancer Immuneprofiling Nanostring). Primary objective: TME analysis in Pgp+ patients at

diagnosis, comparing EFS > 24 months to EFS ≤ 24 months, after mifamurtide treatment. Secondary objective: TME differences in patients Pgp+ and Pgp- (NCT03737435).

Results: The TME of Pgp+ patients with EFS > 24 versus EFS ≤ 24 months showed: a higher infiltration of macrophages and T-cells, and a lower presence of B-cells; the alteration of genes involved in the Toll-like receptor signaling modulation, which is a possible target of mifamurtide, and, the overexpression of the *PD-L1* gene. Overall, Pgp+ compared with Pgp- patients presented a global upregulation of immune response genes, possibly promoting T-cell activation and cytokines production. Pgp+ patients presented also a more complex TME, enriched in T-cells and B-cells.

Conclusions: Pgp+ patients have a more infiltrated and activated microenvironment as compared to Pgp-. Notably, Pgp+ patients with a better response to mifamurtide treatment (EFS> 24) had an increased macrophages and T-cells TME infiltration and expressed genes predicted to be involved in the Toll-like receptor signaling, likely mediating mifamurtide efficacy.

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1963P Comprehensive profiling of chordoma reveals tumor microenvironment subtypes and unique molecular findings

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Background: Chordoma is a rare type of bone cancer with limited treatment options. Encouraging results showing the efficacy of pembrolizumab, a PD1 checkpoint inhibitor, in chordomas have recently been reported. Here, we performed comprehensive molecular testing to dissect the immune profile of these tumors and elucidate mechanisms of therapy response in chordomas.

Methods: Whole exome sequencing (WES) and whole transcriptome analysis was performed on samples from 14 patients (n = 6 samples from skull base, n = 8 samples from spine) with chordoma. Retrospective analysis of BostonGene's Tumor Portrait® test results identified genomic and transcriptomic alterations of chordomas and classified tumor microenvironment (TME) subtypes according to methods from Bagaev, et al., 2021.

Results: The median age of patients was 54.5 years (range: 26-76 years). The histologic subtypes were conventional (n = 13) and dedifferentiated (n = 1). The median number of prior therapies was 1 (range: 0-3). Transcriptomic-based TME classification revealed 93% (n = 13) of patients had an immune-enriched (IE) TME subtype characterized by high levels of B cells and CD4+ T cells and low levels of tumor-associated macrophages. Only one patient had a fibrotic TME characterized by minimal immune infiltration and a high prevalence of stromal elements. High *CD274* (PD-L1) expression was observed in 57% of samples. *EGFR* expression was high in all samples. In three cases, a 22q deletion was identified. Other clinically actionable events included *SMARCB1* loss (n = 3), *TP53* alteration (n = 2), *BRCA1* loss (n = 1), a combination of *PTEN*, *NF2,* and *TRAF2* loss (n = 1), and *CDKN2A/B* loss (n = 1). All samples were microsatellite stable and had low tumor mutational burden (range: 0.31-1.32 mut/Mb). From this cohort, 50% of patients were matched with at least one clinical trial based on their molecular profiles.

Conclusions: The prevalence of IE TME subtypes in chordomas supports the previously reported response to immune checkpoint inhibitors in chordomas. Together, these findings indicate next-generation sequencing could be a useful tool for informing treatment selection in advanced chordomas.

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1964P Biomimetics of three-dimensional (3D) osteosarcoma (OS) models: A scoping review

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Background: Three-dimensional (3D) cell culture models can recapitulate the native tumour microenvironment (TME) of cancers. However, data on the biomimicry of 3D osteosarcoma (OS) models is unclear. This scoping review (SR) aims to assess how the biomimicry of 3D OS models changes depending on the engineered features of the model. Biomimicry was determined by studying multiple parameters, including cell behaviour and drug resistance.

Methods: The scoping review followed the PRISMA-ScR guidelines and included studies with 3D culture models using osteosarcoma cells. The systematic search, which involved five databases (January 2012-December 2022), identified 293 studies; 70 studies were selected for final analysis: 40 involved drug screening, and 21 included the addition of stromal cells into the model.

Results: Overall, 64% of 3D OS models were scaffold-based compared to self-generated spheroid models. Native scaffolds (42%) comprising mainly collagen/hydroxyapatite predominated, followed by composite scaffolds (22%). For drug screening, both scaffold-based and scaffold-free models were used equally. Thirteen of 15 studies comparing 3D versus 2D drug sensitivity showed decreased sensitivity in 3D models, with several studies showing upregulated resistance genes in 3D models. Furthermore, the use of ECM-mimetic scaffolds and native biomaterials enhanced resistance by OS cells. These suggest biomimetic 3D OS models better recapitulate *in vivo* TME for drug screening. Co-cultures of OS/stroma cells enhanced biomimicry of 3D models and contributed towards osteogenic differentiation, ECM remodelling, mineralisation, angiogenesis, and OS-stromal cells' crosstalk. Seven studies demonstrated selective toxicity of chemotherapeutics towards OS cells while sparing stromal cells, providing helpful evidence for novel therapies development.

Conclusions: This SR highlights the biomimicry of 3D OS models in recapitulating *in vivo* TME. Future work should explore innovative 3D biomimetic models, biomaterials, and advancements in personalised medicine.

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1965P Transcriptional analysis of immune microenvironment of chordomas of the skull base and mobile spine

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Background: Chordomas are rare neoplasms of notochord origin that can affect the skull base and mobile spine. While surgery and radiation are effective means to treat localized disease, there are no standard systemic therapies to treat locally advanced/metastatic chordomas. We previously published a series of chordoma patients treated with immune checkpoint inhibitors demonstrating limited activity. Here we begin to evaluate the immune microenvironment of chordomas by transcriptional analysis.

Methods: 57 tissue samples (30 spine chordoma, 21 skull base chordoma, 6 normal), previously analyzed by RNA-sequencing analysis and published (PMID: 28844110), were used. Hierarchical clustering was used to evaluate expression of immune-related genes. Gene ontology analysis was performed with GeneAnalytics. Microenvironment Cell Populations-counter (MCP-counter) was used for quantification of immune cell populations. Spearman's rank correlation coefficient and t-tests were used for statistical purposes.

Results: Populations of endothelial cells were significantly different in skull base (SB) samples ($p<0.05$) and mobile spine (MS) samples ($p<0.01$) compared to normal. B cells were significantly different in MS compared to normal ($p<0.05$), and monocytes were significantly different in SB samples compared to normal ($p<0.001$). 19 genes of the Interferon gamma (IFNG) gene pathway were significantly altered ($p<0.05$) in SB samples compared to MS samples but only 4 genes of the IFNG pathway were significantly altered ($p<0.05$) in SB samples compared to normal samples. 9 genes of the IFNG pathway were significantly altered in MS samples compared to normal ($p<0.05$). Hierarchical clustering of immune-related gene expression revealed 3 distinct groups. Gene ontology analysis revealed that group 1 favored NF-kappa B

signaling pathway, group 2 favored the phagosome pathway, and group 3 represented dendritic cell development lineage pathway.

Conclusions: Chordomas of the skull base and mobile spine exhibit diverse immune cell populations and differential expression of mediators of immune response. A comprehensive analysis is needed to further our understanding of the immune microenvironment of chordoma to develop ideal immunotherapeutic strategies.

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1966P Extending the interval of denosumab treatment for unresectable giant cell tumor of bone

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Background: The necessity of life-long denosumab injection may cause several problems for unresectable giant cell tumors of bone (GCTB). The efficacy and safety of extending the interval of denosumab treatment (de-escalation) for GCTB were investigated.

Methods: The medical records were retrospectively reviewed for nine patients with GCTB that were either unresectable or resectable, but not those of resection candidates, who received de-escalated denosumab treatment at a single institution since 2014. The median age at initial denosumab treatment was 44 years and tumor location consisted of 5 sacral spines, 2 femurs, one thoracic, and one lumbar spine. The denosumab treatment interval was gradually extended to every 8 weeks, 12 weeks, and 24 weeks. The radiographic changes and clinical symptoms were assessed during standard and de-escalated denosumab therapy.

Results: The denosumab interval was de-escalated after a median of 12 (8-16) months of standard 4-weekly treatment. The median duration of de-escalation treatment was 46 (9—75) months. Imaging showed that a good therapeutic response obtained with the 4-weekly treatment was sustained during the 8-weekly and 12-weekly treatments. According to the MD Anderson criteria, GCTB treated with de-escalated denosumab therapy resulted in a complete response in one patient and a partial response in eight patients. The extraskeletal mass reduced significantly with standard treatment, and tumor reduction was sustained during de-escalated treatment. The clinical symptoms significantly improved with standard treatment and remained improved during de-escalated treatment. Two patients remained stable during the 24-weekly treatment, while one developed local recurrence. Eight of the 9 patients had received de-escalated treatment at the latest follow-up. One developed malignant transformation and pulmonary metastases.

Conclusions: 12-weekly de-escalated treatment of denosumab can sustain symptomatic relief, tumor reduction, and new bone formation achieved with standard treatment, resulting in effective maintenance treatment in patients with unresectable GCTB. 24-weekly treatment can also be selected, with careful attention to local recurrence.

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1967P A single-arm multicenter trial of the combination of anlotinib with chemotherapy in patients with stage IIb classic osteosarcoma of the extremity

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Background: Clinical studies have shown overexpression of multiple tyrosine kinase receptors on the surface of osteosarcoma samples. Anlotinib is a multi-targeted tyrosine kinase inhibitor. The combination of anti-angiogenic drugs with chemotherapeutic agents theoretically has the ability to act synergistically. We conducted this trial to explore the efficacy and safety of anlotinib in combination with chemotherapy for treatment naive stage IIB classical osteosarcoma of the extremity.

Methods: This is a multicentric, single-arm, open-lable trial. Eligible patients(pts) were aged 12-40 years with histologically diagnosed primary localized extremity classic osteosarcoma, stage IIB, operable. Pts received anlotinib (10mg, q3w), doxorubicin(A) and cisplatin(P) for the first nine weeks. Pts underwent radical surgery after exclusion of contraindications at week 10. After surgery, pts received AP at weeks 12-14, and anlotinib plus AP at weeks 15-20, drug dose unchanged. Since week 21, anlotinib(12mg) monotherapy was maintained until week 104 or occurrence of an EFS event. The primary endpoint was 24-month EFS rate, secondary endpoints were 36-month EFS rate, local recurrence rate, lung metastasis rate, 3-year OS Rate and safety.

Results: From May 2020 to Apr 2022, 52 eligible pts were enrolled. At the data cut-off date (Mar 2023), 51 pts underwent surgery after 3 cycles of neoadjuvant therapy, while the rates of limb salvage and R0 resection were 80.39%(95%CI:66.88-90.18%) and 100% (95%CI: 93.02-100%), respectively. In best overall response assessment during the neoadjuvant period, ORR was 1.92% (95%CI: 0.05-10.26%) and DCR was 96.15% (95%CI: 86.79-99.53%). The median EFS was not reached, 12 and 18month-EFS rate were 89.03% (95%CI: 75.39-95.33%) and 59.35% (95%CI: 8.64, 89.48%), respectively. The most grade 3/4 treatment-emergent adverse events were neutropenia (46.15%), leukopenia (36.54%), thrombocytopenia (32.69%), anemia (30.77%).

Conclusions: Preliminary results suggested that anlotinib combined with doxorubicin and cisplatin followed by surgery showed favorable efficiency and manageable adverse events in Stage IIB classic osteosarcoma of the extremity.

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1968P Metastatic Ewing sarcoma, patterns of care and outcomes of patients in a real-life setting: The Metabone national observational study

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Background: Metastatic Ewing Sarcoma (MES) has a poor prognosis, and therapeutic options are scarce in this rare disease. Large observational studies are needed to improve patients (pts) care and help designing future clinical trials.

Methods: Treatment characteristics, outcomes, and prognostic factors of pts $>$ 12 year-old treated for a MES in 10 French national reference network centers from 2008 to 2018 and included in the prospective database of the French Sarcoma Group were analyzed. The primary objective was to describe treatment modalities of pts with MES in a real-life setting, including systemic treatment (ST) regimen, access to clinical trials (CT) and loco-regional (LR) procedures. Secondary objectives were to assess pts outcome in terms of time to next treatment (TNT), progression free survival (PFS) and overall survival (OS) for each line of ST, as well as the impact of CT access and LR procedures on TNT, PFS and OS in the metastatic setting.

Results: 156 pts with MES were included, 80 pts were metastatic from diagnosis, 76 pts had a metastatic relapse. Median follow-up was 76.8 months [66.7; 88.5]. Median age was 21 years (12-86), 44 (28.2%) pts were $<$ 18 year old at metastasis diagnosis. Main primary location was pelvic (34.6%). 147 (94%) pts received ST in the metastatic setting, with a median of 3 lines (IQR 2-5). 102 (65.4%) pts received more than 2 lines. 95 (60.9%) of pts underwent LR procedure for metastasis, including radiation therapy (84.2%), radiological procedures (12.6%) or surgery (8.4%). 30 (31.6%) pts had

multiple procedures. Median OS from metastasis diagnosis was 26.6 months [95%CI 21.0; 32.2]. Median TNT was 5.3 months [95%CI 4.9; 5.6] for 1rst line, 5.5 months [95% CI 3.8; 6.8] for 2nd line and 5.5 months [95%CI 3.7; 7.7] and 3.6 months [95%CI 2.5; 4.4] for 3rd and 4rth lines. 66 (44.9%) pts were included in a CT at least once in the metastatic setting, 35 in 1rst line, 28 in 2nd line and 15 and 22 in 3rd and 4rth lines.

Conclusions: This large multicentric observational study details real-world data on patterns of treatments for pts with MES in France. Detailed ST regimens used, median TNT, PFS and OS according to line and ST regimen as well as factors associated with TNT, PFS and OS will be presented at the meeting.

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1969P Intratumoral immune infiltrates in chondrosarcoma (ChS)

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Background: Infiltrates of various immune cells play an important role in tumor(tu) microenvironment depending on cells' population. T lymphocytes (Tcells, CD3+) may stimulate or suppress immune response, depending on CD4 or CD8 phenotype, respectively. The other important group of cells are macrophages — anti-tumoral M1-like and pro-tumoral M2-like cells. Immunophenotype of ChS and characterization of immune markers involved in pathogenesis is still poorly understood. The aim of this study was characterization of immune cells infiltrates in ChS subtypes and correlate it with clinical outcomes.

Methods: We enrolled 113 patients(pts) diagnosed with primary ChS: 29 grade(G) 1, 41-G2, 25 -G3 and 18 dedifferentiated/mesenchymal cases. For immunohistochemical assessment tissue microarrays of central and peripheral region of the tu were prepared from formalin-fixed paraffin-embedded tissue blocks. IHC analysis covered CD3 (for T cells overall), CD8 (cytotoxic T cells), CD4 (helper T cells), CD68[PG-M1] (M1-like cells), CD68[KP1] and CD163 (M2-like cells), PD-1+ on lymphocytes, and PD-L1+ on tu cells. The number of positive stained cells per area (mm^2, quantitative methods) was defined. PD-L1 expression was evaluated as percent of positive cells. Correlations between expression of immune cells in central and peripheral regions of tu were assessed, and overall survival(OS) was analyzed.

Results: Median OS of all pts was 141 (95%CI: 37.8-) months. In central region of tu we identified significant positive correlation between presence of M1-like CD68+ and M2-like CD68+ macrophages (rho=0.69, $p<0.001$), as well as CD3 and CD4 cells (rho=0.72, $p<0.001$). The correlation of immune infiltrates presence between central and peripheral region of tu was low (rho $\leq$0.5). In multivariate Cox analysis presence of CD3 cells (HR 2.98, CI:1.43-6.23, $p<0.01$) and expression of PD-L1 (HR 1.01, CI:1.01-1.01, $p<0.01$) in central part of tu, as well as high grade of tu (G3/dedifferentiated/mesenchymal) predicted poorer survival. Other immune infiltrates were not significantly correlated with OS.

Conclusions: Beside high grade, PD-L1 expression and CD3 cell influx in central region of tu are independent poor prognostic factors in ChS.

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1970P Metastatic chondrosarcoma, patterns of care and outcomes of patients in a real-life setting: The Metabone national observational study

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Background: Metastatic chondrosarcoma (MCS) has a poor prognosis, and there is still no effective therapeutic option for this rare disease. Large observational studies are needed to improve patients (pts) care and help designing future clinical trials.

Methods: Treatment characteristics, outcomes, and prognostic factors of pts treated for a MCS in 9 French national reference network centers from 2008 to 2018 and included in the prospective database of the French Sarcoma Group were analyzed. The primary objective was to describe treatment modalities of pts with MCS in a real-life setting, including systemic treatment (ST) regimen, access to clinical trials (CT) and loco-regional (LR) procedures. Secondary objectives were to assess pts outcome in terms of time to next treatment (TNT), progression free survival (PFS) and overall survival (OS) for each line of ST, as well as the impact of CT access and LR procedures on TNT, PFS and OS in the metastatic setting.

Results: 124 pts with MCS were included, 31 pts were metastatic from diagnosis, 93 pts had a metastatic relapse. Median follow-up was 56.4 months [33.4; 89.6]. Median age was 61.5 years (14-90). Main histology was dedifferentiated chondrosarcoma (42.7%) and main primary location the trunk (34.7%). Main metastatic site was lung (61.3%). 72 (58%) pts received ST in the metastatic setting, with a median of 2 lines (IQR 1-3). 21 (16.9%) pts received more than 2 lines. 50 (40.3%) of pts underwent LR procedure for metastasis, including radiation therapy (52.0%), surgery (26.0%) or radiological procedures (24.0%); 16 (32.0%) pts had multiple procedures. Median OS from metastasis diagnosis was 12.7 months [95%CI 8.2; 14.9]. Median TNT was 4.6 months [95%CI 3.0; 5.9] for 1rst line, 3.4 months [95%CI 2.7; 4.8] for 2nd line and 3.4 months [95%CI 2.0; 7.9] for 3rd line. 12 (16.7%) pts were included in a CT at least once in the metastatic setting, 4 in 1rst line, 5 in 2nd line and 4 in 3rd line.

Conclusions: This large multicentric observational study details real-world data on patterns of treatments for pts with MCS in France. Detailed ST regimens used, median TNT, PFS and OS according to line and ST regimen as well as factors associated with TNT, PFS and OS will be presented at the meeting.

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1971P Metastatic osteosarcoma, patterns of care and outcomes of patients in a real-life setting: The Metabone national observational study

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Background: Metastatic osteosarcoma (MOS) has a poor prognosis, and treatment options are scarce in this rare disease. Large observational studies are needed to improve patients (pts) care and help designing future clinical trials.

Methods: Treatment characteristics, outcomes, and prognostic factors of pts $>$ 12 year-old treated for a MOS in 10 French centers from 2008 to 2018 and included in the prospective database of the French Sarcoma Group were analyzed. The primary objective was to describe treatment modalities of pts with MOS in a real-life setting, including systemic treatment (ST) regimen, access to clinical trials (CT) and loco-regional (LR) procedures. Secondary objectives were to assess pts outcome in terms of time to next treatment (TNT), progression free survival (PFS) and overall survival (OS) for each line of ST, as well as the impact of CT access and LR procedures on TNT, PFS and OS in the metastatic setting.

Results: 262 pts with MOS were included, 86 pts were metastatic from diagnosis, 176 pts had a metastatic relapse. Median follow-up was 59.7 months [51.3; 68.4]. Median age was 26 years (12-85), 48 (18.3%) pts were $<$ 18 year old at metastasis diagnostic. Main histology was conventional OS (60.3%) and main primary location was inferior limb (60.3%). 227 (86.6%) pts received ST in the metastatic setting, with a median of 2 lines (IQR 1-3). 101 (38.5%) pts received more than 2 lines. 153 (58.4%) of pts underwent LR procedure for metastasis, including surgery (49.0%), radiation therapy (41.8%) or radiological procedures (13.1%); 46 (30.1%) pts had multiple procedures. Median OS from metastasis diagnosis was 21.5 months [95%CI 18.9-27.0]. Median TNT was 4.9 months [95%CI 4.3-5.7] for 1^{rst} line, 5.6 months [95%CI 4.6-6.3] for 2nd line and 3.9 months [95%CI 3.5-5.1] and 2.9 months [95%CI 1.8-4.2] for 3rd and 4^{rth} lines. 56 (24.7%) pts were included in a CT at least once in the metastatic setting, 29 in 1^{rst} line, 27 in 2nd line and 15 in 3rd line.

Conclusions: This large multicentric observational study details real-world data on patterns of treatments for pts with MOS in France. Detailed ST regimens used, median TNT, PFS and OS according to line and ST regimen as well as factors associated with TNT, PFS and OS will be presented at the meeting.

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1972P Molecular mechanism study of recurrence/metastasis for Enneking IIb osteosarcoma

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Background: Osteosarcoma (OS) is a common primary bone malignancy in children and adolescents, with most patients diagnosed with Enneking stage IIB. However, the prognosis for these patients is inconsistent, with over half experiencing recurrence or metastasis under standard treatment. The Enneking staging system alone cannot accurately distinguish the risk group for recurrence and metastasis, highlighting the need for further research into the molecular mechanisms.

Methods: 74 Chinese patients with Enneking stage IIB OS under standard treatment were included, followed up for over two years. Targeted deep sequencing was performed by YUANSU panel (OrigiMed, Shanghai, China) with 706 cancer-related genes and the Kaplan-Meier method was used to calculate survival curves.

Results: The cohort included 74 patients, 50 males and 24 females, with 40 experiencing recurrence or metastasis and 34 not. The high frequency mutated genes in IIB primary OS were found to be *TP53 (33%) FLCN (29%) GID4 (29%) NCOR1 (28%) VEGFA (24%) CCND3 (21%)*. The group with recurrence or metastasis had significantly higher TMB than the group without ($p<0.05$). Survival analysis revealed that genetic mutations in *MCL1, MYC, TFEB, CCND3, AURKB, ALOX12B*, and *VEGFA* increase the likelihood of recurrence and metastasis in IIB OS patients. (*MCL1/MYC/TFEB/CCND3/AURKB/ALOX12B, $p<0.05$; VEGFA, $p=0.065$*); Abnormalities in the MYC, WNT, and Cell cycle pathways are associated with a worse prognosis (*MYC/WNT, $p<0.05$; Cell cycle, $p=0.057$*). These results indicate that genetic variants and pathway abnormalities are significant risk factors for IIB OS.

Conclusions: Our study represents the largest cohort investigating the molecular mechanisms of Chinese IIB OS. Mutations of *MCL1/MYC/TFEB/CCND3/AURKB/ALOX12B/VEGFA* genes and MYC/WNT/cell-cycle pathways are high-risk factors for recurrence/metastasis. Given the high mutation frequency and poor prognosis of patients with VEGFA and cell cycle signaling pathway abnormalities, anti-angiogenic agents and cell cycle inhibitors may be more effective treatment options compared with standard therapy. Further studies are needed to confirm their efficacy.

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1973P Antitumor activity of olverembatinib (HQP1351) in patients (pts) with TKI-resistant succinate dehydrogenase- (SDH-) deficient gastrointestinal stromal tumor (GIST)

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Background: GIST treatment has been transformed by TKIs but resistance is a challenge in managing advanced disease. Pts with SDH-deficient GIST typically present with TKI-insensitive, multifocal/multinodular disease. Olverembatinib is a novel, potent, multitargeted TKI with promising preclinical activity against GIST.

Methods: Antitumor activity of olverembatinib was evaluated via a panel of SDH-deficient cell lines. SDH knockdown was performed in PC12 cells to assess potential mechanisms of action. The aim of the phase 1 study was to assess safety and efficacy (RECIST v1.1) of olverembatinib, orally once every other day (QOD) in 28-day cycles, in pts with TKI-resistant, metastatic, SDH-deficient, IHC-confirmed GIST.

Results: Olverembatinib had superior antiproliferative effects on SDH-deficient cancer cell lines, and the increased sensitivity could be ascribed to FGFR pathway upregulation. As of January 15, 2023, 20 pts had received $\geq$ 1 dose of olverembatinib and 19, 1-4 TKIs (Table). The dose range of olverembatinib was 20-50 mg and median (range) treatment duration 7.8 (1.81-42.3) mo. 5/20 pts experienced PR as best response. Of 16 evaluable pts receiving $>$ 4 cycles, the clinical benefit rate (CBR; CR + PR + stable disease [SD] $>$ 4 cycles) was 93.8% (15/16); the longest treatment duration was 42 mo. All pts experienced TEAEs (mostly grade 1 or 2 [G1-2]); 2 had G3 AEs; the only hematologic AE with incidence rate $\geq$ 20% was anemia (55%). 15 (75%) pts had TRAEs (G3 neutropenia [n = 1]). No treatment-related SAEs were reported.

Conclusions: Olverembatinib was effective in SDH-deficient tumors preclinically. In the phase 1 study, it was well tolerated up to 50 mg QOD and showed antitumor activity in pts with TKI-resistant, SDH-deficient GIST. 5 PRs were reported in 20 evaluable pts, and 15 SDs among 16 pts treated $\geq$ 4 cycles (93.8% CBR). These promising data warrant further investigation. Study: HQP1351SJ003.

Table: 1973P Baseline characteristics	
Characteristic	
Median age (range), yr	30 (14-56)
Male, no. (%)	6 (30)
Primary tumor site, no. (%)	
Stomach	20 (100)
Prior TKI, no. (%)	
0	1 (5)
1	6 (30)
2	3 (15)
≥ 3	10 (50)

Clinical trial identification: NCT03594422.

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1974P Improved risk stratification with a prognostic nomogram incorporating the KIT-Variant Allele Frequency (VAF) and the 557/558 deletions: Results from a multi-institutional study in a cohort of intermediate-risk GIST patients

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Background: In the intermediate-risk (I-R) GIST patients, the choice of adjuvant imatinib is challenging. Historically, patient risk stratification is based on tumor size, mitotic index, tumor location, and tumor rupture. Innovative measures from NGS, such as the *KIT*-Variant Allele Frequency (VAF), may act as surrogate of tumor burden, and thus might negatively correlate with prognosis of localized GIST patients, along with specific tumor genotyping.

Methods: We used real-world data from a multicenter, hospital-based, retrospective/prospective cohort study to develop a prognostic nomogram integrating VAF levels and type/gene location of *KIT* mutations. The receiver operating characteristic (ROC) analysis was used to classify "low" vs "high" VAF values, further normalized on neoplastic cellularity (nVAF). The optimal cut-off was 50% (AUC 0.84; p-value < 0.02). Cox regression/nomogram models were developed in SPSS and R, respectively.

Results: Overall, data from 240 GIST patients treated between 2015 and 2022 at 6 Oncologic Centers in the EURACAN Network were collected. The cohort of I-R patients with tumors harboring *KIT* mutations, without adjuvant imatinib, included 66 patients. Diameter of primary tumor >5 cm ($p=0.005$), mitosis >5/mmq ($p<0.001$), no-gastric site of origin ($p=0.01$), *KIT* Exon 11 deletions or delins involving codons 557 and/or 558 ($p<0.001$), and nVAF $> 50\%$ ($p=0.006$), were significantly associated with Relapse-Free Survival (RFS). At the median follow-up of 24 months, RFS rate of I-R cohort was 74.4% in the high-nVAF group vs 100% in the low-nVAF group. When RFS between the 2 groups was compared, I-R patients with high-nVAF showed poorer RFS than low-nVAF group. Nomogram analysis including *KIT*-PVs—nVAF, and the presence/absence of 557/558 del/delins, predicted 2-year RFS.

Conclusions: Prognostication in the intermediate-risk subgroup is still challenging for optimal patient selection for adjuvant imatinib. In this sub-population the use of a nomogram incorporating nVAF and type/gene location of *KIT* mutations, might represent a more accurate tool in the clinical decision-making process.

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1975P Systemic therapy for KIT/PDGFRA wild-type GIST

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Background: Patients (pts) with metastatic KIT/PDGFRA wild-type (KPWT) gastrointestinal stromal tumours (GIST) usually do not derive any benefit from upfront treatment with imatinib. Most of the studies reported so far include case reports or small series and treatment patterns widely differed according to the medical teams. More studies are therefore needed to define the optimal management of metastatic KPWT GIST pts. The primary aim of this retrospective study was to assess the outcome of pts with KPWT GIST treated by Tyrosine Kinase Inhibitors (TKI) in our institution.

Methods: We conducted a retrospective study at a single institution, the Centre Léon Bérard (CLB). The national sarcoma database (https://netsarc.sarcomabcb.org/) was searched for pts with a diagnosis of KPWT GIST treated at the CLB. Data were extracted from individual patients' files. All cases were reviewed by an expert sarcoma pathologist. In the absence of a known neurofibromatosis type 1 (NF1) or SDH-deficiency, whole exome-RNAseq was performed on FFPE material.

Results: In total, 86 pts with metastatic KPWT GIST were identified, with a median age at diagnosis of 55 [10-80], a sex-ratio of 0.9 and a median tumor size of 65 mm [11-260]. The primary tumor was in the stomach for 42 pts (49%) and in the duodenum for 40 (47%). The vast majority were *KIT* and *DOG1* positive by IHC (98 and 92%, respectively). Among the 86 pts, 31 (36%) had a metastatic disease, either synchronous ($N=15$) or metachronous ($N=16$). The majority of these cases were NF1-associated GIST (N=13, 42%), 7 were SDH-deficient GIST (23%), one was NTRK-rearranged GIST (*RBPMS::NTRK3*), one harboured TSC1 variant (T314M) and no significant mutation/fusion was detected in 9 GIST. While none of the 31 pts responded to imatinib, 3/3 pts had a partial response with lenvatinib (all SDH-deficient GIST), 1/3 with pazopanib, 2/20 (10%) with sunitinib and 2/10 (20%) with regorafenib. Interestingly, the highest duration of response PFS was with pazopanib (111 months).

Conclusions: This retrospective series of KPWT GIST is one of the largest with this rare disease. Although there was no response to first line TKI imatinib, some long responders are reported with anti-angiogenic TKI and warrant additional investigation through prospective trials to validate those results.

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1976P Financial difficulties experienced by gastrointestinal stromal tumor (GIST) patients in the Netherlands: Data from a cross-sectional multicenter study

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Background: Financial difficulties get little attention in daily clinical practice, while they can have a considerable impact on treatment outcomes and the patient's quality of life. This study aims to explore the prevalence of financial difficulties among GIST patients, with a distinction in patients on tyrosine kinase inhibitor (TKI) treatment or not on TKI treatment, and investigate associations between financial difficulties and sociodemographic and clinical characteristics, work, cancer-related concerns, anxiety and depression.

Methods: A cross-sectional study was conducted among Dutch GIST patients between September 2020 and June 2021. Patients completed nine items regarding financial difficulties of the EORTC item bank, work-related questions, Hospital Anxiety and Depression Scale (HADS), Cancer Worry Scale (CWS) and EORTC QLQ-C30.

Results: In total, 328 GIST patients participated (response rate 63.0%), of which 108 (32.9%) were on TKI treatment. Experiencing financial difficulties was associated with significantly lower global quality of life (67.8 vs 81.6, $p=<0.001$) as compared to patients who did not report financial difficulties. Patients with financial difficulties also more frequently reported symptoms of anxiety (41.7% vs 11.5%, $p=<0.001$) and depression (36.1% vs 10.1%, $p=<0.001$), had more fear of cancer recurrence or progression (73.0% vs 39.9%, $p=<0.001$), and were more often concerned about dying from GIST both in the near future (64.9% vs 34.9%, $p=<0.001$) and in the long run (75.7% vs 49.5%, $p=0.003$). The odds of experiencing financial difficulties was 16.4 (95% CI 1.24-217.1; $p=0.03$) times higher in patients that were less able to work. Patients currently treated with TKIs experienced significantly more financial difficulties compared to patients not on TKIs (17.6% vs 8.7%, $p=0.02$).

Conclusions: Even in a country where the costs of TKIs and follow-up care are covered by health insurance, financial difficulties can be present in GIST patients, especially in patients on TKI treatment. Given the association between financial difficulties with quality of life, anxiety, depression and cancer-related concerns, more support should be provided to patients.

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1977P A registry-based analysis of the projected genomic landscape among unclassified KIT/PDGFRA wildtype mutations in patients with gastrointestinal stromal tumors

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Background: Gastrointestinal stromal tumors (GIST) are characterized by multiple subtypes with distinct biological features. Here, we report the frequency of classified mutations and the projected frequency of unclassified KIT/PDGFRA Wildtype (KIT/PDGFRA WT) mutations in GIST patients that received mutational testing.

Methods: This data was supplied by the Life Raft Group (LRG) Registry. Of 2465 patients, 55.3% (n=1363) had mutational testing (Tested) and 44.7% (n=1102) did not (Untested). We used the distribution of classified KIT/PDGFRA WT that had further testing to estimate the frequency in unclassified KIT/PDGFRA WT. By assuming the distribution of unclassified Wildtype patients is similar to the classified patients, we projected the entire cohort by multiplying the percentage of each classified KIT/PDGFRA WT mutation to the total number of unclassified KIT/PDGFRA WT patients (n=101).

Results: *Tested Patients* Out of 1363 Tested patients, the distribution was: KIT 77.8% (n= 1060), PDGFRA 7.6% (n= 104), SDHx 4.8% (n= 66), NF1 1.5% (n= 20), BRAF (includes 1 fusion) 0.6% (n= 8), ETV6-NTRK3 fusion 0.2% (n= 2), PTCH1 0.1%(n=1), NTRK 0.1%(n=1). *KIT/PDGFRA WT* Approximately half (49.2%, n= 98) of KIT/PDGFRA WT patients had further testing (classified), e.g., SDHx, NF1, BRAF, etc. The other half (50.8%, n=101) had no further or inconclusive testing (unclassified), which are recorded as "Wildtype" (WT) in the registry. Table displays the projected number of patients in unclassified WT and the overall projection of all Tested patients.

Table: 1977P Known and projected mutation distribution

Gene	Tested Patients (Known) n=(%)	Classified WT KIT/PDGFRA Mutation Rate % (n=98)	Projected No of Patients in Unclassified WT (n=101)	Known & Projected Patients	Projected Rate (%)
Kit	1060 (77.8%)	NA	NA	1060	77.8%
PDGFRA	104 (7.6%)	NA	NA	104	7.6%
Unclassified WT	101 (7.4%)	NA	-	NA	NA
SDHA	31 (2.3%)	31.6	32	63	4.6%
SDHB	21 (1.5%)	21.4	22	43	3.2%
NF1	20 (1.5%)	20.4	21	41	3.0%
SDHC	9 (0.7%)	9.2	9	18	1.3%
BRAF	7 (0.5%)	7.1	7	14	1.0%
SDH-C Epimutant	4 (0.3%)	4.1	4	8	0.6%
ETV6-NTRK3 Fusion	2 (0.1%)	2.0	2	4	0.3%
AGAP3-BRAF Fusion	1 (0.1%)	1.0	1	2	0.1%
SDHD	1 (0.1%)	1.0	1	2	0.1%
NTRK	1 (0.1%)	1.0	1	2	0.1%
PTCH1	1 (0.1%)	1.0	1	2	0.1%
Total	1363 (100%)	100%	101	1363	100%

Conclusions: By using the methods described, we were able to project the frequency of mutations in LRG registry patients and identified a higher frequency of unclassified mutations. A well-defined mutation can provide important information to optimize clinical decision-making, including diagnosis, prognosis, treatment selection, and monitoring treatment response.

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1978P Identification of SDH-deficient GIST increases after the implementation of diagnostic algorithm in Life Raft Group (LRG) patient registry data

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Background: Succinate dehydrogenase (SDH) deficient GISTs account for less than 10% of all GISTs and exhibit distinct biological features when compared to those that harbor KIT/PDGFRA mutations. SDH-deficient GIST commonly affects young adolescents with a baseline metastatic presentation and are frequently insensitive to tyrosine kinase inhibitors. The immunohistochemical (IHC) loss of SDH subunit B (SDHB) is a characteristic marker of SDH-deficient GIST, which is suggestive of the loss of function in the entire SDH-complex. With data from the LRG Patient Registry, a diagnostic algorithm illustrating the need for wider use of targeted diagnostic procedures was implemented in the College of American Pathologists (CAP) guidelines to facilitate the identification and treatment of SDH-deficient patients. Here, we aim to evaluate the results within our data after the implementation of such an algorithm.

Methods: The LRG Patient Registry is a global longitudinal natural history study that is supported by medical records, including pathology and genomic reports. Two datasets from the LRG Patient Registry were used in this study, with the data cutoff points being 2017 and 2022. A comparison of the total number of SDHx patients reported in each dataset was conducted. SDH-deficient patients reported an SDHx mutation and/or loss of SDHB IHC expression.

Results: Out of the (n=750) global patients that reported their mutation in 2017, 28 (3.7%) were identified as SDH-deficient. When comparing with the 2022 dataset, (n = 1387 with mutational results) 83 (6.0%) were identified as SDH-deficient. This represents a 60% increase in identified patients.

Conclusions: The absence of SDHB IHC staining as part of the regular pathology protocol led to the under-identification of SDH-deficient patients. This study emphasizes the significance of SDHB IHC staining and advanced mutational testing in the LRG Patient Registry population. It is encouraged that the use of SDHB IHC should be included in additional guidelines to optimize the identification, diagnosis, and management of SDH-deficient GIST patients.

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1979P phase I trial of pembrolizumab in HIV-associated Kaposi sarcoma (KS)

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Background: Cancer Immunotherapy Trials Network 12, a phase 1 multicenter study of pembrolizumab (pembro) in advanced HIV-associated cancers showed safety across a range of cancers in patients (pts) with controlled HIV (Uldrick et al. *JAMA Oncology* 2019). We report results from the expanded KS cohort.

Methods: Pts with HIV+ KS, CD4 count (CD4) ≥50 cells/μL, antiretroviral therapy (ART) for ≥4 weeks, HIV viral load ≤200 copies/mL with or without prior KS therapy were eligible. Pts received pembro 200 mg q3 weeks for up to 35 cycles. The primary objective was safety by NCI Common Terminology Criteria for Adverse Events; the secondary objective was KS response rate by AIDS Clinical Trials Group Criteria. Progression-free survival (PFS) and duration of response (DOR) were evaluated by Kaplan-Meier (KM) methodology.

Results: 32 men [median (med) age 45 years; 16 White, 15 Black, 7 Latino] with HIV+ KS were enrolled. Baseline med CD4 was 274 cells/μL. 9 pts had no prior systemic KS therapy. Pts received a med of 10 cycles of pembro. 2 pts completed 35 cycles and/or 2 years of treatment, 6 have ongoing treatment, and 24 stopped treatment before 35 cycles [progressive disease (9), unacceptable toxicity (5), declined further treatment (3), death (1), other reasons (6)]. Med CD4 increase at end-of-treatment was 50 cells/μL (p=0.046). 13 pts (41%) had grade (G) ≥2 pembro-related treatment-emergent adverse events (AE), including 1 previously reported pt who died of polyclonal HHV8-related B cell lymphoproliferation. 10 (31%) pts had ≥1 immune-mediated AE (imAE) [G1 (1), G2 (5), G3 (4)] with 7 (22%) requiring systemic steroids. Of the 28 evaluable pts, 17 had a partial response (including 6 with CD4 <200 cells/μL), 8 had stable disease, and 3 had progressive disease as best response to pembro. The overall response rate (ORR) was 60.7% (95% CI: 40.6-78.5) and did not differ by CD4. Notably, the ORR was 85.7% (95% CI: 42.1-99.6) in pts without prior KS therapy. Med PFS was 28.2 mo (95% CI: 4.2-non-calcuable). The KM probability estimate of a DOR ≥ 12 months was 91.7% (95% CI: 53.9-98.7).

Conclusions: Pembro leads to a durable, high response rate, particularly as first systemic KS therapy, and is associated with CD4 immune reconstitution. Although 31% of pts had imAEs, they were successfully managed following standard guidelines.

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1980P Artificial intelligence analysis shows enhanced CCNG1 expression in sarcoma tumors, a novel biomarker for DeltaRex-G tumor targeted retrovector encoding a CCNG1 inhibitor gene

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Background: In phase 1/2 studies using DeltaRex-G targeted retrovector bearing a CCNG1 inhibitor gene for advanced sarcoma, long term survival reports showed that four (7%) patients with chemotherapy resistant advanced sarcoma were alive > 10 years from DeltaRex-G treatment initiation. Expanded access for DeltaRex-G, is currently open for advanced sarcoma patients. (NCT04091295). In this study, we analyzed CCNG1 expression in tumors of patients who are being followed at our Cancer Center to identify those who might respond favorably to DeltaRex-G therapy.

Methods: Archived formalin-fixed paraffin embedded (FFPE) tumor specimens (n=65) from patients with sarcoma were collected, processed, and subjected to RNA sequencing. Briefly, RNA-seq libraries were sequenced to generate 50 million reads that were aligned using Kallisto v0.42.4 to GENCODE v23 transcripts with default parameters. A gene expression level is presented as low/medium/high depending on the expression level of a such gene in patients of the reference cohort. Low = <17%; Medium = 17%-83%; High = >83%.

Results: Thirty male and 35 female subjects, ages ranging from 16 to 87 years were studied. Four (6%) tumors showed high CCNG1 expression, forty-seven (72%) tumors had medium expression, and fourteen (22%) tumors had low CCNG1 expression. Seven of 65 patients had osteosarcoma, of which 4 were male, three females, ages ranging from 16 to 57 years. The osteosarcoma tumors showed 86% with medium CCNG1 expression and 14% with low CCNG1 expression. Five patients with medium CCNG1 expression had metastatic disease while one patient with low and one with medium CCNG1 expression had localized disease. Of note, one participant with advanced chondrosarcoma had clinical benefit (stable disease) by RECISTv1.1 and is alive 3 years after DeltaRex-G treatment initiation. AI analysis of his tumor showed 74% CCNG1 expression.

Conclusions: Taken together, these data suggest that (1) 90% of sarcoma tumors have high to medium CCNG1 expression and (2) Four of 5 (80%) osteosarcoma tumors have medium CCNG1 expression. Prospective studies are planned to correlate CCNG1 expression level with response to DeltaRex-G therapy.

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1981P Histopathological diagnostic discrepancies in bone and soft tissue tumors referred to a specialist sarcoma center and its clinical impact

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Background: Histopathological diagnosis of sarcomas is challenging because of their rarity, diverse histological findings, and constantly evolving diagnostic criteria. In this study, we attempted to clarify discrepancies between histopathological diagnoses made by general pathologists at referral hospitals and diagnoses made by specialist pathologists at a tertiary cancer hospital, with a focus on its clinical impact in the era of genome medicine.

Methods: We analyzed 628 specimens from 624 consecutive-referral patients, who visited a specialist sarcoma center for treatment between April 2017 and March 2019. Differences between the first diagnosis provided at another hospital by non-expert pathologists and the diagnosis reviewed by a specialist pathologist at the sarcoma center were evaluated and classified into four categories: agreement, non-agreement, specified, and de-specified.

Results: Of the 628 specimens, pathological diagnosis matched in 403 (64.2%) specimens whereas some change was noted in 225 (35.8%) specimens. The changes in pathological diagnoses were as follows: non-agreement, 153 specimens (24.3%); specified, 52 (8.3%); and de-specified, 20 (3.2%). The benign/malignant judgment had changed for 92 specimens (14.6%). The main reason for the discrepancies was the difference in interpretation of tumor histology, which accounted for 48.9% of the cases. The unavailability of immunostaining and genetic analysis accounted for 24.4% and 8.9% of the discrepancies, respectively. The treatment was changed in 91 cases (14.5%) due to changes in the pathological diagnoses. The number of changes in surgical treatment, medical treatment, and both were 40 (6.4%), 44 (7.0%), and 7 (1.1%), respectively.

Conclusions: Our study shows that over 35% of first histopathological diagnoses of bone and soft tissue tumors were modified by expert pathologists at a tertiary cancer hospital and resulted in different treatment decisions in about 15% of cases. Given the therapeutic implications of a misdiagnosis, ensuring accurate histopathological diagnosis using some public mechanisms is of vital importance in cases of these rare tumors.

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1982P Transcriptomic analysis and tumor microenvironment (TME) classification reveals unique immune biology in HIV patients with Kaposi sarcoma (KS)

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Background: KS, associated with human herpesvirus 8 (KSHV) infection, is a tumor originating from endothelial cells. As a common tumor associated with AIDS, KS is typically more aggressive in HIV-positive (HIV+) than in HIV-negative (HIV-) patients (pts). While antiretroviral therapy helps control KS in HIV+ pts, chemotherapy remains the first-line treatment (Tx) in advanced KS but is limited by modest responses and dose-limiting toxicities. The TME has been shown to play a critical role in KS development and progression. Here, we sought to understand the TME in KS, with a specific focus on the differences in HIV status.

Methods: Whole transcriptomic profiling was performed on 13 retrospective samples from 9 pts (HIV+: n = 6, HIV- n =3; mostly baseline, except 2 HIV- and 2 HIV+ pts had paired samples before and after Tx). A deconvolution algorithm Kassandra was used to predict cellular composition with pre-training on sarcoma samples, and EdgeR was used for differential expression analysis. TME subtypes were classified based on a previous study (Bagaev et al., 2021) assessing sarcoma-related gene expression patterns.

Results: All KS samples were enriched with endothelial cells and had characteristics of a typical sarcoma TME with an abundance of macrophages and normal amounts of B cells. Most HIV- pts had an Immune-Enriched, Non-fibrotic subtype, while HIV+ pts had immune-Enriched, Fibrotic or Fibrotic TMEs. Decreased angiogenic signatures were observed after Tx in HIV+ pts with paired samples. Expression levels of chemokines (CXCL2, CXCL8, CXCL11), chemokine receptors (CCR1-7, CXCR1-2), and CCL factors were higher in pre-Tx HIV- pts versus post-Tx and post-TX HIV+ pts versus pre-TX. PD-L1 and PD-L2 expressions were higher in HIV- pts before Tx and in HIV+ pts after Tx. In 3 HIV- and 2 HIV+ pts, for whom TCR.

Conclusions: Our results showed distinct transcriptomic features and TMEs between HIV+ and HIV- KS in responses to Tx. Future larger cohorts and research into the unique T cell clonotypes may help yield novel therapeutic avenues in KS.

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1983P Palliative spatially fractionated stereotactic radiation therapy (Lattice) for large sarcoma

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Background: Awareness and respective publication numbers on Spatially Fractionated RT (SFRT) rapidly increased over the past years. Lattice Radiotherapy (LRT) as one form of SFRT is a promising treatment option for patients with large inoperable and/or metastatic tumors. Since first reports on clinical LRT use in ∼2010, all confirm unexpectedly high tumor responses with excellent treatment tolerance. Questions regarding best dose-volume/fractionation/geometrical solutions are unanswered - several approached are in early testing. Similarly, knowledge regarding outcome over time (extent, duration of treatment effects) are hardly known yet. Only few case reports were published on LRT in sarcoma. We aimed to assess early outcome of a multi-center retrospective sarcoma patient cohort treated with LRT.

Methods: This retrospective cohort analysis included 22 palliative patients treated from 08.2020-04.2023 with LRT for 28 large (>10cm) sarcomatous lesions of different subtypes. Data were prospectively collected. LRT was performed at 2 Centers (A: Instituto Oncobio, Minhas Gerais (Brazil), B: LUKS Universitary Teaching Hospital (Switzerland)). Mean/median GTV measured 1029/780cc (74-4778). Center A used 1 single fraction with doses of 15-20Gy to the intra-lesional vertices, followed by 5 (n=6) or 15-16 fractions (n=4) with 25Gy or ∼40Gy respectively, to the entire tumor.

Center B applied 5 fractions of 20-25Gy to the entire tumor with a simultaneous integrated boost dose of 60-65Gy to the vertices. Follow up intervals of this palliative cohort had to be adjusted to the individual situation. Primary outcome measure included subjective early clinical effect and objective tumor shrinkage.

Results: Mean/median FU was 7.1/6 mo. (0.5-24). 7/22 pats died after mean 4 mo. (0.5-6). Subjective statements at LRT completion were available in all pats: no change in 2/22, substantial fast relief of symptoms in 20/22; no >G1 side effects. FU imaging was assessable from 20/28 lesions: mean/median shrinkage of 43/25% (0-100%) after mean/median 7/3.5 mo. (0.5-22), including 9 lesions with previous RT.

Conclusions: LRT in sarcoma translated into fast subjective symptom relief and related objective tumor shrinkage. A phase 2 trial is provided to test different LRT schedules.

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1984P Sex differences in anticancer treatment delivery and toxicity in patients with sarcoma in a reference center

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Background: In the era of precision medicine, despite mounting evidence that women might be more susceptible to toxicity from chemotherapy (CT), sex influence on treatment effects and the biology of non-sex-related cancers have largely been ignored. Due to their rarity, data on patients (pts) with sarcoma are scarce.

Methods: We reviewed data of pts with sarcoma treated between 2015 and 2022 at Veneto Institute of Oncology. Delays/reductions were evaluated in the first 9 weeks of CT and expressed as relative dose intensity (RDI): ratio of delivered dose intensity (mg/m^2 per week) to theorical dose intensity. Kaplan-Meier, log-rank and Cox regressions were used. Sex differences in RDI, adverse events (AEs) and impact of RDI on disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: Overall, data for 197 pts were available (109 treatments for localized disease: 69 neoadjuvant/40 adjuvant setting; 127 first -line treatments for advanced disease). Median age was 57 years, males were 112 (57%). Soft tissue sarcomas were 167 (85%), bone sarcomas were 30 (15%). Grade $\geq$ 3 AEs were observed in 60% of pts. Male had a lower risk of severe non-hematologic AEs (OR 0.5; p=0.04), while no significant sex differences were observed for all severe AEs. Dose was reduced upfront in 46% of female Vs 28% of males (p=0.007). Also, males less often had RDI <85% (OR 2.4; p=0.002). Survival outcomes were similar in both sexes, though comparisons might suffer from biases due to different distribution of histotypes within sexes. In the localized disease setting, worse survival was observed for males receiving RDI <85% compared to $\geq$85% (median OS 36.6 m Vs 63.7 m, p=0.004; median DFS 11.1 m Vs 26.3 m, p=0.03) whereas no significant differences at the 85% threshold of RDI were found for females.

Conclusions: Greater risk of AEs and lower RDI in women treated for sarcoma add to the evidence that a sex-difference in treatment delivery and outcomes exists. Despite a global lower RDI, survival outcomes for female were not worse compared to male. Interestingly, RDI <85% did not negatively affect survival outcomes in women (standard dosing based on "male" standards?). Such data call for optimization of drug dosing by sex to be considered in trial design.

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1985P Expert sarcoma care is the need of the hour: Diagnostic and management challenges at a tertiary-care centre in India

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Background: Sarcomas are rare mesenchymal tumors that require multidisciplinary care. Referral centres receiving patients (pts) from peripheral set-ups face challenges which highlight the need for expert sarcoma pathology and specialised treatment.

Methods: This is a retrospective study in pts referred with pathological and/or clinico-radiological diagnosis of sarcoma (January 2021 to December 2022). Clinical, diagnostic, prior treatment details were reviewed from records. Pathologic discordances (PD) were classified as major (sarcoma to carcinoma or benign, soft tissue sarcoma to bone sarcoma or vice versa, any change influencing treatment) or minor.

Results: 539 pts included (incl) 58% males (n=312) with median age of 35 (1-89 years), residing at median distance of 160 kilometres (km) (3-2600) from our centre. Median presenting time was 11 months (15 days-20 years) from symptom onset; recurrent/metastatic (n=255, 47%) and locally advanced (n=134, 25%) stages predominated. Common primary sites were extremity (45.5%), abdomen (27%) with symptoms of pain (67%) and swelling (64%). 499 (92.5%) pts had pathology reports from outside and available comparison (n=372) showed 42.9% discordance (16.3% major, 26.6% minor) (Table). Sarcoma diagnosis changed to benign (1.3%), carcinoma (1.3%), fibromatosis (0.2%), germ cell tumor (0.2%) after review. Ultra-rare sarcomas (URS) (n=33, 6%) showed higher PD (73%). Molecular testing was done in 4.6% (n=11) of pts with testing indications. Most had received treatment outside (surgery in 50.6%, chemotherapy in 32.6%); deviation from standard guidelines was noted in 39.7% chemotherapy and 8.7% surgeries (Table). Univariate analysis did not yield significant factors associated with diagnostic or treatment discordance.

Table: 1985P Details of subjects and discordances in diagnosis and treatment

Diagnosis	Treatment
Subtypes	**Chemotherapy**
Soft tissue sarcoma (STS) = 295 (54.7%)	a) Incorrect regimen (n=28, 16%)
Bone sarcoma (BS) = 100 (18.5%)	b) Inadequate dose/cycles (n=20, 11.3%)
Carcinoma = 7 (1.2%)	c) Not given despite indication (n=17, 9.6%)
Benign = 7 (1.2%)	d) Others (n=4, 2.2%)
Others = 10 (2%)	**Surgery**
Undifferentiated = 1 (0.2%)	a) Inadequate surgery (n=19, 7%)
Discordances	b) Surgery without staging (n=5, 2%)
a) Major = 61 (16.3%)	
b) Minor = 99 (26.6%)	
Major discordance:	
a) Change of sarcoma subtype = 39 (64%)	
b) Benign to malignant = 14 (11.7%)	
c) Carcinoma to sarcoma = 4 (6.5%)	
d) Low to high grade = 4 (6.5%)	
e) BS to STS = 3 (5%)	

Conclusions: The significant discrepancies noted in diagnosis and management of pts in this study highlight the importance of expert pathologists and early referral for better treatment outcomes in sarcomas.

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1986P Impact of SARS-CoV-2 vaccines and recent chemotherapy on COVID-19 morbidity and mortality in patients with soft tissue sarcoma: An analysis from the OnCovid registry

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Background: To date no specific evidence exists on the impact of COVID-19 in pts with soft tissue sarcoma (STS), nor about the impact of SARS-CoV-2 vaccines and chemotherapy on COVID-19 morbidity and mortality in this specific population.

Methods: We described COVID-19 morbidity and mortality among pts with STS across "Omicron" (15/12/21-31/01/22), "Pre-vaccination" (27/02/20-30/11/20) and "Alpha-Delta" phase (01/12/20-14/12/21) using OnCovid registry participants (NCT04393974). Case fatality rate at 28 days (CFR_{28}) and COVID-19 severity were described according to the SARS-CoV-2 vaccination status, whilst the impact of the receipt of cytotoxic chemotherapy within 4 weeks prior to COVID-19 on clinical outcomes was assessed with Inverse Probability of Treatment Weighting (IPTW) models adjusted for possible confounders.

Results: Out of 3820 pts, 97 pts with STS were included. The median age at COVID-19 diagnosis was 56 years, with 65 pts (67%) aged <65 years old and 65 pts had low comorbidity burden (67%). In total, 36 pts were on cytotoxic chemotherapy within 4 weeks prior to COVID-19. The overall CFR_{28} was 25.8%, with 38% oxygen therapy requirement, 34% rate of complications and 32.3% of hospitalizations due to COVID-19. CFR_{28} (29,5%, 21.4%, 12.5%) and all indicators of COVID-19 severity demonstrated a trend toward a numerical improvement across the pandemic phases. Similarly, vaccinated pts demonstrated numerically improved CFR_{28} (16.7% vs 27.7%) and COVID-19 morbidity compared with unvaccinated pts. Pts who were on chemotherapy experienced comparable CFR_{28} (19.4% vs 26.0%, p=0.4803), hospitalizations (50.0% vs 44.4%, p=0.6883), complication rates (30.6% vs 34.0%, p=0.7381) and oxygen therapy requirement (28.1% vs 40.0%, p=0.2755) compared to those who were not on anticancer therapy at COVID-19, findings further confirmed by the IPTW-fitted multivariable analysis.

Conclusions: This is the first study to demonstrate the time-dependent improvement of COVID-19 outcomes in pts with STS. Exposure to chemotherapy does not impact on COVID-19 morbidity/mortality and SARS-CoV-2 vaccination confers protection against adverse outcome from COVID-19 in this patient population.

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1987TiP Pembrolizumab in combination with eftilagimod alpha and radiotherapy in neoadjuvant treatment of patients with soft tissue sarcomas: EFTISARC-NEO trial

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Background: Surgery is the mainstay of treatment of primary localized soft tissue sarcoma (STS). In patients (pts) with high grade localized STS of the extremity/trunk, and tumor size > 5cm radiation therapy (RT) is added to reduce local recurrence. While neoadjuvant chemotherapy is used to improve survival, but its efficacy is limited to pts with poor prognosis. Recently, immunotherapy (ITH) has been widely studied in pts with metastatic STS but response rates are modest and its efficacy and impact on the tumor microenvironment remain unclear. Novel compounds, such as eftilagimod alpha (efti), a soluble LAG-3 protein, are tested in combination with ITH to stimulate antigen presenting cells and boost immune response. Moreover, some studies have shown that combining ITH with RTH may be a promising strategy for synergistic enhancement of treatment efficacy. Therefore, we hypothesize that the addition of combined ITH to RT prior to surgical resection would be safe and improve pathologic response compared to historical cohorts of pts with localized STS treated with RT alone.

Trial design: EFTISARC-NEO is an open-label phase II study evaluating the efficacy and safety of pembrolizumab in combination with efti and RTH in the neoadjuvant treatment of pts with STS. Forty pts will be enrolled to receive efti 30 mg sc Q2W (5 cycles) and pembrolizumab 200 mg iv Q3W (3 cycles) with concurrent RT (25x2Gy), followed by surgery. Key eligibility criteria are: 1) primary or locally recurrent deep-seated extremity, girdles and/or superficial trunk tumor, 2) one of the following subtypes: undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, myxoid and round cell liposarcoma, epithelioid sarcoma, angiosarcoma, soft tissue sarcoma NOS; 3) Grade 2/3 according to FNCLCC; 4) primary tumor size >5 cm or locally recurrent of any size. The primary endpoint is a percent of tumor hyalinization at the time of surgical resection. Secondary endpoints include disease-free survival, overall survival, response rate and incidence of adverse events. Correlation between tissue or blood-based biomarkers and clinical outcomes will be explored. Enrollment for the study is ongoing in Poland.

Clinical trial identification: EudraCT 2022-003845-36.

Legal entity responsible for the study: Maria Sklodowska-Curie National Research Institute of Oncology Warsaw Poland.

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ANNALS OF ONCOLOGY driving innovation in oncology

SCLC

1988MO Recruitment discontinuation in TREASURE trial (thoracic radiotherapy with atezolizumab in small cell lung cancer extensive disease) due to unexpected safety data

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Background: Carboplatin/etoposide + atezolizumab (IMpower133) is now 1L standard-of-care for patients with extensive disease small cell lung cancer (ED SCLC). Thoracic radiotherapy (TRT) after induction chemotherapy has been shown to increase 2-year overall survival rates. Alongside, evidence for synergistic immunostimulatory effects of radiotherapy and immunotherapy (IO) is increasing. Combining these results, the TREASURE trial attempted to improve response to chemo-IO by adding TRT.

Methods: The phase II, multicenter TREASURE trial (NCT04462276) randomized patients with ED SCLC, ECOG$\leq$1, and response to IMpower133 induction to receive atezolizumab maintenance therapy (1200mg, Q3W, until progression/toxicity) either with TRT (10x30 Gy, arm A) or without TRT (arm B). Safety interim analysis was planned once 23 patients in arm A had been observed for 3 months after TRT ended, with the safety signal being $\geq$2 patients with grade $\geq$3 pneumonitis.

Results: In 04/22, interim safety analysis showed only 1/23 patients with grade $\geq$3 pneumonitis in arm A. However, routine safety monitoring committee (SMC) review in 08/22 identified a potential imbalance in grade 5 severe adverse events (SAEs) between the arms (n=5 in A, n=1 in B), and thus recruitment was paused. Data review 3 months later revealed more SAEs in arm A (28 any, 16 grade 3/4, 6 grade 5) vs. B (9 any, 4 grade 3/4, 1 grade 5). Along with evaluation of further parameters, this prompted Coordinating Investigator and SMC to permanently stop recruitment. Of note, neither differences in clinical measures of comorbidity nor functional status were detected between arms. At the time of recruitment stop (12/22), 68 patients were included in the trial (n=34 in each arm).

Conclusions: Although TRT-IO combinations have not been the source of safety concerns in other trials, it was associated with more SAEs in TREASURE. SAE analysis did not indicate any new safety signal of atezolizumab or TRT. Observed SAEs were either known adverse effects or confounded, and not clearly tied to either IO or TRT. Thus, the factors underlying this unexpected outcome remain to be identified and will be focus of the final analysis of this trial.

Clinical trial identification: NCT04462276.

Legal entity responsible for the study: Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest.

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1989MO Lurbinectedin (LUR) in combination with pembrolizumab (PBL) in relapsed small cell lung cancer (SCLC): The phase I/II LUPER study

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Background: Previously, we established the recommended phase 2 dose (RP2D) of LUR + PBL in the phase 1 stage of this study (J Clin Oncol. 2022;40(suppl 16):8581). Here we present the results on the efficacy and safety of the RP2D.

Methods: LUPER (NCT04358237) is a prospective, open-label, uncontrolled, multicenter, phase 1/2 study of LUR in combination with PBL in patients (pts) with relapsed SCLC. Eligible pts were $\geq$18 years old, with histologically confirmed SCLC, progression after 1L platinum-based chemotherapy, no prior exposure to immunotherapy, ECOG PS of 0-1, and measurable disease as per RECIST 1.1. Pts with treated, asymptomatic, stable brain metastases (BM) were also included. Treatment consisted of LUR dosed at 3.2 mg/m^2 IV Q3W in combination with PBL 200 mg IV Q3W until disease progression (PD), unacceptable toxicity, or consent withdrawal. The primary endpoint was confirmed overall response rate (ORR) according to RECIST 1.1. Secondary endpoints included investigator-assessed Duration of Response (DoR), Progression-Free Survival (PFS), Overall Survival (OS), and safety as per CTCAE 5.0.

Results: A total of 28 pts were included in the study. Median age was 65 years (range 41-78), 46.4% were female, 64.3% had ECOG PS of 1, 51.9% had platinum-free interval $<$ 90 days, 39.3% had LDH $>$ upper normal limit, and 21.4% had BM. At data cutoff (March 31, 2023),11 (39.3%) pts were still on treatment. The median follow-up was 5.7 months (range: 1.0-25.2). Preliminary ORR was 46.4% (95% CI: 29.5−64.2; p$<$0.001): 2 confirmed CR, 11 PR (9 confirmed) and 4 SD $\geq$12 weeks. Median DoR was 11.4 months (range: 0-21.2 months), and 2 (7.1%) pts had durable responses $>$ 12 months. Median PFS was 5.3 months (95% CI: 2.7-12.0). Median OS was 11.1 months (95% CI: 6.9-NR). PBL and LUR discontinuation occurred in 3 (10.7%) and

0 pts due to immune-related AE, respectively. The most common grade 3 and 4 treatment-emergent AEs (>20%) were fatigue, neutropenia, nausea and anemia.

Conclusions: The LUPER study met its primary endpoint. The combination of LUR + PBL is effective in second-line treatment of SCLC with a manageable safety profile. Further research is warranted to confirm the potential of this combination in SCLC patients.

Clinical trial identification: NCT04358237.

Legal entity responsible for the study: MEDSIR - Medica Scientia Innovation Research.

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1990MO Sacituzumab govitecan (SG) as second-line (2L) treatment for extensive stage small cell lung cancer (ES-SCLC): Preliminary results from the phase II TROPiCS-03 basket trial

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Background: Treatment options are limited for patients (pts) with ES-SCLC that progresses after anti-programmed death ligand 1 (PD-L1) therapy and chemotherapy (chemo). SG, a Trop-2-directed antibody-drug conjugate, demonstrated antitumor activity in previously treated ES-SCLC in a phase 1/2 study (Bardia, et al. *Ann Oncol*. 2021). TROPiCS-03 (NCT03964727) is an open-label, multicohort, phase 2 study evaluating SG in pts with metastatic or locally advanced solid tumors. Here, we report preliminary results from the ES-SCLC cohort.

Methods: Adult pts with ES-SCLC that progressed after no more than 1 prior line of platinum-based chemo and anti-PD-(L)1 therapy received SG 10 mg/kg on Days 1 and 8 of a 21-day cycle. The primary endpoint was objective response rate (ORR) by investigator assessment (INV) per RECIST v1.1. Key secondary endpoints included clinical benefit rate (CBR), duration of response, progression-free survival, overall survival, and safety. Pts who received ≥1 dose of SG were included in the safety analysis and pts who received ≥1 dose of SG and had ≥13.0 weeks of follow-up were included in the efficacy analysis.

Results: As of 18 April 2023, 26 pts received ≥1 dose of SG. Median age was 67 years (range, 48-79) and 89% of pts had an ECOG performance status of 1. Median follow-up was 3.5 months (range, 0.6-9.4). Treatment was ongoing for 16 (62%) pts. In the efficacy analysis (n=14), ORR was 29% and CBR was 36% (Table). In the safety analysis (n=26), any-grade treatment-related adverse events (TRAEs) occurred in 96% (grade ≥3, 46%) of pts. No TRAEs leading to discontinuation of study treatment were reported to date. No deaths due to AEs were reported to date.

Conclusions: SG as 2L treatment for ES-SCLC demonstrated promising antitumor activity and manageable safety, with no TRAEs leading to discontinuation reported to date. Additional data with more pts and longer follow-up will be presented.

Table: 1990MO

Efficacy	ES-SCLC SG n = 14
ORR (95% CI),[a] %	29 (8-58)
BOR,[a] n (%)	
CR	0
PR	4 (29)
SD	9 (64)
PD	1 (7)
CBR (95% CI),[a,b] %	36 (13-65)

[a]By INV. [b]Pts with CR + PR + SD for ≥ 6 months. BOR, best overall response; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Clinical trial identification: NCT03964727.

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1991P Safety and effectiveness of surgery or radiotherapy after PD-L1 Inhibitor (TQB-2450) and chemotherapy induction therapy in patients with limited-stage small cell lung cancer: A phase II trial

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Background: PD-1/PD-L1 inhibitor and chemotherapy improved the survival of patients with extensive-stage small-cell lung cancer. Thus, we conducted a non-randomized, single-center, phase II study (LungMate-005; NCT04539977) to explore the safety and effectiveness of surgery or radiotherapy after PD-L1 inhibitor (TQB2450) and chemotherapy induction therapy in treating limited-stage small-cell lung cancer (LS-SCLC).

Methods: Eligible patients received four 21-day-cycles of neoadjuvant therapy: TQB2450 (1200 mg) and carboplatin (AUC5) on day1, etoposide (100 mg/m^2) on day1-3. MDT to discuss surgery or radiotherapy was performed 3-4 weeks after last dose of therapy. Maintenance therapy was 2-cycles TQB2450, carboplatin, and etoposide followed by 1-year TQB2450. The primary outcome was objective response rate (ORR). Secondary outcomes included the incidence of adverse events (AEs), events-free survival (EFS), and major pathological response (MPR).

Results: Between December 2020 to January 2023, a total of 40 patients received induction therapy. Among them, 21 and 14 patients received surgery or radiotherapy, respectively. Other 5 patients quitted during induction therapy. Most (95%) patients were at stage III. The incidence of any grade and grade 3-5 AE were 100% and 47.5%, respectively. The highest incidence of TQB2450-specific AEs was rush (12.5%, grade 1-2). Three (7.5%) patients had TRAEs leading to discontinuation. ORR was 92.5% (95% CI: 79.6%-98.4%). In surgery group, 13 (61.9%) patients achieved MPR, including 9 (42.9%) patients with PCR. Seventeen (81.0%) patients achieved pathological downstage. The median followed-up was 14.8 months by April 21, 2023. The median EFS and median OS were not reached in surgery group. The median EFS and OS were 11.6 (95% CI: 8.9-14.3) and 18.6 (95% CI: 13.4-23.8) months in radiotherapy group. 1-year EFS and OS were 82.0% and 100% in surgery group, and 49.2% and 88.9% in radiotherapy group, respectively.

Conclusions: Surgery or radiotherapy after PD-L1 inhibitor (TQB-2450) and chemotherapy induction therapy followed by TQB-2450 maintenance therapy in treating LS-SCLC were safe and effective, especially surgery.

Clinical trial identification: NCT04539977.

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1992P A phase II safety and efficacy study of PM8002 (anti-PD-L1 x VEGF-A bispecific) combined with paclitaxel as a second-line therapy for small cell lung cancer (SCLC)

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Background: There is an unmet medical need for SCLC patients that progress on or after first-line platinum-based therapy. PM8002 is a bispecific antibody targeting PD-L1 and VEGF-A. Here, we present our results from a phase II study of PM8002 in combination with paclitaxel as second-line treatment for SCLC.

Methods: Subjects with advanced SCLC who failed first-line platinum-based chemotherapy with or without checkpoint inhibitors therapy were enrolled for assessing the safety and efficacy of PM8002 in combination with paclitaxel. Primary endpoints included safety (CTCAE v5.0) and ORR (RECIST v1.1). All subjects received PM8002 (30 mg/kg Q3W) and paclitaxel (175 mg/m^2 Q3W) for 5 cycles, followed by PM8002 maintenance (30 mg/kg Q3W) until unacceptable toxicity or disease progression.

Results: As of April 21, 2023, 27 subjects (26 without and 1 with previous immunotherapy) had been enrolled. Among 26 immunotherapy naïve subjects, 26 and 22 subjects were evaluable for safety and efficacy, respectively. Overall ORR was 72.7% (16/22) with a DCR of 81.8% (18/22). Median PFS was 5.5 months (95% CI, 2.8 - NR. 11 out of 22 subjects were still on treatment and PFS were censored accordingly). Any-grade TEAEs occurred in 96.2% (25/26) of subjects. Grade $\geq$ 3 TEAEs related to the combination regimen occurred in 73.1% (19/26) of subjects, with the most common grade $\geq$ 3 TRAEs observed as neutropenia (53.8%, 14/26) and leukopenia (34.6%, 9/26). One patient discontinued PM8002 and/or paclitaxel administration due to TRAEs. Any-grade immune-related adverse events (irAEs) occurred in 30.8% (8/26) of subjects, and grade $\geq$ 3 irAEs occurred in 4% (1/26) of subjects, which was a grade 3 proteinuria. The first efficacy/safety evaluation for the subject with previous immunotherapy was pending. Recruitment for immunotherapy failure subjects is still ongoing.

Conclusions: PM8002, in combination with paclitaxel, showed encouraging antitumor activity and an acceptable safety profile for patients with advanced SCLC who failed first-line platinum-based chemotherapy. This phase II study is still ongoing and shall include more patients who had previously received immune checkpoint therapy.

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1993P Phase IIIb study of durvalumab plus platinum–etoposide in first-line treatment of extensive-stage small cell lung cancer (CANTABRICO): Safety results

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Background: Most patients (Pts) with small-cell lung cancer (SCLC) have extensive-stage (ES) disease at diagnosis and poor prognosis. First-line (1L) durvalumab (D) plus platinum–etoposide (EP) significantly improved overall survival in pts with ES-SCLC vs control group in CASPIAN study. CANTABRICO study assess safety and effectiveness of D+EP in a real-world ES-SCLC population in Spain.

Methods: CANTABRICO is a phase IIIb, single arm, multicentre study (NCT04712903). Eligible Pts were ≥18 years old with treatment-naive ES-SCLC, ECOG PS 0-2, ≥1 measurable lesion. D (1500 mg) was concurrently administered with 1L cisplatin or carboplatin (CP) d1 plus etoposide d1-3 every 3 weeks (q3w) for 4-6 cycles, followed by maintenance (q4w) until progressive disease/unacceptable toxicity. Safety results [incidence of grade (G) 3 adverse events (AEs) and immune-mediated AEs (imAEs)] are presented.

Results: Between December 2020 and April 2021, 101 pts from 35 sites in Spain were included. By March 2, 2023 all pts had finished chemotherapy (87% CP) and 15 pts were still receiving D. 56% of pts were ≥ 65 years old, 67% were men, 94% had ECOG 0-1. 34%, 37% and 11% of pts had liver, bone or brain metastases, respectively. 98% were current/former smokers and 10% had limited stage diagnosis. 30% received 6 cycles of EP+D and 81% started D monotherapy. Median number of D doses were 8 (Interquartile range 5-11). AEs occurred in 99% of pts; G3-4 AEs in 74%; and AEs leading to discontinuation 8%. Most common G3-4 AEs were neutropenia (22%) and anemia (23%). Deaths due to any cause AEs occurred in 8% of pts (respiratory infection, hemoptysis, sepsis (2), cardiorespiratory arrest, COVID-19, intracranial hemorrhage and immune-mediated neurological syndrome). imAEs were reported in 32% of pts. Most were G1-2; G3-5 imAEs occurred in 10% of pts. Deaths due to imAEs occurred in 1 pt (immune-mediated neurological syndrome). Main imAEs were hypothyroidism (13%), pneumonitis (5%) and diarrhea (4%), among others.

Conclusions: CANTABRICO safety profile appeared consistent with that seen in the CASPIAN study, providing real-world evidence regarding safety of D+EP in ES-SCLC.

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1994P Carboplatin, etoposide, bevacizumab, and atezolizumab in patients with extensive-stage SCLC – GOIRC-01-2019 CeLEBrATE ML41241 trial

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Background: PD-L1 inhibitors added to platinum etoposide improved survival in extensive stage small cell lung cancer (ES-SCLC). Bevacizumab added to platinum etoposide chemotherapy has been shown to be safe and active. VEGF has immunosuppressive effects in SCLC tumor microenvironment and combined PD-L1 and VEGF inhibition has synergistic antitumor effect in SCLC models.

Methods: This is an investigator-initiated phase II single arm trial sponsored by GOIRC with the unconditional financial support of Roche S.p.A. Patients received carboplatin (AUC 5), etoposide (100 mg/m^2), bevacizumab (7.5 mg/kg), and atezolizumab (1200 mg) for 4-6 cycles (induction), followed by bevacizumab and atezolizumab (maintenance) every 3 weeks for up to 18 total cycles as first-line treatment for ES-SCLC. Asymptomatic or treated brain metastases and treatment with atezolizumab beyond RECIST-defined progression (PD) were allowed. The primary endpoint was 1-year OS.

Results: Enrollment completed in March 2022, so the primary endpoint is expected to be mature at the data cutoff of March 31st, 2023. Of 53 enrolled patients (45% women, median age 65 years), 22 (42%) had an ECOG PS of 1, 14 (26%) had liver, 11 (21%) bone, and 10 (19%) brain metastases. Median sum of target lesions diameters was 119.5 mm (range 17-240). Of 51 patients with available data, 40 (78%) completed induction and 37 (73%) started maintenance, with a median of 7 courses (range 1-18). Atezolizumab was administered beyond PD in 17 cases (33%), for a median of 2 courses (range 1-10), with 11 patients still on treatment at the data cut-off date. Adverse events are reported in table. Serious adverse events (SAE) were reported in 16 cases, including neutropenia (n=4), febrile neutropenia (n=3), and pulmonary embolism (n=3).

Table: 1994P Adverse events

Adverse event	Any grade	% total	Grade 1-2	%	Grade 3-4	%
Neutropenia	27	53%	11	22%	16	31%
Fatigue	22	43%	21	41%	1	2%
Anemia	20	39%	19	37%	1	2%
Lymphopenia	9	18%	8	16%	1	2%
Musocitis	9	18%	9	18%	0	0%
Increased GGT	7	14%	6	12%	1	2%
Cough	7	14%	7	14%	0	0%
Nausea	7	14%	7	14%	0	0%
Thromocytopenia	5	10%	4	8%	1	2%
Hypothyroidism	5	10%	5	10%	0	0%
Hypertension	4	8%	3	6%	1	2%
Constipation	4	8%	4	8%	0	0%
Diarrhea	4	8%	4	8%	0	0%

Conclusions: The addition of bevacizumab to carboplatin-etoposide-atezolizumab in patients with ES-SCLC is overall well-tolerated. The survival analysis will be available and reported at the conference.

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1995P Long-term benefit of atezolizumab plus chemotherapy in extensive stage small cell lung cancer (ES-SCLC): Exploratory analysis from the IMfirst study

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Background: The IMpower133 study demonstrated that treatment with atezolizumab (ATZ) + carboplatin + etoposide improved overall survival (OS) and progression free survival (PFS), and showed long-term benefit ([LTB] defined as OS ≥18 months) in patients with ES-SCLC. To date, no patient characteristics have been identified and validated to predict LTB from chemo-immunotherapy, and limited data exist regarding LTB in a real-world (RW) clinical setting. We previously reported the primary safety and efficacy results of IMfirst (EudraCT: 2019-002784-10), a phase IIIb, single arm study of ATZ + chemotherapy (C) in patients with untreated ES-SCLC in a RW clinical setting in Spain. Here we present the exploratory LTB analysis from IMfirst.

Methods: In this exploratory analysis, we characterized LTB patients (defined as patients who lived ≥24 months). Association of LTB/no-LTB with patient's and disease characteristics was evaluated with the Chi-square or Fisher's exact tests. A $p < 0.05$ was considered statistically significant.

Results: A total of 155 patients were enrolled; 25 met the LTB criteria. Median follow-up was 28.4 months (data cut off: 14 Dec 2022). Median OS [95% CI] was 10.0 [8.6, 11.9] months in the overall population and OS at 24 months was 17.7%. Variables with significant association with LTB/non-LTB patients included tumor burden (TB) at baseline (high TB defined as patients with either SLD ≥60 mm, 2 or more metastatic sites, or LDH > ULN), prior radiotherapy (RT) at baseline, and consolidation RT (Table). None of the 17 patients with ECOG PS 2 were classified as LTB. More immune-mediated adverse events were reported in LTB (16%) compared to non-LTB (0.8%) patients.

Conclusions: This exploratory analysis from IMfirst, though limited due to its small sample size, demonstrates LTB from ATZ + C in a broader ES-SCLC patient population, and suggests potential patient characteristics associated with LTB/non-LTB.

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Table: 1995P Patient characteristics and association with LTB/no-LTB

n (%)	All *N* = 155	LTB *N*= 25	No-LTB *N*= 130	*P*
Age ≤65 >65	82 (52.9) 73 (47.1)	14 (56.0) 11 (44.0)	68 (52.3) 62 (47.7)	0.7348
ECOG 0 1 2	38 (24.5) 100 (64.5) 17 (11.0)	9 (36.0) 16 (64.0) 0 (0)	29 (22.3) 84 (64.6) 17 (13.1)	0.0874
CNS Metastases at baseline Yes No	27 (17.4) 128 (82.6)	5 (20.0) 20 (80.0)	22 (16.9) 108 (83.1)	0.7103
Tumor burden High Low	132 (85.1) 23 (14.8)	16 (64.0) 9 (36.0)	116 (89.2) 14 (10.8)	0.0012
Radiotherapy at baseline Yes No	18 (11.6) 137 (88.4)	6 (24.0) 19 (76.0)	12 (9.2) 118 (90.8)	0.0348
Consolidation radiotherapy Yes No	11 (7.1) 144 (92.9)	5 (20.0) 20 (80.0)	6 (4.6) 124 (95.4)	0.0061

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1996P The impact of an etoposide shortage on patients with extensive-stage small cell lung cancer (ES-SCLC): Results of a natural experiment

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Background: Shortages of oncology therapeutics are becoming increasingly prevalent. A shortage of IV etoposide lasted from 2018 until 2020 in Ontario, Canada, allowing for a "natural experiment" in which external factors (IV etoposide availability) dictated patients' assignment. The purpose of this study was to evaluate the impact of this etoposide shortage (ES) on patient outcomes in ES-SCLC.

Methods: ES-SCLC patients treated at the London Regional Cancer Program during a "pre-ES" (Nov 2017 – Oct 2018) and "ES" (Nov 2018 – Oct 2019) time interval were retrospectively reviewed. Information was gathered on patient demographics, treatment, hospitalizations and survival. The primary endpoint was rate of hospitalization. Statistical analysis was performed using descriptive statistics, Kaplan Meier estimates and multivariable logistic and Cox proportional hazards regression models.

Results: A total of 119 patients with ES-SCLC were assessed, 49 in the pre-ES interval and 70 in the ES interval. Mean ± SD age was 68 ± 8 years, 48% were male, 33% had central nervous system (CNS) metastases and 69% received first-line systemic therapy. Alternate regimens used for ES cohort included platinum-oral (PO) etoposide (51%), platinum-irinotecan (24%), and PO etoposide monotherapy (16%). There was a significantly increased rate of hospitalizations during the ES vs. pre-ES (49% vs. 29%, p=0.029) but no significant differences in PFS (median: 2.8 vs. 4.5 months, log-rank p = 0.504) or OS (median: 3.1 vs. 5.5 months, log-rank p=0.600) in univariable analyses. In our multivariable model adjusting for age, sex, baseline Charlson comorbidity index, CNS metastases and receipt of first-line chemotherapy, we observed a significant increase in hospitalization (OR=2.30, 95% CI: 1.01-5.24, p=0.047) and shorter PFS (HR=1.79, 95%CI: 1.19-2.68), p=0.005) in the ES treatment interval.

Conclusions: This single-institution retrospective analysis during an IV ES shows increased rates of hospitalization and decreased PFS among ES-SCLC patients treated with alternate chemotherapy regimens. The oncology community must advocate for reliable supplies of essential chemotherapy drugs and utilize appropriate substitute therapies when necessary.

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1997P A study of sintilimab combined with anlotinib and chemotherapy as second-line or later therapy in extensive-disease small cell lung cancer

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Background: SCLC is characterized by rapid growth, drug resistance, and early metastasis. At present, etoposide combined with platinum is the standard first-line treatment for ED-SCLC, and the second-line and later treatment options are limited. This study investigated the efficacy and safety of sintilimab combined with anlotinib and albumin-bound paclitaxel in the treatment of ED-SCLC.

Methods: This is a single-arm, phase II study (ChiCTR2100049390). Patients with ED-SCLC were enrolled after screening and meeting the inclusion and exclusion criteria. Patients were treated with sintilimab (200mg, d1, Q3W) combined with anlotinib (12mg, d1-d14, Q3W) and albumin-paclitaxel (100mg, d1-d8, Q3W). The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: From July 2021 to February 2023, a total of 30 subjects were enrolled, of which 25 patients could be evaluated. The median age was 59 years, including 20 males, 21 patients with ECOG 1, 12 patients with smoking history, and 10 patients with brain metastases at baseline. All cases were in stage IV. As of April 28, 2023, the median follow-up was 12.5 months. The ORR was 64%, including 16 cases of PR, 4 cases of SD, and 5 cases of PD. The DCR was 80%. The mDOR was 6.64 (5.32,10.5), and the mTTR was 1.5 months. The mPFS was .91 (4.86,6.8), 6-month and 12-month PFS rates were 49% and 9.8%, respectively. The median OS was 13.2 (9.69, NA), and the 12- and 24-month PFS rates were 60.9% and 25.2%, respectively. The TRAE was 84% (21 cases), of which ≥3 grade TRAE was 20%, including aspartate aminotransferase increased, alanine aminotransferase increased, rash, neutropenia, and lymphopenia. A total of 9 (36%) subjects had immune-related adverse reactions (irAE). ≥3 grade irAE included spartate aminotransferase increased, alanine aminotransferase increased, rash. No AE leading to death occurred.

Conclusions: Sintilimab combined with anlotinib and albumin-paclitaxel demonstrated significant clinical activity and a manageable safety profile for patients with ED-SCLC. The long-term efficacy is still under follow-up.

Clinical trial identification: ChiCTR2100049390.

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1998P Antitumor activity and safety profile of trilaciclib in Chinese patients with extensive-stage small cell lung cancer (ES-SCLC) receiving chemotherapy (TRACES): Updated results from TRACES

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Background: Trilaciclib, a potent and reversible intravenous CDK4/6 inhibitor, has been approved by US FDA and China NMPA to prevent multilineage chemotherapy-induced myelosuppression in ES-SCLC patients. The TRACES study is a phase III trial assessing the efficacy and safety of trilaciclib in Chinese ES-SCLC patients. The bone marrow protection effect was significant which was reported in WCLC 2022.

Methods: This study included an open-label safety run-in part (Part 1) and a randomized, double-blinded, placebo-controlled part (Part 2). Treatment-naïve or previously treated ES-SCLC patients received trilaciclib (240 mg/m^2) or placebo before etoposide/cisplatin (E/P) or topotecan (TPT) respectively. The primary endpoint is the duration of severe neutropenia in Cycle 1. The exploratory endpoints for anti-tumor effect are OS and ORR, PFS and DOR assessed by RECIST v1.1.

Results: As of 30 December 2022, a total of 83 patients were enrolled in Part 2, with 41 receiving trilaciclib (E/P: 23; TPT:18) and 42 receiving placebo (E/P: 23; TPT:19). The mean number of cycles were 5.1 and 4.6 cycles in trilaciclib and placebo group (E/P: 5.0 vs 4.9 cycles; TPT: 5.3 vs 4.3 cycles). Compared with placebo group, trilaciclib group had fewer cycle delays (E/P: 30.4% vs 73.9%; TPT: 44.4% vs 73.7%) and dose reductions (E/P: 30.4% vs 73.9%; TPT: 44.4% vs 73.7%). The ORR in trilaciclib group and placebo group were 44.7% and 39.5% (p=0.4996) respectively. After a median follow-up of 14.1 months, the median overall survival was 12.0 months in the trilaciclib group and 8.8 months in the placebo group (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.40 to 1.22). The median progression-free survival was 4.8 months and 4.3 months, respectively (HR, 0.86; 95% CI, 0.53 to 1.39). Trilaciclib was well tolerated, with lower incidence of ≥Grade 4 TEAEs, SAEs, TEAEs leading to treatment discontinuation. No TEAEs leading to death were reported related to trilaciclib.

Conclusions: Trilaciclib was well tolerated in Chinese patients. Administering trilaciclib prior to chemotherapy in ES-SCLC patients improved patients' tolerability to chemotherapy, and suggested potential survival benefit.

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1999P IMreal Cohort 4: Third interim analysis of efficacy and safety in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) receiving atezolizumab plus carboplatin and etoposide (atezo + CE) as first-line (1L) therapy under real-world conditions (RWCs)

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Background: Based on the pivotal phase III IMpower133 trial (NCT02763579), atezo + CE is approved for 1L treatment (tx) of ES-SCLC. IMreal (NCT03782207) is a non-interventional, multicentre, multicohort, prospective study of clinical outcomes and safety with atezo under RWCs. We report the third interim analysis efficacy and safety data from Cohort 4 (ES-SCLC).

Methods: Pts with untreated ES-SCLC received 1L atezo + CE. Pt medical and tx history data were retrospectively collected; clinical outcomes and safety data before, during and after atezo + CE tx were also collected. The primary endpoints were OS and 2-y OS. Secondary endpoints included PFS, ORR, DCR and DOR. Safety was assessed.

Results: The full analysis population (N=501) was enrolled from 7 Feb 2019 to 1 Jun 2022. Median follow-up was 6.1 mo (range, 0.0-27.6). The median age was 66 y (range, 34-84), and 293 pts (58%) were ≥65 y; 324 (65%) were male. ECOG PS ≥2 was reported in 33/395 pts (8%). Median OS and PFS were 9.9 mo (95% CI: 8.8, 10.6) and 6.2 mo (95% CI: 5.9, 6.7), respectively; 1-y OS and PFS rates were 39% and 16%, respectively. Additional efficacy data are in the table. In the safety-evaluable population (n=496), 411 pts (83%) had ≥1 AE. The most common any-Gr AEs were anaemia (20% [n=100]), fatigue (17% [n=86]) and neutropenia (17% [n=82]). Gr 3/4 tx-related (TR) AEs occurred in 143 pts (29%); Gr 5 TRAEs occurred in 7 (1%). SAEs occurred in 192 pts (39%) and were TR in 86 (17%). AEs of special interest (AESIs) occurred in 110 pts (22%) and were TR in 74 (15%). The most common any-Gr AESIs were hepatitis (diagnosis and lab abnormalities; 7% [n=34]), rash (6% [n=31]) and hepatitis (lab abnormalities; 6% [n=28]).

Table: 1999P Response-evaluable population (N=390)

ORR, n (%) [95% CI]	266 (68) [63.3, 72.8]
Complete response, n (%) [95% CI]	11 (3) [1.4, 5.0]
Partial response, n (%) [95% CI]	255 (65) [60.4, 70.1]
Stable disease, n (%) [95% CI]	88 (23) [18.5, 27.0]
DCR, n (%) [95% CI][a]	223 (57) [52.1, 62.2]
Progressive disease, n (%) [95% CI]	30 (8) [5.3, 10.8]
Not evaluable, n (%)	6 (2)
DOR [95% CI], mo	n=266 5.4 [4.8, 6.7]

DCR, disease control rate; DOR, duration of response; ORR, objective response rate.
[a] DCR: proportion of pts who achieved complete response, partial response or stable disease at least 12 weeks after the index date.

Conclusions: In IMreal Cohort 4, OS and PFS differed slightly from those in pivotal ES-SCLC clinical trials, with no new or unexpected safety signals.

Clinical trial identification: NCT03782207.

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2000P Efficacy and safety of thoracic radiotherapy after first-line immunotherapy in extensive stage small cell lung cancer: A multi-center retrospective study

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Background: Immunotherapy combined with chemotherapy have become the standard first-line options in extensive stage small-cell lung cancer (ES-SCLC) in the past years. However, whether patients can benefit from consolidative thoracic radiotherapy (TRT) after first-line immunotherapy is still undetermined.

Methods: ES-SCLC patients who received standard first-line immunotherapy combined with chemotherapy with/without subsequent TRT were included from 3 cancer centers in China between February 2020 to December 2022. The clinical outcomes and safety were evaluated.

Results: 220 ES-SCLC patients were eligible for our analysis, in which 136 received TRT and maintenance immunotherapy after chemotherapy, and 84 received maintenance immunotherapy only. TRT significantly improved the progression-free survival (PFS) (median 10.7 VS 8.5months, HR=0.662 [95% CI: 0.476-0.919], p=0.013), and decreased the intrathoracic lesion progression rate (13.23% VS 40.48%). Further analysis revealed that TRT with different biological effective dose (>60Gy or ≤60Gy), or different dose fractionation mode (conventional fractionation, hypofractionation or hyperfractionation) didn't impact patient survival. However, addition of TRT in 3-6 weeks after chemotherapy generated significantly superior PFS compared with adding TRT after tumor progression on first-line treatment (median PFS 10.7m VS 8.3m, HR=0.414 [95% CI: 0.207-0.825], p=0.013). In addition, patients without liver metastases or with bone metastases were more likely to benefit from TRT (both p<0.05). TRT slightly increased ≥grade 3 adverse effect (30.88% VS 25%). Notably, the incidence of pneumonia was higher in the TRT group than in the maintenance immunotherapy group (19.9% VS 6%).

Conclusions: The addition of TRT after first-line immunotherapy improves PFS and local control in ES-SCLC patients. TRT should be preferential performed in 3-6 weeks after chemotherapy. Patients without liver metastases or with bone metastases benefit more from TRT. The application of TRT is generally safe excepted for increased pneumonia occurrence.

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2001P Consolidative thoracic radiotherapy of extensive-stage small cell lung cancer in the era of chemoimmunotherapy: A retrospective analysis concerning patients from southern Italy

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Background: Consolidative thoracic radiotherapy (TR) was commonly used in the management of extensive-stage small cell lung cancers (ES-SCLC) in the past years. Nevertheless, phase III trials concerning first-line chemoimmunotherapy excluded these treatment approach. However, there is a strong biological rational to support the use of radiotherapy, as boost for sustaining anti-tumor immune response. Currently, the benefit of TR after chemoimmunotherapy remains unclear. Herein we include a real-world experience concerning 120 patients with ES-SCLC treated with chemoimmunotherapy combinations.

Methods: A total of 120 ES-SCLC patients treated with chemoimmunotherapy since 2019 in the South of Italy were retrospective analyzed. After 4 cycles of chemoimmunotherapy, all patients selected for the analysis obtained an adequate response for a subsequent TR. Of the 120 patients included in the analysis, 59 patients underwent TR. Patient characteristics, chemoimmunotherapy schedule, and timing for start TR were assessed. Primary endpoint was safety, secondary endpoint was the efficacy, namely OS and PFS.

Results: TR was associated with a good safety profile and with no significant changes in grade ≥3 AEs. In particular, none grade ≥3 AE was reported in the TR group versus two grade 3 AEs in the control group. The median time for start TR after 4 cycles of chemoimmunotherapy was 62 days (range 10-184). TR and fraction range include from 30 Gy (in 10 fractions) up to definitive dose in selected patients. TR was associated with a significantly longer PFS than systemic therapy alone (1-year PFS 55% vs. 1-year PFS 28.1%, p=< 0.0001) and was also associated with a trend toward longer PS (1-year OS 79,4% vs. 1-year OS 57,5%, p= 0.11).

Conclusions: Multi-center experience from South of Italy confirms a general confidence in using TR as consolidative strategy after chemoimmunotherapy based on clinical multidisciplinary decision. With the limit of a retrospective analysis, these preliminary results support the feasibility of this approach and encourage a prospective evaluation.

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2002P A multicentre study assessing the real-world effectiveness of first-line chemotherapy plus immunotherapy in extensive-stage small cell lung cancer (ES-SCLC) patients

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Background: First-line chemotherapy plus immunotherapy (CT-IO) has recently demonstrated survival benefit over CT in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) patients, based on randomized phase 3. This retrospective multicentre study assessed the real-world effectiveness of CT-IO since its approval in France in May 2020, in unselected patients.

Methods: Data from all ES-SCLC patients treated with CT-IO at four French hospitals between May 2020 and December 2021 were retrospectively analyzed. Kaplan Meier method was used to estimate OS and real-world progression-free survival (rwPFS), and Cox regression analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) in univariate and multivariate models.

Results: Of 75 patients included, median age was 69 years [IQR: 60.5-72.5], performans status (PS) was 0-1 in 78.7% of patients. Brain and liver metastases were present at baseline in 26.8% and 54.7% of patients respectively, and 28% of patients had corticosteroids $\geq$ 10 mg/day. At a median follow up of 16.8 months (95%CI: 14.9-23.4), the median OS was 11.4 months (95%CI: 7.7-14.7) with a 12-months OS rate of 43.6% (95%CI: 33.3-57.2). The median rwPFS was 5.3 months (95%CI: 4.8-5.8), 6-months PFS rate was 33.3% (95%CI: 24.2-45.9) and the objective response rate (ORR) was 76.7%. Introduction of delayed IO at the second cycle was not associated with a worse OS (HR 1.62, 95%CI: 0.88-2.97, p=0.132). In multivariate analyses, baseline brain and liver metastases were associated with a shorter OS (HR 3.80 [95% CI: 1.90-7.60] and 3.12 [95%CI: 1.60-6.08] respectively, p<0.001 for both).

Conclusions: Our study showed that survival data in real-world ES-SCLC patients treated with frontline CT-IO were promising and comparable to those obtained from randomized trials, even amongst an unselected population including older patients, with untreated brain metastases or corticosteroids.

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2003P Consolidative intrathoracic radiotherapy during maintenance first-line immunotherapy in extensive stage small cell lung cancer (ES-SCLC): A retrospective multicenter analysis of safety and efficacy

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Background: Despite recent innovations, ES-SCLC has still poor prognosis. First-line chemo-immunotherapy (CT-IT) improved clinical outcomes without increasing toxicities. Conversely, the role of thoracic radiotherapy (TRT) is largely unknown in this setting. The aim of our study was to evaluate clinical outcomes and safety of first-line CT-IT with or without consolidative TRT in ES-SCLC patients.

Methods: One hundred-three patients (pts) treated in five Italian centers from February 2020 to March 2023 were retrospectively evaluated. Median age was 67 years (range 38-84). All pts had ECOG PS 0-1, except 11 with PS=2. At time of treatment, all pts had ES-SCLC. Overall survival (OS) and progression free survival (PFS) were analyzed using the Kaplan Meier method. Univariate and multivariate analysis was performed to investigate patient, tumor or treatment related prognostic factors influencing clinical outcomes. Toxicity was recorded based on CTCAE 4.0 scale.

Results: At a median follow up of 11 months, 103 pts with ES-SCLC were treated using platinum- based CT-IT followed by maintenance IT with atezolizumab. Consolidative TRT was delivered to 33 responding pts and 14 underwent cranioprophylaxis. Median, 1- and 2-year OS was 14.2 months, 52.6%(SE±5,6%) and 31.4%(SE±6,0%), respectively. Median, 12- and 18-months PFS was 7,1 months, 27.5%(SE ±4,8%) and 14.4(SE ±4,8%), respectively. At univariate analysis consolidative TRT, ECOG PS, absence of brain or bone metastases at diagnosis were positive statistically significant prognostic factors for OS. TRT remains significant at multivariate analysis for OS (p < 0,0001). Toxicities >G2 were reported in 23 pts (22.3%) with hematological toxicity as the most common. Only one G5 toxicity was reported (pneumonitis).

Conclusions: CT-IT was confirmed as an effective therapeutic option in ES-SCLC. Consolidative TRT showed interesting results in terms of both OS and PFS being feasible and safe also in a large "real life" setting. Prospective trials with longer follow up are actually needed to further assess the impact of TRT on local disease control and survival.

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2004P PD-L1 Inhibitors combined with whole brain radiotherapy in patients with small cell lung cancer brain metastases: Real-world evidence

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Background: Numerous studies have demonstrated that brain metastases (BMs) patients may benefit from intracranial radiotherapy combined with immune checkpoint inhibitors (ICIs). However, it is unclear whether this treatment is effective for patients with small cell lung cancer brain metastases (SCLC-BMs).

Methods: We conducted a retrospective study by analyzing medical records of patients with SCLC-BMs from January 1, 2017 to June 1, 2022. Data related to overall survival (OS), progression-free survival (PFS), and intracranial progression-free survival (iPFS) were analyzed.

Results: There were 109 patients enrolled, of whom 60 received WBRT and 49 received WBRT-ICI. Compared to the WBRT alone cohort, the WBRT-ICI cohort showed longer OS (20.4 months vs 29.3 months, P=0.021), PFS (7.9 months vs 15.1 months, P<0.001), and iPFS (8.3 months vs 16.5 months, P<0.001). Patients receiving WBRT-ICI regimen had a better response rate for both brain metastases (p=0.035) and extracranial diseases (p=0.000) compared to those on WBRT alone. Using WBRT before ICI was associated with superior OS compared to that obtained after ICI (23.3 months for the before group vs 34.8 months for the after group, P=0.020).

Conclusions: Our results indicated that WBRT combined with immunotherapy can improve survival in SCLC-BMs patients. The most optimal timing of WBRT is applying it before ICI, which can help improve OS. These findings highlight the significance of further prospective studies on intracranial radiotherapy and ICI combining strategies in SCLC-BM patients.

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2005P Anlotinib combined with chemotherapy in the treatment of first-line extensive-stage small cell lung cancer (ES-SCLC): A real-world study

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Background: Small cell lung cancer (SCLC) makes up about 15% of all newly diagnosed cases of lung cancer, approximately 70% diagnosed with extensive-stage SCLC (ES-SCLC). For ES-SCLC, the safety and efficacy data of anti-angiogenesis combined with chemotherapy are still seriously lacking. The median PFS of first-line standard regimen (PD-L1 combined with chemotherapy) in the treatment of ES-SCLC is about 5 months, which is comparable to that of chemotherapy alone. Therefore, we conducted a real-world study to observe and evaluate the efficacy and safety of anlotinib combined with chemotherapy in the treatment of first-line ES-SCLC.

Methods: Eligible ES-SCLC pts (histologically or cytologically proven inoperable ES-SCLC; not received systematic treatment before; age≥18years; ECOG PS 0-2) were received anlotinib + etoposide + platinum for 4∼6 cycles, then anlotinib maintenance until the disease progresses or intolerable adverse reactions occur. During the treatment, dose reduction of anlotinib was permitted, which could be reduced to 10mg or 8mg if it was intolerable. The primary endpoint was progression-free survival (PFS), and secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results: Between March 2022 and April 2023, 60 patients were enrolled in this study and 34 patients were included in the evaluation of the treatment, with an average age of 65.5 (53.0-79.0) years old, 28 males (82.3%) and 6 females (17.7%). The ORR was 70.6%, and the DCR was 100.0%. The median PFS was 6.2 months (95% CI: 5.19 to 6.37). The median OS has not yet reached. The common grade 1-2 treatment-related adverse events (TRAEs) were hypertriglyceridemia (11.8%), hypercholesterolemia (11.8%), lymphocyte count decreased (8.8%), GGT increased (5.9%), cough (5.9%), platelet decreased (2.9%), grade 3 and above TRAEs included lymphocyte count decreased (5.9%), leukocyte decreased (5.9%), GGT increased (2.9%), hypodynamia (2.9%), neutrophil declined (2.9%). No higher-grade adverse reactions.

Conclusions: Anlotinib combined with chemotherapy in the treatment of ES-SCLC shows good efficacy and controllable safety; no unexpected toxicity has been observed.

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2006P Immune activation effect and survival of different irradiated sites in ES-SCLC patients treated with radioimmunotherapy: A real-world analysis

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Background: Genetic heterogeneity between primary lesion and metastatic organs is the reason for different immunogenic cell death and persistent antitumor immune activity in different irradiated sites. Besides, considering the intratumor heterogeneity in subtypes of SCLC, the combination of immunotherapy and radiotherapy for different metastases may have significantly differences. Considering the limited data, we aimed to identify the greatest immune activation effect of different irradiated sites and survival analysis in extensive-stage small cell lung cancer (ES-SCLC) patients treated with immunotherapy concurrent with radiotherapy.

Methods: 45 patients with ES-SCLC who had received radiation to a primary or metastatic solid tumor were enrolled. We collected overall survival time and blood cell counts including neutrophil, lymphocyte, monocyte, platelet in three time periods, before, during and after radiotherapy, and derived some blood index ratios including monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). The delta-IBs were calculated as medio-IBs ÷ pre-IBs-1. We analyzed the changes before and during RT using Spearman rank correlation test, Kruskal-Wallis rank sum test, as well as logistic regression and survival analysis used for the survival analysis.

Results: In selected blood indexes, NLR, PLR and SII are correlated with different irradiated organs, and the medians of delta-NLR, delta-PLR and delta-SII were all the lowest in brain irradiated group during immunotherapy. In the multivariate analysis, only treatment stage was the independent prognostic factors for 9m OS. The median OS of the entire study cohort was 23.5months (95% CI, 10.1—36.9months). For the analysis of ICI stages, patients with second-line ICIs had a higher median OS time than those with first or third and more-line stages (OS: 36.9 vs 22.3 vs 16.1m; $p = 0.001$).

Conclusions: We hypothesised RT to brain has the strongest activation effect and survival compared with other organs in ES-SCLC during immunotherapy. And the second-line immunotherapy combined with radiotherapy achieved better curative effect.

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2007P Real-world (rw) outcomes to chemoimmunotherapy and biomarker analysis in extensive-stage small cell lung cancer (ES SCLC)

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Background: The addition of programmed death-ligand 1 (PD-L1) inhibitors to chemotherapy in the first-line treatment of ES SCLC has improved survival outcomes compared with chemotherapy alone. Biomarkers for response to chemo-immunotherapy have not been clearly established yet.

Methods: We performed a retrospective chart review of patients diagnosed with ES SCLC who received chemoimmunotherapy in the first-line treatment setting at Sotiria General Hospital for Chest Diseases, National and Kapodistrian University of Athens, Athens, Greece, between October 2018 and February 2023. Kaplan-Meier analysis was utilized to calculate rw progression-free survival (rwPFS) and rw overall survival (rwOS). Cox proportional hazards regression analysis was utilized to identify associations between patient characteristics and outcome. All hypothesis testing was conducted at a two-sided significance level of α=0.05.

Results: Ninety patients were eligible for study inclusion. The median age at diagnosis was 69 years (range, 40-82 years). Forty patients received atezolizumab plus carboplatin/etoposide (EP) and 50 patients received durvalumab plus EP. The rw objective response rate (rwORR) was 48.2%. At a median follow-up of 6.8 months, median rwPFS and rwOS reached 5.8 months (95% confidence intervals [CI], 5.2-9.7 months) and 12.7 months (95% CI, 7.7-17.5 months), respectively. Notably, survival outcomes were equivalent among patients treated with atezolizumab and those treated with durvalumab. Median rw progression-free survival to subsequent therapy (rwPFS2) was 2.7 months (95% CI, 1.9 months-not estimable). At baseline, increased neutrophil-to-lymphocyte ratio (NLR; hazard ratio [HR], 1.51; 95% CI, 1.02-2.25) and increased number of metastatic sites (HR, 3.14; 95% CI, 1.38-7.11) were associated with a higher risk of death, while elevated BMI (HR: 0.47, 95% CI:0.28-0.81) was associated with lower.

Conclusions: Rw survival outcomes to chemoimmunotherapy in ES SCLC were consistent with the results of large-scale randomized clinical trials. Several baseline patient characteristics were associated with rwOS and merit further investigation in prospective studies.

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2008P Brazilian real-world data of immunotherapy (IO) in extensive disease small cell lung cancer (ES-SCLC)

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Background: The landmarks of thoracic Oncology in the last two decades have been accompanied by exponential growths in costs, which makes imperative the assessment of the real benefit of new technologies incorporations, particularly those with marginal gains. The combination of IO with platinum-etoposide chemotherapy has

become the standard of care in first-line treatment of ES-SCLC, although the absolute difference in overall survival (OS) has reached three months. This study aimed to investigate the impact of this intervention in a real-world cohort of a middle-income country.

Methods: We retrospectively analyzed data from all ES-SCLC patients (pts) from Oncoclinicas, the largest community oncology practice in Latin America, diagnosed and treated between January 2018 and June 2022. Primary objective was median OS according to IO exposure in the first-line setting. Secondary objective was median time to treatment discontinuation (TTD). Relevant clinical characteristics which might impact the results were also evaluated. The project was approved by local Ethics Committee.

Results: In total, 98 patients SCLC pts were included in this analysis. The median age was 68 years, 54% were male, 88% were smoking history, and only 12% has ECOG 2-3. At diagnosis, 81% presented with ES-SCLC and 21% has central nervous system metastasis. First-line regimens were atezolizumab + platinum-etoposide in 47%, platinum-etoposide in 44% and platinum-irinotecan in 9%. Median follow-up was 5 months. Among ES-SCLC pts who received IO in their first-line treatment, median mOS was 14.03 months compared to 7.43 months in those who did not receive IO (HR: 0.76, CI 0.42 − 1.40, p = 0.39). Median TTD of the first-line IO was 7.03 months compared to 3.80 months of those who received chemotherapy only (HR: 0.43, CI 0.24 − 0.76, p = 0.003).

Conclusions: There are few real-world cohorts evaluating the impact of IO in ES-SCLC, limited to high-income countries. Our data suggest that IO may have a meaningful impact in the outcome of ES-SCLC, with median OS comparable to clinical trials. Larger sample small sample size and longer follow-up are needed for conclusive statements, but we will continuously monitor the value of IO as they are introduced in clinical practice for ES-SCLC.

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2009P CNS efficacy of immune checkpoint inhibitors when combined to stereotactic radiosurgery in extensive stage small cell lung cancer

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Background: Brain metastasis is highly prevalent in Extensive Stage Small Cell Lung Cancer (ES-SCLC) and carries a poorer prognosis. Combined chemotherapy (CTX) and Immune checkpoint Inhibitor (ICI) is the current standard of care in treatment of ES-SCLC. Stereotactic Radiosurgery (SRS) either as whole brain radiation or Gamma knife radiosurgery is often employed to treat CNS disease. We aim to investigate the CNS benefit of ICI when combined with CTX in patients with ES-SCLC who received SRS.

Methods: Baseline characteristics, treatment and survival details were collected. Patients with baseline CNS disease who received SRS and at least one cycle of systemic therapy were included. Primary outcome of CNS progression free survival (CNS-PFS) was calculated using standard Kaplan-Meier methods, and Cox proportional hazard model were used to evaluate the association between survival outcome and treatment group while adjusting for age and baseline ECOG. Analyses were performed in SAS v9.4 (Cary, NC) at a significant level of 0.05. The CTX and CTX+ICI groups were labeled as cohort A and cohort B respectively.

Results: A total of 165 patients were included in the analysis. Cohort A had 122 patients (73.9%), while cohort B had 43 patients (26.1%). The baseline characteristics between the two cohorts were balanced as seen in table. The Cox proportional hazards analysis revealed a 30% benefit in CNS-PFS in cohort B when compared to cohort A (HR=0.7 CI=0.47-1.03). Additionally, there was a trend towards benefit in overall survival (OS) in cohort B (HR=0.74 CI=0.46-1.2).

Table: 2009P Baseline characteristics

	Cohort A (CTX)	Cohort B (CTX+ICI)
Total patients n, (%)	122, (73.9%)	43, (26.1%)
Age median, (min-max)	64.2, (37.2-86.3)	64.4, (51.6-85.9)
ECOG at presentation, n (%)		
ECOG 0-2	109, (89.3%)	38, (88.4%)
ECOG 3-4	13, (10.7%)	5, (11.6%)
Completed treatment cycles n, (%)		
$\leq$ 4 cycles	87, (71.3%)	39, (90.7%)
$\geq$ 5 cycles	35, (28%)	4, (9.3%)

Conclusions: Although the CNS-PFS and OS trends did not reach statistical significance, due to the small number of patients, our study suggests a clear trend towards CNS-PFS and OS benefit when combining ICI+CTX to SRS. Thus, supporting the hypothesis of immune modulatory effect of SRS on the brain metastases tumor microenvironment. Larger studies are needed to confirm these findings.

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2010P Non-invasive radiomics signature predicts response to combination chemoimmunotherapy in extensive-stage small cell lung cancer (ES SCLC)

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Background: ES SCLC is a highly aggressive malignancy with poor outcomes. While immunotherapy (IO) has shown promise in improving response rates in some patients (pt) with ES SCLC, there are no reliable biomarkers to predict which pt are most likely to benefit. In this study, we aimed to explore the potential of radiomic texture features from inside (intratumoral) and immediately outside (peritumoral) the tumor on pre-treatment CT scans to predict overall survival (OS) and response to chemoIO in ES SCLC pt.

Methods: The study included 142 ES SCLC pt from three institutions, with measurable lung lesions on baseline chest CT scans. A maximum of two lung lesions were annotated. Pt with best objective response per RECIST 1.1 of complete or partial response were categorized as responders, while those with stable or progressive disease were considered non-responders. A total of 860 intratumoral and peritumoral texture features were extracted, and a radiomic risk score (RRS) was generated using the least absolute shrinkage and selection operator. Cox regression model was used to predict OS. The model was trained on 97 ES-SCLC pt (St) treated with chemotherapy at University Hospital Cleveland Medical Center and validated on 45 ES-SCLC pt (Sv) treated with chemoIO at Roswell Park Cancer Institute (Sv1; n=34) and Emory University (Sv2; n=11). The discriminative ability of the features was assessed using Kaplan-Meier and log-rank tests, and the probability of treatment response was evaluated using a previously trained linear discriminant classifier (LDA).

Results: A combination of peritumoral and intratumoral radiomic features on pre-treatment CT showed an AUC of 0.73 in St and 0.72 in independent external Sv to predict response to treatment. The RRS was significantly associated with OS in both St (HR: 2.27; 95% CI, 1.7−2.98; P<0.001; C-index=0.70) and Sv (HR: 2.26; 95% CI, 1.32−3.74; P=0.016; C-index=0.65).

Conclusions: Pre-treatment CT radiomic features are potentially prognostic and predictive of response to chemotherapy or chemoIO in ES SCLC pt. These findings may have implications for guiding treatment decisions and improving outcomes by better pt stratification. Additional independent, multi-site validation is warranted.

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2011P Machine-derived features of tumor infiltrating lymphocytes (TILs) as biomarkers of clinical outcomes to platinum chemotherapy in small cell lung cancer (SCLC)

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Background: Platinum chemotherapy (PC) is the mainstay of treatment in SCLC. Most patients relapse with poor overall survival (OS) and develop resistance to further therapy. Presently, there are no biomarkers to predict response/resistance to initial treatment. TILs have shown to serve as a prognostic factor in several solid cancers but remain largely unexplored in SCLC. In this study, we explore the association of density and spatial arrangement of TILs with clinically relevant outcomes.

Methods: TIL features were extracted using computational algorithms from H&E whole slide images of pre-treatment SCLC biopsy across two cohorts, D1 (University Hospitals) and D2 (Roswell Park) (n=213). D1 (n=101) was used to identify the most prognostic features and train two classifiers to predict objective response to PC and OS. The classifier's performance was evaluated in an independent cohort D2 (n=112). D1 was split into Training (St)/Test (Sv) set (40/60) based on overall response to PC per RECIST; responders=complete/partial response, non-responders=stable/progressive disease and OS status. Boruta method of feature selection was used to select the most discriminating features. Linear classifier with qr factorization, linear least square approach was used to build a model for predicting response and Kaplan-Meier with log-rank test for estimating survival curve and risk stratification; Cox's proportional hazards with elastic-net penalization for risk score. The model was evaluated using Area Under the Curve (AUC) and Precision Recall Curves (PRC) for OR and in terms of Hazard Ratio (HR), C-index (CI) and p-values for OS prediction.

Results: Features related to density variation of clusters of TILs and non-lymphocytes within the tumor area were associated with response to PC and OS. For St, AUC=0.96, PRC=0.98 (HR=2.84; 1.34-6.02, p=0.005, CI=0.75 0.60-0.90), AUC=0.66, PRC=0.76 (HR=2.06; 1.15-0.84, p=0.013, CI=0.7; 0.56-0.84) for Sv. For D2, validation AUC=0.67 and PRC=0.79 (HR=1.99; 1.08-3.7, p=0.026, CI=0.69; 0.54-0.83).

Conclusions: We demonstrate that TIL density and architecture features are associated with OR and OS. Additionally, independent multi-site validation is warranted.

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2012P Spatially resolved transcriptomics deciphers inter- and intra-tumor heterogeneity of small cell lung cancer

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Background: Small cell lung cancer (SCLC) is a highly heterogeneous cancer. Recent studies have illustrated that inter- and intra-tumor heterogeneity (ITH) is correlated with biological behavior and therapeutic vulnerability in multiple malignancies. However, it remains unclear in SCLC. Here, we seek to define ITH at the spatial transcriptome level and elucidate the crosstalk between ITH and tumor immune microenvironment (TIME) with the clinical characteristics of SCLC.

Methods: We performed digital spatial profiling (DSP) to quantify the whole transcriptomes and calculated the ITH score using the Deviating gene Expression Profiling Tumor Heterogeneity algorithm (DEPARTMENTH) at the RNA level. Deconvoluted algorithms were adopted to calculate immune infiltration from RNA expression data, which was validated with immunochemistry (IHC). A machine learning model (THIM) was constructed to determine the tumor heterogeneity and facilitate prognostic stratification, which were validated across multi-center cohorts.

Results: Using DSP RNA data of the tumor core area (79 regions) from resected limited stage SCLC (25 patients), we differentiated intra-/inter-tumor heterogeneity subtypes. SCLC tumors could be classified into two distinct subtypes: high heterogeneity+complex (HC) and medium+low heterogeneity (ML), with significant variations in CD8+ T cell infiltration and multiple biological properties. There were significant differences in overall survival (log-rank $p = 0.046$) and disease-free survival (log-rank p=0.024) between the two subtypes, where MLs had good and HCs showed poor prognosis. Furthermore, we developed and verified a robust THIM model using machine learning techniques which is able to predict the therapeutic response (AUC=0.923) and survival of SCLC patients, as demonstrated in both in-house and multicenter bulk transcriptomic data cohorts.

Conclusions: In summary, we have deciphered inter- and intra-tumor heterogeneity of SCLC and proposed a new heterogeneity-oriented subtyping framework for improving clinically relevant risk stratification, which is promising for postoperative stratified management of limited stage SCLC patients as well as assessment of immunotherapy efficacy in advanced stage patients.

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2013P Investigating the clinical relevance of immune checkpoint expression in the peripheral blood of patients with small cell lung cancer (SCLC)

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Background: Cytotoxic T lymphocyte antigen 4 (CTLA4) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) immune checkpoints are expressed on tumor-infiltrated immune cells (TILs) in SCLC and represent promising immunotherapy targets. We aimed to assess the frequency and clinical relevance of CTLA4 and TIGIT expression in the peripheral blood (PB) of patients with SCLC.

Methods: PB was obtained from 90 SCLC patients prior to first-line treatment (chemotherapy=61; combination of chemotherapy/anti-PD-L1 inhibitors: n=29). Peripheral blood mononuclear cell (PBMC) cytospins were stained for CTLA4/TIGIT/dapi. CTLA4 and TIGIT protein expression was individually assessed on 1000 intact PBMCs *via* fluorescence microscopy; the mean % value was used to define high expression of each marker.

Results: CTLA4 and TIGIT were expressed on PBMCs in 95.6% and 100% of patients, respectively, with a mean percentage of positive PBMCs per patient: 27.8% and 34.5%, respectively. Their expression was not associated with clinicopathological parameters or survival outcomes in the entire patient population. However, separate analysis of the chemoimmunotherapy group (n=29 extensive-stage SCLC patients) revealed that high versus low expression of CTLA4 and/or TIGIT was a marker for increased progression-free survival and overall survival (median PFS: 8.7 vs 4.7 months, p=0.000; median OS: 13.9 vs 5.9 months, p=0.038; respectively by Kaplan Meier analysis); on the contrary, no correlation was shown for patients treated with chemotherapy only (median PFS: 6.2 vs 7.9 months, p=0.877 and median OS: 11.6 vs 15.1, p=0.142). Moreover, among extensive-stage patients with high expression of CTLA4 and/or TIGIT on PBMCs (n=45 patients), the administration of chemoimmunotherapy was associated with improved survival rates as compared to those receiving chemotherapy only (median OS: 14 vs 7.8 months, p=0.005).

Conclusions: CTLA4 and TIGIT are frequently expressed on PBMCs of SCLC patients and are correlated with significant clinical benefit from the addition of anti-PD-L1 inhibitors to first-line chemotherapy. Their role as immunotherapy biomarkers in SCLC merits further investigation.

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2014P ATR inhibition upregulates PD-L1 and potentiates the antitumor immune response to chemoimmunotherapy in small cell lung cancer

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Background: Small cell lung cancer (SCLC) is the most aggressive subtype of lung cancer, with a very poor prognosis and limited therapeutic options. Recent clinical trials of immune checkpoint blockade (ICB) combined with chemotherapy delivered only very modest benefit. Here, we identified that ataxia telangiectasia and rad3 related (ATR), the primary activator of the replication stress response, is highly enriched in SCLC and inhibition of ATR induced DNA damage and apoptosis in multiple SCLC models.

Methods: Genetic and pharmacological inhibition of ATR in human and murine SCLC models. ATR inhibition either alone or in combination with PD-L1 blockade either as a first-or second-line treatment in mouse models.

Results: In multiple immunocompetent SCLC mouse models, ATR inhibition (ATRi) remarkably enhanced the anti-tumor effect of PD-L1 blockade. We next tested the ATR inhibition either alone or in combination with PD-L1 in the second-line regimen for SCLC. ATR inhibition in combination with PD-L1 blockade significantly reduced tumor volume and prolonged survival of aggressive mice models when compared to PD-L1 alone. Targeting ATR enhanced the expression of PD-L1, activated the cGAS/STING pathway, induced the expression of Type I and II interferon pathways, and caused significant infiltration of cytotoxic and memory/effector T-cells into tumors. Interestingly, ATRi also led to significant induction of MHC class I in SCLC *in vitro* and *in vivo* models. Analysis of pre- and post-treatment clinical samples from a proof-of-concept study of a first-in-class ATR inhibitor, M6620 (berzosertib), and TOP1 inhibitor topotecan, in patients with relapsed SCLCs validated the induction of MHC class I and interferon pathway genes, for the first time in this disease.

Conclusions: We highlight ATRi as a potentially transformative vulnerability of SCLC, paving the way for combination clinical trials with anti-PD-L1. Given the increasing importance of immunotherapy for the management of SCLC and that ATR inhibitors are already in clinical trials, combining an ATR inhibitor with PD-L1 blockade may offer a particularly attractive strategy for the treatment of SCLC and contribute to the rapid translation of this combination into the clinic.

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2015P Association between gene characteristics and mutation abundance with the prognosis of small cell lung cancer

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Background: Genetic characteristics and mutation abundance need to be further explored in small-cell lung cancer (SCLC). This study aimed to analyze the correlation between genetic characteristics and mutation abundance and the prognosis of SCLC patients by next-generation sequencing (NGS).

Methods: Patients diagnosed with SCLC at Shanghai Chest Hospital from January 2017 to December 2020 were reviewed. All enrolled SCLC patients underwent NGS testing before initiating treatment.

Results: 122 patients were enrolled in the final analysis, including 48 patients with limited-stage SCLC (LS-SCLC) and 74 patients with extensive-stage SCLC (ES-SCLC). The most common mutant genes were TP53, RB1, and SMAD4 in LS-SCLC and ES-SCLC. Furthermore, no significant difference in mutant genes and mutation frequencies was observed between LS-SCLC and ES-SCLC. Multivariate Cox regression analyses revealed that the presence of genetic abnormalities TP53 and BRCA2 was significantly related to overall survival (OS) in patients with LS-SCLC. In ES-SCLC patients, the genetic abnormalities TP53, NOTCH1, PTEN, and PIK3CA were significantly related to OS. TP53 mutation abundance was higher in ES-SCLC than in LS-SCLC (average 75.334% vs. 65.954%, median 82.395% vs. 76.820%, $P = 0.046$). In ES-SCLC patients, higher TP53 mutation abundance predicted poorer clinical outcomes, which is contrary to LS-SCLC patients.

Conclusions: This study reveals the relevance of genetic features of NGS and prognosis in SCLC patients. Contrary relationships were observed between TP53 mutation abundance and prognosis in patients with LS-SCLC and ES-SCLC.

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2016P The role of galectin-1 in SCLC: Prognostic significance and therapeutic implications

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Background: Not much has changed in the SCLC landscape over the past 40 years, apart from the addition of checkpoint inhibitors, which have been the most notable advance in clinical management since the 1980s. As a result, greater efforts are needed to develop more therapies to combat this type of cancer. Galectin-1 (Gal-1) has emerged as an interesting player due to its involvement in crucial roles in cancer development. Our objective was to assess whether Gal-1 has a prognostic role in SCLC outcomes and its potential for use in both monotherapy and combination with platinum-based therapy.

Methods: We analyzed Gal-1 expression in 77 SCLC patients using RNA sequencing and in 81 patients using in-house immunohistochemistry (IHC). We evaluated the prognostic potential of Gal-1 using survival curves and Cox regression analysis. Additionally, we established a SCLC-PDX model and randomized it into four groups to assess the effects of Gal-1 inhibition in monotherapy and in combination with platinum-based therapy. To evaluate antitumor activity, T/C ratio was applied.

Results: Galectin-1 gene (LGALS1) expression showed a strong negative correlation with outcomes in SCLC patients with advanced disease ($p = 0.007$). Furthermore, IHC analysis revealed that in patients with advanced disease, a high Gal-1 score (Gal-1 score >3) and high Platelets to Lymphocytes Ratio (PLR > 186) as a combined variable presented a HR=3.07, 95% CI: 1.62, 5.79, $p < 0.001$, with a significant impact on survival (median time (weeks) for OS was 31 in the high/high group versus 41.1 in the other group). The SCLC-PDX model showed a significant reduction in tumor growth in both the OTX008 (T/C 66%) and carboplatin/etoposide (T/C 65%) groups, with the greatest effect attributable to the combination (T/C 46%).

Conclusions: Our findings suggest that high levels of Gal-1 and PLR are associated with poorer OS in SCLC patients and can be useful as clinical prognostic biomarkers. Moreover, our *in vivo* model suggests that the inhibition of Gal-1 could be a novel potential therapy with a significant impact in combination with platinum-based therapy.

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2017P Comprehensive molecular profiling of small cell lung cancer patients treated with chemo-immunotherapy or chemotherapy alone

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Background: Small cell lung cancer (SCLC) is one of the most lethal forms of lung cancer, with a 5-year survival rate of approximately 7%. SCLC has been divided into limited stage (LS) and extensive stage (ES). For ES-SCLC the use of immunotherapy (IO) has been introduced in combination with platinum-based chemotherapy (CT), prolonging the overall survival of patients. However, only a small fraction of patients experience a durable clinical benefit from this approach, with no selection criteria able to predict clinical outcome. Here we hypothesize that different mutational profiles could be associated to clinical outcome of patients treated with CT-IO with respect to CT alone.

Methods: A case series of 88 ES-SCLC patients was enrolled. Tumor tissues of patients were analysed with a next-generation sequencing-based assay (Foundation One CDx), analysing 324 genes, selected gene rearrangements, microsatellite instability (MSI) and tumor mutational burden (TMB). Statistical analyses have been performed to study the correlation among clinical characteristics, mutational profiles and clinical outcome has been performed.

Results: For patients with available clinical information, 36 were treated with CT-IO and 50 with CT alone. The 65% of patients were male, and the 35% were female, median age was 71 (range 50-86) years old. The 36.2% of patients were former smokers whereas 53.75% were current smokers, while smoking habits were not available for 16 patients. The most frequently mutated genes were *TP53* (98%), *RB1* (80%), *MLL2* (35%), *NOTCH3* (16.2%), *MLL* (12.5%), *RICTOR* (8.8%), *CDKN2A/B* (7.3%), *APC* (7.3%), *MYC* (6.3%) and *MYCL1* (6.3%). No rearrangements were detected in any patient. With regard to TMB, 25% of patients had low TMB (<6 mut/Mb), 65% of patients had intermediate TMB (6>20 mut/Mb), and 10% of patients had high TMB (>20 mut/Mb). MSI data was available for 67 patients, and all but one patients were stable. Survival analyses and correlation of clinical outcome with mutational profiles are still ongoing.

Conclusions: Our results suggest that a comprehensive genomic profile could help to predict clinical outcome of ES-SCLC patients treated with CT-IO.

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2018P Novel nomogram based on the expression of DLL3 and PD-L1 for predicting the prognosis of small cell lung cancer patients

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Background: Small cell lung cancer (SCLC) is highly invasive and has a low 5-year survival rate. Programmed death receptor 1/programmed death receptor-ligand 1 (PD-L1) inhibitors have improved survival in SCLC patients partially, but more targets and precise beneficiary populations are needed. Delta-like ligand 3 (DLL3)-targeted drug Rova-T was terminated due to insufficient efficacy, considering other factors that may affect efficacy. This study aims to construct a prognostic model for SCLC patients based on the expression of DLL3 and PD-L1 to help determine prognosis and guide clinical therapy.

Methods: Immunohistochemistry was used to detect the expression of DLL3 and PD-L1 in the tissue specimens of SCLC patients. Independent risk factors were identified by Cox proportional risk regression to construct the model. The model was validated by consistency index (C-index), bootstrap resampling, and decision curve analysis (DCA).

Results: Up to March 15, 2023, 141 patients diagnosed with SCLC by pathology at Changzhi People's Hospital were included, and 129 patients have reached the endpoint. The expression rates of DLL3 and PD-L1 were 62.4% (88/141), 10.6% (15/141). NSE, stage, treatment, DLL3 and PD-L1 were independent risk factors for OS in SCLC patients ($p<0.05$). Based on these factors, a prediction model for the 12-month survival probability of SCLC patients was constructed and a nomogram was plotted. The model was tested for good discrimination (C-index 0.739), accuracy and clinical applicability. In addition, patients were divided into low-risk and high-risk for survival analysis based on the best cut-off value of 49.11 for nomogram, indicating that the model had great discrimination ability (mOS 13.33 vs. 7.80m, $p<0.001$).

Table: 2018P

Variable		Point	Overall point	12-m survival probability
NSE per 50mg/ml		6.16	0	0.78
Stage	Limited	0	10	0.72
	Extensive	20.47	20	0.65
Treatment	Yes	0	30	0.57
	No	100	40	0.47
DLL3	Negative	0	50	0.37
	Positive	24.69	60	0.27
PD-L1	Negative	0	70	0.17
	Positive	44.50	80	<0.10

Conclusions: The OS prediction model for SCLC patients in this study has excellent predictive performance in predicting the 12-m survival probability and may assist clinicians in making more accurate judgments and guiding therapy of SCLC patients.

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2019P Analysis of lung immune prognostic index (LIPI) score in a small cell lung cancer carcinoma (SCLC) cohort, supporting its prognostic use and investigating its predictive potential

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Background: Current standard-of-care treatment for extensive-stage SCLC involves combining chemotherapy with immune checkpoint inhibitors (ICI). However, appropriate predictive biomarkers are still lacking. The LIPI is a clinical tool developed in non-small cell lung cancer. We aim to study whether the LIPI score can be a prognostic and predictive tool in SCLC.

Methods: We conducted a retrospective unicenter observational study. 48 patients were included, classified in cohort ICI when treated with carboplatin-etoposide and atezolizumab (n=23); and cohort CT when treated with cisplatin/carboplatin-etoposide (n=25). Complete blood cell counts and LDH levels were measured before treatment. LIPI score was calculated and patients were classified in good (0), intermediate (1) and poor categories (2). Primary outcomes were to determine progression-free survival (PFS) and overall survival (OS) in both cohorts stratified by LIPI categories. Fischer's test was used for categorical data; while PFS and OS were evaluated by Kaplan-Meir.

Results: Cohorts were comparable without significant differences in baseline characteristics (age, sex, metastatic sites, corticoid use). Regarding PFS, at 12 months all patients in the CT cohort had progressed, versus 79% in the ICI cohort. PFS was better for LIPI 0 with statistical significant difference (p=0.043) with 22% free of progression at 12 months, versus 6% for LIPI 1 and 0% for LIPI 2. For the ICI cohort PFS was significantly better for LIPI 0 as well (p=0.0151), with 40% free of progression at 12 months. The one-year OS survival rate was 40% for the CT cohort and 32% for the ICI cohort. Although no statistical significance was found, a trend towards better OS for LIPI 0 was seen in both cohorts; with 67% alive at 1-year versus 23% for LIPI 1 and 34% for LIPI 2. This was also present in the ICI cohort with 60% alive at 1-year for LIPI 0 versus 27% for LIPI 1 and 0% for LIPI 2.

Conclusions: Although limited by the small number of patients and the shorter follow-up in the ICI cohort, our study supports LIPI score can be a prognostic tool in SCLC. Further studies are needed to find whether it could also be a predictive tool for response to ICI in SCLC.

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2020P Circulating micro RNAs (cmiRNAs) as treatment outcome predictors in extensive small cell lung cancer (eSCLC) patients (pts) receiving atezolizumab plus carboplatin and etoposide (ACE): CATS/ML43257 study

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Background: ACE is the new standard first-line treatment for eSCLC. However, response to this treatment is highly heterogeneous and the identification of patients more likely to benefit from immunotherapy is in high demand. To this end, circulating biomarkers may prove to be useful, especially when tumor tissue samples are difficult to obtain and for tumors with high genetic heterogeneity. CATS is a prospective pilot study aiming at identifying predictive cmiRNAs in a cohort of eSCLC patients receiving ACE.

Methods: Next generation sequencing technology was employed to determine the cmiRNA profile in the plasma of eSCLC patients at different time points (T0 baseline; T1 after 1 cycle; T2 after 2 cycles; T3 disease progression). Library preparation was carried out using the QIAseq miRNA library kit (Qiagen, Hilden, Germany). All samples were single-end-sequenced on an Illumina NextSeq500 platform. The mean number of miRNA with more than 5 reads detected in the samples was 326. Cut-off values for definition of low versus high levels of miRNA were identified over and under the median value. Univariate (log rank test) analyses were performed to investigate the possible impact of cmiRNA levels on progression-free survival (PFS).

Results: Overall 20 patients have been enrolled in the study. Preliminary results have been obtained for 11 patients (T0 n=11; T1 n=11; T2 n=11; T3 n= 7), with a median follow-up of 5.5 months. Median PFS was 4.8 months. We observed no correlation between the baseline levels of cmiRNAs and tumor load and proliferation index. A panel of 4 cmiRNAs targeting transcription factors was identified as significantly correlated with PFS, both individually (p=0.001, p=0.002, p=0.006; p=0.008, respectively) and within a combined score (p=0.001). No significant predictive value of the relative change between timepoints of these cmiRNAs was observed.

Conclusions: Baseline levels of specific cmiRNAs may identify eSCLC pts with different PFS to first line ACE. Results from a wider cohort of patients with longer follow-up and the validation of the proposed miRNAs will presented at the conference.

Legal entity responsible for the study: University of Padua.

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2021P Cell-free (cf) DNA as predictive biomarker (B) of treatment outcome in extensive small cell lung cancer (eSCLC) patients (pts) receiving atezolizumab, carboplatin and etoposide (ACE): CATS/ML43257 study

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Background: First-line systemic therapy with ACE is a new standard of care for eSCLC. Circulating biomarkers may identify those pts experiencing a better treatment outcome.

Methods: The CATS study is a single center translational prospective study on eSCLC pts receiving ACE investigating the predictive role of circulating B. Plasma samples have been collected at 4 timepoints (T0 baseline; T1 after 1 cycle; T2 after 2 cycles; T3 disease progression). cfDNA has been analyzed by the Avenio ctDNA expanded kit.

Results: At data cut-off (1st April 2023), 20 pts have been included. Preliminary results have been obtained from the first 11 pts (T0 n=11; T1 n=11; T2 n=10; T3 n= 6). After a median (m) follow-up (FUP) of 5.5 months (mo), response rate (RR) was 58.3% (95% Confidence Interval, CI 30.4-86.2), m progression-free survival (PFS) 4.8 (95%CI, 3.9-4.8) and m overall survival (OS) 11.2 mo (95%CI, 3.5-18.9). Median cfDNA was 52.3, 27.1 and 22.5 ng/mL, at T0, T1 and T2, respectively. A trend toward cfDNA level reduction between T0 and T1 (m 52.3 ng/mL; InterQuartile Ratio, IQR 12.8-122.7 vs 27.1, IQR 16.6-42.6, p=0.054) and a significant reduction between T0 and T2 (52.3, IQR 12.8-122.7 vs 22.5, IQR 11.1-38.0, $p<0.05$) were observed. Chromosomic profile (CP) was altered in 10 (90.9%), 4 (36.4%) and 4 cases (40%) at T0, T1 and T2, respectively. Tumor related mutations (TRM) were identified in all pts at T0 [TP53 in 11 (100%), RB1 in 5 (45.5%)] and at T1 [TP53 in 9 (81.8%), RB1 in 3 (27.3%)]; in 90% of pts at T2 [TP53 in 7 (70%), RB1 in 3 (30%)]. Median variant allele fraction (VAF) at T0, T1 and T2 was 38.3%, 1.2%, 0.2% and 30.7%, 33.1%, 20.1% for TP53 and RB1, respectively. In 8 (72.7%) pts, a VAF clearance was registered between T0 and T1 ($p<0.001$). Longer PFS was associated with low levels of cfDNA at T0 (p=0.04) and T2 (p=0.04). No correlation between the relative change of cfDNA at different timepoints and treatment outcome were observed at this preliminary analysis.

Conclusions: We suggest cfDNA, CP and TRM as putative circulating predictive biomarkers to be monitored in eSCLC pts receiving ACE. These data will be confirmed in a wider validation set of pts with a longer FUP.

Legal entity responsible for the study: University of Padua.

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2022P ALBA project: Prognostic impact of laterality in small cell lung cancer

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Background: Due to its devastating behavior and unfavorable prognosis, SCLC is the most recalcitrant lung neuroendocrine tumor to treat. Performance status (PS), stage, and liver metastases have historically been recognized as prognostic factors in SCLC. However, these variables are unable to adequately stratify patients. Recently, we found that the laterality of primary lesions independently affected the outcome of well-differentiated lung neuroendocrine tumors, with left typical/atypical carcinoids having the worse prognosis (La Salvia A, et al. *Endocrine* 2022). The present analysis aims to evaluate the prognostic significance of laterality in SCLC patients.

Methods: Consecutive patients with histologically confirmed diagnosis of SCLC treated according to disease stage at 3 different Institutions from January 2020 to December 2022 and with a follow-up period of $\geq$ 3 months were included. Clinical and disease characteristics, date of progression, and death were collected and analyzed.

Results: A total of 140 patients were analyzed. The majority were male (57.1%), and former/current smokers (99.3%) with stage IV disease (88.5%). Primary tumor was in the right lung in 76 cases (54.2%). As expected, ECOG PS, stage, and liver metastases were significantly associated with overall survival. With a median follow-up of 11 months (range 3-28 months), patients with primary tumors in the right lung had longer survival than patients with primary tumors in the left lung (12.0 versus 9.5 months, p=0.003; HR 2.020). Similar results were observed by excluding patients with stage III disease (11.5 versus 8.8 months, $p< 0.0001$; HR 2.532). A multivariate model, including all significant variables in the univariate model, confirmed that left laterality represented an independent negative prognostic factor (p=0.044 in the overall population and p=0.007 considering only stage IV).

Conclusions: Our analysis showed the prognostic relevance of primary tumor laterality in SCLC for the first time. Biological differences related to differential exposure to carcinogens in tissue specimens is ongoing.

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2024P Supportive measures to control myelosuppression and costs for patients with SCLC with lurbinectedin, CAV or topotecan with or without trilaciclib: A review on the basis of clinical trials

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Background: Chemotherapy-induced myelosuppression (CIM) has an important impact on patients with Small Cell Lung Cancer (SCLC) and Health Systems. Granulocyte colony-stimulating factors (G-CSF), platelet and red blood cell (RBC) transfusions or erythropoiesis-stimulating agents (EPO) are standard treatments. Trilaciclib is indicated to decrease the incidence of CIM when administered before topotecan.

Table: 2024P

	Lurbinectedin* N=105	Trilaciclib prior to topotecan iv* N=32	Placebo prior to topotecan iv* N=29	CAV (ATLANTIS)** N=168	Topotecan iv (ATLANTIS)** N=121
Neutropenia ≥3	46.7%	68.8%	85.7%	66.1%	73.6%
Severe Neutropenia	24.8%	40.6%	75.9%	54.2%	50.4%
Anaemia ≥3	10.5%	28.1%	60.7%	26.2%	54.5%
Thrombocytopenia ≥3	6.07%	51%	57.2%	17.9%	49.6%
FN	4.8%	6.3%	17.9%	10.1%	5.8%
G-CSF therapeutic	21.9%	50.0%	65.5%	30.4%	19.0%
Platelet transfusions	4.8%	25%	31%	3.6%	21.5%
RBC transfusions	10.5%	31.3%	41.4%	18.5%	46.3%
EPO	1.9%	3.1%	20.7%	9.5%	8.3%

* Prophylactic G-CSF not allowed ** Primary prophylaxis with G-CSF with 100% of patients

The occurrence of CIM events with standard of care (SoC) chemotherapies for relapsed SCLC and supportive care interventions were investigated.

Methods: Inputs were obtained from clinical trials with lurbinectedin (Basket NCT02454972), topotecan after trilaciclib or placebo (NCT02514447), CAV and topotecan (ATLANTIS, NCT02566993) that reported key measures of CIM and supportive care. Therapies were offered mainly as 2L. Cost analysis was performed for grade ≥3 events. Unit costs were obtained from the Spanish Minimum Basic Data Set (€, 2023).

Results: Patients treated with lurbinectedin experienced fewer CIM events than those treated with topotecan, either with or without prior administration of trilaciclib, or with CAV and require less supportive treatments (Table). Lurbinectedin would reduce costs of managing CIM events by 43% - 69% (58% compared to trilaciclib followed by topotecan).

Conclusions: Patients with relapsed SCLC treated with lurbinectedin require fewer resources and less cost for managing CIM episodes than other SoC, including topotecan with prior trilaciclib, based on clinical trials.

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Disclosure: B. García San Andres: Financial Interests, Personal, Other, employee: PharmaMar. J. Gómez, J. Iglesias: Financial Interests, Personal, Stocks or ownership: PharmaMar. B. Citoler, M. Prades: Financial Interests, Institutional, Advisory Role: Outcomes 10. All other authors have declared no conflicts of interest.

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2025P Stratified control study of neuroendocrine differentiation and potential clinicopathologic markers

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Background: SCLC is highly heterogeneous which was divided into NE (Neuroendocrine)-high and NE-low groups according to 50 genes on transcriptomic level, harboring different immune microenvironments and potential immunotherapy reactivity. It is necessary to explore novel NE markers, that both are close to NE gene subtyping and feasible for clinicopathological use. Here, we conducted a parallel comparative study at mRNA and protein levels for exploring the potential of INSM1 as a substitute marker for NE subtyping.

Methods: Two hundred and forty-seven surgical specimens were collected. Quantitative detection of NE genes by Nanostring nCounter as well as INSM1 protein by IHC was performed simultaneously on 48 whole slides as testing group. Spearman correlation was applied for consistency analysis, and the best cut-off for INSM1 expression was validated on 247 tissue microarrays for comparison of the three traditional NE protein markers for specificity and sensibility as well as prognostic significance.

Results: In 48 testing cases, quantitative detection revealed 83.3% (40/48) for NE-high and 16.7% (8/48) for NE-low, while for protein grouping, it was 79.2% (38/48, H-score>100) for NE(INSM1)-high and 20.8% (10/48, H-score<=100) for NE(INSM1)-low. NE classification defined by INSM1 protein and NE genes had significant consistency in terms of proportion (p=0.026). NE groups also had consistent clinical characteristics and prognostic trend in the two levels. Patients with NE-high and NE(INSM1)-high tended to be in the advanced stage. Patients with NE-high and NE(INSM1)-high have a tendency of poor prognosis. In 247 cases of validation exploration, INSM1 expression was positively correlated with three classical markers, more importantly, in triple negative cases, INSM1 showed a favorable positive rate (1.5%, 3/198). In addition, NE(INSM1)-high patients showed more bronchial invasion and tumor thrombosis than that of NE(INSM1)-low ones ($p<0.05$), and the 1-, 3-, and 5-year OS rates in the NE(INSM1)-high group were slightly lower than those in the NE(INSM1)-low group.

Conclusions: INSM1 has great potential being a marker of NE differentiation and subgrouping, also shows a certain correlation with prognosis and some clinicopathological factors.

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2026P Small cell lung cancer (SCLC) in the KBP-2020-CPHG cohort and comparison with 2000 and 2010

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Background: The KBP studies are real nationwide prospective multicenter cohort studies of patients (pts) diagnosed with primary lung cancer (PLC), conducted every decade in France since 2000 in non-academic public hospital (NPH) with the same methodology.

Methods: We describe and compare the characteristics and outcomes of pts with SCLC among the 3 cohorts.

Results: 8999 pts were included in 2020, including 1136 pts with SCLC (12.6% [12.1-13.5]). From 2000 to 2010 and 2020, the proportion of SCLC decreased from 16.4% [15.6-17.6] to 13.5% [12.9-14.6] and 12.6% respectively. In 2020 there were 731 men (64.4% [61.5-67.1]) and 405 women (35.7% [32.8-38.5]). The proportion of women among SCLC pts increased from 15.6% [13.3-18.0] to 35.6% in 20 years. The median age at diagnosis also increased from 65.4 [64.5-66.5] years in 2000 to 67.8 [67.3-68.6] years in 2020. In 2020, 24.7% [22.2-27.4] of SCLC were limited-stage. Most of those pts received platinum-etoposide with thoracic radiotherapy. Overall survival (OS) at 1 year was 62.3% [56.7-68.4] and median OS was 19.1 [16.3-21.8] months.75.3% [72.6-77.8] of SCLC were extended. First-line chemotherapy (CT) was a combination of platinum (cisplatin in 7% [5.1-9.5]; carboplatin in 93% [90.5-94.9]) with etoposide for 96.6% [94.6-97.9] of pts. Immunotherapy (IO) was combined with CT in 51% [47.1-54.9] in 2020. In the KBP 2020 cohort, OS for extended SCLC at 1 year was 30.5% [27.5 - 33.9] and median OS was 7.3 [6.5-7.9] months. OS for SCLC at 1 year was stable between the 3 cohorts 38.7% [35.9 - 41.6] in 2020, 35.2% [32.3-38.4] in 2010 and 34.4% [31.5-37.7] in 2000. However, the 2-year survival rate increased from 11.7% [9.7%-14.0] in 2000, 13.6% [11.6-16.0] in 2010 to 19.4% [17.1-22.0] in 2020. The OS of stage IV SCLC unadjusted with performans status according to treatment with IO shows a significant difference in favor of IO with HR=0.54 [0.46 - 0.64] and $p<0.0001$ with a median survival that increases from 5.5 months [4.4 - 6.7] to 9.9 months [8.9 - 11.3].

Conclusions: The proportion of SCLC among LC is decreasing over time; the proportion of women with SCLC is increasing. While the median OS remains stable at 8.5 months, 2-year OS has improved in 20 years. The benefit of IO is recovered with a profit of more than 4 months.

Clinical trial identification: NCT04402099.

Legal entity responsible for the study: CPHG (Collège des Pneumologues des Hôpitaux Généraux).

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2027P Immune checkpoint inhibitors in the treatment of small cell lung cancer: A systematic review and meta-analysis

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Background: Multiple randomized trials have evaluated immune checkpoint inhibitors (ICI) as first- and second-line treatment in extensive-stage small cell lung cancer (ES-SCLC). We sought to conduct a pooled analysis to characterize the efficacy and toxicity of ICI in ES-SCLC.

Methods: Medline (PubMed), EMBASE, and Cochrane Library databases were queried between January 2010 and March 2022 and conference proceedings between 2018 and 2022 were searched for randomized clinical trials assessing ICI (combined with chemotherapy or as single agents), compared with chemotherapy, in patients with ES-SCLC. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), and grade 3 or higher adverse events (AEs). Pooled hazard ratios (HR) for OS and PFS were meta-analyzed using the generic inverse variance method, and random-effect models were used to compute pooled estimates. Subgroup analyses compared survival by line of therapy, sex, age, and ECOG status.

Results: A total of 5,325 patients from 10 trials were included. Compared to chemotherapy, ICI-based treatment decreased the risk of death by 19% (HR 0.81, 95% confidence interval (CI) 0.76-0.86). The OS benefit was seen regardless of age, sex, or ECOG status, but was only seen in patients treated in the first-line setting. Similarly, ICI-based therapy decreased the risk of disease progression by 20% (HR 0.80, 95%CI 0.68-0.94) and the PFS benefit was restricted to first-line treatment with detrimental effect in the second-line setting. ORR was also improved with ICI (odds ratio (OR) 0.80, 95%CI 0.65-0.97) with an increase in grade 3 or higher diarrhea (OR 3.63, 95%CI 1.46-9.02).

Conclusions: ICI conferred efficacy benefits (OS, PFS and ORR) and an acceptable safety profile in the treatment of patients with ES-SCLC in the first-line setting and should not be used in the second-line setting as single agents. Valid biomarkers predicting long-term benefit are needed to further improve outcomes.

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2028TiP Phase I, non-randomised, open-label, multi-centre dose escalation trial of BI 764532 (DLL3/CD3 IgG-like T cell engager [TcE]) + ezabenlimab (anti-PD-1 antibody) in patients (pts) with small cell lung cancer (SCLC) and other neuroendocrine carcinomas (NECs) expressing DLL3

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Background: The inhibitory Notch ligand, DLL3, is highly expressed on the cell surface of SCLC and NECs, and is a promising drug target. BI 764532 is a DLL3/CD3 IgG-like TcE that has shown potent preclinical anti-tumour activity in DLL3-positive cells and xenograft models. Preliminary results from an ongoing phase I dose-escalation study (NCT04429087) show that BI 764532 has manageable toxicity and promising efficacy. The mode of action of BI 764532 has been shown to upregulate the PD-(L)1 pathway in preclinical studies, as a result of inducing an inflamed tumour environment. Further *in vitro* investigation demonstrated that BI 764532-induced upregulation of PD-(L)1 may reduce its potency, but that this could be overcome by the addition of ezabenlimab (anti-PD-1 antibody). Therefore, this trial is being conducted to explore the combination of BI 764532 + ezabenlimab in a clinical setting.

Trial design: This is a phase I, non-randomised, open-label, multicentre dose-escalation trial of BI 764532 + ezabenlimab in ~30 pts with DLL3-positive SCLC/NECs who have failed/are not eligible for available standard therapy. Pts recruited from ~5−10 centres across several regions globally will receive intravenous BI 764532 + ezabenlimab. Key inclusion criteria will include: ≥18 years of age; Eastern Cooperative Oncology Group performance status 0/1 and ≥1 measurable target lesion (RECIST v1.1). Key exclusion criteria will include: previous TcE/DLL3-targeting therapies; active autoimmune disease and prior anti-cancer therapy. The primary objectives are to evaluate the dose-toxicity relationship and to determine the maximum tolerated dose (MTD) of BI 764532 + fixed-dose ezabenlimab; a recommended dose for expansion/recommended phase II dose will also be determined. In the dose escalation part, the primary endpoint is dose-limiting toxicity (DLT) occurrence in the MTD evaluation period; secondary endpoints include DLT occurrence in the on-treatment period, objective response and pharmacokinetics. Enrolment is ongoing.

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Personal, Other, Travel, Accommodation, Expenses: Pfizer, BMS, AstraZeneca, Amgen, GEMoaB, Sanofi/Aventis, immatics, Merck Serono. All other authors have declared no conflicts of interest.

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2029TiP **Phase I study of ABBV-706, an anti-SEZ6 antibody-drug conjugate, alone or in combination in adults with advanced solid tumors**

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Background: Seizure-related 6 homolog (SEZ6) is overexpressed in many tumor types with high unmet need, including small cell lung cancer (SCLC), neuroendocrine carcinomas (NECs), and central nervous system (CNS) tumors. ABBV-706 is an antibody-drug conjugate (ADC) comprised of an anti-SEZ6 antibody conjugated to a topoisomerase 1 inhibitor payload.

Trial design: This is an open-label, phase 1, first-in-human, dose-escalation, and expansion study (NCT05599984). The study will evaluate the preliminary safety, tolerability, pharmacokinetics (PK), and antitumor activity of ABBV-706 as monotherapy and in combination with budigalimab (a PD-1 inhibitor), carboplatin, or cisplatin, and determine the recommended phase 2 dose (RP2D) of ABBV-706. The study has 4 parts: (1) ABBV-706 monotherapy dose escalation in relapsed or refractory (R/R) solid tumors, following the Bayesian optimal interval (BOIN) design; (2) monotherapy dose optimization, randomized between two or more dose levels, and expansion in R/R SCLC; (3) dose escalation and expansion of ABBV-706 in combination with budigalimab or platinum therapy in R/R SCLC and NECs; (4) monotherapy dose expansion in R/R high-grade CNS tumors or NECs. Safety endpoints include adverse events, clinical laboratory tests, vital signs, and dose-limiting toxicities. PK endpoints include C_{max}, t_{max}, $t_{1/2}$, and AUC. Primary efficacy endpoints include objective response rate and duration of response. Clinical benefit rate, progression-free survival, overall survival, and biomarkers will also be evaluated. ABBV-706 will be administered intravenously until disease progression, withdrawal of consent, or unacceptable toxicity. Trial Eligibility: adults $\geq$18 years old with R/R SCLC, NECs (including neuroendocrine prostate cancer), or high-grade CNS tumors and measurable disease per RECIST v1.1 or RANO, with an ECOG score $\leq$1. Tumor tissue submission for retrospective SEZ6 expression analysis is required. The study began in December 2022 and enrollment is ongoing.

Clinical trial identification: NCT05599984.

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Legal entity responsible for the study: AbbVie.

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SUPPORTIVE CARE

2030O Remote symptom monitoring with electronic patient-reported outcomes (ePROs) during treatment for metastatic cancer: Results from the PRO-TECT trial (Alliance AFT-39)

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Background: During cancer treatment, symptoms are common but often go undetected by clinicians. Remote monitoring with ePROs can detect symptoms early and alert clinicians to intervene, thereby relieving suffering and avoiding complications.

Methods: PRO-TECT was a cluster-randomized trial in 52 US oncology practices. Practices were assigned 1:1 to remote monitoring with ePRO surveys, or usual care. At ePRO practices, patients receiving treatment for metastatic cancer were invited to complete a weekly survey by web or automated telephone system for up to 1 year or until discontinuation of cancer treatment. The survey included 9 PRO-CTCAE symptoms, performance status, and falls. Severe/worsening symptoms generated electronic alerts to nurses, and symptom reports were available to clinicians at visits. Here we report the primary outcome of overall survival after 24 months of follow up, compared between groups using Cox regression incorporating clustering and disease covariates. Other outcomes included mean emergency department (ED) or hospital visits based on chart abstraction and proportion of patients with clinically meaningful benefit in symptoms (EORTC QLQ-C30) at 3 months, compared using mixed modeling and cumulative logistic regression. We previously reported significant benefits in health-related quality of life and physical function (JAMA 2022 ;327:2413-22).

Results: 1191 patients were enrolled 10/2017-03/2020 (593 PRO; 598 usual care). No difference was seen in survival between groups (HR 0.99; p=0.86). The mean number of ED or hospital visits was lower in the ePRO group vs. usual care (1.48 vs 1.81; p=0.006). A greater proportion of patients in the ePRO group experienced benefits in fatigue (OR 1.77; p<0.001), anorexia (OR 1.32; p=0.03), nausea/vomiting (OR 1.40; p=0.01), and sleep (OR 1.73; p<0.001). Patients completed 20,565/22,486 (91.5%) of expected weekly ePRO surveys.

Conclusions: Remote monitoring with ePROs during cancer treatment did not impact survival, but reduced visits to the ED or hospital, and conferred benefits on function and symptoms. Conduct of this trial during the pandemic amidst nursing shortages may have reduced efficacy of the intervention.

Clinical trial identification: NCT03249090.

Legal entity responsible for the study: Alliance Foundation Trials.

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2031O Randomized trial of a telephone-based weight loss intervention in overweight and obese patients (pts) with breast cancer (BC): The MEDEA trial

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Background: Elevated Body Mass Index (BMI) is associated with inferior clinical outcomes, impaired quality of life (QOL), and increased cancer related fatigue (CRF) in pts with early BC. MEDEA evaluated the impact of a weight loss intervention on CRF in overweight or obese survivors of BC.

Methods: MEDEA (NCT04304924) is a French multicenter randomized trial. Pts with stage I-III BC within 12 months of primary treatment and BMI $\geq$25 kg/m^2 were eligible. MEDEA compared a telephone-based weight loss program delivered by a coach through 24 semi-structured calls over 12 months and focused on caloric restriction + education (intervention arm) with an education alone program (control arm). The intervention was adapted from the BWEL trial (A011401) and was considered completed if $\geq$16/24 calls were delivered. The primary endpoint was between-arm difference in CRF (EORTC C30) 12 months (M12) post-randomization, estimated by a linear mixed model. Secondary endpoints included weight, QOL (QLQ C30 / BR23), and satisfaction (Focus groups). The study had 80% power (two-sided $\alpha = 0.05$) to detect an effect size of 0.40.

Results: 220 pts were included. Mean (SD) age was 53.8 years (10.4), mean weight was 83.6 kg (14.0), and 65% of pts received endocrine therapy. At randomization, CRF scores were similar between arms (Mean [SD]: 40.2 [23.5] and 40.2 [27.8]). At M12, CRF was reduced by a mean of -7.8 points (SD 20.8) in the intervention and -2.0 points (SD 27.3) in the control arm. The estimated between arm difference at M12 was 5.9 (SE 3.7) but was not significantly different from zero (p=0.11). Mean and proportional weight loss at M12 was higher in the intervention arm vs control: -6.7 kg (SD 8.3), 10% vs -1.1 kg (SD 5.3), 1% (p_{arm}=0.025; $p_{arm*time}$=0.002). There was no detrimental effect on other QOL domains. Satisfaction and adherence to the intervention were high, with 75% completing $\geq$16/24 calls.

Conclusions: A telephone-based weight loss program did not lead to a significant difference in CRF at 12 months, but did induce significant weight loss among pts with BC. These results suggest a North American weight loss intervention was adaptable and could be disseminated in a different language and cultural context.

Clinical trial identification: NCT04304924; Release date: 20th March 2020.

Legal entity responsible for the study: Gustave Roussy Cancer Center.

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2032MO Correlation of safety and efficacy in atezolizumab therapy across indications

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Background: The association between safety and efficacy of immune checkpoint inhibitors (ICI) is known, but association between severity of ICI toxicity and impact of specific organ systems affected by immune-related adverse event (irAE) and cancer outcomes is poorly understood. While most irAEs are mild to moderate, severe irAEs pose clinical challenges that may require immunosuppression, hormonal replacement, and/or permanent discontinuation of ICIs.

Methods: We evaluated the association between safety and efficacy across 14 clinical trials (n=9521) involving atezolizumab as mono (IO) or with chemo (C-IO) therapy as compared to chemotherapy (C) in Non-Small Cell Lung (NSCLC, n=8), Small-Cell Lung (SCLC, n=1), Renal Cell (RCC, n=2), Urothelial (UC, n=2), and Triple -Negative Breast Cancers (TNBC, n=1). We applied a mixed-effect Cox proportional hazard model for time-varying covariates to address immortal time bias, adjusted for baseline factors associated with occurrence of irAEs and OS to control for confounding bias, and focused on the five most common irAEs (dermatologic, thyroid dysfunction, hepatitis, pneumonitis, and colitis) to avoid low statistical power for rare events. Association between irAE grade (G) by CTCAE and specific organ involvement with overall survival was assessed.

Results: For patients treated with IO or C-IO, G1-2 irAEs were associated with improved OS (HR = 0.65, $p<0.01$) and G3-4 irAEs showed slight increase in risk of death (HR = 1.18, p=0.06) versus patients without irAEs. By specific irAE, G1-2 skin irAEs, thyroid dysfunction or pneumonitis were associated with improved OS. However, G3-4 pneumonitis and colitis were associated with worse OS. There was no association with hepatitis and OS by any grade. Findings were consistent across indications.

Conclusions: This is the largest analysis to date demonstrating correlation between irAEs and improved OS for atezolizumab by severity grade, and most common irAEs by organ. We identify that low-grade irAEs are significantly associated with improved OS, while specific high-grade toxicities are associated with poorer OS, underscoring the importance of early recognition and management of toxicity to further optimize benefit/risk balance of ICI therapy.

Clinical trial identification: NCT01846416, NCT02031458, NCT02008227, NCT02409342, NCT02366143, NCT02367794, NCT02763579, NCT02367781, NCT02657434, NCT01984242, NCT02420821, NCT02425891, NCT02108652, NCT02302807

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2033MO The impact of proton pump inhibitor (PPI) exposure before immune checkpoint inhibitor (ICI) therapy on overall survival (OS): A population-based study

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Background: PPIs have been previously associated with potentially negative impacts on ICIs outcomes due to changes in the gut microbiome. However, many studies were smaller studies with heterogeneity in study design, exposure windows and populations. Here, we performed a population-level retrospective cohort study evaluating the impact of PPI exposure prior to ICI on OS.

Methods: A cohort of cancer patients $\geq$ 65 years of age receiving ICIs from 06/2012 to 10/2018 in Ontario, Canada was identified from population-level administrative data and deterministically linked with databases to obtain socio-demographics, covariates and PPI prescription claims. Multivariable cox-proportional hazard models evaluated the impact of PPI exposure both within 1 year and 60 days prior to starting ICI on OS, adjusted for age, gender, body mass index, comorbidities, autoimmune history, hospitalization in the past year and treatment facility level at start of ICI therapy.

Results: Among 2737 patients, median age 73; 43% received Nivolumab, 41% Pembrolizumab and 13% Ipilimumab; 53% had lung cancer, 34% melanoma. Median PPI exposure for patients receiving PPI within 1 year (45%) and 60 days (26%) prior to ICI were 31 weeks (SD=19) and 10 weeks (SD=4) respectively; the most common PPI prescribed over 1 year was Pantoprazole (30%). Median OS estimate was 306 days. Any PPI exposure within 1 year (aHR=1.21 95% CI [1.09-1.33] $p<0.001$) or 60 days prior to ICI (aHR=1.26 95% CI [1.13-1.40] $p<0.001$) was associated with worse OS. A dose effect was seen based on weeks of PPI exposure 1 year (aHR=1.00 per week [1.00-1.01],p=0.05) and 60 days (aHR=1.01 per week [1.00-1.02] p=0.009) prior to ICI. PPI drug analysis only identified Pantoprazole exposure within 1 year (aHR=1.27 [1.14-1.41] $p<0.001$) and 60 days before ICI (aHR=1.34 [1.19-1.52] $p<0.001$) as being associated with worse OS. Subgroup analysis showed similar results for melanoma and patients receiving Pembrolizumab or Ipilimumab, and for Pantoprazole with lung cancer.

Conclusions: Exposure to PPIs prior to ICI therapy is associated with worse OS. Interventions aimed at altering the gut microbiome may be required to help improve outcomes for patients on ICIs with prior PPI exposure.

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2034MO EAGER: A randomized, controlled, multicenter trial of electro-acupuncture in gastric cancer patients undergoing adjuvant chemotherapy

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Background: Patients with gastric cancer experience quality of life (QoL) decline during adjuvant chemotherapy following gastrectomy. The EAGER (Electro-Acupuncture in Gastric cancER) trial was undertaken to confirm the efficacy of electro-acupuncture (EA) for improving QoL in these patients seen in our pilot study.

Methods: Patients who has accepted R0 resection for gastric cancer, and who will receive adjuvant chemotherapy were randomly assigned to high-dose EA (HA, 7 times each chemo-cycle for 3 cycles), low-dose EA (LA, 3 times each chemo-cycle for 3 cycles), or control (Ctrl) groups. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) was reported by the patients at baseline and then once a week during the therapy. Primary endpoint was the differences on total area under curves (AUCs) of FACT-Ga Trial Outcome Index (TOI) during the 3 cycles of chemotherapy, calculated by linear interpolation, among the groups. Secondary endpoints included the differences on AUCs of FACT-Ga Gastric Cancer Subscale (GaCS) scores, AUCs of FACT-Ga scores, and the disease free survival (DFS).

Results: Of the randomized 240 patients, 222 were analyzed according to intention-to-treat (ITT) principle, and 186 were in the per-protocol set (PPS). Both HA and LA produced significant QoL improvement. AUCs (21 days/cycle $\times$ 3 cycles, the higher, the better) of TOI in the ITT were 5678$\pm$1229, 5558$\pm$1226, and 4735$\pm$1233 (HA *vs.* Ctrl, $P<0.001$; LA *vs.* Ctrl, $P<0.001$), of GaCS were 3458$\pm$725, 3356$\pm$723, and 2919$\pm$726 (HA *vs.* Ctrl, $P<0.001$; LA *vs.* Ctrl, $P<0.001$), and of FACT-Ga were 8164$\pm$1516, 8024$\pm$1516, and 7029$\pm$1521 (HA *vs.* Ctrl, $P<0.001$; LA *vs.* Ctrl, $P<0.001$), in HA, LA, and Ctrl groups, respectively. EA also produced trend of DFS improvement, although not significantly in the ITT population [HA *vs.* Ctrl: HR=0.56 (0.27-1.15), $P=0.1089$; LA *vs.* Ctrl: HR=0.81 (0.59-1.12), $P=0.1979$], while the DFS differences in the PPS were significant [HA *vs.* Ctrl: HR=0.37 (0.15-0.92), $P=0.0258$; LA *vs.* Ctrl: HR=0.72 (0.51-1.02), $P=0.0582$].

Conclusions: EA resulted in a clinically meaningful improvement of QoL in gastric cancer patients undergoing adjuvant chemotherapy. Besides, EA was also associated with promising effect in prolonging DFS in these patients.

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2035P Routine biomarker monitoring does not replace comprehensive clinical assessment in the detection of immunotherapy induced myocarditis

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Background: Multiple international guidelines suggest that pre-treatment cardiac markers should be taken prior to each cycle of treatment to support the early diagnosis and treatment of immune checkpoint inhibitor (ICI) induced myocarditis (1). As a large regional tertiary cancer centre with an established cardio-oncology service early adoption of baseline and subsequent cardiac surveillance has been implemented and its utility evaluated.

Methods: A retrospective analysis of patients whom had undergone baseline cardiac assessment prior to receiving ICI treatment at the Clatterbridge Cancer Centre between October 2022 and March 2023 was performed. Within the regional protocol all patients with abnormal cardiac markers (Pro-B Naturetic Peptide (Pro-BNP) >400 ng/L and or a high sensitivity troponin T (TropT) >14 ng/L) were subsequently monitored with pre-cycle cardiac biochemical monitoring for the first 3 cycles of ICI treatment.

Results: 400 patients who commenced ICI treatment underwent baseline cardiac screening. Of these 169 patients (42.2%) had abnormal biomarkers: 36% (n=61) elevated TropT; 32% (n=54) elevated pro-BNP and 32% (n=54) had elevations in both. Within this cohort 3.3% (n=13) patients were diagnosed with ICI-induced myocarditis; 12 confirmed on cardiac MRI (cMRI) and 1 clinically diagnosed due to clinical instability. Of these 69% (n=9) patients had abnormal baselines and thus had pre-cycle monitoring; 4 did not. Of these 9; 8 were detected through symptoms alone; 1 patient was found to have elevated biomarkers but had already been clinically assessed prior to treatment and had been admitted prior to the biomarker results being reviewed.

Conclusions: Baseline cardiac assessment is useful, as the majority of patients that go on to develop ICI myocarditis have abnormal baseline values. However, the clinical utility of pre-cycle screening has not demonstrated enhanced or earlier detection of myocarditis compared to clinical assessment and represents an area of potential cost saving. Patients are either presenting mid-cycle or are identified via symptomatic review therefore investment is better placed in education and training to optimize clinical recognition and timely management.

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2036P Prevalence and risk evaluation of cardiovascular disease among newly diagnosed prostate cancer population in China

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Background: Cardiovascular disease (CVD) emerged as a leading death cause in prostate cancer (PC) patients in recent decades, bringing great disease burden globally. Men with preexisting CVD were at increased risk for major adverse cardiovascular events when treated with ADT. The prevalence and risk evaluation of CVD among the newly diagnosed PC population in China has remained a blank.

Methods: Clinical data of newly diagnosed PC patients was retrospectively collected from 34 centers in China. CVD was defined as myocardial infarction, arrhythmia, heart failure, stroke, ischemic heart disease and others. CVD risk was estimated by calculating Framingham risk scores (FRS). Patients were accordingly divided into low-risk, middle-risk and high-risk.

Results: A total of 4135 patients was enrolled in the present study, and 26.97% complained a current or history of CVD. The enrolled population distributed in 6 regions of China and about 70% patients lived in urban settings. With imaging and pathological evaluation, most of PC patients were diagnosed at late stage, with 20.80% local progression and 20.80% metastasis. Most of them initiated prostatectomy (46.48%) or regimens involving ADT therapy (45.83%) for prostate cancer. In the present PC cohort, 43.36% were hypertension patients and 50.81% of them lived with poor control of blood pressure. In patients with comorbid PC and CVD, 27.80% had two or more CVDs. With FRS stratification, as expected, higher risk of CVD was related with aging and metabolic disturbance. However, we also found that patients with treatment involving ADT presented an original higher risk of CVD than those without. That was in accordance with the clinical practice, i.e., aged patients or patients at late

oncological stage were inclined to accept systematic integrative therapy, instead of surgery. Among patients accepting medical castration, only 4.37% received GnRH antagonist in stark contrast to the grim situation of CVD prevalence and risk.

Conclusions: Prostate cancer patients in China are diagnosed at a later stage. Heavy CVD burden was presented at the initiation of treatment. Patients accepting ADT-related therapy occupied an original higher risk of CVD but the consciousness of cardiovascular protection was far from sufficient.

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2037P Prehabilitation as a strategy to improve postoperative outcomes in frail cancer patients undergoing elective surgery: A systematic review and meta-analysis

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Background: Prehabilitation is a process that aims to improve a patient's functional capacity before surgery. It may reduce postoperative complications and improve outcomes in cancer patients, particularly those frail. However, the effectiveness of prehabilitation in frail cancer patients undergoing elective surgery is not well understood. This systematic review and meta-analysis aimed to evaluate prehabilitation's effects on postoperative outcomes in frail cancer patients undergoing elective surgery.

Methods: Our search included electronic databases such as PubMed, Embase, and Cochrane and was conducted until January 2022. We had studies that compared a prehabilitation or preoperative optimization program to standard care, postoperative rehabilitation, or a placebo. The primary outcomes of interest were postoperative complications, length of hospital stay, 30-day mortality, and hospital readmission rate. We used R version 4.0.3 and the metafor and meta packages for statistical analysis.

Results: A total of 8 studies met the inclusion criteria for the meta-analysis, with 581 patients in the prehabilitation group and 675 patients in the control group. The results showed that prehabilitation was associated with a significant reduction in postoperative complications (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.69 to 0.98). Prehabilitation was also associated with a significant reduction in length of hospital stay (mean difference -2.32 days, 95% CI -4.34 to -0.29) and a non-significant reduction in 30-day mortality (RR 0.45, 95% CI 0.13 to 1.59). There was no significant difference in hospital readmission rate between the prehabilitation and control groups (RR 1.09, 95% CI 0.38 to 3.15).

Conclusions: Prehabilitation may improve hospital stay and reduce postoperative complications in frail cancer patients undergoing elective surgery. Further research is needed to confirm these findings and determine rehabilitation interventions' optimal duration and intensity. Clinicians need to consider the potential benefits of prehabilitation in caring for frail cancer patients preparing for surgery.

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2038P Perioperative iron deficiency in patients with ongoing cancer treatment scheduled for major surgery: A French prospective multicenter cross-sectional study

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Late withdrawal

2039P Primary endpoints of confirmatory randomized controlled trials for older patients with cancer: A scoping review

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Background: Reliable and validated primary endpoints, such as overall survival (OS), are commonly used in oncologic confirmatory randomized controlled trials (RCTs). However, recent studies suggest that these endpoints may not sufficiently measure the true benefits of therapies in older patients with cancer. We conducted a scoping review of the literature to identify primary endpoints used in geriatric oncology RCTs.

Methods: We searched the literature on confirmatory RCTs specific to older patients with cancer using PubMed (National Center for Biotechnology Information) and CINAHL (EBSCO). Studies fulfilling the selection criteria were reviewed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews, and definitions of primary endpoints were extracted.

Results: A total of 68 RCTs met the inclusion criteria. Data on geriatric assessment and quality of life (QOL) were extracted in 66 (97.1%) and 25 (36.8%) RCTs, respectively. Fifty-two RCTs (76.5%) used traditional outcomes, such as OS, DFS, relapse-free survival, progression-free survival, and response rate, as primary endpoints; however, one RCT used OS adjusted for QOL as a primary endpoint and one RCT used OS and health-related QOL as a combination primary endpoint. Three of the four RCTs using time-to-event endpoint as the primary endpoint included toxic effect as an event in addition to disease progression and death due to any cause. Toxic effect was a primary outcome measure in six RCTs (8.8%) which utilized the National Cancer Institute Common Terminology Criteria for Adverse Events. Health-related QOL, including the EORTC QOL Questionnaire core version 30 items, was a primary endpoint in three RCTs (4.4%). Barthel index for activities of daily living and the confusion assessment method for delirium were used in two RCTs (2.9%).

Conclusions: Although most geriatric oncology RCTs used traditional primary endpoints, some RCTs utilized innovative primary endpoints to more appropriately measure treatment benefit for older patients with cancer. This scoping review should be helpful for methodological discussions among investigators and efficient use of these endpoints.

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2041P The prevalence of hematologic adverse events (HAEs) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) in patients (pts) with advanced high grade ovarian carcinoma (aHGOC) receiving PARP inhibitor (PARPi), with or without a germline BRCA pathogenic variant

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Background: Pts with a germline BRCA pathogenic variant (gBRCA-PVs) and aHGOC report increased HAEs with platinum salts (PSs), for a possible more susceptibility of the hemopoietic stem cells to to DNA damaging agents. Also, MDS/AML cells seem to be enriched in g*BRCA*-PVs. The risk of PARPi-related HAEs and MDS/AML according to g*BRCA*-PV status in currently unknown.

Methods: We conducted a retrospective single-centre study to evaluate HAEs^{3}G2 and MDS/AML in pts with aHGOC receving PARPi, according to the presence of a g*BRCA*-PV. Pts included had received a PARPi as maintenance therapy for $\geq$8 weeks, in any line of therapy, from Feb 2017 to Dec 2022, and had known g*BRCA* status. HAEs were identified by electronic medical record review, classified per CTCAE v5.0 and expressed as proportion of patients with at least one event. Onset of AML/MDS was tracked also beyond the end of treatment with PARPi (possible later occurrence), up to the last follow-up. Correlative analyses were performed (significance at p-value$<$0.05).

Results: 166 pts were included: 95 (57%) had a g*BRCA*-PV. Patient characteristics, HAEs and MDS/AML are reported in in the table. At univariate analysis, g*BRCA*-PV status was not associated with PARPi-related HAEs, but was correlated with appearance of MDSs (9/95 vs. 1/71; p=0.04), which led to most of PARPi-discontinuations due to HAE/MDS/AML (12/95 vs. 2/71; p=0.02); 3/10 MDSs occurred during PARPi.

Table: 2041P Patient characteristics and HAEs

	gBRCA-PV+ N=95	gBRCA-PV- N=71	p
Age at baseline, mean (SD)	56.6 (8.9)	60.1 (9.9)	**.01**
Line of PARPi, median (IQR)	2 (1-3)	2 (1-3)	**.79**
Type of PARPi			<.001
Olaparib - %	61%	19%	
Niraparib - %	21%	29%	
Rucaparib - %	9%	1%	
Previous chemotherapy for other cancers - %	10	4	.79
N° of cycles of PARPi, median (IQR)	11 (8-24)	13 (6-22)	.34
HAEs - % of pts with at least one event			
Any HAE* ^{3}G2	47%	28%	.67
A ^{3}G2	33%	16%	.55
N ^{3}G2	20%	14%	.37
T ^{3}G2	10%	6%	.83
MDS/AML	10%	2%	.16
MDS	**9%**	**1%**	**.04**
AML	2%	1%	1.00
Hospitalization for HAE	3%	2%	1.00
Dose reduction for HAE	25%	16%	.61
Dose delay for HAE	30%	18%	.70
Discontinuation for HAE or MDS/AML	**11%**	**1%**	**.02**

*A (anemia), N (neutropenia) or T (thrombocytopenia).

Conclusions: Unlike PSs, g*BRCA*-PVs are not associated with PARPi-related HAEs in pts with aHGOC. MDSs are more frequent in g*BRCA*-PV carriers. The interaction between g*BRCA*-PV, MDSs and PARPi warrants further investigation.

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2042P Improving breast cancer outcomes for indigenous women

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Background: Breast cancer is the most diagnosed cancer affecting Australian women. While the incidence rate of breast cancer is lower in indigenous women than non-indigenous women the mortality rate is higher, with indigenous women 1.2 times more likely to die from the disease. The are many factors that contribute to this and if we want outcomes to improve for indigenous women with breast cancer, we must identify where practice and policy can change and improve. These findings may inform approaches for indigenous women in other high-income countries who experience similarly poor breast cancer outcomes.

Methods: This research employed the Context-Mechanism-Outcome (CMO) framework to reveal potential mechanisms and contextual factors that influence breast cancer outcomes for indigenous women. The framework explains generative causation, which helps to highlight the relationship between a context, mechanism, and outcome of a program or policy. The mechanisms and contextual factors were stratified into multiple levels; micro (interpersonal), meso (systemic), and macro (policy) levels. "If-Then-Because" statements were used to represent (broadly) the elements of CMO.

Results: The CMO framework allowed us to interpret evidence regarding indigenous women and breast cancer and provided nine practical ways to improve health outcomes and survival rates: 1. Improved health literacy regarding the importance of screening and early detection, delivered in a culturally safe way 2. Increased cultural safety and access to screening services 3. Presence of indigenous health service providers 4. Ensuring health service provider is local and/or familiar with indigenous culture and community 5. Culturally safe screening, diagnosis, treatment and follow-up settings 6. Local indigenous screening champions in the community 7. Protocols for abnormal results are tailored to local setting and community 8. Culturally safe support available for people who receive diagnoses 9. Policy is re-written in consultation with indigenous people and provides solutions to improve health outcomes.

Conclusions: Using the CMO framework, this study has provided nine practical measures to assist in improving the health outcomes for Australian indigenous women with breast cancer.

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2043P Can Charlson Comorbidity Index (CCI) and Clinical Frailty Scale (CFS) assessments predict survival in octogenarians with colorectal cancer?

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Background: Elderly patients are a heterogeneous group, ranging from fit to frail, with varying disease burden, comorbidities and ability to tolerate cancer-directed treatment. Defining treatment strategies in octogenarians with colorectal cancer (CRC) is challenging due to the high risk of complications and the likelihood of death from other causes. The aim of this study was to evaluate whether CCI and CFS can predict survival in octogenarians with CRC.

Methods: Patients aged 80 and over with CRC, seen at the Multidisciplinary tumor board at our center between January 2020 and December 2022 were evaluated in this study. CCI and CFS were calculated in all patients. Kaplan-Meier method was used to estimate the probability of 1-, 3- and 5-year survival rates (OS) regardless of treatment, and to compare OS estimates based on subjects' characteristics, CCI and CFS scores.

Results: We analysed 149 patients, median age 82 (range 80-91), with 53% of patients with stage IV CRC. Death was confirmed in 65 patients (44%) during follow-up. Following CFS scoring, patients were classified as frail (44%), pre-frail (45%) and robust (9%). The univariate 1-, 3- and 5-year survival rate estimates in frail group were 89%, 56% and 29%, and in robust/pre-frail group 92%, 85% and 64%. Median OS estimate in frail group was 13.24 months (5.35-21.13), and in robust/pre-frail 113.02 months (56.41-169.63), which was statistically significant, p$<$0.01. According to CCI scale patients were divided in groups that scored 1-5 (13%), 6-7 (28%), 8-10 (31%) and more than 10 points (24%). In these CCI groups, median OS estimates were as follows: 59.5, NR, 40.4 and 8.28 months, respectively, which proved to be statistically significant (p$<$0.019). A binomial logistic regression was performed to ascertain the effects of ECOG performance status (PS), CFS and CCI on the likelihood that participants will

survive 12 months. Of these three predictor variables, only PS was statistically significant in predicting 1-year survival in this model.

Conclusions: Geriatric assessments (CFS and CCI) were efficient in predicting survival in octogenarians with CRC, with potential implications for shaping the decision-making process for different treatment modalities.

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2044P Bloodstream infections (BSI) in cancer patients: Epidemiology, antibiotic therapy and risk factors related to mortality

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Background: BSI are a frequent and severe complication in cancer. Recent changes in oncological treatment, supportive care and development of new antimicrobial therapies could have affected its epidemiology, management and outcomes. Our aim is to describe clinical and microbiological features, antibiotic therapy, outcomes and mortality-related risk factors of BSI in cancer patients.

Methods: We performed a retrospective, observational, unicentric study. Microbiologically-confirmed BSI episodes in cancer patients between January 2017 and December 2021 were collected. We analysed clinical and microbiological data, empirical antibiotic treatment (EAT) and outcomes. A binary logistic regression model was used to detect variables related to 7 and 30-days mortality. P values <0.05 were considered significant.

Results: 438 episodes of BSI were documented in 362 patients. Most frequent neoplasms were pancreatobiliary (25.1%), colorectal (16.9%), lung (11.9%) and breast (9.1%) tumours. 78.1% were metastatic. 72.1% had received chemotherapy in the previous month. The most common sources of BSI were vascular catheters (26.9%), cholangitis (23.1%) and other abdominal infections (22.8%). Gram-negative bacteria (GNB) were isolated in 60.3% of cases and Gram-positive bacteria in 45.4%. Yeasts were isolated in 3.9% of cases. Most common organisms were *E. coli* (29.7%), *Klebsiella spp*. (15.1%), coagulase-negative staphylococcus (12.6%) and *S. aureus* (10.3%). Most used EAT was piperacillin/tazobactam (43.2%), followed by meropenem (18.3%), amoxicilin/clavulanic acid (16%) and vancomycin (14.8%). Adequate EAT was given to 76.3% of patients. Mortality at 7 and 30 days was 11.2% and 24.4%, respectively. Statistical analysis showed lung cancer, respiratory source, yeasts and *Pseudomonas spp*. as independent risk factors for 7 and 20-days mortality.

Conclusions: BSI is a severe complication associated to elevated mortality in cancer patients. Most frequent sources of BSI are vascular catheters, cholangitis and abdominal infections. Most of them occur in patients with metastatic digestive tumours and are caused by GNB. Lung cancer, respiratory infections, isolation of yeasts and *Pseudomonas spp*. could imply a worse prognosis.

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2045P Patient Reported Outcome Measures (PROMs) capturing therapy adherence of cancer patients: A systematic literature review

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Background: The success of cancer therapy relies on patient adherence, which refers to the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider (WHO 2003). Several PROMs were developed to measure patient adherence to (cancer) therapy. In light of this, our study aims to offer a comprehensive overview of PROMs in the cancer field, with a specific focus on the adherence dimensions captured.

Methods: A systematic review of systematic reviews was performed to identify studies of cancer patients that apply PROMs to measure adherence without restriction to the type of therapy. Databases of Pubmed and Embase were searched up to March 2022 and studies were selected based on predefined eligibility criteria. A qualitative synthesis was used determining measurement of adherence and dimensions of PROMs according to the WHO definition for adherence.

Results: After screening 4483 results a total of 56 literature reviews were included capturing 1064 studies that focused on cancer patients. Out of the 56 literature reviews included in our final analysis, the majority (45) focused on medication adherence, while 18 studies assessed adherence to dietary recommendations, and 13 studies examined adherence to lifestyle changes. Three studies investigated other dimensions of adherence. Data collection was primarily carried out via questionnaires and most studies applied self-developed, non-validated PROMs. PROMs mainly measured one dimension of adherence, even though the content of items were overlapping between medication, diet and lifestyle.

Conclusions: This systematic literature review provides a comprehensive overview of PROMs used to assess adherence in oncology. Our analysis highlights the predominance of studies measuring medication adherence and underscores the need for greater attention to other dimensions of adherence. Our findings can inform the choice of PROMs to monitor patients' adherence in clinical practice and enhance health outcomes.

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2046P The importance of communicating bad news in medical education

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Background: Effective communication between doctors and patients is crucial, especially when delivering bad news that can impact a person's present and future expectations. However, acquiring optimal skills in breaking bad news requires the incorporation of multiple professional competencies that are acquired gradually through years of training. The purpose of this study was to conduct a systematic review of existing literature on medical education programs and interventions aiming to improve communication skills and to critically evaluate the effectiveness of such training.

Methods: We conducted a systematic review following PRISMA guidelines, searching PubMed and Scopus databases at February 2023, using the key words "medical education," "breaking bad news," and "end of life communication."

Results: Our search yielded 21 relevant studies, with 12 randomized studies indicating improvements in trainees found in PubMed, while four Scopus studies referred to workshops and seminars that increased participants' confidence in various communication areas. Furthermore, eight studies referred to training courses on communication techniques that helped medical students and health professionals develop confidence in breaking bad news skills. One study utilized interactive theater and role-play with professional actors to teach breaking bad news to medical students, which can be a potentially powerful tool for teaching breaking bad news during medical education. One study showed that the COVID-19 pandemic has disrupted health education due to social distancing.

Conclusions: Our findings suggest that training physicians at the undergraduate and postgraduate levels in communication skills for breaking bad news can be beneficial for both physicians and patients. However, limitations exist in reaching definitive conclusions. As digital learning has emerged in healthcare education during the post-

COVID-19 period, digital solutions have also been examined for training in the communication of bad news.

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2047P Neutrop: A descriptive, observational study for G-CSF prescription in daily practice

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Background: Despite significant advances in prevention and treatment, febrile neutropenia (FN) remains a common and serious complication of chemotherapy. Leverages data related to G-CSF use are missing. This study aims to (1) describe the practices of G-CSF treatment implementation; (2) identify and measure the decision criteria related to their implementation in patients with breast (BC), lung (LC), or gastrointestinal cancers (GIC), in ambulatory settings, beyond the usual recommendations.

Methods: This non-interventional, cross-sectional, multicenter study required clinical cases presented using conversational interfaces (chatbot), simulating a conversation with one or several virtual interlocutors by voice or text exchange.

Results: The questionnaire was completed by 102 physicians. Most practitioners (84.5%) reported prescribing G-CSF, regardless of tumor type (Table). G-CSF was prescribed more frequently for adjuvant/neoadjuvant therapy than for metastatic cases. Leading factors motivating the prescription were chemotherapy regimen, comorbidities, and age (in 56.7% of cases). Access to care was cited as a reason to prescribe G-CSF.

Table: 2047P Levels and reasons of G-CSF prescription in all 3 cancer types

		Breast cancer	Lung cancer	Gastro Intestinal cancer	Total
Implementation of a G-CSF treatment N (%)	N	77	57	60	194
	Yes	68 (88.3%)	42 (73.7%)	54 (90.0%)	164 (84.5%)
	Not	9 (11.7%)	15 (26.3%)	6 (10.0%)	30 (15.5%)
What should be considered before prescribing a G-CSF for this patient? N (%)	N	68	42	54	164
	Chemotherapy Protocol	23 (33.8%)	9 (21.4%)	7 (13.0%)	39 (23.8%)
	Chemotherapy Protocol + comorbidities	12 (17.6%)	2 (4.8%)	8 (14.8%)	22 (13.4%)
	Chemotherapy Protocol + Age	2 (2.9%)	6 (14.3%)	2 (3.7%)	10 (6.1%)
	Chemotherapy Protocol + comorbidities + age	31 (45.6%)	25 (59.5%)	37 (68.5%)	93 (56.7%)

Conclusions: Our findings suggest that ESMO recommendations are broadly followed. In most cases, G-CSF is prescribed in early stages and in curative intent. Despite a large use of G-CSF, education about febrile neutropenia and risk factors should be disseminated to a wide audience.

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2048P Frequency and clinical relevance of drug-drug interactions with oxycodone among patients with cancer

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Background: Oxycodone is known to have numerous drug-drug interactions (DDIs) that can potentially decrease efficacy or lead to adverse drug reactions (ADRs). However, there is limited research on the frequency of DDIs associated with oxycodone use in patients with cancer. In this study, the frequency and pharmacological and clinical relevance of DDIs between oxycodone and perpetrators were studied in patients with cancer.

Methods: A cross-sectional study was conducted using pharmacy records to study the concomitant use of oxycodone and DDI perpetrators. These perpetrators were registered from oxycodone use trajectories between 1 September 2021 and 1 September 2022 in the Deventer Hospital by consulting Lexicomp®, Micromedex®, the Dutch Kennisbank and the Dutch Commentaren Medicatiebewaking. The clinical relevance of the identified perpetrators was examined by a clinical pharmacologist and a medical oncologist. Additionally, the frequency of multiple interactions was studied.

Results: In 254 oxycodone trajectories, 227 (89.4%) were found to include at least one pharmacologically relevant perpetrator. Of these, 210 (82.7%) were clinically relevant. A total of 80 different pharmacologically relevant perpetrators were identified, with 65 (81.3%) being considered clinically relevant. Interactions were observed in 21 (8.3%) oxycodone trajectories. Dutch compendia generally classified DDIs with oxycodone as less relevant compared to Lexicomp and Micromedex.

Conclusions: A high frequency of pharmacologically and clinically relevant perpetrators of DDIs with oxycodone was observed in our cohort. Moreover, a high number of double interactions involving oxycodone was found. Revision of drug interaction compendia used in Dutch healthcare in accordance with international compendia is recommended to improve pharmacovigilance.

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2049P Osimertinib-related muscle cramps as a common adverse event: A real-world data analysis in the post-approval setting

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Background: Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) that is the standard of care treatment for non-small cell lung cancer (NSCLC) with EGFR driver mutation. Some of the most common treatment-related adverse events (TRAEs) are rash, diarrhea, nausea, paronychia, and stomatitis. This abstract aims to describe muscle cramps as TRAEs associated with osimertinib use.

Methods: EGFR mutant NSCLC patients using osimertinib were included. Data were collected during pharmaceutical consultations and remote telemonitoring between January 2016 and April 2023. In all consultation modalities, drug interactions, drug reconciliation, adherence to treatment using the Morisky Medication Adherence Scale (MMAS) tool, classification and grading of TRAEs according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 were evaluated.

Results: A total of 88 patients were included. Mean age was 68 years and 71% were female. The pharmacist performed medication reconciliation and analysis of drug interactions in all patients and 99% of them showed good adherence to treatment. In the evaluation of TRAEs, 29% reported muscle cramps, with 19% of the sample developing grade 2. The median onset of the event was 2 months after starting osimertinib. Around 57% of the patients had diarrhea, which was managed early after the initial symptoms. Therefore, the occurrence of muscle cramps was not related to hydroelectrolytic unbalance due to diarrhea. The main osimertinib registration studies did not report muscle cramps as TRAEs.

Conclusions: In our cohort muscle cramps were very common TRAEs associated with osimertinib use and have not been directly related to diarrhea. It is an underreported adverse event that can impact on quality of life. Pharmaceutical follow-up is strategic for post-marketing surveillance, playing an important role in identifying new TRAEs. Update on muscle cramps as a very common TRAEs for osimertinib is required to develop supportive measures in conjunction with the multidisciplinary team, support clinical data and add to regulatory agency records.

Clinical trial identification: Research Ethics Committee approval CAAE: 19918319.1.0000.5533.

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2050P Integrating ayurveda herbs with standard of care for management of cancer or cancer treatment related anorexia

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Background: Anorexia is the fourth common symptom seen in half of newly diagnosed cancer patients. It also remains most prevalent and troublesome clinical problem experienced by patients with cancer during and after chemotherapy. Consequently, anorexia adversely influences nutritional status of a patient which further causes a negative impact on quality of life and survival. Various herbs have shown to be having positive effect on treating anorexia. In this study, we analysed the effect of an Ayurveda formulation consisting standardised dry powders of 5 herbs indicated in Ayurveda for treatment of Anorexia.

Methods: We did an assessment of study variables related to anorexia, cachexia and quality of life in a heterogeneous group of stage IV cancer patients (n=45) receiving conventional therapies for cancer and complaining of anorexia. These patients were administered herbal capsule "Ruchir" for treatment of Anorexia. Ruchir is consisting dry herbal powders of Pomegranate (*Punica grantum*), Black pepper (*Piper nigrum*), Ginger (*Zingiber officinale*), Amla (*Phyllanthus emblica*), Cumin (*Cuminum cyminum*). Therapy response on Anorexia was assessed using AC (Anorexia/cachexia subscale) and its impact on quality of life was assessed using Functional Assessment of Anorexia / Cachexia Treatment (FAACT). Weight was recorded at each visit (day 0, day 30, day 90, and day 180) using digital weighing scale. Statistical significance was assessed using nonparametric Wilcoxon Signed Ranks Test.

Results: The mean age of study participants were 64.54 (±5.6) years. Significant improvement was observed in Anorexia sub scale score ($P < 0.01$) and quality of life ($P<0.05$) as compared to baseline. No significant change was observed in weight. Treatment was well tolerated by all patients.

Conclusions: Herbs used in this study have been shown to have significant effects in reducing anorexia and improving quality of life in a heterogeneous group of cancer patients. This study provides preliminary evidence about effectiveness of herbs in treating Anorexia in cancer patients. Further controlled studies in a homogenous group of patients are warranted to integrate herbs with a standard of care in cancer patients for management of Anorexia.

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2051P E-PRO within comprehensive companion program for patients undergoing systemic cancer treatment to reduce emergency visits and inpatient admission in a Peruvian institution

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Background: The implementation process, characteristics and objectives of the companion program have been previously reported. Briefly, the program consisted of a web containing an e-PRO questionnaire platform with real time monitoring for early symptom detection and intervention, a communication channel for resolving doubts and educational resources on diagnosis, treatment and adverse events. We aimed to determine the impact of the program in terms of reduction of emergency visits (ERV) and non-planned inpatient admissions (NIA).

Methods: Case-control analysis of patients with gastrointestinal cancer receiving systemic treatment (chemotherapy, immunotherapy, targeted therapy or combinations) at Oncosalud between June 2021 and July 2022. Patients were divided into two cohorts according to enrollment into the companion. Incidence rate (IR), IR ratios (IRR) and 95% confidence intervals were calculated. Time to first ERV and NIA curves since enrollment were constructed using the Kaplan Meier method and log rank test.

Results: In total, 199 patients were included, 97 enrolled into the program (cases). Mean age was 61.4 (±13.2), 50.3% were women and 94% were in ECOG 1-2. Chemotherapy was the most common treatment (88.4%). There were no differences in these characteristics between groups. The mean follow time was of 8.3 and 6.7 months, for cases and controls respectively. A statistically significant reduction in incidence rates was observed for both outcomes. ERV IR was 20.3 ERV per month in controls (95% CI:17.0-24.0) vs 15.1 ERV per month in cases (95%CI:12.6-18.0) which translated into a 25% decrease in ERV (IRR: 0.75 (95%CI:0.58-0.96; p=0.02)). NIA IR was 9.2 NIA per month in controls (95%CI:7.0-11.8) vs 5.9 NIA per month in cases (95%CI:4.4-7.8) which translated into a 35% decrease in NIA (IRR: 0.65 (95%CI:0.44-0.96; p=0.02)). There were no differences in time to first event for both outcomes.

Conclusions: The results demonstrate that e-PRO monitoring within a comprehensive companion program for cancer patients undergoing systemic treatment achieves clinical benefits as it reduces ERV and NIA. Its potential impact on outcomes and costs is being evaluated and will be reported.

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2052P Adverse events in FLOT chemotherapy for locally advanced gastric cancer: An observational study of pre- and post-operative toxicity profiles

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Background: Fluorouracil plus leucovorin, oxaliplatin and docetaxel (FLOT) is the standard of care for perioperative chemotherapy in resectable locally advanced gastric cancer (LAGC) in Europe. As a triplet combination, FLOT may be associated with increased toxicity. Therefore, it is crucial to investigate whether patients experience similar toxicities before and after surgery. This study aims to evaluate the toxicity profile of FLOT chemotherapy.

Methods: This observational, longitudinal, retrospective study included patients diagnosed with LAGC and treated with FLOT chemotherapy in a Portuguese medical oncology department between January 2018 and December 2020. Adverse events were classified according to Toxicity Grading CTC-AE version 5.0.

Results: Forty-seven patients with LAGC treated with FLOT chemotherapy were included in this study. The median age at diagnosis was 59.3 years (SD 8.1), and the majority of patients were male (n=29, 61.7%) with an ECOG PS of 0 (n=41, 87.2%). During the first four cycles of FLOT given before surgery, a total of 56 adverse events of any degree were observed, with 8 (17%) patients requiring treatment delay and 4 (8.5%) patients requiring dose reduction. In the 5th to 8th cycles given after surgery, there were 62 adverse events of any degree, with 13 (27.7%) patients requiring treatment delay and dose reduction. Notably, the toxicity profile differed between the pre and post-operative periods. In the first 4 cycles, the most common adverse events were nausea (n=16, 28.6%), emesis (n=9, 16.2%), and diarrhea (n=6, 10.7%), mostly with grade 2 toxicity. In the postoperative period, the main adverse events were neutropenia (n=23, 37.1%), nausea (n=6, 9.7%), and neuropathy (n=6, 9.7%). Grade 3 and 4 neutropenia occurred in 15 and 2 patients, respectively. Forty-two patients completed 8 cycles of FLOT.

Conclusions: The observed differences in toxicity between the pre- and postoperative periods highlight the importance of tailoring the treatment approach based on the patient's individual needs. Efforts to minimize dose reduction and chemotherapy delay should be made to maximize the effectiveness of FLOT therapy. Limitations of this study include the lack of data on long-term toxicity.

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2053P Dehospitalization through outpatient drug release in clinical pharmacy as a strategic cost-minimization action in a public oncology hospital in the Eastern Amazon: A quantitative analysis

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Background: In recent decades, the home care initiative has expanded in the health system, mainly linked to hospitals. The mismatch between available financial resources and advances related to cancer therapy requires projects to improve cost minimization processes.

Methods: The variables collected for each sector were described through monthly totals and averages per year. To verify the existence of an association between expenses with material, medication and chemotherapy and the cost avoided with

monthly dehospitalization, Pearson's correlation coefficients and their respective p-values were calculated. Spending on medication and total spending on material, medication and chemotherapy were related to the amount avoided using linear regression models, in order to estimate the effect of increased spending on medication on avoided costs. The same procedure was performed to estimate the effect of increased costs on bed turnover, using linear regressions, and on the number of days of hospitalization avoided per month, using Poisson regression.

Results: Pearson's coefficients confirm a relationship, with a positive sign, between expenses and avoided costs with early dehospitalization, showing a perfect positive relationship between the variables, with a statistically significant p-value. Effect of expenses on total costs with hospitalization avoided on General Hospitalization, Coefficients - Amount spent on medication:100.36; 95% CI (14.26, 186.45); p-value= 0.02. By the linear model, the total avoided cost with discharges was $795,204.52 in the three-year period from 2020 to 2022, for a total of 3,722 avoided hospitalization days and an average cost avoided with discharges of $70,146.06. Effect of expenses on the days of hospitalization avoided (Poisson regression) was statistically significant in all variables (p-value<0.001).

Conclusions: All tests - Pearson Correlation coefficients, Poisson regression, and Generalized Linear Model (p<0.05) confirmed the hypothesis that the discharge managing with outpatient drug release has a significant effect on the final cost avoided with cancer hospitalization.

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2054P Metastatic cancer patients hospitalized at initial diagnosis: When does rescue systemic therapy make sense? ONIRIS - A national, prospective study

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Background: Little is known about metastatic cancer patients who are hospitalized at diagnosis because of impaired performance status and/or severe symptoms. This study aims to explore their prognosis and the effect of systemic anti-neoplastic treatment (SANT) initiation on their outcomes.

Methods: A prospective multicentric study of adult inpatients with a newly diagnosed metastatic solid tumor was conducted in seven cancer-facilities in France. During a three-month follow-up, socio-demographic characteristics, response rate and duration of response for patients receiving SANT, length of hospital stay and survival were collected. Correlation with clinical prognostic and predictive factors was analyzed.

Results: 107 patients were included from November 2021 to April 2022. Seventy-four (69%) underwent SANT. Median overall survival was 1.7 months for the entire cohort. Forty (37%) were alive at 3 months, including 39 patients that started SANT. Factors associated with the initiation of a SANT were young age (OR=0,94 [0,90; 0,98]), low Charlson Comorbidity Index (OR=0,56 [0,42; 0,73]), SANT initiated at patient's or caregiver's request (OR=0,07 [0,02; 0,17] and 0,17 [0,06; 0,42], respectively). Patients with biomarker-based targeted therapy had better outcomes at 3 months, while survival of patients treated with exclusive immunotherapy was poor. PALLIA-10 score superior to 5 was a significant predictive factor for mortality (HR=3,24; p<0,001).

Conclusions: Metastatic cancer patients hospitalized at the time of diagnosis share a similar poor survival. The initiation of SANT does not always impact their outcomes. Larger prospective studies with longer follow-up are needed to better assess the effect of SANT in this population.

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2055P Multidisciplinary Tumor-ICU Board: Enhancing care for critically Ill patients with solid tumors in the ICU

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Background: Patients with solid tumors frequently experience complications that may require ICU admission. The advent of new cancer treatments such as has added complexity and potential adverse events, which frequently mimic severe infections or critical disorders. Therefore, there is a need to evaluate patients with solid tumors in the ICU from multiple perspectives. We aim to establish a Multidisciplinary Board to customize diagnostic and treatment approaches for critically ill patients with solid tumors in the ICU, through a comprehensive evaluation by ICU, Hematology (HEM), Infectious Diseases (ID), and Medical Oncology (MO) specialists.

Methods: Specialists from the Vall d'Hebron ICU, ID, and MO meet weekly to discuss prospectively clinical evolution, how to tailor treatments and further diagnostic steps of patients with solid tumors admitted to the ICU.

Results: From January to April 2023, 46 patients with solid tumors were evaluated by the ICU-Tumor board. The majority (65%) were male, with a median age of 62 years. Gastrointestinal tumors accounted for 44% of the cases, followed by lung cancers (17%), head and neck tumors (11%), and other malignancies (28%). Overall, 17% of the patients were receiving potentially radical treatment (NA or ADJ treatment), and 83% presented with metastatic disease. Respiratory failure (65%), septic shock (11%), metabolic disturbances (10%) and other events (14%) were the most frequent reasons for ICU admission which were caused by infectious events (51%), treatment toxicity (22%), and cancer-related complications (27%). Median time admitted at the ICU was 10 days (1-83 days). The Board's most common recommendations included diagnostic procedures (50%, biopsy or radiological evaluations) therapeutic interventions (30%) (antibiotic, immunosuppression or start chemotherapy in the ICU), and limiting treatment intensity (10%). Mortality within the ICU was 10%, and 30-day mortality was 39%.

Conclusions: The Multidisciplinary ICU-tumor Board's recommendations range from diagnostic to therapeutic interventions and can lead to improved outcomes and tailor therapeutic strategies for these critically ill patients, particularly with the increased complexity of new cancer treatments and complex infections.

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2056P Hospitalization, reconsultations and mortality in the field of oncological emergencies: Who is at higher risk?

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Background: The wider availability of oncological treatment and the improved survival of cancer patients have increased the frequency of emergency consultations and their impact on healthcare. The aim of this study was to investigate the variables that influence hospital admission, re-consultation and clinical outcomes among oncology patients who seek emergency care.

Methods: Single-center, observational and prospective study. We analyzed a sample of 554 oncology patients who consulted in the Emergency Deparment during regular office hours between March-22 and March-23. Statistics: Chi-squared test to assess association between variables. Kaplan-Meier curves and log-rank test for survival analysis. Significance level: p-value <=0.05.

Results: The baseline characteristics of the study participants were: 50.2% females, 21.5% lung cancer, 68.8% stage IV, 25.8% consulted for digestive symptoms, 37% were hospitalized and 16.4% reconsulted in the following 15 days. The overall median survival was 54 weeks. Factors that were associated with a higher likelihood of hospitalization were lung cancer (26.9% of admissions), stage IV (80.7%), monotherapy chemotherapy (CT) (36.3%), first-line treatment for metastatic disease (40.9%), ECOG 2 (36.8%), digestive symptoms as reason for consultation (29.2%) and complications secondary to the tumor itself as definitive diagnosis (32.2%). Factors significantly associated with a higher likelihood of reconsultation within the following 15 days were lung cancer (19.3% of reconsultations), monotherapy CT (38.6%), ECOG 1 (42.1%) and infectious pathology and complications secondary to the tumor itself (28.1% each one). Factors significantly associated with lower overall survival were hospital admission (median: 16 weeks, 95% CI 3.7-28.2), diagnosis of complications secondary to the tumor itself (median: 11 weeks, 95% CI 10.3 - 23.6) and reconsultation (median: 17 weeks, 95% CI 10.3-23.6).

Conclusions: Among oncology patients admitted to the Emergency department, complications secondary to the underlying oncological disease represent the most relevant variable in the field of oncological emergencies due to their impact on the likelihood of hospitalization, reconsultation and survival.

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2057P Prevalence of frailty in long-term prostate cancer survivors after radical prostatectomy and its association with quality of life and emotional health

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Background: Aging-related deficits that eventually manifest as frailty are emerging as an important determinant for quality of life and emotional health in older patients with cancer. Prevalence of frailty in long-term prostate cancer survivors and its impact on quality of life have not been investigated so far. The objective of the current study was (I) to assess the prevalence of frailty and (II) to elucidate the relationship between frailty, quality of life and emotional health in long-term prostate cancer survivors after radical prostatectomy.

Methods: 2979 prostate cancer survivors from the multicenter German Familial Prostate Cancer Database were included. Patients completed the following standardized patient-reported outcome measures of interest: frailty (Groningen Frailty Indicator, GFI), quality of life (EORTC QL2), and emotional health (anxiety/depression symptoms, PHQ-4). Chi-square tests and Wilcoxon-Mann-Whitney tests were used to detect differences of selected variables between frail and non-frail patients. Associations were assessed using multiple linear regression analysis.

Results: The patients' mean age was 79.4 years (SD = 6.4) and mean time since radical prostatectomy was 17.4 years (SD = 3.8). 33.1% (985/2979) of patients were classified as frail (GFI $\geq$4). Regarding mental health and quality of life, frail patients reported more often symptoms of depression (24.0% vs. 4.0%; p<0.001) and anxiety (20.6% vs. 2.0%; p<0.001) as well as lower quality of life (M = 53.4 (SD = 19.2) vs. M = 72.7 (SD = 16.0); p<0.001) compared to non-frail patients. Frailty was significantly associated with depression (OR 1.68; CI 1.49-1.89), anxiety (OR 1.75; CI 1.55-1.97), lower quality of life (OR 0.72; CI 0.67-0.77), higher age (OR 1.04; CI 1.03-1.07), and a missing partnership (OR 1.83; CI 1.37-2.45).

Conclusions: Every third long-term prostate cancer survivor after radical prostatectomy was frail. The associations with lower quality of life and poorer mental health indicates the need for an integrated care approach including further geriatric assessment and possible interventions to improve health outcomes of these patients.

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2058P Reducing waste to improve sustainability and affordability of cancer treatment: Redispensing unused oral anticancer drugs

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Background: Strategies targeting oral anticancer drug (OAD) waste are required to improve sustainability and affordability of these expensive treatments frequently remaining unused by patients. This study aims to quantify waste reduction, cost-savings and environmental impact obtained by redispensing unused OADs compared to standard practice of disposal.

Methods: A prospective, single-arm intervention study was conducted in four Dutch hospitals. Eligible patients were $\geq$18 years, diagnosed with cancer and prescribed an OAD. During twelve months, participants received OAD packages sealed with a time-temperature indicator. If unused, OADs were returned to the pharmacy where quality was assured by checking authenticity, shelf life and storage temperature. OADs of verified quality were redispensed to other patients. Waste reduction was expressed as the percentage returned OADs that were redispensed. Mean annual cost-savings per patient were costs of redispensed OADs minus operational expenses from a healthcare perspective. Impact on environmental indicators was assessed via a cradle-to-grave Life Cycle Assessment. Patient subgroups associated with positive cost-savings were identified with multiple logistic regression. Scenarios analyses on the effect of optimized quality assurance and patient population selection was performed.

Results: 1,071 patients participated, median age 70 years (IQR: 62—75) and 41.9% female. 224 OAD packages (1.7%) of 128 patients (12.0%) were redispensed (2.4% of total drug costs), reducing waste by 68.1% and providing mean annual cost-savings of €576 per patient (95% CI: 444—709). Optimizing quality assurance and targeting patient subgroups (< 24 months OAD use/using targeted therapies) could increase mean annual cost-savings up to €1,348 (1,039 — 1,697) per patient. Waste reduction was associated with mean annual environmental benefits of >1 kg CO_2 per patient, but only with an optimized quality assurance procedure a net beneficial impact on environmental indicators was achieved.

Conclusions: Redispensing unused OADs reduces waste substantially, generates cost-savings and can benefit environmental impact, improving sustainability and affordability of cancer treatment.

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2059P The impact of a dental oncology clinic for patients (pts) prescribed bone-modifying agents (BMA) in a cancer centre

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Background: Two decades ago medication related osteonecrosis of the jaw (MRONJ) was first described in oncology pts receiving BMAs. Pre-existing dental disease is the main initiating factor for MRONJ. Dental disease is the commonest global non-communicable disease. We assessed the impact of integrating a dental oncology service for all incident pts prescribed BMAs.

Methods: A dental clinic was established in March 2022 collocated with a cancer centre and all pts receiving BMAs were assessed by an oral surgeon prior to BMA administration and all necessary dental treatment was completed.

Results: 120 pts included (66% female), 66 were <65 years, were treated over 1 year. 82 pts had metastatic disease. Early stage breast cancer (N=35), metastatic breast cancer (N=36), prostate cancer (N=24), and other malignancies (N=25) were represented in this cohort. 118 pts were planned for intravenous zoledronate and 2 were planned for denosumab. 117 pts were deemed dentally fit to commence their BMA. 29 pts were current smokers, and 24 pts wore dentures. 45 pts had a current dental complaint on presentation, for which 31 complaints related to pain and infection. Assessment of barriers to dental services; 20 pts live alone, 42 pts were not registered with a dentist, and 51 hadn't seen their dentist in ≥3 yrs. 8 pts had intraoral smoking related changes, and moderate dysplasia was identified in 1 pt following a biopsy. The Decayed, Missing and Filled Teeth (DMFT) index median score was 18, and mean DMFT score was 19. 88 pts had a periodontal status of ≥Stage 2 Grade B which demonstrated longstanding and active periodontal disease. The mean bleeding on probing score was 35% and 75 pts had a high Caries Risk Assessment score. 65 pts required an operative dental procedure. 33 pts received a dental restoration, of which 16 pts required a median of 2 dental restorations. 58 pts had teeth extracted, of whom 37 had a median of 3 teeth extracted.

Conclusions: This oncology cohort had poor engagement with dentistry and had a high burden of dental disease prior to BMA treatment. The data highlights their dental treatment needs prior to BMA treatment and the requirement for proactive dental integration by the oncology team. Dental care should be an integral part of multidisciplinary cancer care.

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2060P Prevalence and predictor of poor mental adjustment to cancer before lung cancer surgery

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Background: The aim of the study is to identify the prevalence and predictors of mental adjustment to cancer in patients who were going to resect lung for non-small cell lung cancer in Korea.

Methods: A total of 697 patients were recruited from September 2021 to October 2022 and completed a survey questionnaire of the Korean version of Mini-Mental Adjustment to Cancer (K-Mini-MAC) which higher mean score denote worse mental adjustment, except for positive attitude (PA) domain. Multivariable logistic regression was analyzed to determine potential predictors of poor adjustment to cancer for each domain of K-mini-MAC, which was defined by the mean score of 2.5 or higher, while PA domain was defined by mean score of 2.5 or lower.

Results: The mean age of study population was 63.2 ± 0.4 years old and 50.4% was male. The proportion of poor mental adjustment was 6.0% (Helpless/Hopeless [HH] domain), 29.6% (Anxious Preoccupation [AP] domain), 19.1% (PA domain), and 30.1% (Cognitive Avoidance [CA] domain). The mean score of each domain was 1.60 ± 0.02 (HH), 2.17 ± 0.02 (AP), 2.83 ± 0.02 (PA), and 2.62 ± 0.02 (CA). Younger age (<65 years old, aOR 1.78, 95% CI 1.15-2.76) and having comorbidity (aOR 1.64, 95% CI 1.09-2.45) were associated with poor mental adjustment in AP domain, while current alcohol drinking was associated with better mental adjustment in AP domain (aOR 0.56, 95% CI 0.32-0.96, vs. non-alcohol drinker). Poor mental adjustment in PA domain was predicted based on Lower education level (≤ middle school, aOR 1.97, 95% CI 1.12-3.46; high school, aOR 2.31, 95% CI 1.23-4.36, vs. ≥ university). There was no significant predictor for mental adjustment in HH and CA domain.

Conclusions: Younger, non-alcohol drinker, having comorbidity and lower educational level was associated with a poor adjustment to cancer. Interventions to help with adjustment to cancer should be focused particularly on these group.

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2061P Network analysis of comprehensive concerns in patients with cancer: Differences between the sexes

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Background: Patients' concerns have become more complicated, while the advancements in cancer treatments have improved clinical outcomes. This study aims to comprehensively explore the concerns of cancer patients and to elucidate their interrelationships.

Methods: A fact-finding survey was conducted with 300 cancer patients (male; 127, female; 173) using a 74-item questionnaire. The questionnaire included comprehensive items (rated from 0 [none] to 3 [severe]) related to the concerns of cancer patients. Correlation network analysis was performed to visualize the association between the patients' concerns. Degree centrality was used to assess network centrality, and the Girvan−Newman algorithm was used to detect communities.

Results: Cancer types were as follows: breast cancer (n=84), gastrointestinal cancer (n=82), urologic cancer (n=52), cholangiopancreatic cancer (n=44), gynecologic cancer (n=20), and others (n=18). The mean overall score was significantly higher in females than in males (30.4 vs. 22.5, $p<0.01$). The most frequent concerns were physical decline (81.7 %), fatigue (80.5 %), muscle weakness in the limbs (65.9 %). In the overall network, the concerns with the highest centrality score were muscle weakness in the limbs (0.151), nutritional management (0.123) and fatigue (0.082). The network was classified into three communities: 1) physical decline, including 21 items such as muscle weakness, nutritional management, and fatigue; 2) changes in appearance, including 8 items such as pigmentation and hair loss; 3) social support, including 11 items such as employment and finances. The network analysis by gender showed that the highest centered item was sex life (0.123) in men, and depression (0.137) and anxiety (0.110) in women.

Conclusions: This study illustrated that cancer-related fatigue and weakness were the most frequently and numerous interrelated concerns that plagued patients with cancer. Furthermore, they formed a wide-ranging network with other concerns. Our study also showed that the structure of the network differed between the sexes. A multidisciplinary approach may be necessary to comprehensively solve interrelated patient concerns.

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2062P The psychological distress (PsyD) evaluation in pancreatic cancer (PC) patients (pts): A mono-institutional analysis

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Background: PsyD is frequent in cancer pts and it negatively affects their treatment and quality of life. However, psychological screening is not extensively performed and few data about its impact are available. The aim of our study is to evaluate baseline PsyD in PC pts treated at our Institution and its correlation with clinicopathological features.

Methods: In the last year, we baseline evaluated PsyD of PC pts starting chemotherapy at our Institution, using the Distress Thermometer (DT) and Problem List (PL). The DT score was divided into three levels: no/minimal (0-3), moderate (4-6) and high (7-10) distress. PL was grouped into 6 categories (practical, physical, cognitive, spiritual/religious, emotional and family problems). Clinicopathological characteristics were collected and correlated with PsyD.

Results: A total of 86 PC pts were tested for baseline PsyD. The median age was 65 years, 63% were female, ECOG PS was > 1 in 56% of pts and 72% of pts had one or more comorbidities. The majority of pts (67%) received chemotherapy for metastatic disease. Regarding psychological screening, 31%, 29% and 40% of pts had no/minimal, moderate and high DT score, respectively. According to PL we observed: practical problems in 17% of patients, physical in 9%, cognitive in 42%, spiritual/religious in 9%, emotional in 16%, and family problems in 13% of patients. Regarding psycho-oncological care, 93% of pts received initial counseling, 63% intervention and follow-up.

No significant association between DT score and PL groups with clinicopathological characteristics was observed.

Conclusions: Our mono-institutional analysis showed that the majority of PC pts receiving chemotherapy at our Institution presented a PsyD scored as moderate (29%) or high (40%) by DT at baseline. According to PL, the main problem concerned the cognitive sphere, specifically problems related to concentration and/or memory and self-perception. Additional analyses, including the impact of PsyD on treatment compliance, tolerability and prognosis are going.

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2063P Lifestyle changes as cancer treatment: It is time to get specific with our patients

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Background: In this study we seek to learn more about the lifestyle habits of our cancer patients, with a particular emphasis in exercise and eating behaviours. We choose to focus on these two areas as they have an outsized impact on clinical outcomes such as mortality, risk of relapse, quality of life, sarcopenia, duration of hospitalizations, post-surgical complications, response to immunotherapy and even overall survival rates.

Methods: Observational study across a cross-section of cancer patients at the Medical Oncology Service of the Nuestra Señora de Candelaria University Hospital, Santa Cruz de Tenerife. The statistical significance of lifestyle habit changes is tested through a form and IPAQ, MUST, and SARC-F surveys using chi-squared tests.

Results: We involved 100 patients whose average age was 61 years. 46% of patients had lung cancer, 30% breast cancer and 10% gastrointestinal cancer. 59% patients had stage-four cancer, 48% were receiving first-line treatment and 54% were being treated with immunotherapy or target therapies. 99% of individuals considered their diet as an important pillar in their cancer disease. However, we found that only 47% had discussed aspects of their nutrition with their oncologist, but this was not statistically associated with a reduced risk of malnutrition. 80% considered that a healthy lifestyle could help reduce the adverse effects of the treatment. The validated test results showed that 45% had an intermediate-high risk of malnutrition according to the MUST test and 14% had risk of sarcopenia according to the SARC-F test. Patients receiving immunotherapy or target therapies had a higher risk of malnutrition than those receiving other treatments (50 vs 42%, p=.507). 47% were sedentary according to the IPAQ test and 80% who did not perform physical activity would start an adapted exercise program if it were available.

Conclusions: Our patients present good high-level awareness about the generally positive ways in which lifestyle changes involving healthier eating and exercise habits can impact the outcome of their treatments. However, we appreciate a need for more specific nutritional and fitness recommendations that patients can immediately put into practice, as well their ranked impact on their health.

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2064P Hospitalisation of patients with cancer: Identifying points for improvement in patient care in a university hospital in Spain

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Background: Hospitalisation is an inevitable step in the evolution of many patients with cancer, principally in advanced tumors. This study aims to describe the admissions to a medical oncology inpatient service of our University Hospital between November 2022 and April 2023.

Methods: We conducted a retrospective cross-sectional study of patients admitted to the Medical Oncology Service of Infanta Sofía University Hospital (Madrid) along six months. Database was collected from the electronic health records. The following variables were analyzed: age, sex, type of tumor, stages, origin of the admission, period of hospital stay, diagnoses, assessment by another specialities, type of discharge and readmissions.

Results: In the chosen period, 310 hospitalisations related to 223 patients were studied, because some of them were readmitted in these six months. The average age was 71.49 years, 42.9% women and 57.1% men. The average hospital stay was 10.18 days. Near 77% of the patients had advanced disease. In order of frequency, patients with lung (28.06%), colorectal (15.8%) and genitourinary (11.94%) cancer represented the most of inpatients. Mainly the patients were admitted from the Emergency Department of our Hospital (56.45%). The most prevalent reason for hospitalisation was secondary symptoms of disease progression. Infections were the cause of admission in 24.52% of the cases and 27.42% of them were from respiratory system. Other causes to take into account were the toxicity to the treatment (5.8%). As part of the multidisciplinary approach, during their hospitalisation, 5.26% inpatients required surgical assessment. Interventional radiologists treated 1.29% patients and endocrinologists providing nutritional support in 10.65% of cases. Furthermore, less than 2% of our patients were admitted to the Intensive Care Unit. Palliative Care Unit assessed 37.74% of the inpatients, which 19.35% were being previously followed-up by them. Unfortunately 15.8% of the admitted patients died. We also observed 26.45% had to be admitted again.

Conclusions: It is important to identify the reasons why patients with cancer are admitted to the Hospital because it could help to identify areas for improvement in the quality of care.

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2065P Communication on the first medical oncology appointment: What do cancer patients want?

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Background: Beyond the diagnosis, multiple situations during the natural history of cancer can be pointed out as stressful and hard to convey. The first Medical Oncology appointment is crucial and comprehensive, where patients are invited to understand their diagnosis and grasp the prognostic consequences of cancer and its treatment. Strategies to elicit information while meeting patients' needs are required to overcome the potentially challenging moment, improve clinical outcomes and promote safe, high-quality, patient-centred care. This study evaluated the communication preferences at the first medical oncology approach.

Methods: A total of 169 cancer patients from a Portuguese Medical Oncology department answered the C-FAQ (Communication in first medical oncology appointment questionnaire), a survey representing the SPIKES and MPP (Measure of Patients' Preferences) protocols asking about preferences regarding Content (what and how much information is told), Facilitation (where and when the information is conveyed), and Support (emotional support during the interaction) elements of communication and patient's assign to these items.

Results: The Content elements (M=3.69, SD=0.35) were mentioned as the most important when compared with Facilitation (M=3.56, SD=0.39), $t(30.13) = 17.38$, $p < .001$, or Support (M=3.46, SD=0.44), $t(24.14) = 7.12$ $p < .001$. The physician's knowledge, honesty and being given clear information about cancer and treatment were the areas of greatest importance. Facilitation was considered more important than Support, $t(24.14) = 16.42$, $p < .001$. Globally, all items were mostly evaluated as "very important", Mdn 65.85% (11.525).

Conclusions: All communication components should be considered during the dialogue in this context. Medical teams should overcome barriers by learning skills to communicate with patients and promote engagement. More research is required to understand the complexity of the triad patient, physician, and family and address how patients' preferences can be met in a demanding clinical atmosphere.

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2066P Evaluation of the quality and reliability of ChatGPT and Perplexity's responses about rectal cancer

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Background: This study aimed to assess the usefulness of ChatGPT and Perplexity's responses to frequently asked questions regarding the diagnosis and treatment of rectal cancer.

Methods: Both artificial intelligence systems were asked 20 questions covering disease risk factors, screening, symptoms, treatment, and treatment side effects. In accordance with the ESMO patient guides, the questions were posed in the order specified. According to ESMO patient guide recommendations, responses were graded as "appropriate," "inappropriate," or "insufficient."

Results: While ChatGPT provided appropriate responses to 17 of the questions (85%), the responses to two questions (10%) were deemed inappropriate, and the response to one question (5%) was deemed insufficient. Nineteen (95%) of Perplexity's responses were deemed appropriate. It was determined that both artificial intelligence systems responded improperly to the nutrition question.

Conclusions: The study's findings indicate that ChatGPT and Perplexity provide patients with accurate information about rectal cancer. The accuracy rate of Perplexity was found to be higher than that of ChatGPT. It can be demonstrated that the benefit of Perplexity is that it displays the source for each piece of information. However, especially cancer patients require emotional and psychological assistance, and further research is required to determine the impact of these artificial intelligence systems on the patient's psychology. Moreover, given the complexity and individuality of medical care, AI chatbots should not be viewed as a replacement for medical professionals, but rather as a supplement that can help patients gain access to trustworthy information and support. Overall, this study contributes to the growing body of literature on AI chatbots and their potential use in cancer by highlighting both the advantages and disadvantages of these technologies.

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2067P Influence of psychiatric disorders on survival in patients with lung cancer: Real-world data

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Background: Although the psychological burden of patients with malignant diseases is marked as one of the main aspects in the disease trajectory, anxiety and depression are still unmet need in practice. To determine influence of Anxiety and Depression on survival in patients with diagnosed lung cancer (LC) after 7 years survival follow up (SFU) period.

Methods: During the period January 2014 to May 2015 patients with LC were rated themselves on Hospital Anxiety Depression Scale (HADS). Subjects with history of psychiatric disorders and/or undergone curative surgical procedure were excluded from the study. Last SFU was done on February 28th 2023.

Results: Out of 298 screened patients 206 were included in SFU. Majority of included subjects were male 156 (75.7%), ECOPG PS 1 153 (74.3%), smokers 120 (58.3%) in Stage III 88 (42.7%) and IV 85 (41.3%) with diagnosed lung adenocarcinoma 95 (46.1%) followed by sqamouse cell LC 79 (38.3%) and SCLC 28 (13.6%). Psychiatric disorder was verified in 81 (39.3%) subjects. Out of those depression was found in 35 (43.2%) anxiety in 7 (8.6%) and combined anxiety and depression in 39 (48.2%) subjects. One-year survival was 66,5%, 3-year 26,2%, 5- year 14.1% and 7-year 8.7%. Difference in survival rate was observed between subjects with and without disorders in 1-, 3-, 5- and 7-years survival rate (61.7% vs. 69.6%; 19.8% vs. 30.4%; 11.1% vs. 16.0% and 4.9% vs. 11.2% respectively). Statistically significant difference was found in survival time between subjects with and without psychiatric disorders (25.9 vs. 49.5 Months; p=0.046). The lowest survival time was observed in group with combined anxiety and depression (21.2 Months) followed by only depression or anxiety (30.3 Months) in comparison with subjects without disorders (49.5 Months) (p=0.033).

Conclusions: Based on the results of this research, psychiatric disorders are highly prevalent and also affect the survival time of patients with LC. Despite the evidences psychological aspect is still neglected in patients with diagnosed malignancies. Easy-to-use tools for determination of anxiety and depression such as HADS should be applied regularly in clinical practice in order to recognize those disorders and to introduce adequate treatment.

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2068P Perspectives and concerns on sexuality among adolescents and young adults treated for testicular germ cell tumour: The PRICELESS-study - A qualitative study

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Background: Sexual dysfunction is a frequently seen late effect in patients treated for testicular germ cell tumour (TGCT). Therefore, monitoring of sexual dysfunction is essential. The Utrecht Symptom Diary (USD) helps monitoring cancer symptoms, but items regarding sexuality are missing. Adding these symptoms may provide a better tailored tool, enhance monitoring of late effects on sexuality, and might help to address this topic. Therefore, the aim of this study was to explore perspectives and concerns on late effects regarding sexuality among adolescents and young adults (AYAs) being treated for TGCT to adapt the USD to make it suitable for follow-up care for these patients.

Methods: Individual, semi-structured interviews were conducted with thirteen AYAs from one centre of expertise for TGCT in the Netherlands. Patients were purposively sampled and using maximum variation. Data was analysed using Braun and Clark's thematic analysis.

Results: Interviews revealed seven overarching themes which interact and overlap: fulfilment to have children, rediscover sexuality, insecurity about sexual performance, acceptance of physical change, loss of masculinity, burden on relationship, and need to talk about sexuality. Concerns related to the fulfilment to have children seems to play a major role.

Conclusions: Results help to better understand these men's thoughts and experiences related to late effects regarding sexuality and gives healthcare professionals the opportunity to act on these topics by discussing it in the consulting room. Partner involvement seems beneficial.

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2069P QoL changes of caregivers during first-line palliative chemotherapy for patients with incurable cancer

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Background: We previously reported the impairment of quality of life (QOL) of caregivers of patients with cancer (ann. oncol. 2019, vol.30 supple 9, IX142). A multifaceted longitudinal survey is warranted to establish a valid support system.

Methods: This single-institution prospective cohort study was conducted with the approval of the ethical committee of Ina Central Hospital. 48 pairs of patients with incurable cancer and their caregivers filled out questionnaires according to the Japanese version of EORTC QLQ C-30 before the initial session of the first and the second-line treatment. Patients: 31 men and 17 women with an average age of 68.3±10.6 years. Caregivers: 17 men and 31 women with an average age of 63.5±11.6 years. Primary sites of cancer: gastrointestinal system in 41 patients, lung in 4, head and soft tissue in 2 and neck in 1. Average duration of treatment: 228 ± 171 days, median 161 days. The influence of the treatment outcome ("responder with RECIST PR and CR" or "non-responder with SD and PD") and duration ("shorter than 161 days" or "longer") on the scales were investigated statistically.

Results: All the nine symptomatic scales of EORTC QLQ-C30 were positive in around 20% in caregivers before treatment. After treatment, fatigue (88%), pain (42%), and financial concerns (43%) scales changed more frequently. The emotional function (EF) and cognitive function (CF) scales showed no significant differences in patients and caregivers before and after treatment, unlike other comprehensive scales. The scale declined in 38% of caregivers in physical function, 15% in role function, 33% in emotional function, 28% in cognitive function, 33% in social function, 29% in global health, and 42% in summary score. EF and CF decreased by almost the same proportion in patients and caregivers. The duration and outcome of treatment did not have a correlation with changes in the scales of caregivers.

Conclusions: Consistent insufficiency of emotional and cognitive function in caregivers, similar to that in patients, was revealed throughout the treatment. The outcome and duration of treatment did not affect the caregivers' mental condition. Caregivers of patients with cancer require emotional and cognitive function support throughout the patients' treatment.

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2070P Assessment of healthy lifestyle habits in breast cancer patients

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Background: Healthy lifestyle habits such as avoiding overweight, engaging in moderate physical activity for at least 150 minutes per week, and getting good quality sleep have not only been shown to decrease the incidence of certain cancers, but also have a clear impact on the outcome of patients diagnosed with breast cancer. Adherence to these recommendations has an impact on quality of life, and some studies suggest their beneficial effect on patient survival.

Methods: We included 181 patients diagnosed with breast cancer in different stages, Multivariable ambulatory circadian monitoring of skin temperature, motor activity, light exposure, and sleep patterns was performed for 7 consecutive days through a small watch-like device called Kronowise 3.0. The patients are divided into 3 groups: group 1 includes metastatic patients, group 2 consists of patients with early-stage breast cancer undergoing chemotherapy, and group 3 comprises patients with early-stage breast cancer under follow-up (more than 1 year after the completion of chemotherapy).

Results: The table describes the mean age with standard deviation, physical activity categorized as patients who achieve $\geq$ 150 minutes of moderate physical activity (MPA) per week, $\geq$ 300 minutes of moderate physical activity per week, $\geq$ 75 minutes of vigorous physical activity per week, patients with good sleep hygiene (between 7 and 9 hours of sleep per day), patients with $<$ 10 hours of sedentary behavior, and the percentage of patients with overweight and obesity in each group.

Conclusions: Despite breast cancer patients not being sedentary and having higher levels of moderate physical activity compared to the general population, the occurrence of vigorous physical activity is quite low among these patients. It is imperative to establish proper sleep hygiene in these patients in order to improve parameters and reduce the rates of overweight and obesity, particularly among the metastatic population and long-term survivors, where these rates are significantly higher.

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2071P Identification of top issues and concerns of cancer patients in Korea on social media

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Background: The objective of this study is to identify the major issues and concerns of cancer patients in Korea related to cancer, anti-cancer therapy, and patient care that are mentioned on social media.

Methods: We collected data from open-access forums, blogs, and social networking sites using professional ISO 20252 certified online access tools. We searched the terms "cancer", "cancer treatment", and "patient care" and collected social media posts between October 2021 and September 2022, excluding spam and advertisements.

Results: Total 169,575 social media posts were collected. Among the posts, 51% were related to cancer symptoms, concerns following diagnosis, and cancer etiology, while 39% discussed treatment methods, treatment-related side effects, novel therapies, as well as costs. The remaining posts centered on how to manage in daily life. The most frequently mentioned cancer types were breast, lung, colorectal, stomach, and liver cancer, consistent with common cancers in Korea. Concerning the difficulties experienced, 52% reported physical challenges, 42% reported emotional challenges, and 6% discussed daily life issues, such as diet and sexual relationships. Additionally, patients had high expectations for immune checkpoint inhibitors. Patients tend to view clinical trial participation as an alternative when conventional treatments are ineffective and see it positively as a way to participate without financial burden. However, some express safety concerns. Patients frequently shared tips for managing daily life on social media, such as healthy eating, taking supplements, and light exercise to maintain physical strength.

Conclusions: Our findings suggest that cancer patients in Korea frequently use social media for information. The high frequency of emotional difficulties mentioned indicates that patients face persistent emotional challenges throughout the cancer journey. This study underscores the potential benefits of analyzing social media posts by cancer patients, providing valuable insights for healthcare professionals and patients. Moreover, it emphasizes the importance of the developing and delivering professional information on daily life management for cancer patients.

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Table: 2070P

	Median Age	MPA ≥ 150 min	MPA ≥ 300 min	Vigorous activity ≥ 75 min	Sedentariness < 10 hours	Median night sleep (hours)	Median BMI	BMI 25-30	BMI ≥ 30
GROUP 1	57 ± 9	65%	45%	4%	90%	7.5	25.53	21%	20%
GROUP 2	50 ± 7	88%	73%	15%	100%	6.7	23.26	15%	5%
GROUP 3	55 ± 10	89%	79%	20%	100%	6.5	26	20%	17%

2072P Topical application of mixed agents to reduce oral mucositis during radiotherapy in post operated head and neck cancer

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Background: Oral mucositis is a debilitating condition seen in head and neck cancer(HNC) patients treated by radiotherapy(RT). The aim of study was to evaluate the response of combined new oral agents as local applicant to prevent mucositisand to record the change in mucositis grading during and after RT.

Methods: Sixty threepatients of post-operative HNC planned for adjuvantRT were randomized to treat mucositis by soda bicarbonate gargles only (Control arm: n=30) 4-5 times a day or soda bicarbonate gargle along with new agent comprised of five drugs (ORA-5GEL): one tablespoon each of honey, choline salicylate ointment(8.7w/w), and lignocaine ointment(2%w/w), one tablet of fluconazole 150mg and metronidazole 400mg were mixed to form a paste and applied intraorally starting from 2nd week of RT (Study arm:n=33).

Results: Severity of mucositis was found to be either stable or in downgrading trend after the application of the ORA-5 gel. None of the patients had grade3 mucositis in study arm compared to 15 patients in control arm. Grade 1 mucositis was seen in 64% and 97% of patients at the end of week 3 that progressed to grade 2 in 27% and 70% patients study and control arm, respectively, by the end of 4thweek ($p<0.001$). On univariate analysis, factors associated with higher mucositis grading were: high disease burden (Stage IV), conventional RT technique and concurrent chemotherapy. In study arm reversible trend of grading was observed in this subset of patients also. With the continuous use of soda bicarbonate gargle and symptomatic treatment, the frequency of grade 3 mucositis in control arm decreased, however, there was significant difference in grading in both the groups till week 7($p<0.001$). By the end of the treatment, none of the patients in control arm had grade 0 mucositis compared to 73% in study arm.

Conclusions: ORA-5 GEL effectively acts on all stages of mucositis and prevents not only severity and progression in all patients but also shows reversible grading during RT.

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2073P Medical cannabis: A potential effective treatment for chemotherapy-induced peripheral neuropathy (CIPN)

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Background: Medical cannabis is extensively used by Israeli cancer patients, mostly in the form of natural extracts. We've previously shown that cannabis can alleviate symptoms of Oxaliplatin induced CIPN. Yet, it is still unknown which cannabis component, either tetrahydrocannabinol (THC) or cannabidiol (CBD) contribute to this effect and at which dose.

Methods: A database of 5,063 medical records consecutive patients of medical cannabis clinic ('Tikun Olam') was reviewed. 802 patients reported CIPN related symptoms and 751 met inclusion criteria were included in the analysis. Data included questionnaires regarding Patient Reported Outcome (PROM), Activities of Daily Living (ADL) and Quality of Life (QOL) filled before and six months after cannabis use. Four CIPN symptoms were observed. Improvement was defined as positive change from baseline score. Two patients' clusters were identified using k-mean clustering method to study the association between THC, CBD and change in symptoms, ADL and QOL: CBDhigh/ THClow and THChigh/ CBDlow doses.

Results: Symptoms frequency before cannabis use: paresthesia (549pts, 73%), burning sensation (358pts, 48%), numbness (235pts, 31%) and cold sensation (146pts, 19%). After cannabis use improvement reported in paresthesia (320pts, 58%), burning sensation (217pts, 60%), numbness (112pts, 47%) and cold sensation (67pts, 45%). Burning and cold sensation improvement was 37% and 15% in THChigh compare to 27% and 8% in CBDhigh cluster ($p=0.02$ and $p=0.008$, respectively). ADL and QOL change were higher in THChigh cluster ($p=0.03$ and $p=0.006$, respectively).

Conclusions: The use of natural extracts of cannabis can effectively alleviate CIPN symptoms and improve both QOL and ADL with suggested advantage to high THC levels. Further analysis is required to better correlate specific symptoms to specific components.

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2074P Oral cannabidiol for prevention of chemotherapy-induced peripheral neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is experienced by 37−84% of patients during and/or after end-of-treatment and often results in discontinuation of anti-neoplastic treatment and impairment of health-related quality of life. Cannabidiol (CBD) has shown preventive effects in CIPN animal models without compromising chemotherapy efficacy.

Methods: Patients with cancer referred for adjuvant treatment with capecitabine and oxaliplatin (CAPOX) or carboplatin and paclitaxel (Carbo-Tax) were recruited to participate in the CINCAN-2 study. CBD oil was self-administered two times daily (300 mg daily oral dose) for 8 days total at each cycle of chemotherapy, beginning 24 hours before start of chemotherapy. Patient reported outcomes (EORTC-CIPN20) were captured before start of chemotherapy and at follow-up until one year after end-of-chemotherapy. Vibration Perception Thresholds (VPTs) were collected at 32, 125 and 250Hz on patient dominant hand and at 8, 32, and 125Hz on the patient dominant foot. Controls were obtained from a similar cohort (CINCAN-1) receiving the same chemotherapy regimens, but no CBD.

Results: From March to December 2021, 54 out of 65 eligible patients were recruited. CINCAN-2 patients were significantly older (median age 64 vs 57 years, $p=0.004$) compared to the CINCAN-1 cohort. Patients treated with CBD showed significantly better VPT scores than patients not receiving CBD at 3, 6 and 12 months follow-up. The largest VTP difference was found in patients treated with Carbo-Tax and CBD at 32Hz in metatarsal V at 12 months with -1.86 Z-score, CI-95=[-3.16;-0.49] compared to patients who did not receive CBD. Patients treated with CAPOX and CBD scored significantly better in PRO scores at 3 and 6 month follow-up (-6.75 [-11.54;-1.98] and -9.25 [-13.91;-4.58] points respectively compared to patients treated with CAPOX only. No difference in PRO scores was observed for patients treated with Carbo-Tax. Patients receiving Carbo-Tax and CBD received significantly higher cumulative doses of paclitaxel (1737mg vs 1194mg, $p=0.027$) compared to patients receiving Carbo-Tax only.

Conclusions: Patients treated CBD showed better long term PRO and VPT outcomes than controls. A randomized trial is warranted.

Clinical trial identification: NCT04582591.

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2075P MW05, a novel, long-acting recombinant human serum albumin/human granulocyte-colony stimulating factor(I) fusion protein for the management of chemotherapy-induced neutropenia: Results of a phase III trial

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Background: MW05 is a novel, long-acting recombinant human granulocyte-colony stimulating factor, which is produced by fusion of N terminal of highly active modified G-CSF with C terminal of human serum albumin(HSA). We report results from a randomized, double-blind, phase III study comparing the efficacy and safety of MW05 to approved PEG-rhG-CSF(Jinyouli®) for preventing chemotherapy-induced neutropenia.

Methods: Patients with breast cancer were randomized 2:1 to receive MW05 or PEG-rhG-CSF after standard docetaxel plus cyclophosphamide with/without doxorubicin chemotherapy for 4 cycles. The primary objective was to evaluate the non-inferiority of MW05 to standard PEG-rhG-CSF in duration of severe neutropenia (DSN; Grade 4) in cycle 1.

Results: Eligible patients were randomized to the groups(MW05, n=328; PEG-rhG-CSF, n=164). In cycle 1, the mean DSN was 0.24 days for MW05 and 0.25 days for PEG-rhG-CSF, and the mean difference of DSN[−0.02(95%CI: -0.12, 0.08)days] met the primary endpoint of non-inferiority. In cycle 2-4, the results of DSN were consistent with cycle 1. The incidence of Grade 4 neutropenia in MW05 group was lower than that in PEG-rhG-CSF group, representing 16.5%, 3.0%, 2.7%, 3.4% for MW05 and 19.5%, 9.8%, 6.7%, 6.1% for PEG-rhG-CSF in chemotherapy cycle 1-4 respectively. The incidence of febrile neutropenia(FN) across all cycles was numerically low and not significantly different between two groups, with 7 patients (2.1%) in MW05 group and 6 patients (3.7%) in PEG-rhG-CSF group. Other efficacy endpoints and adverse events results were comparable between two groups. There was 1 death during the study, which was not related to study drug treatment.

Conclusions: These results demonstrate non-inferiority and comparable safety for MW05 versus PEG-rhG-CSF. As a novel, long-acting rhG-CSF modified with HSA, MW05 can effectively shorten DSN induced by chemotherapy and may reduce the incidence of FN and severe neutropenia.

Clinical trial identification: NCT04554056.

Legal entity responsible for the study: Mabwell (Shanghai) Bioscience Co., Ltd.

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Disclosure: P. Wang: Financial Interests, Personal, Full or part-time Employment: Mabwell (Shanghai) Bioscience Co., Ltd. All other authors have declared no conflicts of interest.

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2076P Topical diclofenac for prevention of HFS in patients receiving capecitabine monotherapy: An exploratory subgroup analysis of the D-ToRCH phase III trial

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Background: Hand foot syndrome is a distinct side effect associated with capecitabine. Celecoxib, a cyclooxygenase (COX 2) inhibitor is the only drug effective in randomized trials. However, its use in clinics has declined due to concerns regarding cardiac safety. In our trial, we describe the use of topical diclofenac for prevention of HFS in patients receiving capecitabine monotherapy.

Methods: The D torch trial randomized 264 patients with breast or GI cancers receiving capecitabine to apply either 1% topical diclofenac or placebo gel. Stratified permuted variable size block randomization was done using a computer-generated random numbers sequence. The primary objective was to compare the incidence of grade 2 or higher HFS in diclofenac and placebo arms. Secondary objectives were incidence of any grade HFS, capecitabine dose reduction due to HFS and adherence with application. Here, we report the results of the monotherapy subgroup.

Results: 108 out of 264 patients received capecitabine monotherapy (56 in diclofenac arm and 52 in placebo arm). Baseline characteristics were well matched in both arms. The study group's median age was 47 years (IQR 39.5-57.5). Majority were females (n=101, 93.5%). 67 patients (62%) had an ECOG performance status of 0-1, while the rest were PS 2. 95 patients (87.9%) had carcinoma breast and the remaining 13 patients had various gastrointestinal cancers. 63 patients (58.9%) and 41 patients (38.3%) had stage 3 and 4 disease respectively, whereas only 3 patients (2.8%) had stage 2 cancer. Overall, 12 patients developed grade 2 or higher hand foot syndrome, of which 2 were in diclofenac group and 10 were in placebo group (3.6% vs 19.2%, p=0.01). Any grade HFS was seen in 3 patients (5.4%) in diclofenac arm and 12 patients (23%) in placebo arm (p=0.008). Dose reductions of capecitabine were less frequent in the diclofenac arm compared to placebo (3.6% vs 19.2% p=0.01). Adherence to topical treatment was more in the diclofenac group compared to placebo (93.2% vs 82.2%, p=0.04).

Conclusions: Topical diclofenac gel significantly reduced the incidence of HFS in patients receiving capecitabine monotherapy. Topical diclofenac gel application led to less frequent dose reductions of capecitabine.

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Legal entity responsible for the study: The authors.

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2077P A randomized, placebo-controlled trial assessing the efficacy and safety of the combination of superoxide dismutase, alpha lipoic acid, vitamin B12, B1, B2, B6, E, Mg, Zn and a fatty acid for 6 months in the management of chemotherapy induced neuropathic pain

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Background: To investigate the efficacy of Superoxide Dismutase (SOD, 70 UI), Palmitoyethanolamide (PEA, 300 mg) Alpha Lipoic Acid (ALA, 300 mg),vitamins B6 (1.5 mg), B1 (1.1 mg), B12(2.5 mcg), E (7.5 mg), Nicotinamide (9 mg) and minerals (Mg 30 mg, Zn 2,5 mg) in one tablet in managing neuropathic pain due to cancer chemotherapy.

Methods: In this pilot study, 67 age-matched patients with cancer (41 men) and a mean age of 65.4 years were randomly assigned, either to receive the combination of ten elements (2 tablets/24h) in the active A group, (n=33), or the placebo B (n=34) for six months. Nerve function was assessed by DPN Check [sural nerve conduction velocity (SNCV) and amplitude (SNAP)]. Sudomotor function was evaluated with SUDOSCAN, which measures electRochemical skin conductance in hands and feet (ESCH and ESCF). We used Pain questionnaires: Pain Detect (PD), Neuropathic Pain Symptom Inventory (NPSI), and Visual Analog Scale (VAS) for the estimation of neuropathic pain, also. All patients received Taxanes and platinum analogs as cancer chemotherapy.

Results: At follow-up, measurements from SNCV, SNAP, ESCH and ESCF did not change significantly in both groups. In A group PD baseline vs. final (9.57±7.0 vs. 6.78±4.16, p=0.003), NPSI (28.51±21.26 vs. 19.87±12.6, p<0.001) and VAS (27.78±22.40 vs 21.48±17.79, p=0.003) improved significantly during follow up. In group B PD (7.03±5.19 vs. 9.71±6.61 p<0.001), NPSI (23.50±18.99 vs. 36.25±22.15, p<0.001), and VAS (25.03±23.83 vs 38.75±26.60 p<0.001) deteriorated. No side effects detected.

Conclusions: The combination of the ten elements as supplement in one tablet for six months at a daily dose of two pills in patients improved neuropathic pain due to cancer chemotherapy.

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Disclosure: All authors have declared no conflicts of interest.

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2078P Evaluation of chemotherapy-induced nausea and vomiting beyond the delayed phase: Results of a survey of healthcare providers in Japan

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Background: Chemotherapy-induced nausea and vomiting (CINV) occurs in two arbitrarily defined phases: the acute phase (from 0 to 24 h following chemotherapy (CT) initiation) and the delayed phase (from 24 to 120 h). Almost all antiemetic studies have therefore evaluated efficacy to 120 h after the administration of CT, and the period beyond 120 h is generally perceived to be relatively free of CINV, with some studies reporting continued nausea beyond the delayed phase.

Methods: In July and September of 2022, healthcare providers (HCPs) in Japan were recruited to complete an online quantitative survey. All HCPs were required to work with patients receiving anticancer CT in the hospital setting and have experience selecting, preparing and/or administering antiemetics. As part of this survey responses were collected on whether HCPs had patients who experienced nausea/vomiting (CINV) during Days 5-7 (beyond the delayed phase) after initiation of CT. Responses were also captured by CT regimen; for the physician subset, respondents were grouped by and analyzed only if they were prescribers of the chemotherapy type.

Results: A total of 809 HCPs (174 pharmacists, 102 nurses and 533 physicians) completed the survey. The physician group was comprised of breast surgeons (n = 57), pulmonologists (n = 107), gastroenterologists (n = 74), GI surgeons (89), gynecologists (n = 98), ENTs (n = 54), and oncologists (n = 54). The vast majority of

respondents (98%, 93%, and 88% of pharmacists, nurses, and physicians, respectively) indicated they had patients who experienced CINV 5-7 days after CT. Of the HCPs reporting patients with CINV on Days 5-7, the highest proportions were seen for cisplatin, AC and EC chemotherapy regimens (Table).

Table: 2078P Proportions of respondents with patients experiencing CINV on days 5-7 by chemotherapy regimen

CT Regimen	Pharmacists	Nurses	Physician Prescribers
Cisplatin	78%	71%	80%
Epirubicin/cyclophosphamide (EC)	50%	43%	43%
Anthracycline/cyclophosphamide (AC)	44%	45%	42%
Carboplatin	37%	43%	48%
Irinotecan	41%	37%	37%
Oxaliplatin	36%	32%	28%

Conclusions: This survey highlights a need for continued assessment of CINV beyond the delayed phase after CT to better understand the incidence and to optimize prevention of CINV for the entire period of risk.

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2079P Naloxegol for the treatment of opioid-induced constipation in patients with cancer pain: A pooled analysis of real-world studies (NALOPOOL)

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Background: We aimed to evaluate the efficacy and safety of naloxegol for opioid-induced constipation (OIC) in cancer patients in a real-life setting.

Methods: We pooled individual patient data from three multicenter observational studies conducted with naloxegol in cancer population. Efficacy outcomes included: response rate at week 4 ($\geq$3 spontaneous bowel movements [SBM] per week and an increase of $\geq$1 from baseline); clinically relevant improvement (>0.5 points) in the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) and in the Patient Assessment of Constipation Symptoms (PAC-SYM); and clinically relevant improvement in the Bowel Function Index (BFI $\geq$ 12 points at the endpoint). All analyses were performed using a visitwise approach. Homogeneity was assessed with Cochran's Q test.

Results: 393/427 patients were included in the pooled efficacy/safety analyses, with a median age of 64 years and a slight predominance of males (53%). Lung (25%), breast (18%), prostate (9%) and head & neck (6%) were the most common tumor locations. 66% of the patients had metastases, and 53% were receiving chemotherapy. The most common opioids were fentanyl (43%), oxycodone (39%) and morphine (28%), with a median treatment duration of 8.9 weeks. Most patients (83%) received an initial dose of naloxegol of 25 mg and 86% were receiving laxatives at baseline. Efficacy outcomes are presented in the table. Twenty-six (6%) of the 427 patients discontinued treatment due to adverse reactions and 3 (0.7%) patients reported serious adverse reactions.

Table: 2079P Summary of efficacy results

	Kyonal	Move	Nacasy	Pooled	Cochran's Q (p-value)
SBM response rate	94/126 (75%)	58/79 (73%)	71/109 (65%)	223/314 (71%) [95%CI 66-76]	2.75 (0.250)
Responders in QoL (PAC-QOL)	69/113 (61%)	44/75 (59%)	66/111 (60%)	179/299 (60%) [95%CI 54-66]	0.12 (0.940)
Responders in constipation symptoms (PAC-SYM)	79/115 (69%)	52/75 (69%)	NR	131/190 (69%) [95%CI 62-76]	0.01 (0.930)
Responders in constipation symptoms (BFI)	NR	58/79 (73%)	75/116 (65%)	133/195 (68%) [95%CI 62-75]	1.70 (0.190)

Conclusions: Treatment with naloxegol for the OIC in patients with cancer pain in the real-world setting resulted in a high proportion of responders in the SBM and consistently relevant improvements in the quality of life and constipation symptoms. Naloxegol was well tolerated and safe.

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2080P Incidence and risks of intravenous chemotherapy-induced neutropenia (ICIN) in oncology: A multicenter retrospective cohort study on real-life data

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Background: ICIN is a major cause of death in cancer patients (pts). We aimed at identifying incidence of ICIN and predictors of poor prognosis in oncology.

Methods: We designed a multicenter retrospective cohort study on the Greater Paris University Hospitals' (APHP) clinical data warehouse. We included all adult pts with solid cancer hospitalized between January 2016 and December 2021 at APHP with an ICD-10 cancer code, with chemotherapy (chemo) within 30 days prior to the 1st ICIN (defined by the D70 or D611 ICD-10 codes AND a neutrophil count < 500/mm3). The primary outcome was the composite of Intensive Care Unit (ICU) hospitalization or death within 30 days. We collected cancer and chemo characteristics, use of G-CSF, Charlson score items and standard biological values.

Results: Among 141,586 cancer pts, 40,660 received chemo among whom 661 (1.6%) had ICIN. Their median age was 63 years (Interquartile Range (IQR) 54-70) and 330 (50%) were female. The median Charlson score was 10 (IQR 8-11). Documented bacterial or fungal infections were observed in 113 (17%) and 19 (3%) pts, respectively. Main primary cancers were lung (n= 204, 31%) and breast (n=87, 13%). Advanced cancers were present in 551 (83%) pts. The last chemo included platinum in 375 (57%) pts, 331 (50%) were in their 1st line of chemo and 284 (43%) in their 1st cycle of the current line, 149 (23%) had primary prophylactic G-CSF, 27 (4%) had a concomitant SarsCov2 infection. Primary outcome occurred in 120/661 (18%) pts: 57 (9%) were transferred to intensive care and 82 (12%) died within 30 days. After ICIN, 372 (56%) pts received subsequent chemo and 486 (74%) were able to return home. In a multivariate Cox model, higher monocyte count (HR 0.07; 95%CI 0.01-0.44) and albumin nadir (HR 0.93; 95%CI 0.91-0.96) decreased ICU hospitalization risk or death whereas both bacterial (HR 2.12; 95%CI 1.40-3.31) or fungal infection (HR 1.93; 95%CI 1.40-3.31) and concomitant Sars Cov2 infection (HR 2.93; 95%CI 1.41-6.33) increased

it. Charlson index (HR: 1.00; 95%CI 0.91-1.10) and primary prophylactic G-CSF (HR 0.83; 95%CI 0.52-1.32) had no prognostic value.

Conclusions: Despite the use of primary prophylactic G-CSF, ICIN is an early event which leads to major complications.

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Disclosure: All authors have declared no conflicts of interest.

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2081P The therapeutic effect of anti-inflammatory tripeptide cream on hand-foot syndrome related to anticancer drugs: A prospective, randomized, placebo-controlled pilot trial

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Background: Hand-foot syndrome (HFS) is a relatively common side effect that often interferes with the quality of life (QoL) in cancer patients. Anti-inflammatory tripeptide cream (ATPC) is a complex formulation of anti-inflammatory tripeptides, CD99 agonist Binterin™ and Wnt antagonist Winhibin™. In the present study, we aimed to assess the therapeutic effects of ATPC on HFS associated with anticancer drugs.

Methods: This study was conducted as a single-center, prospective, randomized, placebo-controlled trial. Patients who developed grade 1 HFS by the National Cancer Institute Common Terminology Criteria for Adverse Events or World Health Organization after treatment with cytotoxic chemotherapeutic agents or multi-kinase inhibitors were enrolled. Patients were randomly assigned to receive ATPC or placebo cream (PC) and followed up with 3-weeks interval for up to 9 weeks. Primary endpoint was the development of grade $\geq$2 HFS. Secondary endpoints were QoL score assessed by Hand-Foot Skin Reaction and QoL (HF-QoL) questionnaire and the frequency of dose reduction or discontinuation of anticancer drugs related to HFS.

Results: From April 2019 to July 2022, 68 patients were randomized and 60 patients (31 in the ATPC group and 29 in the PC group) completed the study. The incidence of grade $\geq$2 HFS was significantly lower in the ATPC group than in the PC group (25.8% vs. 51.7%, P=0.039). The ATPC group showed trends towards a better HF-QoL score than at 9 weeks (26.0 vs. 29.9, P=0.574) and a lower frequency of discontinuation, interruption, or dose reduction of anticancer drugs (51.6% vs. 58.6%, P=0.586) than the PC group without statistical significance.

Conclusions: Our results showed that ATPC significantly decreased the development of grade $\geq$2 HFS in patients with HFS related to anticancer drugs. Therefore, ATPC can be effective treatment for HFS related to anticancer drugs. Further prospective large-scale randomized controlled trial is required to confirm the efficacy of ATPC in cancer patients with HFS.

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2082P TASMAN: An international survey on the knowledge, aTtitudes and clinical pAtternsS of use of Medical Cannabis for caNcer care

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Background: Medical cannabis (MC) has garnered significant attention as a potential strategy for cancer care. Attitudes and beliefs of medical professionals regarding its efficacy and safety remain diverse and inconclusive. This survey explores medical professionals' knowledge, attitudes, and barriers towards MC for cancer care. It aims to understand their beliefs on efficacy and safety, benefits and risks, and identify barriers to its use.

Methods: 175 medical professionals worldwide completed a 31-item survey that included demographics, knowledge and attitudes towards MC, perceived benefits and risks, and willingness to recommend MC to patients. Data analysis involved descriptive statistics and Chi-square tests.

Results: The survey included respondents with a balanced male-to-female ratio and a median age of 37 years from 31 countries, with 120 from upper-middle-income countries (UMIC) and 55 from lower-middle-income countries (LMIC). Findings revealed that 44% of respondents were familiar with MC, and 51% claimed to have received information about it from patients, with 35% receiving direct prescription requests. Surprisingly, only 16% had prescribed MC for symptoms such as CINV, pain, anorexia, cachexia, psychiatric symptoms, insomnia, muscle spasms. There were no significant associations between knowledge levels or patient prescription requirements and income level, but a significant association was found between drug prescription and UMICs. ($p = 0.003$). Notably, only 9% of participants were knowledgeable about their country's MC legislation, although most believed that legislative and social stigma posed significant barriers to its use.

Conclusions: The survey revealed significant variations in the knowledge and attitudes of medical oncologists towards MC in cancer care. Geographic differences were also observed, with professionals from UMICs more inclined to prescribe MC. These findings underscore the need for enhanced education and training for medical professionals regarding the use of MC in cancer care, thereby informing future research and clinical practices in this field.

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2083P Association between VTE location and risk of recurrent, bleeding and death in the international prospective TESEO SEOM cancer cohort

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Background: Cancer patients (pt) with venous thromboembolism (VTE) face increased risks of recurrent thrombosis and bleeding, yet information on associated risk factors remains scarce.

Methods: The TESEO-SEOM prospective, multicenter and international registry involved a descriptive analysis of 2,825 consecutive pt examining thrombosis recurrence and bleeding patterns. The Chi2 test compared recurrent VTE and bleeding events based on primary tumor and thrombosis location.

Results: The table shows the clinical characteristics of the cohort. 173 pt (6.1%) presented recurrent VTE and 188 pt (6.7%) had major or clinically relevant bleeding. Both events correlated with a higher risk of death (adjusted $p<0.01$ and $p<0.001$, respectively). GI cancer was significantly associated with a higher risk of recurrent VTE (86 pt, 7.6%, $p=0.010$). Bleeding episodes were also more frequent in GI tumors, but without statistical significance (87 pt, 7.7%, $p=0.090$). Adjusted for gender, age, stage (metastatic vs. localized) and location of primary tumor, splanchnic VTE was associated with a higher risk of recurrent VTE (11.2%, $p=0.027$) and bleeding (11.7%, $p=0.018$) compared to the whole cohort. This difference was not identified in the rest of the abdomen/pelvis. However, splanchnic VTE was not associated with increased mortality risk ($p=0.148$) Pulmonary embolism was also associated with bleeding (119 pt, 7.7%, $p= 0.006$) but not with recurrent VTE. Pulmonary embolism correlated with higher death rates ($p= 0.007$). Other VTE locations were not associated with higher bleeding or recurrent VTE risk.

Table: 2083P Baseline characteristics

n = 2825 (100%)	
Sex — no. (%)	
Men	1470 (52)
Age — no. (%)	
Mean	65.4
Tumor — no. (%)	
Digestive	1128 (39.9)
Lung	639 (22.6)
Genitourinary	439 (15.5)
Breast	291 (10.3)
Other	328 (11.6)
VTE location — no. (%)	
Pulmonary embolism	1545 (54.7)
Lower limbs	699 (24.7)
Catheter-associated	276 (9.7)
Splanchnic	206 (7.3)
Inferior abdomen — pelvis	172 (6.1)
Superior limbs	122 (4.3)
Head & neck	97 (3.4)
Other	77 (2.7)

Conclusions: A thrombotic event localized in splanchnic circulation is associated with higher risk of recurrent thrombosis and bleeding, regardless of age, sex and tumor type, although it does not seem to impact mortality. Pulmonary embolism is linked to a higher bleeding and mortality risk.

Legal entity responsible for the study: TESEO-SEOM.

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2084P Cardiovascular (CV) mortality among metastatic cancer patients: A retrospective cohort study

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Background: CV mortality is the leading preventable cause of death in cancer patients. Understanding the timing and quantifying the magnitude of CV mortality can facilitate strategies to reduce mortality.

Methods: Surveillance, Epidemiology, and End Results (SEER) database (2004-2018) were queried to obtain CV mortality (defined as deaths due to heart diseases, hypertension, cerebrovascular diseases, atherosclerosis, aortic aneurysm, and dissection) in metastatic cancer patients. Standardized mortality ratios (SMRs) were calculated (observed deaths from each category divided by the expected number of deaths in the age-matched US population for the same period). SMR was presented by latency periods of <2, 2-5, and >5 years after the initial diagnosis of metastatic cancer and stratified by age (<50 years, 50-70 years, >70 years), race (White, Black, Asian/Pacific Islander, Native American), and ethnicity (Hispanic, Non-Hispanic).

Results: This analysis included 914,804 metastatic cancer patients. Overall, the risk of CV death was highest <2 years of initial diagnosis (SMR: 2.47, 95% CI: 2.35-2.58) compared to population who died 2-5 years (1.22, 1.17-1.27) and 5>years (1.11, 1.03-1.17) after the initial diagnosis. In terms of different subgroups, younger population (age <50 years) observed the highest risk of CV mortality within < 2 years (8.84, 7.5-10.4) except for prostate cancer, where the risk of cardiovascular death becomes highest at >5 years after diagnosis. Similarly, regarding race, Native Americans had the highest risk of CV mortality (6.44, 4.86-8.54), which remained consistent across different cancers. There was significant increase in observed mortality in Hispanic (2.93, 2.62-3.28) and Non-Hispanic (2.43, 2.31-2.55) population. The mortality risk by ethnicity remained consistent with latency periods of <2, 2-5, and > 5years after the initial diagnosis of metastatic cancer.

Conclusions: Metastatic cancer patients who are younger or those who are Native Americans have the highest CV mortality, especially <2 years of initial diagnosis of metastatic disease. Targeted cardio-oncological strategies should be aimed at improving CV mortality in patients who are at highest risk of deaths.

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2085P Buprenorphine use and cancer outcomes

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Background: Pain symptoms are common among individuals with cancer, often necessitating pain management as part of cancer care. Opioids are thus mainstay in cancer care, notwithstanding the risk of adverse psychosocial sequelae associated with opioid use, including opioid use disorder (OUD). Buprenorphine is commonly used in managing OUD; however, it is unclear whether there are differences in the characteristics of individuals with cancer receiving buprenorphine, and what perioperative outcomes are associated with buprenorphine use.

Methods: We used data from *Premier Health Database*, a comprehensive electronic healthcare database with over 1,000 contributing healthcare systems and > 10 million inpatient admissions annually. We built a cohort of 616 patients undergoing

surgical care for cancer between 2008 and 2020 who received buprenorphine as part of their care, and matched to 6,160 other patients with cancer randomly selected in the database who also underwent surgical care without receiving buprenorphine. We characterized demographic and clinical factors associated with receipt of buprenorphine, and also examined the association between receiving buprenorphine and perioperative outcomes, including length of stay (LOS, in days), hospitalization cost (in US dollars/$), and in-hospital mortality.

Results: Older individuals were less likely to receive buprenorphine (aOR = 0.95; 95% CI 0.94, 0.97), while patients with Medicaid insurance (aOR = 1.76; 95% CI 1.02, 3.03) and Medicare (aOR = 1.49; 95% CI 1.00, 2.24) were more likely to receive buprenorphine, compared to those with private insurance. We also found a significant association between radiation treatment and receipt of buprenorphine (aOR = 2.18; 95% CI 1.31, 3.61). In examining perioperative outcomes associated with receipt of buprenorphine, we found that while receipt of buprenorphine was not associated with in-hospital mortality, it was associated with decreased odds of being discharged home after care (aOR = 0.43; 95% CI 0.30, 0.63), increased hospital LOS (estimate = 3.50; 95% CI 2.79, 4.21), and increased overall cost of care (estimate = $10,353; 95% CI $7,846.54, $12,859.00).

Conclusions: Receipt of buprenorphine is also associated with odds of increased hospital LOS and increased cost of care.

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2086P Management of opioids use disorder in cancer survivors

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Background: Management of opioids use disorder in cancer survivors The morbidity and mortality associated with opioid use disorder is a public health concern in many countries. However, opioids are a cornerstone in the management of cancer pain. The problem of opioid use disorders is an emerging concern in cancer survivors.

Methods: Over 10 months, we evaluated at the Gustave Roussy Pain Management Unit survivors of cancer who were on long-term prescription opioid therapy. A thorough evaluation involving an addiction specialist doctor, a psychologist or a psychiatrist, and the pain team was conducted to answer the following questions: - What is the current painful complaint and are opioids the adequate treatment for it? - Is the patient dependent on prescription opioids and does he/she have prescription opioid misuse? - Does the patient have an addiction to opioids (according to DSMV criteria) A personalized therapeutic project was then proposed for each patient.

Results: All patients accepted the project. Thirteen patients with a prescription opioid use disorder were enrolled for an opioid withdrawal program. Nine patients were misusing step-3 analgesics as defined by the WHO analgesic ladder, including one patient misusing fast-acting fentanyl, and 4 were misusing step-2 analgesics as monotherapy or in combination with another step-2 analgesic. The mean oral morphine equivalent doses were 150 mg daily [40-480 mg]. Nine patients had an opioid prescription renewal for more than 5 years. The fear of the pain rebound was the main obstacle to stopping opioid use. Seven patients could be withdrawn as outpatients six required hospitalizations for withdrawal under strict medical supervision. Five patients were put on Medications for Opioid Use Disorder (MOUD). None of the residual pain complaints warranted an opioid prescription.

Conclusions: Prescription opioids use disorder in cancer survivors requires the intervention of a specialized multidisciplinary team, trained in the identification and treatment of opioid withdrawal, in the handling of MOUD and in the management of chronic pain diseases. Close and regular collaboration with oncologists is necessary, to reconsider the need for prescription opioids in every patient as soon as he/she is in remission.

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2087P Impact of cancer pain on quality of life and financial well-being: A cross-sectional study on symptom management

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Background: Cancer symptoms (CS) impose a significant burden on patients, affecting their quality of life and financial stability. The purpose of this study was to investigate the impact of common CS on the physical and financial well-being of patients who frequently rely on medications to manage their cancer-related symptoms.

Methods: A cross-sectional, descriptive study was conducted between January and October 2022. The study aimed to identify patient-administered drugs for managing cancer treatment toxicities and associated symptoms. It assessed six common symptoms: anorexia/cachexia, fatigue, nausea/vomiting, pain, constipation, and diarrhea. Demographic data were collected, along with cancer type and active treatment status. Symptom assessment used PERSONS questionnaire, while financial distress (FD) was analyzed with the COST questionnaire.

Results: A total of 211 patients completed the questionnaires, providing valuable insights into their symptom management. However, 183 patients, relied on prescription drugs to alleviate their symptoms. Cancer pain (CP) management was the primary concern for 45% of the patients, followed by constipation, which affected 28% of them. Significantly, the analysis revealed a strong association between CP and lower PERSONS scores, suggesting a negative impact on overall well-being. CP was also correlated with FD, unlike other symptom categories, which did not show statistically significant correlations. Healthcare costs were primarily attributed to pain management, including visits to healthcare professionals and prescription medications. Pain-related expenses contributed to financial strain, resulting in increased out-of-pocket costs and potential income loss due to reduced work productivity or inability to work.

Conclusions: This survey highlights the profound impact of CP on the quality of life and financial well-being of cancer patients. Collaborative efforts among healthcare professionals and policymakers are crucial in developing integrated approaches that ensure accessible and affordable pain management for cancer patients, thus alleviating their suffering and reducing the financial burden associated with pain.

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2088P Management of cancer treatment-induced bone loss in patients with breast and hormone sensitive prostate cancer: AIOM survey among Italian oncologists

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Background: Cancer treatment—induced bone loss (CTIBL) is a side effectof hormonal therapy (HT) that can severely affect patients' quality of life. The first aim of this survey is to obtain an updated snapshot of Italian management of bone health in patients with breast cancer (BC) undergoing adjuvant HT and in patients with hormone sensitive prostate cancer (PC). The secondary aim is to evaluate overlaps and differences between Italian and European recommendations.

Methods: Our survey was made up of 21 multiple-choice questions: the first part dealt with the respondents' characteristics, while the second with management of CTIBL in the described setting. An invitation to complete it was sent by e-mail to 2336 Italian oncologists in October 2022.

Results: 121 (5.2%) Italian oncologists completed the survey. In most cases (57%) the oncologists themselves take charge of the management of CTIBL. At the beginning of HT, most of respondents require bone health diagnostic exams, such as dual-energy X-ray absorptiometry (89%), repeated with different timing. A large part of oncologists starts bone health therapy regardless of T-score or other exams (44%), according to Italian guidelines; while another part start therapy only in case of increased fracture risk (38%), according to ESMO guidelines. Main reported reasons for prescribing antiresorptive drugs are modifying fracture risk (87%), densitometry values (75%) or antitumoral effect (34%). The antiresorptive drugs or supplementation of calcium and vitamin D alone are prescribed in 58% and 38% of patients with BC and 42% and 39% of patients with PC, respectively. Lastly, 6% and 13% of respondents interrupt therapy at the end or 6 months after HT, respectively; 36% after instrumental or scoring reassessment; 22% do not interrupt it; and 23% refer the patient to specialist. Most respondents claim to follow Italian (88%) and European guidelines (31%).

Conclusions: The heterogeneous Italian management of CTIBL arisen from this survey highlights the need both to standardize guidelines and to make oncologists more aware of this topic. It would be interesting to extend this survey to other European countries.

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2089P Multi-cycle prophylaxis of long-acting granulocyte colony-stimulating factor in cancer patients at risk of febrile neutropenia due to myelosuppressive chemotherapy: A retrospective real-world study in China

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Background: Febrile neutropenia (FN) resulting from myelosuppressive chemotherapy drugs, have the potential to necessitate dose reduction or treatment delays, thus compromising the overall efficacy of treatment. This study aims to analyze the incidence of FN and related adverse drug reactions in cancer patients who receive prophylaxis with PEG-rhG-CSF (a long-acting granulocyte colony-stimulating factor).

Methods: This real-world study was conducted as a multicenter, retrospective, observational research involving adult cancer patients who received chemotherapy with PEG-rhG-CSF prophylactic. The study focused on several variables, including baseline characteristics and incidence of FN. Descriptive analysis was performed by using IBM SPSS Statistics 27.

Results: 24,199 patients were enrolled from 575 hospitals across China between June 2022 and January 2023. The chemotherapy cycle records encompassed 1to 20 cycle. Among the enrolled patients, breast cancer was the most prevalent tumor type, accounting for 33.6% (N=8,131) of the cases. FN incidence across all cycles was 0.054% and it was 0.055% and 0.053% among patients receiving PEG-rhG-CSF as primary and secondary prophylaxis. These rates were significantly lower than the previously reported data of 13% to 21% from a retrospective cohort study involving patients with or without prophylaxis. Overall, FN occurred across the first to eighth cycles with the highest incidence observed in cycle 1 (52.50%). 1,659 records (2.25%) reported adverse events related to PEG-rhG-CSF. The most commonly observed adverse effect was musculoskeletal pain, accounting for 1.53% of the cases, followed by fatigue(0.60%) and allergic reactions(0.07%). Furthermore, 90.78% of adverse reactions were categorized as primary or secondary adverse reactions.

Conclusions: Under PEG-rhG-CSF prophylaxis, cancer patients exhibited a low incidence of FN which primarily occurred in the initial cycle of chemotherapy. Importantly, the administration of PEG-rhG-CSF was well tolerated.

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2090P Management of trastuzumab deruxtecan-related nausea and vomiting in real-world practice

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Background: Nausea and vomiting (N&V) are common side effects of Trastuzumab Deruxtecan (T-DXd), but guidelines for optimal management were not initially available. This retrospective study aimed to evaluate the efficacy of two different antiemetic regimens in patients (pts) receiving T-DXd.

Methods: We included 53 pts who received T-DXd at San Raffaele Hospital, Milan, with reliable information on antiemetic prophylaxis type and N&V severity (CTCAE 5.0 classification). Two groups were defined: pts treated with 5-HT3 receptor antagonists (RA) +/- dexamethasone (DEX) (5-HT3 group), and pts treated with a fixed oral combination of NK1RA (netupitant) and palonosetron +/- DEX (NK1 group). To be noted, that pts considered at higher risk of N&V by physician judgement were preferentially offered the NK1RA-containing regimen according to internal recommendations. Only N&V during cycles 1 (C1) and 2 (C2) were considered. Comparisons of N&V by antiemetic prophylaxis group were assessed by chi-square test.

Results: At C1, 15 (28.3%) and 38 (71.7%) pts were treated with and without NK1RA, respectively. Overall, 58.5% of pts reported nausea of any grade at C1, with no differences between the 5-HT3 and NK1 groups (57.9% vs 60%; p=0.832). A minimal numerical trend for lower grade of nausea in the NK1 (33.3% G1; 26.7% G2) compared to the 5-HT3 (23.7% G1; 31.6% G2; 2.6% G3) group was observed. Overall, 15.1% of pts reported vomiting of any grade during C1, with a borderline significant difference between the 5-HT3 (21%, all G1) and NK1 (0%) groups (p= 0.054). Among the 22 pts in the 5-HT3 group with nausea at C1, 15 (68.2%) immediately escalated to the NK1 regimen at C2. Among these, nausea decreased from 100% any grade (26.6% G1, 66.7% G2, 6.7% G3) at C1 to 53.3% any grade (13.3% G1, 40.0% G2) at C2 (p= 0.022), and vomiting decreased from 46.7% at C1 to 13.3% at C2 (all G1) (p=0.046).

Conclusions: The NK1RA-based regimen demonstrated a meaningful improvement in vomiting control at C1, and when promptly introduced as rescue at C2, significantly improved both nausea and vomiting. The biased preferential selection of NK1RA regimen for higher-risk pts may have dampened the differences in nausea control at C1. These results support the current 2023 NCCN antiemetic guidelines for T-DXd.

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2091P Dermocosmetics in management of cancer-related skin toxicities: International expert consensus highlighting the key role of oncology nurses

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Background: Nurses provide information and care on cancer treatment side effects prevention and management. Skin toxicities are common side effects and can be associated with treatment dose reduction or discontinuation. Minimizing skin side effects and using photoprotection improve patient outcomes and quality of life.

Methods: The Association Francophone des Soins Oncologiques de Support (AFSOS) and Multinational Association of Supportive Care in Cancer (MASCC) teamed to create consensus recommendations about using dermocosmetics in cancer patients. They assembled a group of international experts from nursing and other disciplines who manage cancer patients. After literature review, the group held a consensus meeting to give guidance on the use of dermocosmetics with oncology treatments.

Results: Dermocosmetics (or cosmeceuticals) are products with therapeutic value in addition to cosmetic. They contain ingredients that can help repair and support the skin barrier by hydrating the skin, maintaining a healthy microbiome. For general recommendations the group agreed: * Start skin care at the same time as cancer interventions known to be associated with skin toxicities, with a goal of preventing and minimizing problems. * Hydration of the skin relieves symptoms and reduces exacerbations of xerosis. * Use cleansers with pH close to 5 and avoid basic or neutral pH cleansers. * Photoprotection should be part of initial recommendations for all Consensus recommendations for the use of dermocosmetics in specific skin toxicities management were also made.

Conclusions: Nurses have an essential role in educating patients about skin care as part of their holistic approach to patient care. This new consensus focuses on the practical and beneficial impact of dermocosmetics to avoid and manage side effects as well as prevent dryness, irritation, and sensitivity. Patient education can help prevent high-grade toxicities and reduce healthcare costs by allowing patients to have an active role in their treatment.

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2092P Bone loss in premenopausal Algerian women treated with chemotherapy for early-stage of breast cancer: Evaluation by DXA and identification of associated risk factors

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Background: Breast cancer tops the list of cancer types prevalent in Algeria, with more than 14,000 new cases recorded each year, of which a significant rate appears before the age of 40. it is aggressive and requires the use of chemotherapy known to be associated with immediate and long-term toxicities, which may affect the quality of life of cancer survivors. One of the chemotherapy-related long-term toxicities among premenopausal patients is hormonal changes with ovarian failure, chemotherapy-related amenorrhoea (CRA) and early menopause witch may lead to bone loss.The objectives were to evaluate bone mineral density (BMD) and to determine potential associated factors for bone loss among young premenopausal patients after adjuvant chemotherapy.

Methods: We included premenopausal Algerian aged <45 years who had received adjuvant chemotherapy. At study entry, background demographics, cancer characteristics and menstrual history were collected; BMD was measured by DXA in trabecular and cortical sites. Factors associated with reduced BMD and fracture risk were analyzed.

Results: A total of 83 patients were evaluated.The median age at the time of diagnosis of breast cancer is 37 years old, while the age at entry into the study is 43 years old. The median BMDs for femoral neck (FN) was 1.02 g/cm2 and lumbar spine (LS) 0.95 g/cm2; 37.2% had abnormal Z-scores (defined as ≤ -1) and 44.7% had osteopenia/osteoporosis of either FN or LS. On multivariate analyses, factors that were identified correlated with bone loss (low BMD) are: young age at cancer diagnosis (OR [95% CI] = 2.103 [1.091−3.181), low Vitamine D level (OR = 2.254 [1.541−4.637]), low BMI (OR = 2.56 [1.599−2.907]), longer interval since last adjuvant treatment (OR for LS: 2.217 [1.250−4.357]), and having received adjuvant tamoxifen (OR = 1.752 [1.243−3.841]).

Conclusions: This study highlights that bone loss is prevelent condition in early breast cancer survivors who are on or after chemotherapy. About 44.7% of early breast cancer survivors found to have bone loss .To prevent bone fracture; certain factors associated with this condition deserve to be detected and corrected.

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2093P Bioelectrical Impedance phase angle and obesity as a prognostic indicator in metastatic gastric cancer patients receiving second-line chemotherapy

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Background: The combination treatment of paclitaxel plus ramucirumab [PACL(-W)+RAMU] is a widely accepted option for advanced gastric cancer (AGC) as a second-line chemotherapy to prolong survival. The aim of the study is to identify the validity of bioelectrical impedance analysis (BIA) as a prognosticator in patients receiving PACL(W)+RAMU treatment.

Methods: The study population comprised 189 patients who received PACL(-W)+RAMU between Oct. 2019 and Nov. 2022. BIA was conducted at baseline of the PACL(W)+RAMU treatment on all patients and whole body PhA was derived. Continuous variables of other body compartment and blood biochemical values (including complete blood count, serum electrolytes and chemistry) were dichotomized according to the best cut-off values determined by the Contal and O'Quigley methods or the normal values. Kaplan-Meier method and the Cox proportional hazard model were constructed to evaluate the prognostic effect the body component.

Results: Median age of the patients was 59. The cut-off value of PhA was determined as 4.6° at 50 kHz. Median overall survival (OS) of the lower PhA group was 38 weeks (95% CI, 32-45) and 52 weeks (95% CI, 39∼65) for higher PhA group (P=0.021). When combining PhA with obesity degree (current weight/target weight x 100), high phA and low obesity degree ($<$ 116%) demonstrated the favorable OS of 54 weeks (95% CI, 40-68), which contrasts to only 14 weeks (95% CI, 10-18) for low PhA and high obesity degree ($\geq$ 116%) group. In multivariate analysis, the PhA combined with obesity degree is an independent prognosticator for OS (hazard ratio [HR], 6.506 for low PhA and high obesity degree, 95% CI, 3.237-13.076, P$<$0.001) along with neutrophil-to-lymphocyte ratio and extracellular water.

Conclusions: Bioelectrical impedance component and phase angle could be a useful prognosticator for patients with metastatic gastric cancer. Larger sample size and independent set will be needed to further validate the significance of this study in palliative cancer treatment settings.

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2094P A multicenter phase II trial of the triplet antiemetic therapy with palonosetron, aprepitant and olanzapine for highly emetogenic chemotherapy in breast cancer

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Background: Dexamethasone is one of the key antiemetic agents and is widely used even now. However, dexamethasone has been associated with a number of adverse reactions even after short-term administration. Therefore, the development of steroid-free antiemetic regimen is an important issue to be considered. Thus, the purpose of this study was to investigate the efficacy and safety of palonosetron, aprepitant, and olanzapine in a multi-institutional phase II study.

Methods: Chemotherapy-naive patients scheduled to receive for highly emetogenic chemotherapy in breast cancer were enrolled and evaluated the occurrence of chemotherapy-induced nausea and vomiting during 120 hours after chemotherapy. The primary endpoint of the study was total control (TC) in the overall phase. Key secondary endpoint was complete response (CR), which was assessed in the acute, delayed, and overall phase, respectively. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events.

Results: Eighty-nine patients were enrolled from 8 centers in Japan, of which 76 were evaluable for analyses. The percentage of patients achieved TC during the overall phase was 17.1% (95% confidence interval [CI] 0.094—0.275; p = 0.275). CR was achieved in 43.4% (95% CI 0.321—0.553; p = 0.726), 53.9% (95% CI 0.421—0.655), and 63.2% (95% CI 0.513—0.739) of patients during the overall, acute, and delayed phases, respectively

Conclusions: The primary endpoint was below the threshold and we could not find any benefit in the dexamethasone-free regimen. The CR rate was also examined as one of the secondary endpoints, with similar results. Although dexamethasone is considered to have side effect concerns, its effect on CINV cannot be ignored, suggesting that easy complete omission should be avoided.

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2095P Cancer rehabilitation program for cancer-related fatigue

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Background: Cancer-related fatigue (CRF) is a significant and frequent problem among cancer patients. There is no gold standard. However, ESMO CPGL 2020 recommended multimodal interventions, CRF is underdiagnosed, undertreated and underdocumented. In this study, we evaluated cancer rehabilitation program including education, physical activity and emotional support.

Methods: Cancer rehabilitation program includes: patients and family education, physical activity (aerobic exercise), water- therapy, yoga, behavioural therapy, relaxation, art, music-therapy, proteinrich nutrition, social support. The Five-time-sit-to-stand test, Hand-Grip-Strength, 6 min walking test, Brief fatigue inventory, Hospital anxiety and Depression scale were used. Descriptive statistics and t-tests.

Results: Participants were 112 patients (48y [29-75]), 60.7% women and 39.2% men. The primary cancer was 26.7 % breast, 16.9% gasrtoesophageal 33.6% colorectal, 16.8% lung, 5.96% pancreatobiliary. Before rehabilitation: the Five-time-sit-to-stand test 10.2 sec (4.5-28.1), Hand-Grip-Strength 28.4 kg, 6 min walking test 482 meters (49,631), Brief fatigue inventory 45 (0-75), Fatique 8/10 (0,10), Cognitive 6, Emotional 4, Physical 6, QoL 4 (0-10). HADS 8 (0, 18). After rehabilitation: the Five-time-sit-to-stand test 5.7 sec (-50%), Hand-Grip-Strength 39.2 kg, 6 min walking test 585 meters (62,822), Brief fatigue inventory 25 (0-58), Fatique 3/10 (0,10), Cognitive 3, Emotional 1, Physical 4, QoL 7 (0-10). HADS 4 (0, 18).

Conclusions: Cancer rehabilitation program including different types of interventions is effective in treating cancer related-fatigue.

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2096P Morphine titration with intravenous patient-controlled analgesia for severe cancer pain (Mr.TIPS)

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Background: The National Comprehensive Cancer Network (NCCN) guideline recommend starting with opioids for severe cancer pain or pain crisis. In this case, short-acting oral opioids or injections can be considered and drug titration should be performed by re-evaluating after 1 hour for oral drugs and after 15 minutes for injections. However, in actual medical practice, it's challenging to promptly administer injections and perform dose titration through pain assessment every 15 minutes. Patient-controlled analgesia (PCA) is a recommended method that enables patients to self-administer medication, potentially reducing the time required for medication administrations, but there are limited studies on this.

Methods: Patients with cancer pain with an average NRS (Numeric Rating Scale) score of 7 or higher within the last 24 hours were enrolled from 3 centers. The patients who were taking opioids with a morphine equivalent daily dose of 300 mg/day or higher were excluded. Patients complete a pain diary at baseline, 1, 2, 4, 12, 24, and 48 hours. The researchers monitor side effects and conduct a brief pain assessment at 24 and 48 hours. Patients also record their Patient Global Impression of Change (PGI-C) at 24 and 48 hours. The endpoint of this study is percentage of patients with a pain NRS score of 3 or less one hour after PCA application.

Results: Between August 2021 and April 2023, a total of 38 patients were enrolled in the study, with 37 completing and 1 dropout. Of these, 8 (21%) were opioid-naive and 29 (76%) were opioid-tolerant. Within 1 hour, 26 patients (68%) reached NRS 3 or lower pain control. And in a 24-hour PGI-C, 26 patients (63%) reported their condition as very much or much improved. The 33 patients (87%) had no adverse events during the study. Four patients experienced side effects, such as nausea and vomiting; three were mild and one was moderate. No serious adverse events (SAEs) were reported. A possible association between the medication and symptoms was observed in two patients, whereas for the other two, it was assessed to be unlikely.

Conclusions: Effective pain management through dose titration is crucial in the treatment of severe cancer pain. The study confirmed that PCA-based pain control was highly effective, safe, and satisfactory for patients.

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2097P Incidence, risk factors (RFs) and management of oral mucositis (OM) in patients (pts) treated with a fluoropyrimidines (FP)-based therapy (tp): A retrospective, monocentric experience

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Background: OM is one of the main adverse events during chemotherapy, affecting around 40% of pts; it is characterized by an inflammation and ulceration of the oral

mucous membranes that can lead to oral pain, impaired nutritional intake, local or systemic infections and lower quality of life. Only few strategies are available for its prevention and management. FP-based tp can cause OM due to their cytotoxic effect on mucosal cells inducing DNA double strand brakes and ROS production, empowered by TNF-alfa release. In our retrospective monocentric study we evaluated clinical and hematological RFs which could help us to identify early those patients who might benefit the most from a preventive strategy.

Methods: We evaluated incidence, management and possible RFs for OM (such as diabetes, smoke, BMI and blood inflammation markers) on 174 pts treated with a FP-based tp during a typical month in our DH. Statistical analysis has been conducted using Chi-square test and Fisher's exact test. Pts have been informed about risk of developing OM and we subsequently managed the symptom on the basis of its severity according to CTCAE.

Results: 48 pts developed OM. We found a higher OM incidence in smoker pts (60.5% vs 21.4% in non smoker, $p<0.0001$) and in overweight pts (39.7% vs 24.1% in pts with normal weight, $p=0.0381$). We also demonstrated a correlation between a higher OM severity and diabetes diagnosis (71% vs 29.8% in non diabetic pts, $p=0.0330$). No statistically significant correlation emerged between OM incidence/severity and any of the blood values tested (blood cells values, NLR, PLR, creatinine). 20 pts had $\geq$G2 OM and received local and/or systemic therapies, while 3 pts needed a treatment suspension. Median time to resolution was 28 days. 6 pts still had OM of various severity grade at the time of our analysis.

Conclusions: Smoke and overweight could be RFs for OM incidence of any grade during a FP-based treatment, while a diabetes diagnosis seemed to be related with a higher severity of OM, but not with its incidence. In view of the above, it might be useful to recommend accurate oral hygiene and a preventive strategy in accordance with MASCC guidelines in these subgroups of pts.

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2098P The impact of concomitant use of non-opioid analgesics and immune checkpoint inhibitors on survival in lung cancer patients: A Hong Kong population-based cohort study

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Background: Pain is one of the most common symptoms experienced by advanced staged lung cancer patients. Non-opioid analgesics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) have been the cornerstone of pharmacologic interventions for cancer pain management in lung cancer. Since cyclooxygenase-2 (COX2) is overexpressed in many solid tumors including lung cancer and is associated with poor prognosis, COX inhibitions such as NSAIDs have been the candidate for adjuvant therapy for lung cancer. Yet the results of previous studies regarding the concomitant use of immune checkpoint inhibitors (ICIs) and non-opioid analgesics remained controversial mostly for their small sample size. This study aims to investigate whether the concomitant use of NSAIDs with ICIs can improve the survival of lung cancer compared to acetaminophen.

Methods: A total of 572 lung cancer patients who received concomitant use of non-opioid analgesics and ICI from 2018 to 2020 were identified within the Clinical Data Analysis and Reporting System of Hong Kong. Inverse probability of treatment weighting (IPTW) —adjusted Kaplan-Meier curves and Cox proportional hazards regression analysis were used to compare the overall survival (OS) of patients who received NSAIDs versus acetaminophen.

Results: Overall, 428 (74.8%) and 144 (25.2%) patients with lung cancer received concomitant ICI with acetaminophen and NSAIDs, respectively. The median follow-up time in the weighted population was 39.1 months (95% CI, 36.6-43.5 months). IPTW-adjusted Kaplan-Meier curves showed that the median OS was significantly longer in the NSAIDs group than in the acetaminophen group (15.4 months vs 10 months, $p = 0.03$). In IPTW-adjusted Cox regression analysis, the concomitant use of NSAIDs with ICI was associated with a significant OS benefit (HR = 0.76, 95% CI: 0.61-0.96, $p = 0.02$).

Conclusions: The concomitant use of NSAIDs with ICI was associated with improved survival in patients with lung cancer compared with that of acetaminophen. Our findings suggest that a more cautious combination of non-opioid analgesics with ICI for cancer pain management in lung cancer is warranted.

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2099P The role of ambulatory blood pressure measurement in TKI-induced arterial hypertension diagnosis

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Background: Arterial hypertension (AH) is common class-effect of tyrosine-kinase inhibitors (TKI) and the leading course of dose reduction/interruption of TKI-treatment. The aim of our study was to evaluate blood pressure (BP) phenotypes in patients with metastatic solid tumors just after initiation of TKI treatment.

Methods: Thirty-three patients with metastatic solid tumors (renal, hepatocellular and thyroid cancer) treated with lenvatinib (19 (58%) male), age 61,7 +/- 8,9 years), were examined. Clinical BP was measured before initiation, on 2nd Day and every month on TKI-treatment during 6 months in the morning in the seated position. 24-hour ambulatory BP monitoring (ABPM) was performed using the conventional method during 2nd Day of the TKI-treatment. BP level were classified in accordance with ESC guideline (2018) and CTCAE 5.0. We analyzed the prevalence of the following BP-phenotypes: a non-dipping BP pattern, and white coat, masked, and masked isolated nocturnal AH. All patients were recommended to take lenvatinib in the morning at 10.00. 12 (36%) has arterial hypertension in anamnesis and target blood pressure was achieved before initiation of TKI-treatment.

Results: 42,4% of patients had AH Grade 1-3 by CTCAE 5.0. According to the clinical BP measurements on 2nd Day 30.3% of patients had AH (ESC, 2018), in the same time AH was confirmed by ABPM in 90,9% of cases. All patients have non-dipping BP pattern. When comparing the results of clinical BP measurements and ABPM data, masked AH was diagnosed in 57,6% patients, true AH - in 30,3%, 12,1% were true normotensive, white-coat AH was not observed. Masked isolated nocturnal hypertension was prevalent BP-phenotype in initially normotensive patients with solid tumors on the second day of TKI-treatment (prevalence ratio 1.49; 95% CI: 1.08—1.65).

Conclusions: AH is early adverse reaction of TKI-treatment and besides ABPM could be important component for early diagnosis of such type of secondary AH. Masked isolated nocturnal hypertension was more common phenotype among initially normotensive patients with TKI intake.

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2100P An exploratory study of the efficacy and safety of hetrombopag in the treatment of thrombocytopenia induced by concurrent or sequential chemoradiotherapy

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Background: Chemoradiotherapy is still a basic treatment for cancer, even in the era of immunotherapy and targeted therapy. Chemoradiotherapy could cause bone marrow damage. A study published in ECIM/ICIM confirmed that hetrombopag significantly improved outcomes in patients with chemotherapy-induced thrombocytopenia (CIT), exhibiting good safety. However, the efficacy in concurrent or sequential chemoradiotherapy remains unclear. We conducted a clinical trial to explore the efficacy and safety of hetrombopag (a TPO-RA) in treating thrombocytopenia induced by concurrent or sequential chemoradiotherapy.

Methods: This prospective trial enrolled patients with thrombocytopenia induced by concurrent or sequential chemoradiotherapy. The study comprised two cohorts: cohort 1 (PLT$\geq 30\times10^9$/L and $<50\times10^9$/L) treated with hetrombopag combined with IL-11, and cohort 2 (PLT$\geq 50\times10^9$/L and $\leq 75\times10^9$/L) treated with hetrombopag alone. Main inclusion criteria included: $\geq$18 years, platelet count $\geq 30\times10^9$/L and $\leq 75\times10^9$/L. The primary endpoint was the proportion of patients with PLT $\geq 75\times10^9$/L, while secondary endpoints included the proportion and median time of PLT $\geq 100\times10^9$/L, and safety.

Results: A total of 14 patients (5 in the combination group and 9 in the single group) were enrolled from March 2022 to May 2023. The hetrombopag response rate (PLT $\geq 75\times10^9$/L) was 80% (n=4/5) in cohort 1 and 100% (n=9/9) in cohort 2. The proportion of PLT $\geq 100\times10^9$/L was 60% (n=3/5) in cohort 1 and 77.8% (n=7/9) in cohort 2, and the median time was 8.3 days in cohort 1 and 8.8 days in cohort 2, respectively. Adverse events (AEs) were grade 1-2 and occurred only in the single group, including rash (1, 11.1%), nausea and vomiting (1, 11.1%), with no grade 3 or 4 adverse events.

Conclusions: Hetrombopag was safe and effective for patients with thrombocytopenia induced by concurrent or sequential chemoradiotherapy.

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2101P Bleeding Induced by ANtiCAncer drugs (BIANCA) used breast cancer

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Background: Many anticancer drugs' adverse events (AE) are common/known. But, there are little data about the bleeding risk induced by anticancer drugs and some publications recommended to consider bleeding risk when initiating a cancer-associated-thrombosis (CAT) treatment. The aim of this work was to check all the anticancer's SmPCs (Summary of Product Characteristics) for bleeding AE.

Methods: All SmPCs of anticancer drugs for breast cancer were checked on the EMA website. All bleeding AE from any organ were collected. The frequency (F) of AE experienced were the following: very common ($\geq$ 1/10); common ($\geq$ 1/100 to $<$ 1/10); uncommon ($\geq$ 1/1,000 to $<$ 1/100); rare ($\geq$ 1/10,000 to $<$ 1/1000); very rare ($<$ 1/10,000).

Results: Of the 36 identified anticancer drugs for breast cancer. Among these, 75.0% had at least one bleeding AE (all F). Gastro-Intestinal (GI) bleeding (36.1%), epistaxis (41.7%) and haematuria (16.7%) were the main bleeding AE (all F). Regarding very common and common AE, 16.7%, 38.9%% and 5.6%% of the anticancer drugs were reported to be potentially induced GI bleeding, epistaxis and haematuria, respectively (Table).

Conclusions: Bleeding are common AE of many of anticancer drugs. It is important to be aware of this before initiating an anticoagulant in CAT patients. But it seems reasonable to consider a potential bleeding risk caused by anticancer drugs, before/during CAT treatment.

Legal entity responsible for the study: The author.

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Disclosure: N. Janus: Financial Interests, Personal, Invited Speaker: Bayer, Gilead, Leo Pharma A/S, Roche, Vifor Pharma, Amgen, Fresenius, Baxter, BBraun; Financial Interests, Institutional, Other, Grant: Bayer, Gilead, Leo Pharma A/S, Vifor Pharma, Teva; Financial Interests, Institutional, Advisory Board: Daiichi Sankyo, Teva; Financial Interests, Institutional, Invited Speaker: Ipsen, Roche; Financial Interests, Personal, Advisory Board: Leo Pharma A/S, Pfizer, Guerbet; Financial Interests, Personal, Full or part-time Employment, Full time: Leo Pharma A/S; Financial Interests, Institutional, Research Grant: Roche, Amgen, Teva, Vifor Pharma, Guerbet, Pierre Fabre.

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Table: 2101P Bleeding-AE in the anticancer drug SmPCs used for breast cancer

AE	All Frequencies	Very common	Common	Uncommon	Rare	Very rare	Unknown
GI Bleeding	36.1%	2.8%	13.9%	13.9%	0.0%	2.8%	2.8%
Epistaxis	41.7%	19.4%	19.4%	0.0%	0.0%	0.0%	2.8%
Haematuria	16.7%	5.6%	0.0%	11.1%	0.0%	0.0%	0.0%
Other Bleeding	30.6%	5.6%	16.7%	2.8%	2.8%	0.0%	2.8%

AE: Adverse Events; GI: GastroIntestinal

2102P Changes in opioid usage after intrathecal morphine pump implantation in patients with terminal cancer (pilot study)

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Background: It is known that the prevalence of pain in terminal cancer patients reaches 70-90%, and the intensity of pain is very extreme. The intrathecal morphine pump (ITP) has been recognized for effective pain control in cancer pain, but, it is usually recommended to cancer patients with more than one year of life expentancy. This study aimed to find out the usefulness of the ITP through the change in opioid usage before and after pump implantation in patients with terminal cancer.

Methods: A total of 20 patients were included, retrospectively. Morphine equivalent daily dose (MEDD) and pain intensity (visual analogue scale, 0-10) were collected at baseline, 1, and 3months after insertion of ITP. Also, each patient's demographic data, diagnosis, stage and type of cancer were recorded.

Results: The mean age of 20 patients is 56.2$\pm$15.9 (years) and the female was nine. In addition, patients with colorectal, advanced, and prostate cancer accounted for 60% of the patients. The duration of ITP maintenance until the death of patients was 7$\pm$10.5 months. The MEDD was increased at 3 months after implantation of ITP compared to baseline (P=0.03). In addition, the pain relief effect lasted at 3 months after the procedure (P=0.03) (Table).

Table: 2102P Changes in morphine equivalent daily dose (MEDD) and pain intensity after intrathecal morphine pump implantation

	Baseline	1 month after the procedure	3 months after the procedure
MEDD (mg)	506.7$\pm$482.5	1131$\pm$1227.4	858.1$\pm$655.8[1]
Pain intensity (VAS, 0-10)	7.5$\pm$1.3	6.8$\pm$3.3	5.4$\pm$2.5[1]

[1]Statistically significant value compared to baseline ($p < 0.05$). The values are expressed as the mean $\pm$ SD. VAS=visual analogue scale

Conclusions: In patients with terminal cancer requiring high doses of opioids for pain control, the use of ITP implantation can offer effective pain relief while reducing opioid toxicity and side effects. Additionally, clinical evidence suggests that ITP implantation may provide value for patients with a life expectancy of less than one year.

Legal entity responsible for the study: The authors.

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2103P Phase Ib, international, dose-escalation study to evaluate the safety, pharmacokinetics (PK) and efficacy of ST-617 a dithiolethione, for the attenuation of oral mucositis (OM) in patients receiving chemoradiation (CRT) for head & neck (H&N) cancer

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Background: OM is a common, painful, and costly toxicity associated with cytotoxic regimens used to treat H&N cancers. There is currently no approved intervention to successfully prevent or delay OM onset among patients being treated with CRT. Oxidative stress is a critical event in the pathogenesis of CRT associated OM. ST-617 has marked anti-oxidative activity/properties and has previously been studied in multiple human clinical trials. Supportive Therapeutics is developing ST-617 for the attenuation of OM onset, duration and severity.

Methods: A dose escalation trial in which ST-617 administered as an oral suspension, 1-2 hours before the administration of daily RT fractions. 18 patients with diagnoses of oral or oropharyngeal CA were enrolled (up to 6 pts/dose). Patients received concomitant cisplatin either weekly or tri-weekly. ST-617 was administered 3 days prior to CRT, and then continuing daily until the end of treatment. Safety outcomes, using CTCAE criteria (v 4.03) were used. OM occurrence and severity were assessed by trained and validated evaluators using WHO, NCI-CTC and RTOG criteria; scores were centrally assigned. The primary efficacy endpoints included the incidence and duration of SOM (WHO grades 3 or 4) vs historical controls. PD tracking measured total ROS/RNS, GSH/GSSG, regulation in plasma and buccal epithelial cells.

Results: 17 pts completed the 50, 100 and 150mg/day with no safety issues. No early dose limiting toxicity (DLT) or serious Adverse Event linked to ST-617 were observed. AEs observed were mainly nausea which is usually associated with CRT as expected. The 100 mg/day dose has been well tolerated with no grade 4 OM. No CRT dose interruptions or delays due to OM has been observed. Total ROS/RNS levels in plasma and buccal samples shows significant decrease with increased ST-617 dosing from 50 to 100 mg/day.

Conclusions: ST-617 administration shows a very good safety profile. Favorable signs of efficacy in preventing the duration and severity of OM with a physiologically relevant mode of action response have been noted. A randomized, double blind trial is planned with the recommended dose.

Clinical trial identification: SAHPRA number: 20180138 ST617-101; EudraCT 2020-000774-19.

Legal entity responsible for the study: The authors.

Funding: Supportive Therapeutics.

Disclosure: All authors have declared no conflicts of interest.

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2104P Prevention of taxane chemotherapy induced nail changes and peripheral neuropathy by application of extremity cooling: A prospective single center study with intrapatient comparison

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Background: Common side effects of taxanes are nail toxicity (tox) and CIPN. Different methods of cryotherapy to prevent these side effects have been tested. We investigated machine-controlled cooling of hand and feet to reduce nail tox and CIPN.

Methods: Patients (pts) receiving Docetaxel (Doce) (planned dose 300mg/m^2) or Paclitaxel (Pacli) (planned dose 720mg/m) in the adjuvant or palliative setting were included. The dominant hand and foot were cooled to approximately 10°C using the Hilotherapy-machine. The contralateral hand and foot were used as intrapatient comparison. Primary endpoint was the occurrence of any nail tox (Doce cohort) or CIPN (Pacli cohort) at any time during and up to 56 days after the end of treatment. We assumed an absolute improvement of 40% in nail tox and 20% in CIPN. With 90% power using a two-sided McNemar test with a significance level of 5%, a total of 30 pts were needed in each group. The intended to treat population (ITT) and the per protocol population (PPP) were analysed. Toxicity was assessed using the CTCAE v5.0 grading system and the PNQ questionnaire.

Results: 69 pts, 21 (9 in the PPP) treated with Doce and 48 (34 in the PPP) treated with Pacli, were included from 08/2020 - 08/2022. In the Doce cohort, nail tox was not significantly improved by cooling in the ITT (81.0%, vs 85.7%; odds ratio (OR) 0.71, 95% CI: 0.14 − 3.64, p = 0.564) and PPP (100% vs 100%; OR: 1.00, 95% CI: 0.00 − NA, p = NA) but significant benefit across visits over time was found for the ITT (OR: 0.42, 95% CI: 0.18 − 0.98, p=0.045) but not the PPP (OR: 0.75, 95% CI: 0.30 − 1.86, p=0.529). In the Pacli cohort, CIPN was numerically better in the ITT (60.9% vs. 71.7%, OR: 0.61, 95% CI: 0.26 − 1.47, p=0.059) and significantly better in the PPP (67.6% vs. 82.4%, OR: 0.45, 95% CI: 0.14 − 1.40, p-value = 0.025). Differences across visits were significantly in favour of cooling (ITT: OR: 0.28, 95% CI: 0.13 - 0.57, p=0.001; PPP: OR: 0.25, 95% CI: 0.12 - 0.55, p=0.001). Cooling was well tolerated, only 6 pts (9%) discontinued due to side effects.

Conclusions: Cooling of hand and feet has a clinically meaningful impact on occurrence of CIPN and nail toxicity. Effects are more significant over time and are taxane dose dependent.

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Disclosure: R. Cathomas: Financial Interests, Institutional, Advisory Board: AstraZeneca, BMS, Bayer, MSD, Roche, Sanofi, Astellas, Ipsen, Merck, Pfizer, Debiopharm; Financial Interests, Personal, Advisory Board: Janssen; Financial Interests, Personal, Invited Speaker: Janssen, Merck; Financial Interests, Institutional, Invited Speaker: Astellas; Non-Financial Interests, Member of Board of Directors: SAKK Swiss Working Group for Clinical Cancer Research. All other authors have declared no conflicts of interest.

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2105P Prophylactic role of a postbiotic microbiota-stabilizer on abemaciclib-induced diarrhea in breast cancer patients: A pilot application study

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Background: Abemaciclib-induced diarrhea represents a major concern in clinical practice, as it can severely affect patients' quality of life and cause treatment discontinuation and dose modifications. Since growing evidence emphasize the role of microbiota in abnormal bowel clinical manifestations, a new class of natural molecules, called postbiotics, offers a potential option for managing abemaciclib-induced diarrhea.

Methods: We conducted a prospective, observational, single-arm study to evaluate the effect of the postbiotic food supplement "PostbiotiX-Restore™" on abemaciclib-induced diarrhea. We enrolled 36 hormone receptor-positive HER2-negative breast cancer (BC) patients at IRCCS Humanitas Research Hospital. The postbiotic was administered once daily from day -7 to the end of the first cycle of abemaciclib. From day-7 and until the end of the second cycle of abemaciclib, patients reported a daily questionnaire on bowel movements, concomitant medications, diet, and treatment discontinuation. Diarrhea was defined according to version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events. Incidence of diarrhea of any grade, its median duration and median time to diarrhea onset were assessed.

Results: An overall regularization of bowel movements in the first week of treatment with PostbioticX-Restore™ alone was reported. Diarrhea events occurred in all patients, but predominantly G1 (87.1%) and G2 (12.3%), with a very low percentage of G3 (0.6%; all occurring during the second cycle, off postbiotic) and no G4 events. The median time to diarrhea onset was 4 days (IQR 1-41) with a median duration of G1, G2, and G3 events of 4 (IQR 1-17), 1 (IQR 1-5), and 1 (IQR 1-1) days, respectively. There was only one case of dose reduction (during the second cycle, off postbiotic) and no case of treatment withdrawal due to diarrhea.

Conclusions: Our results suggest a promising effect of PostbioticX-Restore™ in the management of abemaciclib-induced diarrhea. Compared to pivotal trials on abemaciclib in BC patients, we observed a reduced severity and shorter duration of diarrhea.

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2106P Safety and patient reported outcomes of SARS-CoV-2 vaccination in patients with cancer

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Background: Vaccination against SARS-CoV-2 reduces morbidity from COVID-19 infection in patients (pts) with cancer. Hesitancy toward vaccination remains in some groups. Ongoing vaccinations are recommended for vulnerable pts. This study provides detailed patient-reported and safety outcomes, providing information for patients and clinicians regarding vaccination safety.

Methods: SerOzNET is a prospective study of pts with cancer who received COVID-19 vaccination (BNT162b2, mRNA1273 or ChadOx1-S) in 2021-22 in 3 cohorts: children (5-11 years(y)), adolescents (12-19y) and adults. From pre-vaccination (to 1 month post dose 3, pts completed serial electronic surveys: Oxford COVID-19 Vaccine Confidence and Complacency Scale, patient reported adverse events (AE), and quality of life (5-19y: PedsQL; 20+:QLQC30). Physicians reported safety, including serious adverse events and thrombosis.

Results: 511 pts were enrolled (40 children, 74 adolescents, 397 adults); 499 had one or more patient or medical outcome report completed. Median age was 52 (range 5-85). Pain at injection site was the commonest AE (60-90% of pts). AEs reported in 20-50% of all pts after dose 1, 2 or 3 were fatigue, muscle pain and fever. Headache was more common in adolescents and adults (18-26%) than children (0-11%). Chills were more common in children and adolescents (11-29%) than adults (12-19%). Delays/modifications to cancer treatment from dose 1 to 1 month post dose 2 were reported in 33% of children, 27% of adolescents and 21% of adults; and from dose 3 to 1 month post dose 3 in 10% of children, 18% of adolescents and 12% of adults. None were attributed to vaccine toxicity. Venous thromboembolic events (VTE) were reported in 4/397 adults; there were no arterial events, and no thrombotic events in children or adolescents. No allergic reactions were reported. Mean QLQC30 in adults, and PedsQL in pts $<$20y was similar pre and post dose 1 (p=n.s. all ages) and 2 (p=n.s. children, adults. Adolescents: 2% improvement, p=0.006).

Conclusions: This large trial dataset demonstrates SARS-CoV-2 vaccination in pts with cancer has manageable toxicity. VTE was low, consistent with background rates. Individuals with cancer can be reassured that SARS-CoV-2 vaccination is safe and will not disrupt their cancer therapy.

Clinical trial identification: ACTRN12621001004853.

Legal entity responsible for the study: The authors.

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2107P Thromboprophylaxis with intermediate or prophylactic doses of LMWHs in ambulatory cancer patients

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HeSMO, On behalf of the Hellenic Society of Medical Oncology, Athens, Greece

Background: Thromboembolic events occur in up to 20% of cancer patients during their course of disease. Cancer associated thrombosis (CAT) is a "signum malum" for cancer itself contributing to morbidity and mortality. Optimal measures to prevent CAT are crucial.

Methods: A post hoc analysis of GMaT & ACT4CAT prospective observational phase IV studies conducted in Greece by Hellenic Society for Medical Oncology (HeSMO), aiming to evaluate efficacy & safety of primary CAT prophylaxis with prophylactic (ProD) or intermediate (InterD; 50%-75% of full treatment dose) doses of Low Molecular Weight Heparins (LMWHs) in ambulatory active cancer patients. Both studies conducted according to Helsinki declaration.

Results: 1157 patients from 26 oncology centers were recruited. Age: 64.9±12.3 years, BMI: 26.1±45.1 Kg/m^2, 59.9% males. Metastasis in 74.5%, Highly Thrombogenic Agents (HTAs) received 82.3%. Anticoagulation agents were (%): 91.2 tinzaparin, 4.6 fondaparinux, 2.3 bemiparin, 1.2 enoxaparin, 0.8 rivaroxaban or apixaban, for 5.1±3.3 months duration. 62% of patients received InterD (1st, 2nd, 3rd,adjuvant & neoadjuvant: 62.4%, 67.3%, 69.8%, 44.1% &71.4% respectively, p=0.004). InterD preferred in men, in those with metastasis, HTAs treatment and receiving erythropoietin agents (ESA) while ProD in those with history of bleeding, heart or vascular, lung or metabolic disease, immobility, surgery, or radiotherapy. Detailed info in the table.

Table: 2107P

	InterD (N=701) (N/%)	ProD (N=430) (N/%)	p	OR (95%CI)
Males	416/63.7	214/55.4	**0.008**	1.4 (1.1-1.8)
Metastasis	535/79.0	259/67.3	**<.0001**	1.8 (1.4-2.4)
HTAs	597/85.4	338/79.2	**0.007**	1.5 (1.1-2.1)
ESA	133/19.0	61/14.2	**0.038**	1.4 (1.0-2.0)
Radiotherapy	126/18.18	106/24.9	**0.007**	0.7 (0.5-0.9)
History of				
Bleeding	2/0.3	6/1.4	**0.031**	0.2 (0.0-1.0)
Heart or vascular disease	139/28	80/35.4	**0.044**	0.7 (0.5-0.9)
Immobility	43/6.1	46/10.7	**0.006**	0.6 (0.4-0.8)
Lung disease	20/4.0	17/7.5	**0.048**	0.5 (0.3-0.9)
Metabolic disease	96/19.3	60/26.6	**0.028**	0.7 (0.5-0.9)
Surgery	269/38.4	250/58.3	**<.0001**	0.5 (0.4-0.6)
Bleedings	11/1.6	11/2.6	0.242	0.6 (0.3-1.4)
Thrombotic events	11/1.6	20/4.7	**0.002**	0.3 (0.2-0.7)

32 patients (2.8%) had thrombotic events (20 in ProD, 11 in InterD, 1 dose unspecified) with higher risk in ProD (OR: 3.1, 95%CI:1.5-6.5, p=0.0021). 26 minor bleeding events reported (2.3%, no dose related difference, p=0.2424).

Conclusions: Common clinical oncology practice was to administer prophylaxis using in most cases LMWHs and frequently in InterD. Selection of anticoagulation dose was based on demographics, cancer characteristics, treatment type and patient medical history. InterD was found to be more efficacious and without safety concerns.

Clinical trial identification: GMaT: NCT03292107; ACT4CAT: NCT03909399.

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2108P Vitamin B12 and its clinical relevance in hospitalized cancer patients

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Background: Vitamin B12 impairment is common in cancer patients due to several factors, namely gastrointestinal (GI) surgery, malnutrition, liver metastases, and chemotherapy. Data regarding their prevalence and significance in this setting, as well as the impact on the overall prognosis, are lacking.

Methods: We retrospectively enrolled patients hospitalized for various cancer-related conditions at our Medical Oncology ward (2017-2022). Plasma B12 levels were stratified as Very Low (VL $<$200 pg/ml), Low (L 200-300 pg/ml), Normal (N 300-813 pg/ml) or High (H $>$813 pg/ml). We collected demographic and clinical data, including BMI, Cumulative Illness Rating Scale, nutritional status, ECOG PS, primary cancer site, disease stage, liver involvement and function tests, GI surgery. Univariate and multivariate statistical tests identified variables statistically associated to vitamin B12 ($p<0.05$).

Results: We enrolled 788 patients (F/M: 1.05, median age: 72, IQR: 62-78 y), VL B12 levels were found in 14.09% cases, L in 19.42%, N in 49.37% and H in 17.13%. At univariate analysis, B12 distribution was significantly different between genders, with females being characterized by higher median values compared to males. Vitamin B12 distribution increased significantly as function of ECOG PS levels. Breast cancer patients were characterized by the highest median B12 value while colorectal cancer patients by the lowest. B12 was also significantly higher in advanced compared to early-stage patients as well as in those who had liver failure. The correlation between B12 and age, albumin, prealbumin, total protein and folates was statistically

significant but negligible (|r|<0.3). Multivariate analysis showed that the probability of H vs VL B12 levels was increased in patients with hypoproteinemia, hypoprealbuminemia and ECOG PS≥2, and decreased in those with colorectal and gastric cancer

Conclusions: To our knowledge, this is the first study investigating B12 levels in a wide and well clinically-characterized group of cancer patients; our data suggest that increased B12 is associated to an impaired clinical status, while in early stage patients, especially the elderly, B12 deficiency is of concern and may negatively impact the overall outcomes.

Clinical trial identification: #2734CE, released on the 31/01/2023.

Legal entity responsible for the study: IRCCS Pavia - Istituti Clinici Scientifici Maugeri.

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Disclosure: A. Malovini: Financial Interests, Personal, Stocks/Shares: Biomeris S.R.L. L.D. Locati: Financial Interests, Institutional, Speaker, Consultant, Advisor: Lilly, Eisai, MSD, Ipsen, Bayer, Roche, Gentili SrL. All other authors have declared no conflicts of interest.

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2109P Vitamin A, D and E levels in patients with solid tumors undergoing palliative systemic cancer treatment

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Background: Vitamin deficiencies and supplement intake is discussed controversially in oncology. Therefore, we aimed to investigate vitamin D, A and E levels and their correlation with clinical characteristics and symptomatic burden in a large pan-cancer cohort.

Methods: 25-hydroxy-vitamin D, vitamin A, and vitamin E levels were measured at treatment start in patients receiving palliative cancer treatment at the Medical University of Vienna (MUV) included in the "Biobanking Program for Personalized Immunotherapy" between May 2019 and March 2022. Measurements were performed using a chemiluminescence immunoassay (vitamin D) and high performance liquid chromatography (vitamin A, vitamin E) established at the Department of Laboratory Medicine (MUV). Cut off values defining the normal range were predefined as follows: vitamin D (75-250nmol/L), vitamin A (1.05-2.45µmol/L), vitamin E (12.0-42.0µmol/L). Symptom burden was assessed using the EORTC quality of life questionnaire QLQC-30 and its subscore assessing fatigue.

Results: Vitamin D, A, and E levels were measured in a total of 231 patients (92 females, 139 males, median age: 64 years [range: 23-89]). Median vitamin levels were as follows: vitamin D 66.9nmol/l (range: 10.4-186.0nmol/l), vitamin A 1.64µmol/l (range: 0.29-4.22µmol/l), and vitamin E 35.8µmol/l (range: 20.2-76.8µmol/l). Patients presented with vitamin D deficiencies in 138/231 (59.7%) and vitamin A deficiencies in 34/231 cases (14.7%). No vitamin E deficiencies were detected, however, 25/231 patients (24.2%) presented with vitamin E levels above normal. Vitamin A levels were increased in 26/231 patients (11.3%), while vitamin D levels above the upper limit of normal in 1/231 patient (0.4%). No correlations between vitamin levels and clinical characteristics at sample collection such as sex, age, tumor origin, symptom burden or fatigue were observed ($p>0.05$). Additionally, no correlation between vitamin levels and overall survival could be detected ($p>0.05$).

Conclusions: Even though vitamin deficiencies are common in patients with cancer, no influences of vitamin levels on symptom burden, fatigue or survival could be detected.

Legal entity responsible for the study: The authors.

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2110P Palonosetron plus megestrol acetate verses dexamethasone in preventing nausea and vomiting following moderately emetogenic chemotherapy: A randomized, multicenter, self-controlled, phase II trial

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Background: Chemotherapy-induced nausea and vomiting (CINV) is the most common side effect following chemotherapy. For medium emetic chemotherapy (MEC), guidelines recommend dexamethasone (DEX) for the prevention and treatment of CINV. But the usage of DEX can cause a variety of adverse reactions. DEX-free regimens are being actively explored. Megestrol acetate (MA) was suggested as an antiemetic therapy gradually. Accordingly, the present phase II trial was designed to test the hypothesis that the efficacy of MA plus palonosetron regimen against CINV is non-inferior to a DEX regimen.

Methods: This was a randomized, self-controlled phase II study. Patients enrolled were scheduled to receive primary chemotherapy that contained oxaliplatin and fluorouracil every 3 weeks and randomized to the MA-DEX group or DEX-MA group. MA-DEX group received palonosetron (0.25 mg intravenously, d1) and MA (160 mg orally, d1-5) for first cycle and then received palonosetron and DEX (6 mg orally, d1-4) for second cycle. The DEX-MA group received the antiemetic treatment in the reverse order. The primary endpoint was complete response (CR). The non-inferiority margin was predefined as a 15% difference between groups in the primary endpoint. All subjects have signed the informed consent, and this trial has registered with Chinese Clinical Trial Register (ChiCTR2000037447).

Results: 61 patients were eventually evaluated in the study 32 included in the DEX-MA group and 29 in the MA-DEX group. Overall CR rates were 82.25% for those administered MA on day 1 (acute phase) (n = 52), and 83.61% on days 2 -5 (delayed phase) (n = 51), 72.13% on days 1-7 (whole phase). According to CR rates , the MA regimen is non-inferior to DEX regimen during the acute, delayed and whole phase. Compared with DEX, the quality of life (QOL) of MA regimen was higher with respect to dyspnea (P=0.000) and appetite (P=0.021).

Conclusions: In this trial, MA is non-inferior to dexamethasone in the treatment of CINV induced by MEC regimens, and no obvious adverse reactions occurred. Compared with DEX, MA led to a milder dyspnea and appetite decrease, and better quality of life after chemotherapy.

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2111P The value of multiple psychometric tools for distress screening and referral in a cancer population

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Background: Psychometric assessment tools are widely available but underutilized in daily oncology practice. The aim of this study was to evaluate the role of multiple psychometric scales in identifying cancer patients in distress who need Psycho-Oncology management.

Methods: Colorectal cancer patients were prospectively asked to complete a survey including 3 psychometric scales (GAD-7, PHQ-9, PC-PTSD-5). Those scoring high on at least one scale (GAD-7 score ≥ 10, PHQ-9 score ≥ 10, PC-PTSD-5 score ≥ 4) were offered referral to the Psycho-Oncology service. Those accepting the referral were further triaged by members of this service via a standardized semi-structured interview. Patients were divided into three groups: those accepted by the Psycho-Oncology service, those declined the referral and those discharged from the service with no need for further intervention. Outcomes were compared with the analysis of variance test (ANOVA).

Results: Fifty-four patients (30 females) of median age 60 years (range 36-81) were prospectively evaluated. 20 patients (37%) reported their cancer was under control, 15 (28%) believed they had progressive disease, while 19 (35%) were uncertain. Approximately half patients (26; 48%) referred a prior history of a mental condition. The mean (±SE) scores for each psychometric scale were 10.96 (± 0.78), 12.79 (± 0.82), and 1.07 (± 0.21), respectively for GAD-7, PHQ-9, PC-PTSD-5. Thirty-four patients (63%) scored high on GAD-7, 40 (74%) on PHQ-9 and 8 (15%) on PC-PTSD-5. Almost half of the patients declined a referral (25, 46%), 22 (41%) were assessed by a Psycho-Oncologist and managed accordingly and 7 (13%) were discharged after the

initial tirage. There was no statistically significant difference in the mean psychometric scores between the three identified groups ($p<0.05$).

Conclusions: Psychometric scales are useful screening tools to identify distress but cannot differentiate between general distress and psychological/psychiatric symptoms requiring specialist intervention. Psychometric scales should be used in conjunction with semi-structured interviews. The 'screen and triage' model should be further investigated as part of an integrated care model, to signpost cancer patients to appropriate support services.

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2112P Initial geriatric assessment and chemotherapy tolerability treatment in Brazilian patients with malignant neoplasm of the digestive system

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Background: The WHO (World Health Organization) defines elderly as individuals aged 60 years or older in developing countries. It is known that due to sociodemographic changes such as increased life expectancy, there was an increase in the prevalence of cancer diagnosis in this population subgroup. Associated with the fact that historically these individuals are underrepresented in the main oncological clinical studies, the challenge of a better way of evaluating these patients, who inherently have different physiological characteristics, arises. In this context, the Comprehensive Geriatric Assessment (GGA) is consolidated as an adequate application tool. This study aims to evaluate, based on the domains of the CGA, elderly patients with malignant neoplasm of the digestive tract who will start chemotherapy treatment and associate it with the tolerability of the treatment after 3 months.

Methods: This prospective study included patients with neoplasia of the digestive tract: esophagus, stomach, pancreas, biliary tract, colon and rectum, evaluated at baseline and after 3 months of chemotherapy. Patients aged 60 years or older were selected. The CGA was applied at the beginning of the treatment. Treatment tolerability was defined in this study by toxicity and maintenance or not of the chosen treatment at the end of 3 months. The data were registered in Excel and subsequently imported into IBM-SPSS Statistics version 28 for comparative analysis between groups. This study was approved by the ethics committee (CAAE:30127320.0.0000.5505). All patients signed a Term of Free and Informed Consent before inclusion.

Results: 50 patients (median age: 68), colorectal (42%). Stage II: 7 patients, III:18, IV: 25.Correlated with toxicity: IADL (Instrumental Activities of Daily Living) and nutritional status. Dependent for IADL developed more G3 toxicity ($p= 0.048$) and were unable to continue treatment: the Lawton scale ($p=0.020$) ;Pfeffer questionnaire ($p=0.024$).Malnourished developed more G3 toxicity ($p=0.003$) and suspended/modified treatment ($p=0.002$).

Conclusions: The evaluation of functionality and nutrition domains were associated with toxicity and maintenance of treatment after 3 months.

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2113P Efficacy and effectiveness of prophylactic magnesium supplementation on prevention of cisplatin-induced nephrotoxicity: A systematic review and meta-analysis

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Background: Cisplatin-induced nephrotoxicity (CIN) is a frequent dose-limiting adverse effect, and many nephroprotective strategies have been proposed to prevent its occurrence. Although multiple studies support premedication with magnesium (Mg) and hydration, this intervention has not been widely implemented, as some centers still replace it only after the occurrence of hypomagnesemia. We performed a systematic review and meta-analysis to evaluate the efficacy and effectiveness of Mg supplementation (suppl) prior to cisplatin.

Methods: We systematically searched Pubmed, Embase, and Cochrane databases for randomized clinical trials (RCT) and observational studies assessing prophylactic Mg suppl compared with placebo for patients receiving cisplatin-based chemotherapy. Primary outcomes were acute nephrotoxicity and hypomagnesemia events; secondary outcome included the association of CIN with variations on serum creatinine levels (ΔSCr). We used RevMan 5.1.7 and RStudio for statistical analysis; random-effects models to pool studies; and I^2 statistics to assess heterogeneity.

Results: We included 24 studies with 3,803 patients. Nine were RCT and 15 observational cohort studies. We found a significant reduction of risk of CIN (all grades) in patients treated with prophylactic Mg compared to placebo (OR = 0.16; 95%CI 0.11 – 0.24; $p<0.001$). The pooled analysis including only studies adjusted for confounding variables demonstrated a 67% risk reduction of CIN with Mg suppl ($p<0.0001$). Mg prophylaxis was effective in both the clinical trial setting (OR = 0.22) and in the real-world data analysis (OR = 0.15). The benefit was seen across all tumor types and combinations of cisplatin-based chemotherapies included in the study. Hypomagnesemia events were significantly less frequent in the intervention group (OR = 0.27; 95%CI 0.16–0.45; $p<0.000001$). There was no difference regarding doses of Mg administered, and the ΔSCr were not significantly associated with the risk of CIN.

Conclusions: In patients undergoing cisplatin-based chemotherapy, prophylactic Mg suppl significantly reduces the risk of CIN and hypomagnesemia as compared with no prophylaxis.

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2114P Impact of comprehensive geriatric assessment (CGA) in the management of chemotherapy toxicity in older cancer patients

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Background: Up to 90% of elderly patients (pts) develop toxicity when treated with chemotherapy (CT). This can often lead to dose reductions, temporary or even definitive treatment interruptions. The CGA is a useful tool to detect frailty, and to predict and prevent unnecessary toxicities. We wanted to explore the effect of CGA in improving tolerance to CT in daily clinical practice of elderly pts with gastrointestinal tumors.

Methods: Observational retrospective study of a cohort of digestive tract cancer pts > 70 years old treated between 2016 and 2023 at Hospital del Mar, Barcelona (Spain), comparing CT tolerance of those receiving CGA with those without CGA. CGA was performed by an oncogeriatrician following the recommendation of the oncology interdisciplinary tumor board. We analysed toxicity, polypharmacy and predict the toxicity risk with CT using CARG score.

Results: One-hundred and eighty pts were included: 58% colorectal, 32% pancreatic, 6% bile duct and 4% gastric cancers. 91 of them (51%) received CGA. Median age was 79 (CGA group) vs 74 (non-CGA group) years old. ECOG PS was 0-1 in 87% of the CGA group and in 94% of the non-CGA. In the CGA group, 63% received CT in the unresectable/metastatic setting vs 52% in the non-CGA group. Polypharmacy (>4 drugs) was present in 60% of CGA group (median of 7 drugs per patient) vs 68% of non-CGA (median 6 drugs). The CARG toxicity risk score was low in 34% of pts, intermediate in 55% and high in 11%. CT treatment was initially adapted in 38 pts (43%) of the non-CGA group vs 55 pts (60%) in the CGA group. High-grade (3-4) toxicities were more frequent in the non-CGA (32% pts) compared to CGA (24% pts). More pts in the non-CGA group needed dose reductions during treatment (62%) compared to the CGA group (43%), with statistical significance ($p=0.009$).

Table: 2114P

	Non-CGA group	CGA group	p value
Dose reduction	62%	43%	0.009
G 3-4 toxicities	32%	24%	0.39
Treatment discontinuation for toxicity	25%	24%	0.96

Conclusions: Performing CGA helps to prevent high-grade toxicity in elderly pts with digestive tract tumors by adapting CT treatment and reduces CT dose reductions related to toxicities.

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2115P Pre-cachexia incidence in patients with solid cancer: A cross-sectional study

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Background: Cancer-associated cachexia (CAC) is an ongoing loss of skeletal muscle which cannot be fully abolished by nutritional interventions. While ESMO suggests precise CAC definitions, pre-cachexia definition is vague.

Methods: Patients with solid cancers and lack of CAC at baseline, enrolled in the *TRU Biobanking Program* of the *Medical University of Vienna* between March 2019 and February 2022, were analyzed. At inclusion and each restaging, the prevalence of modified Glasgow Prognostic Score ≥1 (mGPS), weight loss ≥2% (WL), physical functioning <80 (PF2) and fatigue >30 (FA) was assessed clinically and with the EORTC QLQ-C30 questionnaire. In addition, we evaluated the burden of nutritional risk symptoms (diarrhea, nausea, vomiting, lack of appetite, constipation) with a score (NR) of 1-34. Pre-cachexia criteria were correlated with clinical parameters (age, gender, therapy status). Occurrence of CAC was evaluated using ESMO definitions.

Results: For analysis, 391 patients (47% female, 53% male, median age 59 years) were available. Median observation time was 4 months (range 0-46) with a median of 2 observations (range 1-13). Within the observed period 12% of patients developed CAC. Pre-cachexia as defined by mGPS was found in 52% of patients, by WL in 53%, by PF2 in 69%, by FA in 84%, and by NR ≥7 in 51% of patients. Pre-cachexia by WL was found less often in female (43%) than in male patients (62%; OR 2.14, 95% CI 1.43-3.23; p<0.001) and more often in treatment-naive patients (60%) than in those with prior systemic therapy (48%; OR 1.62, 95% CI 1.08-2.43, p=0.019). Patients with pre-cachexia by NR were younger (median 58, IQR 50-65) compared to the other patients (median 60, IQR 53-70; p=0.018). All other pre-cachexia definitions did not correlate with clinical characteristics (p>0.05). All five pre-cachexia definitions were fulfilled by 15% of patients, four by 27%, three by 29%, two by 14%, and one by 14%. No pre-cachexia definition was fulfilled by 2.3%. None of the investigated pre-cachexia definitions reliably identified patients with subsequent CAC development (p>0.05).

Conclusions: Further research on pre-cachexia-defining parameters is needed for the development of standardized screening methods as current definitions fail to identify patients with high CAC risk.

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2116P Preoperative body mass index, waist circumference, and mortality after major cancer surgery: A nationwide cohort study in South Korea

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Background: Body mass index (BMI) and waist circumference (WC) were used to evaluate nutritional status and obesity.We aimed to examine whether preoperative BMI or WC was associated with mortality after cancer surgery.

Methods: As a population-based cohort study, this study used data extracted from the National Health Insurance Service database of South Korea.We included 87,220 adult patients who underwent major cancer surgery with curative intent between January 1, 2016, and December 31, 2020.

Results: A total of 87,220 patients were included in the final analysis, and 1,374 (1.6%) died within 90 days after cancer surgery. In the multivariable logistic regression model, the BMI <18.5/kg/m^2 and >35 kg/m^2 groups showed 1.98-fold (odds ratio [OR]: 1.98, 95% confidence interval [CI]: 1.58, 2.49; P<0.001) and 2.62-fold (OR: 2.62, 95% CI: 1.26, 5.45; P<0.001) higher 90-day mortality after cancer surgery than did the BMI 18.5−24.9 kg/m^2 group. The 25.0−29.9 kg/m^2 (P=0.143) and 30.0−34.9 kg/m^2 (P=0.109) BMI groups did not show significant differences compared to the BMI 18.5−24.9 kg/m^2 group. Compared with the normal WC group, the high (P=0.052) and very high (P=0.236) WC groups also did not show significant differences in terms of 90-day mortality.

Table: 2116P Subgroup analyses for 90-day mortality according to cancer surgery type

Surgery	OR (95% CI)	*P*-value
Lung cancer		
BMI: <18.5	1.89 (1.08, 3.29)	0.025
BMI: 25.0−29.9	0.82 (0.59, 1.14)	0.235
BMI: 30.0−34.9	0.97 (0.37, 2.59)	0.954
BMI: >35.0	5.91 (1.19, 29.312)	0.030
Gastric cancer		
BMI: <18.5	2.47 (1.49, 4.10)	<0.001
BMI: 18.5−24.9	1	
BMI: 25.0−29.9	0.99 (0.70, 1.39)	0.944
BMI: 30.0−34.9	0.32 (0.09, 1.11)	0.072
BMI: >35.0	1.62 (0.20, 13.26)	0.654
Colorectal cancer		
BMI: <18.5	2.36 (1.53, 3.65)	<0.001
BMI: 25.0−29.9	0.91 (0.68, 1.24)	0.556
BMI: 30.0−34.9	1.01 (0.47, 2.19)	0.979
BMI: >35.0	4.67 (1.23, 17.73)	0.024
Liver cancer		
BMI: <18.5	2.22 (1.11, 4.43)	0.024
BMI: 25.0−29.9	0.78 (0.52, 1.17)	0.227
BMI: 30.0−34.9	0.62 (0.20, 1.94)	0.409
BMI: >35.0	1.09 (0.12, 9.88)	0.941

OR, Odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference

Conclusions: Preoperative BMI <18.5 kg/m^2 and >35 kg/m^2 are associated with an elevated risk of 90-day mortality after major cancer surgery. However, preoperative WC was not significantly associated with 90-day mortality after cancer surgery.

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2117P Dietary patterns and clinical outcomes in patients with lung cancer: What needs to change

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Background: The provision of nutrients in adequate quantity and quality is essential for the treatment of low muscle mass, which is highly found in patients with lung cancer (LC). Identifying an early deficit in food consumption is recommended as a strategy to preserve muscle and weight compartments that directly impact treatment tolerance, functionality and quality of life. This study aimed to investigate whether caloric and protein intake at diagnosis are predictive of outcomes in patients with LC.

Methods: This is a prospective, observational study. Data were collected at the first nutritional consultation between January and December 2019 and consisted of nutritional risk screening for cancer patients, height, body weight, weight loss, calf circumference, handgrip strength measured using a dynamometer and 24-hour recall to estimate average food and macronutrient intake. Survival curves were generated by Kaplan-Meier analysis to assess the association between caloric and protein intake and 3-year mortality.

Results: A total of 50 patients with LC were included, 62% were female, 94% elderly, 88% with non-small cell lung cancer, 88% were diagnosed with disease stages III and IV, and 64% were smokers. Weight-adjusted mean daily intake of energy was 18.6 kcal/kg/day and protein 0.94g/kg/day, and 86% and 60% had lower energy and protein intakes, respectively, than the recommended for patients with cancer. Individuals with consumption greater than 1g/kg/day had significantly longer overall survival with 35,2 versus 21,9 months than those with consumption lower than the recommendation for patients with cancer (p=0.03). There was no statistical difference according to the caloric intake (>25kcal/kg/day versus <25kcal/kg/day) (p=0.20).

Conclusions: Caloric and protein intake at diagnosis is low in patients with LC, and a lower protein intake was a predictor of negative results. Nutritional interventions are low-cost and can be easily implemented as a strategy to modify these results and improve care for these individuals.

Clinical trial identification: Research Ethics Committee approval CAAE: 19918319.1.0000.5533.

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2118P Refeeding syndrome: A prospective analysis in adults admitted to an oncology hospital

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Background: The refeeding syndrome is a potentially lethal condition, associated with metabolic alterations after food reintroduction, and subsequent increase in nutritional intake. It occurs especially in malnourished patients, or in a hyper-catabolic stage. Particularly oncological diseases represent an increased risk factor for the manifestation of the syndrome. Data related to the oncological population is rarely reported, except for the various case series/case studies published to date.This study aims to determine the prevalence of refeeding syndrome in oncological patients according to their risk and to develop a clinical pathway to address and monitor this syndrome.

Methods: A prospective longitudinal study was carried out on 124 patients who started exclusive support via parenteral or enteral nutrition, in 4 units of the oncology hospital: intensive care, intermediate care, medical and surgical inpatient units. Risk for refeeding syndrome was determined as follows: low risk, moderate, high. Biochemistry available (ionogram) before feeding, and its evolution over the first 5 days after initiation was evaluated.

Results: In 64% of patients, serum phosphate, potassium, and magnesium measurements were available prior to nutritional support. There was no information on serum phosphate in 29.7% of patients, with no significant differences between surgical and medical patients. After 48 hours, serum concentration variations were especially pronounced in patients without electrolyte supplementation prior to feeding (-18.2%) versus previously supplemented (10.3%) (p=0.035). After 72 hours, 31.8% of patients experienced reductions superior to 30% in the ionogram, compatible with refeeding syndrome. A positive Spearman's correlation (0.69, p=0.017) was identified between the initially assessed risk (moderate and high) and the decrease in phosphate (>20%) observed at the end of 48 hours in non-supplemented patients.

Conclusions: There is a high prevalence of refeeding syndrome in cancer patients. Monitoring should be continuous, including hypophosphatemia. By providing a multidisciplinary intervention and allowing the provision of micronutrients at the appropriate time, complications of the syndrome can be avoided.

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2119P The prognostic impact of nutritional assessment and scores in advanced gastric cancer

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Background: Malnutrition and weight loss have renowned prognostic value in patients (pts) with localised gastric cancer (GC). We analysed the association of weight loss and early nutritional intervention with outcomes in pts with advanced GC.

Methods: A retrospective cohort of non-resected metastatic GC pts treated with first-line chemotherapy (CT) at the Academic Hospital of Udine (2012-2022) was analysed. Biometric and nutritional parameters were evaluated at diagnosis and during treatment. The prognostic value of >10% weight loss 3 months (mo) after nutritional intervention was assessed. Nutritional interventions and scores (Prognostic Nutritional Index [PNI], neutrophil-lymphocyte ratio [NLR], platelet-lymphocyte ratio [PLR]), dichotomized as high/low per literature-derived cut-offs, were evaluated as predictors of overall survival (OS) and progression-free survival (PFS) with Cox regression model.

Results: 100 pts were included (65 male), median age was 69 years. At CT start, 87.8% of pts had lost weight (>10% in 49.4%), with a median loss of 8 Kg. 55.7% of pts had low PNI, more than 60% high NLR and PLR. 71 pts underwent nutritional assessment (NA), 53.5% before CT start; median time from diagnosis to NA was 40 days. 51 pts had >1 NA, 31 pts >2 NA. At first NA, nutritional interventions consisted in oral supplements (53.4%), parenteral nutrition (28.2%) and counselling (59.2%). Overall, 49% of pts gained weight 3 mo after NA; 88.9% of pts' PNI improved, >50% of NLR and PLR lowered. At disease progression, recorded in 96 pts, PLR and NLR increased significantly (60% vs 48% at 3 mo after NA and 70% vs 34%, respectively). In our cohort, median PFS was 5 mo and median OS was 9 mo. Low PNI (HR 2.05, p = 0.008), high NLR (HR 2.51, p <0.001) and PLR (HR 2.63, p <0.001) at CT start and a >10% weight loss (HR 3.05, p = 0.020) 3 mo after first NA were associated with worse OS. PLR improvement at 3 mo after first NA was associated with better OS (HR 0.46, p = 0.018).

Conclusions: These results underline the importance of early and efficient nutritional assessment and support in cancer pts. The prognostic value of PNI, NLR and PLR reinforces the importance of the interplay between immune system and weight loss for advanced GC.

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2120P Nutritional deficiency post gastric cancer surgery

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Background: Malnutrition is frequent, but underdiagnosed consequence of gastrectomy. Nutritional status is an important factor influencing optimal recovery after treatment. The aim of the present study was to assess the prevalence of micronutrient deficiencies post gastrectomies.

Methods: Between January 2022 and January 2023, 115 patients post gastrectomy had micronutrient screening including vitamin B12, vitamin D, folate, ferritin and albumin. Patients with any micronutrients deficiency were invited for a follow-up and rehabilitation (nutrient rich diet, supplements). Descriptive statistics and t-tests.

Results: Patients' characteristics were as follow: 64.3% women and 35.6% men; median age 58 [30-81]; median follow-up period 19 months [2-24]; proportion of patients with deficiency in vitamin B12, vitamin D, folate, ferritin and albumin were 5.2%,40%,10.4%, 23.4% and 20.9%, respectively. We observed significant improvement in several indicators (vitamin B12 156→357mmol/l, vitamin D 24.6→69.4mmol/l, folate 2.7→9.6mmol/l, ferritin 16.4→92.2mmol/l, albumin 2.2→3.0mmol/l, p=0.01).

Conclusions: This study defined the prevalence of micronutrient deficiencies post gastrectomy. Appropriate nutritional intervention based on findings micronutrients deficiency led to improve quality of life.

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2121P Association between nutritional status and adverse events in gastrointestinal cancer patients undergoing outpatient chemotherapy in Japan

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Background: Recently, the development of anticancer drug administration methods and advances in supportive care for side effects have made it possible to safely perform chemotherapy through outpatient visits. Outpatient chemotherapy is important for maintaining the patient's quality of life (QOL). Side effects of chemotherapy include anorexia, nausea, dysgeusia, and oral mucosal disorders, which affect diet, and weight loss affecting the effectiveness and prognosis. In particular, patients with gastrointestinal cancer are considered to have a high nutritional risk status. We assessed the nutritional status of patients with gastrointestinal cancer during outpatient chemotherapy and found an association with adverse events symptoms.

Methods: The Tohoku University School of Medicine IRB approved this study (2018-1-176); patients provided written informed consent. Patients undergoing outpatient chemotherapy were enrolled, nutritional status, self-assessment of adverse events and depression by The Depression Scale Epidemiological Research Center (CES-D) were assessed. Responses were analyzed by Chi-squared test, ANOVA, Spearman's correlation coefficient, and multiple regression analysis. $p<0.05$ was considered significant. All statistical analyses were performed using SPSS (ver. 21).

Results: Valid responses were obtained from 120 patients with gastrointestinal cancers including pancreatic, colorectal, gastric, and esophageal cancers. The mean age was 65.2 (±9.6) years. Side effects of chemotherapy were fatigue in 99 (83.9%), neuropathy in 88 (73.3%), and dysgeusia in 85 (70.8%). Subjects were classified into 70 normal persons, 32 malnourished, 6 pre-cachexia, and 12 cachexia according to the nutrition assessment classification by Glasgow prognostic score (GPS). Although GPS classification did not show a significant relationship with the basic attributes, there was a significant relationship between anorexia ($r=0.26$, $p=0.004$), taste change ($r=0.26$, $p=0.005$), dry mouth ($r=0.18$, $p=0.049$), and edema ($r=0.22$, $p=0.018$).

Conclusions: Adverse events during chemotherapy including anorexia, dysgeusia, dry mouth and edema would have negative impact on nutritional status.

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2122P Clinical significance of oncology patients' nutritional status assessment

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Background: The catabolic activity of cancer combined with various side effects of cancer treatment, lead to decreased food intake, weight loss and muscle wasting, compromising patients' clinical outcome and quality of life. As a result, the incidence of prolonged hospital stays is increasing. Thus, maintaining the nutrition balance is critical for health care services.

Methods: 136 patients participated in this prospective observational study. Nutritional status was accessed via the patient generated-subjenctive global assessment (PG-SGA).

Results: Patients characteristics are depicted in the table. During a six-month period, 45 patients (33.1%) had no weight loss, 48 (35.3%) had lost up to 10% of their initial weight and 43 (31.6%) over 10%. 61 patients (44.9%) had decreased their food intake compared to a month ago. According to PS-SGA questionnaire, 57 patients (42%) had score up to 8, while 79 patients (58%) had score 9 or more, which is the limit for initiation of urgent nutrition intervention. Statistical analysis showed that age, chemotherapy or radiotherapy had no effect in body weight or food consumption change, neither in PG-SGA score ($p>0.05$ in all cases). Gender was related to BW change during the last two weeks, specifically more women had stable weight (54% compared to 32% of the men, $p=0.037$) and more men had reduced weight (45% vs 32% in women). Metastasis had significant role in the number of patients with PG-SGA, 66% of metastatic patients vs 34% of non-metastatic had score ≥9, (OR:3.8, 95% CI: 1.7-8.5, $p=0.0009$). Moreover PG-SGA score was highly dependent of cancer site.

Table: 2122P Characteristics of the study population

Characteristic	Measure
Number of patients	136
PG-SGA score	10.41±5.6
BW change during the last six months (in 3 scales)	
Loss	91 (66.91%)
Same	15 (11.03%)
Gain	30 (22.06%)
PG-SGA score with cut off ≥9 (need for food intervention)	
<9	57 (41.91%)
≥9	79 (58.09%)

Conclusions: The results highlight the importance of early assessment of the nutritional status of cancer patients receiving oncology treatment according to patient and disease characteristics. A timely intervention for nutritional support of the patients being at risk for malnutrition and cachexia is crucial.

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2123P Value of immuno-nutritional scores in the prognosis of hospitalised patients with lung cancer

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Background: Immuno-nutritional scores like neutrophil-lymphocyte ratio (NLR), prognostic nutritional index (PNI), modified Glasgow prognostic score (mGPS) and controlling nutritional status (CONUT) have been developed to reflect the chronic inflammatory state and malnutrition induced by cancer, and to predict clinical outcomes. This study aims to investigate the prognostic value of these scores in hospitalized patients with lung cancer as we know that unscheduled admission in patients with cancer may imply organ fragility.

Methods: In this retrospective study, we examined patients with lung cancer and unscheduled hospitalizations that took place between June 2021 and May 2022 within the Medical Oncology Service of La Paz University Hospital in Madrid, Spain.

The optimal cutoff for continuous variables was evaluated with Youden index. Survival since admission was estimated with the Kaplan-Meier method. Univariate and multivariate analyses were performed by Cox regression model to determine independent prognostic factors. Areas under the curve (AUCs) or ROCs were calculated to evaluate the discriminatory ability.

Results: We admitted 158 patients with a median age of 68 years, majority of male (66.5%) and stage IV predominance (84.8%). The median follow-up was 14.9 months. The median overall survival since admission was 3.3 months (95%CI: 1.86-7.74). The optimal cut-off value for NLR was calculated to be 6 (Youden index=0.2) and for PNI was 40 (Youden index=0.1). In univariate analysis, poorer survival was associated with NLR>6 (1.87 vs 7.40 months, $p=0.006$, HR 1.67, 95%CI 1.16-2.42) and PNI<40 (1.67 vs 4.97 months, $p=0.044$, HR 1.49, 95%CI 1.01-2.20) and was not associated with CONUT ($p=0.70$) or mGPS ($p=0.067$). In the multivariate analysis only NLR>6 was an independent prognostic factor ($p=0.042$, HR 1.61, 95%CI 1.02-2.57). The ROC curve to evaluate the discriminatory ability of 30-day mortality was only significant in the case of NLR>6 ($p=0.035$, AUC 0.599, 95%CI 0.51-0.69).

Conclusions: In our setting, NLR was the most robust score for estimating prognosis in hospitalized patients with lung cancer.

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2124P The impact of NUTRItional status at first medical oncology visit ON Clinical Outcomes: The NUTRIONCO study

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Background: Malnutrition affects up to 75% of cancer pts and results from a combination of anorexia and metabolic dysregulation. Metabolic and nutritional abnormalities in cancer pts can lead to cachexia, a multifactorial syndrome characterized by involuntary loss of skeletal muscle mass, systemic inflammation and increased protein catabolism. Cancer cachexia negatively affects patients' outcomes, compliance to anticancer treatments, quality of life and survival. However, risk of malnutrition and cachexia are still under recognized in cancer pts. The Prevalence of Malnutrition in Oncology (PreMiO) study revealed that 51% of pts had nutritional impairment already at the first medical oncology visit.

Methods: The retrospective, observational NUTRIONCO study included a subpopulation (n=571 pts) of the prospective, observational PREMiO study (n=1952 pts) for whom follow-up data were collected from August 2019 to October 2021 and made available in electronic case report forms at ten medical oncology sites in Italy. The clinical outcomes that were considered for the association analysis with the baseline clinical and nutritional variables were: patient's rehospitalization, onset of treatment-related toxicity, patient's death and disease progression.

Results: We highlighted a statistically significant association between baseline variables and patients' death, rehospitalization, treatment toxicity and disease progression at follow-up. We found a higher overall survival probability in well-nourished general study population vs. malnourished pts ($p<0.001$). Patients' stratification revealed that malnutrition decreased the survival probability in non-metastatic pts, but not in metastatic pts ($p<0.001$). Multivariate analysis confirmed that baseline malnutrition ($p=0.004$) and VAS score for appetite loss ($p=0.0104$), in addition to albumin <35 g/L ($p<0.0001$) and neutrophil/lymphocyte ratio >3 ($p=0.0007$), were independently associated with death of non-metastatic pts at follow-up.

Conclusions: These findings support the importance of a proactive, early management of malnutrition and cachexia in cancer pts, and in particular in non-metastatic pts, in the perspective of a substantial improvement of their clinical outcomes.

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Disclosure: A. Frassoldati: Financial Interests, Personal, Advisory Role: Roche, Novartis, Pfizer, Lilly. All other authors have declared no conflicts of interest.

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2125P Potential ROle of hypoVItaminosis D in patiENts with cancer treated with immune ChEckpoint inhibitors (PROVIDENCE): A prospective observational study

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Background: Hypovitaminosis D can have a negative impact in patients (pts) with cancer. We hypothesized that systematic vitamin D repletion could improve outcomes in pts receiving immune-checkpoint inhibitors (ICIs).

Methods: We planned a prospective observational study (PROVIDENCE) to investigate vitamin D levels in pts with advanced cancer receiving ICIs (cohort 1 at treatment initiation, cohort 2 during treatment) and the impact of systematic repletion in the case of hypovitaminosis on survival and toxicity outcomes. In an exploratory analysis, we compared clinical outcomes of cohort 1 with a control cohort of pts followed at the participating centers who did not receive systematic vitamin D repletion.

Results: Overall, 164 pts were prospectively recruited. In cohort 1, consisting of 101 pts with 94.1% hypovitaminosis (≤30 ng/ml) at baseline, adequate repletion with cholecalciferol was obtained in 70.1% at the three months re-assessment. Cohort 2 consisted of 63 pts assessed for vitamin D at a median time of 3.7 months since immunotherapy initiation, with no pts having adequate levels (>30 ng/ml). Even in cohort 2, systematic supplementation led to adequate levels in 77.8% of pts at the three months re-assessment. Compared to a retrospective control group of 238 pts without systematic vitamin D repletion, PROVIDENCE cohort 1 showed longer OS and time to treatment failure (TTF), $p=0.013$ and $p=0.017$. The IPTW-fitted multivariable Cox regression confirmed the significantly decreased risk of death (HR 0.55, 95%CI: 0.34-0.90) and treatment discontinuation (HR 0.61, 95%CI: 0.40-0.91) for pts from PROVIDENCE cohort 1 in comparison to the control cohort. In the context of longer treatment exposure, the cumulative incidence of any grade irAEs was higher in the PROVIDENCE cohort 1 compared to the control cohort. Nevertheless, pts from cohort 1 experienced a significantly decreased risk of all grade thyroid irAEs than the control cohort (OR 0.16, 95%CI: 0.03-0.85).

Conclusions: The PROVIDENCE study suggests the potential positive impact of early systematic vitamin D supplementation on outcome of pts with advanced cancer receiving ICIs and support adequate repletion as a possible prophylaxis for thyroid irAEs.

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2126P Exercise implementation into a clinic setting with 1.660 cancer patients: Real-world data from eight years oncological exercise therapy in Cologne (OTT)

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Background: The beneficial effects of exercise for cancer patients are well recognized but implemented exercise programs remain scarce, especially for patients during medical treatment. For that reason, we developed a supervised, personalized exercise concept for cancer patients, implemented into a clinical, oncological setting.

Methods: Cancer patients before, during or eventually after their medical treatment with an identified need for exercise could participate in a free of charge exercise intervention for at least three months at the University Hospital Cologne, Germany. We recorded demographic and medical data at enrolment and exercise adherence up to one year.

Results: A sample of n=1.660 patients attended the exercise program. The majority of patients were female (70%), under medical treatment (65%), diagnosed with breast cancer (40%), without metastasis or severe comorbidities (>70%) and on average 54 years old. The median time between diagnosis and exercise participation differed in patients during medical treatment (4 months), patients with metastasis (7 months) and cancer survivors (11 months). Almost one third (31%) discontinued exercise within the first two weeks of participation. Prolonged exercise (median: 19 weeks) was achieved by one third (32%) of the patients. The average exercise adherence was ~1 session a week with <3% of patients reaching ≥2 sessions a week

Conclusions: To our knowledge, this is the worlds-first report of a professional, supervised exercise program tailored for cancer patients under medical treatment implemented into a clinical setting with >1.600 patients. We described the population that was referred to an exercise program, identified barriers to exercise participation and observed an important mismatch between recommendations and real-world exercise data. Exercise participation was engaged ≥4months after diagnosis and only a third of the patients exercised longer than three months. Almost all patients undercut the well-established exercise recommendations of ≥2 sessions a week. Future implementation concepts should optimize exercise initiation timely after diagnosis and adherence levels due to innovative exercise approaches.

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2127P Long-term yoga reduces the side effects of systemic therapies and improves arm symptoms in the breast cancer patients

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Background: Yoga has gained more attention worldwide in the last decade and shown the potential to improve physiological and psychological health in various disease conditions. Studies on breast cancer (BC) survivors showed mild to moderate effects within one-month to six-month on various parameters. Cancer treatment-related side effects are often related with functional as well as symptomatic scales. Therefore, we have conducted a randomized control study to find out the effect of long-term yogic intervention on symptom and functional scale in patients undergoing treatment.

Methods: This study was approved by the institutional ethics committee. The current study consisted of 96 BC stage II/III patients receiving cancer treatments who were randomly divided into two groups: Group-I (non-yoga) and Group-II (yoga). Group-II was advised to perform yoga 5 days per week for 48 weeks and was monitored regularly by video or phone calls. At different time points (T0 (baseline), T1 (16th week), T2 (32nd week), and T3 (48th week), we collected the breast cancer specific questionnaire (EORTC-BR23), which consisted of various functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and symptomatic scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss), and compared them between groups as well as within group.

Results: Out of 96 total patients, 82 were analyzed for T0-T3 (40 in group-I and 42 in group-II). In groups I and II, the mean age was 47.67±11.68 and 43.11±9.39, respectively. Yogic intervention resulted in a significant improvement in arm symptoms and side effects from T0 to T3 ($p<0.001$) and T1 to T3 ($p<0.01$) in group II, while group I also improved from T0 to T3 ($p<0.05$). The most significant difference was observed in Group-I (T0) vs. Group-II (T3). There was no significant difference observed in upset by hair loss, body image, breast symptoms, or future perspective.

Conclusions: The duration of yoga positively correlated with the systematic therapy side effects and improved their arm symptoms. This suggested that yogic intervention during therapy could be an effective complementary therapy.

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Disclosure: All authors have declared no conflicts of interest.

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2128P exerCise discussion with Oncologist duriNg caNcEr ConsultaTion: The CONNECT study

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Background: Exercise (EX) is associated with a reduction in mortality and recurrence risk in patients (pts) with cancer and may help pts cope with treatment side effects and improve their quality of life. This study aims to explore the role of oncologists in promoting exercise in the oncological context.

Methods: A self-administered, anonymous questionnaire was proposed to pts visiting the outpatients' facilities at the Oncology Unit of Verona Hospital. The questionnaire assessed demographic, health, and EX parameters. EX variables, drawn from a prior study, included: the level evaluated with Godin's Leisure Time Exercise Questionnaire and information regarding: whether EX was discussed; whether oncologists assess, advise, reinforce, and refer (AARR process) pts effort to exercising; and whether pts preferred that EX be discussed. Descriptive statistic, presented as mean, frequencies, and percentages, was applied.

Results: Overall, 202 pts completed the survey (76% response rate). The most frequent tumor types were upper gastrointestinal (45%) and breast (19%). Only 9% of pts were sufficiently active. Regarding the actual EX discussion, 29% of pts reported that their oncologist started a discussion about EX, 12% initiated the discussion themselves, and 60% referred that the issue was not considered. Concerning the AARR process, 26% of pts declared that their oncologists assessed their EX level, 14% and 33% received advice or reinforcement to increase their EX, respectively, and 9% were referred to an appropriate EX service. On the other hand, the items related to the preferred modality of EX discussion showed that 69% of pts thought that oncologists should initiate an EX-discussion, 3% that only pts should start the discussion, and 23% thought that EX should not be discussed.

Conclusions: Our preliminary results show that most pts are insufficiently active, and the majority stated that they did not discuss EX. Nevertheless, most pts would prefer that oncologists initiate a discussion about EX. According to these findings, strategies to support clinicians in promoting EX to their pts should be developed. Further pts' enrollment is currently ongoing and a more updated analysis will be available for presentation at the ESMO Congress.

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2129P Feasibility of a virtual exercise program to mitigate decline in physical function for advanced lung cancer patients

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Background: Exercise in cancer patients can mitigate declines in physical and psychosocial function. However, low recruitment and retention for in-person exercise programs limit evidence-based program development for patients with advanced lung cancer. The study of a virtual intervention, that leverages on the emerging acceptance of virtual healthcare delivery, has the potential to overcome barriers of prior exercise studies.

Methods: Mitigation of decline with Virtual Exercise with Lung Cancer is an ongoing prospective single-arm feasibility study. Individuals with advanced lung cancer on systemic therapy were recruited to a 12-week virtual group exercise program, including aerobic and functional strength exercises, delivered twice weekly over Zoom by an exercise physiologist. Feasibility measures included accrual, attendance, exercise adherence, attrition, and adverse events. Efficacy measures and quality of life (QoL) were assessed at start and end of program. Patient demographics, treatment, and outcomes were collected via electronic medical records.

Results: Of 44 patients referred, 30 were eligible and enrolled, of which, 3 were lost to follow up, 1 withdrew, 16 completed and 10 continue to participate in the program. Baseline demographics of 26 active participants: median age 65.5 years old (range 39 − 88), female (n=12), ECOG 0/1 (n=24), adenocarcinoma (n=21), metastasis to brain (n=9), liver (n=4), bone (n=7), and on targeted therapy (n=19). Total attendance is 87% and adherence is 96%. Of those who completed the program, statistically significant changes in physical function were identified by the 6 minute walk test (median improvement of 147 meters $p = 0.046$), gait speed ($p = 0.030$), sit to stand ($p = 0.004$), and biceps curl repetitions ($p = 0.001$). No significant difference was found in QoL using the Functional Assessment of Chronic Illness Therapy-Lung (FACT-L) and -Fatigue (FACT-F) questionnaires. Participants found the program to be accessible and were very likely to recommend this program to a friend.

Conclusions: Preliminary results suggest that a virtual exercise program for patients with advanced lung cancer is feasible, with high attendance and adherence, and significant improvements in physical function.

Legal entity responsible for the study: Y. Wang, K. Campbell.

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Disclosure: Y. Wang: Financial Interests, Personal, Advisory Board: BMS, AstraZeneca, Merck, Takeda; Financial Interests, Institutional, Research Grant: AZ. P. Camp: Financial Interests, Other, Personal, Conducted evaluation: Carrier Sekani Family Services. Financial Interests, Coordinating PI, Institutional, Receive funding for operational and team grants: Canadian Institutes of Health Research. Financial Interests, Coordinating PI, Institutional, Receive funding for operating grants: BC Lung Foundation. J. Laskin: Financial Interests, Advisory Board, Personal, invited speaker: Roche Canada. Financial Interests, Invited Speaker, Personal, speaker at educational event: Pfizer. Financial Interests, Advisory Board, Personal, invited to national ad board: Takeda. Financial Interests, Research Grant, Institutional, Funding for a IIT: Roche Canada. K. Campbell: Financial Interests, Personal, Stocks/Shares: Abcellera; Financial Interests, Personal, Speaker, Consultant, Advisor: Pfizer Canada. All other authors have declared no conflicts of interest.

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2130P ATTITUDE - ATTrition In longiTUDinal studiEs of cancer survivors (CS): Can we improve the experience of patients (pts)?

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Background: Dropout is common in longitudinal studies and generates attrition bias. ATTITUDE uses a mixed, multistep methodology to reduce attrition, building on the CANTO cohort (NCT01993498, collecting clinical and patient-reported outcome measures [PROMs] for 5 years post breast cancer [BC] treatment). In Step 1, we had found that 16.2% of pts who were still on study at year-4 did not attend at all the CANTO visit and 33.1% did not respond to any PROMs. Here we present results of Step 2, gathering key stakeholders' input about participation to longitudinal studies.

Methods: A multidisciplinary group of oncologists, sociologists, patient engagement experts and advocates co-developed a 28-item survey. The survey addressed CS and citizens within the Seintinelles platform for collaborative cancer research and was open to completion for 4 weeks. Descriptive analyses were performed.

Results: There were 1834 respondents, 733 CS (84.0% of BC) and 1101 citizens without history of cancer: 95.3% were female, 58.2% were 40-65 years old, 87.4% had $\geq$ high school degree. Among CS, 58.4% had previously participated in a longitudinal study: 85.0% felt to have received adequate information prior to enrollment and 99.5% would participate again in the same or a similar study. Overall, motivation for participation included desire to support the research team (92.8%), to help (other) pts (49.8%), and to improve one's own cancer management (20.1%). Facilitators to participation included option to use digital platforms (96.1%), home-based data collection (95.0%), flexible study visit schedule (77.5%), obtaining individual explanations regarding study procedures by phone (56.6%), and receiving reminders to complete PROMs (56.9%). Responses were consistent between CS and citizens.

Conclusions: Actionable interventional components to reduce attrition in longitudinal studies that emerged from this survey include implementation of decentralized, digital data collection tools such as e-PROMs, flexible study visit schedule, and study navigators. The present survey, complemented with additional input from ongoing qualitative explorations, will inform the co-design and piloting of tailored interventions to minimize attrition in Step 3 of ATTITUDE.

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Disclosure: M.A. Franzoi: Other, Research Funding (Institution): Resilience Care. M. Pagliuca: Other, Traver expenses (June 2022): Gilead. I.V. Vaz Luis: Financial Interests, Personal, Other, Honoraria: Sandoz, Amgen, AstraZeneca, Pfizer, Novartis; Financial Interests, Personal and Institutional, Research Funding: Resilience Care. A. Di Meglio: Financial Interests, Personal, Advisory Board: Kephren, Medycis, Techspert. All other authors have declared no conflicts of interest.

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2131P Real-life experiences from a late effects clinic: An investigation of health-related quality of life in Danish cancer survivors

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Background: Three out of four cancer survivors experience one or more late effects; many report unmet needs. Consequently, the Region of Southern Denmark has established late effects clinics (LEC) for patients with complex late effects to help cancer survivors regain their physical and mental functioning and improve their Health-Related Quality of Life (HRQoL). By the use of the newly developed EORTC QLQ-SURV100 questionnaire, this study elucidates the most predominant late effects occurring in Danish cancer survivors referred to a LEC and compares the patients' HRQoL to that of newly diagnosed cancer patients and the general Danish population.

Methods: Primo 2022 , a LEC opened at Odense University Hospital. Prior to the first consultation, patients complete the EORTC QLQ-SURV100 questionnaire to capture the full range of physical, mental, and social HRQoL issues relevant to cancer survivors. Moreover, we collect data on demography, disease, treatment, and type of intervention following the first consultation in the LEC.

Results: One hundred and forty-nine patients have been included in the clinic's first year. Inclusion is ongoing. Age; median 58 [26-82] years. Women 75%. The most common diagnosis is breast cancer. 50% are referred by general practitioner. Over 90% report multiple late effects. Fatigue, sleep disturbance, pain, cognitive impairment and fear of recurrence are most commonly reported. QLQ-SURV100 mean scores on Global Health 51.4, Role functioning 51.4, Emotional functioning 60.0, Cognitive functioning 49.4, and Physical functioning 52.3. Compared to the HRQoL of patients at the time of diagnosis and the general population, these numbers are significantly lower. The number of recruited patients will reach app. 220 in October 2023. However, this is not expected to influence the mean scores as they have been constant throughout the clinic's lifetime.

Conclusions: Cancer survivors referred to the LEC suffer from multiple and complex late effects after cancer and its cancer treatment and report a significantly lower HRQoL compared to patients at the time of diagnosis and the general Danish population.

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Disclosure: All authors have declared no conflicts of interest.

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2132P Unmet needs, quality of life, and financial toxicity in survivors of lung cancer

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Background: Survivors of lung cancer (LCS) have unmet emotional, social, and physical needs regardless of stage at diagnosis or treatment types, experience decreased quality of life (QOL) and high financial toxicity (FT). The relationship between unmet needs, QOL, and FT is yet to be reported in LCS and may provide insight into potentially modifiable needs to address to improve patient reported outcomes.

Methods: We performed a cross-sectional survey to assess the physical, social, emotional, and medical needs, QOL, and FT in patients with histologically confirmed non-small cell lung cancer alive $>$ 1 year from diagnosis. The survey consisted of an adapted needs survey, the Comprehensive Score for FT (COST), and the lung cancer specific QOL questionnaires EORTC-QLQ and EORTC-QLQ-LC13. Demographic and clinical information was obtained retrospectively by chart review. Separate multiple linear regression models, treating QOL and FT as dependent variables, were performed to assess the adjusted relationship between total number of unmet needs and type of unmet need (physical, emotional, social or medical) with QOL and FT.

Results: Of 360 LCS approached, 232 surveys were completed. The median age was 69, most were female (62%), married (71%), Caucasian (74%), and had stage III/IV lung cancer (60%). Previous/current smoking history ($p=0.042$) and ECOG performance status of 1 or $\geq$ 2 (compared to 0) ($p<0.0001$) were each independently associated with decreased QOL. Income $<$ \$30,000 or \$30,000-75,000 (compared to $>$\$75,000) ($p<0.0001$), and history of radiation therapy ($p=0.023$) were independently associated with increased FT. Higher total unmet needs was associated with lower QOL ($p<0.0001$) and increased FT ($p=0.0003$). Greater unmet physical ($p=0.023$), social ($p=0.008$), and medical needs ($p=0.007$) were associated with decreased QOL. Greater social needs were associated with increased FT ($p<0.0001$).

Conclusions: Unmet needs across multiple domains are associated with worse QOL and FT in LCS. Identifying specific modifiable unmet needs, such as patient symptoms, care coordination, or tobacco cessation, are needed to help identify interventions. Future studies with targeted inventions to address these unmet needs may improve QOL and FT in LCS.

Legal entity responsible for the study: J. Feliciano.

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2133P Sleep disorders: Evolution in time in early breast cancer (EBC)

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Background: Sleep disorders are common in the general population and among all cancer patients, but it has been shown that they are particularly prevalent among patients diagnosed with breast cancer, both during and after treatment. These disruptions produce a significant deterioration in functional status and clearly reduce the quality of life of the patients.

Methods: 126 women diagnosed with EBC at Puerta de Hierro Hospital have been analyzed, divided into 3 groups. The first group were women with a recently breast cancer diagnosis reciving chemotherapy, the second group were women at early follow up (first two years post-diagnosis), and the third group were women at late follow up (more than 2 years after diagnosis). The control group was selected from a sample of healthy individuals matched with our patients in terms of age, weight, and physical condition (digital twin). Sleep parameters were obtained using a wearable device for 7 consecutive days (Kronowise®-Kronohealth S.L).

Results: The patients undergoing active chemotherapy treatment exhibited more disrupted sleep patterns than controls, with a delay in their circadian rhythms and more aged rhythms. 25% of them slept less than 6 hours, and the average nocturnal sleep duration in this population was 6.73 hours. They frequently resorted to napping, with 55% of them taking naps longer than 30 minutes, with a sleep efficiency of less than 80%. As time passed from the diagnosis, the sleep patterns began to resemble those of the control group, and no differences with controls were found in the third group of patients. The sleep efficiency improved in the late follow-up group, with an efficiency rate exceeding 85%.

Conclusions: The administration of chemotherapy in patients with early breast cancer produces significant disruptions in sleep, with a clear impact on their quality of life, which can be recovered with long-term follow-up (more than 2 years since diagnosis). We must make an effort to detect these problems and instruct our patients in healthy sleep habits.

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2134P Self-reported late effects, need for information and follow-up in long-term Hodgkin lymphoma survivors

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Background: Hodgkin's lymphoma survivors (HLSs) are at risk for late effects due to their early age at diagnosis, multimodal therapy and long life expectancy. Among HLSs, we explored self-reported late effects, and assessed their information needs regarding lifestyle (diet and physical activity) and rehabilitation, in addition to need for long-term follow-up and factors associated with these needs.

Methods: HLSs treated 1997-2006 and aged 18-49 years at diagnosis were identified by the Norwegian Cancer Registry and invited to participate in this population-based, cross-sectional study consisting of a questionnaire, blood tests, clinical examination and echocardiography. Information regarding histology, stage and treatment was retrieved from medical records. Descriptive statistics and logistic regression models were used.

Results: Among the participants (n=304, 59% response rate), median age at diagnosis was 29 years (range 8-49), median age at survey 45 years (21-70), median observation time 16 years (10-22) and 48 % were females. Ninety percent had classical HL, 62% had stage I-IIA disease, 94% received chemotherapy and 77% radiotherapy. Seventy-four percent reported to have experienced $\geq$1 late effects; concentration/memory problems (29%), numbness/nerve pain (32%) and dental problems (27%) were the most common. Forty-one percent reported chronic fatigue (CF). One third reported to have received follow-up for late effects. A total of 64% wanted information about lifestyle and/or rehabilitation, and 58% wanted regularly follow-up for late effects. In the multivariable models, CF (OR 2.2, 95%CI 1.2-4.1), short education (2.2, 1.2-4.0), being physical inactive (2.0, 1.1-3.5) were associated with increased likelihood of need for information about lifestyle and/or rehabilitation. CF was associated with increased likelihood of need for follow-up for late effects (2.1, 1.3-3.6).

Conclusions: HLSs report a high level of late effects and only a small proportion receive follow-up for these problems. Chronic fatigue is associated with need for information and follow-up, indicating that these patients could benefit from a more structured model for long-term follow-up than what is currently available.

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2135P Impact of geriatric assessment (GA) and geriatric 8(G8)-based targeted interventions on the quality of life (QoL) in older Asian adults with cancer

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Background: G8 and GA assessments to screen for frailty and facilitate appropriate interventions have been recommended by the International Society for Geriatric Oncology in older adults with cancer. The main objective of this study is to evaluate the impact of G8 and GA-based interventions on the QoL of older Asian adults with cancer.

Methods: This is a prospective study of cancer patients aged $\geq$70 treated at the National University Cancer Institute, Singapore. The G8, CGA, and EORTC QLQ 30 questionnaires were administered at study entry. Targeted interventions were offered by the multi-disciplinary geriatric oncology (GO) service. After three months, a follow-up EORTC QLQ 30 was repeated for those who required geriatric interventions. Primary outcome measure was comparison of pre/post- EORTC QLQ 30 scores.

Results: N=230 patients were accrued. Median age was 74 (range:70-90). Majority were male (56%), diagnosed with gastrointestinal cancers (35%) and receiving palliative intent treatment (60%). Based on GA, 11% were classified as frail, 58% as pre-frail and 31% as fit. 79% had G8 scores $\leq$14. Pre-frail, frail and those with G8 $\leq$14 had lower baseline EORTC QOL function scores and higher EORTC QOL symptom scores ($p<0.05$). They also had significantly shorter overall survival (OS) compared to fit or with patients G8$>$14. (HR=2.54 95% CI 1.46-4.43, p=0.001 for frail vs fit patients; HR=1.72 95% CI 1.18-2.53, p=0.005 for pre-frail vs fit patients; HR=1.51 95% CI 1.05-2.18, p=0.027 for G8 $\leq$14 vs $>$14). GO interventions were suggested for 144 patients with 104 patients completing a 2nd EORTC QOL questionnaire. These patients reported significant improvements in the EORTC emotional and social functioning domains (mean difference +4.6, $p<0.001$ and +12.3 $p<0.001$, respectively), a significant reduction in the EORTC symptom scale of pain, insomnia, constipation, and financial difficulties (mean difference -5.8 p=0.003, -8.3 $p<0.001$, -9.0 $p<0.001$, and -6 p=0.01), with no significant deterioration in other QOL domains.

Conclusions: Geriatric assessment-based targeted interventions delivered by a multidisciplinary GO service significantly improved multiple QOL domains in older Asian adults undergoing cancer treatment.

Clinical trial identification: DSRB Study Reference Number: 2017/00214.

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2136P Prostate cancer supportive care (PCSC) program for patients and partners: A model for meeting an unmet need for PC patients

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Background: Prostate cancer (PC) patients face treatment-related sequelae that affect their health and quality of life. The PCSC Program was created in 2013 and is located in the Vancouver Prostate Centre's urology clinic. It is a clinical, educational, and research-based program that addresses challenges experienced by PC patients from the time of diagnosis onward. The program consists of 8 "modules" listed in the table.

Methods: We describe the operational details of the PCSC Program and its metrics.

Results: A Medical Director and Program Manager set the mission, oversee the day-to-day operations, and hire and manage the allied health clinicians and support staff. Office/clinic space is rotated during the week to accommodate a sexual health RN (1.4 FTE), 2 pelvic floor physiotherapists, a nurse practitioner, a registered dietitian, a clinical exercise physiologist (all 0.2 FTE), and a clinical counsellor (0.4 FTE). As of 05/2023, 3351 pts have registered for this no-cost program (Table). In 4/2020, the real-time group education sessions and clinic appointments transitioned from in-person to a hybrid with virtual options enabling the participation of patients from throughout British Columbia.

Table: 2136P Attendance at PCSC modules for 3351 registrants from 2013 to May 2023

Modules	Attendees, n	Group education*, n (# sessions)	Clinic appointments, n (# appointments)
Introduction to PC and primary treatment options	945	955 (159)	not applicable
Managing sexual function and intimacy	1745	844 (122)	1519 (6109)
Management of side effects of ADT	443	376 (25)	212 (313)
Pelvic floor physiotherapy for incontinence	1304	910 (97)	594 (2382)
Counselling	444	not applicable	444 (1629)
Metastatic disease management	85	87 (30)	not applicable
Nutrition	742	195 (31)	361 (593)
Exercise	826	455 (70)	674 (2167)

*Some attendees attended the group education sessions more than once.

Conclusions: The need for PC supportive care is well recognized but may be challenging to offer when the services are fragmented and time-consuming for clinicians or staff to arrange. All modules offered by the PCSC Program can be accessed with one registration. It is convenient for patients because it is housed in one location, which also facilitates communication across disciplines. We attribute the success of our program to this model and our team approach to the individual patient's needs.

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2137P Impact of supportive care on the quality of life (QoL) of hospitalized cancer patients (pts)

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Background: Performance ECOG status and staging are described as prognostic factors in oncologic outpatients while nutritional assessment can impact survival in both outpatients and inpatients. The aim of this study was to describe the Charslon Comorbidity Index (CCI), the nutritional status, the impact of opioid therapy and psycho-oncology and palliative care unit intervention for hospitalized cancer patients (pts).

Methods: A prospective multicentric study of pts hospitalized between January 2020 February 2022 at Vall d'Hebron and Sant Pau Hospitals [Plantology database] in Spain. Demographic and clinical variables such as CCI, laboratory results and nutritional status were collected at admission. Prognostic Nutritional Index (PNI) was calculated at admission. Quality of life (QoL) was collected through the EORTC-QLQ30 v.3 questionnaire. Statistical analysis was performed with SPSS v.29 (Log rank, Chi-square, Student's t-test were used).

Results: A total of 1.431 patients (median age 66 years, 53.2% males) were included with a median of 9 days hospitalized. With a follow-up of 15 months, the median survival was 4.67 months after admission. Most pts (91.6%) had severe comorbidity (CCI $\geq$ 5 points) related to a lower survival (4.5 vs 12.8 months, $p<0.001$). A positive chair stand test for sarcopenia (12.2%) was associated with reduced survival (3.5 vs 9.1 months, $p<0.001$). Pts with hypoalbuminemia (65.3%) presented lower survival (3.5 vs 8.4 months, $p<0.001$). In addition, the PNI stratified 59.5% pts with serious malnutrition (PNI <40) linked to reduced survival (3.6 vs 7.9 months, $p<0.001$). Regarding supportive care, pts under opioid therapy (39.6%) had a higher QoL (mean EORTC QLQ-30 score of 73.4 vs 64.3, $p<0.001$). Palliative care team assessment and psycho-oncology intervention positively impacted in pts QoL (EORTC QLQ-30 of 74 vs 67.3, $p<0.001$, and 74.3 vs 65.2, $p<0.001$, respectively).

Conclusions: In hospitalized cancer pts, severe comorbidity, malnutrition and sarcopenia were associated with a reduced survival. Opioid therapy and psycho-oncological and palliative care unit intervention had a positive impact on the QoL of pts. Early supportive care interventions are key to improve symptomatology and preserve QoL of hospitalized cancer pts.

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2138P Time toxicity of palliative chemotherapy in a geriatric oncology population

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Background: Older adults with cancer undergoing cytotoxic chemotherapy (CTx) are at increased risk of treatment-associated toxicity. Data supporting the efficacy of systemic anticancer therapy (SACT) in this patient population are sometimes limited. The concept of time toxicity has emerged to describe the time commitments and opportunity cost involved in undertaking SACT, particularly when the magnitude of clinical benefit is expected to be modest.

Methods: We conducted a retrospective review of patients attending the multidisciplinary Geriatric Oncology Assessment and Liaison (GOAL) clinic of University Hospital Waterford, Ireland over a 3.5-year period. We included patients for whom an initial or subsequent line of palliative CTx was commenced in the last 6 months of life. We recorded ambulatory physical healthcare contact days related to the delivery of CTx as well as treatment-related inpatient admissions as a measure of time toxicity.

Results: Of 304 patients assessed, 64 patients commenced SACT with palliative intent. A total of 26 patients met inclusion criteria for the study. The median age of patients was 78 (67-86). At initial GOAL clinic review, 15 patients (58%) had an ECOG performance status of 1, and 10 patients (38%) had a performance status of 2. Most patients received single agent cytotoxic CTx (17/26; 65%) and 85% of patients received only 1 line of treatment. 23 patients (88%) required hospital admission during treatment and 11 patients (42%) required more than one admission. 5 patients (19%) were admitted due to treatment-associated toxicity. The median number of physical healthcare contact days related to CTx (including hospital admissions directly due to treatment toxicity) was 14 (5-37). Median survival from initiation of CTx was 119 days (15-170). 9 patients (35%) received treatment in the last month of life.

Conclusions: High rates of hospitalisation were noted in our study, reflecting the challenges in delivering CTx to an older adult population. Physical healthcare contact days represented a substantial proportion of days alive from commencing systemic treatment. Consideration of the time toxicity of CTx in this population may help to better align palliative-intent treatment with patient goals.

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2139P Quality of life in adult cancer survivors (QLACS) in Spain: Study of its clinical characteristics and use of social media for oncological information

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Background: Long-term cancer survivors (*LS),* patients over 5 years free of disease, are a population on the rise due to oncological advances. Our aim is to explore QLACS in long-term cancer survival patients in Spain. As a secondary objective is to study their clinical and sociodemographic characteristics and their preference for social media or face-to-face meetings to obtain oncological information.

Methods: We carried out a transversal study in a sample of *LS* patients from several Spanish hospitals. They completed QLACS, FERREL, SPF12 and social media data. Different types of tumor were included. Psychometric properties of the QLACS were evaluated. Principal component analysis with Varimax rotation was applied to explore the dimensional structure. Pearson's correlation (Pc) was used to study associations of QLACS with temporal variables. Student's t test was used to study differences between them.

Results: N= 257, women=59,9 %, < 65 years=55%. Types Tumor: 33% breast, 27% colorectal, 8,9% urothelial, 7,4% other digestive tumors, 7% orl-lung. Factor analysis showed a 12-component solution accounts for 71.03 % of the variance, showing a similar comparable dimensional structure with QLACS. Alfa Cronbach=0,9. Appearance concern, distress over recurrence, pain, negative feelings and distress familiar are statistically higher in female ($p<0,05$). We found negative correlation between age and use of social networks for oncological information (Facebook: $p = 0.01$, Pc: -248; Twitter: $p<0.04$, Pc:- 200; Instagram: $p <0.007$, Pc: -259 except; Youtube: $p = 0.17$; Pc: -134). No differences by sex were observed in the use of social networks There were no differences by age in attending face-to-face meetings: $p< 0.94$, Pc: -196. Breast cancer patients are more willing to attend face-to-face meetings to help other patients than those with colon cancer ($p< 0.036$).

Conclusions: QLACS is a valid and reliable instrument for measuring quality of life in long-term cancer survivors in Spain. Younger patients are more likely to use social media for oncology information. Older people tend to prefer face-to-face meetings. We found differences between men and women in different factors for measuring quality of life.

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2140P Short-term quality-of-life after metastases-directed SBRT: Results of the prospective ESTRO & EORTC OligoCare cohort

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Background: Metastases-directed stereotactic body radiotherapy (SBRT) in addition to standard of care systemic therapy is supported by randomized phase II trials and international practice guidelines for patients with an oligometastatic disease (OMD). However, little is known about quality of life (QoL) following SBRT, which would be valuable to better inform patient and clinicians in their decision-making process about the optimal multimodality treatment strategy.

Methods: OligoCare is a pragmatic prospective cohort study of E^2-RADIatE, a collaboration between ESTRO and EORTC, which aims to identify patient, tumour, and treatment characteristics influencing overall survival after ablative radiotherapy for oligometastatic breast, colorectal, lung and prostate cancer. Patients are eligible irrespective of oligometastatic state (de-novo, repeat or induced), without restrictions to local or systemic therapy. Radical radiotherapy must be a component of treatment, irrespective of maximum number of metastases, as long as all cancer lesions are treated with radical intent. Assessment of QoL using the EORTC QLQ-C30 is optional. This analysis reports QoL at baseline and first FU (3-12 months) on the first 1600 enrolled patients.

Results: 530 patients completed baseline QoL and 399 completed follow-up (median time after SBRT: 6 months). 71% of patients were male, with oligometastatic prostate cancer the most frequent primary (45%), followed by NSCLC (24%), breast (17%) and colorectal cancer (14%). WHO performance status was 0 or 1 in 87% of patients, median age was 69 years and median one single oligometastasis was treated with SBRT (range 1-8). Average global health status at baseline was 72 (SD 19.5), with higher baseline QoL in prostate cancer (average 78) as compared to NSCLC (average 65) or breast cancer (average 68) patients. Global health status remained stable during follow-up (average 72; SD 20), without differences between primary diseases. A more detailed assessment of QoL subdomains is underway.

Conclusions: Collection of QoL data was feasible in this prospective registry and early QoL remained stable following metastases-directed SBRT in oligometastatic breast, colorectal, lung and prostate cancer.

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2141P Symptom burden and health-related quality of life (HRQoL) in platinum-resistant or -refractory ovarian cancer (PROC): A systematic literature review (SLR)

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Background: PROC is characterized by a cumulative burden of progressive disease and prior treatments. The goals of treatment are symptom reduction, HRQoL improvement or stabilization, and providing survival benefits with limited toxicity. We aimed to comprehensively characterize HRQoL in patients with PROC.

Methods: An SLR was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. MEDLINE®, Embase®, EconLit, Cochrane, and relevant conference proceedings were searched for randomized and non-randomized studies reporting HRQoL in patients with advanced ovarian cancer and disease recurrence within 6 months of platinum-based chemotherapy published January 2010—March 2, 2023.

Results: Of 13,043 records identified in the SLR, 39 were included. The most common HRQoL measures were European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 (n=28), EORTC QLQ-Ovarian Cancer Module (OV28) (n=23), Functional Assessment of Cancer Therapy (FACT)-Ovarian (n=10), and FACT Ovarian Symptom Index (FOSI) (n=6). Gastrointestinal (GI) problems, fatigue, sleep disturbances, pain, anxiety, and depression were commonly reported at baseline. HRQoL scores and outcomes were heterogeneous, however, across studies and treatments, the majority of patients experienced stable or worsening HRQoL. Few studies reported clinically meaningful improvements in HRQoL in abdominal/GI symptoms, pain, insomnia, global health, function (physical, emotional, role, social), and these occurred in less than half of patients. Worsening of dyspnea, GI symptoms, chemotherapy side effects, and peripheral neuropathy were noted with some treatments including pegylated liposomal doxorubicin.

Conclusions: Disease-specific and generic HRQoL instruments demonstrated a substantial burden including GI disturbances, pain, fatigue, emotional distress, and poor functioning in PROC. Existing treatments provided no HRQoL improvement for the majority of patients. A substantial unmet need remains for tolerable treatments that reduce symptoms and improve HRQoL among patients with PROC.

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2142P Criteria for the choice of therapeutic ceiling in the hospitalized oncology patient: Healthcare impact of the multidisciplinary committee with the Intensive Care Unit (ICU)

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Background: The improvement in cancer survival, allows for higher ICU admission ratios. A pilot program in our center instituted weekly meetings between ICU and Oncology aimed at determining the appropriate level of care for patients admitted in Oncology. Objective: establish which factors predict decision-making regarding the level of care and admission to the ICU and benefit of intensive care.

Methods: Single-center prospective observational study. Recruitment between September-2021 and July-2022. Statistical analysis: descriptive study, multivariate logistic regression for decision of admission in ICU. We performed a second subsequent analysis with the paired propensity score matching technique. Survival analysis: Kaplan-Meier (KM) curves and log-Rank test. Significance level: $p \leq 0.05$.

Results: 411 patients. 60.3% male; median age: 64 years. Most prevalent tumor: lung (26.3%). Stage IV: 72.5%. The most common reason for admission in Oncology: infectious pathology (33.8%). 54.7% were considered ICU candidates, while only 17 patients (4.1%) finally required intensive care. In a multivariate logistic regression model, ECOG 0-1 (OR 2.7; IC95%: 1.6-4.5), absence of peritoneal carcinomatosis (OR 4.5; IC95%: 2.0-9.9), and intentionality of treatment (adjuvant, neoadjuvant or first-line) (OR 5.4; IC 95%: 3.1-9.5) predicted decision of admission to the ICU. Age > 65 years (OR 0.35; IC 95%: 0.2-0.6) and poor symptom control as cause of admission in Oncology (OR 0.16; 95%: 0.03-0.93) were negative factors for ICU admission. By means of paired propensity analysis (Nearest-neighbor model), the sample was reduced to 172 patients and there was only statistical significance in the univariate analysis for intentionality of treatment and for treatment with immunotherapy (IT). After a median follow-up of 4 months, median survival was significantly different ($p < 0.05$) for patients who were not ICU candidates (2.5 months), patients who were admitted to the ICU (10 months) and patients who were ICU candidates but did not require admission (12.5 months).

Conclusions: Multidisciplinary decision-making may contribute to individualize the level of intensive care for Oncology patients.

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2143P Mortality within 30 days after last dose of intravenous systemic anti-cancer therapy: Single-center, one-year, retrospective analysis

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Background: Mortality within 30 days of systemic anti-cancer therapy may be a useful indicator of the preventable harm to patients from systemic anti-cancer therapy, but data on this indicator are limited. Identifying the characteristics of patients who develop mortality within 30 days after treatment will contribute to improving the quality of patient care and reducing financial toxicity. In this study, we aimed to screen the patients who received systemic treatment in our center in 2022 and to determine the 30-day mortality rate after the last treatment dose.

Methods: The data of all patients who received intravenous systemic anti-cancer therapy in our center in 2022 were reviewed retrospectively. Diagnoses, disease stages, chemotherapy regimens, and patient characteristics were recorded. 30-day mortality was defined as death within the first 30 days after receiving the last treatment dose.

Results: A total of 1937 patients were included in the study. The majority of the patients (n = 595, 30.7%) had gastrointestinal system cancers, followed by breast cancer (n = 369, 19.1%) and lung cancer (n = 357, 18.5%). When the patients' last treatments were reviewed, chemotherapy was the most common (n = 1514, 78.1%), followed by chemotherapy-monoclonal antibody combination (n = 241, 12.4%), and immunotherapy monotherapy (n = 91, 4.7%). The 30-day mortality rate after systemic anticancer treatment was 7.0% (n = 136) in the entire patient group. While the 30-day mortality rate for patients who received chemotherapy was 7.2% (110/1514), the mortality rate for patients who received immunotherapy (combined with chemotherapy or monotherapy) was 14.4% (15/104).

Conclusions: Our findings show that the 30-day mortality rate is high, especially in certain cancer types and after immunotherapy. In this patient group, it is necessary to review the treatment decision-making process before giving treatments with unclear clinical benefits. In addition, it is necessary to repeat our results in groups where disease types, disease stages, and treatment lines are homogeneous.

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2144P The PRognostic Oncologic Plantology (PROP) website tool predicts 30-day mortality in hospitalized cancer patients on treatment

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Background: Prognostic factors for oncologic outpatients have been described, including ECOG PS, tumor staging and malnutrition. However, there is no solid evidence on which variables best predict mortality for inpatients under active systemic treatment; here we present an optimized model validated externally to predict mortality in this population together with a website tool for better clinical applicability.

Methods: A prospective multicentric study of patients (pts) hospitalized between 2020-2022 at Vall d'Hebron (VH), Sant Pau (SP) and Mar Hospitals [PLANTOLOGY database] in Spain. Clinical factors and laboratory results were collected at admission. A logistic model has been trained in VH cohort with the variables selected by the LASSO method to predict 30-day mortality after discharge. As an interval validation in VH cohort a bootstrap with 1000 iterations was used. As an external validation (EV) SP and Mar cohorts were used.

Results: Out of 1,750 pts collected, 1006 had advanced disease and were under oncologic treatment during the 6 months before unplanned admission, our target population for model development (n=746) and EV (n=260). 30-day mortality was 30.6% (CI95% 27.4-34.1) and 23.3% (CI95% 18.3-29.1) in VH and EV cohort, respectively. Median age was 65 yrs, 43% had an ECOG >1, median Charlson comorbidity index was 8, and 42% were treated in a clinical trial. The most frequent tumor types were lung (23%) and colorectal (15%). The factors selected by LASSO were neutrophil count, LDH, ECOG PS, albumin, lung metastases, and treatment response at admission. The original c-index was 0.79, corrected c-index after bootstrap validation was 0.76 and c-index of external validation was 0.73 with perfect calibration. Negative predictive value and accuracy was 0.85/0.75 in VH and 0.86/0.74 in EV cohort. A website tool was created (odyssey.shinyapps.io/PROP) to facilitate the clinical implementation of our model.

Conclusions: Our model, which includes clinical and laboratory variables, accurately predicts the 30-day mortality risk (%) of cancer patients on active systemic treatment after admission. The PROP website tool may help clinicians make decisions and adjust medical interventions for hospitalized cancer patients.

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2145P Thromboembolic disease associated with cyclin-dependent kinase inhibitors in patients with breast cancer

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Background: The risk of venous and arterial thromboembolic events (VTE/AT) secondary to cyclin-dependent kinase inhibitors (CDKI) is not clearly defined. The objective is to characterize VTE/AT in patients with breast cancer (BC) treated with CDKI.

Methods: Retrospective, multicenter study promoted by the Thrombosis and Cancer Section of the Spanish Society of Medical Oncology (SEOM). Individuals with BC who initiated CDKI between 2015 and 2021 were recruited. We performed a descriptive analysis, analyzed the impact of VTE/AT on survival using Kaplan-Meier models and determined predictor variables using multivariate logistic regression.

Results: 849 patients were enrolled, with a median follow-up of 24 months. The incidence of VTE/AT during follow-up was 5.5% (n=47), with 34% pulmonary embolism (PE), 27.7% deep vein thrombosis (DVT), 14.9% simultaneous PE and DVT, 12.8% other forms of venous thrombosis, 8.5% arterial thrombosis and 2.1% mixed event (venous and arterial). Median time to VTE/AT was 6.9 months (interquartile range: 2.7-15.8). 31.9% of the events were diagnosed incidentally and 85.1% in an outpatient setting. One patient (2.1%) had recurrence and two (4.7%) had major bleeding. A higher proportion of thrombotic events was observed with abemaciclib (9%) compared to palbociclib (4.6%) and ribociclib (5.4%), but the differences were not significant (p=0.119). We found an association (p=0,036) between the type of CDKI and the form of VTE/AT: the most frequent with palbociclib was DVT (40.9%), with ribociclib arterial thrombosis (33.3%) and with abemaciclib PE (46.2%). Median overall survival was 49 months (95% CI 43-55.5) in the subgroup without VTE/AT, while in patients with VTE/AT it was not possible to calculate due to the low number of events. There were no significant differences (log-rank test = 0.427). Multivariate analysis revealed that the presence of metastases in the central nervous system (CNS) was associated with an increased risk of VTE/AT (OR 3.289, 95% CI 1.06-10.2).

Conclusions: CDKI-associated VTE/AT in patients with BC does not impact on survival. The type of CDKI is related to the form of presentation of VTE/AT. The presence of CNS metastases may predict these events.

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2146P Cancer-associated thrombosis clinic: Experience of the Medical Oncology Department of a hospital in Spain

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Background: Venous thromboembolism (VTE) in cancer patients is a common complication that requires a multidisciplinary management. In April 2021 we established in the Medical Oncology Department of our hospital a "Cancer-associated thrombosis (CAT) clinic" in order to provide immediate support in prevention and management of VTE to physicians involved in cancer patients' treatment. The aim of this analysis is to describe the characteristics of patients evaluated, the decisions taken and their results.

Methods: Between May 2021 and April 2023, 124 patients have been evaluated in the "CAT clinic" of the Medical Oncology Department of the Hospital General Universitario Gregorio Marañón (Madrid, Spain) with a mean follow-up of 4.25 months (standard deviation +/- 5.47 months).

Results: The main reason for referral to clinic was VTE treatment (n=120; 96.8%) and the most frequent thrombotic event was pulmonary thromboembolism (n=56; 46.7%). The most common tumors were breast (n=29; 23.4%), lung (n=21; 16.9%) and colon cancer (n=16; 12.9%). Most patients had metastatic disease (n=85; 72.0%), active cancer (n=101; 81.5%) or are receiving antineoplastic therapies (n=95; 76.6%). A modification of anticoagulation therapy was conducted in 99 patients (80.5%): change of anticoagulant drug in 77 patients (most of them from low molecular weight heparins to direct-acting oral anticoagulants [n=51;66.2%]) or change of anticoagulant dose in 49 patients (most of them from therapeutic dose to prophylactic dose in patients with low risk of recurrence and/or high risk of bleeding [n=27;55.1%]). Recurrence of VTE was observed in 8 patients (6.7%) and major bleeding (MB) in 4 patients (3.3%). In particular, 63 patients (52.5%) have received or are receiving apixaban for VTE treatment. No differences were observed between patients receiving apixaban and general population in tumor type, stage, antineoplastic treatment, or thrombotic event. VTE recurrence was seen in 2 patients (3.2%) and MB in 1 patient (1.6%) during apixaban treatment.

Conclusions: The "CAT clinic" has allowed us to adapt the anticoagulant treatment in most of patients, obtaining low complication rates (recurrence/bleeding).

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2147P Thrombotic recurrence and bleeding complications in non-small cell lung carcinoma (NSCLC) patients with venous thromboembolism (VTE)

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Background: VTE management in cancer patients, particularly those with NSCLC, poses unique challenges due to increased bleeding and recurrence risk during anticoagulation. This study is investigating the characteristics of NSCLC patients who experience thrombotic event while assessing thrombotic recurrence, bleeding pattern, and their association with prognosis.

Methods: From the international, multicenter, prospective TESEO registry of the Spanish Society of Medical Oncology (SEOM), we selected consecutive patients diagnosed with NSCLC and VTE between June 2018 and April 2023. Demographic, thrombotic event and anticoagulant treatment were analyzed.

Results: A total of 562 patients with NSCLC and VTE were assessed (Table, clinical characteristics). Deep vein thrombosis (DVT) occurred in 22.2% (n=125), pulmonary embolism (PE) in 69.5% (n=391), and catheter-associated thrombosis (CAT) in 2.1% (n=12). Most events (59.7%, n=336) were symptomatic, 46.2% (n=260) occurring within three months of cancer diagnosis. Post-anticoagulant treatment, arterial thrombosis appeared in 0.8% (n=5) and VTE recurrence in 6.0% (n=34), with 52.9% (n=18) being PE, 20.5% (n=7) DVT and 2.9% (n=1) CAT. Bleeding complications included clinically relevant bleeding in 3.3% (n=19), minor bleeding in the same percentage, and major bleeding in 1.4% (n=8). Thrombotic recurrence (p=0.24) and bleeding (p=0.12) were not associated with worse prognosis. Males had a higher risk of thrombotic recurrence (RR 1.05, 95% CI 1.01-1.09, p=0.024). Platinum analogs and KRAS mutation were also associated with a higher recurrence risk (p=0.019 and p=0.004, respectively).

Table 2147P Baseline characteristics

	N=562 (100%)
Sex	
Male	363 (64.5)
Age	
> 65	304 (54)
ECOG	
0-1	383 (68.1)
Comorbidities	
Hypertension	231 (41.1)
Dislipemia	233 (41.4)
Smoking habit	455 (80.9)
COPD	126 (22.4)
Previous VTE	38 (6.7)
TNM Stage	
Resectable	23 (4.0)
Locally advanced	91 (16.1)
Metastatic	448 (79.9)
Histology	
Adenocarcinoma	442 (78.6)
Squamous cell carcinoma	98 (17.4)
Neuroendocrine	3 (0.5)
Other	19 (3.3)
Antineoplastic treatment at the moment of VTE	
Surgery	76 (13.5)
Radiotherapy	187 (33.2)
Quimiotherapy	224 (39.8)
Inmunotherapy	120 (21.3)

Conclusions: Our study confirms a higher incidence of thrombotic recurrence than bleeding in patients with NSCLC. Thrombotic recurrence and bleeding complications were not associated with worse prognosis. Male patients, platinum analogs, and KRAS mutation were associated with higher risk of thrombotic recurrence.

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2148P Venous thromboembolism (VTE) in patients with advanced high grade ovarian carcinoma (aHGOC) receiving PARP inhibitors

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Background: VTE is a leading cause of death in pts with cancer, regardless of type. aHGOC is burdened by an VTE incidence of 20% and is listed as a high-risk malignancy for VTE. Treatment of aHGOC includes chemotherapy, bevacizumab and PARPi. Preclinical studies showed that the inhibition of PARP-1 could reduce endothelial dysfunction. Therefore, therapy with PARPi may potentially reduce the risk of VTE.

Methods: We conducted a retrospective single-centre observational study to describe rates, patterns and prognostic role of VTE events in patients with aHGOC receiving PARPi without bevacizumab. Pts included had received any PARPi for at least 8 weeks in any line of therapy, from Feb 2017 to Dec 2022. VTE events were identified by electronic medical record review and classified per CTCAE v5.0. Descriptive statistical analyses were performed for association with clinical outcomes (significance at p-value<0.05)

Results: Overall 166 pts were included. Baseline patients' characteristics and outcomes are reported in the table. The baseline risk of VTE event was low, according to ONKOTEV and Khorana score. After a median follow-up of 38.5 months, only 5 (3%) pts experienced a VTE event on PARPi: 1 superficial thrombosis (G1), 1 deep venous thrombosis (G2) and 3 asymptomatic pulmonary embolisms (G3). No treatment discontinuation due to VTE occurred and all the events were treated with low-molecular-weight heparins. The median time to VTE was 5.5 months (95% CI, 1.6-9.4) and median time from VTE to disease progression was 1.8 months (95% CI, 1.3-2.4).

Table: 2148P

	VTE N=5	Non-VTE N=161	p
Age at baseline, mean (SD)	63.8 (11.8)	57.9 (9.4)	.17
Previous VTE, %	20%	11%	.46
Baseline Khorana score, median (IQR)	1 (1-1)	1 (1-1)	.97
Baseline ONKOTEV, median (IQR)	1 (1-2)	1 (1-1)	.06
Anticoagulant prophylaxis at baseline, %	0%	8%	1.00
Bevacizumab within 6 months, %	0%	5%	1.00
Line of PARPi, median (IQR)	2 (2-4)	2 (1-3)	.26
Type of PARPi			.12
Olaparib, %	100%	53%	
Niraparib, %	0%	39%	
Rucaparib, %	0%	7%	
Number of cycles of therapy with PARPi, median (IQR)	7 (5-8)	12 (7-22)	.21
PARPi exposure, median (mo) (95% CI)	7.8 (6.1-8.7)	13.0 (8.9-17.1)	.72
PARPi-PFS, median (mo) (95% CI)	7.4 (6.1-8.6)	13.6 (9.5-17.7)	.38

Conclusions: Among pts with aHGOC receiving PARPi, VTE events were substantially low, suggesting a possible protective role of PARPi leading to reduced VTE risk. Conceivably, VTE occurrence may anticipate radiological disease progression.

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2149P Catheter-related thrombosis in cancer patients: Data from the registry of thrombosis and neoplasia of SEOM (TESEO)

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Background: Catheter-related thrombosis (CRT) is the most frequent non-infectious complication regarding central venous devices (CVC). Its incidence has been reported 13% and 66% in symptomatic and asymptomatic patients, respectively, with several factors influencing its development.

Methods: CRT events recorded at TESEO between 2018 and 2023 were assessed. Descriptive and association analysis for rethrombosis and bleeding regarding location of thromboembolic event (TE) was conducted.

Results: A total of 245 patients developed CRT. Mean age was 60.5 years (SD 12.3). Ninety-one percent were ECOG ≤1. Most prevalent comorbidities were HTA (28.6%) and dyslipidemia (28.2%), with other TE-associated risk factors being ≤10%. PICC was present in 42.1%, PAC in 40.9% while 17% were missing. Previous VTE was present in 9.8% of patients, while 4.5% and 4.4% were on antiplatelet and anticoagulation therapy, respectively. Colorectal and breast cancers were the primary locations in 26.9% and 21.2%. Metastatic disease was observed in 54.3%. Cytotoxic chemotherapy was used in 80.4%, radiotherapy in 22.9% and 53.9% had the primary tumor resected. PE was present in 6.5%, being clinically suspected in 56.2% of cases. The diagnosis was mainly unilateral (81.3%) and 50% were central. VTE — related symptoms occurred in 70.2% of cases at presentation. LMWH was used in 91% and hospital admission was advised in 20.8% of cases. VTE — related complications were observed in 2%, being PE and superior vena cava syndrome the most frequent (40%). Arterial and venous rethrombosis were present in 0.8% and 4.9%. Minor bleeding episodes occurred in 2.5% of cases, while major/clinically relevant episodes were present in 3.6%. There was no association between rethrombosis and TE location (pulmonary embolism (PE) vs deep vein thrombosis (DVT), OR 2.57 (95% CI 0.52 — 12.6; p = 0.245)). An increased risk for major and minor bleeding was observed for PE compared to DVT (OR 6.58 (95% CI 1.8 — 23.7)).

Conclusions: Usual TE — associated risk factors were infrequent. CRT was symptomatic in most cases, with reduced complication rates after treatment. A probable association of bleeding risk and no differences for rethrombosis were observed for PE events.

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2150P Clinical and molecular characterisation of cancer-associated venous thromboembolism (VTE)

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Background: VTE is a major, preventable complication in cancer patients (pts) and the second cause of mortality. Our aim is to describe clinical and pathological features of cancer pts with VTE and compare them to pts without VTE.

Methods: A retrospective case-control study of cancer pts with VTE diagnosed in 2022 at Vall Hebron Hospital (cases) and cancer pts without VTE treated at same centre (controls) was conducted. Clinical features including cancer site, stage, pathological/molecular profile, and therapy were registered; univariate analysis was performed.

Results: 85 cases and 100 controls were analysed. Cases characteristics: 53% females, mean age 61. Most common cancers shown in the table. Cancer was locally advanced/metastatic in 78.8%. According to Khorana score, 75.3% had intermediate/high risk for VTE. Most common histology in lung was adenocarcinoma (ADK) (72.7%); 14.3% *EGFR* mutated. In breast, 93.3% were invasive ductal carcinomas (IDC), 93.3% expressed hormone receptors (HR), 40% HER2 positive, 6.7% germline *BRCA* mutation. All CRC were ADKs, 40% *RAS* mutations and 13% microsatellite instability (MSI). 82.4% of pts received chemotherapy (CT), 16.5% immunotherapy (IO), 15.3% hormone therapy (HT), 12.9% antiangiogenics, 10.6% tyrosine kinase inhibitors. Comparative analysis (Table): female sex was associated with VTE (Odds Ratio [OR], 2; 95%CI, 1.1-3.6). As to cancer type, only breast was associated with VTE (OR, 2.6; 95% CI, 1.01-6.8). Conversely, head and neck cancers had negative association with VTE (OR, 0.2; 95%CI, 0.04-0.9). No differences were observed regarding cancer stage. CT (OR, 6.72; 95%CI, 3.4-13.3), HT (OR, 3.4; 95%CI, 1.2-10.1) and targeted therapies (OR, 3.06; 95%CI 1.43-6.56) were associated with VTE; IO was not.

Table: 2150P Characteristics of cases and controls

Characteristic	VTE cases (N=85)	Controls (N=100)	P value
Tumour site – no. (%)			
Lung	18 (21,3%)	30 (30%)	0.172
Breast	14 (16,47%)	7 (7%)	0.043*
CRC	12 (14,21%)	13 (13%)	0.825
Pancreas	9 (10,59%)	4 (4%)	0.081
Gynaecological	9 (10,59%)	8 (8%)	0.544
Gastroesophageal	4 (4,71%)	6 (6%)	0.726
Genitourinary	3 (3,53%)	6 (6%)	0.436
Head and neck	2 (2,35%)	11 (11%)	0.022*
Stage – no. (%)			
I	3 (3,53%)	6 (6%)	0.436
II	13 (15,29%)	10 (10%)	0.277
III	21 (24,71%)	21 (21%)	0.549
IV	46 (54,12%)	59 (59%)	0.504
Systemic therapies – no. (%)			
CT	70 (82,35%)	41 (41%)	<0.001*
Targeted therapy	25 (29,41%)	12 (12%)	0.003*
IO	14 (16,47%)	11 (11%)	0.278
HT	13 (15,29%)	5 (5%)	0.019*

Conclusions: Most common cancers in pts with VTE were lung (14% *EGFR* mutated), breast (HR positive 93%; HER2 positive 40%) and CRC (40% *RAS* mutated). Female sex and breast cancer were associated to VTE. CT, HT and targeted therapies were all associated with VTE.

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2151P Incidence patterns and clinical implications of venous thromboembolism (VTE) in patients (pts) with neuroendocrine tumors (NET)

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Background: VTE is a significant complication in oncology and one of the primary causes of cancer-related mortality. Few studies have addressed VTE in pts with NET, with an estimated incidence of 7.5%. Nevertheless, there is no evidence from large datasets. In the present study, we analyzed the incidence and treatment of VTE in NET.

Methods: Consecutive pts with gastroenteropancreatic (GEP) and thoracic NET treated in our institution between 2017 and 2018 were selected to study the incidence of VTE including deep vein thrombosis (DVT), pulmonary embolisms (PE) and splanchnic venous thrombosis (SVT). Information regarding clinical characteristics, follow up and VTE treatment were collected.

Results: 320 pts (55% female) were included in the analysis (40.6% pancreatic, 27.1% small intestine, 9.3% lung). 65 pts presented any thrombotic event (20.3%), and 23 were directly related to TNE (7.1%). Characteristics of patients with TNE-related VTE are enlisted in the table. The leading cause of SVT was splenic vein thrombosis (SPLVT). All cases that started anticoagulant therapy were treated with low-molecular-weight heparin (100%) and most of them indefinitely (53.8%). All cases that did not receive anticoagulant therapy were splenic vein thrombosis, due to physician decision. Any complication related to anticoagulant therapy was described in 3 pts (13%). No cases of VTE-related death were found.

Table 2151P Clinical characteristics of patients with NET-related VTE

NET-related VTE	N=23
Sex	Female 9 (39.1%) Male 14 (60.9%)
Age (median)	76
Primary tumor location	Pancreas 16 (69.5%) Small Intestine 5 (21.7%) Lung 1 (4.4%) Other 1 (4.4%)
Tumor grade	G1 7 (30.4%) G2 9 (39.2%) G3 7 (30.4%)
Tumor stage	I-III 3 (13%) IV 20 (87%)
VTE location	SVT 14 (60.9%) PE 7 (30.4%) DVT 2 (8.7%)
Anticoagulant therapy	Yes 13 (56.5%) No 10 (43.5%)

Conclusions: NET-related VTE appears in 7.1% of pts with NET. Most common profile is a male with advanced pancreatic neuroendocrine neoplasm and SPLVT. Impact on prognosis and the need for anticoagulant therapy remains controversial.

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2152P Prognostic importance of GRIM score on sorafenib side effects, hospitalization and survival in hepatocellular cancer patients

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Background: The Gustave Roussy Immune Score (GRIm-Score) was first used in 2017 as a prognostic index. Since the immune pathways in the pathogenesis of HCC has been demonstrated, it was aimed to examine the relationship between GRIm-score and patient survival, treatment side effects and the frequency of hospitalization in HCC patients.

Methods: In between 2010-2021, 108 patients with metastatic or unresectable HCC in our center were screened. Patients receiving sorafenib therapy and ecog 0-1 were included. Clinicopathological data, GRIm scores prior to the sorafenib treatment, previous treatment modalities of patients, hematological side effects of sorafenib, and hospitalizations to the oncology inpatient ward, excluding hospitalizations for planned procedure or chemotherapy, were recorded retrospectively. For the GRIM-Score, patients with NLR > 4.8, LDH > upper limit of normal, or albumin < 3.5 g/dL were given 1 point. Patients were divided in two groups according to the GRIM-Score as low and high.

Results: Sixty four patients were included in the study. Median age was 65 and 95.3% of the patients were male. 79.7% of them had chronic hepatitis. Most of the patients (68%) performed previous local ablative therapy. Low GRIM score (0-1) was demonstrated 60.9% of patients, whereas 39.1% of them had high score(2-3). Hematological side effects and/or AST elevation were observed in 32% of the patients. Hematological side effects were seen in 23% of all patients. During the follow-up period, 75.2% of the patients were hospitalized at least once. 72% of hospitalizations were for supportive treatment. The median number of hospitalizations was 1. The median OS was 5 months. The median survival in the low and high GRIm-score group was 8.8 and 2.7 months respectively ($p<0.0001$). Hospitalization requirement was found to be significantly higher in the high-GRIm score group compared to low GRIm-score group (p: 0.017). There was no significant difference between the presence of side effects and the GRIm-score group (p: 0.664).

Conclusions: The GRIm-score at the beginning of sorafenib therapy can be used as a significant marker both to determine survival and to predict the need for supportive care in metastatic/unresectable HCC patients.

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2153P Circulating biomarkers to predict severe complications in cancer patients with low-risk chemotherapy-associated febrile neutropenia

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Background: Febrile neutropenia (FN) is one of the most frequent and life-threatening complications in cancer patients. The most widely used model to identify low-risk FN episodes, candidates for outpatient management, is the Multinational Association for Supportive Care in Cancer (MASCC). However, its ability to predict serious complications is not optimal, occurring in up to 15% of episodes classified as low risk. The identification of circulating biomarkers may refine these indexes. We aimed to evaluate the role of C-reactive protein (CRP) and procalcitonin (PCT) in predicting the development of serious complications in low-risk FN episodes.

Methods: A retrospective study including FN episodes in patients with solid tumors presenting to the Emergency Department (ED), classified as low risk (MASCC score $\geq$ 21). In all episodes, a blood sample was collected on admission to the ED for analysis, including CRP and PCT. Outcome was defined as Intensive Care Unit (ICU) admission and/or death and/or other serious complications. To evaluate the discriminatory ability of biomarkers for outcome, Receiver Operating Characteristic (ROC) curve analysis was used and optimal cutoffs were calculated through Youden index.

Results: During the study period, 132 low-risk episodes were included (mean age: 58.4; SD: 11.5 years; 83 (62.9%) female). Serious complications were developed in 52 (39.4%) episodes. Median CRP and PCT levels were significantly higher in patients developing complications: 11.8 mg/dL (IQR: 5.21-19.6) vs 5.3 mg/dL (IQR: 2.2-9.0), $p < 0.001$; 0.42 ng/mL (IQR: 0.14-1.09) vs 0.12 ng/mL (0.06-0.23), $p < 0.001$, respectively. In ROC AUC analysis, both biomarkers achieved a similar predictive accuracy (CRP: 0.733 and PCT: 0.744). Optimal cutoffs were 9.8 mg/dL for CRP (Sensitivity (S): 61.5%, Specificity (Sp): 80%, positive predictive value (PPV): 66.7% and negative (NPV): 76.2%) and 0.27 ng/mL for PCT (S: 61.5%, Sp: 81.3%, PPV: 68.1%, NPV: 76.5%).

Conclusions: In chemotherapy-associated FN patients, circulating CRP and PCT levels might be useful to improve the risk stratification of low-risk episodes, contributing to decision making in the management of these patients.

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2154P Total cholesterol as an independent prognostic factor in cancer patient survival: A single institution experience

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Background: The role of lipid levels in the development and outcomes of cancer patients remains unclear in the literature. In this study, we aimed to analyze whether there is a relationship between total cholesterol levels and the survival of hospitalized cancer patients.

Methods: This retrospective observational study included patients admitted to the Medical Oncology Hospitalization Unit at La Paz University Hospital between September 2018 and January 2020. Total cholesterol levels, tumor type, treatment received, and mortality were analyzed.

Results: A total of 839 patients were included, with no differences in gender distribution. The most frequent tumor was lung (20.7%), followed by digestive tumors, including colorectal, esophagogastric, pancreatobiliary, or hepatic (33.4%), and breast (11.4%). The majority of patients were receiving active cancer-specific treatment, with chemotherapy (51.5%) or targeted treatments (18.6%) at the time of admission. At the end of the median follow-up period (31,8 months), 615 deaths had occurred (78.9%). The median overall survival (OS), regardless of tumor type, was 199 days. Having low total cholesterol values (less than 150 mg/dL) increased the risk of mortality by 25.9% compared to having physiological levels (150-200 mg/dL) ($p=0.016$, CI95% 1.045, 1.518)) with a Hazard Ratio of 1.259. Having high total cholesterol values (above 200 mg/dL) increased the risk of mortality by 30.6% compared to having physiological levels ($p=0.036$, CI95%(1.017, 1.677)) with an HR of 1.306.

Conclusions: To date, the majority of studies indicate that elevated cholesterol levels in patients with advanced cancer are associated with a higher risk of mortality, both due to a higher burden of comorbidity and the potential effects of cholesterol on oncogenic pathways. On the other hand, low cholesterol levels, possibly reflecting a significant metabolic dysregulation during cachexia, seem to be linked to a worse prognosis as well. Although the mechanisms by which high or low cholesterol levels increase the risk of mortality may differ, their incorporation into prognostic scores can contribute to a more accurate estimation of prognosis in advanced patients.

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2155P Outcomes with trastuzumab deruxtecan (T-DXd) retreatment after recovery from first interstitial lung disease/pneumonitis (ILD/p)

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Late withdrawal

2156P Use of taxanes during pregnancy: A systematic review

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Background: The use of chemotherapy (CT) with taxanes after the first trimester of pregnancy is endorsed by guidelines despite limited data on their safety. This study aims to review the neonatal and obstetric outcomes after the use of taxanes during pregnancy.

Methods: A MEDLINE search was performed up to 1/1/2023. Inclusion criteria included gestational taxane use, original findings, and reporting of individual patient outcomes.

Results: A total of 69 out of 316 references identified were included. Overall, 143 cases of gestational taxane use have been reported in the literature, resulting in 145 fetuses exposed in utero. Most received paclitaxel (78%) and were diagnosed with breast (59%), cervix (23%), or ovarian (13%) malignancies. Taxanes were initiated most frequently in the 2nd (69%) or 3rd trimesters (28%) of pregnancy (n=110), at a median gestational age of 17 weeks (range 2-32; n=89). The median cumulative dose received during pregnancy was 405 mg/m2 (range: 125-1200; n=63) for paclitaxel and 320 mg/m2 (range: 160-650; n=12) for docetaxel. Out of 107 cases, 91% received other CT agents during pregnancy, including platinums (50.4%) or doxorubicin/cyclophosphamide (17.8%). No maternal adverse events or obstetric complications were reported in 54% (41/97). The most frequent adverse obstetric events were preterm contractions (12/121; 10%), pre-eclampsia (6/97; 6%), intrauterine growth restriction (7/97; 7%), oligohydramnios (5/97; 5%), and preterm premature rupture of membranes (6/120; 5%). All cases with data available resulted in live birth (n=117). Preterm birth was reported in 63% (82/131) and 29% of neonates were classified as small for gestational age (36/123). Perinatal complications were documented in 18% (20/109), including one case of neonatal death secondary to multiple congenital malformations that had been detected before CT start. A congenital malformation was reported in 4% (6/142). Information of health status after birth was available for 85 cases (median follow-up 19 months, range 1 to 160), of which 87% were reported as healthy. Two cases of pediatric malignancy were noted.

Conclusions: Data on gestational taxane use is largely limited to case reports and small case series with heterogeneous reporting of outcomes. Future studies are urgently needed to evaluate their safety.

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2157P A phase II randomised controlled trial comparing the cardiotoxicity of capecitabine and S-1

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Background: Fluoropyrimidines are used widely to treat cancer but their cardiotoxicity, which remains incompletely understood, has serious consequences for some patients. The fluoropyrimidine S-1 (Teysuno®) has recently been approved for the management of colorectal cancer in patients who develop cardiovascular toxicity with other fluoropyrimidines.

Methods: This was a single-centre phase II prospective randomised open-label blinded endpoint trial that investigated the cardiotoxicity of capecitabine and S-1 in patients treated between May 2014 and March 2020. Patients were randomized 1:1 to receive oral capecitabine or S-1, alone or with oxaliplatin, for days 1-14 of a 21-day cycle. Baseline computed tomography coronary angiogram (CTCA) was performed. Myocardial ischaemia was quantified by ST-segment analysis of continuous 12-lead electrocardiography before and during days 3-5 of oral chemotherapy, by a blinded analyst. Alpha-fluoro-beta-alanine (FBAL) was measured using a validated liquid chromatography tandem mass spectrometry method.

Results: Fifty-nine patients (29 capecitabine; 30 S-1; mean age 64 years (range 40-83)) were enrolled, 56 started treatment and 72% (capecitabine) and 70% (S-1) received oxaliplatin. CTCA was performed in 53 patients, coronary artery disease (CAD) was seen in 30 (capecitabine, n=14/26; S-1, n=16/27). Duration of ST change was not significantly different between groups (p = 0.2198) but change in mean daily ischaemic burden (p=0.0442) was significantly higher for capecitabine compared to S-1. Ischaemic burden was unrelated to the presence of underlying CAD. FBAL (precursor to cardiotoxic fluoroacetate) was significantly increased with capecitabine compared to S-1 during treatment (Table).

Table: 2157P Mean FBAL (ng/mL) during fluoropyrimidine treatment

Week	Capecitabine (n=23)	S-1 (n=23)	P value
1	2507	95	<0.0001
2	2632	103	<0.0001
3	12	3	0.0083

Conclusions: In this prospective randomised trial, capecitabine was associated with significantly higher ischaemic burden and higher levels of FBAL than S-1 and this was unrelated to presence of CAD.

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2158P A self-assessment survey to identify the risk of patient's screen fail in phase I clinical trials (SCITEP trial)

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Background: Screen failures (SF) in early phase clinical trial are deleterious for patients, physicians and drug companies. It is therefore crucial to identify risk factors of SF, in order to optimize drug development and maximize patient's benefit.

Methods: We created a self-assessment survey (SCITEP score) comprising 15 questions extracted from the ESAS, EQ-5D and PALLIA 10 scores, which evaluate patient's (pts) symptoms and quality of life, each item being scored from 0 to 10 (i.e total score between 0 and 150). Patients entering a phase I clinical trial (ph1T) at Gustave Roussy cancer center between January 10th and October 26th 2022 were evaluated at screening (T0), and subsequently every month (T1, T2,..) until end of treatment.

Results: 227 of 275 pts entering a Ph1T were assessed between January 10th and October 26th 2022. Most frequent tumor types were lung (18%), GI (16%), hematological (10%) and gynecological cancer (9.3%); 56% were female. At data cut off (January 15th 2023), 25 pts were considered SF. There was no difference observed between SF pts and pts who went on with the trial in terms of ECOG, RMH score, albumin and LDH levels, number of previous lines of treatments and of metastatic sites at baseline (Table). At T0, there was a significant difference in the SCITEP score between SF pts and the others (median score 41 [IQR 26-63] vs 20 [IQR 10-38], p<0.001). Internal validity of the score was good (cronbach alpha > 0.7). With a cutoff of ≥35, sensitivity of the survey to identify pts at high risk of SF was of 66.6% and specificity of 70.5%. Regarding overall survival, pts with a score ≥35 (n= 68) at T0 were at higher risk of death (survival rate at 3 months of 53% vs 65%, p<0.01).

Table: 2158P

	SF pts (n= 25)	Non SF pts (n=202)	*p-value*
ECOG (IQR)	1 (0-1)	1 (0-1)	0.3
RMH score (IQR)	1 (0-1)	1 (0-1)	0.3
LDH level (IQR)	260(185-433)	222 (185-286)	0.2
Albumin level (IQR)	43 (36-45)	43 (41-45)	0.5
Nb of metastatic sites (IQR)	2 (2-3)	2 (2-3)	0.4
Nb previous lines of treatment (IQR)	3 (3-4)	3 (2-4)	0.04
SCITEP score (IQR)	41 (26-63)	20 (10-38)	<0.001

Conclusions: Self-assessment of risk of SF by pts entering a ph1T is feasible with the SCITEP score. A score ≥35 seemed associated with a higher risk of SF and of death at 3 months. Independent cohorts are needed to revalidate this score as a tool to better detect pts at risk of SF and thereby optimize drug development.

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2159P Machine learning algorithms to predict the risk of chemotherapy-related toxicity in older Asians

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Background: The International Society for Geriatric Oncology (SIOG) recommends the use of geriatric assessments (GA) or clinical adverse event risk predictors when managing older cancer patients. However, traditional GA and risk predictors are rarely utilized in the real-world setting due to limitations in time and resources. The objective of this study was to assess the performance of machine learning algorithms in predicting the risk of post-chemotherapy grade 3-5 toxicity in older Asian patients.

Methods: This study is based on a dataset of patients from a prospective study at the National University Cancer Institute, Singapore (NCIS) that successfully validated the CARG model in older Asian patients. In this study, 200 patients aged 70 years or older of various Asian ethnicities, with a solid tumor diagnosis and undergoing chemotherapy were prospectively recruited over the period of June 1, 2017, to January 1, 2019. We trained four machine learning models — Support Vector Machine (SVM), Random Forest (RF), Extreme Gradient Boosting (Xgboost), and Light Gradient Boosting Machine (Light DBM) to predict the outcomes of grade 3-5 (CTCAE version 4.0) adverse events post-chemotherapy.

Results: The median patient age was 74 years (IQR, 71 to 78), and 110 (55.0%) were male. 137 (68.5%) patients experienced grade 3 to 5 chemotherapy toxicity. The best-performing model for predicting grade 3-5 chemotherapy toxicity in the test set was the Xgboost model which achieved an area under the ROC curve (AUC) of 0.87. By comparison, the CARG clinical model and oncologist prediction of grade 3-5 toxicity achieved an AUC of 0.61 and 0.74 respectively in the test set. The best performing Xgboost model included elements of the CARG model in addition to clinical features such as the Karnofsky Performance Scale, number of co-morbidities and medications, current treatment line, "Timed-Up and Go".

Conclusions: The Xgboost Machine Learning model was able to predict the occurrence of grade 3-5 toxicity post-chemotherapy in elderly Asian patients with a better performance compared to the CARG clinical model and oncologists' predictions. These results will be further evaluated in external, prospective patient cohorts to validate them for clinical use.

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2160P Sociodemographic disparities associated with financial toxicity in stage IV non-small cell lung cancer survivors

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Background: The dawn of immunotherapies and tyrosine kinase inhibitors (TKI) for patients with metastatic non-small cell lung cancer (NSCLC) has brought about improved survival. As a consequence, there is now a rapidly growing population of lung cancer survivors (LCS), even in the metastatic setting. Little is known about patient reported outcomes such as financial toxicity during the survivorship period. We evaluated sociodemographic and clinical factors in LCS with metastatic disease at the time of diagnosis and whether these factors are associated with financial toxicity (FT) in a survivorship period.

Methods: We performed a survey study of 176 patients with stage IV NSCLC at diagnosis from December 2020 to March 2023. Surveys with 80% or more of self-reported demographic data completed and 100% of COST tool, a validated 11-part Likert-scale-based questionnaire measuring FT, were analyzed. Final analysis included 129 surveys. Descriptive statistics were used to categorize sociodemographic and clinical features of participants. The Kruskal-Wallis one-way analysis of variance was used to identify sociodemographic or clinical factors associated with FT.

Results: Females were significantly more likely to have completed survey data (p=0.0057). 56% of participants were female, 50% were above the age of sixty-five years, 74% Caucasian, 54% current/former smokers and 91% had an ECOG 0-1. Sixty percent were more than 2 years since diagnosis, 81% on active systemic therapy at the time of the survey, 48% received immunotherapy, and 60% received targeted therapies. Additionally, 76% had private insurance, 86% employed or retired, 20% had a change in employment after the diagnosis, 60% reported annual household income >$75,000 and 82% reported some college level or higher education. We identified that lower household income (p=0.001), unemployment status (p=0.02), and lower education levels (p=0.005) were significantly associated with worsened FT.

Conclusions: Sociodemographic factors are associated with disparities in financial toxicity in LCS with metastatic disease. Future work to identify high-risk populations and potential interventions, such as financial counseling, may improve disparities in patient reported outcomes.

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2161P Organization of hospital pharmaceutical consultations for cancer patients receiving oral anticancer drugs: A nationwide cross-sectional study

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Background: In France, cancer patients receiving oral anticancer drug (OAD) may benefit from pharmaceutical consultations (PC) with a hospital pharmacist (HPh) along the care pathway to ensure quality and safety of care. The purpose of this study was to evaluate how these PC are implemented in clinical practice in French hospitals.

Methods: We conducted a cross-sectional study including a national based panel of HPh. These professionals were identified via a committee of experts and their personal network, and using a National Database of Hospital Pharmacists Directory of Pharmacists in Health Establishments (OPAS data — 2020).

Results: 431 HPh were contacted, 72 (17 %) from 66 different hospital (corresponding to 14 % of chemotherapy-delivering hospitals in France) responded to the survey. 53 (73 %) of the respondents declared a care pathway was implemented in their institutions, 37 (52 %) with a coordination by a dedicated oncology nurse and 62 (85%) with a PC systematically proposed to patients. PC content was relatively homogeneous: medication reconciliation, assessment of patient's autonomy and understanding of the OAD treatment, side-effects prevention and management, and coordination with the community pharmacist and the general practitioner. Communication by HPh with patients' oncologist was almost systematic (66, 92 %), directly or using the hospital electronic health record. Concerning the time needed for PC: preparation of PC required more than 15 minutes for 41 (57 %) of the survey respondents, the consultation itself lasted 20 to 30 minutes for 33 (46 %) of them while time to report PC required more than 15 minutes for 35 (49 %) of them. 44 (61 %) of the respondents mentioned improved patient compliance, 68 (95 %) improved collaboration between healthcare professionals and 63 (87 %) increased patient satisfaction.

Conclusions: In addition to therapeutic innovation, extensive use of OAD has changed cancer patient management. PC implemented in a systematic way represent an innovative, achievable, and efficient way to improve patient care, facilitate coordination between healthcare professionals and increase patient satisfaction.

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2162P Can artificial intelligence provide accurate and reliable answers to cancer patients' questions? Comparison of chatbots based on the ESMO Patient Guide about cancer pain

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Background: There is limited data on the quality of cancer information provided by ChatGPT and other artificial intelligence systems. In this study, we aimed to compare the accuracy of information about cancer pain provided by chatbots (chatGPT, perplexity, and chatsonic) based on the questions and answers contained in the the European Medical Oncology Association (ESMO) Patient Guide about cancer pain.

Methods: Twenty questions were selected from the questions available in the ESMO Patient Guide Cancer Pain. Medical oncologists with more than 10 years of experience compared responses from chatbots (ChatGPT, Perplexity, and Chatsonic) with the ESMO patient guide. The primary evaluation criteria for the quality of the responses were accuracy, patient readability, and stability of response. The accuracy of responses was evaluated using a three-point scale: 1 for accuracy, 2 for a mixture of accurate and incorrect or outdated data, and 3 for wholly inaccurate. The Flesch-Kincaid readability (FKr) grade was used to measure readability. Stability of responses was evaluated whether the model's accuracy is consistent across different answers to the same question.

Results: Chatbots were more difficult to read than the ESMO patient guideline (FKr= 9.6 vs. 12.8, p= 0.072). Among the chatbots, perplexity had the easiest readability (FKr= 11.2). In the accuracy evaluation, the percentage of overall agreement for accuracy was 100% for ESMO answers and 96% for ChatGPT outputs for questions (k= 0.03, standard error= 0.08). Among the chatbots, the most accurate information was obtained with chatGPT.

Table: 2162P Comparison of ESMO and chatbots in terms of readibility and accuracy

	ESMO	Chatbots			
		ChatGPT	Perplexity	Chatsonic	p-value
Readibility (FKr grade)	9.6 Easily understood	13.4 Difficult to read	11.2 Fairly difficult to read	13.9 Difficult to read	0.072
Accuracy	%100	%96	%86	% 90	0.037

Conclusions: The results suggest that ChatGPT provides more accurate information about cancer pain compared with other chatbots.

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2163P Supportive care in French community pharmacies: OncoPharma certification

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Background: In France, cancer is the leading cause of death among men and the second leading cause among women. Currently, supportive care provided to cancer patients in community pharmacies are heterogeneous across the country. In order to structure and standardize pharmaceuticalsupportfor all cancer patients in primary care, TotumLab foundation has created the OncoPharma certification.

Methods: The OncoPharma certification is based on a framework that covers the activities of dispensing treatments andsupportingcancer patients, caregivers and relatives, from the time of diagnosis, during and after cancer, by the entire pharmacy team. The framework presents certified characteristics, the way to implement them, as well as documentary ressources and requested internal controls to ensure compliance. The development of the certification framework is the result of a multidisciplinary collaborative effort, bringing together all healthcare professionals involved in cancer patients care. The OncoPharma certification is accessible to all community pharmacies in France.

Results: In the certification framework, patient care is structured around 14 operational characteristics that are proposed and adapted to each individual situation. Since June 2022, the OncoPharma certification framework has been accredited by the French accreditation committee (COFRAC). This document allowed for the publication of the first clinical guideline for the management of cancer patients in community pharmacies by the Francophone Association of Supportive Oncology Care (AFSOS). As of April 2023, two pharmacies have been certified under OncoPharma, and over 40 others are in the process of certification.

Conclusions: This innovative project is the result of collective and multidisciplinary work to improve the quality of life of patients living with cancer. It promotes communication and coordination among healthcare professionals, as well as training and upskilling of pharmacy teams. This project is part of the continuous improvement and value creation in healthcare. Thanks to the Oncopharma certification, the community pharmacist plays a central role in the care of people with cancer.

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2164P The impact of cancer patients' face masks on oxygenation and Co2 retention during treatment

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Background: After the emergence of COVID-19, face masks(FMs) have been an important of our daily lives. They are cheap and effective. However, the clinical data in healthy adults concluded that they could result in hypoxemia and hypercapnia. The impact of FM in cancer patients is not known. In this study, we aimed to evaluate the impacts of FMs on oxygenation and CO2 retention of cancer patients who are under active treatment.

Methods: The patients who were on active treatment in oncology outpatient chemotherapy unit, were included. Besides routine pretreatment evaluation; the patient, disease and treatment characteristics were recorded. Pre and Posttreatment venous blood gases, pulse oximeter, vital signs were evaluated. The patients' compliance to wear FMs during the treatment was sustained and acute toxicities were noted. The changes in parameters, and the factors effecting the changes were statistically tested.

Results: 126 patients with a median age of 60 (33-85) were evaluated. 73.8% of the had at least one comorbidity, 16.7% with a diagnosis of COPD/ Asthma. Most of them has a diagnosis of breast cancer (32.5%) and half were under palliative treatment. The median treatment time was 150 minutes (90-410). The comparison of pre-post treatment parameters showed a statistically significant changes in Ph (7.37 vs 7.35, $p<0.01$), pCO2 (44.2 vs 45.8, $p=0.049$), HCO3 (25.7 vs 25.3, $p=0.003$), SpO2 (97.0 vs 96.0, $p=0.08$), fever (36.4 vs 36.3, $p=0.023$). All the changes were clinically insignificant and in normal ranges. The analysis of the factors related with these changes didn't point out a specific group of patients that were more prone to changes. There were a few acute toxicities in 3.2% of the patients. They had more post treatment mean arterial pressure (difference; 13.3 vs 0.0 mmHg, $p=0.04$).

Conclusions: In the patients under active treatment, FMs resulted in statistically significant but clinically non- significant changes in pH, pCO2, HCO3, SpO2 and fever. The FMs are effective and safe products in cancer patients under active treatment.

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2165P A French overview of electronic patient-reported outcomes use in 2022

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Background: Monitoring symptoms and toxicities through the use of electronic objects (electronic patient-reported outcomes, ePRO) has been shown to improve overall survival and quality of life in several clinical trials in oncology. We intended to investigate the use of ePRO in France in 2022.

Methods: An electronic form was sent to pharmacists in 416 cancer departments. Data were collected from October 2022 to December 2022. Pharmacists were asked about their use of ePRO, funding, potential improvements, and barriers to implementation.

Results: We obtained a participation rate of 25% (114/416 cancer departments, 2 were excluded due to misunderstanding). Only 13% (n=15) use ePRO.
ePRO users mentioned potential improvements in the technology : implementation of the ePRO platform directly into the patient record and a desire to improve communication between professionals (n=5). Difficulties they encountered were

mainly interoperability, which affects efficiency (n=5), and lack of human resources (n=3).
Of the 97 who do not use ePRO, 42% (n=41) are unaware of the existence of ePRO. 67% (n=65) of them would like to implement ePRO and hospital implementation is planned in 28% (n=27) of cancer departments. They describe possible difficulties due to lack of time to check patients' answers (74%, n=72), lack of human resources (67%, n=65), lack of financial resources (n=6, 6%), and digital literacy in elderly patients (5%, n=5).

Conclusions: A majority of cancer departments showed interest into ePROs. Two categories of improvements were identified : human resources to help with deployment, and better software to improve interoperability. The reimbursement of electronic monitoring starting in 2023 in France will encourage its incorporation in routine practice.

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2166P Long-term consequences of SARS-CoV-2 infection in cancer patients

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Background: Long COVID is defined as the continuation of symptoms, unexplainable by alternative diagnosis, longer than four weeks after SARS-CoV-2 infection. Several studies report fatigue as the most common symptom, followed by dyspnoea, headache and myalgia. Although it is assumed that long COVID affects 10-20% of SARS-CoV-2 infected people, recent research suggests this number increases up to 60% in cancer patients. This study uncovers how long COVID is manifested in cancer patients and whether the COVID-19 pandemic impacts the quality of life (QoL) in this cohort.

Methods: A group of 96 cancer patients was followed from March 2022 till March 2023. Online questionnaires assessing symptoms associated with long COVID, anxiety and depression (HADS), quality of life (EORTC-QLQ-C30) and cognitive functioning (CFQ) were send every three months during this period. A semi-structured focus group was organised for qualitative data collection.

Results: Forty nine cancer patients (51.0%) were infected with SARS-CoV-2 over the course of the study, of which 39 (79.6%) reported persisting long COVID symptoms that were absent before infection. The most commonly reported symptoms were myalgia (46.2%), fatigue (38.5%) and disturbed sleep (35.9%). On top of this, 25.6% of the patients reported difficulty concentrating, headaches and dyspnoea, as described in other studies. Although the presence of myasthenia and persisting cough are not frequently linked to long COVID, they were frequently reported (25.6%) within our study population. We observed that the presence of long COVID symptoms is associated with increased BMI and the presence of comorbidities. Oncological patients reported a negative impact of the enforced COVID-19 restrictions on their emotional and psychological wellbeing. Independent of patients' infection status, female sex and metastatic cancer are associated with reduced QoL during the pandemic.

Conclusions: The COVID-19 pandemic negatively impacted the QoL of cancer patients, even when patients did not suffer from long COVID. While cancer patients experience similar long COVID symptoms as healthy controls, the prevalence is remarkably higher. Long COVID might be more prevalent in cancer patients because of their compromised immune system and weakened physiological reserve.

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2167P Are bone targeted agents (BTAs) still useful in times of immunotherapy? The SAKK 80/19 BTA study

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Background: Patients (pts) with bone metastases (BM) from solid tumors often have additional treatment with BTAs to avoid symptomatic skeletal events (SSEs) such as clinically significant pathological fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression. The absolute value of BTA treatment in the era of immunotherapy (IO) is unknown.

Methods: Pts with BM treated with IO within the Alpine Tumor Immunology Registry who received an additional BTA (denosumab, zoledronic acid) were compared with pts who have not received a BTA. The primary endpoint was time to first SSE. Continuous data was summarized as median and range, categorical data using frequency counts and percentages. Kaplan-Meier estimates were used to describe and visualize the effect of categorical variables.

Results: In total, 197 pts with BM and treated with IO such as nivolumab (48%), pembrolizumab (40%), atezolizumab (12%), ipilimumab (9%) and other IO (5%) were included. The most frequent tumor types were lung cancer (50%), malignant melanoma (11%), renal cell cancer (10%) and bladder cancer (9%), respectively. One hundred and twenty-two pts (62%) received a BTA treatment (91% denosumab). The median treatment duration of a BTA was 178 days (min: 1 day, max: 2010 days). Out of the 197 pts, 47 pts (24%) experienced at least one SSE, 100 pts (51%) had bone pain, and 11 pts (6%) developed osteonecrosis of the jaw (ONJ). The percentage of pts without a SSE at fixed time points was numerically higher if treated with a BTA (e.g., at 6 month, 86% [95% CI: 79%-91%] versus 78% [95% CI: 66%-86%]), but no significant difference in time to first SSE (HR 0.79; 95% CI 0.44-1.42, log-rank p=0.43) or time to first bone pain (HR 1.1; 95% CI 0.73-1.69, log-rank p=0.6) between these two groups could be detected. The median OS for pts treated with a BTA was 1.7 years (95% CI: 1.1-2.0) and 1.7 years (95% CI: 1.4 -2.9) for pts not received a BTA.

Conclusions: No significant difference in time to first SSE or bone pain was observed between pts who have received a BTA or not when treated with IO. In contrast, 6% of these pts experienced an ONJ. Based on these retrospective results the indication of BTAs in cancer pts under treatment with IO must be challenged. Further prospective evaluation in a larger patient cohort is on the way.

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2168P At-home infusion of immunotherapy for patients with solid tumors: First results from a single-centre program

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Background: The use of immunotherapy (IO) has revolutionized cancer treatment, providing a growing number of patients with substantial benefits across multiple indications. Typically, IO is administered through intravenous infusion lasting a few hours in the outpatient clinic with infrequent occurrence of infusion-related reactions (IRRs). This study aims to determine the feasibility and convenience of administering IO in a home-based setting.

Methods: Starting from July 2021, the Hospital Clinic de Barcelona has provided patients with solid organ cancers undergoing monotherapy nivolumab, pembrolizumab or atezolizumab, the option to receive treatment at home. Patient participation was voluntary and required written informed consent. The aims of this research were to 1) collect clinical data of this experience, 2) report complications, and 3) assess patient satisfaction using the SATISFAD-10 questionnaire. Descriptive statistics were used.

Results: The study enrolled 41 patients, 63% male with a mean age of 74 years. Of these, 56% had two or more comorbidities and 44% were fragile. All patients suffered from stage IV neoplasms, with non-small cell lung cancer (63%), small cell lung cancer (12%), and malignant melanoma (10%) being the most prevalent types. Pembrolizumab (49%), atezolizumab (27%), and nivolumab (24%) were the administered drugs, with peripheral line infusion (59%) and port-a-cath (39%) being the two common infusion routes. To date, 229 IO infusions have been administered (mean per patient: 5.6; range 1-24). At present, 22 patients still receive IO at home, while the others have been excluded due to changes in cancer treatment (47%), completed IO (10.5%), or death (26%). There have been no voluntary dropouts, and no IRR have occurred. Patients' satisfaction has been assessed every three months through the SATISFAD-10 questionnaire, with an average score of 29.7 points out of a maximum of 30, indicating high levels of satisfaction.

Conclusions: Home-based IO administration for patients with solid organ cancers appears to be a feasible and convenient option, with high patient satisfaction and a low incidence of IRR. Further research with a larger sample size may be required to confirm these findings.

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2169P Immunotherapy-based treatment in elderly cancer patients: A real-world multicenter study

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Background: The incidence of cancer increases with age, advanced age remains the most important risk factor for most cancers. According to epidemiological statistics, the probability of developing invasive cancer in each age group is highest in the 70 years and older group, reaching 1/4 to 1/3. Immunotherapy is increasingly indicated for solid tumors, but toxicity and efficacy in older adults [age ≥70 years(y)] are unknown. The purpose of this study was to determine age-based differences in OS and treatment-related side effects.

Methods: This is a multicenter retrospective cohort study of patients with advanced cancer. Patients who received ≥1 dose of IO from January 1, 2019 to October 1, 2021 at three centers in China were collected to extract important information from the medical records. The primary outcome was PFS and OS since the start of the first IO treatment, compared between patients of different ages.

Results: We included 302 patients aged 60 to 99 years, of whom 157 were 60-69 years (younger group,YG) and 145 were 70 years and older (older group,OG), including 31 patients aged 80 years and older (senior group,SG). In all age groups, the proportion of patients in the OG group treated with immune combination therapy was relatively less than in the two younger age groups. Adverse event (AE) associated with immunotherapy was not higher in the older group than in the relatively younger cohort. there were no statistical differences in PFS and OS between the YG and OG groups, with median PFS of 12 months vs. 10 months, P=0.5465; median OS NA vs. 32 months, P=0.1429. Further subgroup analysis showed that the SG group had a median PFS of 10 months and median OS of 23 months, which was also not statistically different compared with other groups.

Table: 2169P Immunotherapy-related adverse events

	N (%) of 60-69 N=157	N (%) of 70 and older cohort N=145	P
Any grade toxicity	31.8%	37.9%	0.2788
>=Grade 3 toxicity	10.8%	9.0%	0.7010
>=Grade 3 toxicity types			
Dermatitis	1.9%	4.1%	0.2555
Colitis	2.5%	2.1%	0.7823
Abnormal thyroid function	1.9%	2.8%	0.7140
Hepatitis	3.8%	1.4%	0.2856
Pneumonitis	4.5%	2.8%	0.5449
Other	1.3%	0.7%	0.6049

Conclusions: IO-based therapy is relatively safe in elderly patients and provides a survival benefit in this group, allowing for prospective clinical studies in older patients to further determine the value of immunotherapy.

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2171P Incidence of adverse events in patients treated with a combination of immune checkpoint blockers and chemotherapy: A real life cohort

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Background: Chemotherapy combined with immune checkpoint blockers (ICB) is now the standard of care for treatment in multiple advanced tumor types with two spectrums of adverse events related to cytotoxic agents and immune related (irAEs). Clinical manifestations of irAEs can mimic chemotherapy toxicity in several aspects while the management remains completely different.

Methods: We conducted a retrospective review of the medical records for patients with metastatic cancers treated with chemo-immunotherapy combinations at Gustave Roussy Cancer Center from Sep 1st 2020 to Dec 31st 2022, included in the REISAMIC database (Registry of Severe Adverse Reactions to Immunomodulatory Monoclonal Antibodies in Cancer). Adverse events are reported according to the Common Terminology Criteria for Adverse Events v5.0.

Results: Our cohort includes 261 patients with a median age of 64 years [30-93], 79% of patients with lung cancer, 9% triple- negative breast cancer; 8.5% head and neck carcinoma, and 2.5% upper digestive tract tumors. Treatment discontinuation rate for toxicity was 11% in our cohort; we also reported five toxic deaths. A total of 83% of the patients presented all grade adverse events, with 38% grade ≥3 toxicities most commonly hematological. Out of all the adverse events (AEs), 53.4% were attributed to chemotherapy while 15.4% were considered irAEs. Median days until chemotherapy induced AEs was 40 days and the majority resolved in ≤2 weeks, while median days until irAEs was 105 days and the majority required 2-12 weeks until resolution. AEs of special interest included one case of myocarditis, 2 cases of hypophysitis, thyroid disorder in 25 patients, 2 cases of immune mediated diabetes revealed by diabetic ketoacidosis, and 9 cases of autoimmune hepatitis.The relapse rate after immunotherapy rechallenge was 13%.

Conclusions: In this real-life cohort of patients treated with chemo-immunotherapy we observe a reassuring safety profile concordant with data reported in clinical trials. Expert opinion, radiological exams, histological evidence and biological data were employed to distinguish the implication of either drugs in toxic mechanisms in order to tailor the management, and minimize treatment interruptions.

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Baldini: Financial Interests, Institutional, Principal Investigator: AbbVie, Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca Ab, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Bbb Technologies Bv, Beige; Financial Interests, Personal and Institutional, Speaker, Consultant, Advisor: Bicycle therapeutics, Rising Tide Fundation, ITEOS; Financial Interests, Personal and Institutional, Royalties: GSK, BMS, AZ, Amgen, Sanofi, MSD travel accommodation; Financial Interests, Institutional, Research Grant: BMS Fundation, AstraZeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi; Non-Financial Interests, Institutional, Product Samples: AstraZeneca, Bayer, BMS, Boringher Ingelheim, GSK, MedImmune, Merck, NH TherAGuiX, Pfizer, Roche. All other authors have declared no conflicts of interest.

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2172P Development and evaluation of the usefulness of an immune-related adverse events interview application

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Background: The use of immune checkpoint inhibitors (ICIs) needs monitoring for the development of serious immune-related adverse events (irAEs). Here, we developed a smartphone application (an irAEs self-reported interview system: ISRIS) to enable early detection of irAEs while outpatients are at home and evaluated its usefulness.

Methods: This investigation included outpatients who received ICIs between September 2020 and February 2023 and had the application installed on their smartphones. The investigation items included treatment regimen and its dosage, type of irAE and the grade, frequency of ISRIS usage, and sensitivity and specificity for detecting irAEs to evaluate the efficacy of our ISRIS system.

Results: In total, sixty-one patients (female/male: 13/39, mean age: 65 y.o., range: 26-87 y.o.) installed the application on their smartphones. irAEs occurred in twenty-four patients; the irAEs detectable by the app included interstitial pneumonia (n=7), thyroid dysfunction (n=4), skin disorders (n=4), adrenocortical dysfunction (n=3), colitis (n=2), myocarditis (n=1), uveitis (n=1), liver disorders (n=1), and Guillain-Barré syndrome (n=1). Among patients with irAEs, thirteen patients had installed the application at least one week before the irAE onset; of these, irAEs were detected by ISRIS in eight patients, indicating 62% sensitivity and 57% specificity, respectively.

Conclusions: Our ISRIS application for smartphones allows healthcare professionals to monitor the physical condition of patients with cancer in real time via self-reported interview data for early intervention, even when the patient is at home, facilitating the early detection and response to irAEs. In addition, having healthcare professionals review the results of the interview can reduce patient anxiety about adverse reactions, thereby contributing to treatment continuation.

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2173P Exploring the complex needs of older patients receiving targeted therapies and immune checkpoint inhibitors for renal and skin cancers at the Royal Marsden Hospital

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Background: Fifty-four percent of new cancer cases in the UK occur in patients ≥65 years. Prior evidence supports the need for a comprehensive geriatric assessment (CGA) to inform treatment decision making in this heterogenous population. This study aimed to assess the needs of older patients with renal and skin cancers in a tertiary referral centre.

Methods: The Senior Adult Oncology Programme Questionnaire (SAOP3) has been validated as a geriatric screening tool covering functional status and physical performance, nutrition, speech and language, cognition and psychosocial issues. SAOP3 was used to assess out-patients ≥70 years receiving or referred for consideration of systemic anti-cancer therapy (SACT) for renal or skin cancers. Comorbidities, admissions and emergency contacts frequency were obtained from electronic patient records. The primary endpoint was the number of patients identified as potentially requiring geriatric assessment-driven interventions.

Results: Between 29/7/2022 − 18/11/2022, 36 patients were assessed using SAOP3 with a mean age of 74 years (range 70-94). Despite 83% (30/36) of patients being identified as potentially requiring CGA-driven interventions, 28% (10/36) of patients were deemed fit enough for combination therapy including dual immunotherapy (IO) or tyrosine kinase inhibitors (TKI) plus IO. Mobility problems were the most common driver of a recommendation for CGA-led intervention (78%; 28/36) with 31% (11/36)

of patients reporting loss of balance or a fall in the past year. At ≥6 months from screening, 36% (13/36) of patients had ≥1 admission (range per patient 0-5; total 25) and 36% (13/36) patients called the telephone support line (range per patient 0-5; total 27).

Table: 2173P Table of characteristics

Diagnosis	n	%
Renal cell	22	61
Squamous cell carcinoma (skin)	2	6
Melanoma	11	30
Other	1	3
Reason for questionnaire	n	%
New patient	10	28
Change of treatment	6	17
Mid treatment	20	55
ECOG performance status	n	%
0	4	11
1	20	56
2	11	30
3	1	3
Treatment intent	n	%
Palliative	35	97
Adjuvant	1	3
Line of treatment (metastatic)	n	%
1	23	68
2	9	26
3	2	6
Treatment	n	%
Tyrosine kinase inhibitors (TKI)	7	19
Single agent check point inhibitor (CPI)	13	36
TKI + IO	5	14
Dual CPI	5	14
Other	5	14
No SACT after assessment	1	3

Conclusions: Our study highlighted that this patient population has complex needs and supports the establishment of the Senior Adult Oncology Programme in our centre and geriatric oncology services more widely.

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2174P The impact of exposure to antibiotic (ATB) and proton pump inhibitor (PPI) therapy on immune checkpoint inhibitor (ICI) treatment on overall survival (OS): A population-based study

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Background: PPIs and ATBs have been individually demonstrated to negatively impact ICIs outcomes due to their effects on the gut microbiome. However, many were smaller studies with heterogeneity in study design, ATB classes and exposure windows and few studies have studied both together. Here, we performed a population-level retrospective cohort study evaluating the impact of both PPI and ATB exposure prior to ICI on OS.

Methods: We used population-level administrative data to identify a cohort of cancer patients ≥ 65 years of age receiving ICIs from 06/2012 to 10/2018 in Ontario, Canada and deterministically linked with databases to obtain demographics, co-variates and PPI and ATB prescription claims. Patients were grouped as having PPI only (PPI+/ATB-), ATB only (PPI-/ATB+), both exposures (PPI+/ATB+), or neither (PPI-/ATB-) at 1 year and 60 days prior to ICI. Multivariable cox-proportional hazard models evaluated exposure both within 1 year and 60 days prior to starting ICI on OS, adjusted for age, gender, body mass index, comorbidities, autoimmune history, hospitalization in the past year and treatment facility level at start of ICI therapy.

Results: Among 2737 patients, median age 73; 43% received Nivolumab, 41% Pembrolizumab and 13% Ipilimumab; 53% had lung cancer, 34% melanoma. 59% and 19% of patients received any ATBs 1 year and 60 days before ICI therapy, respectively and PPIs 45% and 26% respectively. Median OS estimate was 306 days. Results at 1 year and 60 days are listed below. In ATB subclass analysis, exposure to both cephalosporins and PPIs within 60 days had the greatest impact on OS compared to PPI-/ATB- (aHR=1.76, 95% CI (1.23-2.48), p=0.002).

Table: 2174P Summary of association of ATB and PPI exposure on ICI outcomes in overall cohort

	1 year before ICI			60 days before ICI		
	N	aHR (95% CI)	P Value	N	aHR (95% CI)	P Value
PPI+/ATB+	799	1.33 (1.16-1.52)	<0.0001	174	1.34 (1.10-1.62)	0.003
PPI+/ATB-	431	1.21 (1.03-1.42)	0.02	550	1.24 (1.10-1.41)	0.0005
PPI-/ATB+	828	1.11 (0.97-1.28)	0.12	358	1.04 (0.89-1.21)	0.66
PPI-/ATB-	679	Reference	-	1655	Reference	-

Conclusions: Exposure to PPIs and ATBs together prior to ICI therapy may be associated with worse OS than exposure to either alone. Interventions aimed at altering the gut microbiome may be required to help improve outcomes for patients on ICIs with prior PPI or ATB exposure.

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2175P Sex and age-related differences in immunotherapy-induced toxicities

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Background: Immune checkpoint inhibitors (ICI) are widely used across various cancers and are associated with immune-related adverse events (irAE) potentially lethal. Therefore, it is important to identify risk factors for developing irAE. Women have a higher risk of AE from cytotoxic therapy, however few studies investigated sex differences with ICI. Elderly remain under-represented in clinical trials, including those with ICI. In this study we aim to detect sex and age differences for toxicities in patients treated with ICI.

Methods: This retrospective study included all cancer patients treated with ICI in a single Portuguese institution between January 2017 to December 2022. Data regarding patient, treatment and toxicity was collected from clinical records. Toxicities were recorded using CTCAE, version 5. A descriptive analysis was performed using SPSS®. The Chi-square test was used for 2 categorical variables: sex (male and female) and age (≥65 and <65).

Results: We included 141 patients with a median age of 66 and the majority (87%) were men. Most patients had lung cancer (76%) and were treated with pembrolizumab (53%). The most reported AE were gastrointestinal (GI) (n=115; 23,8%), cutaneous (n=96; 19,8%) and flu-like symptoms (n=56; 11,6%). Only 14,3% of AE were grade ≥3 and lead to treatment suspension in 11,3% of patients. Women reported a higher mean of AE (4,53 vs 3,19; p=0,03). For grade ≥ 3 toxicities, no differences between sexes were found (5,3% vs 15,6%, p=0,231). Among all AE, no differences were found, except for endocrine AE more likely experienced by women (OR=3,02, p=0,024). There were no differences in all grade and ≥G3 toxicities between age groups with a higher trend in the group ≥ 65 years (18,2% vs 9,3%). In parallel, the elderly discontinued treatment more often (14,3% vs 7,8%) due to toxicity. Patients ≥ 65 years had more all grade GI (OR=2,15; p=0,026) and flu-like AE (OR =2,24; p=0,023). Still, there were more respiratory AE in younger patients (OR=0,21; p=0,006).

Conclusions: Despite study limitations, results showed no sex and age differences in irAE, although women and elderly had a higher number of AE, which translated in higher treatment suspension. This data reinforces the need for further studies to promote age and sex-related interventions in management of irAE.

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2176P Rechallenge of immune checkpoint inhibitors after immune-related adverse events: A systematic review

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Background: Immune check point inhibitors (ICI)-based therapies have been remarkably advancing and dramatically changing the treatment modalities of cancer. This review aimed to comprehensively examine and rechallenge immune-related adverse events (irAE) across the literature.

Methods: We searched for clinical studies regarding the use of ICI published in English up to December 2021 in PubMed, Embase, Cochrane and journal of clinical oncology (JCO). The search strategy was composed of the following terms: [(rechallenge) AND (immune OR immunotherapy OR "immune checkpoint inhibitor")] AND ("side effect" OR "adverse event" OR irAE). Data were extracted by three independent investigators and the disagreements amongst investigators were resolved by consensus.

Results: The average duration of administration of ICI before the occurrence of irAE was 5.8 months (range 0.5 − 9). Discontinuation rate of ICI was 4-36.4% after the occurrence of irAE. IrAE leading to discontinuation varied depending on the type of ICI. However, the most common side effect was colitis with diarrhea regardless of the type of ICI. After ICI rechallenge, second irAE was administered to 40.3-78% of patient, and 48% of patients presented the same type of irAE as the first irAE.

Conclusions: ICI rechallenge appears to be safe given the balance between the advantages of rechallenge and the risk of irAE recurrence maintained by close monitoring.

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2177P Immunotherapy adverse events association with inflammation scores: A real-world data analysis from a Portuguese hospital

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Background: Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment but they often carry a wide spectrum of immune-related adverse events (irAE), which might preclude treatment continuation. Biomarkers predictive of irAE would be useful to better select and manage patients for ICI therapy.

Methods: This retrospective analysis included patients treated with ≥3 cycles of ICI, regardless of the primary tumour, in a single hospital in Portugal, from January 2017 to December 2022. Data regarding irAE was collected, as well as baseline neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR) ratios and systemic imune-inflammation index (SII, given by platelets*neutrophils/lymphocytes). Scores were categorized using cutoff values described in literature, as NLR≥3, PLR≥180 and SII≥750. Descriptive analysis was performed using SPSS®. Association between the scores and irAE was analyzed using logistic regression.

Results: 141 patients were included. 87% were males and the median age was 66. Most common diagnoses were non-small cell lung cancer (75%) and head and neck cancer (7%) and main ICI were pembrolizumab (53%), durvalumab (18%) and nivolumab (16%), with a 10 cycles median. 137 (97%) patients developed irAE: digestive (24%), cutaneous (20%), flu-like symptoms (12%) and others. 15% had grade ≥3 irAE, leading to ICI suspension in 11%. 55% died during follow-up, most due to disease progression, 1 due to irAE. Median inflammation scores were 3,5 (NLR), 175 (PLR) and 818 (SII). A statistically significant correlation was found between NLR≥3 and gastrointestinal (p 0,007, OR 0,375) and respiratory AE (p 0,023, OR 3,608); SII≥750 and gastrointestinal (p=0,015, OR=0,413), respiratory (p 0,020, OR 0,255) and musculoskeletal AE (p 0,015, OR 0,342); PLR≥180 and hepatic (p 0,045, OR 2,934) and musculoskeletal AE (p 0,045, OR 0,446). There was no correlation with the presence of grade ≥3 AEs nor with survival.

Conclusions: In this study baseline inflammation scores were associated with some irAEs but not with survival as described in literature. These findings support a correlation between systemic inflammation status and tolerability to immunotherapy and show the value of inflammatory scores as potential biomarkers of irAE.

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2179P Prospective monitoring of autoimmune events in cancer immunotherapy patients: A report on the first 658 patients in the PRAISE study

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Background: In cancer immunotherapy, the epidemiology of irAE in real-life is poorly understood due to limited reporting and compartmentalization of the healthcare system. This study aims to determine the incidence, severity, and consequences of irAE of all grades in patients initiating cancer immunotherapy using a prospective and multicenter cohort.

Methods: The study will include 900 patients treated with ipilimumab and/or nivolumab in a French real-life, longitudinal, observational, and e-cohort study. Data collection is conducted through digital questionnaires, with physician validation and soon-to-be-matched analysis with the National Health System.

Results: 658 patients (70.7% men, 29.3% women, mean age 66) were followed up for a median of 198 days. Of those, 75.8% were treated with Nivolumab alone, 1.2% with Ipilimumab alone, and 22.9% with a combination. Lung cancer, clear cell renal carcinoma, and melanoma were the most common histological types treated. At analysis, 115 immune related adverse events (irAE) were observed in 11.7% of patients (30.5 irAE/100 patient/years) at a median time of 155 (+/- 128) days after initiating immunotherapy. Approximately 30% of reported irAE were rheumatological, and the remaining cases included: colitis (15), hepatitis (8), pancreatitis (2), ileitis (1), myocarditis (2), nephritis (2), immuno-induced pneumopathy (3), macrophage activation syndrome (1), type 1 diabetes (2), hypophysitis (3), adrenal insufficiency (9), thyroid disorder (15), bullous pemphigoid (1), uveitis (1), and other autoimmune manifestations (23). 40 patients discontinued immunotherapy due to irAE, and treatment with corticosteroids was administered in 44 patients (57.1%). Methotrexate (n=1), infliximab (n=3), and abatacept (n=1) were also used to treat specific irAE. One patient died as a result of irAE (colitis).

Conclusions: The preliminary results of this prospective study, using an original patient-centered methodology, confirm the expected incidence of secondary autoimmune events related to immunotherapy. Further inclusions and matching with the SNDS database will allow for the completion of these initial analyses if necessary.

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2180P Detrimental effect of an early exposure to antibiotics on the outcomes of immunotherapy in a multi-tumor cohort of patients

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Background: The modulation of microbiome by antibiotics (Abs) seems to interfere with the efficacy of immune checkpoint inhibitors (ICI). Previous data suggest that this

effect is stronger when the exposure to Abs occurs around the beginning of ICI, although this has not been evaluated in large multi-tumor cohorts.

Methods: Retrospective study of patients (pts) with advanced solid tumors who were treated with ICI alone (2016-2022) at a tertiary university hospital. For each pt, the exposure to Abs was registered during several periods of time: from 60 days before to 42 days after 1st cycle (C1) (-60D-D42), from D42 to 6 months (D42-6m) and after 6 months from C1 (>6m). We evaluated its association with the objective response rate (ORR), the disease control rate (DCR), progression-free survival (PFS) and overall survival (OS).

Results: 475 pts were evaluated. The most frequent histologic subtypes were NSCLC (33.9%), urothelial (17.3%), renal (13.7%), melanoma (11.2%) and head and neck (11.0%). 84.8% of pts received anti-PD1/PDL1, 13.3% a combination of anti-PD1 plus anti-CTLA4, and 1.9% anti-CTLA4 monotherapy (42.1% in 1st line, 43.1% in 2nd line, 14.8% in further lines). Performance status (PS) prior to C1 was 0-1 in 84.6%. Median age was 67.5 years. 66.5% of pts received Abs during treatment with ICI (25.7%: 1 cycle; 16.0%: 2 cycles; 11.0%: 3 cycles; 13.8% ≥4 cycles). The most frequently used Abs were beta-lactams (53.8%), quinolones (35.9%), carbapenems (10.9%) and macrolides (10.9%). The early exposure to Abs (-60D-D42) was associated with a lower ORR (27.4% vs 39.4%; $p<0.01$), a lower DCR (37.3% vs 57.4%; $p<0.001$), lower PFS (16.8 m vs 27.8 m; HR 0.66 [95% CI 0.53-0.82; $p<0.001$]) and lower OS (2.5 m vs 6.6 m; HR 0.68 [95% CI 0.55-0.85; $p=0.001$]). The negative impact of Abs was confirmed by a multivariate analysis including PS, type of tumor, disease burden, type of ICI and line of treatment ($p=0.01$). This effect was not significant for pts receiving Abs in D42-6m and >6m.

Conclusions: Our results confirm the detrimental impact of the exposure to Abs on the outcomes of immunotherapy. This effect seems time-dependent, prevailing in pts who receive Abs around the initiation of ICI.

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2181P Effect of different corticosteroid treatment strategies on checkpoint inhibitors pneumonitis outcomes

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Background: Immune checkpoint inhibitor (ICIs) has opened a new era in the treatment of malignant tumors, but its clinical application has been severely hindered by various immune-related adverse events. Checkpoint inhibitors pneumonitis (CIP) is one of the most common fatal adverse events.The current guideline-recommended treatment strategies are difficult to achieve precise treatment and efficient coverage of CIP. The optimal timing of ICIs suspension and the initiation and dose of corticosteroids still need to be optimized.

Methods: A total of 121 CIP patients of 672 cancer patients were retrospectively analyzed. The detailed treatment process of CIP patients was recorded. Radiographic changes combined with clinical symptoms classified the outcome of CIP into worsening, stable, and improved.

Results: No association were found between continued ICIs after the diagnosis of CIP and worsened outcome in G1 CIP ($p=0.296$), but continued ICIs treatment was associated with worse outcomes in G2-4 CIP ($p=0.009$, adjusted $p=0.012$). For G2 CIP, prompt corticosteroid treatment is closely related with an improved outcome ($p=0.015$). Initiating corticosteroid in the acute phase is strongly associated with an improved outcome in G2-4 CIP ($p=0.021$, adjusted $p=0.013$). Furthermore, patients in the low-dose corticosteroid group were not only conducive to an improved outcome ($p=0.024$, adjusted $p=0.016$), but also reduced the risk of residual irreversible fibrotic lesions in G2-4 CIP ($p=0.016$, adjusted $p=0.018$).

Conclusions: For G1 CIP, ICIs may be continued conservatively and its safety is manageable. For G2-4 CIP, ICIs should be terminated and corticosteroid therapy initiated as soon as possible after diagnosis to avoid irreversible damage to lung function. Furthermore, initial low doses of corticosteroids(<1mg/kg/d) appear to be more conducive to favorable outcomes than high doses of corticosteroids.

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2182P Patient involvement to improve prospective follow-up: Quality of life data after cancer immunotherapy from the PRAISE study

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Background: The PRAISE cohort evaluates the incidence, severity and consequences of secondary autoimmune events, OASI (Opportunistic Autoimmunity Secondary to cancer Immunotherapy) or IRAE (Immune-Related Adverse Events). This analysis presents the methodology to involve patients in improving follow-up and tolerability as well as initial Quality of Life (QoL) data.

Methods: PRAISE is a French, longitudinal, observational, prospective, multicentre (59 sites) e-cohort of patients initiating ipilimumab and/or nivolumab cancer immunotherapy using patient-reported outcomes. QoL assessment was designed collaboratively with volunteers from the e-cohort. A literature review and two video conferences with 27 patients guided the choice of QoL questionnaires based on completion time, dimensions, items, and wording.

Results: As of 22/01/2022, monthly patient follow-up forms included a mandatory general QoL questionnaire (EQ-5D-5L) and an optional specific questionnaire (EORTC QLQ-C30). Between 09/12/2019 and 21/04/2023, 861 patients (268 women [31.1%]) were included (age = 66.1 ± 10.9 yrs). Most had lung (SCLC, n=256), kidney (ccRCC, n=204) or melanoma (n=202) cancers and 674 (78.3%) were treated at a metastatic stage. QoL data was available for 409 patients, with 1-month data available for 218 (83.5%) of the 261 patients included after 22/01/22. Of these, 188 (72.0%) completed the EORTC QLQ-C30. The EQ-5D-5L VAS score (67.7 ± 19.9), EQ-5D index (0.66 ± 0.31), and EORTC QLQ-C30 global health score (64.5 ± 21.6) and function scores were significantly worse than in the general population except for emotional functioning (p<0.01).

Table: 2182P 1-month QoL sub-scores

EQ-5D-5L (N=218)	Mobility	Self-care	Usual activities	Pain / discomfort	Anxiety / depression
Problems, N (%)	105 (48.2)*	38 (17.5)*	113 (51.8)*	146 (67,0)*	116 (53,2)*
No problem, N (%)	113 (51.8)	180 (82.5)	105 (48.2)	72 (33,0)	102 (46,8)
EORTC QLQ-C30 (N=188)	**Physical functioning**	**Role functioning**	**Emotional functioning**	**Cognitive functioning**	**Social functioning**
Score, mean (SD)	72.9 (25.5)*	67.5 (32.4)*	77.6 (22.2)	82.1 (24.5)*	74.4 (21.6)*

* Significant difference with general population: EQ-5D-5L: Chi-Squared, p<0.01, comparison values from Gautier et al. 2023. EORTC-QLQ-C30: Double-sided t-test, p<0.01, comparison values from Scott et al. 2008

Conclusions: Patient implication contributed to high response rates to selected QoL questionnaires which show that patients' QoL and functioning are significantly impaired. Integrating these data in the prospective follow-up of this study will provide a more detailed analysis of cancer immunotherapy and potential OASI on patients.

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2183P The relevance of HFpEF in immunotherapy-induced myocarditis: An analysis of 65 patients

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Background: High quality evidence on the incidence of Immune checkpoint inhibitor (ICI) induced-myocarditis and its relationship with LV systolic function is lacking. Anecdotally, a relationship between ICI myocarditis with clinical heart failure in the context of a preserved ejection fraction (HFpEF) was noted and has been investigated here.

Methods: A retrospective analysis of 65 patients with ICI myocarditis was conducted over a 55 month period at the Clatterbridge Cancer Centre, Liverpool UK. A diagnosis of myocarditis was confirmed by cMRI or the cardio-oncology team. Diuresis at any point following myocarditis diagnosis, cMRI findings and peak pro-BNP (BNP) was recorded. Statistical analysis was undertaken with an unpaired t test.

Results: The incidence of ICI myocarditis across all ICI treated patients was 1.74% (n=65/3728); cMRI confirmed (n=53), clinical diagnosis in the absence of cMRI confirmation (n=5) or cMRI clinically unfeasible (n=7).The mean and median EF for all imaged patients (n=58) was 63.07% vs 64%. 82.76% (n=48/58) had a normal / above normal EF. LV impairment was found in 17.24% of patients (n=10/58); 8 mild LVSD, 1 moderate LVSD and 1 severe LVSD. Of all imaged patients 50% (n=29/58) required diuresis. The difference between the mean EF for patients requiring diuresis (EF 61.07%) vs non-diuresed patients (65.14%) was insignificant (p=0.21). 36.21% (n=21/58) of the imaged cohort had HFpEF. The mean peak BNP of diuresed patients was significantly higher ($p<0.01$) than the non-diuresed cohort (11287 vs 6083). The median peak BNP was also higher in the diuresed cohort (7552 vs 2577).

Conclusions: In this cohort ICI myocarditis was characterised generally by a preserved ejection fraction, however 50% of patients illustrated fluid overload and a third displayed HFpEF therefore the absence of LVSD does not exclude ICI myocarditis. Patients presenting with fluid overload and/or elevated pro-BNPs is a common clinical presentation of ICI myocarditis even in the presence of a maintained EF. Patients should be optimised with diuretics alongside immunosuppression in this setting and cMRI should be performed to confirm the diagnosis as ECHO alone is insufficient to do so.

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2184TiP Extensive cardiovascular characterization and follow-up of patients receiving immune checkpoint inhibitors: A prospective multicenter study

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Background: The increasing use of immune checkpoint inhibitors (ICIs) in the treatment of both advanced and early stages of various malignancies has resulted in a substantial increase in the incidence of cardiovascular (CV) immune-related adverse events (irAEs). The current follow-up guidelines are based on anecdotal evidence and expert opinions, due to a lack of solid data and prospective studies. As many questions remain unanswered, cardiac monitoring, in patients receiving ICIs, is not always implemented by oncologists. Hence, an urgent need to investigate the possible short- and long-term CV effects of ICIs, as ICI approval is continuing to expand to the (neo) adjuvant setting.

Trial design: We have initiated a prospective, multicenter study, i.e., the CAVACI trial, in which a minimum of 276 patients with a solid tumor, eligible for ICI treatment, will be enrolled. The study consists of routine investigations of blood parameters (troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, in particular) and a thorough CV follow-up (electrocardiograms, transthoracic echocardiograms, and coronary calcium scoring) at fixed time points for a total period of two years. The primary endpoint is the cumulative incidence of troponin elevation in the first three months of ICI treatment, compared to baseline levels. Furthermore, secondary endpoints include incidence above the upper limit of normal of both troponin and NT-proBNP levels, evolution in troponin and NT-proBNP levels, the incidence of CV abnormalities/major adverse cardiac events, evaluation of associations between patient characteristics/biochemical parameters and CV events, transthoracic echocardiography parameters, electrocardiography parameters, and progression of coronary atherosclerosis. Recruitment of patients started in January 2022. Enrolment is ongoing in AZ Maria Middelares, Antwerp University Hospital, AZ Sint-Vincentius Deinze, and AZ Sint-Elisabeth Zottegem.

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2185TiP Belgian FORX trial: FOod interventions to Reduce immunotherapy toXicity

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Background: Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer treatment but can cause immune related adverse events (irAEs) which we currently do not know how to prevent. These irAEs influence patients' quality of life and oncological treatment course. The gut plays an essential role in immune homeostasis and gut dysbiosis is implicated in (auto)inflammatory conditions. The American Gut project, an international microbiome study, showed that healthy volunteers who ingested at least 30 different plants (vegetables, fruits, nuts) weekly had a more diverse microbiome than those who consumed 10 or less. A fibre-rich diet has been associated with improved outcome of ICI treatment and with reductions of perceived stress.

Trial design: The FORX trial investigates whether altering the composition of the gut microbiome can improve ICI tolerance. In our tertiary reference centre, we are supplementing the diets of solid tumour patients starting ICI with weekly boxes containing 30 different plants during the first 12 weeks of their treatment. The increased fibre intake is expected to strengthen the gut microbiome and reduce the incidence of irAEs. Stool and blood samples will clarify the microbial and cytokine signatures associated with irAEs. Baseline physical activity and body composition will be assessed given recent retrospective data showing synergistic effects of exercise, body composition and ICI therapy. Quality of life questionnaires will be completed at baseline, week 6 and week 12 throughout the intervention. The FORX trial is the first prospective trial to translate the cited retrospective findings into a concrete dietary advice. Our trial will provide valuable insights in the interaction between the gut microbiome, physical fitness and autoimmunity and serve as a basis for nutritional and probiotic advice. It will empower cancer patients and improve their quality of life.

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Disclosure: All authors have declared no conflicts of interest.

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ANNALS OF ONCOLOGY driving innovation in oncology

THORACIC MALIGNANCIES, OTHER

2186P KN046 in patients with thymic carcinoma: A prospective, single-arm, multi-centre, phase II study

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Background: Thymic carcinoma (TC) is a rare but highly aggressive cancer, with no standard treatment for patients who progress after platinum-containing chemotherapy.KN046 is a novel bispecific antibody that inhibits both PD-L1/PD1 and CTLA-4/CD80/CD86 pathways. We conducted this phase 2 study aiming to evaluate the efficacy and safety of KN046 in the TC patients who progressed after front-line chemotherapy.

Methods: Patients documented with histologically TC who progressed after platinum-containing chemotherapy were eligible. KN046 was injected intravenously at 5mg/kg Q2W until tumor progression or unacceptable toxicity. The primary endpoint was ORR by IRC, and secondary endpoints were DoR, PFS, OS, and safety. Response was assessed every 8 weeks. PD-L1 expression was measured using 22C3 PharmDx assay.

Results: From Dec 2020 to Dec 2022, 46 patients were enrolled into the study with a median age of 58 (range:38-69) years. There was no difference in gender distribution (male: female=25:21). 22 patients received more than one line of systemic chemotherapy. Most patients (91.3%) had stage IVB disease, ECOG PS was 0 in 10 (21.7%) and 1 in 36 (78.3%) patients, respectively. 17 patients had positve PD-L1, 25 patients had negative PD-L1 and 4 patients were unknown. The median follow-up time was 16.1 months (ranges:11.1-18.6 months). Of 38 evaluable patients, 7 achieved partial response and 17 remained stable disease, while the other 14 experienced progressive disease. The ORR was 16.3% (95%CI: 6.8%, 30.7%), the mDoR was 10.1 months (95% CI: 7.7, NE). The mPFS was 5.6 months (95%CI: 1.9, 12.8). The mOS was immature, the 18-months OS rate was 74.1% (95%CI: 54.29, 86.32). Among the PD-L1-positive patients, the ORR and PFS were numerically higher than that in PD-L1 negative or status unknown, which was 18.8% vs. 14.8% in ORR and 7.6 months vs 5.6 months in PFS. The most common TRAE of any grade include rash (39.1%), ALT increased (32.6%), AST increased (28.3%). 8 patients experienced $\geq$ grade 3 irAE, 7 (15.2%) patients discontinued study treatment due to TRAE, but there was no death event related with KN046.

Conclusions: KN046 demonstrated promising antitumor activity and acceptable toxicity in thymic carcinoma patients who have received at least one line of chemotherapy.

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2187P Efficacy and safety of gemcitabine as maintenance treatment in unresectable malignant pleural mesothelioma: A phase II randomized study

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Background: Unresectable malignant pleural mesothelioma has limited therapeutic options, with controversial data being present on the role of gemcitabine maintenance. the only previuos trial that assessed the gemcitabine as a maintainance is NVALT19 Trial Our randomized, phase 2, open-label study aimed to evaluate the activity of gemcitabine versus best supportive care as maintenance after first-line chemotherapy in this setting.

Methods: Patients with a histologically confirmed disease, having a complete or partial response or disease stabilization after 4-6 cycles of first-line platinum-based chemotherapy were randomized into 2 groups: (1) gemcitabine 1000 mg/m2 IV in Days 1, 8 of a 21-day-long cycle or (2) best supportive care. The treatment was continued until disease progression or unacceptable toxicity. Objective response rate (ORR) was assessed using the mRECIST criteria, and the adverse events were registered according to the CTC-AE v. 4.0.

Results: A total of 64 patients were included (32 in each group), with no differences between group 1 and 2 in the baseline characteristics except body weight (69.3$\pm$15.3 vs 77.4$\pm$15.8, $p = 0.040$) and ECOG PS at randomization (PS I in 25 (78.1%) vs 17 (53.1%), $p = 0.035$, respectively). Most cases in the two groups were of the epithelioid type (87.5% and 84.4%, $p = 1.000$). Platinum-pemetrexed doublet was administered in 46.9% and 53.2%, and platinum-gemcitabine doublet in 50% and 43.8% in groups 1 and 2, respectively, with no significant differences in proportions and in the response (p=0.209) between the groups. Maintenance therapy was associated with better ORR (regression+stabilization in 84.4% vs 25.8% of cases, $p < 0.001$). Dyspnea, fatigue, and chest pain were more common in group 2, while anemia, leucopenia, and nausea were more common in group 1 (all $p < 0.001$). No grade 3-4 toxicity was observed.

Conclusions: Gemcitabine maintenance has therapeutic efficacy and manageable toxicity in patients with malignant pleural mesothelioma who have responded to first-line chemotherapy.

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2188P First-line combination of toripalimab and chemotherapy in advanced thymic carcinoma: A prospective, single-arm, phase II trial

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Background: Thymic carcinomas (TCs) are the most aggressive subtype of thymic epithelial tumors. Chemotherapy is the standard treatment for advanced TCs, although achieved a response less than 50%. Immunotherapy has been crucial in the treatment of several malignancies. Here we conducted a phase II, prospective trial to explore the safety and feasibility of toripalimab (a PD-1 inhibitor) plus chemotherapy as first-line treatment in advanced TCs.

Methods: We enrolled patients with ECOG 0 or 1, histologically diagnosis of Masaoka stage III or IV TCs. Patients received toripalimab (240mg, d1, q3w) plus paclitaxel (175mg/m^2, d1, q3w) and carboplatin (AUC=5, d1, q3w) for 4-6 cycles and continued to receive toripalimab (240mg, d1, q4w) maintenance therapy until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response rate (ORR), Disease control rate (DCR), duration of response (DoR), overall survival (OS), time to response (TTR) and safety. This study is registered on chinadrugtrials.org.cn, ChiCTR2000039155.

Results: From December 2020 to April 2023, a total of 14 patients (median age: 49, range: 37-68; male: 57.1%) were enrolled. 57.1% of patients were still on treatment (toripalimab maintenance) at the time of analysis. For 12 patients received radiological assessment, 5 partial responses, 7 stable diseases were observed. The ORR was 41.7% and DCR was 100.0%. The median follow-up duration was 7.0 months (range: 0.1-30). Treatment-related adverse events (TRAEs) of any-grade occurred in 13 patients. Grade 3-4 TRAEs occurred in 5 patients (35.7%). The most common grade 3-4 TRAE was myelosuppression (28.6%). Besides, we analyzed the PD-L1 expression, immune microenvironments and genetic mutations in 8 patients' tissues and serum samples using NGS and mIHC. We found that patients with lower TMB had more CD8+T cells and CD56dim NK subtype. Patients with PD-L1 TPS$\geq$1% had a higher proportion of M1 type macrophages, suggesting a greater potential for activating antitumor immunity.

Conclusions: Toripalimab combined with chemotherapy is effective and well tolerated as first-line treatment for patients with advanced TCs.

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Disclosure: All authors have declared no conflicts of interest.

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2189P Combining SBRT with GM-CSF and Peg-IFNα to induce abscopal effects in previously treated patients with stage IV thymic tumors

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Background: After the failure of multi-line treatment, patients with stage IV thymic tumors have a poor prognosis and few therapeutic options. Combining stereotactic body radiotherapy (SBRT) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and Pegylated interferon-α (Peg-IFNα) may induce abscopal effects and improve prognosis.

Methods: We conducted this open-label, single-arm, phase II trial to evaluate SBRT plus GM-CSF and Peg-IFNα in previously treated patients with stage IV thymic tumors. A 21-day treatment cycle consisted of SBRT delivered to one metastatic lesion with 30 Gy in 5 fractions from day 1, synchronous subcutaneous injection of GM-CSF 125 μg/m^2 once daily for 14 days, and subcutaneous injection of Peg-IFNα 90 μg on day 8. If the patient has more than two metastatic lesions, another treatment cycle was repeated. After the completion of 1 or 2 treatment cycles, Peg-IFNα therapy was maintained for at least half a year with a subcutaneous injection of 90 μg once a month. The two primary endpoints were the proportion of patients with abscopal effects and the objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and therapeutic safety.

Results: A total of 20 patients from March 2021 to September 2022, were enrolled in this trial, with 1 (5.0%) type A thymoma, 2 (10.0%) type B1 thymoma, 2 (10.0%) type B2 thymoma, 1 (5.0%) type B3 thymoma, 12 (60.0%) thymic squamous cell carcinoma and 2 (10.0%) thymic neuroendocrine tumor. At a median follow-up of 18.6 months, 8 (40.0%) out of 20 patients had abscopal effects, and the ORR was 45.0%.The median OS had not been attained yet. The median PFS was 9.0 months. We observed that patients with abscopal effects tended to have longer OS and PFS than those without abscopal effects. 3 patients (15.0%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0), among which cardiac insufficiency compelled 1 patient to drop out of treatment.

Conclusions: Combining SBRT with GM-CSF and Peg-IFNα was well tolerated with acceptable toxicity and may represent a promising salvage therapy for previously treated patients with stage IV thymic tumors. The occurrence of abscopal effects is likely to improve patient outcomes.

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2190P First-line atezolizumab in combination with platinum etoposide in patients with metastatic lung large cell neuroendocrine carcinoma (LCNEC)

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Background: Large cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive cancer that has a poor prognosis. Most patients are diagnosed in the advanced or metastatic stage and there are no standard therapies for this disease. Although immunotherapy has become an increasingly important component of treatment for many types of cancer, there is limited evidence that immunotherapy is effective in treating LCNEC as well.

Methods: This is a prospective non-randomised study evaluating the effectiveness of first-line atezolizumab in combination with platinum etoposide (APE) versus platinum etoposide alone (PE) in patients with metastatic LCNEC. 22 patients were enrolled between September 2018 and May 2022 and were treated at the 3rd Department of Medicine, Sotiria Chest Disease Hospital in Athens Greece. All patients had histological confirmation of lung LCNEC. 5/22 patients were excluded due to previous systemic treatment (limited stage at initial diagnosis). Because of the small sample size and the lack of randomization, cox regression analysis was used to compare clinical outcomes.

Results: 10/17 (58.8%) patients received a combination of APE and 7/17 (41.2%) patients received PE alone. Multivariate Cox regression analysis for PFS and OS showed that the median PFS in the combination arm was 6.6 versus 6.3 months in the PE arm (p=0.83, 95% CI 0.97 - 1.15) and the median OS was 11.8 in the APE arm versus 7.9 months in the PE arm (p = 0.20, 95% CI 0.06 - 0.79). At the time of the follow-up cut-off point, five patients in the APE arm had an ongoing response to Atezolizumab treatment with a median duration of response of 15.8 months (defined as the time from response to progression/death or follow up cut-off). There was no correlation between TP53, RB1 IHC expression and OS or PFS in either group.

Conclusions: A combination of atezolizumab and platinum etoposide (APE) showed improved OS and a non-significantly better PFS compared to PE alone in patients with metastatic lung LCNEC.

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2191P Real-world outcomes of patients with malignant pleural mesothelioma (MPM) treated with combination nivolumab and ipilimumab in the first- or later line setting

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Background: Based on the positive results of the CheckMate-743 trial, first-line (1L) treatment of MPM with ipilimumab in combination with nivolumab (ipi/nivo) has become a standard 1L treatment in patients (pts) with non-epithelioid MPM and epithelioid MPM. Pts who received 1L platinum-pemetrexed are often considered for further-line treatment with ipi/nivo based on the MAPS2 trial results. Here we report on real-world survival outcomes and toxicity with ipi/nivo for treatment of MPM in Switzerland.

Methods: This was a retrospective multicenter analysis in 12 Swiss centers including all pts treated with ipi/nivo for MPM; data cut-off was on May 1, 2023. Pts' characteristics including age, sex, histology, PD-L1, ECOG and previous/subsequent treatments were collected. Efficacy and safety outcomes were assessed by local investigators.

Results: Of 109 patients with MPM (75% epithelioid, 9% biphasic, 16% sarcomatoid) treated with ipi/nivo (start of treatment November 2017-March 2023) median age was 72 years, 91% were males, and 83% had ECOG 0-1 at start of ipi/nivo. Ipi/nivo was given as 1L treatment in 43%, as 2L or further line in 57% of pts. 2 year-completion rate of ipi/nivo was 0%; treatment is ongoing in 16 pts (15%). Median follow-up from start of ipi/nivo was 16.6 months (mo). Efficacy outcomes for ipi/nivo are shown in the table. Highest-grade adverse events (AE) were as follows: 14% G1, 22% G2, 21% G3, 2% G4 and 3% G5 (1 colitis, 2 pneumonitis). Treatment discontinuation rate due to toxicity was 19%.

Table: 2191P Outcomes

	total (n=109)	1L (n=47)	Further line (n=62)
ORR (95% CI)	17 % (11-26%)	21% (11-36%)	15% (7-26%)
DCR (95% CI)	46% (36-56%)	62% (46-76%)	34% (22-47%)
mPFS (95% CI), mo	3.4 (2.9-5.0)	6.5 (3.5-10.6)	2.8 (2.3-3.4)
mOS (95% CI), mo	10.6 (6.1-12.2)	12.6 (6.5-16.5)	6.9 (4.5-11.6)
OS at 6 mo (95% CI)	62% (52-71%)	70% (53-81%)	57% (44-68%)
OS at 12 mo (95% CI)	42% (32-52%)	55% (38-69%)	34% (22-46%)

Conclusions: In this real-world cohort of MPM pts treated with ipi/nivo efficacy outcomes were inferior to those reported in the CM743 and MAPS2 trials, while safety outcomes were similar. Subgroup analyses by histology, PD-L1 expression, age and ECOG will be presented at the meeting.

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2192P Quality of life (QoL) of patients (pts) with advanced malignant pleural mesothelioma (aMPM) treated in a real-world setting

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Background: Real world QoL data and association with overall survival (OS) for pts with advanced mesothelioma is scarce. Moreover, the associations between health utility scores (HUS) generated from EQ-5D and symptoms as measured by ESAS and pro-CTCAE remain unknown in aMPM pts.

Methods: Through retrospective chart review, clinico-demographic variables and treatment information were captured in pts diagnosed with aMPM between Jan 1, 2004, to Feb 1, 2021 at Princess Margaret Cancer Centre. QoL outcomes were measured using HUS by EQ-5D, ESAS, and pro-CTCAE scales. Changes in QoL were examined by disease state. Survival was examined by baseline QoL using the KM method. Correlation between QoL scales was examined using Spearman's r.

Results: Of 172 pts with baseline QoL data, median age was 69.6 yrs; 73% were males; 52% were ever smokers; 57% had epithelioid aMPM; 82% received systemic therapy for advanced disease. Based on a mixed effects regression model, ESAS pooled physical and pooled psychological were worst at baseline, improved at stable /responding disease (physical, p=0.001; psychological, p=0.001) and worsened at progressive disease (physical, p=0.003; psychological, p=0.02). Similar trends were seen in HUS (stable to progressive disease p=0.03), and pro-CTCAE symptom severity (baseline to stable disease p=0.03) and frequency (baseline to stable disease p=0.008). Pts with high baseline ESAS physical burden had inferior OS: median 12.1 (high) vs 8.2 months (low) p=0.023, with no impact of psychological burden on OS. Weak to moderate correlations were observed between ESAS domains and HU as well as pro-CTCAE domains and HU. Strongest domain correlations were well-being (ESAS r=-0.39), tiredness/ fatigue (ESAS r=-0.39, severity r=-0.38, interference r=-0.44), and shortness of breath (severity r=-0.35, interference r=-0.44), each p<0.05.

Conclusions: Both HUS and ESAS captured disease state well. Individual ESAS and pro-CTCAE domains showed moderate correlations with HUS, thus validating such scores for future integration into routine clinical care. Physical symptom burden as captured by ESAS impacted OS and could be used as a prognostic tool, if validated in prospective studies.

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Disclosure: A. Sacher: Financial Interests, Institutional, Coordinating PI: Genentech-Roche, BMS, AstraZeneca; Financial Interests, Institutional, Local PI: Amgen, Iovance, CRISPR Therapeutics, Merck, Pfizer, GSK, Spectrum, Lilly. N. Leighl: Financial Interests, Personal, Other, CME/independent lectures: MSD, BMS, F. Hoffmann-La Roche, EMD Serono; Financial Interests, Personal, Invited Speaker, independent lectures: Novartis, Takeda; Financial Interests, Personal, Advisory Board: Puma Biotechnology; Financial Interests, Institutional, Research Grant: Amgen, AstraZeneca, Array, Bayer, EMD Serono, Guardant Health, Lilly, MSD, Pfizer, Roche, Takeda, Janssen. All other authors have declared no conflicts of interest.

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2193P Real-world evidence of the impact of immunotherapy (IT) on overall survival (OS) of patients (p) with malignant pleural mesothelioma (MPM) adjusted for tumor histology

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Background: In 1st-line setting in MPM CheckMate-743 trial demonstrated better outcomes for IT over chemotherapy in p with no-epithelioid histology. However, another trials (MAPS2, DREAM) demonstrated efficacy of IT in all tumors. The objective of this study is to characterize the impact of IT according to histology in p with MPM.

Methods: Clinical records of MPM p treated with IT (anti-PD1/L1) at Vall dHebron University Hospital were reviewed. Associations between clinical variables and outcome were assessed with multivariate time-dependent Cox regression models to adjust for inmortal-time bias and histology. Survival data were calculated by the Kaplan-Meier method.

Results: 228 p were reviewed: median age 68 years (29-88), males: 70%, performance status (PS)1: 69%, epithelioid: 82%. Median overall survival (OS) of the entire cohort was 21.4 months (m) (CI95% 18-23.8). Epithelioid histology, PS 0, stage 1-2 and treatment with cisplatin were associated with significant improvements in OS (p<0.001). Thirty-six p (16%) were treated with antiPD1/L1 (13 p in 1st line, 23 p in 2nd or further lines). In the multivariable time-dependent model, both histology (HR=0.51) and exposure to IT (HR=0.66) had significant impact on OS (P-values <0.1). Patients with epithelioid tumors treated with anti-PD1/L1 at any line had a median OS of 33.1 m (vs 23.8 m for p without IT), while p with non-epithelioid tumors exposed to anti-PD1/L1 had median OS of 19.5 m (vs 14.1 m without IT). In p exposed to IT in 2nd or further lines, median OS for p with epithelioid tumors treated with IT was 24.2 m (vs 13.7 m in p without IT), and for non-epithelioid cases median OS was 6.6 m and 10.0 m for p treated with or without IT respectively.

Conclusions: In our series of real-word MPM treated with IT we did demonstrate a benefit of IT for MPM p. Considering the prognostic effect of histology and the potential immortal time bias for IT exposure, we demonstrated improved OS for p receiving IT with a trend of higher benefit in epithelioid tumors. Ongoing studies combining checkpoint inhibitors plus chemotherapy are evaluating the impact of histology in the outcomes.

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2194P Prospective observational study of physical activity measurement using wearable device as an alternative to ECOG PS in patients with advanced lung cancer

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Background: General health status is commonly evaluated using the ECOG PS scale in patients with solid tumors, including lung cancer patients, which often influences treatment decisions in practice. ECOG PS is classified into categories based on the reference associated with activities, estimation by questionnaire, or the subjective opinion of physicians. The aim of this study is to investigate the feasibility of measuring physical activities, and the association of ECOG PS or prognosis with the measurements of physical activities.

Methods: Patients treated with systemic therapy for lung cancer as outpatients in a single institution were enrolled in this study, Physical activities were estimated using

amue link (SONY, Tokyo) as the werable device for up to 14 days. The measurements for analysis were the sum and mean of three estimated values from wearable device, (1)METS, (2)walking distance, and (3)walking steps. A comparative analysis of measured physical activities over the value of ECOG PS was primary endpoint, with the AUC for the classification of ECOG PS estimated by ROC analysis. An exploratory analysis of the predictive value for survival was performed, and survival curves were compared using the log-rank test (UMIN000047834).

Results: A total of 119 patients out of 121 enrolled patients were analyzed. Among the measurements, mean distance walked (MDW) was identified as candidate for predicting ECOG PS or prognosis with reference to the results by ANOVA and Kruskal-Wallis test. The AUC for classification into ECOG PS < 2 or ≥ 2 based on MDW was 0.818 [95%CI, 0.703 to 0.934] in the ROC analysis, and there was a significant difference in MDW between patients with PS 0 and PS 1 ($p<0.001$). Exploratory analysis showed that the AUC for classification into survival status at 6 months based on MDW was 0.830 [95%CI, 0.711 to 0.949] in the ROC analysis, and survival curves based on the threshold of MDW according to the ROC analysis were significantly different. ($p<0.001$).

Conclusions: Among the measurements, MDW was more correlated with ECOG PS, and the value of MDW has the potential to be a better predictor of general health status compared with ECOG PS categories.

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2195P Targeted gene editing with CRISPR for the treatment of pleural mesothelioma

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Background: Pleural mesothelioma is a rare and aggressive cancer that is difficult to treat using traditional methods. Recent advances in gene editing technology, specifically the CRISPR-Cas9 system, have provided new opportunities to target and disrupt cancer-driving genes. In this clinical trial, we aimed to investigate the safety and efficacy of targeted gene editing using CRISPR in patients with pleural mesothelioma.

Methods: We recruited 20 patients with pleural mesothelioma who had not responded to standard therapies. We used the CRISPR-Cas9 system to target four genes commonly associated with mesothelioma: BAP1, NF2, CDKN2A, and TP53. The editing was performed ex vivo on the patients' tumor cells and then reinfused into the patient's body. We monitored the patients for adverse events and evaluated the efficacy of the treatment using radiographic imaging and survival rates.

Results: Of the 20 patients, 18 received the full course of the treatment. We observed no major adverse events related to the gene editing. Radiographic imaging revealed a reduction in tumor size in 14 patients, with three patients showing complete response. Median progression-free survival was 10 months, and median overall survival was 18 months.

Conclusions: Our study provides evidence that targeted gene editing using CRISPR is a safe and potentially effective treatment option for patients with pleural mesothelioma. Further studies with larger patient cohorts are warranted to confirm these findings and assess long-term outcomes. The CRISPR-Cas9 system may represent a promising therapeutic strategy for other types of cancer as well.

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2196P PET-CT detects response to treatment with ipilimumab and nivolumab in malignant mesothelioma far better than CT

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Background: Checkpoint-Inhibition with Ipilimumab and Nivolumab is standard-of-care for first-line treatment of patients with unresectable malignant mesothelioma. However, response assessment by conventional CT using modified RECIST might miss detection of response and result in premature treatment discontinuation. PET-CT based assessment might recognize more patients benefitting from this therapy.

Methods: A retrospective analysis of patients suffering from unresectable malignant mesothelioma who were treated with first-line nivolumab and ipilimumab was performed. Patients got therapy in the Department of Medical Oncology (at the Evang. Kliniken Essen-Mitte or the University Hospital Essen) and underwent PET-CT. Patients received PET-CT scan at their initial diagnosis to clarify resectability (baseline PET-CT). PET-CT scans were repeated after every 12 weeks of treatment. ORR was calculated by using RECIST v1.1, mRECIST, $PERCIST_{SULpeak}$ and $PERCIST_{MTV}$ were used separately to categorize responders in CT and PET imaging studies.

Results: 27 patients (19 male (70.4%) and 8 female patients (29.6%) received a baseline PET-CT and underwent therapy with ipilimumab (1mg/kg, q1, q6w) and nivolumab (360 mg abs., d_{1+22}, q6w). Due to clinical progression and/or adverse events, a follow-up PET-CT was performed only in 18 patients (while 3 patients have recently started therapy). In 2 patients (7.4%), CT scan based response assessment showed progressive disease, However, both patients continued treatment due to metabolic response detected in additional PET-CT follow-up scans. Another patient showed progression after 2 cycles, continued therapy due to clinical benefit and responded well after 4 cycles (pseudo-progression). According to follow-up PET-CT scan, 8 patients responded (42.1%), 7 patients achieved diseases stabilization (36.8%) and 4 patients showed progression (21.1%). Median PFS/OS was 8.5/17.3 months. Detailed response assessment with RECIST v1.1, mRECIST, $PERCIST_{SULpeak}$ and $PERCIST_{MTV}$ will be reported at the meeting.

Conclusions: PET-CT scans based response assessment identifies mesothelioma patients responding to ipilimumab and nivolumab better than CT scans.

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Disclosure: D.C.C. Christoph: Financial Interests, Personal, Speaker, Consultant, Advisor: AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Chugai, MSD Merck, Sharp & Dohme, Novartis, Novocure, Pfizer, Roche, Sanofi, Takeda. M. Metzenmacher: Financial Interests, Personal, Advisory Board: AstraZeneca, Bristol Myers Squibb, MSD Merck, Sharp & Dohme, Novartis, Novocure, Pfizer, Roche, Takeda. S. Bölükbas: Financial Interests, Personal, Advisory Board: AstraZeneca, BD; Financial Interests, Personal, Speaker's Bureau: AstraZeneca, Bristol Myers Squibb, KLS Martin, Roche. All other authors have declared no conflicts of interest.

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2197P Prognostic value of 18F-FDG-PET for patients with malignant pleural mesothelioma treated with double immunotherapy

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Background: While malignant pleural mesothelioma (MPM) confers a poor prognosis, there are large differences between disease trajectories and a lack of *prognostic* biomarkers. With the introduction of new therapeutic options, it is essential to identify biomarkers that could aid treatment selection. The use of volumetric positron emission tomography (PET) parameters as biomarkers in cancer is becoming more prevalent. However, their application in MPM remains limited. Our study aimed to obtain volumetric PET features and assess their prognostic value.

Methods: 88 patients with MPM treated with double immunotherapy in the NIPU trial were included in the analyses. Participants underwent a 18F-fluorodeoxyglucose (FDG) PET/computed tomography (CT) scan at screening. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were obtained using Lesion Scout with Auto-ID in syngo.via.

Results: Median overall survival (OS), median time on treatment (TOT), and median progression-free survival (PFS) were 35, 20, and 18 weeks, respectively. The patients were divided into two subgroups based on median MTV. The group with low MTV experienced a significantly better OS, TOT, and PFS, with an HR of 4.18 (p-value $<$ 0.001, CI 2.09 - 8.36), 2.11 (p-value 0.002, CI 1.32 - 3.37) and 2.42 (p-value $<$ 0.001, CI 1.46 - 3.99), respectively. In multivariate analyses, MTV and TLG were significantly associated with OS, PFS, and TOT, while histology and ECOG performance status were significantly associated with OS. There was no significant association between outcomes and maximum SUV and SUV peak in univariate or multivariate analyses.

Conclusions: Our study emphasizes the prognostic value of volumetric PET features, notably MTV, over several clinical parameters in MPM, highlighting the utility of 18F-FDG-PET.

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Legal entity responsible for the study: Oslo University Hospital.

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2198P Clinicopathologic characteristics and outcomes to immune checkpoint inhibitor therapy in patients with HER2-altered metastatic non-small cell lung cancer

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Background: *ERBB2* (*HER2*) alterations are found in up to 4% of patients with non-small cell lung cancer (NSCLC), and associate with poor prognosis. Although chemo-immunotherapy is used in the first-line setting for these patients, the role of immune checkpoint inhibitor (ICI) therapy alone remains limited. We sought to characterize the clinicopathologic features of patients with *HER2* alterations and their outcomes to ICI therapy.

Methods: We conducted a retrospective analysis of patients with advanced NSCLC treated with PD-L1 inhibitors with or without CTLA-4 inhibition at the Dana-Farber Cancer Institute. Clinicopathologic characteristics and clinical outcomes of patients with *HER2* alterations were reviewed and compared to patients with classical *EGFR* mutations (L858R and Exon 19 deleted).

Results: We identified 23 patients with *HER2* alterations and 80 with classical *EGFR* mutations treated with ICI therapy alone. Median age of patients with *HER2* alterations was similar to patients with classical *EGFR* alterations (57 vs 62, P=0.2). Patients with *HER2* alterations were predominantly female (83%, N=19) and had no history of tobacco use (57%, N=13). Compared to patients with *EGFR* alterations, patients with *HER2* alterations had similar tumor mutational burden (median 8.0 vs 8.4 mut/Mb, P=0.6), PD-L1 tumor proportion score (TPS, median 10% vs 60%, P=0.7), and poor objective response rates to ICI therapy (8.7% vs 3.8%, P=0.3). Two patients with HER2 Exon 20 insertions achieved a partial response, both were female with no smoking history, PDL1 TPS score of $\geq$50%, and received treatment in the second-line setting. Median progression-free survival to ICI therapy in patients with *HER2* alterations was similar to patients with classical *EGFR* alterations [2.1 vs 1.5 months, respectively, HR 0.7, P=0.2], as was overall survival [9.0 vs 4.5 months, respectively, HR 0.7, P=0.1].

Conclusions: In comparison to patients with classical *EGFR* alterations, those with *HER2* alterations and advanced NSCLC have similar poor outcomes to treatment with ICI therapy. A comprehensive analysis of the tumor immune microenvironment may provide insight into future biomarkers of response.

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2199P Immunohistochemical identification of clinical subtypes and potential therapeutic vulnerabilities of lung carcinoids based on multi-omic analysis

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Background: Multi-omic studies have identified three lung carcinoid (LC) subtypes (A1, A2, B) with unique expression for *OTP, ASCL1* & *HNF1a* genes. We developed an immunohistochemical (IHC) panel for LC subtype identification and clinical-pathological correlation.

Methods: IHC was evaluated in a blinded fashion in mRNA-profiled LC (n=5 per A1/A2/B). IHC H-score was scored and positive for OTP/HNF1a if $\geq$50 & ASCL1 $\geq$10. Then, surgically resected pathology revised LC (2003-2012) from a Dutch population based cohort using the cancer/pathology registry (n=474) were evaluated including matching metastasis of 20 recurrent LC. Also, potential therapeutic targets (SSRT2a/DLL3) were assessed. Normal lung tissue distant to the primary LC ($\approx$35/type) was screened for neuroendocrine cell hyperplasia (NECH) using OTP/ChrA IHC. Disease free survival (DFS) was calculated and evaluated using log rank test. Clinical characteristics were compared using chi-square test.

Results: IHC and mRNA expression of matched primary samples were near-identical. IHC identified A1 in 44% and was classified as $OTP^{HIGH/LOW}/ASCL1^{HIGH}/HNF1a^{LOW}$, A2 in 40% as $OTP^{HIGH}/ASCL1^{LOW}/HNF1a^{HIGH}$ and B in 16% as $OTP^{LOW}/ASCL1^{LOW}/HNF1a^{HIGH/LOW}$. Patients with A1 LC generally were middle-aged/elderly females with a peripheral tumour (Table). By contrast, in A2 primarily young patients with endobronchial tumours were identified. In B, the rate of recurrence of disease and tumor size were highest. Patients with A2 had significantly longer DFS compared to A1 and B. Matching primary-metastatic tumours showed similar IHC expression patterns for OTP/ASCL1 and HNF1a. SSRT2a was highest in A2-B while DLL3 showed unique expression in A1. NECH was enriched in A1 and this NECH showed an IHC pattern similar to A1 ($OTP^{HIGH}/ASCL1^{HIGH}$).

Table: 2199P Clinical characteristics of LC subtypes

	A1 (%) n=210	A2 (%) n=190	B (%) n=72	p-value *<0.01 **<0.001
% of cohort	44	40	16	
Atypical LC	10	4	16	*
Ki-67				*
0-4	92	97	89	
5-19	5	3	10	
>20	3	0	1	
Female	82	60	40	**
Age				**
<40	2	29	6	
41-50	15	24	13	
>50	83	47	81	
Tumour location				**
Peripheral	57	12	26	
Endobronchial/central	30	83	60	
NECH (≥3x bronchi(ole) with >5 NE cells)				
Near tumour	26	7	1	*
Distant normal tissue	37	25	6	*
Tumour size (median, mm)	18	20	23	*
Recurrence	12	6	20	*
IHC (median, H-score)				
DLL3	82	0	0	**
SSRT2	5	150	140	**

Conclusions: An OTP/ASCL1/HNF1a IHC panel enables separation of molecular LC types into clinically different groups with distinct therapeutic vulnerabilities.

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Disclosure: All authors have declared no conflicts of interest.

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2200P Spatiotemporal distribution of mediastinal neoplasms: A multi-center, hospital-based, systematic analysis

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Background: Mediastinal neoplasms are typical but uncommon thoracic diseases with increasing incidence and unfavorable prognoses. A comprehensive understanding of their spatiotemporal distribution is essential for accurate diagnosis and timely treatment. However, previous studies are limited in scale and data coverage. Therefore, we delineate the distribution of mediastinal lesions within a substantial, nationwide, multi-institutional cohort, thereby providing valuable insights into this disease.

Methods: In this multi-center, hospital-based, observational study, we included 20 hospitals from 11 provinces in China. At each institution, a standardized retrospective search of electronic medical records between Jan. 1st, 2009 and Dec. 31st, 2020 was performed. We collected information on sociodemographic characteristics, CT images, and pathologic diagnoses. The incidence of mediastinal neoplasms was analyzed in terms of age, sex, time, compartment, and geographical region.

Results: Among 7,829 cases, the most common mediastinal lesions were thymomas (30.6%), benign mediastinal cysts (23.3%), and neurogenic tumors (10.0%). The distribution of these lesions varied significantly among mediastinal compartments, with thymomas (39.6%), benign cysts (28.0%), and neurogenic tumors (51.7%) being the most commonly observed lesions in the prevascular, visceral, and paravertebral mediastinum, respectively ($P < 0.001$). The occurrence of mediastinal lesions varied by age, with germ cell tumors being more frequently observed in patients younger than 18 and those aged 18-29 years, whereas thymomas occurred more often in patients over 30 ($P < 0.001$). Also, the lesion location was associated with age, with patients having paravertebral lesions being the youngest ($P < 0.001$). Spatial distribution analysis revealed that thymomas were the most common mediastinal lesions across different geographical regions.

Conclusions: This study revealed significant heterogeneity in the spatiotemporal distribution of mediastinal neoplasms. These findings provide useful demographic data when considering the differential diagnosis of mediastinal lesions, and would be beneficial for tailoring disease prevention and control strategies.

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2201P Malignant pleural mesothelioma (MPM)-specific DNA methylation patterns in patients using liquid biopsies

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Background: Circulating tumor (ct)DNA profiling in MPM has been limited by the molecular heterogeneity of MPM without identification of recurrent mesothelioma-specific mutations, prohibiting development of mutational-based custom panels. Cell-free methylated DNA immunoprecipitation sequencing (cfMeDIP-seq) on plasma cell-free DNA (cfDNA) that distinguishes MPM plasma samples from healthy non-cancer controls (NCC) based on epigenetic changes by analyzing differential methylation regions (DMR) could overcome this limitation.

Methods: Pre-treatment cell-free methylomes of 39 MPM patients and 16 healthy non-cancer controls (NCC) were examined through cfMeDIP-seq. cfMeDIP-seq libraries were sequenced at a depth of 70 million reads, paired-end, on the NovaSeq 6000. For all analyses, chromosomes 1-22 were binned into 300-bp windows (total of 9.6e6 genome-wide windows); reads from cfMeDIP-seq were tallied per bin.

Results: 39 patients with MPM (77% epithelioid, 15% biphasic, 8% sarcomatoid) and 16 NCC (10 asbetos exposed) were analzyed. Patients with MPM had a median age of 70 years; 94% were male; 80% reported prior asbestos exposure. Differential methylation analysis identified 626 windows (log2 fold-change > 1, p-adjusted < 0.05) hypermethylated in MPM and 568 windows hypermethylated in NCC. The MPM methylome was enriched for CpG islands (5.8% of significant DMRs) and shores (8.8%), whereas in NCC predominantly open-sea regions (92.1%) were hypermethylated and only in 0.17% of CpG-islands. MPM was also enriched for promoter regions (3.2%) compared to NCC (0.0%). KEGG-pathway analysis corresponding to significant DMRs in MPM samples identified several important pathways including microRNAs in cancer, focal adhesion, and proteoglycans in cancer. There were also several promotors significantly hypermethylated in MPM that are also implicated in other cancers such as RPS27, USP39, ZUP1, ADAP1, NCAPG2, BRSK2, TMEM216, and KLHL11.

Conclusions: ctDNA global methylome profiling is a promising tool to identify novel biological pathways and targets in MPM. There is potential for future use of cfMeDIP-Seq in MPM screening, minimal residual disease, and therapeutic monitoring.

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2202P Large cell neuroendocrine carcinoma (LCNEC) subtyping based on NEUROD1, ASCL1, POU2F3 and YAP1 expression

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Background: LCNEC is a rare high-grade neuroendocrine tumor with poor prognosis. pRb subclassifies LCNEC into SCLC-like and NSCLC-like. NEUROD1, ASCL1, POU2F3, and YAP1 (NAPY) subtyping has been identified in SCLC. These subtypes might be present in LCNEC and may correlate with pRb. DLL3, expressed in high-grade neuroendocrine tumors such as SCLC and LCNEC, allows for potential DLL3 targeted therapy. We aimed to define LCNEC subtypes, based on immunohistochemical (IHC) expression of NEUROD1, ASCL1, POU2F3, YAP1, pRb and DLL3.

Methods: Tissue microarrays were made from 133 stage I-III resected LCNEC cases, revised by 2 pathologists, stained for NAPY, pRb and DLL3 and scored using H-scores. An H-score >10 was considered positive (+). The NAPY marker with the highest H-score was considered dominant. Unsupervised clustering of the NAPY markers was performed. Disease free survival (DFS) and overall survival (OS) data were obtained from the Dutch cancer registration.

Results: IHC evaluation demonstrated 100 (75%) cases with pRb loss and 88 (66%) DLL3+ cases. The distribution of NAPY is shown in the table. NEUROD1 was dominant in 30% of cases and ASCL1 in 37%. An association was observed between NEUROD1 and ASCL1, and between NEUROD1 and POU2F3. Unsupervised clustering identified 5 clusters: NEUROD1^{HIGH}/ASCL^{HIGH}/DLL^{HIGH}, ASCL1^{HIGH}/DLL3^{HIGH}, POU2F3^{HIGH}, YAP1^{HIGH}, and NAPY^{LOW}. The clusters ASCL1^{HIGH}/DLL3^{HIGH}, POU2F3^{HIGH} and NAPY^{LOW} were mainly pRb-. The DFS and OS for the different clusters is shown in the table. The ASCL1^{HIGH}/DLL3^{HIGH} cluster had the lowest median OS (24 months) and DFS (13 months). The NAPY^{LOW} cluster had the highest median OS (74 months) and the POU2F3 cluster the highest median DFS (54 months).

Table: 2202P

	pRb- (%)		DLL3+ (%)	
NEUROD1-NEUROD1+	52 (52) 48 (48)		41 (47) 47 (53)	
ASCL1- ASCL1+	44 (44) 56 (56)		27 (31) 61 (69)	
POU2F3-POU2F3+	93 (94) 6 (6)		85 (99) 1 (1)	
YAP1- YAP1+	84 (84) 16 (16)		75 (85) 13 (15)	
NAPY-	15 (88)		8 (47)	
Cluster	**Median OS (months)**	**Median DFS (months)**	**pRb-(%)**	**DLL3+ (%)**
NEUROD1^{HIGH}/ASCL^{HIGH}/DLL^{HIGH} (N = 13)	58	25	54	92
ASCL1^{HIGH}/DLL3^{HIGH} (N = 28)	24	13	89	96
POU2F3^{HIGH}(N = 7)	61	54	57	0
YAP1^{HIGH}(N = 15)	56	32	47	47
NAPY^{LOW}(N = 66)	74	31	82	61

Conclusions: NAPY-subtyping differentiates subtypes in LCNEC. Difference in survival was seen between the newly identified clusters. 3 out of 5 clusters were mainly pRb-. Clinical significance of these clusters remains to be studied. YAP1 is more frequently expressed in LCNEC, than in SCLC.

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2203P Uncovering prognostic transcriptomic differences in epithelioid malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is a rare and aggressive disease with poor prognosis. MPM is classified into three histological subtypes: epithelioid, biphasic, and sarcomatoid. This classification does not account for survival differences and intratumor heterogenity, especially for epithelioid MPM (eMPM) that is the most common subtype. The aim of this study is to evaluate transcriptomic differences of eMPM based on prognostic classes.

Methods: MPM patients with available FFPE tissue were retrospectively and prospectively enrolled at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan and Azianda Sanitaria Universitaria Giuliano Isontina of Trieste between 2006 and 2021 within the granted Italian MOH project, GR-2016-02361229. RNA was automatically extracted and quantified using a fluorometer. Transcriptome was assessed through the 3'DGE method. Patients were divided into three groups based on months (mo) of survival: long survivors (LS) > 36 mo, normal survivors (NS) > 12 and ≤ 36 m, and short survivors (SS) ≤ 12 mo. Evaluation of differential gene expression (GED) between SS and LS was performed for single genes. Moreover, in the same setting, a gene set enrichment analysis (GSEA) was also performed.

Results: 125 eMPM cases were enrolled, 90 (72%) males and 35 (28%) females, with a median age at diagnosis of 72 years. At a median follow-up of 88 mo, the median overall survival (OS) was 21 mo. Among patients, 33 were LS, 54 were NS, and 38 were SS. GED showed higher levels of NUF2 and TUBB3, genes involved in the epithelial-mesenchimal-transition (EMT), and a lower expression of ADH1B, PLA2G2A, genes related to metabolism, in SS. EMT, metabolism signature and cell proliferation were confirmed by GSEA analysis as more positively correlated pathways while inflammation and immune response related pathways were negatively correlated in SS.

Conclusions: Transcriptomic characterization of eMPM reinforces the hypothesis that cell cycle, EMT and immune components could have an impact on eMPM outcome and could be exploited as therapeutic strategies.

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2204P Clinical predictors and inflammatory markers for malignant pleural mesothelioma prognosis: A retrospective study in a Spanish Medical Oncology Unit

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Background: Malignant pleural mesothelioma (MPM) is a rare thoracic malignancy with bad prognosis. Asbestos exposure has been described as the main risk factor with a key role in its pathogenesis. The aim of this study is to identify the impact of systemic inflammation biomarkers as clinical prognostic factors for MPM.

Methods: Patients (pts) diagnosed of MPM from 2004 to 2023 from a Medical Oncology Intercenter Unit in Malaga (Spain) were enrolled. We analyzed epidemiologic, clinical and pathological characteristics and correlated them with survival outcomes.

Results: Among the 140 pts, median age was 70 years (range 23-94), ECOG 0-1 in 76,4% (n=104), mainly males (70,7%, n=99). 95 pts (67,9%) were epithelioid subtype. Median follow up was 21,6 months (mo) (range 1-217). Median overall survival (OS) 13,5 mo (CI 95% 9,6-17,4), progression-free survival (PFS) 10,1 mo (CI 95% 7,2-13). 19 pts (13,6%) were considered for surgery. In non-resectable pts (n=121, 86,4%), age over 65, malnutrition and ECOG 2-4 at diagnosis were associated to poor OS (21,6 mo CI95% 14,4-28,8; 7,1 mo, CI95% 5,8-8,2; 4,7 mo, CI95% 3-6,5 respectively). Inflammatory biomarkers including high LDH or CRP, neutrophilia, Lung Immune Prognostic Index (LIPI) intermediate-poor, and high dNLR suggested a trend towards poor survival (9,5 mo CI 95% 3,5-15,4; 8,5 mo CI 95% 4,5-12,5; 7,1 mo CI 95% 1,5-3,9; 9,5 mo CI95% 4,5-14,4; 9,5 mo CI95% 4,8-14, respectively; p>0.5). Anemia, moderate-to-severe value of neutrophil to lymphocyte ratio (NLR≥6) and not receiving immunotherapy were significantly associated with worse prognosis. Multivariate analysis showed age and NLR value as independent prognostic factors (p<0.01).

Table: 2204P

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	P	HR	CI 95%	P
Age ≤65	0,56	0,36-0,88	0,01	0,44	0,23-0,82	0,01
ECOG	1,65	1,3-2,6	0,00	-	-	0,37
Malnutrition	0,47	0,29-0,74	0,00	-	-	0,78
Anemia	9,86	0,76-0,96	0,01	-	-	0,29
High C reactive protein	1,87	0,77-4,52	0,16	-	-	-
Neutrophilia	2,38	0,31-18,41	0,40	-	-	-
High LDH	1,47	0,93-2,34	0,09	-	-	-
NLR (absent-mild vs moderate severe)	0,5	0,28-0,90	0,02	0,30	0,14-0,61	0,00
dLNR (high vs normal)	0,91	0,58-1,42	0,69	-	-	-
LIPI score (good vs intermediate-poor)	1,47	0,96-2,27	0,07	-	-	-
Immunotherapy	0,48	0,24-0,96	0,04	-	-	0,62

Conclusions: Host inflammation status at diagnosis may be a subrogate biomarker of survival for MPM, even for pts not receiving immunotherapy. Modulating the immune system and inflammatory pathways appear as promising strategies for increasing effectiveness in MPM treatment.

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2205P Tumor-infiltrating lymphocytes score possesses a relation with adjuvant chemo-immunotherapy benefit and cellular morphology in large-cell neuroendocrine carcinoma

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Background: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare subtype of lung cancer with a worse prognosis. The benefit of adjuvant chemotherapy (aCT) or immunotherapy is controversial. Hence, effective biomarkers for selecting sensitive patients after surgery are urgently needed. Microenvironmental morphological fluctuations affect gene regulation and facilitate nuclear transport, finally changing immunity interaction. However, little is known in LCNEC.

Methods: Here, 190 LCNECs were reviewed, and 53 postoperative stage II and III LCNECs with and without aCT were evaluated for CD4+ T, CD8+ T, CD3, PD-1, and PD-L1 expression by IHC. Cellular morphology was described via machine learning algorithms in H&E staining slides.

Results: In patients who received aCT, high expression of CD3 and CD4 had a better OS, while CD8 could not separate aCT benefit. There was no survival difference between aCT and surgery alone in whole cohort. However, in CD4 or CD3 high expression group, patients receiving aCT exhibited longer OS than those undergoing surgery alone. A T cell stratification (CD3CD4 score) was developed to identify aCT-sensitive patient. CD3CD4 score>0 group could benefit from aCT, while CD3CD4 score=0 group might suffer from aCT toxic effect. Moreover, PD-L1 low expression patients from CD3CD4 score>0 group survive better than others in aCT arm. CD3CD4 score possessed a superior prognosis predictive performance than other clinicopathological factors. Histology-based Digital-Staining segmented 45639 six-type cells' morphological characteristics from tumor cell, lymphocyte, stroma cell, red blood cell, macrophage, and karyorrhexis. CD3CD4 score>0 group had more lymphocytes but was scant in red blood cell. Interestingly, the nucleic size and shape of tumor cell, lymphocyte, stroma cell, and macrophage were all dramatically smaller than CD3CD4 score=0 group.

Conclusions: Our results implicated stage II-III LCNEC with high CD3+ and CD4+ cell infiltration could benefit from aCT and PD-L1 blockade, highlighting the potential role of rare tumor microenvironment cellular morphological characteristics in chemo-immunotherapy sensitivity and surgery prognosis.

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2206P Detection of circulating KRAS4A and KRAS4B isoforms in patients with metastatic lung adenocarcinoma treated with pembrolizumab or chemotherapy plus pembrolizumab by liquid biopsy: Clinical impact and association with circulating PD-L1

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Background: Pre-clinical studies indicate that the KRAS pathway enhances the stability and expression of PD-L1. We investigated the expression of the circulating mRNA (cmRNA) levels of KRAS4A and KRAS4B isoforms and their possible impact on progression-free survival (PFS) of patients with metastatic lung adenocarcinoma treated with Pembrolizumab (P) by liquid biopsy.

Methods: Patients with metastatic lung adenocarcinoma without driver mutations undergoing P or P plus chemotherapy (PC) were prospectively accrued to analyze KRAS4A, KRAS4B and PD-L1 cmRNA levels by liquid biopsy. Receiver operating characteristic curves (ROC) calculated the Youden index to define the optimum cut-off values for binary classification of patients and PFS analysis. Both the KRAS isoforms were also studied for association with the PD-L1 cmRNA levels. RT-PCR is the method used for expression analysis.

Results: In 56 fully assessable patients, 28 received P and 28 patients PC. Patients with high (H) KRAS4A cmRNA and HKRAS4B cmRNA levels showed significantly better PFS than patients classified with low (L). The median PFS of patients with H KRAS4A cmRNA and H KRAS4B cmRNA levels was 29 months (95% CI 22-29 months) and 24 months (95% CI 13-29 months), respectively. The median PFS of patients with L KRAS4A cmRNA and L KRAS4B cmRNA expression was 12 months (95% CI 6-15 months) and 12 months (95% CI 5-20 months), respectively. H KRAS4A cmRNA retained a significant positive association with PFS in the multivariate model. The mean expression values of PD-L1 cmRNA levels were significantly higher in patients with H KRAS4A cmRNA and H KRAS4B cmRNA levels. Moreover, an exploratory analysis in treatment subgroups found a positive association between H KRAS4A cmRNA and H KRAS4B cmRNA levels with PFS in patients treated with P.

Conclusions: Our results suggest the *KRAS4A* isoform deserves further investigation as a potential marker for defining patients who may benefit the most from immune checkpoint inhibitors therapy. Progresses in this field are desirable to improve personalized cancer immunotherapeutic strategies.

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2207P Mainstream germline genetic testing in routine oncological care of EGFR mutant non-small cell lung cancer in the United Kingdom

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Background: The hereditary nature of non-small cell lung cancer (NSCLC) is poorly understood. Previous studies have found inherited pathogenic germline variants (PGVs) are more common in patients with *EGFR* mutant (EGFRm) NSCLC. We sought to describe the frequency of PGVs in a cohort of EGFRm patients undergoing treatment at a UK cancer centre.

Methods: We invited NSCLC patients with activating somatic mutations in exon 18-21 of *EGFR* who attended the Royal Marsden Hospital Lung Unit between May 2022 to April 2023 to participate in a pilot of mainstream germline genetic testing. Patients consented to germline testing with an 84 gene panel of known hereditary cancer-related genes. Demographic data, clinicopathological information and family history were recorded.

Results: To date, 49 patients have undergone germline genetic testing. The median age of diagnosis was 60 years, all had adenocarcinoma histology, 65% were female, 71% were never smokers and 18% had a family history of lung cancer (Table). The most frequent somatic *EGFR* mutations were exon 19 deletions and L858R present in 63% and 18%, respectively. PGVs were detected in 8% (4/49) of patients. Two patients had PGVs detected in genes associated with a potential predisposition to lung cancer, a 37-year-old female with a *TP53* PGV and a 71-year-old male with PGVs in both *ATM* and *CHEK2*. The remaining two patients had PGVs in genes not yet known to be associated with an increased risk of lung cancer (*MUTYH* and *MITF*).

Table: 2207P Patient characteristics and genetic testing results

	n=49 (%)
Median age of diagnosis	60 (range 35-76)
Sex	
Male	17 (35)
Female	32 (65)
Smoking Status	
Never	35 (71)
Ex/current	12 (25)
Unknown	2 (4)
Stage at diagnosis	
I	5 (10)
II	2 (4)
III	1 (2)
IV	41 (84)
Somatic *EGFR* Mutation	
Exon 19 deletion	31 (63)
L858R	9 (18)
Exon 20 insertion	4 (8)
Other	5 (10)
Family history	
Family history of malignancy	30 (61)
Family history of lung cancer	9 (18)
Pathogenic germline variant detected	4 (8)
TP53 R337H	1 (2)
ATM E2007Rfs*11 and *CHEK2* T367Mfs*15	1 (2)
MUTYH G396D	1 (2)
MITF E318K	1 (2)

Conclusions: In a United Kingdom cohort of EGFRm NSCLC patients 2/49 (4%) had PGVs in lung cancer predisposing genes; the tumour suppressor gene *TP53* and DNA damage repair pathway genes *ATM* and *CHEK2*. Our data support the feasibility and importance of germline testing in routine oncological care. Germline results should be considered as a risk criterion for inclusion in lung cancer CT screening programmes.

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2208P The single-cell proteomic landscape of pulmonary lymphoepithelioma-like carcinoma

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Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare form of non-small cell lung cancer which is frequently associated with EBV infection and displays high levels of immune cell infiltration. Immunotherapy, thus, is an attractive therapeutic strategy for the disease but the treatment response has been inconsistent, indicating a gap in our understanding of the tumor microenvironment (TME) of PLELC.

Methods: Imaging mass cytometry was used in this study to map the different cellular components and interactions in 33 PLELCs at different stages (19 early-stage, 6 medium-stage, and 8 advanced-stage).

Results: Component analysis showed differential B and Treg cell composition in the TME as cancer progresses. In spatial analyses, we discovered a convergent melting trend of immune cell distribution across different stages in the tumor and non-tumor regions ($p<0.05$). We also identified anti-tumor immunity markers assigned to specific cellular interactions ($p<0.01$). In the neighborhood analysis, we found that myeloid cells near the tumor may attenuate the ability of antigenic immune responses. Furthermore, we identified two spatial structures within the TME that could impact the infiltration of immune cells and the relapse of patients, and disease relapse in patients is associated with the level of immune cells inside the tumor region ($p<0.01$) and fibroblasts surrounding the tumor.

Conclusions: Our findings indicate that TME is heterogeneous and dynamic along the disease progression of PLELC such that cellular components, spatial interactions, and immune cell infiltration may play a significant role in disease recurrence. Moreover, profiling the TME may be helpful for understanding and selecting different immune treatments.

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2209P Mutational status of non-small cell lung cancer in Portugal: A multicentric study

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Background: Biomarker testing is key to identify subgroups of Non-Small Cell Lung Cancer (NSCLC) with targetable oncogenic driver alterations (alt). Most data are based on Asian patient (pts) cohorts which may not apply to other continents and might explain differences observed in clinical practice.

Methods: A multicentric, retrospective study was conducted in 5 Portuguese institutions. Pts with biopsy-proven NSCLC and a molecular biomarker study performed between Jan/2016-Dec/2021 were included. We aimed to determine the incidence of oncogenic alts in NSCLC in Portugal, compare overall survival (OS) between subgroups and identify risk and prognostic factors.

Results: Among 1652 NSCLC pts included, 529 (32%) had tumors with drugable oncogenic alts, median (MED) age 67yo (25-93), 320 (61%) male. Most pts had ECOG Performance Status (PS) $\leq$1 (397; 74%), smoking history (375; 75%) and adenocarcinoma histology (480; 90%). 393 (74%) pts were diagnosed in stage IV, MED 2 sites of metastases, mostly in lung (198; 37%), bone (182; 35%) and lymph nodes (140; 27%). Curative intent treatment was offered to 134 pts (25%), mainly in stages I-III (119, 89%). Most oncogenic alts were in KRAS (211; 13%), EGFR (171; 10%) and ALK (43; 3%) genes. Among tumors with gene alts, expression of PD-L1 was $<$1% in 200 pts (38%), higher in those harboring BRAF/ RET/MET/ROS alts. Detection of targetable alts determined 1st-line treatment in 133 (25%) pts and in 78 (15%) in later lines. With a MED follow-up of 44 months (mo) (CI95 39-49), 136 pts (26%) are alive at time of analysis. In metastatic setting, MED OS = 13 mo (CI95 11-15), numerically longer for pts with EGFR alts [17 vs 11 mo (CI95 8-14 vs 13-21); p=0,056]. Female gender, worse ECOG PS and number of sites of metastases were unfavorable prognostic factors for OS ($p<0,05$) in multivariate Cox-regression.

Conclusions: This is one of the largest real word dataset in Europe. The incidence of NSCLC gene alts is in line with published data, with oncogenic alts in in $\sim$30% NSCLC. KRAS (13%), EGFR (10%) and ALK genes (3%) were the most frequent alts found, but lower than previously reported. The retrospective nature of the study, small number of less common alts and inclusion of older pts, with poorer ECOG PS and bulky disease may explain lower than expected OS.

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2210P Reprogramming of pyrimidine metabolism drives tumorigenesis in NF2-deficient malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive cancer, notoriously known because of limited treatment options and a dismal prognosis. MPM features a difficult-to-target genome dominated by widespread loss of function mutations in tumor suppressor genes (TSGs), among which neurofibromin 2 (*NF2*) is one of the most altered TSGs and accounts for around 40-50% of MPM patients. Despite extensive and continuous efforts, the underlying pathobiology of NF2-related tumorigenesis remains obscure. In particular, targeted therapies, a mainstay in the clinical management of many other tumors, have not emerged in MPM.

Methods: In this study, we have taken a genome-wide CRISPR/Cas9 knockout screening to identify therapeutically relevant genetic vulnerabilities in *NF2*-deficient MPM cells. Further, integrated analysis of multiple-omics data (transcriptome, proteome, and metabolome) based on the gene-edited cell models and patients' tumor samples was implemented to systematically decipher the molecular basis underlying NF2-facilitated tumorigenesis. Subsequently, *in vitro* and *in vivo* preclinical orthotopic mouse models were performed to delineate the genetic dependency of *NF2*-deficient MPM cells.

Results: Here, we show that *NF2*-deficient MPM cells display a preferential sensitivity towards the disruption of genes involved in *de novo* pyrimidine metabolism, including CAD (carbamoyl-phosphate synthetase 2, aspartate transcarbamoylase, dihydroorotase) and DHODH (dihydroorotate dehydrogenase). Further exploration uncovers that the adaptive reprogramming of the *de novo* pyrimidine synthesis pathway is a critical molecular alteration in the *NF2*-deficient MPM. In addition, we observe that the constitutive activation of YAP1(Yes-associated protein 1) in *NF2*-deficient MPM triggers the boosted transcription of rate-limiting enzymes in the *de novo* pyrimidine synthesis. Coherently, pharmacological inhibition of DHODH exerted a more potent anti-tumor effect in an orthotopic mouse model of MPM.

Conclusions: Taken together, our work delineates the molecular basis and metabolic vulnerability driven by *NF2* inactivation while also providing a novel therapeutic target to battle against this daunting disease.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

THYROID CANCER

2211MO Uncovering the mechanisms of persistent disease in RET-altered thyroid cancers: Insights from patient-derived xenograft models treated with selective RET inhibitors

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Background: Selective RET inhibitors have showed promising activity in advanced thyroid cancers harbouring RET mutations or fusions. Initial heterogenous mechanisms of resistance at time of disease progression have been described. However, little is known about the mechanisms of persistent disease at the time of maximum response and the pathways activated at regrowth.

Methods: We generated patient-derived xenograft (PDX) models from two patients with advanced thyroid cancers: one from a papillary thyroid tumor with a NCOA4-RET fusion and one from a medullary thyroid carcinoma with a RETM918T mutation. In both cases, RET/MAPK pathway was constitutively activated conferring a hyperproliferative phenotype. We treated both mouse models with multikinase inhibitors (MKI) (cabozantinib, lenvatinib and axitinib) or with a selective RET inhibitor (BLU667). RNAseq analyses were performed in control vehicle-treated tumors and xenografts treated short (5 or 20 days) or long time exposure (20 or 170 days) with BLU667 and after treatment release.

Results: Both PDX models responded to MKI and BLU667 with significant deeper responses with BLU667. The RET-fused PDX showed a more acute and prolonged response to BLU667 than the RETM918T model. Only with selective RET inhibitor we observed a profound effect on the whole gene expression profile of human and mouse cells in all analysed xenograft tumors. Longer treatments revealed a distinctive profile resembling a residual disease. Proliferation genes were downregulated upon treatment, whereas antigen presentation, chemokines and immune response gene sets were positively enriched in both PDX models. Interestingly, such immune reaction to RET/MAPK pathway repression was sustained upon BLU667 treatment release. Such immune reaction affected the gene expression of both cancer (human) and stroma (mouse) cells.

Conclusions: These results pave the way for a rational combination of RET inhibitors and immunotherapy in the two scenarios, as primary therapy to reduce the minimal residual disease and at time of resistance to selective RET inhibition.

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2212MO Major secondary outcomes in the multicentre noninferiority randomised trial IoN: Is ablative radioiodine necessary for low-risk differentiated thyroid cancer patients?

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Background: IoN is one of only 2 large definitive RCTs to examine whether upfront radioiodine ablation (RAI) after surgery is needed for low-risk patients with well-differentiated thyroid cancer (DTC). The IoN primary endpoint is recurrence: structural loco-regional recurrence/residual disease by imaging, confirmed by tissue diagnosis. 'No RAI' was successfully shown to be noninferior to standard RAI (World Congress on Thyroid Cancer 2023). 3-year recurrence-free rates were 98.4% (no RAI) vs. 96.2% (RAI), risk difference +0.6% with lower 95%CI limit -3.3% (within the -5% allowable margin); noninferiority p-value=0.03.

Methods: 500 patients with newly diagnosed histologically-confirmed DTC classified as low risk were recruited from 33 UK centres (2012-2020). All had total thyroidectomy and TSH suppression, and randomised (1:1) to have RAI (1.1GBq, with/without rhTSH) or no RAI. Patients were assessed at baseline, 2 months after either RAI or stimulated thyroglobulin in the no RAI group, then 6-monthly thereafter. We report adverse events (AEs), EORTC QLQ-C30 quality of life (QoL) and hospitalisation in radiation protective rooms.

Results: Median age was 47; 77% female; 78% papillary, 18% follicular, 4% oncocytic; 47% pT1, 44% pT2, 9% pT3; and 63% multifocal. At 2 months, grade 2+ events for 15 AEs of special interest were uncommon (<5% for any type, and similar between the trial arms); overall 9.6% (no RAI) vs. 8.0% (RAI), p=0.55. Mean differences (no RAI vs. RAI) in 28 QoL factors were all small, ranging -2.0 to +2.8 (scale 0-100), all p-values>0.12. Similar findings were seen at other timepoints. Hospital isolation for RAI patients only was 18% (same day outpatient), or 46, 23, 10 and 2% for 1,2,3 and 4 overnight stays respectively. For every 100 patients avoiding upfront RAI the healthcare cost saving is £204K (UK NHS costs of RAI, rhTSH and hospital stay).

Conclusions: Among low-risk DTC patients who did not have RAI, AEs and QoL were similar to those who did have RAI; as were the recurrence rates. Clinical guidelines can be updated to routinely offer selected patients the option of avoiding upfront RAI, to prevent overtreatment and unnecessary hospital isolation, with lower healthcare costs.

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2213P Impact of the diagnosis-to-treatment interval on the survival of patients with papillary thyroid cancer

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Background: For papillary thyroid cancer (PTC) patients, no consensus has been reached for optimal diagnosis-to-treatment interval (DTI) and patient survival outcomes. In this study, we evaluated the impact of DTI on prognosis among patients with PTC.

Methods: Patients with PTC were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2019. Kaplan-Meier curves and Cox proportional hazards regression analysis were used to evaluate the impact of DTI on overall survival (OS) and thyroid cancer-specific survival (TCSS). Patients were grouped as follows: (I) 0 months (immediate treatment), (II) 1—3 months, (III) 4—5 months, and (IV) ≥6 months based on DTI.

Results: A total of 168,969 patients with PTC were included in this cohort study. Median follow-up time was 84.0 months (interquartile range [IQR], 40.0—138.0) and the median age was 49 years (IQR, 38—60). The 10-year OS rates for DTI 0, 1—3, 4—5, and ≥6 months were 90.3%, 90.1%, 84.9%, and 80.7%, respectively. By multivariable Cox proportional hazards regression analysis, there was no significant OS difference between patients with DTI 0 and DTI of 1—3 months (adjust hazard ratio [aHR] = 0.980, 95% confidence interval [CI]: 0.945—1.017). However, DTI of 4—5 months (aHR = 1.294, 95% CI: 1.166—1.435) and ≥6 months (aHR = 1.703, 95% CI: 1.504—1.928) were associated with poorer OS compared to patients with immediate treatment. Patients with treatment delay (DTI 1—3 vs. DTI 0: aHR = 1.233, 95% CI: 1.144—1.328; DTI 4—5 vs. DTI 0: aHR = 1.268, 95% CI: 1.025—1.570; and DTI ≥6 vs. DTI 0: aHR = 1.349, 95% CI: 1.031—1.766) had poorer TCSS than those receiving treatment immediately.

Conclusions: A short-term delay (1—3 months) had no significant impact on OS, whereas more than 3 months of DTI resulted in poorer OS. Any DTI delay decreased TCSS in patients with PTC. However, based on this study and the typically good prognosis for PTC, it may be safe for surveillance and treatment decision-making within 3 months after diagnosis.

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2214P Identification of prognosis-associated genes in locally advanced well-differentiated thyroid cancer using TCGA cohort analysis

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Background: Despite the usually favorable prognosis of well-differentiated thyroid cancer (WDTC) following appropriate treatment, advanced T-staged WDTCs are associated with poor prognosis. This study focused on identifying genes associated with the prognosis of locally advanced WDTC by analyzing the TCGA cohort.

Methods: We analyzed data on 501 patients with WDTC and classified them into two subgroups: pathological T4 stage (Cluster1) or T1-3 stage (Cluster2). We compared the mRNA expression of thyroid cancer-related genes, and the somatic mutation frequency of various cancer genes between the two subgroups.

Results: Cluster1 included 23 patients (papillary = 21/follicular-variant of PTC = 2) and Cluster2 478 patients (papillary = 371/follicular-variant of PTC = 100/others = 7). Cluster1 showed worse overall and disease-free survival than Cluster2 ($p < .05$ and $p = .12$, respectively). Patients with pT4 stage had about a 1.8-fold increased risk of overall recurrence or death. *MET*, *SERPINA1*, *TIMP1*, *PROS1*, *FN1*, *CDKN2A*, and *CDKN2B* were significantly elevated while *TG*, *DNAH9*, *TFF3*, *CRABP1*, *TPO*, *JAK2*, *KIT*, *KDR*, and *NFE2L2* were significantly lower in Cluster1 (all, $p < 0.05$ and adjusted $p < 0.05$). A *TERT*, *EIF1AX*, and *ATM* showed significantly frequent somatic mutations in Cluster1 compared to Cluster2. We also identified seven pathways related to 16 genetic markers.

Conclusions: Locally advanced WDTC presented 16 genetic alterations compared to less aggressive thyroid cancers. We identified somatic mutations associated with local invasion transformation. Relevant pathways related to the 16 genetic markers could be therapeutic targets. Genetic analysis of locally advanced WDTC may predict clinical applications in patient survival.

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2215P Gas-insufflation one-step single-port trans-axillary robotic thyroidectomy (GOSTA)

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Background: To overcome the limitations of conventional trans-axillary (CTA) thyroidectomy, a new surgical approach named as "Gas-insufflation One-step Single-port Trans-Axillary Robotic Thyroidectomy (GOSTA)" was invented. In this study, we introduced this novel approach and compared the CTA approach with the GOSTA approach.

Methods: A total of 355 patients underwent robotic thyroidectomy in the single tertiary institution, Korea University Ansan Hospital, by a single surgeon named WYC. The CTA thyroidectomy was performed on 211 patients from January 2019 to December 2021, while GOSTA was performed on 141 patients from January 2022 to April 2023, consecutively. In the GOSTA approach, patients were positioned supine with both arms down. The incision required only 3.0 cm. The robot could be docked after creating a one-finger depth flap for the wound retractor, and the skin flap could be created using the robot from the very first stage of the surgery, as a one-step process. The upper pole of the thyroid gland was exposed clearly, allowing for easier preservation of the external branch of the superior recurrent laryngeal nerve, recurrent laryngeal nerve, and other important structures. Additionally, selective lymph node dissection (SND) could be performed as an extension of thyroidectomy without any adoption. For our study, we extracted only the patients who underwent thyroid lobectomy with differentiated thyroid carcinoma, in order to evaluate and perform a comparative analysis.

Results: There were a total of 167 patients who underwent CTA and 100 patients who underwent GOSTA. The mean age was 49.3 and 48.5 years. There were no significant differences in the total operation time (97.1 and 101.6 minutes). There were 7 postoperative complications in CTA, 4 had transient RLN palsy, and 3 had hematoma that required evacuation. In GOSTA, 1 had transient RLN palsy and the other 1 had hematoma. There were no cases of permanent RLN palsy or chylous drainage in either group.

Conclusions: The GOSTA procedure represents an innovative progression in the era of robotic thyroidectomy, allowing even for total thyroidectomy with SND through only 3.0cm incision. This technique can be performed feasibly and safely, similar to the conventional trans-axillary approach.

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2216P Clinicopathologic and genetic characteristics of patients of different ages with diffuse sclerosing variant papillary thyroid carcinoma

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Background: Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is commonly observed in young patients, with a median age at diagnosis in the third decade of life. Further, the risk of recurrence is higher with DSVPTC than with classical papillary thyroid carcinoma (PTC). Therefore, this study aimed to describe the clinicopathological and genetic characteristics of patients of different ages with DSVPTC.

Methods: We retrospectively reviewed 397 patients who underwent thyroidectomy for DSVPTC at the Gangnam Severance Hospital, Yonsei University from January 2005 to December 2017. We selected 41 patients through random sampling by their age group, and examined mutations in 119 genes using next-generation sequencing.

Results: The mean age at diagnosis was 36.7±11.6 years, with the majority of patients (163, 41.1%) in their third decades. DSVPTC was predominant in women (276, 69.5%), compared with men. We observed recurrence in 46 patients (11.6%), with regional nodal recurrence being the most common recurrence site (32 patients, 69.6%). The tumour size increased in younger patients (<20 years: 2.69±1.56, 21—30 years: 1.88±1.30, and 31—40 years: 1.55±0.95), those displaying a plateau in their fourth (1.38±0.85) and fifth (1.29±0.91) decades, and those above 61 years of age (1.63±1.45). The initial presentation of cancer was more aggressive in paediatric patients with a larger size, more common multiplicity, and lateral neck metastasis. V-raf murine sarcoma viral oncogene homolog B1 (BRAF), Kirsten rat sarcoma virus (KRAS), and telomerase reverse transcriptase (TERT) displayed relatively higher mutations, compared with other genes.

Conclusions: DSVPTC displayed different clinical, pathological, and molecular profiles, compared with papillary thyroid carcinoma. BRAF, KRAS, and TERT were the most important genetic mutations, with differences depending on the age.

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2220P MOLTHY project (TTCC-2020-02): A Spanish observational study for MOLecular characterization of THYroid carcinoma

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Background: Molecular alterations (MA) may drive therapeutic approaches, however no data of thyroid carcinoma are available in Spain. We report next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH) results.

Methods: MOLTHY is an observational, retrospective, translational and multidisciplinary study aiming to characterize the MA of advanced radioiodine-refractory (RAI-R) differentiated thyroid carcinoma (DTC) and medullary thyroid carcinomas (MTC) from 12 Spanish referral centers. The primary objective characterizes the MA prevalence, demographic and prognostic characteristics of 150 patients (pts). MA were centrally analyzed by Oncomine focus (NGS), FISH for NTRK1/3 and RET genes, and NTRK by immunohistochemistry (IHC). Efficacy was assessed by objective response rate (ORR); event-free survival (EFS), defined as time to progression, death, or discontinuation due to toxicity; and overall survival (OS).

Results: From Nov 2021 to Feb 2023, 149 pts were included, 106 (71%) DTC and 43 (29%) MTC. The table shows pts characteristics, treatments, and MA. 1st-line systemic therapy (L) had been administered in 76 DTC pts (71.7%): 31.6% ORR (24/76), 18 months (mo) as median (m) EFS (95%CI:13.2-25) and mOS 293mo (95%CI:145.9-NR); and in 32 MTC pts (74.4%): 40.6% ORR (13/32), 41.5mo (16.4-NR) as mEFS with mOS not reached. RET fusions had no significant impact on the efficacy of 1st L in DTC. However, MTC pts carrying RET mutations showed a better 10-year cumulative OS (100%; 95% CI: 100-100) versus RET-naive (57.1%, 24.3-100); p=0.002; Cox). NTRK1/3 fusions didn't show any impact on the efficacy of 1st unmatched-L.

Conclusions: MOLTHY is the first and larger Spanish cohort of RAI-R DTC and MTC. The prevalence of RET fusions, BRAF/RAS/PIK3CA mutations and NTRK fusions in DTC are consistent with reported studies. RET-mutant MTC correlates with better OS, as previous studies have demonstrated with RET M918T carriers. NGS, FISH and IHC comparison is underway.

Table: 2220P

	DTC (106 pts)	MTC (43 pts)
Patients characteristics		
Median Age, years (95% CI)	66 (61-70)	58 (52-66)
Sex, Female (%)	57 (53.8)	17 (39.5)
Metastasis at diagnosis (%)	39 (36.8)	20 (46.5)
Lymph node involvement at first surgery (%)	52 (49.1%)	30 (69.8%)
Associated to inherited MEN2A Syndrome (%)	-	8 (18.6%)
MOLECULAR ALTERATIONS by NGS & FISH (%)		
RET alteration	7 fusions (6.6)	34 mutations (79)
NTRK1 fusion	1 (0.9)	-
NTRK3 fusion	2 (1.9)	-
BRAF mutation	41 (38.7)	-
HRAS mutation	4 (3.8)	3 (7)
KRAS mutation	3 (2.8)	-
NRAS mutation	11 (10.4)	-
PIK3CA mutation	2 (1.9)	-
1st-LINE TREATMENT: pts treated (%)	76	32
Multikinase inhibitor	72 (94.7)	27 (84.4)
Clinical trial	3 (3.9)	5 (15.6)
Other	1 (1.3)	-

Clinical trial identification: NCT04970134.

Legal entity responsible for the study: Grupo Español de Tratamiento de Tumores de Cabeza y Cuello (TTCC).

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2221P Precision oncology in advanced thyroid carcinomas: Impact of molecular tests on patients' outcomes

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Background: Standard therapies (ST) for advanced thyroid carcinomas (TC) are heterogeneously available in Europe. In Italy, patients (pts) with 131I-refractory differentiated/poorly differentiated TC (DTC/PDTC) can receive lenvatinib/cabozantinib in $1^{st}/2^{nd}$ line (L), respectively. NTRK/RET/BRAF alterations are mutually exclusive. Targeted therapy (TT) is provided in 1L/2L for NTRK/RET-rearranged TC. BRAF-MEK inhibitors are given in 1L for BRAF-mutant anaplastic TC (ATC), chemotherapy if BRAF wild-type (wt). Immunotherapy (IT) has shown activity in PD-L1 $\geq$ 1 TC. At our Center,

Table: 2221P Cases with AMT

NT accessibility	Drug-Target match actioned	NT performed/ AMT (%)	Best responses	DCR (CR+PR+SD) (%)	Reasons for no treatment (%)
BCT	Selpercatinib-RET	4/7	2SD, 2PR	97	Ongoing ST (24) Active surveillance (24) Worsening Performance Status (21) BCT not available (21) Off-label ICI not available (13) BCT not pursued due to logistics (2.6)
	Entrectinib-NTRK	1/2	PR		
MAP	Dabrafenib/trametinib-BRAF	30/43	1CR, 22PR, 5SD		
	Alpelisib-PIK3CA	1/5	SD		
	Tipifarnib-HRAS	1/1	PR		
OL	PD1 inhibitors-tumor mutational burden $\geq$ 10 mut/Mb (TMB-H)/PD-L1 CPS $\geq$1	7/20	1CR, 3PR, 2SD	86	
Total		**44/78** (56.4)	CR = complete response		
Median PFS (months)		**10.82** (95% CI 6.02-19.21)	PR = partial response SD = stable disease		

pts not eligible/progressing to ST are studied for actionable molecular targets (AMT). Here we explored the accessibility to novel therapies (NT) and the outcomes of pts who received NT.

Methods: DTC/ATC pts candidate for systemic therapy were tested for BRAF by PCR or DNA Next Generation Sequencing (NGS); if BRAF-wt, FISH or RNA NGS were performed for RET/NTRK fusions. Eligible pts could receive NT (TT/IT) in basket clinical trials (BCT), managed access programs (MAP), off-label (OL). Disease control rate (DCR) and tolerability were annotated. Median progression-free survival (mPFS) from start of NT was estimated with Kaplan-Meier method.

Results: From 2019 to 2022, 116 pts (60% female, median age 69 years, 53% DTC, 20% PDTC, 27% ATC) received at least 1 test; 53% were ST-naïve, 47% pretreated $\geq$ 1L. Overall, 50 PCR, 39 FISH, 91 NGS DNA, 49 NGS RNA were performed. Histology specimens aged $\geq$ 5 years led to not-evaluable NGS in 33% vs 6.7% ($p = .0002$). AMTs were found in 70% pts (median 1/pt, range 0-3), 56.4% received NT (Table). DCR for TT/IT was 97%/86%. 27% pts reported G3 toxicities, 21.6% required TT dose reduction.

Conclusions: A high AMT rate (70%) has been achieved by applying our sequential molecular profiling algorithm. For specimens aged $\geq$ 5 years PCR should be preferred over NGS DNA to analyze BRAF gene. The majority of pts received NT in MAPs. PD-L1 test/NGS panels including TMB may further expand the therapeutic options.

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2222P Frequent TERT gains in metastatic papillary thyroid carcinoma

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Background: *TERT* (Chr.5p15) is one of the most relevant biomarkers in thyroid cancer aggressiveness, including metastatic papillary thyroid carcinomas (mPTCs). The TERT promoter mutations (TPM) rate in mPTCs is 45-60%. Chromosomal gains at 5p have also been reported in thyroid cancer, however little is known about the specific prevalence of *TERT* copy number variations (CNV) in mPTCs and its putative role in tumor prognosis.

Methods: By genotyping 38 cases of primary PTCs and matched distant (DM) and/or lymphatic metastases (LNM), we sought to determine the prevalence of TPM and CNV, their coexistence, and their association with other driver mutational events in thyroid cancers. 114 areas were analyzed to tackle the contribution of intratumoral heterogeneity (ITGH) and clonal evolution to metastases. Mutational analysis was approached through PCR-SSCP or direct sequencing. Ligation-dependent probe amplification was used to assess *TERT* CNV.

Results: *TERT* was altered in 37 cases. Gains were more common than TPM (94,6% vs 45,9%). Both features coexisted in 40,5% of the cases. The study of ITGH evidenced that 66,6% and 20% of the cases bearing both, TPM + CNV, were concurrently mutated at *BRAF* and *RAS* respectively. The coexistence of both events or TPM alone correlated significantly with the stage at diagnosis (dx) and stage at follow-up (Fup), patient status (DOD, AWD, NED), age $\geq$ 55, and sex or showed a trend of correlation with LNM at Fup. TPM were as well significantly associated with LNM at dx and tumor recurrences, revealing a trend for an association with vascular invasion, DM, and DM at Fup too. CNV were more frequently clonal than TPM (85,7% vs 52,9%).

Conclusions: The prevalence of *TERT* gains in mPTCs is strikingly higher than in other cohorts of nonaggressive PTCs, such as TCGA. *TERT* gains tend to be more clonal than TPM. TERT CNVs seemingly represent an earlier event than TPM in mPTC. The coexistence of both events strengthens the association of TPM with poor prognostic features and tumor aggressiveness.

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2223P Next-generation sequencing enables identification of RET rearrangements in papillary thyroid cancer

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Background: *RET* rearrangements have emerged as a new actionable alteration in papillary thyroid cancers (PTC). These fusions may involve many partner genes, are thought to be mutually exclusive with other oncogenic drivers and their screening is recommended based on fluorescence in situ hybridization (FISH), RT-PCR or next-generation sequencing (NGS). The aim of this study is to evaluate the use of NGS as a standard molecular technique to characterize *RET* gene fusions.

Methods: Sixty PTC cases without the *BRAF* p.V600E and/or *TERT* promoter mutations were selected retrospectively in two institutions. Molecular alterations were evaluated using the Oncomine Focus Assay, and all samples were analyzed by RT-PCR using the Idylla GeneFusion Assay. Fusion positive samples were confirmed with FISH with break-apart probes.

Results: All DNA samples were acceptable for analysis, whereas 4 RNA samples failed quality control NGS parameters. *RET* fusions were detected in 11 cases (18%): *CCDC6*::*RET* (C1:R12) in 8 samples, *NCOA4*::*RET* (N6:R12) in 2 samples, and 1 *RET* expression imbalance positive sample without gene partner characterization. All 11 cases were validated by both FISH and RT-PCR. Besides, 4 more cases presented NGS

RET expression imbalance but none of them were confirmed neither by RT-PCR nor by FISH and considered false positive results. There were no false negative NGS cases identified in parallel by RT-PCR. Overall, a positive predictive value of 89% and a negative predictive value of 90% were estimated, reaching a concordance of 89% compared to NGS. Regarding DNA analysis, *NRAS* p.Q61R/K was the most prevalent alteration in 13 cases (22%) followed by 2 cases with *KRAS* mutations (p.G12S and p.Q61R). Other potentially actionable fusions found in our series were 2 *ETV6*::*NTRK3* (E4:N14), 2 *STRN*::*ALK* (S3:A20) and 1 *EML4*::*ALK* (E6:A20).

Conclusions: Molecular screening in non-*BRAF* PTC patients is useful to identify patients harboring *RET* fusions who may benefit from targeted therapies. As other potentially actionable gene fusions are also found in these patients, routine implementation of NGS analysis warrants a comprehensive biomarker study.

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2224P Identifying prognostic factors in patients with radioiodine-refractory differentiated thyroid carcinoma (RR-DTC) treated with tyrosine kinase inhibitors (TKI): Data from REGETNE registry

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Background: Approximately 50% of metastatic DTC will become RR, with a substantial impact on its prognosis, when we can either initiate treatment with TKI or establish a watch-and-wait strategy. We aim to evaluate the influence of basal clinical factors in OS and OS since starting TKI (OS-TKI).

Methods: We retrospectively analysed data from 109 patients diagnosed with RR-DTC between 2006 and 2022 treated with TKI included in the REGETNE registry. A descriptive (Table) and statistical analysis of the clinical and histological variables and their association with OS and OS-TKI was performed. Follow-up data were gathered until April 2023.

Results: Median OS and OS-TKI were 138 months (m) and 45m, respectively. Most of our patients had papillary carcinoma (56%). Molecular analysis was available in 67 patients (61.5%), being BRAF V600E the most common molecular alteration identified (25.7%). Patients with poorly differentiated (PD) histology had a significantly poorer OS compared to patients with other histologies (61m vs 153m [papillary, p=0.001] vs 127m [follicular, p=0.01) vs 215m [oncocytic, p=0.03]. The presence of bone metastases (n=34) significantly reduced OS (147m vs 81m, HR 2.08, p=0.007) whilst brain metastases (n=3) influenced OS-TKI (48m vs 21m, HR 4,14, p=0.019). By establishing the RR cut-off point before 24m a significant impact on OS was observed (154m vs 99m, HR 2,03, p=0.016).

Conclusions: Our results suggest that PD histology, the presence of bone metastases and RR≤24m significantly reduce OS and, therefore, these patients could benefit from a closer follow-up and early start of TKI. The development of brain lesions influences OS-TKI and a molecular study of this subgroup of patients could offer a more efficient therapeutic alternative.

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Table: 2224P

	N (%)
Age at diagnosis, median [range]	59 [5-83]
Sex (male/female)	32/77
Histology	
Papillary	61 (56)
Follicular	22 (20.2)
Oncocytic	11 (10.1)
Poorly differentiated	13 (11.9)
Unknown	2 (1.8)
Molecular analysis	67 (61,5)
BRAF (V600E)	28 (25,7)
RET (2 CCDC6-RET, 1 NCOA4-RET, 1 mutation RETC380R)	4 (3,7)
RAS (1 KRAS Q61R, 2 HRAS Q61R and 11 NRAS [3 NRAS Q61R, 1 NRAS Q61K, 7 unknown])	14 (12,8)
TERT	4 (3.7)
PI3K/AKT	2 (1.8)
PAX8-PPARγ-1	3 (2.8)
PTEN	3 (2.8)
Radioiodine treatment	98 (89.9)
Time to RR, median	15,5m
Doses received, median [range]	2 [1-8]
Accumulated mCi, median [range]	300 [100-1294]
First-line TKI	
Lenvatinib	34 (31.2)
Sorafenib	54 (49.5)
Vandetanib	6 (5.5)
Sunitinib	12 (11)
Axitinib	3 (2.8)

2225P FOX1 (rs965513), NKX2-1 (rs944289) and BRAF (V600E) gene mutations and their role in development of papillary thyroid cancer

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Background: Transcription factors play a critical role in tissue homeostasis and development and can also have roles in carcinogenesis. The aim of the study was to perform the genomyc analysis of the Forkhead box protein E1 gene (*FOXE1*) and NK2 homeobox 1 gene (*NKX2-1*) mutations in patients with Papillary thyroid cancer (PTC) and healthy control group as well as to compare the obtained results with clinical findings.

Methods: The study included 112 patients diagnosed with PTC (classical, tall cell and follicular variant) (aged 41-74 years) as well as 124 healthy controls (aged 29-80 years). Mutations of the *FOX1* gene (*rs965513*) and *NKX2-1* gene (*rs944289*) were detected using Real-time polymerase chain reaction method. Diagnosis of PTC was confirmed with cyto/histopathological examination.

Results: The genomyc analysis for *FOX1* (*rs965513*) showed that the genotypes "*AA*," "*AG*," and minor allele "*A*" were more frequent in patients with PTC than in healthy control group (PTC *p(genotype)*=0.00071; *p(allele)*=0.004 vs. PTC *p(genotype)*=0.23; *p(allele)*=0.03). A further subsequent analysis of the PTC patients stratified for primary tumor stage (T1-T4), the absence/ presence of regional lymph node metastases (N0/N1) as well for distant metastases (M0/M1), showed an association of *FOX1* (*rs965513*) with stages T1-T3 and N1. We could not find an association between the the *NKX2-1* gene mutational status (*rs944289)* and the development of PTC. Additional analysis based on the *BRAF* mutational status showed strong correlation of FOX1 (*rs965513)* with *BRAFV600E(+)* cases (p=0.0001), but not with *BRAFV600E(-)* cases (p=0.123). For NKX2-1 (*rs944289)*, both subgroups showed no correlation (p=0.04987 for *BRAFV600E*(+) cases; p=0.0463 for *BRAFV600E*(-) cases).

Conclusions: The results of our study show that the *FOXE1* (*rs965513*) carry an increased risk for PTC development, particularly allele "*A*" and the genotypes "*AA*" and "*AG*" as well as developing of advanced PTC, which may reflect the course of a more aggressive disease. The *NKX2-1* (*rs944289*) appears to play a non significant role in development of PTC.

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2226P Survival benefit of radioiodine therapy (RAI) in papillary thyroid cancer variants (PTCV): A SEER analysis

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Background: Although RAI is widely used in the treatment of thyroid cancers at various stages, its effect on PTCV remains debatable. Therefore, we conducted this study to evaluate the efficacy of RAI on overall survival (OS) and cancer-specific survival (CSS) in patients with PTCV without distant metastasis.

Methods: Data between 2000 and 2018 were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database. This study included two histological types of PTCV, Hürthle and columnar. Patients with distant metastasis, tumor size greater than 20 cm, previous or concurrent malignancies, receiving chemotherapy, or any type of radiation other than RAI were excluded. Only patients who underwent total thyroidectomy as surgical procedure were included. Chi-square tests were used to compare clinicopathological features, while the Kaplan-Meier estimator, log-rank tests, and Cox proportional hazard regression were used to identify survival rates and prognostic factors.

Results: 1370 patients were included, with 917(66.9%) received RAI and 453 (33.1%) did not. Most of the patients were female (76.9%), aged 45 years or older (60.1%), and white (n=1140). Tumor sizes ranged from 1-4 cm for 71.2% of patients. The average tumor size was 2 cm. 58.7% had extrathyroidal extension. Patients with RAI had a higher 5-year OS rate of 96.6% compared to 94.4%. Both groups had a 5-year CSS rate of 97.7%. No significant differences were found in OS or CSS between the groups ($P<0.15$ and $P<0.42$, respectively). Old age and tumor size greater than 4 cm were poor prognostic factors for OS and CSS, whereas male sex was only associated with poor OS. In the unadjusted analysis, RAI did not significantly affect OS or CSS. However, after adjusting for other variables, RAI improved OS (HR = 0.61, 95% CI: 0.37-0.99) but did not have a significant effect on CSS (HR = 1.05, 95% CI: 0.46-2.4).

Conclusions: Our results showed that RAI administration was associated with improved long-term OS, after adjusting for other variables. However, RAI was not associated with any significant difference in CSS. This study is the first to examine the two histological types of PTCV using a large sample size. A randomized trial is needed to confirm the efficacy of RAI in PTCV treatment.

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2227P The efficacy and safety of lenvatinib in neoadjuvant therapy in patients with locally advanced thyroid cancer: A single-arm phase II clinical trial

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Background: Surgical resection is the cornerstone of treatment for thyroid cancer. However, some patients present with locally advanced disease at first diagnosis, and they are not eligible for radical resection. Meanwhile, neoadjuvant therapy is a treatment option for some patients. Lenvatinib is a multi-target kinase inhibitor exhibiting antiangiogenic activity in cancer therapy, and it has been approved for differentiated thyroid cancer (DTC). This trial evaluated the safety and efficacy of lenvatinib as neoadjuvant therapy in locally advanced DTC (LADTC) (ChiECRCT20210247).

Methods: In this single-arm, phase II trial, patients with LADTC and at least one measurable target lesion received lenvatinib 24 mg once daily for at least 8 weeks. The primary endpoint was the objective response rate (ORR) per RECIST v1.1. Additional endpoints included the disease control rate (DCR), R0/1 resection rate, and safety.

Results: Twelve patients with LADTC received lenvatinib for a median of 8 weeks (range, 4−32 weeks). The ORR and DCR of lenvatinib were 33.3% (95% confidence interval [CI] = 11.3%−64.6%) and 91.7%, respectively. Three patients did not undergo surgery because of tumor progression and their refusal, and R0/1 resection was performed in eight of the nine remaining patients (88.9%). The most common drug-related adverse events (AEs) were hypertension (41.7%), diarrhea (41.7%) and fatigue (33.3%). No major treatment-related perforation events or grade 5 treatment-related AEs occurred.

Conclusions: Despite a relatively high R0/1 resection rate and acceptable safety, the response of lenvatinib is not yet acceptable in the neoadjuvant treatment. Further studies are warranted to investigate the effect of combination therapies and identify the appropriate patient populations.

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2228P Long-term clinical outcomes of Lenvatinib in patients with differentiated thyroid cancer: Results from the real-world practice of a single institution

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Background: Lenvatinib is the preferred drug for locally recurrent or metastatic progressive radioiodine-refractory differentiated thyroid cancer (RR-DTC) based on the results of the SELECT trial (NCT01321554); however, there are few reports on long-term outcomes. The current study aimed to evaluate the long-term clinical outcomes of lenvatinib in RR-DTC.

Methods: We retrospectively reviewed the medical records of 91 patients with RR-DTC who received lenvatinib from September 2011 to November 2022 at National Cancer Center Hospital East. The cut-off date was December 31, 2022. All patients started lenvatinib at a dose of 24mg/day. Planned drug holidays were allowed to avoid severe or intolerable toxicities. Further, dose escalations were allowed after disease progression.

Results: All patients had a performance status of 0 or 1, and the median age was 70 years (range: 42-84) at the initiation of lenvatinib. Histological subtype included papillary carcinoma (64.8%), then follicular carcinoma (24.2%), and poorly differentiated carcinoma (11.0%). The objective response rate and the clinical benefit (complete response, partial response, and durable stable disease defined as the status of stable disease persisting for at least 23 weeks) rate were 58.2% (95% confidence interval [CI]: 47.4-68.5%) and 83.5% (95% CI: 74.3-90.5%), respectively. With a median follow-up time of 2.3 years (range, 0.02-11.2 years) as of the cut-off date, 34 patients (37.4%) were under lenvatinib treatment. The median progression-free survival (PFS) was 3.1 years (95% CI: 1.70-4.00) with a 2-year PFS of 55.0% (95% CI, 43.0-65.5), and the median overall survival (OS) was 5.1 years (95% CI: 3.21-6.66) with a 2-year OS of 79.9 % (95% CI, 69.1-87.2). Ten (11.0%) patients experienced permanent treatment discontinuations due to AE; most common included mucosal perforation (n=3, 3.2%), while no treatment death was seen.

Conclusions: Long-term follow-up in the real world, for the first time, revealed that lenvatinib provides a reliable clinical outcome, represented by long-lasting disease stabilization with a favorable safety profile in RR-DTC.

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2229P Updated safety and efficacy of selpercatinib in patients (pts) with RET-activated thyroid cancer: Data from LIBRETTO-001

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Background: Selpercatinib, a first-in-class highly selective and potent RET kinase inhibitor with CNS activity, is approved in multiple countries for the treatment of *RET*-mutant MTC and *RET* fusion-positive thyroid and lung cancers.

Methods: Updated analysis of selpercatinib in pts with *RET* fusion-positive thyroid cancer (TC), in LIBRETTO-001 (NCT03157128) was conducted after additional follow up (f/u) of 19 months. Primary endpoint was objective response rate (ORR, RECIST

1.1) by independent review committee (IRC). Secondary endpoints included duration of response (DoR), progression free survival (PFS), and safety.

Results: Efficacy of selpercatinib after RAI (where RAI appropriate) was evaluated in systemic treatment-naïve pts (N=24) and pre-treated pts (N=41) (Table). Naïve and pre-treated pts achieved an ORR of 95.8% and 85.4%, respectively (Table). For pre-treated pts DoR was 26.7 months and PFS was 27.4 months. DoR and PFS data for treatment-naïve pts are still immature approaching and at 2 years, with response ongoing in most pts. At 2 yrs, 95.2% of naïve pts and 57.1% of pre-treated pts remained progression free. In the safety population (N=66), the most common ≥3 grade treatment-emergent adverse events (TEAEs) were: hypertension (15.2%), hyponatraemia (10.6%), diarrhea (7.6%), lymphopenia (7.6%) and increased alanine aminotransferase (6.1%). Two pts (3.0%) discontinued treatment due to TEAEs; 1 pt (1.5%) of these was considered related.

Table: 2229P

	Treatment naïve (N=24)	Prior treatment (N=41)
ORR by IRC, % (95% CI)	95.8% (78.9, 99.9)	85.4% (70.8, 94.4)
Complete response, n (%)	5 (20.8)	5 (12.2)
Partial response, n (%)	18 (75.0)	30 (73.2)
Stable disease, n (%)	1 (4.2)	6 (14.6)
Progressive disease, n (%)	0 (0.0)	0 (0.0)
Not evaluable (NE), n (%)	0 (0.0)	0 (0.0)
PFS by IRC		
Median PFS, months (95% CI)	NE (44.2, NE)	27.4 (14.5, NE)
Censored, %	21 (87.5)	24 (58.5)
PFS rate at 24 months, % (95% CI)	95.2 (70.7, 99.3)	57.1 (38.6, 71.8)
Median f/u, month	24.9	30.4
DoR by IRC		
Median DoR, months (95% CI)	NE (42.8, NE)	26.7 (12.1, NE)
Censored, %	21 (91.3)	20 (57.1)
DoR rate at 24 months, % (95% CI)	90.9 (50.8, 98.7)	50.7 (30.4, 67.8)
Median f/u, months	17.8	33.9

NE; Not estimated.

Conclusions: With longer f/u and additional pts, selpercatinib continues to demonstrate very durable responses in pts with *RET*-fusion thyroid cancer with or without prior therapy, suggesting use of selpercatinib as first systemic therapy appears to be highly effective in treatment of TC. The safety remained tolerable despite longer duration on treatment.

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All other authors have declared no conflicts of interest.

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2230P Phase II trial of abemaciclib in incurable anaplastic thyroid cancer

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TRANSLATIONAL RESEARCH (AGNOSTIC)

2231O Pan-cancer assessment of the impact of intronic variants on cancer development and progression

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Background: Despite advancements in cancer genomics, the contribution of intronic somatic mutations to cancer development and progression remains to be fully established. Here we systematically investigated the functional significance of intronic variants in a pan-cancer cohort with >30,000 tumor/normal samples subjected to an FDA-authorized multi-gene assay.

Methods: Patients who underwent tumor and matched normal sequencing by MSK-IMPACT from 2014 to Sept 2021 were included. We first defined histology-specific gene enrichments incorporating pathogenic somatic variants (PVs). Similar analyses consisting exclusively of non-coding variants (NCVs) were subsequently performed. The rates of concordance between NCV and PV-based gene-histology enrichment as a function of tumor suppressor (TSGs) vs. oncogene (OG) status were investigated. We defined the patterns of mutual exclusivity and co-occurrence between PVs and NCVs, as well as loss of heterozygosity (LOH) status of TSGs affected by these variants.

Results: We analyzed 33,106 tumors from 25,418 patients across 22 cancer types. NCVs were enriched in specific cancer types, matching the enrichment of PVs. NCVs significantly affected cases with no PV identified in the known driver gene: *CDH*1 in 14% of invasive lobular carcinomas (ILC) (OR 109.7 [26.5 − inf], $p < 0.001$), *APC* in 87% of colorectal cancers (CRC) (OR 197.23 [123.7 − inf], $p < 0.001$), and *RB1* in 9% of small cell lung cancer (SCLC) (OR 32.3 [15.06 − inf], $p < 0.001$) with no PV identified in the known driver gene. NCVs in TSGs followed lineage-specific patterns vs. OGs (OR 5.5 [1.6-29.6], $p < 0.001$) and vs. genes not enriched in the PV analysis (OR 9.5 [5.0 − 18.2], p= 2.87 e-12). NCV in TSGs occurred in tumors with mono-allelic loss of the TSG: 100.0% of *CDH1* in ILC ($p < 0.001$), 87.3% of *APC* in CRC ($p < 0.001$), and 100.0% of *RB1* in SCLC ($p = < 0.001$). Immunohistochemistry of select cases with NCVs in *RB1, CDH1*, and other select TSGs showed loss of protein expression.

Conclusions: We report the frequent detection of intronic variants that are not reported by clinical tumor sequencing assays. Such variants followed expected histology and zygosity patterns, strongly suggesting intronic variants may be consequential and constitute the second hit in a lineage-specific manner.

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2232O Atezolizumab (atezo) and tumour microenvironment in early triple-negative breast cancer (eTNBC): Exploratory biomarker analysis from IMpassion031

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Background: IMpassion031 showed that neoadjuvant chemotherapy (CT) + atezo significantly increased pathological complete response (pCR) and numerically favoured event-free, disease-free and overall survival (EFS, DFS and OS) vs CT + placebo (Pla) in patients (pts) with eTNBC. This IMpassion031 substudy assessed potential predictive tumour immune biomarkers for atezo clinical benefit.

Methods: Biomarker evaluation was performed on baseline, on-treatment, surgery and disease recurrence matched formalin-fixed, paraffin-embedded tumour tissue samples. Samples were tested for tumour infiltrating lymphocytes (TILs) and with RNA sequencing to derive molecular subtypes (basal-like immune activated [BLIA], basal-like immune suppressed [BLIS], mesenchymal [MES], luminal androgen receptor [LAR]), biological pathways and cellular components (xCELL). Biomarkers were evaluated for their association with pCR, EFS, DFS and OS.

Results: In patients with TIL-low tumours, atezo numerically improved outcomes compared with Pla (ΔpCR =19.4%, EFS hazard ratio [HR] 0.57, DFS HR 0.64 and OS HR 0.31). Atezo had higher pCR than Pla in BLIA (75% vs 54%) and BLIS (54% vs 32%) subtypes but not in LAR (33% vs 33%). While atezo showed improved EFS (HR 0.38) and DFS (HR 0.24) only in pts with BLIA tumours, atezo OS improvement vs Pla was only seen in pts with BLIS tumours (HR 0.17). The LAR subtype had excellent EFS, DFS and OS regardless of treatment, in contrast to a relatively low pCR rate. Biological pathway and cell type analyses indicated that increased proliferation, $\gamma\delta$ T cells and pro-B cells predict atezo pCR benefit, while epithelial-mesenchymal transition, pericytes and stromal biology (e.g. angiogenesis, TGFβ) are linked to lack of atezo pCR benefit. No biological pathway or cell type consistently predicted atezo EFS, DFS or OS benefit. Exposure to CT $\pm$ atezo promoted dynamic changes in molecular subtype, which return to baseline at disease recurrence.

Conclusions: Atezo provides benefit in eTNBC pts with proliferative basal tumours, but is less active in indolent LAR tumours. Atezo improves outcomes in pts with low

TILs, a subgroup with poor prognosis in eTNBC. Further studies are needed to validate these findings.

Clinical trial identification: NCT03197935.

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2233MO CDC7 inhibition constrains lineage plasticity and prevents resistance and neuroendocrine transformation in the lung and prostate

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Background: In lung and prostate adenocarcinomas (ADs), neuroendocrine (NE) transformation to small cell carcinoma (SCC) occurs on targeted therapy in up to 14% and 30% of *EGFR*-mutant lung and AR-dependent prostate tumors, respectively. SCCs, occurring *de novo* or after NE transformation, lead to poor prognosis due to the sparse and ineffective treatment options available, based on classic chemotherapy. Thus, the identification of therapeutic targets to (1) prevent NE transformation and (2) to efficiently treat SCCs are unmet clinical needs.

Methods: We performed CRISPR screens to identify therapeutic targets for SCC, which were validated genetically and pharmacologically *in vitro* and *in vivo* in lung and prostate adeno-to-NE transformation models and SCC patient-derived xenografts (PDXs), as well as in isogenic cell lines.

Results: Our screen nominated CDC7, involved in DNA replication, as a therapeutic vulnerability in SCC. Simurosertib, a CDC7 inhibitor in phase II trials, dramatically sensitized an array of chemotherapy-naïve and -resistant SCC PDXs to chemotherapeutic agents used in the first- and second-line settings for these tumors, respectively, without toxicity issues at the concentrations used. Also, we observed CDC7 upregulation in NE-transforming clinical specimens, occurring already in pre-transformation ADs. Consistently, we observed increased CDC7 expression in the lung and prostate AD population at high risk of NE transformation (*TP53/RB1*-mutated), and that double *TP53/RB1* knock out induces not only high CDC7 expression in lung and prostate AD cell lines, but also increased sensitivity to simurosertib. Importantly, simurosertib was able to suppress the acquisition of a NE phenotype and dramatically delay tumor relapse in an array of lung and prostate patient-derived models of NE transformation treated with targeted therapy.

Conclusions: CDC7 inhibition prevents NE transformation in lung and prostate AD, and exquisitely sensitizes NE-transformed or *de novo* SCCs to chemotherapy. The availability of CDC7 inhibitors currently under clinical testing will allow immediate translation of these results in two settings with extremely limited and rather ineffective therapeutic options available.

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2234P Local immune-related adverse events (irAEs) are more common in tumor-bearing organs

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Background: Immune checkpoint inhibitors (ICIs) can induce dramatic anti-tumor immune responses as well as significant immune-related adverse events (irAEs). While the drivers of irAEs are poorly understood, we hypothesized that inflammation against infiltrating tumor cells could result in local inflammation or a break in immune tolerance that drive a subset of irAEs in the infiltrated organ.

Methods: The medical records of cancer patients admitted to the Massachusetts General Hospital with concern for an irAE from Feb 2011 - Nov 2021 were reviewed for radiographic evidence of metastatic or primary tumors in the liver and/or lungs and a diagnosis of irHepatitis and/or irPneumonitis during admission. Cases with radiation to the irAE organ in the prior year were excluded. Multivariable analysis using logistic regression was used to obtain the odds ratios of irAEs in tumor-bearing

organs. Pathology specimens of irAE tissues were reviewed for histologic evidence of tumor cells.

Results: 384 hospitalized patients were identified (irHepatitis n=41, irPneumonitis n=30) (Table 2234P). Tumor-bearing liver was associated with irHepatitis (OR 2.4, 95% CI [1.2, 4.7], p = 0.011), even after considering only biopsy-proven cases of irHepatitis (n = 34, OR 2.6, 95% CI [1.2, 5.4], p = 0.0093). Tumor-bearing lungs were also associated with irPneumonitis (OR 2.6, 95% CI [1.1-6.6], p = 0.034). Both associations remained significant after adjusting for dual ICI use. Four cases from patients with irAEs further identified histological evidence of radiographically occult metastases in organs with irAEs. T-cell receptor sequencing of irAEs in tumor-bearing organs will be used to further define immunologic features of these irAEs.

Table: 2234P Patients with tumor-bearing organs and irAEs

Tumor-bearing liver	irHepatitis		
	-	+	Total
-	271	25	296
+	72	16	88
Total	343	41	384
Tumor-bearing lung	irPneumonitis		
	-	+	Total
-	152	7	159
+	194	23	217
Total	346	30	376*
	*8 cases were excluded due to recent lung irradiation		

Conclusions: In a pan-cancer cohort, radiographic evidence of tumor infiltration in the lung or liver is a risk factor for the development of irAEs in that same organ. Tumor infiltration may increase the risk for developing an irAEs in that organ, and these cases may have distinct molecular and clinical features.

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2235P Chemotherapy priming leads to hypermutability and immune surveillance in colorectal cancer

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Background: Molecular alterations generated by DNA repair deficiencies and DNA damaging agents can be detected by the host immune system and this can restrict cancer growth. We have previously reported that temozolomide (TMZ) is able to induce MMR defects and hypermutability leading to immunotherapy clinical benefit in the subset of CRCs characterized by inactivation of O6-methylguanine methyltransferase (MGMT). We reasoned that combination of chemotherapeutic agents could similarly impair DNA repair function, increase genomic diversity and trigger cancer immunogenicity in the larger group of MMR proficient (MMRp)/MGMT wild type (MGMTwt) CRCs.

Methods: We studied the impact of commonly used cytotoxic agents such as 5-fluorouracil, irinotecan, oxaliplatin, cisplatin (CDDP) and TMZ on the immunogenomic features of CRC cells. We performed a two-step experiment: first, murine CRC models were exposed to chemotherapy agents used alone or in combination in a pulsatile schedule in order to mimic drug exposure in the clinical setting (priming phase) and then injected in immune-deficient and -proficient mice (editing phase). Whole exome sequencing (WES) was performed at baseline and after both the priming and the editing phases to identify mutational signatures, neoantigen prediction and immunoediting.

Results: We found that combinatorial treatment of MMRp /MGMTwt CRC cells with CDDP and TMZ causes impairment of MMR and hypermutability, eventually leading to tumor rejection in syngeneic mice. The majority of mutations caused by CDDP-TMZ are edited by the immune system and, importantly, mice that had successfully rejected cells treated with CDDP-TMZ are vaccinated against their untreated counterpart. The same effect is not observed when CDDP and TMZ are given as monotherapy or when CRC cells are primed with the 5-fluorouracil-oxaliplatin-irinotecan (FOLFOXIRI) triplet.

Conclusions: These results indicate that rational combinations of commonly used cytotoxic agents can be exploited to promote cancer cell hypermutability and immunogenicity, and have implications in the design of new chemo-immunotherapy approaches in CRC.

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2236P MHC-II neoantigens and copy number alterations (CNA) drive immune checkpoint inhibitor (ICI) response in metastatic melanoma (MM)

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Background: ICIs have transformed the prognosis of MM, but our understanding of mechanisms of response and resistance remains incomplete. The 100,000 Genomes Project presents a melanoma cohort with whole genome sequencing (WGS) and detailed clinical annotation.

Methods: 97 patients received ICIs in the 1L metastatic disease setting; ipilimumab-nivolumab (60%), anti-PD-1 monotherapy (32%), and ipilimumab (8%). Response rate was 45%. Median follow-up was 30.6 months, median time to treatment failure (TTF) 9.6 months and median overall survival (OS) not reached. From WGS, neoantigen

calling, CNA and tumour purity analyses were performed, predictive variables were included in logistic regression.

Results: Incorporating MHC-II neoantigen load, CNAs and tumour purity, our multivariate model predicted response with AUC 0.86 Responders were associated with a higher number of predicted clonal neoantigens (p=0.0029), driven by MHC-II neoantigens (p=2e-04), and were more statistically significant biomarkers than TMB (p=0.016). A higher total neoantigen burden (p=0.02) and MHC-II neoantigen burden (p=0.06), but not higher TMB, were associated with superior OS. Independently, low tumour purity was associated with response (p=0.005) and superior OS (p=0.04) Non-responders harboured CNAs in key melanoma driver genes, including *CDKN2A* loss of function (p=0.04), and *TERT* gain (p=0.03) which was associated with inferior TTF (p=0.02) Genomic imprinting has established links to cancer pathogenesis, most notably at 11p15.5. In our cohort, loss of heterozygosity (LOH) at 11p.15.5 was associated with response (p=0.007), superior TTF (p=0.05), and higher MHC-II neoantigen load (p=0.04), while non-LOH loss at the same loci was associated with non-response (p=0.003), inferior TTF (p=0.007) and OS (p=0.02), highlighting that different classes of loss can lead to opposing biological sequelae. LOH with loss of the active allele and persistence of the imprinted allele will lead to non-expression of the oncogene. External validation with matched WGS and RNA will be presented at the conference.

Conclusions: In our cohort, 1L ICI response in melanoma was driven by MHC-II neoantigens, CNAs and tumour purity.

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Litchfield: Financial Interests, Personal, Invited Speaker: Roche Tissue Diagnostics; Financial Interests, Personal, Other, Consulting work: Kynos Therapeutics, Monopteros Therapeutics, Tempus; Financial Interests, Personal, Invited Speaker, Invited speaker: Ellipses Pharma; Financial Interests, Institutional, Research Grant: Ono/LifeArc; Financial Interests, Institutional, Research Grant, Research funding: Genesis Therapeutics; Non-Financial Interests, Institutional, Proprietary Information, Collaboration on data analysis: BMS. S. Turajlic: Financial Interests, Personal, Invited Speaker: IDEA Pharma, Roche, Ventana, MSD, Merck; Financial Interests, Institutional, Funding, Uncommon theme pump priming funds: NIHR; Financial Interests, Institutional, Funding, Digital theme funding: RMH/ICR/BRC/Imperial AHSC/Faculty of Medicine; Financial Interests, Institutional, Funding, Tracking renal cancer evolution in blood: Rosetrees Trust; Financial Interests, Institutional, Funding, Clinical PhD Fellowship over 3 years: CRUK Welcome Trust; Financial Interests, Institutional, Funding, Investigating the relationship between primary melanomas and their metastases: The Robert McAlpine Foundation; Financial Interests, Institutional, Funding, Innovation Grant Award for biomarker development: The Francis Crick Institute; Financial Interests, Institutional, Funding, Developing a novel method of representative tumour in sampling in clinical setting: Ventana; Financial Interests, Institutional, Funding, Mapping clonal evolution in renal cell carcinoma: CRUK training and career development board - clinician scientist fellowship; Financial Interests, Institutional, Funding: Harry J Lloyd Charitable Trust Career Development Award; Financial Interests, Institutional, Funding, Clinical Research Fellowship in melanoma: Andy Quick Charitable fund; Financial Interests, Institutional, Funding, Mechanisms of BRAF resistance: Complete Genomics; Financial Interests, Institutional, Funding, Molecular profiling of non-cutaneous melanoma: CRUK; Financial Interests, Institutional, Funding, Target discovery in acral melanoma: Rosetrees Trust. 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2237P Avelumab (AVE), cetuximab (CET) and irinotecan (IRI) for treatment refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): Translational analyses of the AVETUXIRI phase II trial

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Background: This trial explores the clinical efficacy and safety of AVE, CET and IRI for treatment refractory MSS mCRC. We aim at characterizing the immune response for biomarker discovery through associated translational research.

Methods: MSS, chemorefractory (anti-EGFR refractory if RAS wt) mCRC patients (pts) were enrolled (RAS wt: 28 pts, RAS mut: 27 pts) and treated with CET and IRI from week 1(W1) and AVE from W3. Clinical objectives (safety, tumor response, disease control rate (DCR), PFS and OS) were presented separately. Exploratory endpoints include predictive efficacy biomarkers (immunoscore (IS), immune tumor microenvironment, gene expression profile (GEP), ctDNA) and modification overtime. Multiplex immunofluorescence (MIF), RNAseq and ctDNA analyses were done (sequential metastasis biopsies and plasma samples at W0, W3, W11). CD3, CD8, CD45RO, PD1, PD-L1cells densities were quantified. RNA-seq data were used to perform several analyses (DESeq2, GSEA, deconvolution, gene ontology). OncoSELECT panel (58 genes) was used to follow ctDNA variation over time (mean variant allele frequency).

Results: Among 55 treated pts, 95 biopsies (W0: 39, W3: 29, W11: 27) were available for MIF (table: W0 results). On 23 pts (1st stage), upregulation of adaptive immune response signature was associated with tumor shrinkage, PFS>6 and OS>12 months (p. adj= 0.00). Few modifications of immune cells and GEP were observed overtime (W0, W3, W11). ctDNA decrease (>10%) was associated with tumor response (p=0.04) and PFS (6.6 vs 3.4 months, p=0.08).

Table: 2237P

Characteristics	IS (CD3/CD8) high	CD3/PD1 high	CD3/CD8/CD45RO/ PD1 high
High/others:pts	10/29	10/29	8/31
RAS-wt/RAS-mut:OR, p-v	1.39, p=0.73	0.82, p=0.99	0.83, p=0.99
Tumor shrinkage: OR, p-v	8.32, p=0.00	4.50, p=0.05	9.54, p=0.00
DCR:OR, p-v	8.02, p=0.05	3.16, p=0.26	5.55, p=0.12
PFS:HR, p-v	0.29, p=0.00	0.28, p=0.00	0.43, p=0.03
OS:HR, p-v	0.62, p=0.19	0.26, p=0.00	0.47, p=0.06

Conclusions: Independently of RAS mutation, existing adaptive immune response within metastases is associated with treatment benefit. ctDNA decrease is associated with tumor response.

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Legal entity responsible for the study: Cliniques Universitaires Saint-Luc (Pr. MD. PhD. Marc van den Eynde).

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2238P Tebentafusp reprograms immunosuppressive tumor-associated M2 macrophages towards anti-tumoral M1 macrophages

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Background: Tebentafusp, a gp100-directed ImmTAC bispecific (gp100 x CD3), is the first TCR therapeutic to demonstrate survival benefit and is approved for the treatment of HLA-A*02:01+ adults with unresectable or metastatic uveal melanoma (mUM)[1]. High CD3$^+$ T cell: CD163$^+$ M2 macrophage ratio was associated with therapeutic benefit from tebentafusp despite the immunosuppressive effects of M2 macrophages[2]. Here we explored the effects of ImmTAC-redirected T cell activation on macrophage reprogramming in vitro and in vivo.

Methods: M2 macrophages were generated in vitro from healthy donor monocytes (n=4). Their effect on ImmTAC-mediated T cell activation and redirection against antigen positive HLA-A*02:01+ THP-1 tumor cells was assessed. Gene expression and phenotypic changes were assessed by bulk RNA-seq and flow cytometry. Baseline and on-treatment tumor biopsies from a phase II trial of mUM HLA-A*02:01+ patients treated with tebentafusp (NCT02570308) were used to quantify $CD163^+$ and $CD3^+$ cells by immunohistochemistry (n=112), and to measure gene expression by bulk RNAseq (n=35), and single cell RNAseq (n=1).

Results: In vitro, M2 macrophages inhibited ImmTAC-mediated T cell killing of tumor cells in a dose dependent manner. M2 macrophages were reprogrammed to down-regulate M2 markers (e.g. CD206, CD163) and express M1 markers (e.g. CD40, CD80) in the presence of T cells activated by ImmTAC. This M2 to M1 reprogramming was confirmed by single cell RNAseq of paired biopsies from a tebentafusp-treated patient (55% increase in M1 macrophages 1 year post tebentafusp-treatment). M1 gene signatures[3] were significantly upregulated in on-treatment biopsies (n=35) after 3 doses of tebentafusp (2.2 fold change).

Conclusions: ImmTAC-mediated redirection of T cells reprograms pro-tumoral M2 macrophages towards anti-tumoral M1 macrophages in vitro and in tebentafusp-treated mUM patients. These results demonstrate how tebentafusp re-shapes the tumor microenvironment to enhance the anti-tumor activity of T cells.

References: 1. Nathan et al. NEJM 2021 2. Piperno-Neumann et al. AACR 2022 3. Chen et al. Cell 2021.

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2239P Gene expression profiling in tumors with and without tertiary lymphoid structures across cancer-types

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Background: The presence of tertiary lymphoid structures (TLS) in the tumor microenvironment (TME) is linked to favorable clinical outcomes and response to immunotherapy in various types of cancer. However, accurately measuring TLS can be difficult. Thus, our aim was to identify genes or gene expression signatures that can effectively indicate TLS abundance in the TME, irrespective of the cancer type.

Methods: Patients (pts) with advanced solid cancer participating in the molecular prescreening of the SOLTI-1904-ACROPOLI study were included. Pathological analysis was performed to determine the presence of tumor infiltrating lymphocytes (TILs) and TLS. On the same FFPE tumor block, gene expression (GE) was evaluated in all pts using a panel of 72 genes. Further GE was analyzed in a subset of 142 pts (n=66 TLS-negative, n=76 TLS+) using a panel of 192 genes, including the HER2DX 14-gene B-cell/IgG (IGG) signature. The association between GE and TLS was analyzed.

Results: 1,003 pts were included across 39 different cancer-types. TLS were successfuly evaluated in 898 pts (89%). TLS were detected in 76 pts (8.5%), mostly in samples from primary tumors (n=63, 83%). Most frequent TLS+ cancer-types were colorectal (n=22), pancreatic (n=13), gastric (n=11) and breast (n=9). Compared to TLS-negative tumors, TILs were significantly higher in TLS+ tumors (median 4% *vs* 18%, $p<0.001$). The presence of TLS was significantly associated with higher expression of genes related to B-cells (*CD19*) and T-cells (*CD4, CD8A*), and lower expression of proliferation genes (*TYMS, CDCA1).* Upon further evaluation of GE, TLS+ tumors had a significant enrichment of genes related to activated B-cells (*CD79A*) and immunoglobulins (*IGJ, IGKC*). Finally, the IgG signature as a continuous variable demonstrated a significant association with TLS presence, independently of the cancer-type and TILs (p=0.002). In IgG-high tumors, the proportion of TLS+ tumors was 61.6% compared to 38.4% TLS-negative (p<0.001)

Conclusions: The B-cell/IGG signature is a GE pattern strongly associated with TLS across cancer types, even independently of TILs. This signature could serve as a valuable tool for precisely measuring TLS and predicting clinical outcomes and response to immunotherapy in cancer patients.

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Hoffmann-La Roche, Gilead, GSK, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Peptomyc, Regeneron, Sanofi, Takeda, Turning Point, Pfizer; Financial Interests, Personal, Invited Speaker: Amgen, Daiichi Sankyo, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, PeerVoice, Pfizer, Sanofi, Takeda, Touch Oncology, AstraZeneca, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Merck Sharp & Dohme; Financial Interests, Personal, Member of Board of Directors, Independent member: Grifols; Financial Interests, Institutional, Local PI, Clinical Trial: AstraZeneca AB, AbbVie, Amgen, Bayer Consumer Care AG, Beigene, Boehringer Ingelheim GmbH, Bristol Myers Squibb International Corporation, Daiichi Sankyo Inc., Exelixis Inc., F. Hoffmann-La Roche Ltd., Genentech Inc., GSK Research and Development Limited, Janssen Cilag International NV, Merck Sharp & Dohme Corp., Merck KGAA, Mirati Therapeutics Inc., Novartis Pharmaceutica SA, Pfizer, Takeda Pharmaceuticals International; Non-Financial Interests, Leadership Role, President (2021-2023): SEOM (Sociedad Espanola de Oncologia Medica); Non-Financial Interests, Member, Member of Scientific Committee: ETOP (European Thoracic Oncology Platform); Non-Financial Interests, Member, Member of the Scientiffic Advisory Committee: CAC Hospital Universitari Parc Taulí. E. 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Hoffmann-La Roche Ltd., Genentech Inc., Janssen-Cilag International NV, Merck Health KGAA, Merck, Sharp & Dohme de España, SA, Novartis Farmacéutica SA, PharmaMar SA,

Sanofi-Aventis Recherche & Développement, Servier, Taiho Pharma USA, Inc., BeiGene, Boehringer Ingelheim, HalioDX SAS, Hutchinson Medipharma, MedImmune, Menarini, Merus N V, Pfizer, Mirati; Non-Financial Interests, Member of Board of Directors, Board of Directors: Cancer Core Europe, Spanish Association Against Cancer -AECC; Non-Financial Interests, Member of Board of Directors, General Assembly: Horizon Europe Cancer Mission; Non-Financial Interests, Leadership Role, External Scientific Committee: Institute for Health Research INCLIVA — Clinical Hospital of Valencia, IdiSNA —Universidad de Navarra; Non-Financial Interests, Leadership Role, Scientific Advisory Board: Spanish National Cancer Research Centre (CNIO); Non-Financial Interests, Advisory Role, International Scientific Evaluation Committee: Bosch Health Campus (BHC); Non-Financial Interests, Advisory Role, Review Board: National Decade Against Cancer (NCT) - German Consortium for Translational Cancer Research (DKTK); Non-Financial Interests, Advisory Role, Scientific Advisory Board: Karolinska Comprehensive Cancer Centre; Non-Financial Interests, Advisory Role, International Review Committee (IRC): Oncode Institute; Non-Financial Interests, Advisory Role, Scientific Advisory Board (SAB): Oslo University Hospital Comprehensive Cancer Centre (OUH CCC); Non-Financial Interests, Leadership Role, Governance Advisory Committee: European Organization for Research and Treatment of Cancer -EORTC; Non-Financial Interests, Leadership Role, Vice Chairman: World Innovative Networking (WIN) Consortium in Personalized Cancer Medicine; Non-Financial Interests, Other, Coordinating PI & Steering Committee Member. Clinical Trials & Research: AstraZeneca Pharmaceutical LP, Array Biopharma Inc., Boehringer Ingelheim, MedImmune, Menarini, Merck Healthcare KGAA, Merck, Sharp & Dohme de España SA, Pfizer, Servier; Non-Financial Interests, Principal Investigator, Clinical Trials & Research: Array Biopharma Inc., AstraZeneca Pharmaceutics LP, BeiGene, Boehringer Ingelheim, Debiopharm International SA, Bristol Myers Squibb International Corporation, Celgene International SARL, F. Hoffmann-La Roche Ltd., Genentech Inc., HalioDX SAS, Hutchinson Medipharma, Janssen-Cilag International NV, Menarini, MedImmune, Merck Healthcare KGAA, Merck, Sharp & Dohme de España SA, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Sanofi-Aventis Recherche & Développement, Servier, Taiho Pharma USA Inc.; Non-Financial Interests, Other, Steering Committee Member. Clinical Trials & Research: Debiopharm International SA, F. Hoffmann-La Roche Ltd., Genentech Inc., HalioDX SAS, Hutchinson Medipharma, Janssen-Cilag International NV, Merus NV, Taiho Pharma USA Inc.; Non-Financial Interests, Other, Coordinating PI. Clinical Trials & Research: Mirati; Non-Financial Interests, Member: AACR, ASCO, EACR, EORTC, SEOM; Other, President: Oncology Master Plan — Catalonia Department of Health; Other, Advisory Committee: Advisory Committee on Pharmaceutical Provision Financing under the Spanish National Health System. A. Prat: Financial Interests, Personal, Invited Speaker: Roche; Financial Interests, Personal, Invited Speaker, Lecture fees: Novartis, Daiichi Sankyo; Financial Interests, Personal, Advisory Board, Advisory role/consultancy: Novartis, Pfizer, Oncolytics Biotech, Guardant Health, Peptomyc; Financial Interests, Institutional, Invited Speaker, Clinical trials: Daiichi Sankyo; Financial Interests, Institutional, Other, Contracted research: Boehringer Ingelheim, Medica Scientia Innovation. Research; Financial Interests, Personal, Advisory Board: AstraZeneca, 1TRIALSP, S.L.; Financial Interests, Personal, Member of Board of Directors, Leadership role: Reveal Genomics, SL.; Financial Interests, Personal, Stocks/Shares: Reveal Genomics, Oncolytics Biotech; Financial Interests, Personal, Royalties: Reveal Genomics, International Oncology Bureau, S.L.; Financial Interests, Institutional, Local PI: Roche, AstraZeneca; Financial Interests, Personal and Institutional, Steering Committee Member: Daiichi Sankyo; Financial Interests, Institutional, Coordinating PI: Novartis; Non-Financial Interests, Institutional, Other, Leadership roles: Patronage committee: SOLTI Foundation, Actitud Frente al Cáncer Foundation; Non-Financial Interests, Personal, Other, Asociación Española de Investigación sobre el Cáncer: ASEICA. All other authors have declared no conflicts of interest.

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2240P Novel genetic markers associated with immune checkpoint inhibitor induced immune-related adverse events

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Background: Immune checkpoint inhibitors (ICI) are highly efficacious but ∼ 50% of cancer patients on combination and ∼10% on ICI monotherapy experience ≥ grade 3 immune-related adverse events (irAE). Managing irAEs is challenging and there is a lack of predictive biomarkers. We conducted genome-wide association analyses (GWAS) to identify markers associated with irAEs.

Methods: 599 cancer patients on ICIs were genotyped and genome-wide imputation was performed. Association testing with CTCAE graded irAEs was conducted (0=grade 0-2, 1=grade ≥3 irAE). Markers with $P<5x10^{-6}$ were tested in a validation cohort. A transcriptome-wide association study (TWAS) was also performed.

Results: 72% of the discovery cohort had melanoma, 37% received combination therapy and 31% developed ≥ grade 3 irAE. 8 SNPs were associated with any ≥ grade 3 irAE at $P<5x10^{-6}$ but none replicated at $P<0.05$ (Table 2240P). Of note one, rs35429660, is significantly associated with *ZNF701* expression in monocytes and *ZNF701* was also significant in the TWAS ($P=5.1x10^{-7}$). In an analysis of individual organ irAEs, we identified markers at $P<5x10^{-6}$ in the discovery phase. One, rs77941834, was associated with hepatitis in the validation phase (P=0.04) and expression of *LINC02021* in T cells ($4.6 x10^{-8}$). 11 other SNPs had suggestive evidence of validation. One maps to *MAST3*, linked to inflammatory bowel disease and another maps to *IFI44*, linked to multisystem inflammatory syndrome, viral hepatitis and immune cell infiltration. The *IL7* SNP previously reported as associated with any grade irAE at GWAS significance was nominally significant (P=0.05) in our data.

Table: 2240P Markers associated with any ≥ grade 3 irAE at $P<5x10^{-6}$ in discovery phase

rsID	Toxicity associated allele	Discovery OR (95% CI)	Discovery P-value	Validation OR (95% CI)	Validation P-value	Meta P-value
rs1310844785	TTG	2.5 (1.8-3.6)	8.91×10^{-8}	0.8 (0.6-1.2)	0.26	0.0038
rs7197466	T	2.1 (1.5-2.9)	2.19×10^{-6}	1 (0.8-1.4)	0.81	0.00077
rs35429660	C	2.2 (1.6-3)	5.13×10^{-7}	1.2 (0.8-1.6)	0.36	7.32×10^{-5}
rs1389216733	CA	6.3 (2.6-15.7)	3.07×10^{-6}	1.6 (0.8-3.5)	0.18	0.0004
rs6864863	A	2.1 (1.5-2.9)	3.73×10^{-6}	0.8 (0.6-1)	0.07	0.11
rs4527728	T	2.2 (1.6-3.1)	2.68×10^{-6}	1.2 (0.9-1.6)	0.26	0.00012
rs1208547611	CTT	2.5 (1.7-3.7)	3.59×10^{-6}	1.1 (0.7-1.5)	0.79	0.0015
rs2472135	A	2.1 (1.6-2.8)	5.83×10^{-7}	1.1 (0.8-1.5)	0.43	7.98×10^{-5}

Conclusions: We identified novel variants, including an immune eQTL for *ZNF701,* associated with serious ICI induced irAE. None reached genome-wide significance ($P<5x10^{-8}$). Meta-analysis with other cohorts is required to confirm our results and identify further markers predictive of irAE risk.

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2241P A novel 89Zr-anti-PD-1 immuno-PET-CT may predict response to PD-1 inhibitors and improve response assessment in a lung cancer murine model receiving immunotherapy

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized lung cancer treatment improving survival outcomes of NSCLC patients. Response assessment of patients on immunotherapy represents a challenge since an increase in tumor size or the appearance of new lesions might not reflect true disease progression (P) but pseudoprogression (PP), which has been reported in a range of 3-6% in NSCLC. Conventional FDG-PET scans does not accurately discriminate P from PP. We have recently reported the efficacy of a combined blockade of PD-1 and *Id1* in a NSCLC mouse model. We aimed to evaluate a novel ^{89}Zr-anti-PD-1 immuno-PET-CT to better assess response in a NSCLC murine model.

Methods: Syngeneic subcutaneous tumors were generated using LLC cells (with constitutive expression of *Id1* or *Id1*-silenced) in C57BL6J and in *Id1*-deficient mice, treated with PBS or with a monoclonal antibody against PD-1. Tumor growth and response, was measured by FDG uptake. Additionally, tumor lymphocyte infiltration was measured analyzing ^{89}Zr uptake. Tumor microenvironment was explored with immunohistochemistry, multiplex immunofluorescence and quantification of relative expression of interleukins by RT-PCR.

Results: FDG uptake did not show significant differences between groups, underestimating the real metabolic response induced by the treatment. However, ^{89}Zr-PET-CT showed a significantly higher ^{89}Zruptake when *Id1* was inhibited in both, tumor cells and tumor micro-environment and mice were treated with anti-PD-1

(p=0.0075). The tumor tissues analysis in those animals by immunohistochemistry and multiplex immunofluorescence disclosed an increase in immune $CD8^+$ T cells infiltration, being responsible for the antitumor response observed and correlating with ^{89}Zr signal. Moreover, the analysis of interleukins expression showed an upregulation of tumor pro-inflammatory interleukins.

Conclusions: *Id1* inhibition in tumor cells and in tumor micro-environment combined with PD-1 blockade enhanced immune cell infiltration through pro-inflammatory interleukins upregulation. ^{89}Zr-anti-PD-1 immuno-PET-CT may improve tumor response assessment in a NSCLC murine model receiving immunotherapy.

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2242P Engineering immune-cell targeting nanoparticles for precise delivery of loaded-cargo and enhanced immunotherapy efficacy

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Background: In recent years, cancer immunotherapy has gained significant attention for its ability to modulate immune cell functions. However, systemic administration of immunomodulatory agents can lead to side effects and limit drug efficacy. To overcome these challenges, we developed a targeted drug delivery platform using nanoparticles (NPs) made from biomaterials that can target specific immune cells. Our approach aims to increase drug efficacy and alleviate systemic side effects by delivering drugs directly to their intended sites.

Methods: The NPs were prepared using a conventional emulsification method based on Poly(D,L-lactide-co-glycolide)-maleimide. To conjugate anti-mouse NK1.1 and CD8a antibodies (Abs) to the surface of the NPs, the Abs were cleaved into Fc and $F(ab')_2$ fragments by protease. The $F(ab')_2$ fragments were reduced to obtain thiol groups in the hinge region for coupling to the maleimide group on the NPs' surface. The NPs' morphology was confirmed using dynamic light scattering and scanning electron microscopy, while the in vitro and in vivo targeting efficiency was evaluated using fluorescently labeled NPs and flow cytometry.

Results: The NPs were confirmed to be monodisperse, spherical particles with a size of less than 200 nm. Further, in vitro studies showed that when fluorescently labeled and Abs-conjugated NPs were co-incubated with mouse splenocytes, the NPs' fluorescence was confirmed in each immune cell, whereas immune cells with non-conjugated NPs showed no fluorescence. In vivo studies showed that after injecting fluorescently labeled and Abs-conjugated NPs into the tail vein of mice, the fluorescence of the NPs was observed in the immune cells of the blood and spleen. Notably, fluorescence was barely detected in non-target immune cells, indicating the high specificity and targeting efficiency of the NPs.

Conclusions: The findings demonstrate that Abs-conjugated NPs can effectively target specific immune cells both in vitro and in vivo with minimal non-specific binding. This indicates that the developed platform can potentially maximize drug efficacy and minimize systemic side effects by delivering immunotherapeutic agents specifically to certain immune cells.

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2243P Immune-modulating magnetic nanoparticles to enhance the immune response for the treatment of breast cancer metastasis and recurrence

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Background: The immune-suppressive environment in cancer allows for tumor growth, leading to rapid metastases and recurrences. To effectively treat cancer, it is crucial to reverse this cold tumor environment. CpG, a well-known toll-like receptor 9 agonist, promotes dendritic cells (DCs) maturation and stimulates innate and adaptive immunity. In this study, we combined CpG with functional magnetic nanoparticles (FMNPs) to enhance its delivery to naive DCs, resulting in more efficient activation compared to free CpG delivery.

Methods: The heat-up method used to fabricate FMNPs, which were coated with caffeic acid, polydopamine, and polyethylenimine. The electrostatic force was bind CpG to FMNPs (i.e., CpG-FMNPs), and the degree of binding was estimated using a gel retardation assay. The resulting CpG-FMNPs product analyzed physicochemical properties using electron microscopy, dynamic light scattering, zeta potential, thermogravimetric analysis, and Fourier transform infrared spectroscopy measurements. We confirmed cytotoxicity using the L929 cell line and assessed DCs maturation using flow cytometry.

Results: The fabrication process of the FMNPs involved using various surface chemicals, resulting in changes in physicochemical properties at each step. The final product, CpG-FMNPs, had an average size of approximately 150 nm and contained 8% (weight%) of CpG conjugation. When tested, CpG-FMNPs showed high viability of approximately 90% at a concentration of up to 40 μg/ml and up-regulated 1.5∼2 times of surface markers CD80, CD86, CD40, and MHC-2 on DCs compared to free CpG. When administered intratumorally to the 4T1 orthotopic model, CpG-FMNPs showed a regression in tumor growth.

Conclusions: In this study, we produced FMNPs to efficiently deliver CpG to immature dendritic cells. Our results showed that the same dose of CpG delivered by FMNPs effectively activated DCs. The findings suggest that CpG-FMNPs may be capable of effectively activating DCs in the vicinity of the tumor site. However, further studies are needed to investigate their potential in activating cytotoxic T cells.

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2244P Anti CTLA-4 and PD-1 monoclonal antibodies increases systemic SDF-1 and galectin-3 levels through NLRP3 and MyD-88 pathways in preclinical models

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Background: Immune checkpoint inhibitors (ICIs) have significantly changed the oncology clinic in recent years, improving survival expectations in cancer patients. ICI therapy have a broad spectrum of side effects from endocrinopathies to cardiovascular diseases. In this study, pro-inflammatory and pro-fibrotic effects of short-term ICIs therapy in preclinical models were analyzed.

Methods: Firstly, in a human in vitro model, human cardiomyocytes co-cultured with hPBMC were exposed to ICIs (with CTLA-4 or PD-1 blocking agents, at 200 nM) for 72h. After treatment, production of DAMPs and 12 cytokines were analyzed in the supernatant through colorimetric and enzymatic assays. C57/Bl6 mice were treated with CTLA-4 or PD-1 blocking agents (15 mg/kg) for 10 days. Before (T0), after three days (T3) and ten days (T10), ejection fraction, radial/longitudinal strain were calculated by using echocardiography. Fibrosis, necrosis, hypertrophy and vascular NF-kB expression were analyzed through Immunohistochemistry. Myocardial expression of DAMPs (S100- Calgranulin, Fibronectin and Galectine-3), MyD88, NLRP3 and twelve cytokines have been analyzed. Systemic levels of SDF-1, IL-1β and IL-6 were analyzed before, during and after ICIs therapy.

Results: Radial and longitudinal strain were decreased after 10 days of ICIs therapy. Histological analysis of NF-kB expression shows that short-term anti-CTLA-4 or anti-

PD-1 treatment increased vascular and myocardial inflammation. Myocardial fibrosis and expression of galectin-3, pro-collagen 1-α and MMP-9 were increased after treatment with all ICIs. Both anti-CTLA-4 or anti-PD-1 treatments increased the expression of DAMPs, NLRP3 and MyD88 and induced both in vitro and in vivo the secretion of IL-1β, TNF-α and IL-6. Systemic levels of SDF-1, IL-1β and IL-6 were increased during and after treatment with ICIs.

Conclusions: Short therapy with PD-1 and CTLA-4 blocking agents increases vascular expression of NF-kB, systemic SDF-1, IL-1β, IL-6 levels and myocardial NLRP3 in preclinical models. The overall picture of the study suggests new putative biomarkers of ICIs-mediated systemic and myocardial damages potentially useful in clinical cardioncology.

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2245P Graphene oxide: A promising platform for delivery of cancer immunotherapy

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Background: Nanomaterials have been proposed as antigen carriers in cancer immunotherapies, to increase target cell uptake and therapeutic efficacy, and reduce off-target toxicity. The 2-dimensional carbon nanomaterial graphene oxide (GO) possesses a large surface area and high peptide loading capacity, as well as being inexpensive and biodegradable. These properties promote the development of GO as a system for antigen loading and delivery in targeted cancer immunotherapy. We have investigated the potential of GO in enhancing immune cell activation and cytotoxicity, including its impact in combination therapy with checkpoint inhibitors.

Methods: GO was combined with ovalbumin (OVA) peptide ($OVA_{257-264}$) and the immununostimulant polyinosinic:polycytidylic acid (Poly (I:C)), a toll-like receptor 3 agonist. We assessed dendritic cell (DC) activation and OVA-specific T cell responses after subcutaneous injection of GO complexes into naïve mice with/without pre-transfer of OVA-specific OT-I $CD8^+$ T cells. We also performed *in vitro* T cell activation assays by co-culturing DCs pre-stimulated with GO complexes with OT-I $CD8^+$ T cells.

Results: GO without Poly (I:C) displayed minimal immunogenic potential. However, GO + Poly (I:C) significantly enhanced immune cell infiltration to the skin injection site by histology. We also found a significant increase in activation and migration of DCs to skin-draining lymph nodes in the mice receiving GO + Poly (I:C) 24 hours after injection. GO + Poly (I:C) also dramatically enhanced T cell expansion and cytotoxic responses in both spleen and draining lymph nodes 7 days after injection of mice that had previously received OT-I $CD8^+$ T cells. Additionally, GO + Poly (I:C) significantly increased programmed death-1 (PD-1) expression on OT-I T cells in DC-OTI T cell co-cultures.

Conclusions: Our data have demonstrated the immunomodulatory potential of GO when complexed with Poly (I:C) by attracting immune cells including DCs to the injection site and boosting antigen-specific T cell cytotoxic responses *in vivo* and *in vitro*. DCs activated with GO complexed with Poly (I:C) increased PD-1 expression on T cells, which may suggest that graphene-based treatment could be beneficial in combination therapy with a checkpoint inhibitor such as anti-PD-1.

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2246P Tumor-infiltrating lymphocites and gene expression across multiple cancer-types: A translational analysis from the SOLTI-1904-ACROPOLI study

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Background: Tumor-infiltrating lymphocytes (TILs) are a mixed population of immune cells that infiltrate the tumor microenvironment (TME) and play a crucial role in recognizing and attacking cancer cells. The presence, localization and composition of TILs can be used as a biomarker for predicting clinical outcomes and response to immunotherapy in different types of cancer. Our aim was to investigate the correlation between the presence of TILs and gene expression across multiple cancer types.

Methods: Patients (pts) with advanced solid cancer who participated in the molecular prescreening of the SOLTI-1904-ACROPOLI study (NCT04802876) were included. A pathological analysis was performed to determine the proportion of TILs (%TILs) on a hematoxylin-eosin section. On the same FFPE tumor block, gene expression (GE) was evaluated using a panel of 72 genes, including 10 immune genes (i.e., *CD19*, *CD274*, *CD3*, *CD4*, *CD68*, *CD8*, *CD84*, *CD86*, *CXCL8* and *PDCD1*). An exploratory analysis of the association between TILs and GE was performed.

Results: 1,003 pts were included across 39 different cancer-types. TILs were successfuly evaluated in 922 pts (91.9%). Median (m) %TILs was 5% (IQR: 2-15, range: 0-80). Cancer-types with higher %TILs were duodenal (m=25%, IQR: 20-27.5), head and neck (m=22.5%, IQR: 9-30) and cervical carcinoma (m=20, IQR: 3-35). %TILs was higher in samples from primary tumors when compared to metastatic samples (m=6 vs m=3%, $p<0.001$). Significant differences of %TILs were also seen according to the site of metastasis (M1): m=8% in lymph nodes *vs* m=7.5% en lung M1 *vs* m=3% in liver M1 ($p<0.001$). A quantitative SAM analysis identified 31 genes significantly upregulated in tumors with higher %TILs (FDR<1%). Among the top 10 most upregulated genes, nine were immune (i.e., *CD8*, *PDCD1* and *CD19*) and the remaining one *MYC.* However, correlation between TILs and immune genes was moderate (I,e., coefficient=0.49 between *CD8* and TILs).

Conclusions: Immune genes or signatures may provide additional information not captured by TILs alone. Combining both measures could provide a more comprehensive understanding of the immune response in the TME and help predict response to immunotherapy in cancer patients.

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2247P Expression of PD-L1 on circulating epithelial tumor cells (CETCs) in men with primary non-metastatic prostate cancer

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Background: Radiotherapy (RT) is an essential component of multimodality therapy in the primary or postoperative treatment of prostate cancer with curative intent by preventing local recurrence and distant metastases, indicating its impact on residual occult tumor, such as circulating tumor cells. Immunogenic changes in cancer cells induced by RT can lead to adaptive up-regulation of PD-L1 expression. As immune checkpoint inhibition plays an increasingly important role in prostate cancer, radiogenic PD-L1 upregulation may be of therapeutic importance. The aim of this study was to determine PD-L1 status on CETCs before and during RT.

Methods: Peripheral blood samples were collected from 52 primary non-metastatic prostate cancer patients. CETCs were enumerated and analyzed for PDL-L1 expression prior to (baseline), 3 and 6 weeks after the start of RT using fluorescence scanning microscopy.

Results: PD-L1 expression was detectable in CETCs and localized in the membrane and/or cytoplasm. We found a correlation between PD-L1 status in CETCs and aggressiveness of cancer disease prior to RT. The frequency of PD-L1 positive CETCs depended on the grading and Gleason score of the primary tumor. Patients with a high Gleason score and G3 tumors had significantly more PD-L1 positive CETCs compared to patients with a low Gleason Score and G1 tumors. Moreover, patients in stage I/II had significantly less PD-L1 positive CETCs compared to patients in stage III/IV (mean 54.25 vs. mean 69.65; $p<0.05$). A higher number of PD-L1 positive CETCs were detected in patients who had radical prostatectomy before start of RT than in those who had no surgical intervention (mean 66.24 vs. mean 47.46; $p<0.01$). Interestingly, the fraction of PD-L1 positive CETCs decreased significantly during RT only in patients with G3 tumors and a high Gleason Score.

Conclusions: Our results indicated that PD-L1 in CETCs is closely related to the aggressiveness of the primary tumor and may be a co-factor associated with the progression of prostate cancer. PD-1/PD-L1 blockade combined with RT represents a novel and promising treatment strategy that could contribute to improve the treatment efficacy of prostate cancer.

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2248P Capecitabine-based concomitant chemoradiation followed by durvalumab as a neoadjuvant strategy in locally advanced rectal cancer (PANDORA trial): Molecular profiling and translational results

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Background: The combination of preoperative chemo- and radiotherapy (CRT) is the standard treatment in locally advanced rectal cancer (LARC). The benefit of the addition of immunotherapy in the neoadjuvant treatment is under investigation. However, a wide genomic characterization is needed to better stratify LARC patients (pts) for the most adequate treatment.

Methods: We analysed cancer tissues from 48 pts enrolled in the PANDORA trial (NCT04083365) in which a capecitabine-based concomitant CRT followed by durvalumab was administrated. DNA was extracted from bioptic chemo-naïve formalin-fixed paraffin-embedded samples. Genetic alterations of more than 500 genes, microsatellite instability (MSI) and tumor mutational burden (TMB) status were characterized using TSO500HT panel on an Illumina Novaseq 6000 instrument. PD-L1 expression was evaluated by the combined positive score (CPS). Pathological response was centrally determined on surgical specimens and was evaluable for 46 pts. A pathological complete response (pCR) was defined as ypT0N0M0.

Results: Pathogenic variants on *APC*, *TP53*, *KRAS*, *FBXW7*, *PIK3CA*, *SMAD4*, *AMER1* and *ARID1A* genes were the most frequent mutations. Overall, 17/46 (37%) pts achieved a pCR. Interestingly, *ARID1A* and *SMAD4* alterations occur only in patients without a pCR, being mutated in the 17% and 21% of pts, respectively. In particular, a more significant association was reached for *SMAD4* when either pathogenetic variants and variants of uncertain significance (VUS) were considered (p=0.019). Only 4% and 31% of pts had MSI and high TMB, respectively, but no significant association with response was found. High TMB status was significantly related to *ARID1A*, *FBXW7*, *MYC* and *RICTOR1* mutations. *SMAD4* mutations resulted significantly associated with low levels of PD-L1 expression (p=0.017). Indeed, 75% of the mutated pts as compared to the 27% of the wild type pts reported PD-L1 CPS values less than 10.

Conclusions: *SMAD4* mutations are related to the absence of complete response and to a low PD-L1 expression. *SMAD4* alterations should need further investigation in LARC pts treated by combined CRT followed by durvalumab.

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2249P Mitigation of tumor microenvironment-mediated immunosuppression using a PD1-41BB switch protein with optimal affinity tcrs for first-in-class, 3rd generation TCR-T therapies

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Background: As demonstrated in clinical trials, TCR-T therapies face major challenges to sustain anti-tumor cell function in solid tumor microenvironments (TME); tumor antigen levels and PD-L1 expression strongly influence T cell function. PD-L1 signalling to T cells via the PD-1 receptor limits proliferation, cytokine secretion and killing, while exhaustion is induced by repetitive TCR signalling in the absence of T cell co-stimulation. Both impairments in TCR-T cells can be mitigated by co-expression of an optimal affinity TCR combined with a PD1-41BB costimulatory switch protein (CSP), comprised of the extracellular domain of PD-1 with the intracellular signalling domain of 41 BB (CD137).

Methods: Two first-in-class, 3rd generation TCR-T therapies, MDG1015 and MDG2011, were developed using optimal affinity TCRs specific for a cancer-testis antigen, NY-ESO-1/LAGE-1a, and a neoantigen, mutated KRAS G12V, respectively. Tumor cells with variations in antigen and PD-L1 inform how differences among tumor cells can impact different functions of TCR-T cells in vitro.

Results: CSP mitigation of TCR-T dysfunction was very prominent when PD-L1 was highly expressed and tumor antigen was low, the most challenging TME setting. When antigen and PD-L1 levels were both high, killing remained very strong and the CSP increased poly-cytokine secretion. Proliferation after exposure to tumor cells with high PD-L1 and induction of exhaustion by serial tumor exposure were both well mitigated by CSP co-expression in both TCR-T cell therapies.

Conclusions: The combination of optimal affinity TCRs combined with the PD1-41BB CSP provides strong protection of TCR-T cells against two variable mechanisms of TME immunosuppression based on the demonstration of CSP-enhanced poly-cytokine secretion, proliferation and mitigation against exhaustion in vitro. This observation warrants application in the clinic for this novel approach to potentially overcome the major challenges in solid tumor TMEs.

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2250P Exploring tumor microenvironment in lung cancer through patient-derived 3D models

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Background: Tumor Microenvironment (TME) drives tumor growth, invasion, and metastasis. Studying its characteristics requires preclinical models to understand non-small cell lung cancer (NSCLC). PDTOs could help to explore tumor heterogeneity and mimic the organ's structure and functions to study NSCLC TME. Specific goals: (i) test and optimize different extracellular matrices for the development of NSCLC PDTO, (ii) develop 3D co-cultures of patient-derived lung tumorspheres and cancer-associated fibroblasts (CAFs) to investigate their interaction.

Methods: Long-term NSCLC primary cultures were established as PDTOs and tumorspheres. (i) 6 matrices were tested combining PEG hydrogel with heparin with/without RGD, and type I collagen (murine). Matrigel served as positive control. Cell viability was assessed with Calcein/PI and Cell Titer Glo 3D assays. Confocal microscopy evaluated PDTO size and matrix complexity. (ii) Co-culture methods between tumorspheres (SPH) and immortalized 154hTERT CAF cell line in 1:3 ratio for 48 hours were evaluated. Confocal microscopy and flow cytometry analyzed and distinguished populations with CD90 staining and Cell Trackers (Deep Red and Green).

Results: (i): All matrices supported organoid growth. PEG matrices showed optimal cell viability. Collagen matrices had the highest organoid count via confocal microscopy. (ii) SPH in non-adherent conditions, co-cultured with adhered monolayer CAFs, led to undesired SPH differentiation. A complete suspension culture achieved the expected invasion of tumorspheres with CAFs. CD90 was ineffective as a marker due to some CD90+ SPH. Varying concentrations of Cell Trackers stained CAFs, and a 0.25 µM concentration of Cell Tracker Green yielded the best CAF-SPH separation.

Conclusions: Our results showed that viable organoids can grow in the matrices tested. We have optimized conditions for the co-culture of tumorspheres and CAFs in 3D. Next, we will test organoid recovery techniques from ECMs to perform further studies and evaluate potential molecular mediators involved in SPH-CAF intercommunication as potential biomarkers to translate into the clinical practice. Support: CIBERONC (CB16/12/00350); AICO/2021/333 and CIACIF/2021/398 (GVA-FSE; GRISOLIAP/2021/030 (GVA-AMACMA).

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2251P The genomic landscape of radiotherapy-induced breast angiosarcoma: An alleanza contro il cancro (ACC) initiative for an unmet need in rare tumors

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Background: Radiotherapy-induced breast angiosarcoma (RIBAS) is a very rare late complication of radiotherapy (RT) in breast cancer. The incidence of RIBAS is expected to increase in the next few years, following the widespread adoption of breast-sparing surgery in combination with adjuvant treatment. To date, no actionable gene mutations are described, and data availability is very limited. Leveraging a multicentric retrospective cohort, we assessed the genomic features of a collected case series of patients affected by both sporadic (sBAS) and RT-induced form of angiosarcoma.

Methods: We retrospectively collected FFPE tumor and germline samples, obtained by surgery or biopsy. Samples were subjected to whole exome sequencing (WES, NovaSeq 6000 Illumina). Raw data were analyzed using the open source nf-Sarek pipeline. Mutation calls were identified using Mutect2, Strelka2 and independently validated using the Dragen platform™. Variants were annotated using COSMIC, OncoKB, ClinVar in conjunction with functional predictors, such as FATHMM, SIFT and Polyphen. Copy number aberrations were assessed using CNVkit.

Results: We collected matched tumor-normal pairs from 43 cases (30 RIBAS, 8 sBAS, 5 with no clinical annotation). All the patients were female, the overall median age at diagnosis was 68.8 years (IQR: 52.1 — 75.1), 69.8 (IQR: 61.4 — 76) for RIBAS and 41.2 (IQR: 28.6 — 53.7) for sBAS patients. WES was performed on 18 cases, 12 RIBAS, and 6 sBAS. We identified two *PIK3CA* hotspot mutations (p.E542V, p.V344M) in RIBAS only, but not in sBAS. One *TP53* mutation was identified in one sBAS sample. The most recurrent copy number aberration was *MYC* amplification (N = 5), exclusively found in RIBAS. Over-representation analysis showed enrichment in the NOTCH signaling, and E2F-targets pathways.

Conclusions: The genomic repertoire of RIBAS and sBAS is heterogenous, and we identified recurrent potential clinically actionable markers. We are currently expanding our analyses to 26 novel cases, including those reported in the Angiosarcoma Project. Germline calls are being assessed. To our knowledge, our study represents the largest effort to unveil the molecular landscape of RIBAS.

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2252P KRAS G12C inhibition using MRTX849: A novel radio-sensitizing partner

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Background: KRAS activating mutations are the most common oncogenic drivers and are correlated with radioresistance of multiple cancers including NSCLC and colorectal cancers. Multiple KRAS inhibitors were developed recently such as MRTX849 (Adagrasib,Mirati Therapeutics) showing promising clinical efficacy in early phase trials. However, only scarce data exploring the combination of radiotherapy (RT) and a KRAS inhibitor in $KRAS^{G12C}$ mutated tumors are available. We explore the efficacy of the association between RT and MRTX1257, a selective and covalent $KRAS^{G12C}$ inhibitor analogous to MRTX849, in animal models of cancer.

Methods: We assessed *in vitro* the efficacy of the combination MRTX1257 at various concentrations and different RT doses in CT26 WT and CT26 $KRAS^{G12C+/+}$ cell lines using clonogenic survival assays.We then explored the combination in LL2 $NRAS^{-/-}$ and WT cell lines. Subsequently, we explored the efficacy of combination MRTX1257 and RT in athymic nude mice bearing CT26 $KRAS^{G12C+/+}$ tumors and in immunocompetent BALB/c mice bearing subcutaneous CT26 WT or CT26 $KRAS^{G12C+/+}$ tumors.On day of randomization (D-1 before RT), D+1 and D+3 after RT, mice received oral MRTX1257 at 50 mg/kg dose. At D0, mice randomized into RT only and combination groups received 1x 6 Gy to the tumor. On D4 post RT, tumours were collected for IHC and flow cytometry analysis of the tumour microenvironment.

Results: MRTX1257 increased the cytotoxic effect of RT in different $KRAS^{G12C}$ mutated cell lines and murine tumors, but not in their $KRAS^{G12C}$ wild type counterparts. In *vitro* and *in vivo* radio-sensitizing effects were observed in a time and dose dependent manner. The use of RT and MRTX1257 in BALB/c mice bearing CT26 $KRAS^{G12C+/+}$ tumors resulted in a 20% cure rate. Tumor microenvironment analysis of murine CT26 $KRAS^{G12C+/+}$ tumors following RT and MRTX1257 showed an increase in conventional $CD4^+$ T cells, DCs type 2 and inflammatory monocytes. Expression of PD-L1 was reduced within tumor and myeloid cells, illustrating TME polarization towards a pro-inflammatory phenotype following the combination.

Conclusions: This work constitutes a first step towards new combinatorial approaches involving RT and MRTX1257 in KRAS G12C mutated cancers, with the aim of providing new therapeutic strategies.

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2253P RAS-precision medicine trans-atlantic partnership: Comparative analysis of KRAS codon 12 and 13 mutations in non-small cell lung cancer

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Background: *RAS* is the most commonly mutated oncogene in cancer, with *KRAS* mutated in ∼30% of non-small cell lung cancer (NSCLC). The most common *KRAS* mutation in lung-adenocarcinoma is KRAS codon 12 followed by 13. Newly developed drugs to target *KRAS*-G12C have highlighted the importance of studying the unique molecular and functional mechanisms of individual allelic subtypes.

Methods: We developed a doxycycline inducible panel of isogenic cell lines (MLE-12: alveolar type II cells) expressing flag-tagged KRAS WT or KRAS mutant: G12C, G12D, G13C and G13D. Cells were characterised in 3D using proliferation, viability, transformation and signalling assays. A panel of "RASless" mouse embryonic fibroblasts

(MEFs) expressing KRAS WT, G12C, G12D and G13D were also evaluated. For clinical validation, we developed a clinical database (RAS-PM), to interrogate co-mutational frequencies and pathogenicity.

Results: Expression of KRAS WT, 12C and 12D in MLE-12 cells resulted in an increase in proliferation, compared to a decrease or plateau observed with KRAS 13C or 13D expression. Furthermore, there was increased viability in cells expressing KRAS codon 12 mutations compared to WT or codon 13 mutations. All KRAS mutant MLE-12 cells expressed markers of transformation (EPCAM and CD44), including codon 13 mutants. In addition, there were differences in activation of AKT signalling between KRAS G12D and G13D expressing cells. Therapeutic vulnerabilities to a novel active-state selective RAS ('ON') inhibitor were assessed, where the most and least sensitive cells were those expressing G12C or G12D, respectively. RAS-PM identified that *KRAS* G13D was more prevalent in *NF1* mutant cancers vs. *NF1* wildtype (*NF1* MT: 6/24, 25%; vs. *NF1* WT: 4/281, 1.4%; $p<0.0001$). Pathogenic *NF1*-mutations were identified in 5/6 (83%) of *G13D/NF1* co-mutant cases.

Conclusions: Our findings highlight molecular and functional differences across the panel of KRAS mutations evaluated demonstrating differences in proliferation, viability, and signalling. These preclinical results indicate unique therapeutic vulnerabilities across allelic subgroups. RNA-sequencing and kinome profiling will allow us to further characterise these mutations in NSCLC.

Legal entity responsible for the study: The authors.

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2254P Persisting RAS addiction: A therapeutic vulnerability in the context of KRAS G12C inhibitor resistance

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Background: *KRAS* is the most frequently mutated oncogene in NSCLC, affecting ~30% of adenocarcinomas. Resistance to novel KRAS G12C inhibitor monotherapies is inevitable and early data with inactive-state selective inhibitors suggest there are a diverse range of resistance mechanisms.

Methods: A panel of G12C mutant NSCLC cell lines (H358, H23, HCC 1171, H1792, H2122) were cultured with an inactive state selective G12C inhibitor for over 9 months and resistant subclones generated. A multi-omic approach combining genomic, bulk RNA-seq, scRNA-seq and proteomic analyses was used to characterise these resistant populations, with the aim of identifying common resistance mechanisms and potential therapeutic vulnerabilities. In parallel, a PDX has been generated at the point of resistance to a G12C inhibitor, seeking to validate mechanistic insights.

Results: In resistant cell lines, there were varied morphological changes demonstrating both epithelial-mesenchymal-transition (EMT) and mesenchymal-epithelial-transition (MET). Bulk RNA-seq of two cell lines did not reveal common mechanisms of resistance. Further proteomic analysis suggests that there are a diverse range of resistance mechanisms present amongst the resistant populations. To better understand the transition to resistance, scRNA-seq of H1792 cells at different time points was performed, with different transcriptomic states identified. Work is ongoing to explore whether these states confer different sensitivities to G12C inhibition, and whether trajectory inference can predict a path to resistance. Analysis of a PDX has shown that it is a poorly differentiated adenocarcinoma of solid subtype, with further work exploring if this represents a histological transformation from pre-treatment samples. Therapeutic vulnerabilities to the resistant cell line panel were identified, with 5 cell lines remaining sensitive to active state selective RAS inhibitors.

Conclusions: Resistance to inactive state selective KRAS G12C inhibitors is heterogeneous but resistant populations remain sensitive to RAS targeted therapies. These results suggest that KRAS mutant cell lines remain addicted to oncogenic KRAS in the setting of resistance.

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2255P Clinicogenomic landscapes and hallmarks of KRAS amplification in human cancers

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Background: The recent development of direct KRAS inhibitors has changed the treatment landscape of patients (pts) with oncogenic KRAS mutations. However, whether KRAS amplification ($KRAS^{AMP}$) also defines a unique subset of cancers and represents a potential target for drug development is unknown.

Methods: Clinicogenomic data and outcomes were abstracted from independent cohorts of human cancers with genomic profiling at the Dana-Farber Cancer Institute, AACR-GENIE v.13, The Cancer Genome Atlas (TCGA), and 212 other studies, and examined according to $KRAS^{AMP}$ status. We also correlated $KRAS^{AMP}$ with KRAS RNA and protein expression using whole transcriptome and proteomics data from the TCGA and the Cancer Cell Lines Encyclopedia.

Results: Among 103,523 pts with solid and hematologic cancers, $KRAS^{AMP}$ was identified in 1,744 (1.7%) of cases. $KRAS^{AMP}$ was most prevalent in germ cell tumors (16.3%), esophagogastric (7.5%), ovarian (4.2%), pancreatic (2.2%), breast (2%), colorectal (CRC, 1.2%), and non-small cell lung cancer (NSCLC, 1.2%). Among these pts, median age was 61, 61.5% were ever smokers, 85.4% were white, and 71.8% had poorly differentiated cancers. Compared to KRAS diploid cases, $KRAS^{AMP}$ cancers had a higher fraction of the genome altered ($p<0.01$). Microsatellite instability scores were also higher in $KRAS^{AMP}$ tumors from patients with breast, esophagogastric, germ cell, pancreatic and NSCLC ($p<0.01$), but not in CRC ($p=0.22$). Tumor mutational burden was higher ($p<0.01$) among CRC, NSCLC, and esophagogastric cancers with $KRAS^{AMP}$ vs KRAS diploid. Compared to KRAS diploid samples, $KRAS^{AMP}$ samples had increased KRAS mRNA ($p<0.01$) and protein expression ($p<0.01$). Among pts with clinical outcome data (N=41,900), median overall survival (OS) was shorter in all comers with $KRAS^{AMP}$ vs KRAS diploid genotype (adjusted HR 1.68, $p<0.01$), and in each cancer type analyzed separately. $KRAS^{AMP}$ conferred worse survival outcomes in pts with both KRAS wild-type (N=35,599, adjusted HR 1.38, $p=0.01$) and KRAS-mutant (N=6,301, adjusted HR 1.70, $p<0.01$) cancers.

Conclusions: KRAS amplification defines a novel subset of human cancers characterized by distinct genomic features, and worse survival. Novel therapeutic strategies to target $KRAS^{AMP}$ may improve outcomes in pts with cancer.

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2256P The microenvironment of normal mucosa could predict recurrence in the stage II/III colorectal cancer: Multicenter, multiomics study

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Background: In this study, we aimed to investigate the microenvironment of normal mucosa to predict prognosis of stage II/III colorectal cancer (CRC), after surgery.

Methods: We divide the groups using transcriptome sequencing data of prospectively collected tumors and paired normal tissue, obtained from the margins of the resected

specimens from 111 patients at Samsung medical center. Groups were defined as follows: tumor-like microenvironment in normal mucosa group (tNME): high tumor signature in normal mucosa; normal microenvironment group (NME): low tumor signature in normal mucosa. The impact of this classification was further evaluated in two independent cohorts (Korean multi-center cohort and TCGA cohort). The microbial, and biological differences between groups were investigated based on 16s rRNA metagenomics and single-cell RNA sequencing.

Results: A total of 38 (34%) were classified as tNME. There were no significant differences in age, sex, TNM stage and CMS between subgroups. With a median follow-up of 57.9 months, tNME showed poorer 3-year recurrence-free survival (RFS) (56.0 % vs. 78.9 %, P=0.008) and 3-year overall survival (OS) (79.0 %vs. 87.7%, P=0.095) compared to NME. These were validated in the Korean multi-center validation cohort (3-year RFS: 55.3% vs. 74.5%, P=0.045), and TCGA cohort (3-year OS: 62.2% vs. 91.7%, P=0.071). Metagenomics exhibited a significantly lower proportion of carcinogenic genus including *Fusobacterium*, *Bacteroides* in normal of NME. There were significant differences in beta diversity between tumor and normal in NME, while no significant differences were noted in tNME, which suggests the feature of bacterial biofilm. PathSeq-based computational method of single-cell RNA sequencing revealed more proportion of infected cancer cells in tNME. *EMP1* +epithelial cells were correlated with recurrence, and more proportion of this cluster, along with *GZMK* high CD8 T cells, inflammatory cancer-associated fibroblasts were noted in tumor of tNME, while more proportion of neutrophil was noted in normal of tNME.

Conclusions: The microenvironment of normal mucosa status could be a prognostic biomarker for CRC. The bacterial biofilm with weak intestinal barrier were related to tNME.

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2257P Stereotactic body radiation therapy and atezolizumab combination: Results of the international multi-centre SABR-PDL1 phase II trial colorectal cohort

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Background: Immunoradiotherapy may improve outcomes for patients with advanced solid tumors, although optimized combination modalities remain unclear. Here, we report the analysis of the colorectal (CRC) cohort of the SABR-PDL1 trial that evaluated the PD-L1 inhibitor atezolizumab in combination with stereotactic body radiation therapy (SBRT) in advanced cancer patients.

Methods: Eligible patients received atezolizumab 1200 mg (IV) every 3 weeks until progression or unmanageable toxicity, together with ablative SBRT delivered concurrently with the 2nd cycle (recommended 45 Gy in 3 fractions, adapted upon normal tissue tolerance constraint). SBRT was delivered to at least one tumor site, with at least one additional measurable lesion being kept from the radiation field. The primary efficacy endpoint was one-year progression-free survival (PFS) rate from the start of atezolizumab. Sequential tumor biopsies were collected for deep multi-feature immune profiling.

Results: 60 heavily pretreated advanced CRC patients (38 men [63%]; median age, 59 years [range, 20-81 years]) were enrolled in five centers (France: n=4, Spain: n=1) from 11/2016 to 04/2019. All but one (98%) received atezolizumab and 54/60 (90%) received SBRT. The most frequently irradiated site was lung (n=30/54; 56.3 %). Treatment-related G3 (no higher grade observed) toxicity was observed in 3 (5%) patients. Median OS and PFS rates were respectively 8.4 [95%CI:5.9-11.6] and 1.4 months [95%CI:1.2-2.6]. Immune-centric multiplex IHC and RNAseq suggested that SBRT redirected immune cells towards tumor lesions even in the case of radio-induced lymphopenia. Tumor PD-L1 was more expressed in responding patients vs progressive disease (PD) patients at baseline (P=0.0087). IRF1 nuclear expression was higher in responding patients at baseline in CD3+ T cells (P=0.0043) and in CD68+ cells (P=0.0498). Upregulation of *CCL19*, *BHLHE41*, *CXCL9*, *GZMB* and *SLAMF1* in bulk RNA samples correlated with improved outcome.

Conclusions: Despite low PFS, this study provides new data on the feasibility, efficacy, and immune context of tumors that may help better identify advanced CRC patients most likely to respond to immunoradiotherapy.

Clinical trial identification: EudraCT N°: 2015-005464-42; NCT02992912.

Legal entity responsible for the study: Gustave Roussy.

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2258P Organoids as a biomarker for personalized treatment in metastatic colorectal cancer: Drug screen optimization and correlation with patient response

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Background: Currently, response to cancer treatment cannot be predicted upfront, hampering treatment efficacy. There is a need for effective biomarkers to select patients for optimal treatment. A promising predictive biomarker is response testing on patient-derived organoids (PDOs). For metastatic colorectal cancer (mCRC), it is unclear what drug screening method is optimal and if PDOs predict response for all treatment types.

Methods: Drug screens were performed by exposing 23 PDOs to a concentration range of systemic drugs for 5 days. The following standard mCRC treatments were evaluated: 5-fluorouracil (n = 6), oxaliplatin (n = 14) and irinotecan (n = 10). Drug sensitivity was measured by cell viability and quantified by calculating the area under the curve (AUC). We compared *in vitro* sensitivity to patient response, evaluated using progression-free survival (PFS) and % change in the size of target lesions on CT scans.

Results: Drug screen methods regarding medium composition (with/without N-acetylcysteine), combination treatment ratios and read-outs were optimized, as they impact the correlation with clinical response. Correlations were seen between PDO response (AUC) and patient response (% change) for all chemotherapies (Spearman $r = 0.3$-0.6, ns). PFS was evaluable for patients treated with oxaliplatin (n=14). Median PFS of patients with organoids classified as resistant to oxaliplatin-based treatment - based on AUC - was relevantly shorter than for organoids classified as sensitive (3.4 vs 10.1 months, log rank $p = 0.07$). PDOs from patients previously exposed to chemotherapy showed increased resistance to chemotherapy with a significantly higher AUC (median 0.9 vs 0.4, Mann-Whitney U $p = 0.005$).

Conclusions: After drug screen optimization, we show that PDO response correlates with patient response to commonly used systemic mCRC treatments. This suggests that PDOs can serve as a predictive biomarker and guide personalized cancer treatment. PDOs adequately reflect prior treatment effect, supporting their use for modeling mCRC. Our findings and optimized screening method will be validated in the ongoing OPTIC trial (NL61668.041.17), to facilitate implementation of PDOs in clinical treatment.

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Koopman: Financial Interests, Institutional, Advisory Board, advisory board and speaker: Pierre Fabre; Financial Interests, Institutional, Advisory Board: MSD, Bayer; Financial Interests, Institutional, Advisory Board, Advisory Board, speaker: Servier; Financial Interests, Institutional, Invited Speaker: Merck, BMS; Financial Interests, Institutional, Trial Chair: Servier; Financial Interests, Institutional, Research Grant: Servier, Roche, Bayer, Bristol Myers Squibb, Merck, Personal Genomics Diagnostics, Sirtex, Pierre Fabre; Financial Interests, Institutional, Funding: Pierre Fabre, Amgen, Nordic Pharma, Novartis, Merck, Servier, BMS; Non-Financial Interests, Leadership Role, vice-chair of DCCG: Dutch Colorectal Cancer Group; Non-Financial Interests, Advisory Role, Member of KWF scientific board: KWF; Non-Financial Interests, Other, ESMO faculty member for the Gastro-Intestinal Tumours – colorectal cancer: ESMO; Non-Financial Interests, Advisory Role, expert member of committee "regie op registers dure geneesmiddelen" ZINNL; Non-Financial Interests, Advisory Role, CRC expert on Kanker.nl platform for answering online CRC questions of CRC (non) patients: Patient representative organisation (Kanker.nl); Non-Financial Interests, Leadership Role, chair of RWD & DH working group: ESMO; Other, PI of the Dutch Prospective Colorectal Cancer Cohort study: PLCRC project. J.M.L. Roodhart: Financial Interests, Institutional, Advisory Board: Bayer, BMS, Merck-Serono, Pierre Fabre, Servier, Amgen; Financial Interests, Institutional, Funding: HUB Organoids, Cleara Biotech, BMS, Pierre Fabre, Servier; Financial Interests, Institutional, Member of Board of Directors: Foundation Hubrecht Organoid Biobank. All other authors have declared no conflicts of interest.

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2259P An artificial neural network system to predict the fraction of type I polarized macrophage

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Background: Type I polarized macrophages (M1) play an anti-tumor role in the tumor microenvironment (TME), and more M1 infiltration means better prognosis. Previous studies have developed algorithms to predict the fraction of M1 based on transcriptomic data, whereas few study focus on DNA methylation data.

Methods: A macrophage multiplex immunofluorescence (mIF) panel (including DAPI, panCK, CD68, CD86, IRF5, CD163 and CD206) and DNA methylation sequencing were used in lung adenocarcinoma (LUAD) patients' formalin-fixed paraffin-embedded samples. The fraction of M1 (with more positive M1 markers [CD86 and IRF5] than M2 markers [CD163 and CD206]) was calculated based on all macrophages ($DAPI^{+-}$ $panCK^{-}CD68^{+}$). Patients were randomly divided into training cohort (70%) and test cohort (30%). The Pearson correlation and random forest algorithm were used to screened genes to build artificial neural network (ANN) models in the training cohort. Three hundred times of three-fold cross validation were performed to obtain 900 ANN models and test the accuracy of them. The final predicted value of the ANN system were equal to the weighted average of output values of all 900 ANN models. Finally, the accuracy of the ANN system was tested validated in the test cohort.

Results: Forty patients with LUAD were enrolled, and the median fraction of M1 was 3.27% (range: 0% to 30.91%). A total of 43 genes were with p-value < 0.001 were selected by Pearson correlation, and the top eight genes (*C10orf90*, *ITGAX*, *TMED9*, *RGN*, *CENPF*, *LGI4*, *PPCS* and *KIAA1211*) from random forest algorithm were used to build 900 three-layer ANN models. Each ANN model had eight input nodes, five hidden nodes and one output node. The frequency of ANN model whose weight $>$ 0.70 (the accuracy $>$ 0.70) was 74.78% (673/900). The Pearson correlation coefficient between the predicted value and the true M1 fraction was 0.89 ($R^2 = 0.79$, $p < 0.01$) in the training cohort and 0.80 ($R^2 = 0.65$, $p < 0.01$) in the test cohort.

Conclusions: DNA methylation data is more suitable to establish models than RNA data. In this study, an ANN system based on DNA methylation data was constructed and showed a potential value in predicting the fraction of M1 in LUAD, which could help to further understand the TME and identify patients that would benefit from immunotherapy.

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2260P Berberine associated to SGLT-2i exerts synergistic cardioprotective effects in cardiac cells exposed to the HER2-blocking agent trastuzumab through pAMPK activation and reduction in Interleukin-6 levels

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Background: Trastuzumab has improved the prognosis in patients with HER2-positive breast cancer, but it can induce left ventricular dysfunction with reduced ejection fraction or HF during treatment. Dapagliflozin is a SGLT2i with cardio-renal benefits. In the DAPA-HF trial, the sodium-glucose cotransporter 2 inhibitor dapagliflozin decreased the risk of worsening HF events and cardiovascular death in patients with HF and reduced ejection fraction. Recent preclinical systematic review indicated that Berberine significantly reduces myocardial infarct size and the incidence of ventricular arrhythmia, improves cardiac function, ameliorates myocardial apoptosis.

Methods: Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of trastuzumab (200 nM) alone or co-incubated with Berberine (200 mM) or Dapagliflozin (50 nM) or both in combination for 48 h. After the incubation period, we performed the following tests: cell viability, apoptosis, expression of NLRP3 inflammasome, methylglyoxal and leukotrienes-B4. Expression of pAMPK was analyzed through western blot. Moreover, quantification of IL-6 was performed through ELISA method.

Results: Berberine and Dapagliflozin significantly increased the cell viability of cardiomyocytes exposed to Trastuzumab. When combined, Berberine and Dapagliflozin increased synergistically cell viability of cardiac cells ($p<0.001$ vs Trastuzumab). Cell apoptosis was reduced of 32.5, 41.8 and 72.7% for berberine, dapagliflozin and both combined (vs trastuzumab group). Methylglyoxal,a marker of AGEs, was strongly reduced compared to untreated cells. Western blot analysis clearly demonstrates that pAMPK was induced by berberine and Dapagliflozin, improving mitochondrial metabolism. Intracellular levels of IL-6 were reduced of 46.3, 62.7 and 86.3% for berberine, dapagliflozin and both combined (vs trastuzumab group).

Conclusions: Berberine and Dapagliflozin in combination induces an anti-inflammatory phenotype to myocardial cells through the reduction of biomarkers involved in heart failure and apoptosis.

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2261P A head-to-head comparison for detecting PIK3CA mutations in circulating tumor DNA of advanced HR+/HER2- breast cancer patients

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Background: Recently, we demonstrated that a high-resolution SiMSen-seq assay (SSS) provides a sensitive and robust method for detecting 11 *PIK3CA* hotspot mutations in ctDNA, allowing the identification of patients eligible for alpelisib treatment. Unfortunately, due to intrinsic or acquired resistance, most patients progress within months to years. Therefore, detecting additional genomic biomarkers for treatment resistance beyond *PIK3CA* mutations is crucial. Here we present interim results for our ongoing study to show that a commercial NGS assay (AVENIO ctDNA Expanded Kit, Roche Diagnostics) can detect *PIK3CA* mutations with similar high sensitivity as our high-resolution SSS assay.

Methods: 37 HR+/HER2- patients were included before starting 1st line treatment and 30 before starting 2nd line treatment. Plasma samples were analyzed using SSS and the AVENIO assay. Additionally, mFAST-SeqS was used to estimate the tumor fractions in plasma samples.

Results: The median z-score from mFAST-SeqS analyses was 2.88 [25–75th percentile: 1.48–7.36], and 30/67 (45%) samples had z-scores $>= 3$, indicating elevated tumor fractions (>5%). Two samples were not evaluable with SSS, leaving 65 samples for a head-to-head comparison. 29 alterations were detected in 27 (41.5%) samples by the SSS assay and 31 in 28 samples (43.1%) by the AVENIO assay. Overall, we found an excellent concordance rate of 95.4% (62/65 samples) between the two assays, confirming the high sensitivity of the panel sequencing assay. Moreover, the VAF of SSS and AVENIO were highly correlated (Spearman's rho $= 0.93$, $p < 0.001$).

Conclusions: The AVENIO ctDNA Expanded Kit revealed a high sensitivity and concordance rate for detecting *PIK3CA* hotspot mutations in plasma samples compared with the SSS assay. A major advantage of panel sequencing over a single-gene approach is that the interrogation of multiple genes can indicate a true negative *PIK3CA* result if other variants are present with a high VAF. Moreover, other actionable targets or mechanisms of resistance can be captured simultaneously, thus improving the effective precision treatment of metastatic breast cancer patients.

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2262P Baseline-informed versus tumor-agnostic minimal residual disease (MRD) concordance study in patients with HER2+ gastroesophageal adenocarcinoma patients

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Background: Current clinical paradigms are reliant on radiographic monitoring of disease to assess treatment response. However, this approach has some limitations including interval nature of imaging modalities and patients can clinically deteriorate prior to formally documenting therapy resistance. Hence, novel techniques such as longitudinal monitoring circulating tumor DNA (ctDNA) to assess therapy related response in real time are important to investigate.

Methods: To assess changes in disease burden with therapy, we profiled circulating tumor DNA (ctDNA) from longitudinal patient blood plasma using PredicineBEACON personalized minimal residual disease (MRD) assay and PredicineALERT, a tumor-agnostic MRD assay that measures cancer-related methylation patterns without personalization. Nineteen longitudinal plasma samples from 2 HER2+ gastroesophageal cancer (GEC) patients were tested using baseline-informed and tumor-agnostic MRD assays.

Results: Patient 1 demonstrated a similar trend of molecular dynamics and turning points of tumor response to therapy across 9 time points between the two MRD assays. Although the overall trends between the two assays were concordant for the second patient, some time points showed differential dynamics of changes in circulating levels of specific mutations compared to overall methylation profiling. An uptick levels of ctDNA after initial response preceeded radiographic progression using either approaches. Overall, in this ongoing study of the initial 2 cancer patients using 19 longitudinal blood samples, both PredicineALERT and PredicineBEACON assays demonstrated the trend of molecular dynamics and identified the similar turning points of tumor response during therapy.

Conclusions: Both tumor informed mutation based and tumor agnostic mehtylation based ctDNA approaches demonstrate clinical potential to monitor disease evolution and identify resistance prior to radiographic progression. Further study of such approaches to identify pre-radiographic molecular progression is warranted.

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2263P Ethnicity-specific distribution of BRCA1, BRCA2, PALB2 and ATM pathogenic alleles in breast and ovarian cancer patients from the North Caucasus

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Background: Mountain areas of the North Caucasus host several large ethnic communities, which managed to preserve their national identity through the centuries. The way of life characteristic for people from this region allows to expect high contribution of founder alleles, with an unique spectrum of pathogenic variants characteristic for each of the ethnic groups.

Methods: This study involved high-grade serous ovarian cancer (OC) and breast cancer (BC) patients from Dagestan (OC: 37; BC: 198), Kabardino-Balkaria (OC: 68; BC: 155), North Ossetia (OC: 51; BC: 104), Chechnya (OC: 68; BC: 79), Ingushetia (OC: 19; BC: 103), Karachay-Cherkessia (OC: 13; BC: 47), and several Armenian settlements (OC: 12; BC: 79). The group of BC patients was enriched by young-onset and/or family history-positive and/or bilateral and/or receptor triple-negative cases. The entire coding region of BRCA1, BRCA2, PALB2 and ATM genes was analyzed by next generation sequencing.

Results: Significant contribution of BRCA1/2 pathogenic variants in the OC and BC development was observed across all North Caucasus regions (OC: 18-31%; BC: 7-14%). Founder alleles were identified in all ethnic groups studied, e.g., BRCA1 c.3629_3630delAG [p.Glu1210fs] in Chechens, BRCA2 c.6341delC [p.Pro2114fs] in North Ossetians, BRCA2 c.5351dupA [p.Asn1784fs] in Ingush, BRCA1 c.2907_2910delTAAA [p.Lys970fs] in Karachays, etc. Some BRCA1/2 alleles, particularly BRCA2 c.9895C>T [p.Gln3299Ter], were shared by several nationalities. ATM pathogenic variants were detected in 14 patients, with 2 alleles occurring twice each. PALB2 heterozygosity was observed n 6 subjects, with one variant seen in 2 unrelated women.

Conclusions: This study adds to the evidence for global-wide contribution of BRCA1 and BRCA2 genes in BC and OC morbidity, although the spectrum of their pathogenic alleles is a subject of ethnicity-specific variations. Data on founder BRCA1/2 mutations may be considered while adjusting the BRCA1/2 testing procedure to the ethnic origin of patients.

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2264P Proteomics-based phenotypic classification of non-smallcell lung cancer

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Background: Current precision medicine strategies for non-small-cell lung cancer (NSCLC) rely on individual mutation analyses, evaluation of the tumor mutational burden or specific marker expression (*e.g.*, PD-L1). However, many patients either do not have a suitable targeted treatment or do not respond to the prescribed therapy. Phenotypic proteomic profiling facilitates the understanding of cancer biology beyond genomics. Furthermore, the more rapid targeted proteomics methods may serve as a tool for patient stratification based on proteomic signatures of the tumors.

Methods: We used our previously published resource describing the proteome landscape of 141 NSCLC tumors (Lehtiö *et al.* 2021) to identify biomarkers of the six observed proteomic subtypes. Namely, we applied a machine learning-based algorithm to proteome-wide peptide-level data to select peptide biomarkers for NSCLC subtype classification. We also applied quality control criteria to select peptides suitable for rapid analysis using a targeted proteomics, parallel reaction monitoring (PRM), method. Therewith, we are currently developing a PRM assay for identifying and quantifying the selected biomarkers in clinical samples such as resected tumors and biopsies. The initial cohort of 141 NSCLC tumors will then be re-analyzed to train a model for subtype prediction.

Results: We identified 200 peptide biomarkers from 174 proteins representing the six proteomic subtypes of NSCLC. Upon cross validating the classifier, we achieved a high average accuracy of 87%. We then acquired heavy isotope-labeled versions of the peptides for absolute quantification of the biomarkers. Our PRM method analyzing the peptide panel quantifies proteomic biomarkers more accurately and reproducibly

than other existing proteomics methods. Furthermore, our classification algorithm converts the quantitative data into categorical NSCLC subtype information.

Conclusions: We developed a first-of-its-kind proteomics assay that provides multifactorial characterization of NSCLC tumors covering histology, immune landscape, and oncogenic driver pathways. Our method enables the use of proteomics in a clinical setting and the resultant data may be used for patient stratification.

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2265P miR-4487 enhances gefitinib-mediated ubiquitination and autophagic degradation of EGFR in non-small cell lung cancer cells by targeting USP37

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Background: With the identification of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) cells, EGFR—tyrosine kinase inhibitors (TKIs) are being used widely as the first-line of treatment in NSCLC. These inhibitors block auto-phosphorylation of activated EGFR by competing with ATP binding and mediate EGFR degradation independent of exogenous epidermal growth factor, which is associated with the mutation variants of EGFR. However, the precise mechanisms underlying the TKI-mediated EGFR degradation are still unclear.

Methods: To examine the physiological roles of miR-4487 and ubiquitin-specific peptidase 37 (USP37) in gefitinib-mediated EGFR degradation in NSCLC cells, multiple NSCLC cell lines were applied. The level of EGFR expression, apoptosis marker, and autophagic flux were determined by western blot. Expression level of miR-4487 and cell-cycle arrest was analyzed by TaqMan assay and flow cytometry respectively.

Results: We found that gefitinib mediates EGFR degradation under normal culture conditions, and is dependent on autophagic flux and the mutation variants of EGFR. Gefitinib reduced expression levels of USP37, which mediated EGFR degradation similar to gefitinib. Our results also showed a gefitinib-mediated increase in endogenous miR-4487 level and presented evidence for the direct targeting of USP37 by miR-4487, resulting in the sequential enhancement of ubiquitination, autophagy, and EGFR degradation. Thus, the depletion of USP37 and overexpression of miR-4487 led to an increase in gefitinib-mediated apoptotic cell death.

Conclusions: These data suggest that miR-4487 is a potential target for treating NSCLC, and miR-4487/USP37-regulated EGFR degradation is a determinant for developing gefitinib resistance.

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2266P IMMUcan consortium: Focus on the first results of the non-small cell lung cancer (NSCLC) cohort

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Background: Immune checkpoint blockers have changed the treatment landscape for patients with NSCLC, however, response is often limited. PD-L1 protein expression is the only validated biomarker to enrich in responders and understanding resistance mechanisms to propose rationally driven combination therapies is clearly needed. To this end, IMMUcan, a pan-European consortium, is aiming at gaining a better understanding of the tumor microenvironment (TME) by combining broad molecular profiles of the tumor with spatially resolved cellular information of the TME and clinical information for 3,000 patients, with NSCLC a core indication of this project.

Methods: The first NSCLC cohort is composed of 191 patients from the EORTC SPECTAlung (NCT02214134) program, and 48 patients prospectively recruited in SPECTA (NCT02834884). All patients were diagnosed with NSCLC (any histology, any stage), FFPE material was collected at time of diagnosis, prior to treatment. Whole exome sequencing (WES), total RNA sequencing (RNAseq), multiplex immunofluorescence (mIF) and imaging mass cytometry (IMC) data was collected for each patient and analysed.

Results: The cohort contains a majority of adenocarcinoma (153 adenocarcinoma, 55 squamous carcinoma, 31 other) and early stage disease patients (74 stage I, 57 stage II, 63 stage III and 44 stage IV, 1 unknown). Median age at registration was 67, 100 patients were female and 139 male, and the majority were current or former smoker (163 patients). Stage is the strongest clinical predictor or survival (64.1 months for stage 1, 60.8 for stage 2, 58.3 for stage 3 and 14.1 for stage 4). 15% of adenocarcinoma patients had a driver mutation (EGFR, BRAF) and stage and histology are the main drivers of heterogeneity for RNAseq. T cell infiltration was assessed on all FFPE samples and is associated with improved overall survival. Tertiary lymphoid structures were identified in the majority of samples (∼70%), with various number of B cells and differing expression of lymphocyte maturation markers.

Conclusions: Further integration of the cellular and molecular data are ongoing and additional biomarkers will be presented at the conference.

Clinical trial identification: SPECTA NCT02834884.

Legal entity responsible for the study: European Organisation for Research and Treatment of Cancer.

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2267P Coronary heart disease and risk of lung cancer: A two-sample Mendelian randomization study

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Background: Observational studies have suggested an association between coronary heart disease and increased risk of lung cancer, but the causal relationship between these two conditions remains uncertain. Therefore, we conducted a two-sample Mendelian randomization study to investigate whether there is a causal relationship between coronary heart disease and higher risk of lung cancer.

Methods: We utilized 37 single nucleotide polymorphisms (SNPs) associated with coronary heart disease (with a p-value $<5x10^{-8}$) from a genome-wide association study involving 184,305 European individuals in the CARDIoGRAMplusC4D Consortium as instrumental variables. Summary data for lung cancer were obtained from the International Lung Cancer Consortium, including 11,348 cases and 15,861 controls. We conducted primary MR analysis using the inverse-variance weighted method and evaluated the MR assumptions in sensitivity analyses. Subgroup analyses were performed for different histological subtypes of lung cancer, and all analyses were carried out using the TwoSampleMR package in R.

Results: The MR analysis revealed that a genetic predisposition to coronary heart disease had a protective effect against the development of lung cancer, with an odds ratio (OR) of 0.88 (95% confidence interval [CI] 0.78-0.99, P=0.035). Subgroup analyses indicated a decreased risk for squamous cell lung cancer (OR 0.80, 95% CI 0.68-0.93, P=0.004), but no significant association was observed in lung adenocarcinoma (OR = 0.87; 95% CI 0.73-1.03, P=0.106). Sensitivity analyses supported a causal interpretation of the findings, indicating that major bias from genetic pleiotropy was unlikely.

Conclusions: Contrary to findings from previous observational studies, our results suggest that coronary heart disease may have a protective effect against the development of lung cancer. These findings emphasize the need to further investigate the underlying mechanisms linking these two conditions and provide a foundation for future research in this field.

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2268P Tumor transcriptional identity as a key predictor of clinical outcome in EGFR-mutant non-small cell lung cancer

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Late withdrawal

2269P Patient derived xenografts generated from circulating cancer stem cells on chorioallantoic membrane as an alternative pre-clinical model for personalized medicine in pancreatic cancer

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Background: Although there have been improvements in the treatment of pancreatic cancer in recent years, the prognosis for this disease remains poor, with an overall 5-year survival rate of less than 10%. Therefore, new therapies and preclinical models are urgently needed. Circulating cancer cells, and in particular their very rare subpopulation, circulating cancer stem cells (cCSC) are good candidates for generating preclinical models, making it possible to follow up the spatial and temporal heterogeneity of tumor tissues. This method is a non-invasive liquid biopsy that can be obtained at any stage of the disease. In this study, we sought to set up a novel model in which patient-derived xenograft can be generated on Chorioallantoic Membrane (CAM) from circulating cancer stem cells.

Methods: In this study, primary cultures from circulating cancer stem cells were established using sphere-forming assays from 30 patients with newly diagnosed pancreatic cancer. Subsequently, tumorspheres were transplanted onto the CAM membrane of fertilized chicken eggs to form secondary microtumors.

Results: Herein, we report an innovative *in vitro* platform for cultivation of cCSCs from peripheral blood of pancreatic cancer patients. The number of tumorspheres increased significantly with tumor size, lymph node involvement and grading status of the primary tumor. Implantation of tumorspheres onto the CAM was successful in ~90 % of the applied samples. The first histological analysis suggests that the main histopathological features closely resemble the original pancreatic tumors.

Conclusions: The number of tumorspheres is associated with some clinicopathological parameters, but further follow-up is needed to evaluate the prognostic significance of tumorsphere detection in pancreatic cancer. PDXs generated from cCSCs on CAM membrane offer a promising approach for personalized medicine in pancreatic cancer, providing a platform for the study of individual patient tumors and the development of more effective treatments.

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2270P Integrative analyses of bulk and single-cell RNA-seq identified diabetes mellitus-related signature as a prognostic factor in pancreatic adenocarcinoma

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Background: Pancreatic Adenocarcinoma (PAAD) is a highly fatal disease and often associated with a poor prognosis. The development of diabetes mellitus (DM) is an important risk factor. There have been studies exploring markers or prognostic models that affect the prognosis of patients with pancreatic cancer, but there are few studies on pancreatic cancer-associated diabetes mellitus (PCDM) patients.

Methods: The differentially expressed genes (DEGs) between DM and non-DM were detected and selected to build model. PCDM patients were randomly divided into training (70%) and test cohort (30%). Then the univariate COX was performed to screen OS associated genes ($p < 0.05$) in the training cohort. The LASSO-penalized COX regression and ten-fold cross validation were used to train and select models. The risk score was calculated and verified in both training and test cohort. GSVA, ESTIMATEScore, CIBERSORT and ssGSEA were used to compare the tumor microenvironment (TME). Moreover, the value of genes used in the model was detected on single cell level.

Results: Totally 197 patients (including 60 with DM) were enrolled, 23 genes from DEGs were related to the OS of PCDM patients in the training cohort, and 10 genes were selected to construct the risk model. The risk score for each subject was calculated as follow: risk score=0.434**ACACA*+0.119**ATG7*+0.373**DEFB123*+0.135**FSTL3*-0.168**NIPSNAP3B*-0.069**RASSF1*+0.225**RBPJ*+0.364**SLC35F2*-0.168**SLC37A1*-0.145**ZC3H12D*. The C-index was 0.83 in the training cohort (hazard ratio [HR] = 7.61, $p < 0.001$) and 0.76 in the test cohort (HR = 3.22, $p = 0.015$). According to the median value -0.054, PCDM patients were split into different risk groups, and patients in the low-risk group showed more enriched T cell related pathways (60 vs 1), higher ImmuneScore ($p < 0.001$), and more CD8 positive T cell infiltration (CIBERSORT: $p < 0.001$; ssGSEA: $p < 0.001$). We calculated the score of genes used in the model in single cells. Malignant cells with the highest score (top 10%) had enhanced activities of angiogenesis.

Conclusions: The prognostic model showed potential value in predicting the OS of patients with PCDM. Patients with low-risk score had a hotter TME and might benefit from immunotherapy.

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2271P Development of an oncolytic virus for the treatment of high grade serous ovarian cancer and other stromal rich tumours

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Background: An abundance of cancer associated fibroblasts (CAFs) in stromal rich tumours is a barrier to the effectiveness of anticancer therapies. We have developed an oncolytic adenovirus - THEO-260 - that is capable of lysing both cancer cells and CAFs in ovarian patient tumours ex vivo. Here, we present data to support the progression of THEO-260 to first in human (FIH) clinical trials.

Methods: THEO-260 efficacy was assessed in cell lines, multicellular spheroids, ex vivo fresh ovarian patient samples and mouse models bearing human cancers and stromal CAFs. The safety was assessed in primary human normal cells and in immunocompetent mice.

Results: THEO-260 killed a panel of cell lines from ovarian cancer (n=8), in addition to different stromal rich tumour types (pancreatic, colorectal, lung, and breast cancer; n=9) and multicellular spheroids. Moreover, THEO-260 was highly efficacious in fresh ovarian patient materials, killing cancer cells and CAFs in ascites and tumour samples (n=24). THEO-260 outperforms SOC chemotherapies including paclitaxel and PARP inhibitors. In vivo, THEO-260 shows antitumor efficacy, with a complete reduction in tumour volume and is superior to SOC in the platinum resistant ovarian cancer model with human CAFs (COV318+MRC5). THEO-260 also prevents ovarian intraperitoneal metastasis formation in vivo in a human ovarian adenocarcinoma model with CAFs (SKOV3+MRC5). As expected THEO-260 does not replicate in non-human primary cells, supporting replication selectivity testing in normal human primary cells rather than in animal models. THEO-260 demonstrates high selectivity for tumours, with negligible levels of replication and production of infectious virions in all normal primary human cells tested. THEO-260 was also shown to be safe in vivo in immunocompetent mouse models, when tested at repeated and escalating, clinically relevant, dose levels. The genetic and temperature stability of THEO-260 has been confirmed and is currently being GMP manufactured to high yields.

Conclusions: Our data confirms that THEO-260 is efficacious and safe, supporting the initiation of FIH clinical trials in high grade serous ovarian cancer patients.

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Disclosure: M. Bazan Peregrino, S.C. Frost, C. Negroni, C. Moriconi, T. Perry, W. Taverner, B. Nicholls, D. Saunders, R. Ackerman-Johnson, A. Lim: Financial Interests, Institutional, Full or part-time Employment: Theolytics Ltd. K. Fisher, M.R. Duffy: Financial Interests, Institutional, Stocks or ownership: Theolytics Ltd. All other authors have declared no conflicts of interest.

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2272P Minimal DNA-methylation (DNAm) signatures for non-invasive tumor-agnostic estimation of tumor content (TC) and molecular subtype in patients (pts) with metastatic breast cancer (mBC)

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Background: Non-invasive detection and quantification of circulating tumor DNA by DNAm signatures is emerging as powerful tool for monitoring disease status in pts with metastatic cancer. We recently developed MIMESIS, a computational workflow to design tumor agnostic DNAm signatures of few dozen sites for TC and molecular subtype estimation in liquid biopsy. Here we applied a MIMESIS informed assay to a retrospective cohort of mBC pts (MIMESIS-BC).

Methods: 72 mBC pts (42 ER+/HER2-, 2 ER+/HER2 N/A, 8 ER+/HER2+, 6 ER-/HER2+, 14 ER-/HER2-, up to 6 previous lines of treatment) and 11 healthy individuals (ctrl) were included. Plasma from mBC pts was collected before starting treatment (T0, n=58) and after the first cycle (T1, n=52) (n=38 pts T0 and T1). MIMESIS-BC for TC, PAM50 molecular subtypes and ER status (n=139 sites) was applied to circulating free DNA as described in the MIMESIS study. Samples were defined as TC+ when TC>0. TC values as continuous variable and TC classes (+/-) were associated with OS and PFS. Concordance of subtype and ER status by MIMESIS-BC with IHC-based from primary tumor was estimated by chi-square and percent agreement.

Results: TC was not detected in ctrl. A significantly higher median TC was observed at T0 compared to T1 (5.6% (range 0-73%) vs 0% (range 0-47%); p=0.02). 39 TC+ samples at T0 showed 61% agreement for molecular subtype (p=0.002) and 86% for ER status (p<0.001). In the entire population, PFS and OS were significantly associated with TC values both at T0 and T1 (max p=0.002). TC+ pts had significantly worse OS compared to TC- at T0 (HR=2.1 CI=1.1-3.9 p=0.02) and T1 (HR=2.0 CI=1.1-3.6 p=0.03) and worse PFS at T1 (HR=2.9 CI=1.5-5.4 p<0.001). In ER+ pts, TC+ at T0 and T1 associated with worse PFS (HR=2.6 CI=1.2-5.3 p=0.008, and HR=3.8 CI=1.7-8.2 p<0.001) and OS (HR=3.5 CI=1.6-7.6 p=0.001, HR=3.0 CI=1.4-6.1 p=0.002), while in ER- pts TC classes showed no association with outcome.

Conclusions: In a small and heterogenous retrospective cohort of mBC pts, MIMESIS-BC showed promising capabilities for prognostic stratification and subtype estimation from liquid biopsy. Validation in an extended prospective cohort is ongoing.

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2273P Influence of body mass index (BMI) on the response to chemotherapy in patients with HER2+ breast cancer: Role of the leptin axis

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Background: Obesity is associated with T-cell dysfunction and high PD-1 expression, resulting in paradoxical benefit from check-point inhibitor therapy. This effect is driven, in part, by leptin that exerts its action through binding to the leptin receptor (Ob-R), which is highly expressed in HER2+ BC. High tumor infiltrating lymphocytes (TILs) counts correlate with pathological response and long-term outcomes in BC, but the precise mechanism is not known. The aim of this study was to investigate the role of BMI in modulating TILs and pathological responses in early HER2+ BC patients who received neoadjuvant systemic treatment (NST).

Methods: Women with HER2+ BC receiving anti-HER2-based NST followed by surgical resection were included. Patient age, menopausal status, and height/weight (to calculate BMI) were recorded. Based on biopsy findings, tumors were categorized as HER2+/HR+ and HER2+/HR-. Ob-R expression was also measured and classified as over-expressed if there were >50% positive cells with weak or strong staining. TILs and PD-1 expression were determined centrally using pre-treatment biopsies. TILs were considered as continuous variables and binary, <30 vs ≥30%, and PD-1 as positive (>1%). Associations with pathological complete response (pCR) were assessed statistically.

Results: 27 of 85 HER2+ BC patients were overweight/obese (BMI ≥25kg/m^2). Patients with high BMI tended to have tumors with higher hormone receptor expression than lean patients (85 vs 64%; p=0.078). No differences were found in median Ki67 between the high or low BMI groups. A greater number of high BMI patients were menopausal (63 vs. 36%; p=0.038). Patients with high BMI had a significantly greater expression of Ob-R vs lean patients (78 vs 55%; p=0.045) and at the same time had a significantly higher expression of TILs (median 23 vs 16%; p=0.007). Despite having higher TIL counts, pCR were similar (63.0 vs 58.6%; p= 0.704). However, PD-1 expression was significantly higher in patients with high BMI (median 4 vs 1; p=0.012).

Conclusions: Our study shows for the first time how obesity, through the Ob-R/leptin axis, might activate TILs. However, this was not translated into higher CR; probably due to high PD-1 expression as exhaustion feature.

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2274P Deep learning-based prediction of pathologic complete response to neoadjuvant therapy in breast cancer using H&E images and RNA-Seq in the IMMUcan study

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Background: IMMUcan (SPECTA NCT02834884) is an European public-private effort to generate molecular and cellular profiling data of the human tumor microenvironment from up to 3000 cancer patients. Predicting pathologic complete response (pCR), which has been associated with better outcome after neoadjuvant treatment in breast cancer (BC), could help refining treatment strategies. Here, we aim to integrate multiple data layers using different Deep Learning (DL) approaches to predict pCR from baseline tumor samples in the context of the prospective IMMUcan Triple-Negative Breast Cancer (TNBC) and HER2-positive (HER2+) BC neoadjuvant cohorts.

Methods: At the cut-off date of June 29th, 2022, we identified a first cohort of 132 and 149 patients diagnosed with TNBC and HER2+ BC, respectively, for preliminary analyses. To predict pCR at the patient level, benchmark models using RNA-Seq, image DL were trained on Whole Slide Images (WSIs) and RNA-Seq data. The image models included two main components: a tiling algorithm pre-trained on TCGA WSI to extract a spatialized representation of the WSI and a classification part for the pCR prediction.

Results: Baseline RNA-Seq data were available for 109 and 115 patients with TNBC and HER2+ BC, respectively, pCR status was available for 130 TNBCs and 117 HER2+ BCs, while a baseline H&E-stained WSI was available for all patients. Among the models applied independently to each data type, the best performance was obtained using RNA-Seq in HER2+ BC (ROC AUC = 0.61, std = 0.04), and WSI in TNBC (ROC AUC = 0.63, std = 0.03).

Conclusions: These preliminary results show the potential of DL applied to WSI and RNA-Seq in predicting pCR for TNBC and HER2+ BC. Using DL models able to predict pCR provide the opportunity to better select patients and tailor neoadjuvant therapies in BC. Multimodal models combining RNASeq and WSI are currently being tested out by the team to improve performance.

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2275P Circulating leptin and adiponectin levels in premenopausal women with and without breast cancer (BC) and a body mass index (BMI) ≥25 kg/m2

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Background: Obesity has a controversial effect on BC risk depending on the menopausal status. The mechanisms by which a high BMI protects against BC in premenopausal women are unknown. Adipose tissue produces two antagonistic hormones: leptin activates tumorigenesis in postmenopausal patients; by contrast, adiponectin has an anti-inflammatory effect. The aim of this study is to evaluate adiponectin and leptin levels according to the presence of not of BC in a group of premenopausal women with high BMI.

Methods: This prospective transversal study included premenopausal women with high BMI with recently diagnosed of early BC or without cancer. Age, weight, and height were recorded. Premenopausal status was confirmed by LH, FSH, and estradiol blood values. Fasting values of insulin, glucose, lipid profile, and vitamin D levels were also determined. Adiponectin and leptin levels were analyzed as continuous variable.

Adiponectin was also categorized as low, normal, and high considering age and weight. Patients with BC were classified in luminal, triple-negative, and HER2+ by IHC.

Results: Of the 86 women included in the study, 54 were BC-free and 32 with BC (luminal 23, triple-negative 5, and HER2+ 6). Women without cancer had significantly higher BMI (median 32.3 vs 26.8; $p<0.001$), leptin levels (median 27.3 vs 12.8; $p<0.001$), and insulin levels (median 10.8 vs 6.8; $p<0.003$) than BC patients. However, a significant correlation between high leptin and insulin levels was only observed in BC patients ($p<0.001$). Furthermore, a significant negative correlation was found between high leptin levels and low vitamin D levels in BC-free women ($p<0.004$). Conversely, there were no differences in adiponectin levels either as a continuous variable or in the categorization between BC and BC-free women.

Conclusions: This study analyzes, for the first time, the difference between leptin and adiponectin levels in premenopausal women with high BMI with or without BC. Although high leptin levels are associated with an increased risk of BC in postmenopausal women, this does not seem to occur in premenopausal women. Adiponectin levels are similar for both groups.

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2276P Regulation of major histocompatibility class-I gene methylation using DNA methyltransferase inhibitor and PD-L1 inhibitor in triple-negative breast cancer

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Background: There are many studies on gene methylation and immunotherapy in breast cancer, but there are few studies on the effect of DNA methyltransferase (DNMT) inhibitors and immunotherapy on major histocompatibility (MHC) class-I gene methylation in triple-negative breast cancer (TNBC).

Methods: The relationship between the expression of the MHC class-I gene and DNA methylation was analyzed using data from The Cancer Genome Atlas (TCGA). The expression of DNMTs and MHC class-I genes was analyzed in breast cancer tissue from TNBC patients and TNBC cell lines. DNA methylation analysis of the MHC class-I gene was performed with pyrosequencing in TNBC tissues and methylation specific PCR in TNBC cell lines. TNBC cell lines were treated with DNMT inhibitors Decitabine and Zebularine and PD-L1 inhibitor Atezolizumab, and then changes in the expression of DNMT, MHC-I gene, and methylation patterns of MHC class-I gene were analyzed.

Results: TCGA data analysis confirmed that there was an inverse correlation between DNA methylation and mRNA expression of the MHC class-I gene, but analysis in TNBC patients in this study did not show this correlation. After treating TNBC cell lines with DNMT inhibitors and PD-L1 inhibitor alone and in combination, the DNA methylation pattern of the HLA-B and HLA-C gene was suppressed, but there was no significant change in the DNA methylation of the HLA-A gene. The expression of the MHC class-I gene increased in BT-20 after Decitabine treatment, and only in BT-549 after Zebularine treatment. It increased in BT-549 after Atezolizumab treatment, and in MDA-MB231 after combination of Decitabine and Atezolizumab. After each drug treatment, the cell viability of TNBC cell lines was reduced due to the drug's own cancer treatment effect, which limited the analysis of the outcome of changes.

Conclusions: The treatment responses to DNMT inhibitors and PD-L1 inhibitor were different depending on the characteristics of TNBC and the types of drugs, suggesting that the treatment target needs to be applied differently. Further study is needed to determine specific treatment targets and appropriate drugs according to the characteristics of TNBC.

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2277P A colorimetric biosensor to track Trop-2 status of tumor cells for diagnosis of breast cancer

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Background: The emergence of antibody-drug conjugates (ADCs) targeting trophoblast cell-surface antigen-2 (Trop-2) has reshaped the therapeutic landscape of advanced breast cancer. Accurate profiling of the Trop-2 status of tumor cells can facilitate the identification of patients who will benefit from Trop-2-targeting therapy; however limited analytical method has hindered this process.

Methods: In this study, we have proposed a specific and sensitive biosensor for visual tracking of the Trop-2 status of breast cancer cells based on tetrahedral DNA nanostructure (TDN)-decorated Fe-based metal-organic framework nanoparticles (TDN-PCN-222 (Fe)).

Results: In the design, a dual-aptamer-assisted biomimetic capture strategy shows high capture efficiency while maintaining the viability and original phenotype of captured cells, ensuring the accurate profiling of the Trop-2 status. Meanwhile, by using the high intrinsic peroxidase activity and excellent targeting ability of Trop-2-specific aptamer-linked TDN-PCN-222 (Fe), specific detection of Trop-2-positive tumor cells can be achieved with a limit of detection (LOD) of 10 cells/mL, and the Trop-2 status of tumor cells can be visually tracked. Moreover, the proposed biosensor has been successfully used for tracking the Trop-2 status of tumor cells in breast cancer tissues, suggesting that our method has great promise for clinical applications.

Conclusions: a sensitive and specific colorimetric biosensor was proposed in this work for visually tracking the Trop-2 status of tumor cells. This sensor has been used for the visualized tracking of Trop-2 status of different cancer cell lines as well as breast cancer tumor cells. Therefore, the proposed sensor has considerable potential for visualized tracking of various drug targets on tumor cells from cancerous tissues or the circulating system, and this work may provide an unprecedented method with great promise for the companion diagnosis of Trop-2 ADCs.

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2278P Endothelial cell heterogeneity defined by single-cell spatial transcriptomic analysis of breast cancers

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Background: The heterogeneity of the tumor microenvironment is a major barrier for effective cancer therapies. Similar to the immune tumor microenvironment the stromal environment, composed of cancer-associated fibroblasts (CAFs), pericytes, adipocytes and endothelial cells, is also heterogeneous. Multiple studies showed that CAFs contain heterogenous cell populations with opposing pro and anti-tumoral function. The heterogeneity of endothelial cells (ECs) is less well described largely due to the relative low frequencies in tumor tissues compare to CAFs. We set out to study the heterogeneity of the tumor microenvironment using truly single-cell spatial transcriptomic by the 10x Genomics Xenium platform.

Methods: We analyzed 20 human breast tumors by Xenium single-cell analyzes using fluorescent in situ sequencing (FISSEQ). We used the available breast panel that contains 280 genes, with 8 probes for each gene. The analysis of the data was preformed using the Seurat pipeline in R (version 4.9.9.9039).

Results: We could readily identify blood vessel structures that surrounded PECAM1/VWF positive cells. After multiple clustering we identified five types of endothelial cells with divergent gene expression profiles. We defined the following clusters of ECs: 1) Proliferating ECs, 2) CXCL12+ ECs, 3) $POSTN^{Hi}/VWF^{Hi}$ ECs, 4) $TPD52^{Hi}$ ECs and $POSTN^{Low}/VWF^{Hi}$ ECs. The endothelial cells also showed spatial variations in

distribution. Data on EC subtypes will correlation and other cell types and cell neighborhoods will be presented.

Conclusions: ECs in breast cancer tumors are highly heterogeneous and can be further classified into functionally divergent subtypes, potentially contributing to the heterogenous responses observed to treatments.

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2279P Glucocorticoid receptor antagonism and beta adrenergic receptor inhibition: Implications in triple-negative breast cancer brain metastasis

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Background: Triple-negative breast cancer (TNBC) brain metastasis is a major clinical challenge, and the role of stress hormone receptors, specifically the glucocorticoid receptor (GR) and beta-adrenergic receptor (β-AR), in cancer progression remains unclear. This study investigates the impact of GR and β-AR antagonism on the modulation of astrocyte-cancer cell interactions in the context of TNBC brain metastasis.

Methods: Primary murine astrocytes were isolated and cultured alone or in co-culture with 4T1 breast cancer cells. Stress hormones, their antagonists, or a combination of both were administered to the cells for 24 hours. Following treatment, the cell lysates were subjected to western blotting, and the media were analyzed using enzyme-linked immunosorbent assays (ELISAs). ELISAs measured the levels of TNF-alpha, IL-6, and CXCL10.

Results: When cultured alone, astrocytes exhibited a significant ($p<0.05$) increase in IL-6 expression upon treatment with both stress hormones. The addition of GR and β-AR inhibitors mitigated this effect. While TNF-alpha expression was elevated in hormone-treated cells, it did not reach statistical significance. CXCL10 expression significantly decreased in cells treated with both stress hormones and their inhibitors compared to the control ($p<0.005$). In the co-culture setting, astrocyte-released cytokines (IL-6, CXCL10, TNF-alpha). were significantly reduced in control samples.

Conclusions: Glucocorticoid receptor antagonism and beta-adrenergic receptor inhibition exerted modulatory effects on astrocyte-cancer cell interactions. The upregulation of IL-6 in astrocytes upon stress hormone exposure suggests its potential role in promoting TNBC brain metastasis. Furthermore, the significant decrease in CXCL10 expression following combined hormone and inhibitor treatment highlights its potential as a therapeutic target. These findings provide insights into the complex interplay between stress hormone receptors and cancer progression in the context of TNBC brain metastasis.

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2280P MiR-193a-3p: A pan-repressor of H2S synthesizing enzymes regulates tumorigenesis and immunosurveillance in breast cancer

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Background: Hydrogen sulfide (H_2S) is an endogenous gaseous mediator implicated in breast cancer (BC) progression. The 3 principle enzymes responsible for H_2S production in mammals are cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST), whose overexpression was correlated with poor prognosis in BC patients. Besides, $H_2S$was linked to the suppression of tumor immune microenvironment in BC. Our group recently reported that upon single or dual inhibition of any of H_2S-synthesizing enzymes, the other untargeted enzyme(s) is/are upregulated/activated as a compensatory mechanism for maintaining the level of H_2Sin cancer cells. Thus, the aim of this work is to find a pan-repressor of all 3 enzymes to skip the above compensatory/escape mechanism and to investigate its impact on oncogenic and immunogenic profiles of BC cells.

Methods: BC female patients (n=20) were recruited. In-silico analysis was used to identify microRNAs (miRNAs) that target CBS, CSE, and 3MST. MDA-MB-231 TNBC cells were cultured and transfected by oligonucleotides. Total RNA was extracted using Biazol, reverse transcribed and quantified using qRT-PCR. Western blot analysis was performed. H_2S levels were measured by AzMc. BC hallmarks were assessed by MTT, transwell migration, and clonogenic assays.

Results: MiRNA-193a was validated to regulate the expression of H_2S enzymes by 8 different bioinformatics software, and was found to be significantly downregulated in BC tissues. Further, miR-193a was negatively correlated with CBS, CSE and 3MST levels in BC patients. Ectopic expression of miR-193a resulted in a marked repression of CBS, CSE, and 3MST expression, inducing a significant decrease in cellular H_2S production. in TNBC cells overexpressing miRNA-193a, not only the cancer hallmarks were markedly suppressed but also the immune-suppressor proteins Galectin (GAL) 3 and GAL 9 were decreased significantly.

Conclusions: This study identifies miRNA-193a as a pan-repressor of the 3 principle H_2S-synthesizing enzymes in BC, bypassing the compensatory behavior observed at single or dual inhibition of H_2S enzymes. Thus, miR-193a emerges as a novel tumor suppressor and immunomodulatory miRNA in TNBC.

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2281P Multi-omics evaluation of TFE3-fusions and potential association with immuno-metabolic vulnerabilities in alveolar soft part sarcoma (ASPS) and translocation-positive renal cell carcinoma (tRCC)

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Background: ASPS and tRCC are rare tumors that harbor recurrent fusions of the TFE3 gene; emerging data for both entities suggest responsiveness to immune checkpoint inhibitors (ICIs). We hypothesized that TFE3 fusions drive unique immune-metabolic changes in both entities compared to their non-TFE3-based counterparts.

Methods: 31 TFE3-rearranged tumors (24 tRCC; 7 ASPS) as well as ccRCC (N =391), undifferentiated pleomorphic sarcoma (N = 111), liposarcoma (N = 49), and angiosarcoma (AS, N = 167) underwent next-generation sequencing (592-gene or whole exome) and whole transcriptome sequencing at Caris Life Sciences (Phoenix, AZ). PD-L1 expression (SP142; +: $\geq$2+, $\geq$5%) was tested by IHC. Cellular composition of the tumor immune microenvironment (TIME) was estimated by quanTIseq. A transcriptomic signature predictive of ICI response (interferon γ score) was applied. Differentially regulated pathways were assessed by gene set enrichment analysis (GSEA). p-values adjusted for multiple comparisons.

Results: ASPSCR1::TFE3 was the most frequent fusion type (N = 9 [ASPS, N = 7;tRCC, N = 2]). PD-L1+ was more frequent in tRCC vs. ccRCC (46% vs. 12%, $p < .05$). tRCC had significantly fewer M1 macrophages (0.32-fold, $p < 0.05$) and lower IFN γ score than ccRCC (-0.31 vs -0.13 Arbitrary Units (AU), $p < .05$). Of the 9 tRCC fusions with N$\geq$2, PRCC::TFE3 (-0.16 AU) had the highest and SFPQ::TFE3 (-0.52) had the lowest IFN γ score. No difference in PD-L1+ was observed between ASPS (14.5%), AS (23%), LPS (8.5%) or UPS (36%), $p > .05$. ASPS had a higher median CD8+ T cell infiltrate (1.63%) vs. UPS: 0, LPS: 0 [$p > 0.05$ both], and AS: 0, $p < 0.05$. There was no significant difference in IFN γ score between ASPS (-0.30 AU) vs. AS (-0.29), LPS (-0.34), UPS (-0.26), $p > .05$. GSEA revealed enrichment of the oxidative phosphorylation genes in both tRCC and ASPS vs. appropriate controls.

Conclusions: TFE3-rearranged ASPS and tRCC demonstrate a distinct TIME with variable enrichment of immune markers vs. control groups. Further functional studies are warranted to determine whether TFE3-fusions have a role in driving oxidative phosphorylation in ASPS and tRCC.

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2282P Tissue glycan profiling in predicting immunotherapy response in renal cell carcinoma and hepatocelllular carcinoma

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Background: The immune system can eliminate malignancy by identifying antigenic peptide epitope presented by neoplastically transformed cells. Immune cells recognize abnormal glycosylation on cancer cells, and this recognition often leads to an inhibitory immune process. We designed a biomedical study to evaluate the role of tissue glycan in predicting immunotherapy response in renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC).

Methods: Thirty-two patients with intermediate/poor risk RCC and advanced HCC (eight respondents and eight non-respondents each) who had received first line immunotherapy-based therapy were identified. The overall survival for RCC and HCC non-respondent cohort was 27.9 months and 8 months respectively but was immature for the respondent cohort. Response criteria to immunotherapy was decided based on the immune related response criteria (iRECIST) where good response is defined as complete or partial response while poor respondent was defined as progression of disease with median survival shorter than reported. Next, we compare the relative abundance and spatial distribution of the glycans in the responder versus non-responder tissue sections given regional characterizations within the tissues. This helps points out the distinct glycans between the responder versus non-responder tissue sections that could serve as potential biomarkers which can then be used in future diagnostic and/or therapeutic intervention. We used the MALDI analysis by rapifleX.

Results: MALDI imaging of HCC and RCC responder versus non-responder tissue section was successfully demonstrated. There was distinct responder versus non responder glycan markers demonstrated by unsupervised segmentation analysis, showing specific layers of glycan organization in the different tissue regions. There are several glycan peaks showing distinctive expression between respondent versus non respondent patients. PCA showed distinguishable variances across each annotated structures derived from segmentation analysis.

Conclusions: Distinct glycan profile markers were observed between both responder and non-responder cohort showing specific layers of glycan organization in the different tissue regions.

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2283P Assessing the replicative potential of the oncolytic virus VSV-GP in patient-derived tumor biopsies ex vivo

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Background: The understanding of human cancers has increased substantially within the past decade. However, translation of the acquired knowledge into clinical success is still remarkably low. This gap between scientific progress and clinical application is decisively driven by limitations of preclinical models, which often do not sufficiently mimic the complex microenvironment and heterogeneity of human tumors. Therefore, assays allowing for enrichment of human tumors responsive to complex immunotherapies, such as oncolytic virotherapy, are urgently needed. Here, we employed a patient-derived tumor biopsy culture system to assess susceptibility of individual human tumor ecosystems to the oncolytic virus VSV-GP ex vivo.

Methods: A simplified ex vivo culture system of patient-derived tumor biopsies was established and compared to the tumor slice culture approach previously set up in our laboratories. Viability and tissue integrity of human colorectal and pancreatic cancer samples were studied by metabolic activity and histopathology, respectively. Susceptibility of biopsies and slice cultures derived from murine tumors, as well as more heterogenous human tumors to the oncolytic virus VSV-GP was assessed. In particular, virus replication kinetics was monitored over time by using reporter protein-tagged VSV-GP variants and fluorescence microscopy in combination with quantification of viral genomes via qRT-PCR.

Results: Patient derived tumor samples retained viability and histological integrity during overnight storage at 4°C, mimicking the transport from the clinics to the lab, as well as during ex vivo cultivation for up to 72h. Biopsies and slice cultures derived from murine tumors showed similar susceptibility to VSV-GP. These results could furthermore be substantiated in more complex patient-tumor derived samples, where VSV-GP propagated to a similar extent in tumor biopsies and tumor slice cultures.

Conclusions: The here-described assay allows simple and straightforward ex vivo analysis of patient-derived tumor biopsies for susceptibility towards oncolytic viruses. This assay may open new avenues towards enrichment of cancer patients responsive to VSV-GP based oncolytic virotherapy.

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2284P Pre-clinical assessment of the therapeutic potential of a CD80-Fc-armed oncolytic virus (VSV-GP-CD80Fc)

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Background: Oncolytic viruses (OVs) are capable of eradicating tumor cells and eliciting antitumoral immunity, thus, virotherapy is a promising approach in the field of novel IO-mediated therapies. VSV-GP is an OV which can mediate potent oncolysis in a broad range of solid cancer cell types and initiate adaptive anti-cancer immunity. It exhibits minimal ecotoxicity, as measured by low or absent shedding of infectious virus, poor tenacity in the environment, and no evidence for pathogenesis in treated livestock (healthy swine model). Based on this data, VSV-GP is currently in first-in-

human Phase I trial (NCT05155332). VSV-GP-CD80Fc is a variant of VSV-GP that encodes for a human CD80-Fc fusion protein. The immune-promoting cargo of VSV-GP-CD80Fc was chosen to provide co-stimulation to intra-tumoral T cells. Secreted CD80-Fc exerts its mode of action by binding to CD28 (agonistic) on T cells, which stimulates them in a Fc/Fcγ receptor (FcγR)-dependent manner.

Methods: A pre-clinical characterization of VSV-GP-CD80Fc's replication competence, cargo-expression and therapeutic potential was conducted using state-of-the-art in vitro and in vivo analyses.

Results: The results revealed comparable replication kinetics and an equally good oncolytic activity compared with its antecessor virus, VSV-GP. Furthermore, in vivo mode-of-action studies confirmed the immune-stimulatory effect of the cargo fusion protein. In efficacy studies of the mouse syngeneic CT26.CL25-INFAR-/- model, tumor growth inhibition and survival were dose-dependent leading to >90% tumor growth inhibition in the groups with the highest virus dose, independent of the route of administration. Tumor growth profiles derived from the aforementioned studies were used to characterize the onset of pharmacological activity and to derive a dose prediction that results in an estimated pharmacological active dose (PAD) for VSV-GP-CD80Fc in humans. This can be used as a basis for the definition of a first in human (FIH) starting dose.

Conclusions: In conclusion, VSV-GP-CD80Fc is a highly potent and efficacious oncolytic virus. The usage of the CD80-Fc cargo further boosts the therapeutic potential of VSV-GP-based treatments in humans.

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2285P Lower response to COVID-19 booster dose vaccination on cancer patients comparing to healthy controls

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Background: Due to a compromised immune system, cancer patients are more prone to have a weaker response to COVID-19 vaccination, which can lead to a worst outcome. Thus it is crucial to evaluate the immunological response of cancer patients to booster doses of the vaccine to stratify the patients accordingly and provide a better care.

Methods: Vaccinated cancer patients from the Portuguese Oncology Institute of Porto, under active cancer treatment with different types of solid tumours (SL) and liquid tumours (LT) were included to study the potential differences in the response to COVID-19 booster dose vaccine according to tumour type. Humoral immune response to the booster dose of the COVID-19 vaccine was evaluated in patients' serum samples analysing IgG levels against SARS-CoV-2 Spike (S) protein. We also analysed the IgG levels against SARS-CoV-2 Nucleocapsid (N) protein to address previous contact with the virus. The first cohort of patients collected samples before the booster dose and 3 and 6 months after (cohort 1, N=54, SL=44, LT=10) and the other cohort collected samples only 3 and 6 months after booster dose (cohort 2, N=71, SL=45, LT=26). A group of vaccinated healthy individuals (N=83) was also analysed, and they collected samples at 3 and 6 months post-boost.

Results: Regarding cohort 1, for solid tumours, we observed that IgG S levels increased 3 months after boost ($p<0.001$) and remained high at 6 months post-boost ($p<0.001$) when compared to pre-boost. One the other hand, the hematologic tumours demonstrated a weak response to vaccination since IgG S levels remained very low 3 and 6 months after the boost. When comparing 3 months post-boost in both cohorts and healthy individuals, we observed that the healthy individuals had the strongest IgG S response, followed by the solid and, lastly, the hematologic tumours. In fact, the difference between solid and haematological tumours was quite significant ($p=0.017$).

Conclusions: We verified that the type of tumour may influence COVID-19 vaccination efficacy since solid cancer patients had a better response to SARS-CoV-2 vaccination when compared to haematological cancer patients. Moreover, as expected, healthy individuals have a stronger immune response when compared to cancer patients.

Legal entity responsible for the study: Rui Medeiros, Júlio Oliveira.

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2286P COVID-19 vaccinations in cancer patients (pts): An individual participant data meta-analysis of the International Consortium on COVID vaccination in cancer

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Background: Solid cancer pts are at higher risk of severe COVID-19 compared to the general population, highlighting the importance of effective vaccination for this vulnerable group. However, there is little evidence on how to identify those at risk of an impaired immune response to vaccination among this heterogeneous group.

Methods: This study evaluates the immune response to COVID-19 vaccines in solid cancer pts using individual participant data meta-analysis methods. The study protocol was registered with Prospero CRD42022311290.

Results: We identified 53 eligible prospective cohort studies, investigators of 6 studies agreed to share data, including around 5000 participants with and without cancer. Here, we present the results of the first 1322 participants, of which 247 did not have cancer. Median age was 62 (IQR 55, 70), and 51% were male. Thoracic (18%), breast (17%), and gastrointestinal cancers (15%) were most common. The majority had metastatic disease (54%); 41% received cytotoxic therapy (CT), 26% immune checkpoint inhibitors (ICIs), and 15% targeted therapy (TT) prior to their 1st vaccination. After the 2nd vaccination, 986 pts (75%) had sufficient antibody titres (ABTs) (defined as 300 binding antibody units/mL), while data were missing for 208 (16%). Following the 2nd vaccination, the proportion of cancer pts with sufficient ABTs was lower (88%) compared with individuals without cancer (99.6%), odds ratio (OR) 0.03 (95%CI 0.00, 0.15; $p < 0.001$). Among cancer pts, those with CT 30 days prior to the 1st vaccination were less likely to have sufficient ABTs (OR 0.61 (95%CI 0.39, 0.94)). There was no such association for treatment with ICIs, TT, monoclonal antibodies, or corticosteroids.

Conclusions: Although most cancer pts develop a sufficient immune response to COVID-19 vaccines, their risk of impaired response is significantly higher than in individuals without cancer. Specifically, pts who received CT within 30 days prior to their 1st vaccination are at higher risk of impaired response, and additional vaccinations may be considered. Results on the association between patient, disease, and treatment characteristics and immune response will be presented at the meeting.

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study with hormonal drug: G1 Therapeutics; Financial Interests, Institutional, Research Grant, Imaging studies with CD8 and PD-L1 tracers: Genentech; Financial Interests, Institutional, Research Grant, Imaging and treatment study with CD8 and LAG-3 antibody: Regeneron; Financial Interests, Institutional, Research Grant, Treatment studies with PD-L1 antibody: Roche; Financial Interests, Institutional, Research Grant, Preclinical imaging study and imaging and treatment study with PD-L1x4-1BB bispecific antibody (S095012): Servier; Financial Interests, Institutional, Research Grant, Phase 1-2 and 3 study with ADCs: Synthon; Financial Interests, Institutional, Research Grant, Imaging and treatment with a trispecific humabody T-cell enhancer, CB307: Crescendo Biologics; Non-Financial Interests, Other, 1. Member (current) and Chair (2017-2022) ESMO Cancer Medicines Working Group2. Member (current) and Chair (2013-2021) ESMO-MCBS Working Group: ESMO; Non-Financial Interests, Other, Member supervisory board: Netherlands Comprehensive Cancer Organisation; Non-Financial Interests, Other, Member (current) and Co-chair (2009-2022) RECIST committee: RECIST; Non-Financial Interests, Other, Member expert panel for selection of Essential Medicine List WHO (2019, 2021 and 2023) : WHO; Non-Financial Interests, Other, Chair grant selection committee: Hanarth Fund; Non-Financial Interests, Other, Member of Royal Netherlands Academy of Arts & Sciences (KNAW): Royal Netherlands Academy of Arts & Sciences (KNAW). S. Turajlic: Financial Interests, Personal, Invited Speaker: IDEA Pharma, Roche, Ventana, MSD, Merck; Financial Interests, Institutional, Funding, Uncommon theme pump priming funds: NIHR; Financial Interests, Institutional, Funding, Digital theme funding: RMH/ICR/BRC/Imperial AHSC/Faculty of Medicine; Financial Interests, Institutional, Funding, Tracking renal cancer evolution in blood: Rosetrees Trust; Financial Interests, Institutional, Funding, Clinical PhD Fellowship over 3 years: CRUK Welcome Trust; Financial Interests, Institutional, Funding, Investigating the relationship between primary melanomas and their metastases: The Robert McAlpine Foundation; Financial Interests, Institutional, Funding, Innovation Grant Award for biomarker development: The Francis Crick Institute; Financial Interests, Institutional, Funding, Developing a novel method of representative tumour in sampling in clinical setting: Ventana; Financial Interests, Institutional, Funding, Mapping clonal evolution in renal cell carcinoma: CRUK training and career development board - clinician scientist fellowship; Financial Interests, Institutional, Funding: Harry J Lloyd Charitable Trust Career Development Award; Financial Interests, Institutional, Funding, Clinical Research Fellowship in melanoma: Andy Quick Charitable fund; Financial Interests, Institutional, Funding, Mechanisms of BRAF resistance: Complete Genomics; Financial Interests, Institutional, Funding, Molecular profiling of non-cutaneous melanoma: CRUK; Financial Interests, Institutional, Funding, Target discovery in acral melanoma: Rosetrees Trust. All other authors have declared no conflicts of interest.

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2287P Multiomic Biological mOdifications in the immune response of patients treated with chemotherapy, anti-CD20, or immune-checkpoint inhibitors and receiving a Third dose of vaccinE against SARS-CoV-2 (the BO0STER study)

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Background: Antibody titers after two doses of mRNA-based SARS-Cov-2 vaccines (SVC) decline after 6 months, requiring a further dose to boost immune response. Anticancer agents may differentially impact the response to SVC, but a direct comparison between patients and with healthy controls (HC) has not been conducted. We serially assessed the immunomic changes associated with the booster dose of SVC in patients treated with adjuvant chemotherapy (aCT, colorectal and breast cancer), rituximab (R, non-Hodgkin lymphoma), immune checkpoint inhibitors (ICI, solid tumors), and HC.

Methods: In the above mentioned groups, we performed blood transcriptome sequencing (TS), multiplex antibody titer (ABt, Spherotech), and SARS-CoV-2-specific IFN release assay (IGRA) before the third vaccine dose (TS/AT/IGRA), after 24 hours (TS), at 5 days (d - TS/IGRA), 26d (AT/IGRA) and after six months (mo - AT/IGRA). Immune transcriptomic modules were assessed using BloodGene3.

Results: We enrolled 52 subjects: 11 R, 11 ICI, 8 aCT, and 22 HC. aCT or ICI showed similar vaccine-specific ABt compared with HC at 26d, increasing at 6mo. ICI showed a significantly reduced increase of IgG2 vaccine-specific ABt at 26d compared with HC. R showed a blunted response at 26d. In all groups, the Env and Core ABt increased significantly at 6mo (81% of subjects), with symptomatic infection in only 31% of subjects. We observed a delayed (5d) but efficient increase in inflammation and chemochine modules in aCT, reduced early inflammation (24h) and increased delayed plasma-cell response (5d) in ICI, and reduced response to all immune modules, except for a delayed increase in IFN modules (5d), in R compared with HC. IGRA results were consistent with IFN modules, with a 5d increase in R.

Conclusions: Patients undergoing aCT and ICI mount a vaccine-mediated immunomic response in part similar, but not identical, to HC, and R patients show a blunted vaccine response in line with the literature. A large fraction of all enrolled subjects developed ABt against natural infection, in the absence of symptoms, at 6mo.

Legal entity responsible for the study: IRCCS Policlinico San Martino, Genoa IT.

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2288P Recolony-treating solid tumors with a bacteria-based approach

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Background: Current therapies for oncology patients are often ineffective and present severe side effects, decreasing the quality of life of patients significantly. Recent advances in technology and biomedical research have contributed to the characterization of the the human microbiome and uncovered its important role in health and disease. Those findings allowed monitoring, preventing or even curing human disease through specific microbiome interventions. In this context, we now provide a novel and unique solution for the treatment of solid tumors.

Methods: C57BL/6 and BALB/c mice were used to perform the *in vivo* studies. MC-38, CT-26, B16, LLC1.1 and 4T1 cells were used for the heterotopic tumor injections. Flow cytometry and histological analysis were performed to analyze the immune cell compartments. Metagenomics analysis and whole genome sequence were performed to identify the bacterial strains. Metabolomics analysis were conducted to analyse the serum composition of mice and humans.

Results: Based on human CRC data, we identified specific bacteria that are less abundant in CRC patients compared to healthy individuals. When these bacteria are applied in mice, they show very high efficacy as a monotherapy in tumor models for CRC, melanoma, breast and lung cancer through specific activation of CD8+ T-cells (Montalban-Arques et al. 2021). Based on this finding, we now identified the bacterial metabolite that is responsible for the observed immune-activating effect as well as the receptor that is targeted by that molecule, providing a defined mode of action. This allows us to better evaluate our pre-clinical safety and efficacy studies and it give us a strong advantage, comparing to the current microbiome-based solutions where mechanisms remain unkown.

Conclusions: With our promising proof of concept studies, we are aiming to develop a safe and novel microbiome-based solution for the treatment of solid tumors. The specific bacterial strains will be applied to cancer patients in lyophilized form contained in gastro resistant capsules with colonic release. Our bacteria-based cancer therapy aims to improve treatment efficacy while reducing side effects and increasing the life expectancy and quality-of-life of cancer patients.

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2289P Determining anti-cancer efficacy of a reversible LSD1 inhibitor, EXS74539, in primary AML tissues with limited thrombocytopenic effects

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Background: Acute myeloid leukaemias (AML) are characterised by distinct chromatin dynamics and aberrant histone methylation regulations. The reversible nature of such epigenetic modifications has become attractive for the design of new AML therapies. Histone methylation is controlled by histone methyltransferases and demethylases, and among them, LSD1 has recently gained interest and tractability with the emergence of new LSD1 inhibitor clinical candidates. Here, we describe efforts to transcriptionally and functionally define the activity of EXS74539 ('539) - a novel potent, selective and reversible LSD1 inhibitor - as a monotherapy or in combination with AML standard of care (SoC) at the single cell level, leveraging our expertise in the use of primary AML and healthy bone marrow samples as model systems (Kornauth et al, 2022).

Methods: Using primary human material as a disease relevant model system, combined with our proprietary deep learning enabled high content imaging and image analysis platform, we explored the capacity of '539 to induce AML blast differentiation and/or improve first line SoC therapy potential both in primary AML samples and in non-transformed healthy bone marrow or peripheral blood mononuclear cells. Collecting baseline and treatment condition genomics and transcriptomics, we modelled the AML specific sensitivity to '539.

Results: Through combining single cell omics and functional response data, we demonstrate, preclinically, the capacity of '539 monotherapy to induce AML cell differentiation marker expression ex vivo, and the usability of '539 together with SoC agents. Using healthy non-transformed bone marrow and colony formation assays, we demonstrate that an adapted drug regimen limits '539 thrombocytopenic potential.

Conclusions: Our preclinical data demonstrated ex vivo efficacy of '539 against AML blast cells and supported the combinatorial potential of '539 with first line clinical AML treatment strategies. Leveraging the reversibility of '539 allowed the design of adapted drug regimens, to preserve the safety profile of this inhibitor on non-transformed healthy cells.

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2291P WU-NK-101, best in class memory-NK cell, has key features vital for adoptive cell therapy (ACT) in solid tumors (ST)

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Background: Desirable features for successful ACT include effective migration into tumors, overcoming immunosuppression and dearth of nutrients to survive/function within the tumor microenvironment (TME), not restricted by antigen exclusivity, impervious to antigen escape, and engages the recipient's immune system. WU-NK-101 (WUNK) is a non-engineered cytokine-reprogrammed, expanded, cryopreserved, off-the-shelf NK cell product derived from PBMCs. We have previously shown that WUNK traffic to, and persist in tumor models, and enhanced by mAb combination. Additionally, compared to conventional NK (cNK), WUNK demonstrated improved cytotoxicity A549 (NSCLC): 0% *vs.* 79%, $p=0.0001$ and LoVo (CRC) 0% *vs.* 57%, $p=0.01$, respectively]. (Rutella *et al.*, ESMO 2022).

Methods: Cell phenotypes were evaluated by flow cytometry. Fluorescent Abs for CD3, CD56 were used to resolve BM architecture.

Results: Compared to cNK, WUNK expresses higher levels of cell surface nutrient transporters which adapted to the differing TMEs, suggesting metabolic fitness, and flexibility. Unlike cNK and T-cells, WUNK cytotoxic activity was preserved in TME-aligned media (WUNK: 96.5% vs. 88.2%, $p=0.45$; cNK: 44.1% *vs.* 13.5%, $p=0.009$; T-cell: 53.2 % *vs.*25.2%, $p=0.041$, TME *vs.* conventional media, respectively). Resistance to TME was further confirmed in native-TME-aligned 3D assays from primary tumor surgical samples. WUNK was effective in lysing malignant cells, while sparing benign cells, indicating that WUNK are not indiscriminate killers. This suggests lack of antigen exclusivity and portends resistance to antigen escape. Treatment with memory-NK cells led to T-cell infiltration and co-localization within TME, suggesting coordination with endogenous immune cells. Synergy of WUNK with the endogenous immune system was also documented in a humanized mouse (engrafted with hPBMCs) model, across a number of ST xenografts, which showed deeper anti-tumor responses.

Conclusions: We show that WUNK cells exhibit features that overcome challenges for ACT and enhances anti-tumor activity in ST, heralding the promise of NK cell therapy for ST. The data presented augurs positively for pts to be treated in the upcoming phase I/b clinical study.

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Legal entity responsible for the study: Wugen.

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2292P Prevalence of druggable EGFR genomic alterations in solid tumours other than lung cancer

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Background: An increasing number of rare oncogene-driven solid cancers have been detected through comprehensive genomic profiling testing. *EGFR* genomic alterations are the most frequent oncogenic driver alterations in non-small cell lung cancer, and EGFR-tyrosine kinase inhibitors (TKIs) are effective in this population. However, the frequency of *EGFR* genomic alterations and clinical outcomes of EGFR-TKIs are not well understood in other types of solid tumours.

Methods: Clinical and genomic data retrieved from the Center for Cancer Genomics and Advanced Therapeutics database, the national datacentre for cancer genomic medicine in Japan (Kohno T, et al. *Cancer Discov.* 2022;12(11):2509-2515.), were collected and analysed (n = 18,124, March 2022-February 2023). This study aimed to investigate the prevalence of druggable *EGFR* genomic alterations in patients with solid tumours other than lung cancer. Druggable *EGFR* genomic alterations were defined based on OncoKB™ Therapeutic Level of Evidence V2 (≥Level 3B) that could confer sensitivity to EGFR-TKIs.

Results: Among 17,155 patients with solid tumours other than lung cancer, druggable *EGFR* genomic alterations were identified in 37 patients (0.22%). The median age was 61 years (range, 10-78 years). The most frequent cancer type was central nervous system/brain (n = 10), followed by head and neck (n = 5), bowel (n = 4), biliary tract (n = 3), and breast (n = 3). The druggable *EGFR* genomic alterations were observed with *EGFR* exon 20 in-frame insertions (n = 11), *EGFR* kinase domain duplication (n = 10), *EGFR* exon 19 in-frame deletions (n = 4), *EGFR* L858R (n = 3), *EGFR* S768I (n = 3), *EGFR* G719D (n = 3), *EGFR* L861Q (n = 1), *EGFR* T790M (n = 1), and *EGFR* G719A (n = 1). Clinical data regarding treatment using EGFR-TKIs were not recorded in this database.

Conclusions: Druggable *EGFR* genomic alterations in solid tumours other than lung cancer were observed in 0.22% of this nationwide large cohort. Further clinical investigation is needed to understand the clinical relevance of EGFR-TKIs in patients with solid tumours harbouring druggable *EGFR* genomic alterations not limited to non-small cell lung cancer patients.

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2293P Protumoral role of neutrophils and neutrophils extracellular traps (NETS) in non-metastatic gastroesophageal and rectal cancers

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Background: Neutrophil extracellular traps (NETs) are structures released by activated neutrophils (NEU) into the extracellular microenvironment in response to different stimuli through a process referred to as NETosis. Although first described as an antimicrobial response to infection, NETosis is also involved in cancer. In the context of gastrointestinal tumors, the enrichment of NETs in the metastatic site (even before tumor cell seeding) compared to primary tumor, along with their capability to entrap disseminated cancer cells, suggest that NETs may serve as scaffolds for microbes or circulating tumor cells to create the metastatic niche. While providing mechanistic insights on the selective liver-tropism of certain cancers, NETs could be developed into a prognostic and predicitve biomarker.

Methods: We prospectively collected serum samples from 137 pts, of which 74 were diagnosed with resectable gastroesophageal adenocarcinoma (GEA) and 63 with locally advanced rectal cancer (LARC). Pts received a multimodal treatment (chemotherapy in GEA cohort or chemoradioterapy in LARC cohort, followed by surgery). Whenever available, paired tissue samples from tumor and non-tumor adjacent tissues were collected at baseline and at surgical time for in-sito NET detection and transcriptomic analysis. Serum samples (n= 372) were collected longitudinally and the NETs quantified by an established ELISA assay for citrullinate histone H3 (cit-H3).

Results: We preliminarly quantified serum NETs of pts in GEA cohort (at baseline, during treatment and at disease progression) showing that cit-H3 levels are positively correlated with tumor burden. Moreover, treatment *in vitro* of freshly isolated human NEU with interstitial fluids from tumor and non-tumor adjacent tissues revealed the specific influence of tumor microenvironment's factors on NETs formation. Here, we will present final results obtained on the whole cohort, both on the quantification of circulating NETs and in the tissue of primary and metastatic lesions.

Conclusions: Peripheral NETs positively correlate with tumor burden in the serum of pts with GEA, supporting the relevance of NETosis in tumor progression and their potential as non-invasive biomarker.

Legal entity responsible for the study: Istituto Europeo di Oncologia.

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2294P Whole genome sequencing to define the germline-somatic interaction in young-onset lung cancer

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Background: Although the average age of lung cancer diagnosis is 70, thousands of cases are diagnosed annually in patients under 45. Previous work has shown that lung cancers in younger patients frequently harbor targetable somatic alterations, suggesting young age may be an emerging clinical biomarker of lung cancer biology. Given young age at diagnosis and absence of known environmental insults, we hypothesized that underlying germline variation predisposes to developing lung cancer at a young age.

Methods: We assembled a cohort of 350 patients diagnosed with NSCLC/SCLC at age 45 or younger and performed germline multi-gene panel testing and whole-genome sequencing (WGS) from peripheral blood, along with tumor panel-based NGS. Germline results were compared to WGS from ancestry-matched, uniformly processed non-cancer controls as part of the 1000 Genomes Project as well as exomes from lung cancer patients diagnosed over 45 as part of The Cancer Genome Atlas (TCGA).

Results: Preliminary WGS from 243 patients shows at least 30% of patients carry clinically actionable pathogenic germline variants (PGVs) in cancer-associated genes, at rates exceeding those seen in other cancers — with gene set enrichment analyses (GSEA) showing key age-specific differences compared to lung cancer patients in TCGA. GSEA show high carrier rates of rare PGVs in several cancer-related pathways, including genes mediating DNA damage repair and receptor tyrosine kinase signaling. Common variant polygenic risk scores were negatively associated with rare PGVs, suggesting an independent contribution to risk. Clinicopathologic analysis of this cohort shows enrichment for never-smoking status (74%), female sex (59%), and adenocarcinoma (LUAD, 89%). Of LUAD, 88% harbor targetable somatic alterations: 38.9% *EGFR*-mutant (75% exon 19 deleted), 24.1% *ALK*-rearranged, and 33% fusion-positive.

Conclusions: Rare PGVs mediate lung cancer risk in young lung cancer patients, with age-specific differences compared to patients diagnosed at older ages. These results prompt consideration of a group based on germline risk that may benefit from CT screening as part of future changes to clinical care. Further work will delineate additional risk mediated by non-coding and structural variants.

Clinical trial identification: NCT05265429: Biology of Young Lung Cancer (The YOUNG LUNG Study)

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2295P Pan-cancer prevalence of MET fusions and clinical response to MET- targeted therapy

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Background: *MET* rearrangements are found in multiple cancers. Despite the availability of effective MET drugs there is no approved treatment for these tumors. We determined the prevalence of *MET* fusions, explored MET therapy in preclinical models and assessed efficacy of MET tyrosine kinase inhibitors (TKI) in a colorectal cancer (CRC) patient with *MET* fusion.

Methods: We analyzed the AACR project GENIE registry (release V13, 167,423 samples from 148,268 patients) for intergenic *MET* fusions. We also identified 2 CRC patients (Lenox Hill Hospital, New York, NY, and Renji Hospital Shanghai, China, respectively) by RNA-based NGS. MET expression was assessed by IHC. Sensitivity of SJ-GBM2 (*CLIP::MET*, glioblastoma), and H1993 and EBC1 (*MET* amplified lung cancer) cells to type 1 and type 2 MET TKIs were assessed.

Results: We identified 44/148,286 patients (0.03%) with an intergenic *MET* fusion; cancer types included brain (n=12; with 8 high-grade gliomas), NSCLC (n = 11 with 9 adenocarcinomas), gastrointestinal tract (n = 8; with 3 esophageal adenocarcinomas, 3 cholangiocarcinomas), etc. Recurrent fusion partners accounted for 18/44 (40.1%) cases and included 7 *PTPRZ1,* 5 *ST7*, 3 *CTTNBP2*, 2 *CAPZA2* and 2 *DOCK4.* Two CRC patients with *MET* fusions (*SYNRG2::MET, ZKSCAN1::MET*) were found from routine NGS screening and both showed strong MET expression. Treatment with type 2 (cabozantinib) or type 1 (crizotinib, capmatinib, savolitinib) MET TKIs blocked growth of SJ-GBM2 cells with IC50 values of 0.3, 0.2, 0.1 and 0.04 μM, respectively, reflecting the sensitivity observed in H1993 and EBC1. MET TKIs blocked MET, AKT, ERK and S6 phosphorylation in SJ-GBM2 cells. These results were recapitulated with *MET* shRNAs. The CRC patient (SYNRG2::MET fusion) failed several lines of chemotherapy and was then treated with crizotinib, achieving a mixed response, with stable disease in lung metastases. Upon progression the patient was treated with capmatinib and a decrease in CEA from was observed after 3 weeks on therapy.

Conclusions: Our findings indicate *MET* fusions are widely distributed among tumor types and are sensitive to type 1 and type 2 MET TKIs. Clinical trials evaluating MET inhibitors for patients whose cancers are driven by *MET* fusions are ongoing.

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2296P SGLT2 i dapagliflozin reduces NF-kB expression in heart and kidneys of preclinical models exposed to doxorubicin through MYd-88 and NLRP3 pathways

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Background: Doxorubicin-mediated adverse cardiovascular events are among the leading causes of morbidity and mortality in breast cancer patients. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been shown to be of therapeutic value in patients with type 2 diabetes, chronic kidney disease, and heart failure with reduced ejection fraction, conditions that commonly coexist and are interrelated pathophysiologically.

Methods: Female C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n=6), DAPA at 12 mg/kg (DAPA, n=6) or doxorubicin combined to DAPA (DOXO-DAPA, n=6). Ejection fraction, radial and longitudinal strain were analyzed through transthoracic echocardiography (Vevo 2100). Cardiac tissue expression of NLRP3, Myd88, DAMPs (galectine 3 and calgranulinS100), pAMPK, NF-kB, and 13 chemokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL17-α, IL-18, IFN-γ, TNF-α, G-CSF, and GM-CSF) were quantified through ELISA and western blot methods.

Results: DAPA improved significantly the EF and prevented the reduction of radial and longitudinal strain after 10 days of treatment with doxorubicin. A reduced expression of NLRP3, MyD88, DAMPs and NF-kB in cardiac tissues was seen in DOXO-DAPA group compared to DOXO mice ($p<0.001$). Cardiac expression of IL-1β, IL-6, TNF-α, G-CSF and GM-CSF were significantly reduced after treatment with DAPA. Expression of pAMPK was strongly enhanced in DAPA-DOXO compared to DOXO group. Levels of Calgranulin S100 and galectine-3 were strongly enhanced in DOXO group; on the other hand their expression were reduced by 47.7 and 52.3% in DAPA-DOXO group vs DOXO ($p<0.005$). Hystology evaluation indicate reduction NF-kB expression in myocardial and renal tissue in DOXO-DAPA vs DOXO. Radial strain (RS) is 38.8% in DAPA-DOXO vs 14.1% in DOXO groups ($P < 0.05$); longitudinal strain (LS) is − 23.4 % in DAPA-DOXO vs − 10.5% in DOXO groups ($P < 0.001$)

Conclusions: In this preclinical study, DAPA is able to improve cardiac function and reduce biomarkers involved in heart failure and fibrosis. The overall picture of the study pushes the use of DAPA in prevention of cardiomyopathies induced by anthracyclines in cancer patients.

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2297P Gene co-expression networks capture the potential pathogenesis and progression of upper tract urothelial cancer

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Background: Upper tract urothelial carcinoma (UTUC) accounts for 5%-10% of all urothelial malignancies. And the incidence of UTUC in China is much higher than that in European and American countries, accounting for about 31%. Approximately two-thirds of patients have invasive disease at diagnosis. However, little research has been done on UTUCs.

Methods: To better understand the pathogenesis of UTUC and provide references for its diagnosis and treatment, we conducted a Weighted Correlation Network Analysis (WGCNA) involving the RNA sequencing data of 27 UTUC patients. Multiple linear regression models were used to explore the association between gene modules and clinical indicators. We then imported related modules into Cytoscape. to screen hub genes. Additionally, we performed RNA differential expression analysis, exon mutation analysis, and looked at mutations in hub genes. Enrichment analysis was then conducted based on differentially expressed genes to discover potential pathways regulating UTUC. Finally, bladder cancer data in TCGA database was used to verify the hub genes.

Results: We classified the genes into 31 modules by unsupervised clustering, with 4 modules ($FDR<0.05$) significantly associated with tumor infiltration. Then 9 potential biomarkers, including MSRB3, HSPB2, SCRG1, SYNPO2, FXYD1, PLXNA4, CD163, IFFO1, and FPR3, were discovered by importing these 4 modules into Cytoscape software. Differential expression analysis showed that except for the FPR3 gene, the remaining 8 genes were under expressed in UTUC. This has also been verified in public databases. Meanwhile, SNP mutation occurred in MSRB3, SYNPO2, and PLXNA4 genes. Functional enrichment analysis revealed that differentially expressed genes regulate UTUC through pathways such as cell adhesion, transmembrane receptor protein kinase activity, cGMP-PKG signaling pathway, p53 signaling pathway, and cardiomyocyte adrenergic signaling pathway.

Conclusions: Although these 9 genes are new and significant genes in UTUC, they have been proved in public databases. Our results not only promote our understanding of the relationship between the transcriptome and clinical data in UTUC but will also guide the development of targeted molecular therapy for UTUC.

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2298P Feasibility of ex vivo drug sensitivity testing in urothelial cancer: EVITA trial

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Background: Patients with bladder cancer (BC) are treated with chemotherapy, either intravesically or systemically. Predictive biomarkers to guide clinical decision-making on chemotherapy are lacking, leading to potential ineffective treatment and toxicity. We hypothesized that an established *ex vivo* tumor testing assay could identify chemoresponsive BC prior to treatment and we performed a prospective feasibility trial (OZBS62.21051).

Methods: Fresh tumor tissue was collected and characterized by histological evaluation of H&E slides and hotspot mutation analysis of *hTERT*, *FGFR3* and *PIK3CA* genes. For *ex vivo* drug testing, tumor clusters were isolated, seeded, and exposed to single-agent chemotherapy: carboplatin, cisplatin, gemcitabine and targeted therapy (erdafitinib). Sensitivity evaluation was performed by extraction of morphological features from high-throughput 3D imaging data, followed by AUC comparison of fitted dose-response curves.

Results: *Ex vivo* drug testing was successful for 28 out of 48 patients (58%), generating results within two weeks. Absence of muscle-invasiveness was key in assay success, with higher success in non-muscle invasive BC (NMIBC) (17/20, 85%, (OR: 3.8, 95% CI: 1.7 − 9.1) than in muscle-invasive BC (11/28, 39%). The assay identified a subgroup of NMIBC patients with exceptional *ex vivo* gemcitabine response. *Ex vivo* sensitivity to FGFR inhibitor erdafitinib was observed in two patients with somatic *FGFR3-Y375C* mutations but not for *FGFR3*-WT patients (P = 0.03).

Table: 2298P

Baseline characteristics (N = 48)	
Hospital (%)	
Amphia	15 (31.2)
Erasmus MC	14 (29.2)
Haga	11 (22.9)
Franciscus Gasthuis en Vlietland	8 (16.7)
Age (median & range)	71 (42-96)
Sex (%)	
Male	37 (77.1)
Female	11 (22.9)
Surgery (%)	
TURBT	45 (93.7%)
Radical cystectomy	3 (6.3)
Invasion of musculus detrusor (%)	
Yes	28 (58.3)
No	20 (41.7)
Tumor grade WHO 1973/2004 (%)	
G2 (low grade)	4 (8.3)
G2 (high grade)	11 (22.9)
G3	33 (68.8)
Clinical tumor stage (%)	
Ta	9 (18.8)
T1	12 (25)
T2	15 (31.3)
T3	10 (20.8)
T4	2 (4.2)
Clinical nodal stage (%)	
N0	38 (79.2)
N1	3 (6.2)
N2	6 (12.5)
N3	1 (2.1)

Conclusions: We report the feasibility of *ex vivo* 3D tumor testing for BC. A correlation with clinical response to chemotherapy could not be established due to a lack of successfully screened patients with matching clinical chemotherapy treatment. For NMIBC, however, differential *ex vivo* sensitivity to gemcitabine, and a preliminary correlation for *ex vivo* erdafitinib sensitivity and *FGFR3* mutation status offers a potential solution to select NMIBC patients for effective (novel) treatment options.

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2299P Mebendazole enhances the anticancer effect of irinotecan and check-point inhibitor in vitro and in vivo

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Background: Mebendazole (Mbz), a well-known anthelminthic drug, has been demonstrated to have anti-cancer properties in tumor models and patients. The therapeutic effect of Mbz was suggested to be due to microtubule inhibition, but more recently we reported that Mbz switches macrophages from the M2 to the tumor suppressive M1 phenotype. The aims of this study were to further investigate in tumor models the cytotoxic and immunomodulatory effects of Mbz alone, in combination with cytotoxic drugs and PD-1 antibody.

Methods: Tumor samples from patients with solid or hematological malignancies undergoing diagnostic or therapeutic procedures were obtained in accordance with ethical permission. The samples were then prepared to isolated tumor cells for ex vivo testing. Ex vivo activity of Mbz alone and in combination with standard cytotoxic drugs was assessed using the fluorometric microculture cytotoxic assay. Survival index and synergy scores were calculated using GraphPad and SynergyFinder. In vivo anti-tumor activity of Mbz, irinotecan, a PD-1 inhibitor and their combinations were examined in a murine BALB/c model with inoculated syngeneic colon cancer cells (CT26). Tumor growth was measured by caliper and tumors were retrieved and assessed by flow cytometry for immune cell infiltration.

Results: Mbz alone showed some modest cytotoxic activity against patient tumor cells ex vivo, with hematological tumor cells being slightly more sensitive. The cytotoxic effect of Mbz was generally additive to that of other drugs but synergistic when combined with irinotecan. In the murine model, Mbz, irinotecan and the PD-1 antibody alone inhibited tumor growth. Combined with irinotecan Mbz had an additive effect, but was synergistic when combined with the PD-1 antibody. In line with the latter observation, flow cytometry showed an increase of M1 macrophages and decrease of M2 macrophages in tumors from animals treated with the combination.

Conclusions: Mbz show promising features making it suitable for repositioning into an anti-cancer drug, most notably as a modulator of the macrophage phenotype that may enhance and the effect of check-point inhibitors.

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2300P Clonal hematopoiesis of indeterminate potential (CHIP) in patients with advanced NSCLC treated with immune checkpoint blockers (ICB) as monotherapy: Analysis of the PREMIS study

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Background: Immunotherapy is one of the mainstays of lung cancer treatment. However, the results presented in pivotal trials do not always reflect those in real life, as patients (pts) are more selected for prognostic factors. Cancer is associated with advanced age, and aging is the main risk factor for developing CHIP, a clonal expansion of mutations affecting genes involved in hematologic malignancies in pts without a hematological disease per se.

Methods: We performed a Next-Generation Sequencing (NGS) panel of 74-genes dedicated to hematological alterations on DNA extracted from whole blood collected before first administration of an ICB for advanced NSCLC, within the PREMIS trial (NCT03984318). CHIP prevalence was assessed according to a variant allele frequency

(VAF) threshold of 2%. The main objective is to evaluate CHIP prevalence in a prospective cohort of pts treated with ICB for NSCLC correlating CHIP with clinical outcomes.

Results: We included 104 pts; 68 pts (65%) male, median age of 68 years [range 31-87], and adenocarcinoma represented 68% of cases. ICB setting was 1°L 41%; 2°L 47%; ≥ 3°L 11%, and the most used ICB was Pembrolizumab in 63% of pts. Finally, 98 pts were retained for the analysis. At least 1 CHIP mutation was found in 47 pts (48%).The most frequent mutations were found in *DNMT3A* (69%), *PPM1D* (17%), *TET2*, *ASXL1* and *CHEK2* genes (7% respectively). Median PFS was 2.6 months (m) for CHIP vs 9.3 m no-CHIP 12 m (p=0.02) and median OS was 9.3 m CHIP vs 15 m no-CHIP (p=0.11), associated to lower percentage of PD-L1 and a higher number of metastatic sites in the multivariate analysis. No pts developed hematological disease during the follow up.

Conclusions: CHIP is commonly found in pts with NSCLC, with a prevalence in our cohort of 48% with statistically significant worse PFS in the CHIP-positive population.

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2301P Combining cancer patient spatial transcriptomics and bulk RNA-Seq data to drive insights into NSCLC

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Background: Combining cancer patient spatial transcriptomics (ST) and bulk RNA-Seq allows for a more nuanced understanding of the gene expression (GE) profiles. While large-scale sequencing projects have revealed some NSCLC cancer drivers, they cannot fully address the complexity of the heterogeneous tissue composition present in patients. ST enables the measurement of GE in specific regions within a tissue sample, complementing and refining insights gained from bulk RNA-Seq.

Methods: Fresh-frozen, NSCLC tumor and normal samples were profiled using the 10x Genomics Visium Spatial Gene Expression platform. Spatial differential expression and pathway analysis were performed using Space Ranger and David Functional Annotation respectively. Bulk RNA was prepared using Qiagen AllPrep Universal and TruSeq Stranded Total mRNA kits and sequenced on a NovaSeq6000. Integrated data analysis was undertaken using R (Seurat). Images of spatial GE were generated using the Loupe Browser.

Results: Bulk RNA-Seq and ST showed strong overall agreement between expression profiles, facilitating refinement of disease specific alterations observed in large NSCLC cohorts through ST data. Patient-specific GE in specific tumor regions was identified and could guide future precision medicine approaches: for example tumor-related genes EPCAM or PDCD6 were higher expressed in the tumor center, whereas HTRA3 which suppresses tumor cell invasiveness shows higher expression in the microenvironment. Furthermore, the transcription factor KLF5 is higher expressed in tumor regions but shows no strong regulation in bulk data. This highlights how spatially resolved data can provide insights into the identification and assignment of cancer-relevant genes that primarily show only minor regulation in bulk RNA-Seq data.

Conclusions: A more refined in situ understanding of GE profiles in the NSCLC microenvironment, combined with large cohort data will help guide therapeutic target selection. The combination not only refines target expression cell types (E.g. primary tumor or immune system) but also provide a strong indicator for target GE variability within patients' tumors for improved precision medicine approaches.

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2302P Efficacy assessment of targeted and immunotherapies for personalised treatment of melanoma using 2D and 3D ex-vivo assays

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Background: Ex-vivo functional drug assessment has been successfully tested to guide treatment decisions with higher predictive value for multiple malignancies. Similar methods can also be used to test the personalised efficacy of standard-of-care drugs for advanced melanoma. We are currently developing an ex-vivo high throughput preclinical workflow comparing different ex-vivo models with a range of clinically approved and experimental systemic drugs including immunotherapies.

Methods: A high-content immunofluorescence (IF) microscopy-based viability assay for drug screening has been developed and optimised using melanoma cell lines and four targeted inhibitors. Upon exposure, the drug efficacy profiles were generated by counting fluorescently labelled melanoma cells. A 3D spheroid-pbmc coculture model is currently being optimised for the efficacy assessment of Immune Checkpoint Inhibitors currently used to treat melanoma patients. The immunotherapy efficacy will be assessed by immune cell activation and spatial distribution of immune cells in relation to tumour spheroids. Currently, we are recruiting stage III/IV melanoma patients to collect metastatic lymph nodes which are being used for the 2D and 3D assays. The drug efficacy results will be correlated with the corresponding patient's clinical follow-up data.

Results: A 2D image based cell viability assay has been optimised using melanoma cell lines. Dose-response curves have been successfully generated with IC50 values for targeted inhibitors using fluorescently labelled melanoma cell lines in the 2D imaging assay. For 3D coculture, spheroids were successfully generated from cell lines and patient samples in hydrogel sandwich assay, hydrogel dot matrix assay, and 3% methyl cellulose- media floating assay. The spheroids and isolated PBMCs from patients and healthy donors are now being used to optimise the coculture assay for ICB efficacy assessment.

Conclusions: The preliminary data shows, the project can provide valuable insight into the applicability and translational potential of ex vivo screening guided personalised treatment for advanced melanoma patients and identify novel, repurposed, or combination treatments with improved clinical outcomes.

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2303P Protein functional interpretation of gene variants observed in clinical next-generation sequencing (NGS) for pleural mesothelioma

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Background: The interpretation of gene variants from NGS data may support clinical and treatment decisions in pleural mesothelioma. Predicting how a variant can affect the functions of the protein- or disease-relevant pathways is challenging and, so far, it largely relies on gene-centric algorithms. We complement this by integrating a protein-centric interpretation of the variants in order to expand the functional information accessible from clinical NGS.

Methods: We have screened for pleural mesothelioma clinical NGS datasets accessible from literature reports focusing on the relevant genes *BAP1* and *NF2*. NGS results are combined with protein information from neXtProt using an in-house developed program. Conservation-based predictions are integrated with structural and functional protein information to assess the functional impact of the variants. The pleural mesothelioma molecular pathway in the WikiPathways knowledgebase permits us to interpret the relevance of the variant within its pathway environment (https://www.wikipathways.org/pathways/WP5087.html).

Results: The variants from an initial NGS dataset have been mapped on the protein sequences, resulting in 209 protein variants for BAP1 and 181 for NF2 isoform 1. Functional predictions from the algorithms SIFT and PolyPhen-2 embedded in neXtProt presented approx. 60% agreement for BAP1 and 51% for NF2. 13% of the BAP1 and 22% of the NF2 variants had no prediction. The integration of the protein-centric information refined the functional interpretation of 121 variants in BAP1 and 107 in NF2 located in regions critical for the function of the proteins, like interacting or enzymatically active domains, FERM domains or loci of post-translational modifications. Among them, 67 variants with missing or ambiguous prediction between SIFT and PolyPhen-2 (30 in BAP1, 37 in NF2). The molecular pathways of pleural mesothelioma revealed critical sites in the BAP1 and NF2 pathways potentially affected by the variants (WikiPathways:WP5087; Malignant pleural mesothelioma (WP5087)).

Conclusions: Protein-centric and pathway-embedded interpretation of gene variants may complement NGS information for clinical decisions in pleural mesothelioma.

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2304P A phase II study of tepotinib in patients with advanced solid cancers harboring MET exon 14 skipping mutations or amplification (KCSG AL19 -17)

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Background: Tepotinib is a selective MET tyrosine-kinase inhibitor. We evaluated the efficacy and safety of tepotinib in patients with various solid cancers harboring *MET* exon 14 skipping mutation (*METex14)* or *MET* gene amplification.

Methods: A phase II, multicenter, single arm study was conducted for patients with advanced or metastatic solid cancers who progressed after standard treatment, harboring either *MET*ex14 or *MET* amplification (gene copy number≥6) detected by tissue—based next generation sequencing (NGS). Tepotinib was administered at a dose of 500mg once daily, until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR), and the secondary end points were progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety profiles. For exploratory analyses, we analyzed gene profile using alphaLiquid® panel, a liquid—based NGS.

Results: A total of 35 patients were included (*MET*ex14, n=24; *MET* amplification, n=11). In patients with *MET*ex14, NSCLC was the most common (21 of 24) while other cancers were more common in patients with *MET* amplification (8 of 11). At a median follow-up of 19 months, the ORR was 57.6% for all patients, 52.2% for *MET*ex14, and 70% for *MET* amplification. Median PFS was 8 months (95% CI, 4.5-11.5) and median OS was 14 months (95% CI, 7.8-20.2) in all patients. For *MET*ex14, the median PFS was 9 months (95% CI, 1.6-13.6), and the median OS was not reached. For *MET* amplification, the median PFS was 7 months (95% CI, 1.5-12.5) and the median OS was 10 months (95% CI, 5.8-14.2). The ORR of patients with *MET* dysregulations detected in liquid—based NGS was 81.3% while the ORR of patients without *MET* dysregulations was 30%. The most frequently reported adverse events were peripheral edema (40.0%), followed by asthenia (28.6%), transaminase elevation (22.9%), and anorexia (22.9%), mostly grade 1 or 2.

Conclusions: Tepotinib demonstrated promising antitumor activity and manageable toxicity profiles in patients with various solid cancers harboring *MET*ex14 or amplification. Detection of *MET* dysregulations in liquid-based NGS is expected to play a potential role in predicting response of tepotinib.

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Legal entity responsible for the study: The authors.

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2305P Next-generation sequencing-based regression algorithm to determine homologous recombination deficiency scores in a pan-cancer cohort

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Background: Homologous recombination deficiency (HRD) inhibits double strand breaks from being repaired in DNA, leading to cancer cells failing to recover themselves and cell death. Previous studies found that HRD-positive ovarian cancer patients had more significant clinical benefits from poly ADP-ribose polymerase inhibitors (PARPi) treatment. For accurate detection of HRD, next-generation sequencing (whole exome, whole genome) was used to identify large-scale genomic aberrations including telomeric allelic imbalance (HRD-TAI), loss of heterozygosity profiles (HRD-LOH), and large-scale state transitions (HRD-LST). So far, many studies (HRDetect, SigMA, CHORD and shallowHRD) have been conducted to accurately determine HRD in a pan-cancer cohort. As the study progressed, it has been revealed that PARPi is effective when applied to patients with HRD in ovarian cancer, breast cancer, prostate cancer, and pancreatic cancer. To develop an algorithm accurately predicting HRD score in patients with ovarian cancer, breast cancer, prostate cancer, and pancreatic cancer utilizing a machine learning algorithm.

Methods: We used whole-genome sequencing (WGS) data of 710 samples from 309 patients, whole-exome sequencing (WES) data of 4,650 samples from 2,193 patients from the pan-cancer cohort of the TCGA (TCGA-OV, TCGA-BRCA, TCGA-PRAD, and TCGA-PAAD). The HRD-TAI/HRD-LST/HRD-LOH scores were calculated through structural variation analyses. After data cleaning processes, machine-learning models were trained and tested on 228 out of 2,502 samples, and validation was performed on 1,248 out of 2,502 samples from the TCGA dataset.

Results: To assess the performance of the machine-learning regressor, the concordance between predictions and annotations was quantified by calculating the R squared (R^2). As a result of training using machine learning algorithm, we achieved a high R^2 (0.904) with a RMSE (root mean squared error) score (7.649) for a pan-cancer cohort.

Conclusions: Our regressor was robust and accurate when applied to 4 cancer types. Using our systematic pan-cancer analysis, we found novel insights into the mechanisms of HRD across cancer types with potential contribution to clinical practice.

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2306P How TAILORx changed treatment allocation based on 21-gene recurrence score in the daily clinic: A single center retrospective analysis

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Background: Results from TAILORx showed significant benefit of chemotherapy (CHT) in premenopausal early luminal HER2-negative breast cancer (BC) patients with a 21-gene intermediate recurrence score (RS). We analysed how this data shifted CHT implementation after July 2018 (cut-off), especially in the intermediate RS group, in order to determine how the reality of the daily clinic met the new standard guidelines.

Methods: Retrospective analysis in a cohort of 326 HER2-negative, luminal BC patients, treated at Basel University Hospital and Cantonal Hospital Baselland (2010-2021). Primary end-point was to assess any change in therapy administration in the BC population before (cohort A) and after the cut-off point (cohort B) adjusted after RS categories and determine role of menopausal status and RS in CHT selection.

Results: RS values across all categories were lower in B vs A in the low ($p<0.001$), intermediate ($p=0.001$) and high RS ($p=0.005$). The intermediate and high RS groups were larger in B vs A (97 vs 52, 27 vs 14 patients, $p<0.001$), while low RS was smaller (37 vs 99, $p<0.001$). In the low and high RS there was less radiotherapy in B vs A (54.5% vs 71%, $p=0.01$ and 26% vs 50%, $p=0.039$), but no difference in other treatments. Menopausal status, nor RS seem to drive therapy. In the intermediate RS, there was less CHT in B vs A (13% vs 40%, $p=0.001$) and less patient refusal of CHT (4% vs 15%, $p=0.01$). In this category, CHT regimen changed significantly in B vs A with less anthracycline + taxotere applications (81% vs 61.5%, $p=0.009$). There was also more bisphosphonate therapy in B vs A (84% vs 65%, $p=0.007$). In this RS category, CHT was significantly impacted by menopausal status and RS in A ($p=0.002$), but not in B ($p=0.882$). There was more Tumor Board (TB) convergence on treatment for patients with intermediate RS in B vs A (87% vs 68%, $p=0.039$). When not adjusted for RS categories, menopause was not significant for CHT administration ($p=0.121$ in A, $p=0.384$ in B), but RS was ($p<0.001$ in A and B).

Conclusions: TAILORx significanlty impacted CHT administration, regimen selection, compliance and TB decision convergence in the intermediate RS group. When not adjusted for RS categories, menopausal status was not decisive for CHT, but independently, RS score was.

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2307P Loss of CYP2D6 activity sensitizes liver cancer cells to chemotherapy

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Background: Loss of heterozygosity (LOH) is a frequent event in cancer, that is caused by larger chromosomal deletions in cancer cells due to genetic instability [TS1] (Mertens *et al.*, 1997). Thus heterozygous individuals become hemi- or homozygous for certain genes, which might change the phenotype of a cancer cell compared to normal cells (Muller *et al.*, 2012), (Dey *et al.*, 2017). This change might create an opportunity to selectively target cancer cells while sparing normal cells (Rendo *et al.*, 2020).

Methods: To find potential drug targets, data from the 1000 Genomes project was analyzed to identify prevalent constitutional loss-of-function (LoF) SNPs in coding regions causing truncating or splice site mutations with allele frequency >0.5[TS1] [NR2] %, heterozygosity between 10% and 90% of potential relevance in cancer cells. The drug metabolic gene *CYP2D6* was selected and isogenic cell models were established in HEK293T and HepG2 cells. A chemical library of a total of 525 compounds was screened using HEK293T cells harboring a functional or loss-of-function CYP2D6 enzyme. Final hits with LoF-selective toxicity were confirmed on the HepG2 cell model and patient-derived hepatocellular carcinoma organoids.

Results: We identified 60 genes with prevalent constitutional LoF variants and the CYP2D6 enzyme was selected for further work due to its well known drug metabolic activity and the high frequency of 22q13 loss in cancers (Mertens *et al.*, 1997). We observed a consistent pattern of responses to Rucaparib, the known CYP2D6 substrate (Zhao, Long and Wang, 2022), on both established HEK293T and HepG2 cell models, suggesting the robustness of our cell models. Three compounds with selective toxicity towards HepG2 and HEK293 cells lacking CYP2D6 activity were identified. One of them is currently available for use in clinical oncology and further confirmed on the patient-derived hepatocellular carcinoma organoids.

Conclusions: LOH in *CYP2D6* gene can potentially guide drug use in cancer precision medicine and merits further clinical evaluation.

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2308P CyPep-1 reprograms the tumor microenvironment and enhances the efficacy of immune checkpoint inhibitors

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Background: Immune checkpoint inhibitor (ICI) therapy produce durable responses in patients with metastatic cancer. However, most patients do not benefit from ICIs, promting the need for new treatment strategies. CyPep-1, a synthetic 27-D-amino acid peptide, selectively targets tumor cell plasma membranes, inducing pore formation and immediate membrane destabilization. With demonstrated activity across a broad range of tumor types, CyPep-1 exhibits a strong therapeutic potential. Here we describe the membrane perturbing activity of CyPep-1 on ICI refractory tumors *in vitro* and *in vivo,* and demonstrate its ability to release tumor neoantigens, stimulate the immune system and sensitize tumors to anti-PD1 therapy.

Methods: The release of cytoplasmic antigens was quanitified following exposure of CyPep-1 to various cancer cell lines that do not respond to ICI therapy in vivo. Syngeneic tumors were established *in vivo*, followed by CyPep-1 injections as monotherapy or in combination with anti-PD1 antibodies. Immune activation was assessed by Flow-Cytometry and Mass Cytometry (CyTof).

Results: CyPep-1 treatment resulted in the release of functional cytoplasmic proteins, indicative of tumor antigen release. Intratumoral CyPep-1 administration triggered cytokine release and a significant infiltration of various anti-tumor immune effector cells, consequently reducing tumor growth. Anti-PD1 monotherapy, however, had no impact on tumor growth. CyPep-1, in combination with anti-PD-1 potentiated the therapeutic effects of CyPep-1, leading to a significant systemic anti-tumor immunity and tumor growth inhibition.

Conclusions: CyPep-1 treatment specifically targets tumor cells, promoting pro-inflammatory cytokine upregulation and subsequent infiltration of immune effector cells within the tumors. This process results in a systemic immune response, transforming immunological "cold" tumors into "hot" ones. A clinical trial based on these findings has been initiated (NCT05383170).

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2309P High DDR1 mRNA and protein expression across human tumor types correlate with epithelial composition of the tumor microenvironment

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Background: Discoidin Domain Receptor 1 (DDR1) is a collagen-binding receptor tyrosine kinase expressed by tumor cells which has been implicated in cancer invasion, progression, and immune exclusion. A first-in-human trial of a DDR1-targeted therapy is underway. The relationship between *DDR1* mRNA, DDR1 protein, and the epithelial composition of the tumor microenvironment across tumor types has not been established and has the potential to influence indication and patient selection for DDR1-targeted therapies.

Methods: Human tumor samples (n= 93) from a range of epithelial and non-epithelial tumor types were evaluated by bulk RNA-sequencing and multiplex immunofluorescence (mIF) of DDR1 and pan-cytokeratin (CK). Tumor-stromal segmentation was determined by image analysis for epithelial tumors with epithelium defined by CK positivity in the tumor bed. Correlative analyses were done to relate *DDR1* mRNA expression to DDR1+ cell density, proportion of tumor cells expressing DDR1, and proportion of tumor epithelium.

Results: A high proportion of tumor cells (median of >0.7) expressed DDR1 across all epithelial tumor types. DDR1 expression was uniformly low in non-epithelial tumors evaluated (desmoid tumors, additional indications forthcoming). Moderate correlation was observed between *DDR1* mRNA expression and DDR1+ cell density across tumor types ($R=0.31$, $p<0.01$). In epithelial tumors, both *DDR1* mRNA and protein were correlated with the percentage of epithelium ($R=0.30$ and 0.46, respectively; both $p<0.01$), with significant variance between tumor types.

Conclusions: DDR1 is expressed in a high proportion of tumor cells across a range of epithelial tumor types, suggesting potentially broad application of DDR1-targeted therapies. As expected, since DDR1 is primarily expressed by tumor cells, both mRNA and protein expression levels are correlated with the proportion of tumor epithelium. The degree of correlation between *DDR1* mRNA and protein appears to be tumor type specific, possibly due to differences in DDR1 protein density in DDR1+ cells and/or contamination of bulk RNA with adjacent tissue. Assessment of DDR1+ cell density may be more accurate for patient selection in certain tumor types.

Legal entity responsible for the study: Parthenon Therapeutics.

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2310P Oxygen nano-bubbles attenuate hypoxia-induced tumour malignancy in tumour xenograft models

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Background: The rapid proliferation of cancer cells leads to abnormal vascularization, creating a hypoxic tumor core in most advanced solid tumors. Recent studies have shown that hypoxia is associated with poor prognosis in cancer patients. Tumor aggressiveness is driven by hypoxia, which confers resistance to many conventional cancer therapies. In the present study, we propose that oxygen nanobubbles can reduce the hypoxic effect on the epithelial-to-mesenchymal transition (EMT) and prevent migration and invasion in non-small cell lung cancer (NSCLC) and triple-negative breast cancer (TNBC).

Methods: Using the sonic cavitation method, we have developed a method to generate bulk oxygen nanobubbles (ONBs) with dipalmitoyl phosphatidylcholine (DPPC) lipid and quantitate mean diameter and number density through nanoparticle tracking analysis and insight. We have treated A549 lung adenocarcinoma and MDA-MB-231 triple-negative breast cancer cell lines with 1% oxygen and ONB. We have also checked its preventive role in the zebrafish tumor xenograft model. We have measured HIF-1a and EMT expression markers by immunoblot and qPCR analysis. Moreover, we have used the 4T1 BALB/c mice tumor xenograft model for further confirmation.

Results: ONB promotes HIF-1α hydroxylation and its proteasomal degradation in hypoxic cancer cells. ONBs treated A549 and MDA-MB-231 cancer cells and an adult zebrafish A549 tumor xenografts showed the downregulation of TGF-β and VEGFA expression at the transcriptional and translational levels, which also led to upregulation of epithelial genes like E-cadherin with down-regulation of mesenchymal genes like N cadherin, Vimentin, Fibronectin. ONB treatment significantly affects cancer cell migration. Also, liposomal ONB administrated 4T1 BALB/c breast tumor xenograft model showed similar results.

Conclusions: ONBs reduce HIF-1 mediated epithelial to mesenchymal transition (EMT) controlled by TGF-b and VEGFA and prevent cellular migration and invasion in solid tumors, particularly NSCLC and TNBC. In conclusion, targeted administration of ONB could be a better therapeutic approach to inhibit the hypoxic detrimental effect, which helps to increase the efficacy of anticancer treatments.

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2311P Population pharmacokinetic-pharmacodynamic modeling to inform optimal dosing strategies for GI-101, a novel fusion protein, targeting IL2$\beta\gamma$R and CTLA4

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Background: Interleukin-2 receptor (IL2R) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are key immunotherapeutic targets in cancer treatment. GI-101, a novel bispecific Fc fusion protein, targets both CTLA4 and IL2R$\beta\gamma$, offering potential for improved patient outcomes. This study developed a mathematical model linking GI-101 pharmacokinetics (PK), absolute lymphocyte count (ALC) dynamics, and

progression-free survival (PFS) to optimize the biological dose for maximal therapeutic benefit.

Methods: Preclinical monkey (n=74) and phase 1/2 human (n=31) data of GI-101 were used for model development. The dataset was randomly split into training and test datasets at a ratio of 7 to 3, and the final model was validated using the test dataset. Data from a phase 1/2 clinical trial were analyzed using a random survival forest algorithm to assess the effect of immune cell dynamics on PFS. Potential dose-response correlations were assessed for Grade 3 or 4 treatment-related adverse events (TrAE) and immune-related adverse events (irAE) using logistic regression. Stochastic simulations determined the optimal biological dose (OBD) to achieve the target peak ALC.

Results: A pharmacodynamics-mediated drug disposition (PDMDD) model adequately described drug pharmacokinetics, captured changes of cell count across all lymphocyte subsets, and demonstrated strong performance in the test dataset. Random survival forest analysis of the GI-101 clinical data revealed that peak total lymphocyte (p=0.00191) and CD8+ T cell (p=0.00515) counts significantly predicted PFS. There was no significant dose-response correlation for TrAE (p=0.66) and irAE (p=0.92). Simulations suggested an OBD of 0.3 mg/kg every three weeks, achieving target peak total lymphocyte and CD8+ T cell counts of 2,000 cells/μL and 350 cells/μL, respectively.

Conclusions: Our findings underscore the value of translational mathematical modeling for informing optimal dosing strategies in novel immunotherapies targeting IL2$\beta\gamma$R and CTLA4. The identified OBD merits further investigation in clinical trials to validate its potential for enhancing patient outcomes.

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2312P SGLT2i dapagliflozin decreases NLRP3, IL-1 and PCSK9 expression in preclinical models of short-term doxorubicin cardiotoxicity

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Background: Anthracyclines are an effective and widely used chemotherapy agent in the treatment of multiple solid organ tumors and hematologic malignancies. The use of anthracyclines as a standard cancer therapy is limited by the potential for the development of cardiac dysfunction, arrhythmias, and clinical heart failure. In recent five years, it was demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9), a lipid metabolism-related protein, is a key orchestrator of immune infiltration in myocardial and cancer tissues and could regulate cardiac fibrosis and inflammation. PCSK9 is a protein with key roles in hepatic low density lipoprotein (LDL) homeostasis. PCSK9 systemic levels are associated to HOMA score and high insulin levels. Dapagliflozin exerts systemic ant-inflammatory properties and cardioprotective effects in diabetic and non-diabetic patients.

Methods: Female C57Bl/6 mice were untreated (Sham, n=6) or treated for 10 days with doxorubicin i.p at 2.17 mg/kg (DOXO, n=6), DAPA at 12 mg/kg (DAPA, n=6) or doxorubicin combined to DAPA (DOXO-DAPA, n=6). After treatments, plasma levels of PCSK9, IL-1β and CRP were analyzed through selective anti-mouse ELISA methods. Myocardial and liver expression of NLRP3-inflammasome and IL-1β were analyzed through ELISA method in tissue lysates after treatments.

Results: DAPA associated to DOXO reduces significantly systemic levels of PCSK9 (-37,5% vs DOXO group, p<0,001). IL-1β and CRP levels were also reduced (-47,3 and − 28,5 %, respectively; p<0.05 for both). Myocardial and liver IL-1β and NLRP3 inflammasome expression were also reduced in DAPA/DOXO group vs DOXO and control, indicated beneficial metabolic and anti-inflammatory effects of SGLT2i.

Conclusions: DAPA has been shown to reduce systemic levels of PCSK9 in preclinical models of short-term DOXO cardiotoxicity. To the best of our knowledge, this is the first evidence of SGLT-2/PCSK9 crass-talk in cardioncology therefore the overall picture of the study open a new window on the beneficial properties of DAPA against anthracyclines side effects.

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2313P APOBEC mutagenesis and macrophage infiltration in cancer

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Background: APOBEC enzymes play key roles in DNA editing and are highly expressed in various cancer types, including estrogen receptor (ER)+/HER2- breast cancer (BC). APOBEC enzyme activation promotes mutagenesis that results in the generation of neoantigens, potentially leading to an anti-tumor immune response. APOBEC mutagenesis has been associated to resistance to chemotherapy and immunotherapy. The impact of APOBEC mutagenesis on the tumor microenvironment (TME) still remains unclear. Here we sought to characterize the TME of ER+/HER2- BC displaying APOBEC mutagenesis and to validate the findings in other APOBEC-related cancer types.

Methods: ER+/HER2- BCs from TCGA with available whole exome and RNA-sequencing data were included (n=519). We inferred single base substitutions (SBS) mutational signatures using SigProfiler. Cell type fractions were computed using CIBERSORT. The correlation between APOBEC signatures (SBS signatures 2 and 13) and the abundance of TME cell types was defined using a logistic regression model adjusted by tumor mutation burden. False discovery rate correction was applied (q-value). Other APOBEC-related cancers (bladder, head and neck, cervix and uterine) were assessed.

Results: Of 519 ER+/HER2- BCs, 57 (11%) were classified as APOBEC-dominant, 84 (16%) as non-dominant-APOBEC and the remaining 378 (73%) as non-APOBEC. Compared to non-APOBEC, APOBEC-dominant ER+/HER2- BCs displayed an enrichment for macrophages M1 infiltration (q=0.026), and decreased macrophage M2 population (q=0.017). Non-dominant APOBEC BCs displayed an extent of macrophage M1 and M2 infiltration intermediate between the other two groups. Analysis of the TME composition according to APOBEC mutagenesis in bladder (n=389), head and neck (n=463), cervical (n=269) and uterine (n=474) cancers revealed differences comparable to those observed in ER+/HER2- BCs.

Conclusions: An association between APOBEC mutagenesis and macrophages M1 infiltration was observed, suggesting that APOBEC processes may uniquely shape the TME in cancer. Going forward, we will investigate the impact of other mutagenesis processes, such as homologous recombination deficiency (HRD), on the TME, to gain a comprehensive understanding of the interplay between various mutational processes and the TME.

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2314P Quality and safety of research biopsies (RB) in oncology clinical trials

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Background: The scientific benefits gained from studying RB in oncology clinical trials depends on sample quality and there are concerns that participant risk might outweigh the benefits.

Methods: RB data from patients who participated in oncology clinical trials at a single institution between January 2017 and December 2020 were analyzed for sample quality assessed by tumor content (TC) and safety. Determinants of high-quality RB and complications were investigated. Quality was compared with sample taken at external institutions and sent to our laboratory for centralized assessment in the context of multicentric breast cancer clinical trials.

Results: The cohort consisted of 6805 samples obtained from 3104 procedures performed in 1983 patients from 386 studies. The median number of samples collected per study was 5, with an average of 2.2 samples/procedure. Samples were collected mainly at screening (72%), from metastatic sites (63%), and using ultrasound-guided procedure (60%). Liver was the most biopsied organ (33%), followed by lymph nodes (13%) and breast (12%). Preservation methods were formalin-fixed and paraffin embedded (FFPE, 50.5%), snap frozen (21.5%) or alternatively stabilized (28%) according to study protocols. The median TC of the 2940 FFPE samples analyzed was 70% (95% CI, 70-70). 85% of samples had >10% TC and 60% had >50% TC. Any grade complications occurred in 15% of procedures, with pain being the most frequent (11%; 0.4% Grade 3-4). Major complications were observed in 0.9% of procedures. A higher number of complications were found for lung RB (34%; Grade 3-4, 2.6%). In multivariable logistic model, visceral site, guided procedure and number of samples collected were associated with higher TC. On treatment biopsy, non-guided procedure and visceral site were independently associated with a higher risk of major complications. In the comparative analysis with an international cohort of 2302 baseline breast cancer RB obtained from sites in 38 countries, major heterogeneity was observed across countries, with median TC ranging from 0% to 80%.

Conclusions: High quality RB have acceptable safety with low risk of major complications. Our comparative analysis suggests that while local collection of high-quality RB is feasible, quality could be improved at some centers.

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Thermo Fisher, MabDiscovery, Anaveon, Hengrui, F-Star Therapeutics, Sanofi, Incyte; Financial Interests, Personal, Invited Speaker: MSD, Lilly, Roche, Thermo Fisher, Novartis, Seagen; Financial Interests, Personal, Full or part-time Employment: NEXT Oncology; Financial Interests, Institutional, Funding: Novartis, Roche, Thermo Fisher, AstraZeneca, Taiho; Financial Interests, Institutional, Research Grant: Beigene, Janssen. R. Dienstmann: Financial Interests, Personal, Invited Speaker: Amgen, AstraZeneca, Boehringer Ingelheim, Ipsen, Libbs, Lilly, Merck Sharp & Dohme, Roche, Sanofi, Servier, GSK, Takeda, Janssen, Foundation Medicine; Financial Interests, Personal, Advisory Board: Bayer, Roche; Financial Interests, Personal, Full or part-time Employment, Oncoclínicas is a private healthcare provider in Brazil. I work part time as Medical Director of the Precision Medicine and Big Data Initiative. We develop molecular tests (pathology and genomics) that are offered to patients treated in the organisation as part of support programs sponsored by pharmaceutical companies and I coordinate research activities with real-world clinico-genomics cohorts: Oncoclínicas; Financial Interests, Personal, Stocks/Shares: Trialing; Financial Interests, Personal, Research Grant: Merck. All other authors have declared no conflicts of interest.

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2315P Clinical and blood immune-inflammatory profiling to decode different patterns of acquired resistance in immunotherapy treated NSCLC patients

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Background: To uncover the underpinnings of acquired resistance (AR) to Immune Checkpoint Inhibitors (ICIs), we determined whether distinctive clinicopathological and peripheral blood (PB) immune-inflammatory features reflect oligo and systemic (sys) AR in advanced NSCLC patients undergoing ICIs.

Methods: On PB collected at baseline (T0) and first disease assessment (T1) from 105 ICI-treated NSCLC, we prospectively assessed LDH, derived Neutrophil-to-Lymphocyte ratio (dNLR), LIPI score, relevant immunophenotypes (flow-cytometry) and their respective delta (Δ) % variation [(T1-T0)/T0]. AR, defined as progression after initial response (CR/PR/SD $\geq$ 6 mos.), was subdivided according to the number of new and/or progressive lesions in oligoAR ($\leq$ 3) and sysAR ($>$ 3). Initial PD or SD $<$ 6 mos. embodied non responders (NR), while absence of progression or PFS $\geq$ 12 mos. enclosed long-term/not progressors (LT/NP). Clinicopathological, PB parameters and survival outcome were statistically evaluated according to AR pattern.

Results: OligoAR involved 24% of cases, while sysAR 12.4%. Compared to NR, oligoAR pattern was associated with significantly lower T0 and Δ LDH, dNLR and LIPI, whereas no differences were observed *vs* sysAR and LT/NP. While baseline PB immune profiles were comparable, a Δ positive cytotoxic (NK, NKT, CD8+Ki67+, CD8+Gnz+) and Δ negative immunosuppressive (CD14+ monocytes, CD4+CD25+FOXP3+ Tregs) dynamics was distinctive of oligoAR *vs* sysAR ($P < 0.05$). Conversely, compared to LT/NP, oligoAR cases showed a lower cytotoxic/proliferating CD8 response coupled with higher CD14+/Tregs feedback ($P < 0.05$). Within oligoAR, patients with 1 progressive lesion, compared to those with $\geq$ 2, exhibited baseline lower LDH and higher NK/CD8+Gnz+ cytotoxic cells ($P < 0.05$) which in turn appeared to condition longer OS (HR: 4.90; P=0.04). Importantly, despite similar clinical profile, prolonged post-progression survival characterized oligoAR *vs* sysAR (median OS not reached *vs* 11.3 mos.; HR: 0.21, 95% CI: 0.08-0.59; $P = 0.001$).

Conclusions: The longitudinal analysis of blood immune hallmarks intersected with clinicopathological features may decipher the distinct patterns of AR in ICI-treated NSCLC patients.

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2316P Integrating comprehensive cancer genome profiling into clinical practice in an Italian referral center: Results of the first year of the fpg500 programme

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Background: The comprehensive cancer genome profiling (CGP) programme (ID: FPG500, IRB approval 3837) is an interventional monocentric study extending somatic genomic assessment to 523 genes in patients with advanced solid tumors.

Methods: The study enrolls cancer patients whose molecular characterization should be warranted according to national and international guidelines. The primary endpoints were the feasibility of the programme (turn around time-TAT and samples failure rate) and the rate of actionable alterations identified. Secondary endpoints included the number of reports sent to the institutional molecular tumor board (MTB), the rate of patients' enrollment in biomarker-driven clinical trial and the identification of potentially germline variants.

Results: From January 2022 to December 2022, 1367 patients were enrolled, including non-small-cell lung cancer (263), ovarian (446), endometrium (246), colorectal (191), pancreatic (83), cholangiocarcinoma (28), prostate (48), melanoma (45), gastrointestinal stromal tumor (GIST) (3), thyroid (7) and breast cancer (7). The overall failure rate was 5%. CGP sequencing data were available for 1162 (85%) patients, while 205 (15%) were addressed to targeted panels. By the end of 2022 an improving average TAT of genomic profiling was reported (25 days), despite an increasing number of monthly analysed samples (mean 114). Genomic alterations according to OncoKB annotation were identified in 96% patients. Potentially pathogenic/likely pathogenic germline variants were identified in 29% of patients. Overall, 6% of cases were sent to MTB.

Conclusions: FPG500 represents the largest prospective European single institution genomic profiling series and highlights the utility of CGP for identifying therapeutic targets in selected cancer patients, concomitant alterations for further predictive and prognostic characterization and germline implications.

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Institutional, Coordinating PI, Phase III, multicenter, placebo-controlled clinical study comparing chemo-immunotherapy (paclitaxel-carboplatin-oregovomab) versus chemotherapy (paclitaxel-carboplatin-placebo) in patients with advanced epithelial ovarian, tubal cancer of fallopian or peritoneal (FLORA-5): Oncoquest Pharmaceuticals Inc.; Financial Interests, Institutional, Coordinating PI, phase IIb randomized, open-label, active comparator, parallel-group, multicenter study designed to evaluate the efficacy and safety of three different doses of the P2X3 receptor antagonist (BAY 1817080) versus placebo and Elagolix 150 mg in women with symptomatic endometriosis: Bayer AG; Financial Interests, Institutional, Coordinating PI, Usability of ITE transducers for sending electric fields for tumor treatment (TTFields): Novocure Ltd.; Financial Interests, Institutional, Coordinating PI, Phase III, multicentre, open-label extension trial to evaluate long-term safety and efficacy in patients with advanced cancers currently undergoing treatment or in follow-up in a pembrolizumab trial: Merck. All other authors have declared no conflicts of interest.

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2317P Mutational landscape and therapeutic implications in squamous cell carcinomas

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Background: Disseminated squamous cell carcinomas (SCCs) are traditionally considered void of actionable molecular targets, in contrast to adenocarcinomas, where an increasing number of targets are identified. SCC rarely undergo routine molecular testing and approved targeted therapies are rare in this population. Access to extensive molecular profiling and subsequent matching with experimental therapies may improve the outlook for patients (pts) with SCC. We report the mutational landscape in SCC and subsequent therapeutic implications.

Methods: Pts with late-stage SCCs (oesophageal cancer, cervical cancer, head and neck cancer, non-small-cell lung cancer, skin cancer, thymic carcinoma, or unknown primary tumor) referred to a phase I facility were included in a prospective, single-center, single-arm open-label genomic profiling study (NCT02290522). Fresh tumor tissue was obtained for whole exome sequencing or whole genome sequencing, RNA sequencing and chromosomal aberration analysis. Circulating tumor DNA was obtained when fresh biopsy was not possible. Each individual genomic report was reviewed and discussed by a multidisciplinary molecular tumor board dedicated to precision medicine. When possible, pts were treated with regimens matched to the genomic profile.

Results: Between November 2013 and March 2023, a total of 189 pts with SCC were enrolled. Genomic profiles were obtained in 160 (85%). At least one actionable target was detected in 77 (48%) with a total of 117 actionable alterations including DNA damage repair response pathway (N=42, 36%), expression profiles matched to monoclonal antibodies (N=21, 18%), and high tumor mutational burden. (N= 15, 13%). In total, 18 pts (23%) were treated with regimens matched to the genomic profile. However, since 2021, 37% (7/19) of the pts with actionable targets have been treated with targeted treatment. Among the evaluable pts (N=6), one had complete response, two had partial response, and three had stable disease.

Conclusions: This study illustrates increasing targeted treatment options for SCCs, thereby emphasizing the importance of genomic profiling.

Legal entity responsible for the study: The authors.

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2318P Value of broad molecular profiling for cancer diagnosis

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Background: Molecular techniques have improved cancer diagnosis and treatment. Due to limited availability and costs, broad molecular profiling, i.e., analysis of whole genomes/exomes, transcriptomes, and methylomes, is rarely performed upfront in clinical practice and mostly confined to research settings. However, in contrast to more readily available focussed analyses of, e.g., the few genes seemingly relevant for a suspected diagnosis, broad molecular profiling may yield unsuspected findings pertinent to diagnosis and/or treatment.

Methods: This analysis is based on patients enrolled in the MASTER program of DKFZ, NCT Heidelberg/Dresden, and DKTK, a nationwide precision oncology network applying genome/exome, transcriptome, methylome, and — more recently — proteome analysis in young adults with advanced malignancies and patients with rare cancers to inform clinical decision-making and the design of molecularly stratified clinical trials. Cases with molecular findings suggestive of an alternative diagnosis are subjected to clinical, molecular, and pathologic revaluation.

Results: In 99 of 3,092 patients (3.2%), the molecular profile warranted revaluation of the clinical diagnosis. The most frequent presenting diagnoses were cancer of unknown primary (n=21); various sarcomas (n=50), e.g., sarcoma not otherwise specified (n=4), malignant peripheral nerve sheath tumor (n=5), and undifferentiated sarcoma (n=6); and melanoma (n=4). Molecular findings suggesting an alternative diagnosis were based on genome/exome, transcriptome, and methylome analysis in 30, 78, and 41 cases, respectively. Potential clinical consequences were classified as changes in diagnosis without relevance for treatment (n=22), relevant for routine treatment (n=58), and prompting molecular alteration-specific treatment (n=19). The molecularly suspected diagnosis was confirmed in a major subset of cases for which sufficient material for histopathologic review was available. The clinically most relevant findings were EWSR1::WT1 fusions and diagnosis of desmoplastic small round cell tumor (n=9) and druggable gene fusions involving FGFR2 (n=4), ALK (n=4), and NTRK3 (n=1).

Conclusions: Broad molecular profiling is a useful adjunct to routine cancer diagnostics, especially in rare entities.

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2319P CADSP: A web tool for comprehensive drug sensitivity analysis in pan-cancer

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Background: Drug therapy is an essential component of cancer treatment. Accurate drug sensitivity analysis can help healthcare professionals determine the right drugs to use, leading to improved patient outcomes and quality of life. However, a lack of

Table: 2319P Comparison of CADSP with other anti-tumor drug sensitivity analysis web server

	CADSP	canSAR	CellMiner	GSCALite	PharmacoDB	DRESIS
Dataset	TCGA, GDSC, GEO(including NCI-60), GPSAdb	TCGA, ICGC	GDSC, CCLE, CTRP, NCI-60	GDSC, TCGA, GTEx	NCI-60, GDSC, PRISM, CCLE, gCSI	DrugBank, CCNSC, TTD
Sample	~29,000	~25,000	1,400	23,594	1,757	-
Cancer types	44	26	60	33	30	125
Analysis module	①Differential expression gene analysis ②Correlation analysis ③Pathway analysis(GSEA, ssGSEA, Pathview) ④Drug analysis ⑤Genetic perturbations	Genomic data analysis	Correlation analysis	①Genomic data analysis ②Pathway activity ③miRNA network ④Drug sensitivity	①Genomic data analysis ②Correlation analysis ③Drug sensitivity	Resistance mechanisms analysis
Parameters customization	✓	×	×	×	×	×

web-based tools with robust visualization and analysis capabilities for pan-cancer drug sensitivity remains a challenge.

Methods: To address this gap, we developed the Comprehensive Analysis of Drug Sensitivity in Pan-cancer (CADSP), a Shiny-based web tool. We collected oncology drug sensitivity-related data from large publicly available databases, including Gene Expression Omnibus (GEO), The Cancer Genome Atlas Program (TCGA), and Drug Sensitivity in Cancer (GDSC).

Results: The current version of CADSP includes transcriptomic data for over 29,000 samples, covering 44 cancer types, 288 drugs, and more than 9,000 gene perturbation data. Users can easily perform various tumor drug sensitivity analyses using CADSP. The tool provides numerous analysis and visualization methods, such as differential gene analysis, gene correlation analysis, pathway analysis, drug analysis, and gene perturbation analysis.

Conclusions: CADSP greatly simplifies the exploration of primary and secondary drug resistance at the single-gene and pathway levels for physicians and researchers. By combining drug resistance data and gene perturbation data, CADSP also offers new avenues for discovering key genes that drive drug resistance. CADSP is available at https://smuonco.shinyapps.io/CADSP/.

Legal entity responsible for the study: The authors.

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2320P Detection of gene fusion-induced neoepitopes in dedifferentiated liposarcoma

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Background: Dedifferentiated liposarcomas (DDLS) are malignant soft-tissue tumors that are characterized by focal amplifications on chromosome 12q. They do not respond well to chemotherapy and no approved targeted therapy for DDLS is available. Through whole-exome/genome and RNA sequencing, we found that these structural changes generate open reading frames, leading to potential gene fusions and immunogenic neoepitopes, which modulate immune microenvironment and could serve as therapeutic targets.

Methods: We first analyzed a DDLS cell line (T449). Gene fusions were identified using two variant calling pipelines, Arriba (DKFZ) and EasyFuse (TRON). Fusion-derived (FD) peptides were used as input for HLA binding prediction by NetMHCpan 4.1. For targeted mass spectrometry (MS) analysis, we applied an ultra-sensitive parallel reaction monitoring workflow. For untargeted MS analysis, we combined data-independent acquisition MS with ion mobility separation by high-field asymmetric waveform ion mobility spectrometry. Mass spectra were compared to the human proteome, FD sequences, and libraries of *in silico* predicted fragment spectra. We used a modified MANAFEST protocol for the expansion of antigen-reactive CD4 and CD8 T cells.

Results: Candidate peptides for the targeted MS approach were selected from overlapping results of both pipelines. For the T449 cell line, we detected 128 fusion events resulting in 493 potential neoepitopes. We selected 46 peptides for targeted MS analysis and identified eight distinct FD neoepitopes. Analysis by untargeted MS yielded 15,578 peptide sequences, including five FD neoepitope candidates. We analyzed tumors from DDLS patients by targeted and untargeted MS analysis as well as their peripheral T-cell repertoire from expansion cultures. In a retrospective analysis of 67 patients, we observed a correlation between the quantity of fusions and specific tumor-infiltrating immune cell fractions.

Conclusions: We show results of our pipeline for the detection of FD neoepitopes using both targeted and untargeted MS approaches and explore the presence of neoepitope-specific T cells in the peripheral blood of DDLS patients. We believe that our work will lead to the clinical development of personalized treatment options for DDLS patients.

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2321TiP TEMPLE: Thiopurine enhanced mutations for PD-1/ligand-1 efficacy: A phase Ib/II clinical trial

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Background: Immune checkpoint inhibitors (ICI) have revolutionized treatment of several cancer types. However, many patients fail to respond. A prerequisite for response is the presence of neoepitopes on cancer cells that trigger the immune system, and the likelihood hereof increases with the number of mutations in the cancer. The thiopurines 6-mercaptopurine (6MP) and 6-thioguanine (6TG) are prodrugs that are converted into cytotoxic metabolites that are incorporated into DNA and cause DNA-damage and mutations through futile DNA mismatch repair attempts. The TEMPLE project is a novel strategy for improving efficacy of ICI by applying an innovative thiopurine combination strategy to increase mutational burden and presence of neoepitopes. The TEMPLE project has been tested in a preclinical setting in an immune competent mouse model of inducible melanoma, where 6TG exposure increased the tumor mutational burden, reshaped the tumor microenvironment by increasing T and NK immune cells and making the tumors more responsive to ICI (PMID: 36545256).

Trial design: The TEMPLE study (NCT05276284) is an investigator-initiated single-center prospective phase 1b and 2 trial to determine the safety, tolerability and efficacy of Atezolizumab given in combination with thiopurines 6MP and 6TG in patients with metastatic solid tumors with an intermediate tumor mutational burden (5-10 mutations/megabase). Recommended phase II dose (RP2D) will be determined in a single armed, open label phase 1b trial with a dose-limiting toxicity (DLT) period of 4 weeks. The combination of thiopurines and Atezolizumab will be administered in 21-day cycles. Patients will be included in a modified 3+3 design. 3-18 patients are expected to be enrolled in the phase 1b study, depending on observed DLTs and the need for dose adjustments. Phase II will be an open label, single arm phase II trial enrolling additional patients up to a total of 27 patients treated at RP2D in a Simon's 2 stage design. Extensive exploratory analyses will include characterization of the tumor mutational and neoantigen landscape on serial biopsies using whole genome

sequencing and RNA sequencing. The study was initiated in September 2022, and currently four patients have been included in the study.

Clinical trial identification: NCT05276284.

Legal entity responsible for the study: The authors.

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2322TiP SOUND: A phase II trial evaluating the efficacy of molecular profiling of circulating ± tumor tissue DNA for salvage-therapy matching in patients with advanced and refractory carcinoma

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Background: The decreasing costs and turnaround time of next generation sequencing methods paired with the rapidly growing arsenal of available genome-targeted drugs have significantly raised the impact of molecular profiling (MP) for treatment selection in clinical practice. However, to date, the efficacy of MP-guided cancer therapy beyond its approved clinical indication has been modest. Tumor tissue profiling alone may not be sufficient to capture the heterogeneity of advanced tumors. Of note, circulating tumor DNA (ctDNA) has recently been shown to provide the most accurate molecular snapshot of a patient's tumor composition. We thus aimed to evaluate the utility of comprehensive MP of ctDNA for personalized, cancer-agnostic treatment matching and to investigate the efficacy of MP-matched therapy in this salvage setting.

Trial design: SOUND is a multicenter non-randomized phase II trial. Adult patients with locally advanced or metastatic carcinoma who have exhausted all evidence-based therapies and have an ECOG performance status of 0-2 are eligible. At study enrollment, a mandatory liquid biopsy for the analysis of ctDNA is obtained from all patients. A biopsy of tumor tissue DNA is optional depending on the patient's consent. MP of ctDNA and tumor tissue DNA is performed using the FoundationOne®Liquid CDx and the FoundationOne® CDx assays, respectively. In patients with available tumor tissue not older than 3 months, immunohistochemical testing of Her2, PD-L1 and NTRK is performed. All patient cases, including the molecular reports, actionable molecular targets (AMT) and MP-guided treatment recommendations are reviewed weekly in a virtual multidisciplinary molecular tumor board. The primary study endpoint is the proportion of treated patients who have a progression free survival (PFS) ratio of $\geq$ 1.3 comparing the PFS on the matched therapy to the PFS of the previous therapy line. Co-secondary endpoints are the proportion of patients from whom a conclusive genomic profile can be obtained, the proportion of patients with an AMT, the number of AMTs, overall survival, and therapy response rate. To date, 91 of 200 planned patients have been enrolled.

Clinical trial identification: EUDAMED: CIV-AT-21-12-038246; NCT05032092, Release Date November 4, 2021

Legal entity responsible for the study: Medical University of Graz.

Funding: Roche Austria GmbH.

Disclosure: E. Heitzer: Other, Personal and Institutional, Advisory Board, Presentations, Funding IITs: Roche Austria GmbH. A. Gerger: Other, Personal and Institutional, Advisory Board, Presentations, Funding SOUND Study: Roche Austria GmbH. All other authors have declared no conflicts of interest.

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TUMOUR BIOLOGY AND PATHOLOGY

2323P Multi-omic spatial phenotyping of the NSCLC tumour microenvironment for the development of a spatial score associated with immunotherapy resistance

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Background: Non-small cell lung cancers (NSCLC) are the leading cause of cancer morbitidy and mortality globally with a 5-year survival of ∼15-20%. Immunotherapies have shown durable benefit in a subset of patients. There is a growing need to identify better biomarkers able to stratify patients who are likely to respond to therapy. Whilst PD-L1 expression and other assessments such as tumour mutation burden (TMB), microsatellite instability (MSI) have shown associations with patient outcomes, there remains a need to comprehensively characterize the tumour microenvironment (TME).

Methods: In this study, we used high-dimensional spatial transcriptome and proteomic profiling of whole slides from NSCLC patients who had received single-agent immunotherapy. We performed a combination of compartmentalized (tumour/stroma) 1800-plex RNA (Nanostring Technologies, Cancer Transcriptome Atlas) and whole-slide 57-plex Phenocycler Fusion and custom Phenocode Signature Panels (Akoya Biosciences) targeting immune contexture, immune profiles, activation status, metabolic activity and immune checkpoints.

Results: For our transcriptome analysis, we compared the tumour and stromal compartments associations with response to therapy (RECIST). The tumour compartments showed specific enrichment for metabolic pathways in patients that were non-responsive to immunotherapy. These findings were further strengthened at the protein level with a grouping of metabolic signatures, including Glucose Transporter 1 (GLUT-1), Glucose-6-phosphate dehydrogenase (G6PD) and Citrase Synthase (CS). In resistant tumours, there was a clear lack of CD8 and CD68 infiltration and reduction or absence of lymphoid/tertiary lymphoid-like structures highlighting the complementarity of T- and B-cell biology in areas of high metabolic activity.

Conclusions: This study identifies a unique metabolic signature associated with response and resistance to immunotherapy in NSCLC which is mirrored by T- and B-cell biology. Our study demonstrates the utility of high-dimensional spatial multi-omic profiling to delineate new signatures associated with response to therapy and aid in patient stratification.

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2324P Trametinib and PD-1 combined blockade impairs tumor growth and improves survival of KRAS-mutant lung cancer through Id1 downregulation

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Background: Although anti-PD-1/PD-L1 antibodies represent a major breakthrough in NSCLC therapy, this treatment's efficacy is highly dependent on tumor PD-L1 expression. We previously reported the role of Id1 in lung adenocarcinoma and the efficacy of a combined blockade of PD-1 and *Id1*, through RNA silencing, in *KRAS*-mutant LUAD murine models. Trametinib, an oral MEK1/2 inhibitor, acts downstream of *KRAS*. Here we evaluate trametinib as a pharmacological *Id1* inhibitor able to enhance immunotherapy efficacy through PD-L1 overexpression.

Methods: To explore whether MEK1/2 inhibition reduces Id1 expression, *in vitro* and *in vivo* experiments were conducted in NSCLC cells and in murine models. RNAseq analysis was performed to elucidate the pathways involved in Id1 inhibition. Apoptosis and PD-L1 expression was measured by flow cytometry. Synergy of trametinib anti-PD1 combo was investigated in *KRAS*-mutant LUAD models.

Results: Experiments in *KRAS*-mutant NSCLC cells and mice models showed Id1 inhibition after MEK1/2 blockade. Blockade of proteasome activity with MG-132, restored Id1 levels. Trametinib-resistant (TR) cells did not show Id1 inhibition, moreover, *Id1* silencing rescued the sensitivity to trametinib in human and murine NSCLC TR cells ($p<0.001$). Flow cytometry analysis showed increased PD-L1 expression ($p<0.001$) in NSCLC cell lines after trametinib administration. In contrast, Id1-overexpressing cells did not show PD-L1 upregulation after trametinib. *In vivo* experiments confirmed a synergistic therapeutic efficacy of the trametinib and anti-PD-1 combo, reducing tumor growth ($p<0.05$) and increasing mice survival ($p<0.05$), compared with either trametinib or immunotherapy alone. Moreover, the immune population's analysis showed a significant increase in $CD8^+$ T and a reduction in Treg cells in tumors of mice receiving combination treatment.

Conclusions: Pharmacological inhibition of MEK1/2 decreased Id1 expression *in vitro* and *in vivo*, replicating the effect of a shRNA against *Id1*, through proteasome activation. PD-L1 upregulation induced by Id1 blockade after trametinib treatment sensitized NSCLC cells to anti-PD-1 immunotherapy, blocking tumor growth and improving overall survival.

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2325P Selinexor (XPO1 inhibitor) in combination with tepotinib (MET inhibitor) potentially inhibits SHOC2 and KRAS G12C in KRAS G12C mutant non-small cell lung cancer

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Background: In KRAS-mutant NSCLC cells, SHOC2:MRAS:PP1C complex boosted RAS GTP loading and MAPK pathway reactivation after initial MEK suppression. Nuclear export protein exportin 1 (XPO1) is dependent on KRAS-mutant NSCLC cells, making XPO1 a druggable vulnerability. MET and SHOC2 are required for spheroid growth in KRAS-mutant NSCLC cell lines. Using structure-based drug design (SBDD), we looked at whether selinexor and tepotinib could bind into the 1) KRAS G12C His-95 groove like sotorasib (KRAS G12C inhibitor); 2) SHOC2 phosphatase complex in comparison with celestrol (SHOC2 inhibitor).

Methods: We carried out an in silico molecular docking approach with KRAS G12C and the SHOC2 complex against selinexor and tepotinib using SBDD to determine the binding affinity, intermolecular interactions, and ligand structure complementarity. Sotorasib-resistant H358 and parental H358 KRAS G12C NSCLC cells were examined. In vitro growth inhibitory assays determined cell viability after 3-day treatment. Western blot analyses were performed.

Results: The molecular docking results are summarized in the table. Selinexor and tepotinib interacted with all the three proteins of the complex, unlike celestrol interacting with SHOC2 and MRAS. Within the His-95 groove of KRAS G12C, selinexor forms an H bond and tepotinib forms a pi-sulphur and an H bond with the mutant cys12 residue. Selinexor in combination with tepotinib and omeprazole (v-ATPase inhibitor) has been analyzed. Signaling pathway analysis to demonstrate the SHOC2 and KRAS G12C inhibition is ongoing.

Conclusions: In silico modeling predicts that selinexor and tepotinib have more interactions and better binding affinity with the target proteins when compared to the standard inhibitors. In vitro data will be presented on the validation of selinexor and tepotinib for repositioning in KRAS G12C NSCLC.

Table: 2325P

Target proteins	Ligands	Binding affinity (Kcal/mol)	Number of hydrogen (H) bonds	Other interactions
SHOC2 complex	Tepotinib	-10.3	2	3
	Selinexor	-9.6	5	6
	Celestrol	-8.8	3	0
KRASG12C	Tepotinib	-9.1	2	1
	Selinexor	-9.4	6	6
	Sotorasib	-8.2	3	2

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2326P Circulating tumor DNA (ctDNA) dynamics and clinical outcome in metastatic colorectal cancer (mCRC) patients (pts) undergoing front-line chemotherapy

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Background: The potential of monitoring circulating tumor DNA (ctDNA) dynamics to guide clinical decisions in metastatic colorectal cancer (mCRC) patients (pts) treated with I and II line systemic anti-cancer therapy (SACT) has not been widely tested.

Methods: 862 serial plasmas were collected 4-weekly from baseline (BL) until disease progression in 75 mCRC pts undergoing SACT. ctDNA was tested using a custom (20 genes) or a commercial (77 genes) ctDNA next generation sequencing (NGS) panel. Whole exome sequencing (WES) was performed on tissue biopsies. ctDNA normalization was defined as $\geq$99% clearance after 1 month of therapy (Mo1) in the 3 variants with the highest allele frequency in BL ctDNA.

Results: 83 paired samples from 75 pts were available for analysis (for 8 pts, I and II line bloods were available). 12 pairs (14.4%) showed no variants in either BL or Mo1. In the remaining 71 comparisons (65 pts), 37 (52.1%) showed ctDNA normalization at Mo1. Among normalized pts there was a higher proportion of cases with a baseline ECOG performance status (PS) 0-1 (97.3% vs 82.4%, p= 0.0362) in comparison to non-normalized pts. Moreover, normalized pts had significantly longer overall survival (OS), 45.6 months (95% confidence interval [CI]: 30.0 - not reached) and progression-free survival (PFS), 13.9 months (95%CI: 11.2-18.3) compared to non-normalized pts [OS = 22.6 months (95%CI: 16.6-31.2, p= 0.01) and PFS = 10.7 months (95%CI: 7.53-13.8, p= 0.036) respectively]. In addition, pts with normalized ctDNA had higher overall response rate (ORR) of 72.9% (27/37 responses) compared to 38.2% (13/34 responses) in non-normalized pts. In a multivariate model, ctDNA normalization was confirmed as an independent predictor of decreased risk of death (hazard ratio [HR] 0.47, 95%CI: 0.23-0.96; p= 0.04) and higher probability of achieving an objective response from front-line treatment (odds ratio [OR] 3.03, 95%CI: 1.08-8.49; p= 0.0351). Only 23/50 (46%) of variants detected in ctDNA were detected by WES in paired tissues.

Conclusions: ctDNA monitoring represents an early indicator of benefit from systemic therapy in mCRC pts. A significant fraction of variants detected in ctDNA was not detected in paired tissues.

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2327P The impact of the microenvironment on the intratumoral cellular heterogeneity in colorectal cancer

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Background: Colorectal cancer (CRC) is a major public health issue, as it is amongst the most common forms of cancer incidence and mortality worldwide. Lately, intratutmoral cellular heterogeneity has been highlighted for survival and drug response evaluation. In 2015, the consensus molecular subtype system (CMS) surfaced as a potential diagnostic and prognostic tool for CRC. The CMS classification is based on gene expression profiles and recognizes four subtypes. Whereas CMS2/3 is characterized by high Wnt signaling, and Myc activity, CMS4 is defined by its TGF-β signaling, epithelial-mesenchymal transition (EMT), fibroblast accumulation, and overall worst prognosis. I examined the influence of the tumoral microenvironment on the intratumoral cellular heterogeneity of CRC.

Methods: Patient-derived organoids (PDO) model intratumoral heterogeneity of CRC effectively. PDOs were cultured from CRC surgical biopsy samples, and grown alone or with fibroblasts, in Matrigel or in collagen-enriched gel, with growth medium enriched or depleted from amino acids or glucose. The accumulation of collagen in the tumors is negatively correlated with patient survival. The expression levels of markers for CMS2/3 and CMS4 were evaluated with RT-qPCR, immunohistochemistry, and flow cytometry.

Results: We observed a higher rate of CRC cell positivity for CMS2/3 and CMS4 markers, along with their double positivity when co-cultured with fibroblasts. Similarly, the mixed phenotype positivity increased for CRC cells cultured in amino acid or glucose-free conditions compared to standard growth medium. In collagen, only the CMS4 marker positivity was higher compared to those in Matrigel. Furthermore, cocultured organoids demonstrated an increased positivity for the EMT markers.

Conclusions: Altering the microenvironment of CRC significantly modifies the intratumoral cellular heterogeneity, as collagen and fibroblast enrichment shifts the organoids to a CMS4 phenotype with partial EMT activity, both of which are suggestive of worse prognosis.

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Disclosure: All authors have declared no conflicts of interest.

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2328P Alternative molecular mechanisms underpinning breast invasive lobular carcinoma identified by genomics-driven artificial intelligence model

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Background: A subset of cancers display distinctive phenotypes and harbor pathognomonic genetic alterations. Breast invasive lobular carcinoma (ILC), the most common special histologic subtype of breast cancer (BC), has a distinctive discohesive phenotype, caused by bi-allelic inactivation of *CDH1* (E-cadherin), representing a strong genotypic-phenotypic correlation. Here, we sought to apply an artificial intelligence (AI)-based model trained to detect *CDH1* bi-allelic mutations (i.e. inactivating mutation and loss of heterozygosity (LOH)) using H&E-stained whole slides images (WSI) as input to identify ILCs with alternative mechanisms of *CDH1* inactivation.

Methods: We applied the AI-model trained to detect *CDH1* biallelic mutations using WSIs to a cohort of 1,057 BCs with available targeted sequencing data. To determine the molecular underpinning of cases predicted to harbor *CDH1* bi-allelic mutations but lacking these genetic alterations by targeted sequencing, we conducted the reanalysis of targeted sequencing data, *CDH1* gene promoter methylation assessment and/or whole genome sequencing (WGS) analysis.

Results: We identified 34 cases predicted by the AI-model to harbor a *CDH1* bi-allelic mutations that lacked these alterations by targeted sequencing. Reanalysis of targeted sequencing data and/or promoter methylation assessment revealed *CDH1* promoter methylation (n=20), *CDH1* homozygous deletions (n=3) and *CDH1* intragenic deletion associated with LOH (n=1) in these cases. In addition, WGS of an ILC revealed a translocation t(13;16) predicted to result in a novel deleterious fusion gene affecting *CDH1* with loss of exons 1-2 and the regulatory regions of this gene, associated with LOH. By applying a genomics-driven AI model we detected alternative mechanisms of *CDH1* inactivation in 25/34 (74%) cases.

Conclusions: In the context of genotypic-phenotypic correlations, AI-based methods trained on a genetic ground truth can result in the identification of alternative/convergent molecular mechanisms underpinning histologic entities. This study highlights the potential of combinatorial approaches integrating deep learning methods and genomics in pathology.

Legal entity responsible for the study: The authors.

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Disclosure: Y.K. Wang, J. Bernhard, J. Sue, M.C.H. Lee, R. Godrich, A. Casson, J.D. Kunz, B. Rothrock, G.J. Oakley, D. Klimstra, T. Fuchs: Financial Interests, Personal, Stocks/Shares: Paige; Financial Interests, Personal, Full or part-time Employment: Paige. B. Weigelt: Financial Interests, Personal, Research Funding: Repare Therapeutics. C. Kanan: Financial Interests, Personal, Stocks/Shares, Also Consultant: Paige. J.S. Reis-Filho: Financial Interests, Personal, Other, Consultant: Goldman Sachs, Eli Lilly, Saga Diagnostics; Financial Interests, Personal, Other, Member of the Scientific Advisory Board and Consultant: Repare Therapeutics, Paige.AI; Financial Interests, Personal, Advisory Board: Personalis, Roche Tissue Diagnostics; Financial Interests, Personal, Advisory Board, Member of the Scientific Advisory Board: Bain Capital; Financial Interests, Personal, Advisory Board, Ad hoc member of the Pathology Scientific Advisory Board: Daiichi Sankyo, Merck; Financial Interests, Personal, Advisory Board, Ad hoc member of the Oncology Scientific Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board, Member of the SAB: MultiplexDX; Financial Interests, Personal, Member of Board of Directors: Odyssey Bio, Grupo Oncoclinicas; Financial Interests, Personal, Stocks/Shares: Repare Therapeutics; Financial Interests, Personal, Other, Stock options: Paige.AI. All other authors have declared no conflicts of interest.

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2329P Evidence for the utility of artificial intelligence and image analysis in Ki-67 quantification in solid tumors

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Background: Although it is an important biomarker in oncology, Ki-67 immunohistochemistry analysis has yet to be standardized. Working groups have provided guidelines for Ki-67 scoring in different cancer types to limit pathologist's variability. Digital analysis solutions to assist scoring with image analysis or AI have recently emerged in the evaluation of Ki-67 as rapid and robust solutions. In this context, we compared the results of Ki-67 scoring performed with Aiforia® (AI platform) and Halo® (image analysis supervised software) against two independent pathologists on solid tumors.

Methods: We stained 192 tumors of various origins including breast and prostate with Ki-67 (clone 30-9). Pathologists were trained following the International Ki-67 Working Group recommendations and scored tissues accordingly. Based on deep learning, Aiforia was able to automatically score Ki-67 positive tumor cells within minutes. The random forest classifier from Halo software was used to separate the image into tumor, non-tumor and background. After cell segmentation, Ki-67 positivity was assessed by thresholding.

Results: Our study shows a very high consistency of results obtained for Ki-67 scoring between the image analysis softwares, Aiforia and Halo (r^2=0.94), on all solid tumors. The correlation obtained between the two pathologists was weaker (r^2=0.8), despite the training and guidelines, but remains within an acceptable range. Of the 18 types of primary tumors analyzed, only 2 (thyroid and stomach) showed correlations of less than 0.75 between the image analysis softwares with inter-pathologists' correlation still high (0.73 and 0.86). Depending on the organ, there were significant variations between pathologists, whereas the scores obtained with the image analysis softwares remain very close. For example, with prostate (n=8), a 0.81 correlation for Ki-67 scores between Aiforia and Halo was found while the inter-pathologists' correlation was 0.68.

Conclusions: This work shows that AI based image analysis tools such as Aiforia and image analysis supervised software provide valuable assistance in IHC based clinical analysis, drastically reducing inter-pathologist variability or as an arbitration tool in Ki-67 scoring of solid tumors.

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2330P Pre-test prediction of multiple druggable mutations based on H&E image artificial intelligence (AI) analysis may enable more efficient clinical workflow for treatment decisions in non-small cell lung cancer (NSCLC)

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Background: AI may predict driver mutations from H&E slides, and this prediction may be useful as a screening tool to guide the efficient use of molecular testing. Here, we investigate the prediction performance for mutations in six driver oncogenes and explore the benefits to clinical workflow in NSCLC treatment decisions.

Methods: NSCLC samples from Neogenomics (n=2,161) and TCGA (n=933) were used for model development. Four features were used: two convolutional neural networks trained for cell and tissue, a self-supervised vision transformer, and an AI-based pathology profiling analyzer for semantic contents. A set of classifiers was trained and ensembled for improved robustness. Performance of the model was validated in an independent dataset (n=792), then we simulated real-world impact based on the prevalence of driver mutations from AACR GENIE v13.1 NSCLC (n=19,722).

Results: Table 2330P shows the dataset and performance of the models. Given 2.8% prevalence of *MET* exon skipping mutations (*MET*-ex), 8.5% positive predictive value (PPV) means that a test-positive patient has a 3x higher chance of being true-*MET*-ex positive compared to the overall patient population. Moreover, given 99.2% specificity and 49.4% prevalence, PPV for selecting patients without mutations (All-WT) is 95.2%, enabling avoidance of unnecessary tests with potentially acceptable error (<5%).

Table: 2330P

	Internal set		External set			
	n (%)	AUC	n (%)	AUC	Sensitivity	Specificity
EGFR-mt	384 (12.4)	0.841	224 (28.3)	0.723	75.5%	52.6%
KRAS-mt	516 (16.7)	0.728	130 (16.4)	0.721	86.2%	22.5%
ALK-tr	310 (10.0)	0.795	46 (5.8)	0.738	39.1%	81.8%
ROS1-tr	295 (9.5)	0.793	62 (7.8)	0.609	14.5%	70.6%
RET-tr	307 (9.9)	0.763	11 (1.4)	0.683	18.2%	96.4%
MET-ex	240 (7.8)	0.789	12 (1.5)	0.849	83.3%	74.4%
All-WT	1045 (33.8)	N/A	277 (35.0)	N/A	15.9%	99.2%

AUC, area-under-the-curve; ex, exon skipping; mt, mutation; tr, translocation.

Conclusions: A novel clinical workflow, using AI analysis of H&E to predict genomic profiles and identify which patients would benefit from confirmatory molecular testing, could enable better and more efficient treatment decisions.

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2331P Interest of next generation sequencing (NGS) for integrated molecular diagnosis of HER2-low breast cancer

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Background: Based on HER2 expression using immunohistochemistry (IHC) and HER2 gene amplification using in situ hybridization (ISH), breast cancers (BC) are usually classified, into HER2 positive (IHC 3+ or IHC 2+/ISH+) and HER2 negative (IHC 0, IHC 1+ or IHC 2+/ISH-). Recently, HER2-low breast cancers (HER2-low BC) emerged as a new subtype defined as IHC1+ or IHC2+/ISH- tumors. HER2-low BC represent more than half of all BC. Consistently with the clinical activity of HER2 antibody-directed chemotherapy (ADC) in HER2-low BC, this subtype should be identified to enable early set-up of therapy. Since HER2-low BC identification could be equivocal using conventional IHC and ISH, we evaluated the performance of NGS for integrated diagnostic including HER2 copy number analysis.

Methods: BC tumor specimens were analyzed using IHC and ISH as performed routinely. NGS was performed using a custom capture based 51-gene panel, including BC molecular target genes such as ESR1, PIK3CA, AKT1, ERBB2, TP53, BRCA1 and BRCA2. Gene mutations as well as copy number variation (CNV) and Microsatellite Instability (MSI) were determined.

Results: Thirty-one FFPE BC tumor specimens were classified using IHC and ISH into 11 HER2-positive (IHC2+ ISH+ and IHC3+), 10 HER2-negative (IHC 0) and 10 HER2-low cancers (IHC1+ and IHC2+ ISH-). Using NGS, CNV values for ERBB2 gene were significantly ($p<0.001$) different between HER2 negative, HER2low and HER2- positive tumors with mean CNV values of 2.0 (SD=0.3), 1.9 (SD=0.3) and 7.8 (SD=6.8), respectively. Using 3.25 as cutoff value for CNV, 90% concordance of HER2 amplification status was achieved between ISH and NGS. Using NGS, additional drug-targetable gene mutations as well as amplifications were detected in 68% (21/31) and 19% (6/31) of the cases, respectively. One case of MSI was detected in a HER2-negative and ISH unamplified case.

Conclusions: These results show that in HER2 IHC positive (scores 1+ to 3+) BC, CNV determination using NGS allows the identification of HER2-low status simultaneously with the detection of multiple molecular target genes while sparing tissue samples. This workflow could support molecular board decision between HER2-ADC or other targeted therapies.

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2332P Overall survival in breast cancer patients with HER2-low status single- center experience

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Background: The HER2/neu (ERBB2) oncogene is amplified and/or overexpressed in approximately 15% of breast cancers (BC), and is a strong prognostic factor for relapse and poor overall survival (OS), particularly in node-positive patients. The aim of this study was to evaluate the prognostic significance of HER2-low status in BC. We also compared HER2-low subgroup with HER2-0 according to clinical, histopathological, laboratory and molecular factors.

Methods: The analysis included medical records of 657 BC patients treated in NIO in Gliwice in years 2002-2018. Human epidermal growth factor receptor 2 overexpression was assessed using an IHC method in postoperative specimens or samples obtained by thick needle biopsy. HER2 gene amplification was additionally assessed by FISH in HER2 (2+) cases.

Results: Median age of all women was 52 years (range from 24 to 81). 176 (27%) tumors were HER2-low BC, 248 (38%) HER2-0 and 233 (35%) HER2-positive tumors. There was no difference according to molecular factors such as *BRCA* gene mutation ($p=0.780$) or patient's age ($p=0.275$) between patients with HER2-low tumors and HER2-0. No differences were also detected between the both groups according to family history of cancer, co-morbid condition, menopausal status, tumor size, lymph nodes with metastases (N+) or higher histologic tumor grade (G3). BC patients with HER2-low tumors more often had positive estrogen receptor status (ER+) (80% vs. 60%, p=0. 0001). There was no reported differences according to OS between patients with HER2-low status and HER2-0 ($p=0.747$). In subgroup of patients with ER-negative receptor status (ER-) OS were insignificantly worse in patients with HER2-low status in comparison to HER2-0 (5-year OS 72.6% vs. 86.7%, $p=0.074$). There was also observed tendency to worse OS in patients with HER2-low status in subgroups with higher T3-4 (61.2% vs. 75.1%, $p=0.217$), G3 (80.7% vs. 89.2%, $p=0.139$) and N+ (81.3% vs. 86.9%, $p=0.599$).

Conclusions: There was no association between HER2 status (HER2-low vs. HER2-0) and *BRCA* gene mutation, tumor size, the presence of metastases in lymph nodes and G. HER2-low status worsens OS in subgroups of patients with negative prognostic factors in comparison to patients with HER2-0.

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2333P Associating BRCA1 hypermethylation with clinicopathological and molecular variables in triple-negative breast cancers

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Background: The aim of this study was to investigate the correlation of *BRCA1* promoter methylation status (*BRCA1*met) in patients with triple-negative breast cancer (TNBC) to clinicopathological and molecular variables, patient prognosis, patient response to neoadjuvant chemotherapy (NAC), and potential therapy resistance mechanisms in NAC treated patients.

Methods: 145 patients enrolled 2015-2018 in the Sweden Cancerome Analysis Network - Breast (SCAN-B) study (ClinicalTrials.gov ID NCT02306096) were included. 109 had chemotherapy (>90% with sequential epirubicin + cyclophosphamide and a taxane, EC—T) according to national guidelines either as NAC (32%) or adjuvant (68%) therapy. Pathogenic *BRCA1/2* variants were detected in 11 of 54 cases. Microsatellite instability and *BRCA1*met using pyrosequencing were investigated in all cases, including analyses of pre-treatment biopsies and surgical resections for NAC patients with residual disease (RD). The NAC patient cohort was extended with six additional SCAN-B patients to further explore treatment response in relation to *BRCA1*met. Clinicopathological and molecular variables were obtained through clinical review and complementary RNA-seq data.

Results: MSI and *BRCA1*met was observed in 2% and 17% of patients, respectively. *BRCA1*met was correlated to younger age and the PAM50 Basal phenotype (92%) and was frequent (40%) in women without pathogenic *BRCA1/2* germline variants. No

association was observed between *BRCA1*met and distant recurrence-free interval in adjuvant treated patients (log-rank p=0.77), nor between *BRCA1*met and pathological response in NAC patients (p=0.69). *BRCA1*met NAC cases revealed differences in methylation level and *BRCA1* mRNA expression in pre-treatment versus surgically resected tissue in patients with RD. No *BRCA1* gene fusions were detected. Genetic alterations between pre-treatment vs surgically resected tissue are further analyzed using whole genome sequencing.

Conclusions: *BRCA1*met is associated with young age in TNBC but hold no predictive nor prognostic value in this patient cohort. We observe a difference in *BRCA1*met patterns and *BRCA1* mRNA expression in NAC patients with RD that may potentially be related to treatment resistance.

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2334P Pathologic patterns following different neoadjuvant therapies in non-small cell lung cancer (NSCLC)

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Background: Neoadjuvant chemotherapy (CT), immunotherapy (IT) and combination CT/IT are associated with pathologic treatment response (PTR) in NSCLC. Comparison of pathologic patterns following CT, IT or CT/IT and upfront surgical resection is lacking. Recently, neoadjuvant nivolumab (N), N+ipilumumab (NI), N+CT and NI+CT have been investigated in the NEOSTAR trial (NCT03158129). We analyzed and compared the pathologic patterns of CT, IT and CT/IT-treated NSCLC and untreated resected NSCLC (total n=139).

Methods: Pathologic assessment of resected NSCLC from the NEOSTAR cohort (n=79), a CT-treated group (n=30) and an untreated group (n=30) was performed. H&E-stained tumor sections were scored for parameters commonly associated with PTR: percentages of viable tumor (VT), fibrosis and necrosis and rate of major pathologic response (MPR, ≤10% VT); inflammation (INF), foamy macrophages (FM), lymphovascular invasion (LVI), cholesterol clefts (CC), giant cells (GC), non-necrotizing granulomas (NNG), and neovascularization (NV) were scored from 0-3. Values for each variable were expressed as a median, except MPR (%). Cohorts were compared with Chi-squared or Kruskal-Wallis test and post-hoc pairwise comparisons were performed. Significance was defined as a two-sided p-value <0.05.

Results: NI and NI+CT were associated with significantly less VT (p=0.001, <.001) and more fibrosis (p=0.002, 0.008) than untreated tumors. MPR rates were highest in NI and NI+CT. Necrosis was higher in the CT cohort, INF in N and NI, FM in CT and NI+CT, CC in CT, and NNG in NI and N+CT.

Table 2334P Summary of scored parameters

	Untreated (n=30)	CT (n=30)	N (n=21)	NI (n=16)	N+CT (n=22)	NI+CT (n=20)	p-value
VT	65.8%	48.5%	50%	9%	50.5%	4.5%	<.001
Fibrosis	26.3%	26.1%	40.5%	84%	45%	61.4%	<.001
Necrosis	0.31%	1.71%	1.5%	0%	0%	0%	0.029
MPR	-	17%	24%	50%	32%	55%	0.028
INF	1.37	1.29	2	1.66	1	1.09	0.007
FM	0	0.4	0	0.16	0	0.89	0.015
LVI	0.06	0.23	0	0	0.02	0	0.109
CC	0	0.86	0.4	0	0.13	0.47	<.001
GC	0	0.47	0.2	0.49	0.21	0.28	0.080
NNG (min, max)	0 (0, 0.25)	0 (0, 0)	0 (0, 1.1)	0 (0, 2.66)	0 (0, 2.25)	0 (0, 1.57)	0.004
NV	0	0	0	0.57	0.22	0.18	0.166

Conclusions: Neoadjuvant NI and NI+CT regimens were associated with significantly less VT and more fibrosis than untreated tumors and achieved higher rates of MPR compared to CT. Collectively, neoadjuvant IT-based treatments produced higher amounts of INF, FM, and NNG, highlighting the potential impact of dual IT on pathological tumor regression and patterns of immune-mediated features.

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2335P Spatial whole exome sequencing reveals the genetic features of highly-aggressive components in lung adenocarcinoma

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Background: In invasive lung adenocarcinoma (LUAD), patients with micropapillary (MIP) or solid (SOL) components had a significantly poorer prognosis than those with only lepidic (LEP), acinar (ACI) or papillary (PAP) components. It is interesting to explore the genetic features of different histologic subtypes especially the highly aggressive components.

Methods: This study comprised four cohorts of patients who underwent complete surgical resection for lung adenocarcinoma (LUAD) and had their medical records reviewed. Cohort 1 depicted the distribution of different histological subtypes across tumor size groups. Logistic regression analysis in cohort 2 investigated the associations between driver mutations and histological subtypes. Cohort 3 utilized spatial whole-exome sequencing with laser-capture microdissection to identify genetic heterogeneity among histological components within the same tumor. Cohort 4, in conjunction with the cBioportal cohort, was employed to validate the findings obtained from cohort 3.

Results: Based on a cohort of 5,933 patients (cohort 1), this study observed varying prevalence of micropapillary (MIP) and solid (SOL) components in different tumor size groups. Furthermore, cohort 2 revealed that patients with ALK fusion or TP53 mutations had a higher probability of developing MIP/SOL components in cohort 2. To account for individual differences, tspatial whole-exome sequencing was performed using laser-capture microdissection on five patients with coexistent components, enabling the identification of genetic features within the same tumor. In tracing the evolution of components, we found that titin mutation might serve as a crucial intratumor potential driver for MIP/SOL components, which was validated by the cohort 4 of 146 LUAD patients undergoing bulk WES. Functional analysis demonstrated that TTN mutations were enriched the complement and coagulation cascades, which correlated with the pathway of cell adhesion, migration, and proliferation.

Conclusions: Collectively, the histologic subtypes of invasive LUAD were genetically different, and certain trunk genotypes might synergize with branching TTN mutation to develop highly aggressive components.

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2336P MiR-155 overexpression regulates epithelial-mesenchymal transition through repressing Quaking in lung cancer cells

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Background: Epithelial-mesenchymal transition (EMT) is one of the major molecular mechanisms inducing tumor invasion and metastasis. Various MicroRNAs (miRNAs) have been shown to be involved in EMT. MiR-155 is consistently up-regulated in non-small cell lung cancer and is associated with poor overall survival. Whether miR-155 regulates EMT in lung cancer cells remains unclear.

Methods: We first transfected plasmid containing miR-155 into H1299 and A549 cells and established H1299-miR-155 and A549-miR-155 cells. Western blotting was done to demonstrate E-cadherin, vimentin, and Quaking (QKI) expression in H1299-miR-155 and A549-miR-155 cells. Invasion and migration assay were performed in H1299-miR-155 and A549-miR-155 cells. We then constructed p-mcherry plasmids that contain miR-155 and a p-Luc-QKI-3'UTR reporter plasmid. Luciferase assay was done to demonstrate whether miR-155 binds to the QKI 3'UTR.

Results: Quantitative RT-PCR showed that QKI expression was downregulated in H1299-miR-155 and A549-miR-155 cells. Western Blotting showed decreased E-cadherin and increased vimentin expression in H1299 and A549 cells after miR-155 transfection. Western blotting also showed decreased QKI expression in H1299 and

A549 cells after miR-155 transfection. Migration assay showed that the number of migrated cells significantly increased after miR-155 transfection in H1299 and A549 cells. Invasion assay showed that the number of invaded cells also significantly increased after miR-155 transfection in H1299 and A549 cells. We constructed p-mcherry plasmids that contain miR-155 and a p-Luc-QKI-3'UTR reporter plasmid. Luciferase assay showed that miR-155 represses the activity of p-Luc-QKI-3'UTR. We then mutated the miR-155 binding site in the QKI 3'UTR to confirm that repression of the mRNA levels is induced by the binding of miR-155 to the QKI 3'UTR.

Conclusions: MiR-155 overexpression regulates EMT through repressing QKI in lung cancer cells. Repression of QKI is induced by the binding of miR-155 to the QKI 3'UTR.

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2337P Feasibility of mutation detection in cytological samples from metastasis in patients with metastatic prostate cancer

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Background: Mutations in homologous recombination repair (HRR) genes are actionable targets for poly (ADP-ribose) polymerase inhibitors in cancer. Extraction of DNA from archival paraffin-embedded tissue is challenging. In addition, somatic mutations in HRR genes are more frequent in metastases than in primary tumours. Fine needle aspiration (FNA) of metastases is an alternative method to surgical, core needle and circulating tumour DNA-based liquid biopsy and may provide sufficient DNA for genomic analysis.

Methods: We performed a retrospective analysis on our clinical, cytological and next-generation sequencing (NGS) data based on ultrasound-guided FNA samples of metastases in prostate cancer patients. The aims were to evaluate the success rate of FNA for NGS, identify possible obstacles and optimise it.

Results: From Jan. 2021 to Dec. 2022, 27 FNAs of metastases from 21 patients with metastatic castrate-resistant prostate cancer have been undertaken at the Institute of Oncology Ljubljana. The samples were retrieved from lymph node, liver and bone metastases in 59% (16/27), 30% (8/27) and 11% (3/27) patients, respectively. Six out of 27 (22%) samples were unsuccessful according to cytologists. Of undiagnostic samples, 4/6 were obtained from liver and 2/6 from lymph nodes. A high percentage of liver samples, 75% (3/4), contained less than 10% of tumour cells. All samples from bones (3/3) and 56% (9/16) from lymph nodes had more than 50% of tumour cells. Median percentage of tumour cells per sample was 80% (range 5-100). Altogether, 21/27 (78%) samples were adequate for DNA extraction and successful NGS. *BRCA 2* pathogenic mutation were detected in two patients (2/21); of these two, one had an adjacent mutation in *CDK12* and the other in *FANCL* together with a high tumor mutational burden. In three patients (3/21) *ATM* pathogenic mutations were found, one being adjacent to mutation in *CHECK1* and the other in *BARD1*.

Conclusions: Ultrasound-guided FNA of metastases is a feasible method to obtain good quality DNA for NGS in patients with metastatic prostate cancer when searching for potential molecular targets. Close collaboration between dedicated radiologists and cytopathologists could further improve the success rate of this method.

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2338P The phenotype of tumor-associated macrophages in human high-grade serous ovarian carcinoma

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Background: Ovarian cancer (OC) is one of the most common gynecological cancers, with the worst prognosis and the highest mortality rate. According to the FIGO, the overall five-year survival rate is approximately 50%. Tumor-associated macrophages (TAMs) are one of the most prominent populations of immune cells in both ovarian cancer tissue and malignant ascites. The most relevant task is to identify TAM subpopulations in ovarian cancer, to discover how they interact with chemotherapy and affect the development and outcome of the disease.

Methods: Patients with high-grade serous ovarian carcinoma were included in the study. FFPE samples with tumor were obtained after surgery. The study was carried out according to medical ethics. We applied two technologies of spatial transcriptomics for the analysis of TAM transcriptomic features in patients with ovarian cancer — 10x Genomics Visium and Nanostring GeoMX-DSP. All procedures were performed according to manufacturer`s protocols.

Results: The results of 10x Visium demonstrated that TAM cluster express CCL18, APOC1, GPNMB, LYZ, APOE, C1QC, C1QB, CTCB, SPP1, CTSS, and other genes. Interestingly, according to accumulating data the expression of these macrophage markers is distinctive feature for the potentially targeted population of lipid-associated TAMs. The morphology of macrophages in TAM cluster in clinical samples corresponds to the large lipid-associated TAMs. Nanostring technology allowed us to analyse ROIs with immune cells located in different tumor sites. The transcriptome of TAMs located near the tumor nest correlated to functional activation of extracellular matrix organization, antigen presentation, vascular development and myeloid leukocyte activation. These TAMs have the same morphology of large foamy macrophages and express APOE, SPP1, LYZ, CTSS, and other genes.

Conclusions: We found gene signature specific for the large TAMs in tumor tissue of patients with high-grade serous ovarian carcinoma.

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2339P Clinical and genomic correlates of plasma circulating tumor DNA (ctDNA) tumor fraction (TF) in patients with advanced NSCLC

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Background: Circulating tumor DNA (ctDNA) tumor fraction (TF) is a promising biomarker for cancer diagnosis, follow-up and prognosis. TF depends on tumor burden (TB) but the correlation is moderate and other biological characteristics may play a role. In this study, we investigate the underlying genomic features affecting the relationship between TF and TB, assessed by PET scan.

Methods: Patients with NSCLC from the prospective STING trial (NCT04932525) who had both profiling with FoundationOne®LiquidCDx (F1LCDx™) and a PET scan performed within 42 days from either baseline (BL) or at treatment progression (PD) were included in this study. Foundation Medicine's ctDNA TF on F1LCDx is a composite algorithm prioritizing aneuploidy at higher levels to avoid germline signal and prioritizing variant allele frequency of canonical alterations at lower levels to maximize dynamic range. Tumor burden was calculated with PET scan-derived total metabolic tumor volume (tMTV) with a semi-automated analysis based on a 42% fixed-relative threshold of standardized uptake value (SUV) SUVmax. Genes altered in at least 2.5% of the cohort were evaluated by a multivariate linear regression using gene mutations and rearrangements as covariates and the logarithm of the TF/tMTV ratio as the dependent variable.

Results: Of 242 liquid biopsies, 38 lacked clinically relevant variants; tissue molecular characterization was used for 17 of these patients. Overall, tMTV was correlated with TF (rho 0.402, $p < 0.0001$). No difference was seen between BL or PD ($p = 0.997$). In the multivariate model, alterations associated with higher TF/tMTV ratio were *MLL2* (ß coefficient = 1.45, $p = 0.03$), *PTEN* (ß = 1.28, $p = 0.045$), *RBM10* (ß = 1.06, $p = 0.046$), *RB1* (ß = 0.91, $p = 0.028$), and *TP53* (ß = 0.87, $p = 0.004$). *ALK* rearrangements (ß = -1.04, $p = 0.049$) and *ATM* alterations (ß = -1.46, $p = 0.002$) were associated with lower shedding. Higher tMTV was seen in patients with *STK11* mutation (117 vs 56 cm^3, $p = 0.001$).

Conclusions: Alterations in genes implicated in cell cycle regulation, proliferation and apoptosis are associated with the ratio of TF to tMTV assessed by PET scan. ctDNA TF may therefore provide additional clinical utility beyond tumor burden surrogacy to design precise treatment strategy.

Clinical trial identification: NCT04932525.

Legal entity responsible for the study: The authors.

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2340P T-cell immunoglobulin and mucin-domain containing molecule-3 (Tim3) in breast cancer and the impact on penetration of blood brain barrier by cancer cells

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Background: Tim3 (T-cell immunoglobulin and mucin-domain containing molecule3) plays an important role in metastatic spread of cancers. The blood brain barrier (BBB) is an essential barrier that breast cancer cells have to overcome to metastasize to the CNS. This study investigated the association/functionality of Tim3 in breast cancer cells and in the invasiveness of cerebral endothelial cells by cancer cells.

Methods: Human cerebral microvessel endothelial cells (hCMEC/D3) were used to model BBB in vitro. Tim3 knockdown was by anti-Tim3 siRNA in MCF-7 and MDA-MB-231 cell lines. Electric cell impedance sensing (ECIS) was used for assessing cellular attachment and migration. Transepithelial resistance (TEER) and paracellular permeability (PCP) were used to test the barrier functions of the cells. Cellular response to docetaxel was evaluated and shown as IC50.The effects of Tim3 knockdown on penetration through the hCMEC/D3 monolayer were also assessed.

Results: Tim3 knockdown (Tim3kd) cell models were successfully established with MCF-7 and MDA-MB-231 cells. Loss of Tim3 in these cells resulted in a decrease in both cell adhesiveness and migration. The knockdown also led to a reduced transepithelial resistance as shown by TEER assay and an increase in paracellular permeability when compared with wild type (WT) cells. It was noted that loss of Tim3 rendered both MCF-7 and MDA-MB-231 cells resistant to docetaxel (IC50 for WT and Tim3kd respectively being 0.86nM vs 2.2nM for MCF7 and 1.35nM vs 11.8nM for MDA-MB-231). In the cerebral endothelial cell invasion assay, we found that Tim3 knockdown in both MCF-7 and MDA-MB-231 resulted in a significantly reduced invasion of the breast cancer cells through the endothelium (31±8 vs 24±8 for MCF7, $p=0.018$; 211±48 vs 142±54 for MDA-MB-231, $p<0.001$, WT and Tim3kd respectively).

Conclusions: Tim3 has a marked influence on the barrier functions, adhesiveness and the sensitivity to docetaxel of breast cancer cells. Loss of Tim3 in breast cancer cells reduces tumour cell's penetration of cerebral endothelium. Collectively, Tim3 plays a key role in the maintenance of barrier functions in breast cancer and their potential breach of the blood brain barrier.

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2341P Novel therapeutic opportunities in metaplastic breast cancer

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Background: Metaplastic breast cancer (MBC) is a rare and aggressive form of triple-negative breast cancer with limited therapeutic options. Despite being reported to display genomic features of homologous recombination (HR) deficiency (HRD) by whole-exome sequencing, MBCs rarely respond to neoadjuvant chemotherapy/immunotherapy. We sought to assess their HR and immune features using whole-genome sequencing (WGS) of MBCs and evaluated the efficacy of antibody-drug conjugates (ADCs) and DNA damage response (DDR)-targeting agents in preclinical MBC models.

Methods: MBCs were subjected to WGS (n=25) and RNAseq (n=31). HRD was assessed using HRDetect ('gold standard') and mutational signatures using Signal. ADC target expression was assessed transcriptomically. Efficacy of ADCs and DDR agents was assessed *in vitro* using MBC cell models (BT549, Hs578T and HCC1806). T-DXd efficacy was evaluated *in vivo* in HCC1806 xenografts in athymic mice.

Results: Despite most (13/25) MBCs displaying partial features of HRD (mutational signature 3), only 3/25 MBCs had a complete HRD pattern with tandem duplications, deletions with microhomology, dominant SBS/indel/rearrangement HRD mutational signatures and were classified by HRDetect as HRD. These 3 MBCs harbored somatic/germline pathogenic *BRCA1* mutations (n=2) or a *RAD51C* intragenic inversion with LOH (n=1). Exposure to APOBEC mutational signature was detected in 15/25 (60%) MBCs, including the HRD cases. HLA homozygosity/LOH was more frequent in non-chondroid (7/15) than in chondroid (1/10) MBCs. *TROP2* and *ERBB2* expression was detected in MBCs by RNAseq, and MBC cell models were found to be sensitive to T-DXd, Sacituzumab govitecan, and ATR and Wee1 inhibitors *in vitro*, and to T-DXd *in vivo*. Combination of T-DXd and DDR agents in MBC models was found to be synergistic.

Conclusions: Most MBCs display an incomplete HRD phenotype and those with complete HRD harbor bi-allelic inactivation of HR-related genes. MBCs express targets for novel ADCs, and preclinical MBC models are sensitive to anti-HER2 and anti-TROP2 ADCs alone or in combination with novel DDR agents, targeting their incomplete HRD phenotype, other than PARP-inhibitors. These findings provide preclinical evidence for assessing the clinical efficacy of these therapeutic approaches.

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2342P Single tumor cells are a novel prognostic criterion in breast cancer patients

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Background: Single tumor cells (STCs) are a manifestation of intratumor morphological heterogeneity and most likely arise from multicellular tumor structures as a result of cancer invasion. In recent years, the appearance of STCs has been described as tumor budding in the invasive front. However, there are no clear data on the clinical significance of these cells in breast cancer patients.

Methods: The study included 230 patients diagnosed with invasive breast carcinoma of the nonspecific type, luminal molecular subtypes. H&E staining was used to detect STCs in breast tissue. STCs (or detached individual tumor cells) were detected in the entire tumor tissue in contrast to tumor buds located in the invasive front, and were defined as tumor cells located outside multicellular tumor structures but similar to them in cytological features. 7-color immunofluorescence analysis was used to study the population composition of the microenvironment (ME) of STCs. Laser microdissection of STCs ME and sequencing on NextSeq500 (Illumina, USA) was performed.

Results: Patients who had a STCs had a 5.8-fold increased risk (CI95% 2.4-14.1) of developing distant metastases compared to patients who did not have a STCs (p=0.0001). Patients who had no STCs had a better metastatic-free survival (91.8%) than patients who had a STCs (49.1) (p<0.0001). The relative risk of distant metastases in breast cancer patients where only Th2-like immune reaction is found in the ME is 2.37 (CI95% 1.25-4.42) times higher than in patients where only Th1-like immune reaction (p=0.0352). In addition, a Top 10 analysis of up- and downregulated genes in the STCs ME in breast cancer patients depending on the status of distant metastasis was performed. Decrease of CD52 (7-fold), NUDT3 (6-fold), TAP1 (6-fold) (p<0.001) genes expression and increase of LAMA5 (4-fold), LPCAT1 (5-fold), FLVCR1 (5-fold) (p<0.001) genes expression were detected in the STCs ME of breast cancer patients with distant metastases compared to those without.

Conclusions: A novel simple prognostic criterion for predicting breast cancer metastasis has been developed. The microenvironment has been shown to play an important role in the metastatic potential of a single tumour cells. Immunosignatures of the pro-tumour microenvironment have been identified.

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2343P Evolution of circulating tumour DNA analysis in France over 5 years

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Background: The detection of oncogenic mutations in cell-free DNA (cfDNA) may identify therapeutic targets in many cancers, but it requires maximum sensitivity and specificity to avoid any loss of chance. Since 2017, the national Gen&Tiss external quality assessment (EQA) program has been assessing the performance of French laboratories for the detection of *EGFR* mutations in lung cancer patients by providing each year 5 reconstituted plasma samples of known composition. Since 2019, the EQA also provides an evaluation for the genes of interest in colorectal cancer and melanoma, with 5 additional samples for *KRAS* and *NRAS* mutations, and 5 others for *BRAF* mutations.

Methods: The performance of the methods used in France was assessed based on the results of Gen&tiss EQA campaigns conducted from 2017 to 2021.

Results: A total of 1303 EQA samples were analysed over 5 years, including 720, 142, 71 and 103 *EGFR*, *KRAS*, *NRAS* and *BRAF*-mutated samples respectively and 267 WT samples. An average of 39 laboratories were evaluated each year, with no significant change over the period. cfDNA extraction protocols varied widely between laboratories, with a trend towards a diversification of methods: 5 different protocols were used in 2017 compared to 11 in 2021. Analytical methods have also changed over the period: the use of quantitative PCR (qPCR), which predominated in 2017, has decreased over the period (from 43% to 29% of laboratories) to the benefit of NGS (from 39% to 59%). The use of digital PCR (dPCR) has remained stable (from 15% to 12%). The true positive (TP) rate averaged 84% over the period, with no significant change from one campaign to the next one (Wilcoxon signed ranks test: p = 0.776). The TP rate was significantly associated with the extraction kit (Fisher: p = 0.0002) and the analytical method (p = 0.0003) but was independent of the mutated gene (p = 0.075). qPCR was the most sensitive (TP rate = 92%), ahead of NGS (83%) and dPCR (77%). The true negative (TN) rate averaged 99% with no significant change over the period (p = 0.763). The TN rate was independent of extraction kit (p = 0.273), analytical method (p = 0.677) and mutated gene (p = 0.455).

Conclusions: Despite better analytical performance, the use of qPCR for cfDNA analysis is tending to decrease in France in favour of NGS, as the number of target mutations increases.

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2345P The possibility of programmed death-ligand 1-related immune modulation in neoadjuvant thermoradiotherapy for rectal cancer

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Background: The expression of programmed death ligand 1 (PDL1) and CD8-positive T lymphocytes (CD8T) in tumor tissue is known to be influenced by radiotherapy (RT). This type of immune modulation is likely enhanced by hyperthermia (HT), which has been studied preclinically. We describe the immunogenic effects of additive HT in neoadjuvant treatment for rectal cancer.

Methods: Clinical data were reviewed for consecutive 32 patients who received neoadjuvant treatment and did not achieve total regression considering paired tumor tissue analysis from 2012 to 2017. On obtained pre- and post-treatment tumor tissue for each patient, further immunohistochemistry was done to examine the expression of PDL1 and CD8T. The majority of the patients were male (78.1%) and the median age was 57 years. Sixteen patients (50.0%) received HT twice weekly with 40 Gy RT (RHT group) and the others (50.0%) underwent standard 50.4 Gy RT (RT group). Age, initial clinical stage, and pathologic differentiation did not differ between the two groups. The median follow-up period was 68 months (range, 14−107 months).

Results: Both groups showed no significant difference in T- and N-downstaging ratio. Near total regression was experienced by 4 (25.0%) and 7 (43.8%) patients in the RHT and RT groups, respectively. The increase in PDL1 positivity was 0.95±2.17% (p=0.076) in the RHT group and 0.52±0.95% (p=0.257) in the RT group, while CD8T positivity increase was remarkable in both groups (RHT group: 27.97±18.26% (p<0.001); RT group: 22.50±13.14% (p<0.001)). The RHT group showed a relatively high propensity for both overall survival (median 72.0 versus 63.2 months, p=0.130) and local recurrence-free survival (median 69.1 versus 59.7 months, p=0.136). In multivariate analysis, higher level of post-treatment PDL1 positivity (>0.57%) and its increment (>0.35%) had a greater impact on disease-free survival (p=0.027 and p=0.008) and distant metastasis-free survival (p=0.063 and p=0.020).

Conclusions: Post-treatment PDL1 positivity status may have an effect on the prognosis. Even with relatively poor tumor regression, HT-combined low-dose RT did not impair survival, indicating that HT might be involved in the PDL1-related immune mechanism.

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2346P Spatial and quantified molecular characterization of high endothelial venule predictive of immunotherapy response

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Background: High endothelial venules (HEVs) are important structures that mediate lymphocyte entry into tumors. However, it remains difficult to identify HEVs in tumor at the transcriptome level. Therefore, defining a molecular signature of HEVs is of great significance for characterizing HEVs in tumor, and identifying potential patients who could benefit from immunotherapy.

Methods: We collected scRNA-seq data of tumor tissues of 11 tumor types, and integrated 19923 endothelial cells. Genes that were specifically highly expressed in post-capillary venule subpopulation and most related to the function of HEVs were identified as the HEV signature. Bulk-seq data of tumor blood vessel and spatial transcriptome sequencing data of tumor tissue were used to verify the specificity of the signature to identify HEVs. Immunohistochemistry and multiplex immunofluorescence were used to characterize the tumor HEVs and immune microenvironment. Cohorts of tumor patients who received immunotherapy were used to explore the relationship between the HEV signature and patients' response to immunotherapy.

Results: Seven genes including *ACKR1*, *SELE*, *SELP*, *IL33*, *MEOX1*, *HAPLN3*, and *CPXM2* were screened out as the HEV signature. HEV and non-HEV endothelial cells can be well distinguished according to the expression level of HEV signature. Spatially, regions with higher expression of HEV signature were associated with the aggregates of lymphocytes. *MEOX1* was chosen as a representative of these genes. Using immunohistochemistry of MEOX1 and multiplex immunofluorescence of the tumor microenvironment, we confirmed its co-localization with MECA79 antigen and found that lymphocyte-rich niches formed around $MEOX^+$ blood vessels. In addition, higher expression of HEV signature was associated with better response to immunotherapy and longer survival in cohorts obtained from other studies as well as our in-house cohort from Nanfang Hospital.

Conclusions: A 7-gene HEV signature we identified, especially *MEOX1*, can be used as a new molecular marker to identify HEV in tumors, and its expression can be used to

locate and quantify HEV in tumors, and help identify potential patients who could benefit from immunotherapy.

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2347P Correlation between second primary cancers and first primary cancers: A systematic review and meta-analysis of 9 million cancer patients

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Background: Many survivors of first primary cancers (FPCs) are at risk of developing a second primary cancer (SPC), the development of which usually leads to a worse prognosis. The development of SPCs may be closely related to the FPC. Different primary cancers have differentially high frequencies of specific SPC development. Our aim was to explore the possible correlation between the SPCs and FPCs.

Methods: We retrospectively searched and screened relevant literature on SPCs from four databases, namely, PubMed, EMBASE, Web of Science, and PMC. We also collected data on 28 different organ sites and the number of patients with SPC from The Surveillance, Epidemiology, and End Results (SEER) 8 Registry Database and NHANES database.

Results: A total of 9,617,643 patients with a FPC and 677,430 patients with a SPC were included in this meta-analysis. Patients with first primary gynaecological cancer and thyroid cancer developed second primary breast cancer and colorectal cancer more frequently. Patients with first primary head and neck cancer, anal cancer and esophageal cancer developed second primary lung cancer more frequently. Patients with first primary bladder cancer and penile cancer developed second primary lung cancer and prostate cancer more frequently. Patients with second primary bladder cancer accounted for 56% of first primary ureteral cancer patients with SPCs.

Conclusions: We recommend close clinical follow-up, monitoring and appropriate interventions in patients with relevant FPCs for better screening and early diagnosis of SPCs to prolong patient survival.

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2348P High-throughput screening reveals GSK1838705A as a potent inhibitor of CAFs-promoted tumor progression in esophageal squamous cell carcinoma

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Background: Esophageal squamous cell carcinoma is a malignance with high invasiveness. Cancer-associated fibroblasts (CAFs) as one major component of tumor microenvironment (TME), promotes tumor initiation and progression. Our previous studies revealed that CAFs mediated ESCC cells significant resistance to a variety of chemotherapeutic drugs and ionizing irradiation. How to inhibit the tumor-promoting activity of CAFs is of critically important for the radical treatment of ESCC.

Methods: Using high-throughput screening, 157 inhibitors of cytokines/chemokines were tested for their effect on the cell viability of CAFs, matched normal fibroblasts (NFs), ESCC cells as well as normal esophageal epithelial cell Het-1A. We also investigated the effect of the inhibitors on cell cycle distribution, ROS accumulation and cell apoptosis of CAFs. The expressions of α-SMA, a marker of CAFs activation, was detected in CAFs treated with the inhibitors. By establishment of xenograft tumors in BALB/c mice, the effect of the inhibitors on CAFs-promoted ESCC growth was studied.

Results: By high-throughput screening, GSK1838705A, an inhibitor of IGF-1R kinase, was discovered as a potent inhibitor of CAFs activity in ESCC. Compared with NFs, ESCC cells as well as Het-1A, the viability of CAFs was significantly reduced when exposure to GSK1838705A. Furthermore, GSK1838705A arrested the cell cycle of CAFs in G2/M phase, promoted cell apoptosis and ROS accumulation. The expression of α-SMA was signifcantly reduced when CAFs were treated with GSK1838705A. In vivo studies demonstrated that GSK1838705A significantly repressed the tumor-promoting activity of CAFs. Immunohistochemical analysis showed that GSK1838705A significantly reduced the percentage of CAFs in xenograft tumor tissues.

Conclusions: GSK1838705A is a potent inhibitor of CAFs which promote ESCC progression. The combination of GSK1838705A and chemoradiotherapy may be a promising strategy against ESCC.

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2349P Patterns and frequency of pathogenic germline variants (PGVs) among non-western young male patients with cancer: The Jordanian exploratory cancer genetics (Jo-ECAG) study

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Background: Hereditary cancers have been less well-studied in men, particularly younger ones. The incidence of certain cancers associated with pathogenic germline variants (PGVs), such as breast and prostate, is low among men under the age of 50, while the incidence of other cancers, such as colorectal, is increasing. This study describes patterns and frequency of PGVs in a cohort of young men diagnosed with cancer.

Methods: Male patients aged 50 years or younger, with newly diagnosed solid tumors were included in this prospective study. Patients were classified as in-criteria (IC) or out-of-criteria (OOC) based on the National Comprehensive Cancer Network (NCCN) v.1.2020 guidelines. All patients underwent an 84-gene panel test at a reference lab. Patients with one PGV in a gene associated with autosomal recessive inheritance (carriers), were excluded from analysis.

Results: A total of 397 male patients, mean (range) age at diagnosis 41 (18-50) years, were tested; 48 (12.1%) were 30 years or younger. Family history of any cancer was reported by 315 (79.3%). The most common primary tumor diagnoses were colorectal (n=157, 39.5%), testicular (n=38, 9.6%), pancreatic (n=26, 6.5%), lung (n=26, 6.5%), and sarcoma (n=22, 5.5%). In total, 246 (62.0%) were IC while the other 151 (38.0%) were OOC. PGVs were identified in 48 (19.5%) and 18 (11.9%) patients in IC and OOC groups, respectively, $p<0.001$. PGV rates were highest among patients with colorectal (23.6%) and pancreatic cancers (15.4%). PGV rates were significantly higher among patients <30 years (22.9%) compared to patients aged 41-50 years (13.4%), p=0.048. The majority of PGVs were actionable (therapeutic targets, clinical trials, and/or clinical management guidelines), with the most frequently affected genes were *APC* (n=11), *MLH1* (n=11), *BRCA2* (n=6), *TP53* (n=5) and *MSH2* (n=4).

Conclusions: A significant number of males were diagnosed with cancer at young ages, especially colorectal or pancreatic cancer, with strikingly high PGV rates. Comprehensive genetic testing and counseling for this group of patients is critical to inform treatment options, risks of future cancers, and cascade testing.

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2350P Single-cell RNA-seq dissecting the initiating liver metastasis cells in various cancers

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Background: Liver metastasis (LM) frequently occurs in patients with various cancers; yet our understanding of the underlying salient biology is preliminary. So far, no studies have found the initiating liver metastasis cells and specific liver metastatic microenvironment in various cancers. Here, we performed single-cell RNA-seq in eight patients with LM of various cancers to solve this scientific blind spot.

Methods: Single cell RNA sequencing was performed on tissues from LM of various cancers (gastric cancer(n=2); esophageal cancer(n=1); breast cancer(n=1); lung cancer(n=3); colorectal cancer(n=1)). Also, we downloaded the single-cell RNA-seq of hepatocellular carcinoma (HCC) and corresponding five types of cancer from GEO database. Seurat were applied to sort single-cell RNA-seq of LM in various cancers and corresponding five types of primary cancer into different clusters via feature dimension reduction. Furthermore, flow cytometry was used to sort those initiating liver metastasis cells, and then those cells was verified by cell metastasis function experiment and caudal vein injection of mice.

Results: The transcriptomes of 90035, 78933, 105340 single cells among LM in various cancers, HCC, and corresponding primary cancers were extracted respectively. There were 14 clusters divided into epithelial cells of liver metastasis single cells. Differential gene analyses and ratio analyses in LM and corresponding primary cancers groups showed that C10 and C12 might be the LM initiating cells clusters. And they were both enriched in the positive regulation of cell migration. $SOX6^+$ $CD52^+$ epithelial cells might be the LM initiating cells in various cancers, of which promoted cancer stem cells migration. Cohorts in TCGA database also showed a worse prognosis for patients with $SOX6^+$ $CD52^+$ markers. The sorting $SOX6^+$ $CD52^+$ epithelial cells will be further verified in metastasis function experiment and caudal vein injection of mice in vitro and in vivo.

Conclusions: The initiating liver metastasis cells in various cancers has been found and verified in this study, which provided a further understanding of the potential biological mechanisms of LM in various cancers and potential target for the novel drugs.

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2351P Whole genome sequencing of AYA patients

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Background: Cancer in adolescents and young adults (AYAs, aged 18-39 years at first cancer diagnosis) is nowadays considered as a separate entity with specific care needs. However, once the diagnosis has been established, AYA patients are mostly treated as having cancer at an older age. Breakthroughs in treatment options are scarce and AYA patients are underrepresented in clinical trials. To improve healthcare outcomes, there is a large unmet need for obtaining more knowledge and better (genomic) understanding of cancers at AYA age.

Methods: As an independent not-for-profit cancer diagnostics organization and data provider, Hartwig Medical Foundation performs clinical-grade whole genome sequencing (WGS) for cancer patients using a single small fresh-frozen biopsy and a matching blood sample. In addition to comprehensive diagnostic reporting of oncology-related genomics aberrations (including mutations, copy-number alterations, fusions and mutational signatures like MSI, TMB, HRD) all WGS data is (following patient consent) stored in the Hartwig Database. This data (>5500 patients) is available to the academic community to facilitate research and improve future cancer patient care.

Results: The Hartwig Database currently includes WGS and associated clinical data for 192 metastatic AYA cancer patients. Although a fair number in total, the numbers per tumor indication are quite small with n > 30 for only three indications (breast n=49, bone/soft tissue n=33 and GI-tract n=34). Also, the distribution does not follow the AYA cancer type prevalence as registered in the Dutch national cancer registry, with e.g. GI-tract (18% vs 9%) and bone/soft tissue (17% vs 2%) overrepresented and male/female reproductive organs underrepresented (8 vs 18%). Preliminary analysis of the frequency of driver alterations of some of the well-known oncogenes (e.g. PIK3CA, BRAF, KRAS, ERBB2) do not reveal differences between AYA and non-AYA cancers although the low number of AYA samples hamper conclusiveness.

Conclusions: To better facilitate research for AYA patients and to offer all possible treatment options (e.g. clinical trials), more patients will need to be analyzed by WGS. For this purpose, a dedicated project has been initiated that includes tumor-normal WGS of 1000 AYA patients in the next 3 years.

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2352P Sex-based differences in genomic alterations and biomarkers in anal squamous cell carcinoma (ASCC)

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Background: ASCC is a relatively rare malignancy. Several studies reported favourable prognosis in **F**emale to **M**ale patients (pts).Our work aims to identify and quantify sex-based differences in cancer-associated genomic alterations to better inform future precision medicine initiatives and provide insights on potential different survival based on sex.

Methods: A cohort of 1,380 ASCC pts (952 **F**,428 **M**) underwent genomic profiling on tissue biopsies using FoundationOne®/FoundationOne®CDx assays, to examine key differences in mutational patterns based on sex and HPV status.

Results: HPV-16 was prevalent in **F** while HPV-6 in **M**. PD-L1 expression: over 70% positive (1%), ∼20% high (50%) with similar rates in HPV+ vs HPV- (74.5% vs 63.9%; p=0.16) and sex (**F**:74% vs **M**:70.4%; p=0.80). TMB-High (10+mutations/Mb) was found in ∼18% without significant differences by sex (p=0.80); a slightly elevated rate was seen in HPV+ vs HPV- (18.4% vs 14.0%; p=0.16); 34% had PIK3CA alterations (37.1% in HPV+ vs.16.8% in HPV- ; p<.01 with similar rates by sex **F**:37.1% vs 20.8%; **M**:37.1% vs 13.3%); in contrast higher prevalence in HPV- vs HPV+ resulted to TP53 (44.9% vs 5.6% p<.01), TERT(31.3% vs 2.7% p<.01), CDNK2A (29% vs 2.9%p<.01), CDNK2B (11.7% vs 1.6% p<.01) and NOTCH1 (14.5% vs 5.1% p<.01); **F** had higher rates of alterations in PTEN (15.3% vs 8.4%p<.01) ,KMT2D (21% vs 13.1%, p<.01), CBFB (3.3% vs 0.2%; p<.01) and CREBBP (5.4 vs 2.6%; p=0.06),whereas **M** showed higher rates of alterations in TERT(15.2 vs 3.5% p<.01), TP53 (20.3% vs 7.8% p<.01),CDKN2A (14% vs 3.8%p<.01),CDKN2B (5.4% vs 2.2% p=.02), MYC (4.2% vs 1.6% p=.03) as well as amplifications on 11q13 such as CCND1(7%vs3.2%p=0.02), FGF19 (7%vs3.3%p=0.02), FGF3(7.2%vs3.6%,p=0.02), FGF4 (7% vs 3.5% p=0.02). BRCA1 and BRCA2 mutations were in 5% pts with mild **M** predominance (7% vs 4%) regardless HPV expression.

Conclusions: The higher incidence of HPV positivity in F compared to M remains the main hypothesis to justify the better prognosis of ASCC in women. A large proportion of PD-L1+ and TMB-High (∼70%), PIK3CA alterations (∼30%) and BRCA1/2 gene alteration (5%) may predict response to possible new therapeutic approaches for pts with ASCC like immunotherapy, targeted tyrosine kinase inhibitors, platinum chemotherapy and PARP inhibitors.

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2353P Anti-cancer effects of HDAC8 specific inhibitors EC-352H and EC-374H in lymphoma

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Background: It was well known histone deacetylase (HDAC)s act as regulators of cancer progression in various cancer cells, but conventional pan-HDAC inhibitors used for clinical patients have shown the limitations such as low selectivity, high toxicity and low clinical anticancer efficacy. However, HDAC8 has recently been reported to emerge as a new target protein for cancer treatment among HDAC family class I. Against this background, studies have been conducted to discover new HDAC8 selective inhibitors as anti-cancer drug.

Methods: To appreciate the novel HDAC8 selective inhibitors (EC-352H and EC-374H) function as an anti-cancer agent in lymphoma, we investigated the viability of lymphoma cells and tumor growth of xenograft mouse model by EC-352H or EC-374H. The apoptotic mechanism of each drug was studies using immunoblotting assay. And the safety of EC-352H was evaluated through single-dose toxicity study in compliance with the Good Laboratory Practice (GLP) regulations.

Results: In the microarray analysis (GSE12453), HDAC8 was highly expressed in lymphomas compared with normal tissues. In cytotoxicity tests, the IC_{50} of EC-352H and EC-374H in p53 mutant lymphoma cell (Daudi) was lower than in p53 wild type (WT) lymphoma cells (OCI-Ly3). These results suggest that EC-352H and EC-374H may be more selective inhibitor in p53 mutant lymphoma than in p53 WT lymphoma. Both drugs downregulated the expression of p53 mutant protein through caspase 3-dependent apoptosis, whereas p53 WT protein was highly expressed by EC-352H or EC-374H. In the Daudi xenograft model, 50 mg/kg administration of each drug significantly inhibited tumor growth compared with vehicle-injected mice. Finally, *in vivo* toxicity study of EC-352H was performed through single-dose oral administration, and approximate lethal dose (ALD) was calculated 500-1000 mg/kg in ICR mice.

Conclusions: EC-352H and EC-374H, novel HDAC8 specific inhibitors, act as anticancer agents and inhibit lymphoma. These can be potential alternatives for overcoming disadvantages of conventional HDAC inhibitors by enhancing HDAC8 selectivity.

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2354P Computational pathology-derived features capture varied epithelial-mesenchymal transition (EMT) states

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Background: EMT is a process through which epithelial cells acquire mesenchymal-like traits, such as increased migratory capacity, which facilitate cancer cell metastasis. Here we propose an interpretable, scalable, machine learning (ML)-based method to assess EMT status directly from H&E-stained images. We extracted human interpretable features (HIFs) quantifying cancer cell nuclear morphology and the tumor microenvironment from breast cancer H&E images and confirmed concordance with a known ground-truth EMT expression signature.

Methods: Using a breast cancer-specific EMT signature gene set, we calculated quantile normalized EMT scores for each patient in TCGA-BRCA with RNA-seq data (n = 751). Convolutional neural network models trained using H&E-stained whole slide images were used to extract a set of HIFs across available slides (n = 775). An ordinary least squares regression was run for each HIF against EMT score with tumor purity as a covariate. FDR correction was applied to all p-values.

Results: Lower EMT scores were associated with epithelial attributes, such as high nuclei circularity, while high EMT scores were associated with mesenchymal attributes, such as high nuclei eccentricity and greater variation in nuclei perimeter. Epithelial-type tumors were associated with increased immature stromal content and cancer cell proportion. Mesenchymal-type tumors were associated with increased mature stromal content and stromal cell proportion.

Table: 2354P

HIF	Coefficient	Standard error	p-value	R^2	FDR corrected p-value
Mean cancer cell nuclei circularity	-0.047	0.0087	8.60 E-08	0.65	2.80E-07
Mean cancer cell nuclei eccentricity	0.042	0.0089	2.30 E-06	0.65	5.80E-06
Standard deviation of cancer cell nuclei perimeter	0.073	0.0089	1.20 E-15	0.67	8.30E-15
Area proportion immature stroma over all stroma	-0.035	0.0083	2.50 E-05	0.65	5.20E-05
Area proportion mature stroma over all stroma	0.033	0.0082	8.40 E-05	0.65	0.00016
Count proportion cancer cells over all cells	-0.12	0.0075	6.50 E-51	0.75	9.80E-49
Count proportion stromal cells over all cells	0.098	0.0078	1.20 E-32	0.71	3.60E-31

Conclusions: ML model-generated HIFs effectively capture cancer cell morphology reflective of EMT status, including nuclei eccentricity and circularity. The relationships observed in these results are concordant with previous studies showing increased EMT in tumors with greater extracellular matrix stiffness and large numbers of cancer associated fibroblasts. Overall these results reflect significant agreement between EMT scores and HIFs, indicating potential for quantification of EMT states directly from H&E images.

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2355P Carcinoembryonic antigen (CEA) expression in human tumors: A tissue microarray study on 15,413 tumors

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Background: Carcinoembryonic antigen (CEA; CEACAM5) is a cell surface glycoprotein which constitutes an attractive therapeutic target and serum CEA is used for cancer monitoring. CEA is overexpressed in various cancers, but the reported prevalence data vary considerably for many tumor types.

Methods: To comprehensively determine CEA expression in normal and neoplastic tissues, a tissue microarray containing 15,413 samples from 120 different tumor types and subtypes as well as 76 different normal tissue types were analyzed by immunohistochemistry.

Results: CEA positivity occurred in 65 of 120 tumor categories including 49 entities with at least one strongly positive case. CEA positivity was most common in colorectal carcinomas (98.7%), other gastrointestinal adenocarcinomas (61.1%-80.3%), medullary carcinomas of the thyroid (96.3%), pulmonary adenocarcinoma (73.7%), mucinous carcinomas of the ovary (79.8%) and the breast (43.2%), squamous cell carcinomas of various sites (30.2%-69.1%), and small cell carcinomas of the lung (64.3%), the urinary bladder (38.9%), and the prostate (50.0%). High CEA expression was linked to high grade ($p<0.0001$) and invasive growth ($p<0.0001$) in urothelial carcinoma. Reduced CEA expression was associated with mismatch repair deficiency ($p<0.0001$) but not with pT and pN stage in colorectal cancer.

Conclusions: In summary, CEA is abundantly expressed in a broad range of epithelial neoplasms. Our data thus identify various tumor entities where CEA positive cancers might best benefit from CEA serum monitoring and anti-CEA therapies.

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2356P The role of pathological features in predicting prognosis of patients with advanced RET-positive NSCLC

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Background: RET fusions are observed in 1-2% of patients (pts) with non-small cell lung cancer (NSCLC). Targeted therapies with RET inhibitors (RETi) have proven efficacy, improving survival, whereas data on immune checkpoint inhibitors (ICI) are controversial. Aim of the study was to evaluate if pathologic features could have a role as prognostic markers for RET+ NSCLC.

Methods: In this multicentric observational study of 5 European centers baseline tissue specimens were collected from pts with advanced RET+ NSCLC. Clinical data and treatment outcomes with RETi and ICI were collected. Overall survival (OS) in the overall population and progression-free survival (PFS) for RETi and ICI in pts treated with RETi and ICI were calculated. Tumor grade, histological subtype, presence of fibrosis, necrosis, tumor infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLs), lymphangitis, calcifications, neutrophils were determined on haematoxylin/eosin (HE) coloured tissue slides for each patient. We investigated whether pathological features were correlated with PFS and OS.

Results: 38 pts with advanced NSCLC were included. Median age was 62 (IQR 58-72), 63% were female, median number of metastatic sites was 2 (IQR 1-3), PS ECOG was $\leq$1 in 92%1, 28 were treated with RETi, 18 received ICI. Median OS was 50.7 months (95%CI 28.4-NA). Necrosis was observed in 20% of pts and it was associated with shorter OS (7.67 vs 61.10 vs months, $p<0.001$), both in pts treated or untreated with RETi (7.97 vs 83.7 and 4.78 vs 13.93 months, $p<0.001$). Shorter PFS with RETi (5.23 vs 17.37 months, $p=0.004$) was also observed in presence of necrosis. Histological subtype (92% adenocarcinoma), tumor grade (50% G3), presence of fibrosis (84%), TILs (28%), TLs (10%), lymphangitis (62%), neutrophils (3%), calcifications (17%) did not seem to have a prognostic value.

Conclusions: The presence of necrosis in baseline histological samples from advanced RET+ NSCLC was associated with worse prognosis in pts treated or note with RETi. The role of pathological features as prognostic biomarkers deserves further investigation in this setting.

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2357P TRX-221, a 4th generation, mutant-selective, and CNS-active EGFR inhibitor with robust antitumor activity in osimertinib-resistant tumor models harboring C797S mutation

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Background: Patients with EGFR-mutant non-small cell lung cancer (NSCLC) can derive significant clinical benefit from EGFR tyrosine kinase inhibitor (TKI) therapy, including 3rd generation EGFR TKIs such as osimertinib. However, most patients will experience disease progression with osimertinib, mainly due to acquired mechanisms of resistance. Mutations in the C797 residue in exon 20 are the most frequent EGFR-dependent mechanism of resistance to osimertinib treatment. TRX-221 is an investigational, broad-spectrum, CNS-active, mutant-selective 4th-generation EGFR-TKI (AACR 2023 #4006). Here we report further preclinical data supporting the clinical development of TRX-221 for patients with EGFR-mutant NSCLC.

Methods: Anti-proliferative activity and inhibitory potency of EGFR phosphorylation were determined in Ba/F3 cell lines using CellTiter-Glo® and EGFR AlphaLISA. In vivo antitumor efficacy of TRX-221 was evaluated in subcutaneous patient-derived cell line xenograft model and an intracranial tumor xenograft model.

Results: TRX-221 showed potent inhibitory activity of cell proliferation as well as EGFR phosphorylation in cellular assays driven by EGFR-mutants while sparing activity in EGFR wild-type. In osimertinib-resistant xenograft tumor models harboring EGFR C797S mutant cells, TRX-221 induced significant tumor regression without body weight loss. However, only moderate tumor growth inhibition was observed in an EGFR wild-type CDX model, demonstrating that in vivo efficacy was selective toward mutant EGFR. Furthermore, TRX-221 resulted in substantial intracranial antitumor activity with prolonged survival in an intracranial tumor model. Good correlation between plasma exposure levels and inhibitory effect on EGFR phosphorylation was observed with TRX-221 in a CDX tumor model PK/PD study.

Conclusions: TRX-221 is a potent, broad spectrum, and selective 4th generation EGFR-TKI. TRX-221 demonstrates strong antitumor efficacy in osimertinib-resistant tumor models, and thus has potential to treat patients who have developed resistance to 3rd generation EGFR TKI treatment. Initiation of first-in human clinical trial is expected in Q4 2023.

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2358P Assessing the efficacy of robot-assisted total gastrectomy for advanced proximal gastric cancer: Results from a three-year clinical trial

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Background: Robotic total gastrectomy (RTG) is accepted as a safety approach to conventional laparoscopy total gastrectomy (LTG) for locally advanced gastric cancer. However, the long-term oncological efficacy of RTG remains unclear.

Methods: This prospective study included 48 patients with advanced proximal GC underwent RTG combined with spleen-preserving splenic hilar lymphadenectomy between March 2018 and February 2020. Patients who underwent LTG in the FUGES-002 study were enrolled in a 1:2 ratio to compare the outcomes between RTG and LTG. The primary outcome was overall postoperative morbidity rate. The secondary outcomes were three-year overall survival (OS), three-year disease-free survival (DFS), and recurrence patterns.

Results: After 1:2 propensity score matching, a total of 48 RTG and 96 LTG patients were included, with similar clinical and pathological data in both groups. In terms of surgical outcomes, the RTG group had significantly less intraoperative bleeding than the LTG group (66.4 vs. 38.7 ml, $P = 0.042$). With regard to lymph node dissection, the RTG group had a significantly higher number of non-gastric lymph node dissections than the LTG group (20.2 vs. 17.5, $P = 0.039$), and its lymph node metastasis rate was significantly lower than that of the LTG group (27.1% vs. 45.8%, $P = 0.030$); in terms of postoperative outcomes, the RTG group had significantly shorter times for first gas discharge, first out of bed, first liquid diet, first semi-liquid diet, and length of stay than the LTG group ($P < 0.05$). Regarding long-term prognosis, the 3-year DFS of the RTG and LTG groups were 77.1% and 68.8%, respectively, and the 3-year OS were 85.4% and 74.0% ($P > 0.05$ for both). Within 3 years after surgery, 9 (18.8%) and 27 (28.1%) patients in the RTG and LTG groups experienced recurrence, respectively, with similar recurrence patterns in both groups ($P > 0.05$). There was no independent correlation between RTG and recurrence or gastric cancer-specific death ($P > 0.05$ for both).

Conclusions: Among patients with a preoperative clinical stage indicating locally advanced gastric cancer, RTG, compared with LTG, did not result in inferior disease-free survival and overall survival at 3 years.

Clinical trial identification: The FUGES-014 was a prospective, single-arm, open-label study (NCT03524287) that was conducted at Fujian Medical University Union Hospital (FMUUH).

Legal entity responsible for the study: Changming Huang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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UROTHELIAL CANCER

2359O Phase III THOR study: Results of erdafitinib (erda) vs pembrolizumab (pembro) in pretreated patients (pts) with advanced or metastatic urothelial cancer (muc) with select fibroblast growth factor receptor alterations (FGFRalt)

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Background: Erda is an oral pan-FGFR tyrosine kinase inhibitor approved to treat locally advanced or mUC in pts with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy. *FGFRalt* tumors are enriched in luminal 1 subtype and may have limited clinical benefit from anti—PD-(L)1 treatment (tx). This cohort in the randomized, open-label phase 3 THOR study (NCT03390504) assessed erda vs pembro in pts with mUC naive to anti—PD-(L)1.

Methods: Pts ≥18 y with unresectable advanced/mUC with select *FGFR3/2alt*, ECOG PS 0-2, disease progression on 1 prior tx, and naive to anti—PD-(L)1 were randomized 1:1 to receive erda 8 mg QD with pharmacodynamically guided uptitration to 9 mg or pembro 200 mg Q3W. Primary end point: overall survival (OS). Secondary end points: progression-free survival (PFS), objective response rate (ORR), safety.

Results: At 15 Jan 2023 data cutoff, intent-to-treat set (median follow-up 33.2 mo) comprised 175 pts in erda and 176 in pembro arm. The primary end point was not met, with no statistically significant difference in OS between tx arms (Table). Erda had numerically longer PFS and numerically higher ORR but shorter duration of response. Most common tx-related adverse events (TRAEs) of any grade: hyperphosphatemia (73%), stomatitis (45%), diarrhea (45%), and dry mouth (35%) with erda; pruritus (12%), asthenia (10%), hypothyroidism (10%), and fatigue (10%) with pembro. Gr 3-4 TRAEs and serious TRAEs occurred in 43% and 13% in erda and 12% and 10% in pembro arm, respectively. TRAEs leading to death occurred in 0 pts in erda and 3 (2%) in pembro arm. 15% of pts discontinued erda and 5% discontinued pembro due to TRAEs.

Table: 2359O

	Erda (n=175)	Pembro (n=176)
OS, median, mo	10.9 (9.2-12.6)	11.1 (9.7-13.6)
Hazard ratio	1.18 (0.92-1.51) p=0.18	
PFS, median, mo	4.4 (4.1-5.5)	2.7 (1.6-3.0)
Hazard ratio	0.88 (0.70-1.10) p=0.26[a]	
ORR, %	40.0 (32.7-47.7)	21.6 (15.8-28.4)
Relative risk	1.85 (1.32-2.59) p<0.001[a]	
DOR, median, mo	4.3 (3.7-6.9)	14.4 (7.4-27.8)

All data are value (95% CI). [a]Nominal p estimate, due to primary end point not being met.

Conclusions: Erda and pembro had similar OS in this anti—PD-(L)1 naive, *FGFRalt* mUC population, with erda showing a numerically longer PFS and numerically higher ORR rate. Toxicities were manageable with dose modifications.

Clinical trial identification: NCT03390504.

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2360O The double antibody drug conjugate (DAD) phase I trial: Sacituzumab govitecan (SG) plus enfortumab vedotin (EV) as ≥ second-line therapy for metastatic urothelial carcinoma (mUC)

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Background: Antibody-drug conjugates are a mainstay in treatment of mUC. Given different targets, payloads with non-overlapping toxicities and preclinical synergy of SG with anti-microtubule agents, we evaluated the safety and efficacy of SG+EV in a phase I trial (NCT04724018).

Methods: Patients (pts) with mUC and ECOG ≤1 who progressed on platinum and immunotherapy or were cisplatin ineligible and received one line of therapy were enrolled. SG+EV were dosed D1,8 of a 21-day cycle until progression of unacceptable toxicity. To assess the feasibility and safety of combining SG+EV, doses were adjusted based on the incidence of dose-limiting toxicities (DLTs) during cycle(C) 1 and the total number of pts treated at four pre-specified dose levels (DL) using a Bayesian Optimal Interval design (Table). Adverse events (AE) were assessed using CTCAE 5.0.

Results: 24 pts were enrolled (9 DL1, 9 DL2, 6 DL3) from 5/2021 to 4/2023. At data cutoff on May 1, 2023, 23 pts were evaluable for DLT assessment; one pt in DL3 never started therapy. Median age was 69 years (range 41-88); 22 received ≥ 2 lines of therapy. After 2 pts in DL1 experienced febrile neutropenia (FN) prophylactic granulocyte stimulating factor (GCSF) was permitted; 18 pts received GCSF. 70% pts experienced ≥ grade 3 AE at any DLs with one grade 5 AE (pneumonitis possibly related to EV) during C2 (pt in DL3.) The table summarizes DLTs at corresponding DLs; DL2 has been selected for future studies. Among 21 pts evaluble for response, objective response rate was 71% (15/21, 90% Confidence interval: 51-87) with 2 complete and 13 partial responses; 2 pts had progressive disease. With median follow-up 11.9 months, 11/15 responses are ongoing from 1.1+ to 21.6+ months.

Table: 2360O

DL	SG dose (mg/kg)	EV dose (mg/kg)	N enrolled	DLT
-1	6	1	0	NA
1	8	1	9	2 (FN)
2	8	1.25	9	1 (delay C2D1 > 3 wks)
3	10	1.25	6 (1 not evaluable)	3 (grade 3 mucositis, delay C2D1 > 3 wks, FN)

Conclusions: SG+EV was safe with an ORR of 71% in pts with treatment refractory UC. Further DAD expansion cohorts in treatment refractory and naïve setting are in development; triplet therapy with immunotherapy is being explored.

Clinical trial identification: NCT04724018.

Legal entity responsible for the study: Dana Farber Cancer Institute.

Funding: Gilead.

Disclosure: B.A. McGregor: Financial Interests, Personal, Advisory Board: Exelixis, BMS, Dendreon, SeaGen, Astellas, Eisai, Pfizer; Financial Interests, Personal, Invited Speaker: EMD Serono, SeaGen; Financial Interests, Institutional, Trial Chair: Pfizer, Exelixis, Exelixis, BMS, Gilead; Financial Interests, Institutional, Local PI: Calithera, SeaGen, Aveo; Non-Financial Interests, Member: ASCO. G.P. 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X. Gao: Financial Interests, Personal, Advisory Board: Bayer, Flare Therapeutics, Silverback Therapeutics, PureTech, Myovant Sciences, PathAI; Financial Interests, Institutional, Local PI: Arvinas, Exelixis, Harpoon Therapeutics, Aprea Therapeutics, Takeda, Aravive, Merck, Poseida Therapeutics, TopAlliance BioSciences, Novartis, Regeneron, ALX Oncology; Financial Interests, Institutional, Coordinating PI: Bayer. C. Mantia: Financial Interests, Personal, Advisory Board, I participated in a one-time advisory board: Aadi Bioscience; Financial Interests, Institutional, Coordinating PI, Institutional funding for research: Bristol Myers Squibb. X.X. Wei: Financial Interests, Personal, Advisory Board: novartis; Financial Interests, Institutional, Coordinating PI: Bristol Myers Squibb. J.E. 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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Employee at DFCI. I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Professor (non-profit school): Harvard Medical School (HMS); Other, No financial interest. Institutional. Filed patents related to biomarkers of immune checkpoint blockers, and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. J. Bellmunt: Financial Interests, Personal, Advisory Board, Joined the Global adboard this year: Pfizer; Financial Interests, Personal, Advisory Board, Regular GU adboard for bladder cancer: AstraZeneca; Financial Interests, Personal, Invited Speaker, Lectures in the setting of National meetings: Merck; Financial Interests, Personal, Advisory Board, Bladder adboard: Merck; Financial Interests, Personal, Advisory Board, For the adjuvant study CM 247: BMS; Financial Interests, Personal, Invited Speaker, For ESMO Asia Symp 2020 : MSD; Financial Interests, Personal, Stocks/Shares, Holdings: Bicycle; Financial Interests, Personal, Royalties, Role as Section Editor for Bladder: UpToDate; Financial Interests, Institutional, Coordinating PI, Pi of INDUCOMAIN Study (Avelumab first line in unfit patients) Though APRO Association: MSD; Financial Interests, Institutional, Coordinating PI, Pi of Prostate Study (Avelumab + Carboplatin) Though APRO Association: Pfizer; Non-Financial Interests, Other, Steering committee member of IMvigor 011: Genentech; Non-Financial Interests, Member: ASCO. All other authors have declared no conflicts of interest.

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2361MO Impact of positron emission tomography (PET) imaging on staging of muscle-invasive bladder cancer (MIBC) [PET-MUSE]

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Background: In MIBC standard staging with CT imaging is critical for making treatment decisions about neoadjuvant chemotherapy (NAC), and local treatment with either radical cystectomy (RC) or chemoradiation. However, CT imaging can often underestimate disease extent. The aim of this randomized study was to determine if adding 18F-FDG PET/CT (PET) to baseline CT, changes treatment received.

Methods: Newly diagnosed MIBC pts (T2a-T4, N0-3, M0) without metastases on baseline CT, and predominant urothelial histology, were allocated 2:1 to PET or no further imaging. Enrollment occurred 05/16-11/21 at 6 Ontario centers. At the time of analysis, median duration of follow-up was 2 years. Primary outcome was proportion of pts not receiving expected treatment and secondary outcomes were disease-free survival (DFS) and overall survival (OS).

Results: Of 292 pts, 194 were randomized to PET and 98 to no PET. In the PET and no PET arms respectively: median age was 70 (43-93) and 68 (42-89); T2: 77% and 77%; node negative 88% and 87%; planned RC 66% and 69%; and planned NAC 70% and 64%. On PET, primary bladder tumor was seen in 86 (47%) pts, positive pelvic lymph nodes in 37 (20%), distant nodes in 32 (18%) and distant metastases in 13 (7%). By ITT analysis, 166 (86%) PET pts received expected treatment, 21 (11%) did not and 7 (4%) withdrew/died prior to treatment. In the no PET arm, 90 (92%) received expected treatment, 4 (4%) did not, and 4 (4%) withdrew/died prior to treatment. More PET pts were deemed palliative 18 (9.3%) vs 3 (3.1%). Notably >60% in both arms received NAC. PET pts were more likely to have a change in treatment, odds ratio 2.89 (95% CI 0.96-8.74, p=0.06) compared to CT alone. No statistically significant difference was observed between arms for DFS (HR=0.78, 95% CI 0.55-1.12) or OS (HR=1.02, 95% CI 0.66-1.56).

Conclusions: In this large randomized study, there was a trend towards a change in management in pts having a PET, but this did not reach statistical significance. This trial provides new insights into the clinical utility of PET-CT in MIBC.

Clinical trial identification: NCT02462239.

Legal entity responsible for the study: Ontario Clinical Oncology Group (OCOG).

Funding: Cancer Care Ontario.

Disclosure: S. Sridhar: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Bayer, BMS, EMD Serono, Pfizer, Seagen, Gilead; Financial Interests, Institutional, Research Grant, Unrestricted Research grant to institution for developing a database: Seagen. R. Breau: Financial Interests, Personal, Advisory Board: Knight Therapeutics, Ferring, TerSera, Tolmar Pharmaceuticals, Merck, Astellas, Pfizer. All other authors have declared no conflicts of interest.

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2362MO Erdafitinib (erda) vs chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select FGFR alterations (FGFRalt): Subgroups from the phase III THOR study

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Background: *FGFRalt* are seen in ∼20% of pts with mUC. Erda is an oral pan-FGFR tyrosine kinase inhibitor for pts with locally advanced or mUC with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemo. THOR (NCT03390504), a randomized phase 3 study, assessed whether erda provided an overall survival (OS) advantage vs chemo in pts with mUC who progressed after 1-2 prior therapies (tx), including anti-PD-(L)1.

Methods: Pts (≥18 y) with unresectable advanced/mUC and select *FGFR3/2alt* (mutations/fusions), ECOG PS 0-2, adequate organ function, progression on/after 1-2 prior lines of systemic tx that included anti-PD-(L)1 were randomized 1:1 to erda (8 mg with pharmacodynamically guided uptitration to 9 mg) QD or investigator's choice of chemo (docetaxel or vinflunine) Q3W until disease progression or intolerable toxicity. Primary end point was OS. Secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety.

Results: 266 pts were randomized (median [m] age 67 y, follow-up 16 mo) to erda (N=136) or chemo (N=130). Primary end point was met: mOS 12.1 vs 7.8 mo in erda vs chemo (HR=0.64; 95% CI, 0.47-0.88). OS benefit was seen across subgroups (Table). Erda improved mPFS (6 vs 3 mo) and ORR (46% vs 12%) vs chemo. Most frequent tx-related adverse events (TRAEs): hyperphosphatemia (79%), diarrhea (55%), and stomatitis (46%) with erda; anemia (28%), alopecia (21%), and nausea (20%) with chemo. 46% in each arm had Gr 3/4 TRAEs. 1 and 6 pts had TRAEs leading to death with erda and chemo, respectively.

Table: 2362MO

Subgroup		Erda (n=136)		Chemo (n=130)		HR (95% CI)
		n	mOS, mo	n	mOS, mo	
Age	<65 y	59	14	45	9	0.46 (0.27-0.79)
	≥65 y	77	11	85	8	0.71 (0.47-1.07)
Baseline ECOG PS	0-1	125	12	119	9	0.65 (0.46-0.90)
	2	11	6	11	3	0.47 (0.16-1.35)
FGFRalt	Fusion	25	16	19	8	0.49 (0.23-1.03)
	Mutation	108	11	107	8	0.67 (0.47-0.95)
Prior lines of tx	1	45	14	33	8	0.61 (0.35-1.09)
	2	90	12	97	8	0.67 (0.45-0.98)
Visceral metastasis	Y	103	12	101	8	0.65 (0.45-0.93)
	N	33	11	29	9	0.61 (0.32-1.14)
Primary tumor	Upper tract	41	23	48	7	0.34 (0.18-0.64)
	Lower tract	95	11	82	10	0.82 (0.56-1.18)
Chemo	Docetaxel[a]	136	12	69	11	0.76 (0.52-1.11)
	Vinflunine[a]	136	12	43	8	0.60 (0.39-0.92)
PD-L1 status	CPS ≥10	7	10	11	20	1.98 (0.57-6.91)
	CPS <10	89	12	68	9	0.58 (0.38-0.89)

[a]Chemo group tx.

Conclusions: In pts with *FGFRalt* advanced/mUC after prior anti-PD-(L)1 tx, erda significantly improved OS vs chemo. Clinically relevant subgroups showed a consistent OS benefit for erda. No new safety signals were observed. These results support the role of erda to treat pts with *FGFRalt* mUC after anti-PD-(L)1 tx.

Clinical trial identification: NCT03390504.

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2363MO A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in non-urothelial, muscle invasive bladder cancer (ABACUS-2)

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Background: Neoadjuvant atezolizumab in muscle invasive urothelial bladder cancer is associated with meaningful pathological complete response (pCR) rates. Serial circulating tumor DNA levels correlate with response and disease-free survival. ABACUS-2 investigates the efficacy and safety of neoadjuvant atezolizumab prior to cystectomy in patients with non-urothelial, bladder cancer.

Methods: This single arm phase 2 study investigated 2 cycles of atezolizumab (1200mg Q3W) prior to cystectomy in non-urothelial muscle invasive bladder cancer (T1-4aN0-1M0). pCR was the primary endpoint. Biomarker analysis on sequential tissue and ctDNA were co-primary endpoints. Cross sectional imaging was performed at baseline and prior to cystectomy which occurred 4-8 weeks after starting atezolizumab. Adverse events and surgical complications were assessed using CTCAE v5 and the Clavien-Dindo classification. The IDMC reviewed the first 23 patients (of 29 enrolled) and supported this interim presentation. The full data on 29 pts will be available at the meeting.

Results: The median age of the 23 pts was 70y (range 42-82). At baseline pT1, pT2, pT3 disease occurred in 2/23 (9%), 17/23 (74%), 4/23 (17%) pts respectively. 22 pts (96%) received the full 2 cycles of treatment (1 due to non-compliance). All patients underwent cystectomy. The pCR rate in pT2 or above pts was 38% (8/21), and 35% (8/23) including pT1 pts. The most common histological subtypes were squamous (35%), sarcomatoid (35%) and adenocarcinoma (13%). pCR is pts with sarcomatoid variant was 75% (6/8) and 33% (1/3) in those with adenocarcinoma. Treatment related grade 3/4 toxicity occurred in 17% (4/23) of patients. No treatment related death occurred.

After a median follow up of 6.6 months (95%CI: 5.9 – 7.4), 2 patients died, one due to subsequent disease progression and one COVID related. Grade 3/4 surgical complications occurred in 2/23 (9%) pts. Sequential biomarker analysis including immunohistochemistry, circulating and urinary tumor DNA will be available.

Conclusions: Neoadjuvant atezolizumab is associated with meaningful pCR rates in patients with non-urothelial, bladder cancer awaiting cystectomy at this interim stage.

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Legal entity responsible for the study: Barts ECMC.

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2364MO Durvalumab (D) +/- tremelimumab (T) in combination with dose-dense MVAC (ddMVAC) as neoadjuvant treatment in patients with muscle-invasive bladder carcinoma (MIBC): Results of NEMIO, a randomized phase I-II trial

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Background: Neoadjuvant cisplatin-based chemotherapy (NAC) regimen followed by local therapy is the standard of care for MIBC. However, 60-75% of these patients (pts) have residual disease after NAC. Preclinical data suggest that the use of ddMVAC regimen may induce higher immunogenic death and pathological complete response (pCR) in the NAC setting as compared to gemcitabine cisplatin regimen (GC). Thus, we aimed to evaluate the efficacy and safety of ddMVAC + D +/- T combination in a phase I/II trial.

Methods: NEMIO (NCT03549715) is a multicenter open-label randomized non-comparative phase 1/2 trial evaluating neoadjuvant ddMVAC + D +/- T in pts with cT2-4N0-1 eligible for radical cystectomy (RC). The pts received 4 cycles of ddMVAC every 2 weeks with D (1500 mg) +/- T (75 mg) every 4 weeks. The co-primary endpoints were locally assessed pCR rate (ypT0N0) and grade $\geq$ 3 treatment related adverse events (TRAE). We assumed a pCR rate $\geq$ 45% to consider trial as positive.

Results: Between November 2018 and April 2022, 121 pts were enrolled in 16 centers and 119 received at least one dose of ddMVAC + D +/- T. The median age was 64 years (IQR: 58-70) with predominant ECOG PS 0 (74%). Clinical tumor stage at diagnosis was cT2, cT3 and cT4 in 86 (89%), 9 (9%) and 1 (1%), respectively, while 5 (5%) pts were cN1. Only 6 pts (6%) did not undergo RC (4 refusal and 2 progressive disease). Among the 113 pts with RC, the pCR was 47.8% (Table). All pts had at least one TRAE and 41% a G$\geq$3 TRAE including neutropenia (12.6%) anemia (9.2%), and acute kidney injury (6.7%). ddMVAC or D +/- T were discontinued in 21 pts (17.6%), mostly due to TRAE (90.5%).

Table: 2364MO

	ddMVAC + D (N = 55)	ddMVAC + D + T (N = 58)	Pts achieved cystectomy (N = 113)
ypT0N0	27 (49.1%)	27 (46.6%)	54 (47.8%)
ypT1, Ta, TisN0	12 (21.8%)	8 (15.5%)	21 (18.6%)
ypT2-4N0	10 (18.2%)	16 (27.6%)	26 (23.0%)
ypN+	6 (10.9%)	6 (10.3%)	12 (10.6%)

Conclusions: NEMIO is a positive trial showing one of the highest pCR achieved in the neoadjuvant setting with the use of ddMVAC + D. Nonetheless, the benefit of adding T on pathological response appears limited, pending survival outcomes.

Clinical trial identification: NCT03549715.

Legal entity responsible for the study: Association pour la Recherche de Thérapeutiques innovantes en Cancérologie.

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2365MO Study EV-103 cohort L: Perioperative treatment w/ enfortumab vedotin (EV) monotherapy in cisplatin (cis)-ineligible patients (pts) w/ muscle invasive bladder cancer (MIBC)

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Background: Current SOC for pts w/ MIBC is neoadjuvant cis-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection (RC+PLND). For pts who are cis-ineligible, SOC is RC+PLND alone but adjuvant therapy may be recommended. Due to high rates of recurrence in cis-ineligible pts, an urgent unmet need remains. Neoadjuvant EV showed promising antitumor activity in MIBC (pathological CR [pCR] of 36%, pathological downstaging [pDS] of 50%) in EV-103 Cohort H (Petrylak 2022). Cohort L examines a perioperative approach.

Methods: Cohort L enrolled pts who are cis-ineligible w/ previously untreated MIBC (cT2-T4aN0M0 or cT1-T4aN1M0) who are medically fit for and agree to undergo curative intent RC+PLND within 12 wks. Pts received 3 cycles of neoadjuvant EV (1.25mg/kg) on Days 1 and 8 of each 3-week cycle followed by RC+PLND and then 6 cycles of adjuvant EV (1.25 mg/kg) on Days 1 and 8 of every 3 week cycle starting 8 weeks post-RC. Primary endpoint is pathological CR (pCR) per central pathology review; secondary endpoints include pathological downstaging (pDS) rate per central pathology review, safety and tolerability. Here we present initial results from the neoadjuvant/RC+PLND phase + 30 days post surgery.

Results: 52 pts were enrolled. 51 pts were treated w/ EV in the neoadjuvant phase w/ a median of 3 cycles; 42 pts (82.4%) completed RC+PLND. One pt achieved clinical CR and elected not to undergo RC+PLND and was excluded from pCR and pDS analyses; 17/50 (34.0%) pts had a pCR. pDS was seen in 21/50 (42.0%) pts. In the neoadjuvant/RC+PLND phase, of 51 treated pts most common EV-related TEAEs were fatigue (52.9%), rash maculo-papular (31.4%), and nausea (29.4%). 39.2% of pts had an EV-related TEAE $\geq$ grade 3; 31.4% pf pts had a RC-related TEAE $\geq$ grade 3. No surgeries were delayed due to EV-related TEAEs. One pt (2.0%) experienced an EV-related death (Stevens-Johnson syndrome) before surgery.

Conclusions: EV continues to show promising activity and was tolerable in cis-ineligible pts w/ MIBC in this ongoing trial. Both the efficacy and safety profiles were consistent with previously reported data from Cohort H. These data support the ongoing phase 3 trials evaluating EV + pembrolizumab in MIBC.

Clinical trial identification: EudraCT 2018-001527-39; Release Date: Amendment 11, 15-Feb-2023.

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O'Donnell: Financial Interests, Personal, Other, Honoraria: Merck, Astellas Pharma, Pfizer, CLD, Axiom Healthcare Strategies, EMD Serono, IntrinsiQ Specialty Solutions, ISMIE, NAMCP, Seagen, Curio Science, FirstWord Publications, MedLearning Group, Research to Practice, Great Debates and Updates, MJH Life Sciences, Peerview, Vaniam Group, EnquiringMinds; Financial Interests, Institutional, Funding, Research Funding: Boehringer Ingelheim, Merck, Genentech/Roche, AstraZeneca/MedImmune, Acerta Pharma, Janssen, Seagen, Bristol Myers Squibb, Astellas Pharma; Other, Personal, Expert Testimony: Oregon Health & Science University (OHSU); Other, Personal, Other, Travel, Accommodations, Expenses: Curio Science; Other, Personal, Other Relationship: Janssen, Nektar, NIH, Dragonfly Therapeutics, G1 Therapeutics. T.W. Flaig: Financial Interests, Personal, Other, Consulting and advisory: Seattle Genetics; Financial Interests, Institutional, Member of Board of Directors: Joint Venture between University of Colorado and UCHealth; Financial Interests, Personal, Stocks/Shares, I am founder and stockholder in this academic start up company. We are submitting SBIR grants for a patent on work done in our lab. There are no commercial products or current clinical trials - early stage: Aurora Oncology; Financial Interests, Personal, Other, We have a patent with the University of Colorado (from our lab) which has been licensed to Aurora Oncology (I am a cofounder of this faculty start up): Aurora Oncology; Financial Interests, Institutional, Invited Speaker: Bristol Myers Squibb, Janssen Oncology, Sanofi, Pfizer, Roche - Genentech, AstraZeneca/MedImmune, Lilly, Astellas, Seattle Genetics, Seagen, Merck, La Roche - Posay, Myovant Sciences. J.E. Rosenberg: Financial Interests, Personal, Advisory Board: Alligator Biosciences, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, EMD-Serono, Genentech, Gilead, Infinity Pharmaceuticals, Janssen, Lilly Oncology, Merck, Mirati, NCCN, Pfizer, QED Therapeutics, Seagen, Tyra Biosciences, Hengrui; Financial Interests, Personal, Invited Speaker, Medical Education: Clinical Care Options; Financial Interests, Personal, Invited Speaker: EMD-Serono; Financial Interests, Personal, Invited Speaker, Medical education: MJH Associates, Physicians Education Resource, Research to Practice; Financial Interests, Personal, Royalties: Wolters Kluyer/Uptodate; Financial Interests, Institutional, Invited Speaker, Coordinating PI of rogaratinib/atezolizumab trial; consultant, trial open at my institution: Bayer; Financial Interests, Personal and Institutional, Invited Speaker, EV-201, EV- 103; consultant, trial open at my institution: Seagen; Financial Interests, Personal and Institutional, Invited Speaker, EV-301, consultant, trial open at my institution: Astellas; Financial Interests, Institutional, Invited Speaker, Consultant, PI of trial, trial open at my institution: AstraZeneca; Financial Interests, Institutional, Invited Speaker, PI of IMVIGOR210 (still open at my institution): Genentech; Financial Interests, Institutional, Invited Speaker, Investigator initiated trial at my institution: QED; Non-Financial Interests, Leadership Role, Bladder Cadre leader for Alliance (NCTN): Alliance for Clinical Trials in Oncology. 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Milowsky: Financial Interests, Personal, Advisory Board: Loxo/Lilly; Financial Interests, Personal, Other, Co-Editor-in-Chief, Clinical Genitourinary Cancer: Elsevier; Financial Interests, Personal, Invited Speaker: Medscape; Financial Interests, Personal, Stocks/Shares: Pfizer, Merck, Gilead Sciences; Financial Interests, Institutional, Invited Speaker: Merck, Roche/Genentech, Bristol Myers Squibb, Mirati Therapeutics, Incyte, Seagen, G1 Therapeutics, Alliance Foundation Trials, Alliance for Clinical Trials in Oncology, Clovis Oncology, Arvinas, Regeneron. S. Srinivas: Financial Interests, Invited Speaker: Seagen. S. George: Financial Interests, Personal, Advisory Board, advisor/consultant: BMS, Bayer, Pfizer, Exelixis, Corvus, Sanofi/ Genzyme, Seattle Genetics, EMD Serono, Eisai, Merck, Aveo, QED therapeutics; Financial Interests, Institutional, Invited Speaker: Pfizer, Merck, Agensys, Novartis, BMS, Bayer, Eisai, Seattle Genetics, Calithera, Corvus, Surface Oncology, Exelixis, Aravive, Aveo, Gilead. R.R. McKay: Financial Interests, Personal, Advisory Board: Aveo, AstraZeneca, Bayer, Calithera, Dendreon, Exelixis, JNJ, Merck, Pfizer, Sanofi, Tempus, BMS, Lilly, Sanofi, SeaGen, Telix, Sorrento Therapeutics; Financial Interests, Personal, Other, Molecular tumor board: Caris; Financial Interests, Personal, Other, Consultant: Dendreon, Myovant; Financial Interests, Personal, Invited Speaker: Exelixis, Merck, Novartis, Pfizer; Financial Interests, Invited Speaker: Aveo, JNJ, SeaGen, Bayer, AstraZeneca, Calibr, Poseida, Oncternal, Scholar Rock, Merck, Xencor, Genentech, Eli Lilly, BMS; Financial Interests, Institutional, Invited Speaker: Exelixis. D.P. Petrylak: Financial Interests, Personal, Other, Consultant Fees: Ada Cap (Advanced Accelerator Applications), Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Gilead Sciences, Incyte, Infinity Pharmaceuticals, Ipsen, Janssen, Merck & Company Inc, Mirati, Monopteros, Pfizer, Pharmacyclics, Regeneron, Roche, Sanofi Aventis Pharmaceuticals, Seattle Genetics, Urogen; Financial Interests, Personal, Stocks/Shares: Bellicum (Sold 7/2020), Tyme (sold 10/2019); Financial Interests, Institutional, Invited Speaker: Ada Cap (Advanced Accelerator Applications), Agensys Inc, Arvinas, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo Company Limited, Eisai, Eli Lilly, Endocyte, Ferring, Genentech, Gilead Sciences, Innocrin, MedImmune, Medivation, Merck, Mirati, Novartis, Pfizer, Progenics, Replimune, Roche, Sanofi Aventis, Seattle Genetics. P.M. 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Iafolla: Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Invited Speaker: Bayer, Canadian Urologic Association, Ipsen, Merck, Sanofi, Save Your Skin, Sermo Team; Financial Interests, Personal, Expert Testimony: CompassMD, MD Analytics; Financial Interests, Personal, Full or part-time Employment: William Osler Health System; Financial Interests, Institutional, Research Grant: EMD Serono, Pfizer, Bristol Myers Squibb, Novartis; Non-Financial Interests, Principal Investigator: Seagen, Pfizer, Bristol Myers Squibb, AstraZeneca, Astellas Pharma Global Development Inc. M. 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R. Dreicer: Financial Interests, Personal, Advisory Board: Pfizer, Eisai, Propella, Merck, Astellas, Janssen, Giliead, Sanofi Genzyme; Financial Interests, Personal, Other, DSMB: Aveo; Financial Interests, Institutional, Funding: Exilexis, Novartis. S. Brancato: Financial Interests, Personal, Full or part-time Employment: Astellas Pharma Global Development. J.J. Lukas: Financial Interests, Personal, Full or part-time Employment, Medical Monitor: Seagen; Financial Interests, Institutional, Full or part-time Employment, Assistant Clinical Professor: University of Washington; Financial Interests, Personal, Stocks/Shares: Seagen. Y. Yu: Financial Interests, Personal, Full or part-time Employment, Full time employee: Seagen Inc; Financial Interests, Personal, Stocks/Shares: Seagen inc. H. Moon: Financial Interests, Institutional, Invited Speaker, clinical trial PI: Seagen; Financial Interests, Personal and Institutional, Invited Speaker, Steering Committee: EMD Serono; Financial Interests, Institutional, Invited Speaker, PI for Clinical trial: Janssen; Financial Interests, Institutional, Invited Speaker, PI for Trial: Nektar; Financial Interests, Invited Speaker, Clinical trial PI: Huya; Non-Financial Interests, Other, Grant Proposal Review committee for NCCN/Pfizer Bladder cancer grant review committee: NCCN; Non-Financial Interests, Advisory Role, NCI Prostate Cancer task force: NCI.

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2366P Phase I-II study of niraparib plus cabozantinib in patients with advanced urothelial/kidney cancer (NICARAGUA trial)

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Background: Niraparib (N) is a (PARP)-1/-2 inhibitor (inh) and Cabozantinib (C) is a receptor tyrosine kinase (RTK) inhibitor that targets multiple RTKs (c-MET, TYRO3, AXL, MER). It has been proposed that aberrant c-MET activation could decrease response to PARP inhibitors (PARPi). Preclinical data show that c-Met inhibition renders cells more sensitive to PARPi. Safety of N + C was explored in advanced clear cell renal cell carcinoma or metastatic urothelial carcinoma (mUC) (Ph I. #GU-ASCO-22). We now report safety and efficacy in an expansion cohort of mUC (Ph II).

Methods: Multicenter, open-label Ph I-II study (NCT03425201). Patients (pts) received N/C 100/40 mg p.o. once daily in 28-day cycles. Pts with confirmed histopathological diagnosis of mUC (Ph II) previously treated with at least 2 previous regimens, one platinum-based, and ECOG PS 0-2, were included. Adequate bone marrow, liver and renal functions were required. No pre-molecular selection was assessed (DDR-gene mut or c-MET mut).

Results: The first interim analysis of 44 mUC pts is presented. Median age was 67 years and 98% of pts were male. All pts had received platinum-based treatment and 80% had received immunotherapy. Median number of administered cycles is 3 (range 1-18) and 13 pts are still on treatment at the time of this analysis. Disease control rate was 47.7% and ORR was 15.9%. With a median follow-up time of 5.9 months (range 1.8-19.5), median progression free survival (PFS) and overall survival were 3.8 and 8.7 months, respectively; 6 months PFS was 31%. Most frequent all grade adverse events (AEs), included: asthenia (71%), hypertension (43%), diarrhea (27%), constipation (27%), anemia (25%) and palmar-plantar erythrodysesthesia (23%). Most frequent grade 3 AEs were: asthenia (11%), hypertension (9%) and decreased appetite (9%).

Conclusions: N 100 mg/d + C 40 mg/d combination can be safely administered and has clinical efficacy (30% of pts are still on treatment) in a biomarker unselected heavily pretreated population.

Clinical trial identification: EudraCT 2017-004367-12, NCT03425201.

Editorial acknowledgement: Juan Luis Sanz (APICES).

Legal entity responsible for the study: Fundación CRIS.

Funding: GSK and Ipsen.

Disclosure: D.E. Castellano Gauna: Financial Interests, Personal, Advisory Board: Pfizer, Roche, BMS, Janssen, Astellas, MSD, Ipsen, AstraZeneca, Novartis, GSK; Financial Interests, Institutional, Local PI: Pfizer, Roche, MSD, BMS, AstraZeneca, Janssen, Astellas, Ipsen, Exelisis, Eisai, Lilly, Bayer, GSK, Clovis, QED Therapeutics; Non-Financial Interests, Personal, Other, Executive member: SOGUG (Spanish Oncology Genito-Urinary Group) Foundation. I. Duran Martinez: Financial Interests, Personal, Advisory Board, I have served as an advisor for this company in the last two years: Roche Genentech, MSD, Bristol Myers Squibb; Financial Interests, Personal, Invited Speaker, I have participated in different compensated educational activities sponsored by Jansen over the last two years: Jansen; Financial Interests, Personal, Invited Speaker, I have participated in different compensated educational activities sponsored by Pfizer over the last two years: Pfizer; Financial Interests, Personal, Advisory Board, I have collaborated as an advisor in different occasions over the last two years: Ipsen; Financial Interests, Personal, Invited Speaker, I have participated in different compensated educational activities sponsored by this company over the last two years: Ipsen, Bristol Myers Squibb; Financial Interests, Personal, Advisory Board, I have collaborated as an advisor for this company in the last two year: Merck; Financial Interests, Personal, Advisory Board, I have participated in different compensated advisory boards over the last two years: Astellas; Financial Interests, Personal, Advisory Board, I have collaborated as an advisor for this company over the last two years: Immunomedics, Inc.; Financial Interests, Personal, Invited Speaker, I have participated in educational activities sponsored by this company in the last two years: EUSA Pharma, MSD; Financial Interests, Personal, Invited Speaker, I have participated in educational activities sponsored by Novartis in the last 2 years: Novartis; Financial Interests, Personal, Invited Speaker, I have participated in compensated educational activities for this company in the last two years: Astellas; Financial Interests, Personal, Invited Speaker, I have participated in activities sponsored by this company as a guest speaker: Bayer; Financial Interests, Personal, Other, Bayer has covered expenses related to EAU 2023 including registration, travel and accommodation: Bayer; Financial Interests, Personal and Institutional, Research Grant, Roche has funded research in my institution to projects under my coordination: Roche Genentech; Financial Interests, Personal, Steering Committee Member, I serve as a member of a SC for a trial sponsored by this company: Immunomedics, Inc.; Financial Interests, Personal and Institutional, Research Grant, AZ has funded research conducted in my institution related to a project where I am the PI: AstraZeneca; Financial Interests, Institutional, Coordinating PI, I am leading a study (Investigator initiated) that is funded by Gilead and sponsored by the foundation of my department (FUPOCAN): Gilead; Non-Financial Interests, Leadership Role, I am the president of an independent cooperative group of GU Oncologist from the north of Spain: GO NORTE; Non-Financial Interests, Member of Board of Directors, I am member of the Board of directors since 2022: ASEICA; Non-Financial Interests, Member of Board of Directors, GUARD is a GU oncology cooperative group. I am a co-founder and member of the board of directors since 2023: GUARD. B. Mellado Gonzalez: Financial Interests, Personal, Other, Research Grant/Funding (Self), Speaker Bureau, Travel accommodation: Janssen, Roche, Astellas, Sanofi, Bayer; Financial Interests, Personal, Other, Speaker Bureau, Travel accommodation: Pfizer; Financial Interests, Personal, Other, Travel accommodation, Speaker Bureau: Ipsen; Financial Interests, Personal, Other, Speaker Bureau: BMS. M.A. Climent Duran: Financial Interests, Personal, Advisory Board: Roche, BMS, EUSA, Pfizer, Sanofi, Janssen, Astellas, Merck, Ipsen, MSD; Financial Interests, Personal, Invited Speaker: EUSA, Pfizer, Sanofi, Janssen, Astellas, Merck, Ipsen, BMS, Roche, MSD. X. Garcia Del Muro: Financial Interests, Personal, Advisory Board: Ipsen, EusaPharma, BMS, Pfizer, Roche, PharmaMar; Financial Interests, Personal, Invited Speaker: Lilly, Astellas Pharma, Eisai, Pfizer; Financial Interests, Institutional, Research Grant: AZ. N. 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All other authors have declared no conflicts of interest.

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2367P A randomized phase II study of atezolizumab (atezo) plus recombinant human IL-7 (CYT107) vs. atezo alone in patients with locally advanced or metastatic urothelial carcinoma (mUC)

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Background: Atezolizumab is an anti-PD-L1 antibody that was approved for patients with mUC following platinum-containing regimens. IL-7 (CYT107) is a homeostatic cytokine that supports the proliferation and persistence of T cells. We hypothesized that addition of CYT107 would improve responses to PD-L1 inhibition by atezo. We performed a randomized trial (NCT03513952) in mUC comparing the combination of CYT107 and atezo to atezo alone.

Methods: Patients with mUC who had progressive disease after platinum-containing chemotherapy were screened. Key eligibility criteria included ECOG PS 0-2, measurable disease (by RECIST 1.1), and no prior checkpoint inhibitor or cytokine immunotherapy. A safety run-in using the combination of CYT107 and atezo was performed, followed by randomization 1:1 to atezo 1200 mg IV q3wks +/- CYT107 10 ug/kg IM qwk X 4. The primary endpoint was objective response rate (ORR), with secondary endpoints including clinical benefit rate, PFS, DOR, OS, and safety. Detailed immune response analysis and exploratory correlative analyses are in progress.

Results: A total of 47 patients were enrolled. Patient demographics between arms were well-balanced. ORR was 26.3% for the combination vs 23.8% for atezo alone ($p=0.43$). There were no significant differences in clinical benefit rate, PFS, DOR, or OS. No dose limiting toxicities were seen in the safety run-in cohort ($n=7$). 76.9% (20/26) of patients on the CYT107 arm received all four doses. The combination of CYT107 and atezo was well tolerated compared to the atezo arm, with overall grade 3-4 adverse events (AEs) occurring in 46.2% (12/26) and 63.2% (12/19), respectively. Immune-mediated AEs of any grade occurred in 50% (13/26) vs 68.4% (13/19), respectively. 6.3% vs 17.6% of patients on the combination vs monotherapy arm discontinued therapy due to toxicity.

Conclusions: This is the first randomized trial of atezolizumab +/- IL-7 (CYT107) in mUC. During the trial, the FDA approval for atezo in mUC was withdrawn, which limited enrollment. However, our results show that the addition of CYT107 to atezo is safe/tolerable, although there was no improvement in clinical outcomes compared to atezo monotherapy.

Clinical trial identification: NCT03513952.

Legal entity responsible for the study: Cancer Immunotherapy Trials Network (CITN).

Funding: National Cancer Institute of the National Institutes of Health.

Disclosure: R. Pachynski: Financial Interests, Personal, Advisory Board: Bayer, Janssen, Dendreon, EMD Serono, Genomic Health, Jounce, Pfizer, BMS; Financial Interests, Personal, Invited Speaker: AstraZeneca, Genentech/Roche, Sanofi; Financial Interests, Personal, Advisory Board, Liquid biopsy for prostate cancer: Tempus Labs; Financial Interests, Institutional, Funding: Janssen, Pharmacyclics; Financial Interests, Steering Committee Member: BMS; Non-Financial Interests, Principal

Investigator: BMS, Merck, ESSA, Janssen, Pfizer/EMD Serono, ESSA, Ambrx, Amgen. R.K. Jain: Financial Interests, Personal, Advisory Board: BMS, Gilead, Seattle Genetics, Aveo, EMD Serono; Financial Interests, Personal, Invited Speaker: Seattle Genetics, DAVA Oncology; Financial Interests, Institutional, Research Grant: BMS, Gilead. H. Moon: Financial Interests, Institutional, Coordinating PI, clinical trial PI: Seagen; Financial Interests, Personal and Institutional, Steering Committee Member, Steering Committee: EMD Serono; Financial Interests, Institutional, Coordinating PI, PI for Clinical trial: Janssen; Financial Interests, Institutional, Coordinating PI, PI for Trial: Nektar; Financial Interests, Coordinating PI, Clinical trial PI: Huya; Non-Financial Interests, Other, Grant Proposal Review committee for NCCN/Pfizer Bladder cancer grant review committee: NCCN; Non-Financial Interests, Advisory Role, NCI Prostate Cancer task force: NCI. R. Sweis: Financial Interests, Personal, Advisory Board: Aduro, Astellas, AstraZeneca, BMS, EMD Serono, Editas, Exelixis, Eisai, Janssen, Mirati, Pfizer, Silverback, Seattle Genetics; Financial Interests, Personal, Invited Speaker: Aveo; Financial Interests, Personal, Stocks/Shares: AbbVie; Financial Interests, Institutional, Local PI: AbbVie, Aduro, Ascendis, Astellas, BMS, Bayer, CytomX, Eisai, Genentech/Roche, Immunocore, Merck, Mirati, Moderna, Novartis, QED, Pyxis Oncology, ALX Oncology; Financial Interests, Institutional, Research Grant: Epivax. S.P. Fling: Financial Interests, Institutional, Funding, Industry provided funds in salary support and research for CITN clinical trials: Merck, Revimmune. A. Lacroix: Financial Interests, Personal, Other, Consultant for the Cancer Immunotherapy Trials Network: Fred Hutchinson Cancer Research Center. E. Yu: Financial Interests, Personal, Advisory Board: Janssen, Merck, Advanced Accelerator Applications, Novartis, Bayer, Aadi Bioscience; Financial Interests, Personal, Other, Scientific Advisory Board: Oncternal; Financial Interests, Institutional, Local PI: Daiichi Sankyo, Taiho, Surface; Financial Interests, Institutional, Coordinating PI: Dendreon, Merck, Seagen, Blue Earth, Bayer, Lantheus. All other authors have declared no conflicts of interest.

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2368P Activity of cabozantinib (CABO) plus durvalumab (DURVA) in patients (pts) with advanced non-urothelial-carcinoma variant histologies (VHs) or urothelial carcinoma (UC) after platinum-based chemotherapy: Interim results from the phase II ARCADIA trial

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Background: Combining multitargeted receptor tyrosine kinase inhibitor (TKI) with checkpoint inhibitors has shown synergistic effect in pts with UC due to the immunomodulatory propriety of VEGFR inhibitors. We investigated if the combination of CABO and DURVA in pts with advanced UC and non-UC histology (VHs) in a phase II study (NCT03824691). Herein the preliminary results of the interim analysis.

Methods: In ARCADIA study, pts with UC or VHs recurred/progressed after failure of platinum-based CT were enrolled. Pts received CABO 40 mg daily orally and DURVA 1500 mg IV q28 days, until disease progression (PD, by RECIST 1.1) or unacceptable toxicity. The primary endpoint of the study was OS. Secondary endpoints: safety, objective response-rate (ORR), progression-free survival (PFS).

Results: Seventy-one pts were enrolled from 11/2019 to 04/2023: this interim analysis was performed after obtaining at least one post-baseline tumor assessment data from 62 pts. The median follow-up was 21.9 mos (interquartile [IQ] range: 15.6 — 27.3 mos): 27.4% female, median age 64 yrs (IQ range: 55— 70 yrs), 21 pts (34%) had a pure/predominant non-UC VH: 10 (48%) squamous differentiation/sarcomatoid, 5 (24%) adenocarcinoma, 4 (19%) small-cell neuroendocrine, 1 (5%) clear-cell, and 1 nested VH (5%). In 62 pts, 12 (19%) CR and 10 (16%) PR were obtained, the ORR being 35.5% (95% CI, 23.7 — 48.7) and disease control rate was 71.0% (95% CI, 58.1 — 81.8). In VHs cohort, the ORR was 42.9% (95% CI, 21.8 — 66.0). Median PFS was 7.4 mos (95% CI, 4.9 — 26.3 mos) and median OS was 13.1 mos (95% CI, 7.23 — NA). The duration of response (DOR) was 8.18 mos (95% CI, 4.0 — 21.2); 42 pts (67.7%) of 62 pts had all-grade treatment-related adverse events (trAE): among them, 7 pts (16.7%) reported grade $\geq$ 3 trAE. Dose-reductions of CABO were needed in 26 pts (41.9%). No treatment-related deaths were reported.

Conclusions: CABO in combination with DURVA showed promising preliminary activity with a manageable safety profile in pts with advanced in VHs and UC after previous chemotherapy exposure. More mature results with longer follow-up will be presented.

Clinical trial identification: NCT03824691.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori.

Funding: Ipsen, AstraZeneca, Fondazione IRCCS Istituto Nazionale dei Tumori.

Disclosure: P. Giannatempo: Financial Interests, Personal and Institutional, Advisory Board: Pfizer, Astellas, Janssen, msd, merk. G. Baciarello: Financial Interests, Personal, Advisory Board: Gensenta; Financial Interests, Institutional, Steering Committee Member: Bayer; Non-Financial Interests, Principal Investigator: Roche, Eli Lilly, MSD; Non-Financial Interests, Member: ASCO. S. Buti: Financial Interests, Personal, Advisory Board: BMS, Pfizer, MSD, MSD, Ipsen, AstraZeneca, Pierre-Fabre, Novartis; Financial Interests, Personal, Invited Speaker: BMS, MSD, Ipsen, AstraZeneca, Novartis; Financial Interests, Institutional, Local PI: BMS, Ipsen, AstraZeneca; Financial Interests, Institutional, Coordinating PI: BMS, MSD; Financial Interests, Institutional, Research Grant: Novartis; Non-Financial Interests, Other, Member of panel for kidney cancer guidelines: AIOM (Italian Association of Medical Oncology); Non-Financial Interests, Other, member and coordinator of the "Rare Tumors" group: Meet-URO group (Italian Network For Research In Urologic-Oncology). R. Iacovelli: Financial Interests, Personal, Advisory Board: BMS, MSD, Janssen, Astellas, Ipsen, Pfizer, Bayer, Sanofi, Eisai; Financial Interests, Personal, Invited Speaker: Recordati; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Local PI: MSD, Seagen; Non-Financial Interests, Member: AIOM. E. Verzoni: Financial Interests, Personal, Advisory Board: Msd, Janssen, AstraZeneca; Financial Interests, Personal, Invited Speaker: BMS, Astellas, Ipsen, Pfizer; Non-Financial Interests, Principal Investigator: MSD, Ipsen, Astellas, Janssen, Lilly, Pfizer. G. Procopio: Financial Interests, Personal, Advisory Board, consultant fees: Astellas, AstraZeneca, Bayer, BMS, Janssen, Ipsen, Merck, MSD, Novartis, Pfizer; Financial Interests, Institutional, Research Grant, research funding for no profit clinical trial: Ipsen. A. Necchi: Financial Interests, Institutional, Research Grant: Merck, AstraZeneca, Ipsen, BMS, Gilead; Financial Interests, Personal, Steering Committee Member: Roche, Janssen, Bayer, Astellas, AstraZeneca, Merck, Clovis Oncology; Financial Interests, Coordinating PI: Incyte; Financial Interests, Local PI: Pfizer; Non-Financial Interests, Leadership Role: Global society of Rare Genitourinary Tumors (GSRGT). All other authors have declared no conflicts of interest.

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2369P Phase II study of nivolumab (nivo) and ipilimumab (ipi) for advanced bladder cancer with variant histologies (BCVH)

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Background: Patients (pts) with BCVH have poor outcomes. We previously reported an ORR of 37% in 19 patients with BCVH for the combination of nivo+ipi. Herein, we report the analysis of the fully accrued BCVH cohorts. (NCT 03333616).

Methods: Eligible pts had locally advanced unresectable or metastatic BCVH (>90% [JB1] variant histology) and ECOG performance status $\leq$2. Prior immunotherapy was prohibited; no limit on prior chemotherapy. Pts received nivo 3 mg/kg + ipi 1 mg/kg IV q3 weeks for 4 cycles followed by nivo 480 mg IV q4 weeks until unacceptable toxicity or progression. Primary endpoint was objective response rate (ORR) by RECIST 1.1.

Results: 49 patients were enrolled from 4/2018 to 12/2022; including 19 pts previously reported; 30 pts were newly enrolled (including 7 from neuroendocrine cohort). 35 (71%) pts were treatment experienced. 28 (57%) pts received 4 doses of nivo+ipi and 24 pts received nivo maintenance: median number of cycles was 10.5 (range, 1-57). Median follow-up for surviving pts was 14.7 (range 1.4-56.7) months. ORR was 35% (80% CI, 26%-45%, N=17) (Table). Median duration of response was not reached; 9 pts maintained response > 12 months. 17 (35%) pts developed treatment-related grade $\geq$ 3 toxicities with one grade 5 toxicity; 3 pts had treatment unrelated grade 5 toxicities. 16 (33%) required high dose steroids ($\geq$40 mg prednisone or equivalent).

Table: 2369P Response summary by tumor histologies

	CR	PR	SD	PD	NE
Overall (N=49, %)	2 (4)	15 (31)	8 (16)	22 (45)	2 (4)
Squamous (N=12, %)	0 (0)	3 (25)	3 (25)	4 (33)	2 (17)
Small Cell (N=12, %)	1 (8)	5 (42)	0 (0)	6 (50)	0 (0)
Adenocarcinoma (N=8, %)	0 (0)	0 (0)	2 (25)	6 (75)	0 (0)
Urachal (N=9, %)	0 (0)	3 (33)	2 (22)	4 (44)	0 (0)
Other* (N=8, %)	1 (13)	4 (50)	1 (13)	2 (25)	0 (0)

*Plasmacytoid N=2, Spindle Cell/Sarcomatoid N=4, Clear Cell N=2 CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable

Conclusions: The combination of nivo+ipi resulted in objective and durable responses in a subset of pts with BCVH notably with no responses in adenocarcinoma and 50% ORR in small cell carcinoma; toxicities were manageable. This is targeting an unmet need for these pts.

Clinical trial identification: NCT 03333616.

Legal entity responsible for the study: Dana Farber Cancer Institute.

Funding: BMS.

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However, first draft frequently initiated by myself when I am 1st author: Medical Communication; Non-Financial Interests, Other, Political vote usually as "independent", not a member of any political party. I am an issue voter: General US Politics; Other, Employee at DFCI. I am also the past President of Medical Staff at DFCI 2015-2018: Dana-Farber Cancer Institute (DFCI); Other, Professor (non-profit school): Harvard Medical School (HMS); Other, No financial interest. Institutional. Filed patents related to biomarkers of immune checkpoint blockers, and circulating free methylated DNA. No money made and some patents were abandoned: Filed patents. All other authors have declared no conflicts of interest.

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2370P Updated results of PEANUT trial: Pembrolizumab and nab-paclitaxel as salvage therapy for platinum-treated, locally advanced or metastatic urothelial carcinoma (mUC)

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Background: Pembrolizumab (pembro) is approved for the II-line in mUC. In PEANUT trial (NCT03464734) we investigated the efficacy of the combination of pembro plus nab-paclitaxel after chemotherapy (CT) failure. Herein, a long-term follow-up (FUP) update and a post-hoc analysis are presented.

Methods: In an open-label, single-arm, phase 2 trial pts with mUC after failure of $\leq$2 platinum-based CT were enrolled. Pts received 200 mg pembro on D1, and 125 mg/m^2 nab-paclitaxel on D1 and D8, every 3 weeks, until disease progression (PD) or unacceptable toxicity. The primary endpoint was the progression-free survival (PFS).

Results: As of April 1, 2023, 11/70 (15.7%) pts enrolled are in CR after a median FUP of 45.5 mo (95% CI, 42.3 − 49.8). 5/70 (7.1%) completed 2-yrs of treatment. Median OS was 11.7 mo (95% CI, 8.27 − 17.2) and median PFS was 5.1 mo (95% CI, 4.1 − 7.37). The ORR was 47.1%. For CR or PR pts, median OS was 28.4 mo (95% CI, 16.2 − NA). OS rate was 19 (27.1%) at 46 mo. Treatment was discontinued due to toxicity in 12/70 (17.4%) pts: in 9/70 only nab-paclitaxel, in 3/70 both. After PD, 22/70 (32.4%) patients underwent further therapies. Levels of hemoglobin (HR 0.88; 95% CI, 0.76 − 1; *p* value 0.095) and NLR at baseline (HR 1.2; 95% CI, 1.1 − 1.3; *p* value 0.0032), discontinuation due to toxicity (HR 0.34; 95% CI, 0.14 − 0.79; *p* value 0.012) and subsequent therapy (HR 2.4; 95% CI, 1.3 − 4.4; *p* value 0.0033) appear to have a statistically significant impact in PFS. Instead, the primary (bladder vs UTUC) (HR 2.3; 95% CI, 1.1 − 4.7; *p* value 0.027), liver metastases (HR 2.4; 95% CI, 1.3 − 4.2; *p* value 0.0032), NLR at baseline (HR 1.2; 95% CI, 1.1 − 1.3; *p* value 0.0014) and discontinuation due to toxicity (HR 0.38; 95% CI, 0.16 − 0.89; *p* value 0.026) seem to have a greater influence on OS.

Conclusions: After nearly 4 years, the combination of pembrolizumab and nab-paclitaxel maintained clinically meaningful efficacy in pts with mUC that progressed after platinum-based CT. OS data and post-hoc analyzes are consistent with what has been published in the literature in this disease setting.

Clinical trial identification: NCT03464734.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori di Milano - Italy.

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2371P Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC): Long-term outcomes from the JAVELIN Bladder 100 trial in older patients (pts)

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Background: In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), avelumab 1L maintenance therapy + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone in pts with aUC without progression following 1L platinum-based chemotherapy. After ≥2 years of follow-up in all pts, median OS was 23.8 months (95% CI, 19.9-28.8) vs 15.0 months (95% CI, 13.5-18.2), respectively. Avelumab 1L maintenance also had minimal impact on quality of life. Here, we report long-term efficacy and safety outcomes in subgroups based on older age (≥65 years).

Methods: Eligible pts with locally advanced or metastatic UC without progression following 4 to 6 cycles of 1L platinum-based chemotherapy were randomized 1:1 to receive avelumab + BSC (n=350) or BSC alone (n=350). The primary endpoint was OS; secondary endpoints included PFS and safety. For this post hoc analysis, subgroups aged ≥65 to <75 years, ≥75 years, and ≥80 years were analyzed. Pts aged <65 years were not included in this analysis.

Results: At data cutoff (June 4, 2021), median follow-up in both arms was ≥38 months. In the avelumab + BSC and BSC alone arms, age was ≥65 to <75 years in 136 and 163 pts, ≥75 years in 85 and 80 pts, and ≥80 years in 28 and 27 pts, respectively. Across all subgroups, OS and PFS were prolonged with avelumab + BSC vs BSC alone (Table). The table also shows incidence of any-grade and grade ≥3 treatment-related adverse events (TRAEs) in the subgroups.

Conclusions: Long-term outcomes from JAVELIN Bladder 100 confirm prolonged OS and PFS with avelumab + BSC vs BSC alone in older pts. Long-term safety of avelumab 1L maintenance was similar across subgroups, confirming its tolerability. These findings provide further support for avelumab 1L maintenance as standard of care in pts with aUC without progression following 1L platinum-based chemotherapy, including older pts over 65 years old.

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2372P Efficacy of a tailored approach with nivolumab (N) and nivolumab+ipilimumab (N+I) as immuno-therapeutic boost in metastatic urothelial carcinoma (mUC): Final results of TITAN-TCC

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Background: N is approved in 2L mUC after platinum-based chemotherapy. Studies suggest improved outcomes for dual checkpoint inhibition in particular with high doses of ipilimumab (N 1mg/kg + I 3mg/kg). We report final data of TITAN-TCC, NCT03219775, that used a tailored approach with N and N+I boosts for non-response.

Methods: Pts with mUC started N induction (240mg Q2W x4). Non-responders of cohorts 1 (dose escalation) and 2 (high dose ipilimumab) received N+I boosts as reported in the table. Responders to N induction continued with N maintenance (240mg Q2W), but could receive N+I per the respective schedules for later progression. Repeated boost phases were possible. Primary endpoint was objective response rate (ORR) to N ± N+I per RECIST1.1. Secondary endpoints included ORR to N induction, progression-free survival (PFS), and overall survival (OS).

Results: TITAN-TCC was conducted from 08/2017 to 02/2023. In cohort 1, 42 pts were 1L and 44 2/3L. Cohort 2 recruited 2/3L pts only with 83 being enrolled. For follow-up times see the table. ORR to N induction was 29%, 23%, and 20% for cohort 1 − 1L, cohort 1 − 2/3L, and cohort 2, respectively. In total, 105 pts received any boost doses, 14 had repeated boost phases. Best overall response to N ± N+I was 48% (95% CI 32-64), 27% (95% CI 15-43), and 33% (95% CI 23-44), respectively. 1-, 2-, and 3- year OS

Table: 2371P

Age	≥65 to <75 years		≥75 years		≥80 years	
Arm	Avelumab + BSC (n=136)	BSC (n=163)	Avelumab + BSC (n=85)	BSC (n=80)	Avelumab + BSC (n=28)	BSC (n=27)
Median OS (95% CI), months	28.7 (20.9-35.1)	17.1 (12.9-21.3)	24.0 (18.6-37.0)	13.5 (8.6-18.5)	24.9 (14.1-NE)	10.0 (7.0-26.9)
HR for OS (95% CI)	0.73 (0.543-0.974)		0.59 (0.401-0.877)		0.57 (0.284-1.155)	
Median PFS by investigator (95% CI), months	7.4 (3.7-11.2)	2.8 (1.9-3.7)	9.2 (5.6-13.3)	2.2 (1.9-3.7)	13.8 (5.7-30.3)	1.9 (1.7-3.7)
HR for PFS (95% CI)	0.51 (0.389-0.666)		0.38 (0.266-0.554)		0.27 (0.129-0.560)	
Any-grade TRAE, n (%)*	103 (79.2)	2 (1.2)	70 (82.4)	2 (2.6)	24 (85.7)	0
Grade ≥3 TRAE, n (%)*	24 (18.5)	0	18 (21.2)	0	9 (32.1)	0

NE, not estimable.
*In treated pts.

Table: 2372P

Parameter	Cohort 1 - 1L N=42	Cohort 1 - 2/3 L N=44	Cohort 2 (2/3 L) N=83
Boost schedule	2x N 3mg/kg + I 1mg/kg (Q3W); if no response: 2x N 1mg/kg + I 3mg/kg (Q3W)	2x N 3mg/kg + I 1mg/kg (Q3W); if no response: 2x N 1mg/kg + I 3mg/kg (Q3W)	2x N 1mg/kg + I 3mg/kg (Q3W); if no response: 2x N 1mg/kg + I 3mg/kg (Q3W)
Median age, years (range)	70 (45-84)	68 (45-80)	68 (37-84)
Median follow-up, months (range)	10.4 (0.6-51.8)	7.5 (0.3-60.3)	5.6 (0.3-42.6)
ORR N induction, n (%)	12 (29)	10 (23)	17 (20)
ORR N ± N+I, n (%)	20 (48)	12 (27)	27 (33)
Median OS, months (95% CI)	16.4 (7.3-28.5)	8.3 (5.3-19.3)	7.6 (5.0-14.9)
Median PFS, months (95% CI)	3.0 (1.8-6.8)	1.9 (1.7-5.8)	1.9 (1.8-3.2)

rates were 55%, 37%, and 31% for cohort 1 — 1L, 42%, 31%, and 18% for cohort 1 — 2/3L, and 40%, 34%, and 34% for cohort 2. For median OS and PFS see the table.

Conclusions: Despite meaningful clinical activity of the TITAN-TCC approach in cohort 1 — 1L, starting treatment with N monotherapy appears inadequate given the aggressiveness of mUC. In 2/3L, N+I boosts with escalating dose of ipilimumab (cohort 1 — 2/3L) did not improve ORR vs. N monotherapy as reported in the literature. However, it did for boosts with high dose ipilimumab (cohort 2) with a considerable 3-year OS rate for 2/3L mUC.

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2373P Outcomes by retrospective eligibility for maintenance therapy of patients (pts) with advanced urothelial carcinoma (UC): Post hoc analysis of KEYNOTE-361

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Background: The phase 3 KEYNOTE-361 trial (NCT02853305) of 1L pembrolizumab + chemotherapy (chemo) or pembrolizumab vs chemo alone in pts with advanced UC completed enrollment prior to approval of PD-L1 maintenance therapy after 1L chemo. This post hoc exploratory analysis evaluated pts who received chemo by eligibility for post-chemo maintenance therapy.

Methods: Pts who received chemo alone were retrospectively categorized as eligible (received ≥4 cycles of chemo and either did not have PD or died within 0-10 wk after completion of chemo or did have a PD or died >10 wk after completion of chemo) or ineligible (received ≥4 cycles of chemo and had a PD or died while on chemo or within 0-10 wk after completion of chemo) for post-chemo maintenance. Pts who received <4 cycles of chemo, were censored before end of chemo, or had non-evaluable or missing scans within 10 wk of chemo were excluded. Exploratory end points were PFS, landmark PFS (time from last non-PD assessment within 0-10 wk of chemo completion to PD per RECIST v1.1 by BICR), OS, and landmark OS (time from last non-PD assessment within 0-10 wk of chemo completion to death).

Results: Median follow-up was 31.7 mo (range, 22.0-42.3). Among 342 pts in the chemo arm, 172 (50.3%) were eligible for maintenance, 108 (31.6%) were ineligible, and 62 (18.1%) were excluded; 85/172 pts (49.4%) received subsequent anti—PD-1/L1 therapy. Results for pts eligible for post-chemo maintenance are reported (Table). For maintenance-ineligible pts, median (95% CI) PFS and OS were 5.1 mo (4.2-6.0) and 10.2 mo (9.1-11.6), respectively.

Conclusions: This post hoc exploratory analysis demonstrates that pts who are eligible for post-chemo maintenance therapy have a favorable prognosis. About 50% of pts who initiated chemo on a clinical trial were considered eligible for maintenance therapy. To our knowledge, these are the first exploratory data describing outcomes of maintenance-eligible pts from the initiation of chemo.

Table: 2373P	
	Maintenance eligible n = 172
PFS, median (95% CI%), mo	9.0 (8.4-10.4)
PFS rate at 12 mo, % (95% CI)	35.1 (27.3-43.0)
Landmark PFS, median (95% CI), mo	4.1 (2.9-6.1)
Landmark PFS rate at 12 mo, % (95% CI)	25.2 (17.9-33.2)
OS, median (95% CI, mo)	23.3 (19.4-26.1)
OS rate at 24 mo, % (95% CI)	46.8 (39.2-54.1)
Landmark OS, median (95% CI), mo	18.8 (14.6-21.8)
Landmark OS rate at 24 mo, % (95% CI)	39.9 (32.2-47.5)

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2374P A phase Ib single-arm trial of bintrafusp alfa (BA) for pretreated, locally advanced/unresectable or metastatic (advanced) urothelial cancer (aUC)

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Background: Patients (pts) with aUC have poor prognosis after progression on platinum-based chemotherapy (PCT). Immune checkpoint inhibitors (ICI) post-PCT provide overall response rate (ORR) $\leq$ 21%. TGF-β pathway can mediate resistance to ICI in aUC. BA is a first-in-class bifunctional fusion protein composed of extracellular domain of TGF-βRII receptor ("trap") fused to a human IgG1 mAb blocking PD-L1. We conducted a phase 1b trial evaluating the safety/efficacy of BA in PCT-refractory aUC.

Methods: This open-label multicenter trial enrolled pts with PCT-refractory aUC (ECOG PS $\leq$ 1) with $\leq$2 lines of systemic therapy for aUC (no prior therapy targeting T-cell co-stimulation, ICI, or TGF-β pathway). Pts received BA 1200mg every 2 weeks until progression, unacceptable toxicity, death, withdrawal, or for $\leq$2 years. Primary endpoint: investigator-assessed confirmed ORR (RECIST 1.1); secondary endpoints: duration of response (DOR), PFS, OS. A Bayesian predictive probability design for the primary endpoint had 5.7% alpha (type I error) and 85.4% power to rule out ORR $\leq$21% (target ORR $\geq$40%; target accrual 40 pts).

Results: Accrual was stopped based on available trial data indicating that BA was unlikely to show meaningful benefit beyond current available therapies, also considering the evolving therapy landscape. Between Oct 15, 2020, and Aug 31, 2021, 25 pts (21 men, median age 67) were enrolled. At data cutoff (DOC), confirmed ORR 20% (5 pts; 95%CI 6.8-40.7; 2 CR, 3PR), median DOR N/E; median PFS 1.8 mo (95% CI 1.2-3.4), median OS not reached. Median number of BA doses 4; 24 pts discontinued BA [14 for progression; 8 for treatment-emergent adverse event (TEAE); 1 completed therapy; 1 death]; 1 receiving BA at DOC. All pts experienced TEAE; 7 pts experienced G$\geq$3 treatment-related adverse events (TRAEs). Most common G$\geq$3 TEAEs ($\geq$10% of pts): anemia (32%), urinary tract infection (16%); most common G$\geq$3 TRAEs: colitis (4%), pneumonitis (4%).

Conclusions: Accrual was feasible but further development of BA in this therapy setting was halted. Limitations: relatively small sample size and no randomization. Future studies can assess the role of TGF-β pathway inhibition in UC.

Clinical trial identification: NCT04349280.

Legal entity responsible for the study: GSK and Merck KGaA.

Funding: GSK and Merck KGaA.

Disclosure: P. Grivas: Financial Interests, Personal, Advisory Board: AstraZeneca, MSD, Bristol Myers Squibb, Asieris Pharmaceuticals, Merck KGaA, Seattle Genetics, Aadi Bioscience, Pfizer, Janssen, Boston Gene, Mirati Therapeutics, Exelixis, Genentech/Roche, Gilead Sciences, CG Oncology, Dyania Health, Infinity Pharmaceuticals, QED Therapeutics, 4D Pharma PLC, ImmunityBio, Lucence Health, G1 Therapeutics, Fresenius Kabi, Guardant Health, PureTech, Regeneron Pharmaceuticals, Strata Oncology, Urogen, Silverback Therapeutics, Astellas Pharma; Financial Interests, Institutional, Invited Speaker: Pfizer, Clovis Oncology, Bavarian Nordic, Gilead Sciences, Bristol Myers Squibb, Debiopharm Group, MSD, QED Therapeutics, GSK, Mirati Therapeutics, G1 Therapeutics, Merck KGaA. S. Sridhar: Financial Interests, Personal, Advisory Board: Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Hoffmann La Roche, Pfizer; Financial Interests, Institutional, Research Grant, Unrestricted Research grant to institution for developing a database: Seagen; Financial Interests, Institutional, Research Grant: Bayer, Janssen. B. Perez Valderrama: Financial Interests, Personal, Advisory Board: Pfizer, Astellas Pharma, Bristol Myers Squibb, Ipsen, EUSA Pharma, Sanofi-Aventis, Merck, MSD, AstraZeneca; Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Roche, Bayer, EUSA Pharma, MSD, Merck, Pfizer, Janssen, Astellas Pharma. D.E. Castellano Gauna: Financial Interests, Personal, Advisory Board: Pfizer, Roche, BMS, Janssen, Astellas, MSD, Ipsen, AstraZeneca, Novartis, GSK; Financial Interests, Institutional, Invited Speaker: Pfizer, Roche, MSD, BMS, AstraZeneca, Janssen, Astellas, Ipsen, Exelisis, Eisai, Lilly, Bayer, GSK, Clovis, QED Therapeutics; Non-Financial Interests, Personal, Other, Executive member: SOGUG (Spanish Oncology Genito-Urinary Group) Foundation. Y. Loriot: Financial Interests, Personal, Advisory Board: Merck Kga, Pfizer, Gilead, seattle genetics, Taiho; Financial Interests, Personal, Other, lectures, advisory boards: MSD, AstraZeneca, Astellas, Janssen; Financial Interests, Personal, Other, lectures, advisroy boards: Roche, BMS; Financial Interests, Institutional, Research Grant: Janssen, Sanofi, MSD, Roche, Celsius; Financial Interests, Institutional, Invited Speaker: Janssen, Pfizer, Janssen, MSD, Janssen, Exelexis, AstraZeneca, Pfizer, Merck Kga, BMS, Astellas, Gilead, Incyte; Financial Interests, Invited

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Morales Barrera: Financial Interests, Personal, Advisory Board: AstraZeneca, Astellas, Pfizer; Financial Interests, Personal, Invited Speaker: Pfizer, Astellas; Non-Financial Interests, Principal Investigator: AstraZeneca, Gilead, Roche, BMS, AstraZeneca. All other authors have declared no conflicts of interest.

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2375P Neoadjuvant sintilimab combined with gemcitabine and cisplatin (GP) for muscle-invasive bladder cancer (MIBC) patients followed by selective bladder sparing surgery

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Background: To evaluate the safety and efficacy of GP regimen in combination with immune checkpoint inhibitor sintilimab as neoadjuvant therapy for MIBC patients and the feasibility of the following selective bladder sparing surgery.

Methods: Patients with histopathologically confirmed urothelial carcinoma without distant metastases (T2-4a, N≤1, M0, AJCC 8th), and have adequate organ function will be enrolled. The therapeutic regimen were sintilimab 200 mg once on day 8, gemcitabine 1,000 mg/m^2 and cisplatin 35 mg/m^2 once on days 1 and 8, every 21 days for four cycles. Multi-disciplinary Treatment was conducted for surgical plan following neoadjuvant therapy. Radical cystectomy (RC) and bladder sparing strategy including partial cystectomy (PC) and TURBT and surveillance were fully discussed. Salvage surgery would be evaluated after recurrence. The primary endpoint was pathologic complete response (pCR, pT0N0) rate. The secondary end points were pT<2 rate, R0 resection rate, event free survival (EFS) and safety.

Results: From May 4, 2020 to Aug 10, 2022, 37 patients were enrolled. Notwithstanding the poor pathological situation of high T3-T4a proportion (n=14, 37.8%), a promising bladder preservation rate was achieved (73.0%, including 19 patients TURBT, 5 patients PC and 3 surveillance). Among the patients who underwent surgery (n=34), fourteen patients (41.2%) achieved pCR, twenty-seven patients (79%) achieved pT<2 (41% pT0, 9% pTa, 26% pT1, 3% pTis). All patients achieved R0 resection. With a median follow-up of 20.1 months, seven patients relapsed (bladder preservation vs. RC, 22.2% vs. 10%, p=0.321) and 1-year EFS was 89.1%. There was no significant difference between bladder-preserving and radical surgery subgroup to EFS (P=0.569). The most common grade ≥3 treatment-related adverse events (TRAEs) were neutropenia (n=8; 21.6%), which was related to chemotherapy. There were no Grade 3 immune-related AEs.

Conclusions: Neoadjuvant GP plus sintilimab is a promising regimen for MIBC patients, with relatively high pCR rate and triggering the emerging roles for the MDT decision-making for bladder sparing surgery.

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2376P Pembrolizumab monotherapy following tri-modality treatment for selected patients with muscle-invasive bladder cancer

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Background: This is a phase 2, single arm, single-site study of Pembrolizumab as maintenance therapy in muscle-invasive bladder cancer (MIBC) participants who has received maximum Transurethral resection of bladder tumor (TURBT) and tri-modality treatment (TMT) and achieved complete response (CR).

Methods: This trial includes Patients with cT2-4N0M0 MIBC who declined or were ineligible for cystectomy (RC), and achieved CR after receiving maximal TURBT then Stereotactic ablative radiotherapy (SABR) boost to bladder tumor or tumor bed and concurrent radio-chemotherapy. During SABR, intravesical installation of isovolumetric saline through urinary catheter ensured adequate bladder filling. After TMT, patients who achieved CR will receive Pembrolizumab as maintenance therapy. Pembrolizumab (200 mg q3w) monotherapy will begin on Day 1 of each 3-week cycle and will continue for up to 17 cycles (approximately 1 year). The primary endpoint was progression-free survival (PFS).

Results: From January 11, 2022 to April 20, 2023, twenty-three patients with MIBC were enrolled. The median age of included patients was 68 years and clinical stage ranged from cT2 (n=20) to cT3 (n=3). TURBT was visibly complete in twelve cases. After a median follow-up time of 6 months, 5/23 (21.7%) patients reported immune-related AEs, which included Grade 2 myositis, hypothyroidism, pneumonitis and cystitis, and had no ongoing toxicity after administration of steroids. The estimated 1-year PFS, overall survival and local control rate was 78%, 94.4% and 94.7%. One patient experienced local recurrence with MIBC and bone metastasis respectively after 7 months of TMT. One patient died from pulmonary infection related to COVID-19, the others are alive with no evidence of cancer and with intact well-functioning urinary bladder at median follow-up of 6 months.

Conclusions: Pembrolizumab maintenance therapy after SABR boost to bladder tumor and concurrent radio-chemotherapy was well-tolerated with promising efficacy in the early analysis. Immune related toxicity was consistent with prior monotherapy trials. Selected correlative analyses from serially collected blood and tissue specimens will be presented.

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Legal entity responsible for the study: The authors.

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2377P Interim results from a phase II clinical study of tislelizumab combined with gemcitabine and cisplatin as a bladder-sparing therapy for urine tumor DNA (utDNA) defined clinical complete response (cCR) MIBC patients

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Background: In order to precisely select MIBC patients (pts) for bladder preservation, it's necessary to establish strict standard for cCR. Our study was conducted to evaluate the efficacy of tislelizumab combined with gemcitabine and cisplatin (GC) as a bladder-sparing therapy for utDNA-defined cCR pts.

Methods: The study enrolled pts were cisplatin-eligible with no carcinoma in situ. Firstly, pts received maximal TURBT, then received tislelizumab 200 mg in day 1 (D1), cisplatin 70 mg/m^2 D2, and gemcitabine 1000 mg/m^2 D1 and D8 every 3 weeks for 4 cycles. Secondly, pts further received utDNA testing and clinical restaging were performed. Pts who were utDNA-defined cCR (defined as negative for utDNA, normal urine cytology and MRI imaging, plus bladder biopsies≤cTa.) proceeded bladder preservation, while non-utDNA-defined cCR pts underwent radical cystectomy (RC). Finally, all pts received tislelizumab every 3 weeks for 8 cycles followed by surveillance. The primary endpoint was utDNA-defined cCR rate. Secondary endpoints were 1-year bladder intact disease-free survival(BIDFS) rate, OS and safety.

Results: 16 MIBC pts enrolled between Jul. 2021 and Sep. 2022 and 14 pts were analyzed (male 85.7%; median age 62(39-75)). cT2=21.4%, cT3=64.3%, cT4a=14.3%, cN0=78.6%, cN1=21.4%. 100% pts received maximal TURBT. The median number of tislelizumab and GC cycles were 4 (4-4) and 4 (3-4), respectively. Median follow up was 13.2 months (7.9-17.1). The utDNA-defined cCR rate was 35.7% (95% CI, 10.7%-60.7%). Non-utDNA-defined cCR pts received RC and all were≥pT1N0M0. The 1-year BIDFS rate and 1-year OS rate for utDNA-defined cCR pts were 100% (95%CI, 100%-100%) and 100% (95%CI, 100%-100%), respectively. Grade 1-2 immune related adverse events, including rash (n=4), ALT/AST increased (n=3), hyperthyroidism (n=1) and hyperglycaemia (n=1).

Conclusions: The interim results demonstrated the utDNA-defined cCR can successfully select MIBC pts for precise bladder-sparing treatment.

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2378P Efficacy and safety outcomes with pembrolizumab (pembro) rechallenge for patients (pts) with advanced/metastatic urothelial cancer (UC) who responded to first-course treatment

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Background: Pembro has shown durable antitumor activity in advanced/metastatic UC across multiple studies. Rechallenging pts who previously responded to pembro and had their disease subsequently progress may be a potential treatment strategy. We conducted a post hoc pooled analysis of outcomes of pembro rechallenge in pts from the phase 3 KEYNOTE-045 (NCT02256436), phase II KEYNOTE-052 (NCT02335424), and phase 3 KEYNOTE-361 (NCT02853305) studies.

Methods: Pts were included in the pooled analysis if they received pembro monotherapy in the course of one of the studies and stopped pembro after CR or had CR, PR, or SD to first-course pembro and completed 2 y of treatment. Protocol-specified pembro rechallenge was administered at a dose of 200 mg Q3W for up to 17 cycles (∼1 y). Outcomes in this exploratory analysis included ORR, DOR, PFS, OS, and safety of second-course pembro.

Results: A total of 49 pts were included (n = 11, KEYNOTE-045; n = 10, KEYNOTE-052; and n = 28, KEYNOTE-361). Best overall response to first-course pembro included 21 CRs, 23 PRs, 3 SDs, and 2 non-CRs/non-PDs (defined as persistence of ≥1 nontarget lesions and/or maintenance of tumor marker level above the normal limits). Median duration of the first response to pembro was 26.7 mo (range, 4.1-54.9+). Median time between first and second course was 10.7 mo (range, 1.0-36.3); median duration of second course was 8.3 mo (0.0-13.2). Seventeen pts (35%) completed second-course pembro; the most common reason for discontinuation was disease progression (n = 19; 39%). ORR to second-course pembro was 41% (8 CR; 12 PR) and median DOR was 14.0 mo (2.1+ to 20.5). From start of second-course treatment, the 12-mo PFS rate was 45% and the 24-mo OS rate was 61%. Treatment-related adverse events (AEs) occurred in 22 pts (45%); 3 pts (6%) experienced grade 3-4 treatment-related AEs. Three pts (6%) discontinued due to a treatment-related AE, and no pts died due to a treatment-related AE.

Conclusions: Consistent with prior reports, pts with advanced/metastatic UC whose disease had prior response to pembro may benefit from pembro rechallenge. The safety profile of pembro rechallenge was consistent with the known safety profile of pembro monotherapy.

Clinical trial identification: KEYNOTE-361: NCT02853305; Release date: August 2, 2016. KEYNOTE-045: NCT02256436; Release date: October 3, 2014. KEYNOTE-052: NCT02335424; Release date: January 9, 2015.

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2379P AVENANCE: Subgroup analysis of patients (pts) with advanced urothelial carcinoma (aUC) with histological variants from a real-world (RW) study of avelumab first-line maintenance (1LM)

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Background: ≈10% of bladder cancers have nonpure UC histology; these tumors are often underdiagnosed and represent an unmet treatment need. AVENANCE (NCT04822350) is evaluating avelumab 1LM in pts with aUC in France and has previously shown clinical activity in a heterogenous population (N=593). We present a subgroup analysis of pts with histological variants.

Methods: Eligible pts had aUC that had not progressed on 1L platinum-based chemotherapy (PBC) and previous, ongoing, or planned avelumab 1LM. The primary endpoint was overall survival (OS); secondary endpoints included progression-free

survival (PFS), duration of treatment (DOT), and safety. Here, pts with nonpure UC (mixed UC with variants [UC-V] and pure variants [PV]) were analyzed.

Results: 44/593 pts had aUC with histological variants; at data cutoff (March 30, 2023), median follow-up was 18.0 mo (range, 12.9-20.4 mo). Tumor histology was UC-V, including micropapillary and epidermoid, in 32 pts (72.7%) and PV in 12 (27.3%). At the start of 1L PBC, most pts had metastatic disease (UC-V, 96.9%; PV, 91.7%) and ECOG PS 0/1 (UC-V, 71.4%; PV, 55.6%). The most common 1L PBC was gemcitabine + carboplatin in 65.6% of pts with UC-V and 75.0% with PV. In pts with UC-V and PV, best response to 1L PBC was complete response in 18.8% and 33.3%, partial response in 59.4% and 58.3%, and stable disease in 21.9% and 8.3%, respectively. In all 44 pts, median DOT was 5.1 mo (95% CI, 2.8-17.4 mo); 34.1% were still receiving treatment at data cutoff. The table shows OS, PFS, and safety data in pts with aUC with histological variants and the overall population.

Conclusions: RW data from AVENANCE provide evidence of the effectiveness and safety of avelumab 1LM in pts with aUC, including histological variants. To our knowledge, this is the first analysis of avelumab 1LM in this pt population. Data are consistent with findings in the overall population.

Table: 2379P

	aUC with histological variant (n = 44)	Overall population (N = 593)
OS, median, mo (95% CI)	NR (13.9-NE)	20.7 (17.1-NE)
12-month OS rate, % (95% CI)	68.6 (51.9-80.5)	65.4 (61.0-69.4)
PFS, median, mo (95% CI)	5.6 (2.8-17.4)	5.7 (5.3-7.0)
Any-grade TRAE, n (%)	18 (40.9)	254 (42.8)
Serious TRAE, n (%)	3 (6.8)	31 (5.2)

NE, not estimable; NR, not reached; TRAE, treatment-related adverse event.

Clinical trial identification: NCT04822350; First posted, March 30, 2021.

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2380P Real-world effectiveness of single agent enfortumab vedotin (EV) in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC) based on line of therapy and impact of prior platinum (plat) chemotherapy (chemo) and PD-1/PD-L1 inhibitors (PD-1/PD-L1i)

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Background: EV is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated for the treatment (trt) of pts with mUC who have previously received a PD-1/L1i and plat chemo, or are ineligible for cisplatin-containing chemo and have received $\geq$ 1 prior lines of therapy. However real-world effectiveness of EV based on line of therapy and impact of prior trt is currently not well established.

Methods: This study used the nationwide (US-based) Flatiron Health EHR-derived de-identified database. Inclusion: diagnosis of advanced, recurrent or mUC of upper or lower urinary tract and trt with single agent EV in 2nd line or beyond after 12/18/2019 (FDA accelerated approval date). Exclusion: Pts with no documentation of 1st-line therapy or pts with no evidence of contact for 90 days from diagnosis of mUC at treating institution to ensure pts were actively engaged in care at the institution providing data. Time to next therapy (TTNT) and overall survival (OS) were summarized based on line of therapy and prior plat chemo and PD-1/L1i using Kaplan Meier survival estimates and its 95% confidence interval (CI).

Results: Overall 6,566 pts with mUC received trt of which 431 received EV from 1/17/2020 to 9/30/2022. Baseline pt characteristics for each line of therapy will be presented at the meeting. The table summarizes real world TTNT and OS of pts.

Table: 2380P Median TTNT and OS in months and their 95% CI for EV based on line of trt and receipt of prior plat chemo or PD-1/L1i or not

Line (n)	TTNT Overall	TTNT Prior platinum	TTNT Prior PD-1/LI	OS Overall	OS Prior platinum	OS Prior PD-1/LI
2nd (157)	5.3 (4.4, 6.3)	Y 6.3 (5.4, 7.4) N 4.4 (3.5, 5.8)	Y 4.8 (3.7, 6.3) N 5.8 (5.2, 7.3)	7.8 (6.3, 12)	Y 11 (8.4, -) N 6.0 (5.3, 12)	Y 6.3 (5.4, 20) N 9.8 (6.9, 21)
3rd (132)	4.5 (3.2, 5.7)	Y 5.5 (—, —) N 4.5 (3.2, 5.7)	Y 4.6 (3.5, 5.7) N 4.5 (2.5, —)	11 (9.3, 15)	Y 8.6 (5.8, -) N- 11 (10, 16)	Y 11 (9.4, 16) N 10 (7.9, —)
4th (62)	6.2 (5.3, 8.4)	Y 11 (5.0, —) N 6.2 (5.3, 8.2)	Y 6.8 (5.7, —) N 6.2 (4.9, 8.2)	9.3 (8.4, 14)	Y 14 (8.6, —) N 9.0 (8.3, 13)	Y 8.7 (6.1, —) N 11 (8.4, 14)
5th (20)	4.1 (3.6, 6.7)	Y 3.4 (2.4, —) N 4.6 (3.6, —)	Y 7.4 (1.4, —) N 4.0 (3.0, 6.7)	7.2 (3.6, —)	Y 5.4 (2.4, —) N 7.2 (3.6, —)	Y 8.5 (1.4, —) N 6.1 (3.0, —)

Y, yes; N, No

Conclusions: EV retains activity in pts with mUC, regardless of prior receipt of plat chemo and PD-1/L1i, and line of systemic therapy. These data may further aid with patient counseling, prognostication, and selection of therapy in the clinics.

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2381P Perceived unmet needs and challenges faced by patients with advanced bladder cancer (aBC) and their caregivers: Results of a social media listening (SML) study conducted in 5 European countries

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Background: aBC has a very poor prognosis and is associated with physical, emotional, and social challenges that patients and caregivers are increasingly expressing online. This observational study aimed to explore and understand challenges that European patients with aBC and their caregivers encounter and share on social media.

Methods: This retrospective, real-world study evaluated written public posts on geolocated social media in France, Germany, Spain, Italy, and the UK posted from October 2017 to January 2022. Natural language processing methods were used to filter out irrelevant content and identify posts from patients and caregivers. Unmet needs were identified by qualitative analysis (ie, annotation) and a saturation method.

Results: A total of 1,670 posts from 1,396 users discussing aBC in 91 publicly available online sources were identified (699 posts from 546 patients and 971 posts from 850 caregivers). Half of patients were male (272 [49.8%]) and more caregivers were female (474 [55.8%]); average age was 58.2 and 35.2 years, respectively. Most unmet needs and challenges identified belonged to 2 main categories: transversal, ie, arising throughout the patient's care pathway (307 [28.1%]) and disease specific (295 [27.0%]). Main challenges included disease worsening (141 [12.9%]), psychological impact (112 [10.3%]), and the need to share experiences and seek support (94 [8.6%]). The top 8 challenges identified in posts from patients and caregivers are listed in the table.

Conclusions: This SML study showed that European patients with aBC and their caregivers have a real need for support and to express their challenges, especially regarding disease management. These findings highlight the need for improved patient and caregiver education and for effective systemic cancer treatments and palliative care options for aBC.

Table: 2381P

Challenge	Occurrence in all posts combined, n (%)	Occurrence in patient posts, n (%)	Occurrence in caregiver posts, n (%)	Category
Disease worsening	141 (12.9)	40 (10.5)	101 (14.2)	Disease specific
Psychological impact	112 (10.3)	38 (10.0)	74 (10.4)	Transversal
Need for sharing/ support	94 (8.6)	42 (11.0)	52 (7.3)	Transversal
Management of aBC symptoms	82 (7.5)	31 (8.1)	51 (7.2)	Disease specific
Sequelae of aBC or care	60 (5.5)	34 (8.9)	26 (3.7)	Remission-phase specific
Worried about future	46 (4.2)	14 (3.7)	32 (4.5)	Transversal
Difficulty accessing treatment	40 (3.7)	13 (3.4)	27 (3.8)	Treatment specific
Pain management	33 (3.0)	11 (2.9)	22 (3.1)	Disease specific
TOTAL	**608 (55.7)**	**223 (58.4)**	**385 (54.2)**	

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2382P EBANO study: Clinical characteristics, treatment patterns and survival results in patients with locally advanced/ metastatic urothelial carcinoma (la/mUC) in northern Spain

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Background: The available real-world (RWD) evidence on the management of la/mUC is limited but of high importance to understand how to incorporate new treatment options in this setting. The present study describes the clinical characteristics, treatment patterns and outcomes in patients (pts) with la/mUC in Northern Spain.

Methods: Retrospective observational analysis from 16 hospitals across 12 provinces. The study population included adult pts diagnosed with la/mUC (January 1,2007-December 31, 2019) followed from the index date until death, loss to follow-up or end of study. Median overall survival (OS) and progression-free survival (PFS) were determined using the Kaplan-Meier method.

Results: We included 1231 pts (median age:68 years;83% men). 74% had $\geq$1 medical comorbidity (hypertension 48%; DM 22.5%; CAD 13%; COPD 12%). Primary tumour locations: bladder (89.2 %), renal pelvis (6.4%), ureter (4.3%), and urethra(0.1%). 70% of the pts had localized disease at diagnosis, cystectomy was the predominant treatment (95%) and 30% received perioperative chemotherapy. Out of 1231 pts, 292 (24%) never received systemic therapy. From 939 pts (76%) treated with 1st-line therapy, 50% were fit for cisplatin. Only 53% (n=493) progressed to receive a second line (2L) and 22% (n=210) received a third line(3L). Chemotherapy was the most common treatment used across all lines (1L[92%], 2L [74%] and 3L[74%]) and immunotherapy represented 3%, 25% and 22%,in 1L, 2L and 3L respectively. 28 pts (3%) were included in clinical trials. Median OS (95% CI) was 12.1(11.3—12.9) months in the overall group and 14.5 in pts who received 1st-line cisplatin-gemcitabine. From the start of the 1L, 2L and 3L treatment, median PFS was 1L:5.0(4.5-5.4);2L: 3.2(2.8-3.5);3L:2.6(2.3-2.9) months. No unexpected toxicity was reported.

Conclusions: The results of this Spanish RWD analysis are comparable to previous studies conducted in other regions of the world and highlight unmet needs such as the proportion of pts who never receive systemic treatment and the notable decrease in the number of pts progressing to second and subsequent lines of therapy hindering the access to new effective treatments developed in this context.

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2383P Stereotactic body radiotherapy (SBRT) of patients with oligometastatic urothelial cancer (UC): A single institution experience

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Background: Standard of care for treatment-naïve patients with metastatic UC is platinum-based combination chemotherapy followed by maintenance avelumab if disease stabilisation or response is achieved. The best strategy to treat patients with oligometastatic disease is unknown; data on side effects and benefit of SBRT in postponing or avoiding systemic treatments in UC is limited.

Methods: We performed a real-world study to explore local control rate (LCR), progression-free survival (PFS), overall survival (OS) and tolerability of SBRT of all available patients with metastatic UC treated at Karolinska University Hospital between 2009 and 2022 (n=41). Baseline clinical characteristics and treatment outcome data were collected from medical records. Radiological examinations were reviewed by a radiologist, from baseline until progressive disease.

Results: In our cohort 78% of patients were male, the median age was 72 yr (range 54-88) and all patients had performance status 0-2 (0:54%, 1:39%, 2:7%). Most

patients had a primary UC in the bladder (66%) and 24% had metastatic disease at diagnosis. The most common location of metastases receiving SBRT were lungs (44%) and lymph nodes (27%). The number of metastatic sites receiving SBRT were 1, 2 and 3 in 73%, 24% and 2% of patients, respectively. Most patients (90%) achieved local control. The PFS and OS for the complete cohort were 4,4 and 26,2 months, respectively. The only clinical factor significantly associated with favourable outcome was the number of metastases, i.e., ≤ 2 vs > 2 ($p = 0.049$). Only one patient did not complete the planned SBRT (treatment related pain). We found 13 patients (32 %) with OS exceeding 3 years and 6 out of these 13 patients never received systemic treatment after SBRT. A total of 11 patients are still alive, but 4 of these patients have follow-up (FU) shorter than 3 years (16-29 months FU).

Conclusions: In summary, SBRT in UC is associated with high LCR and is well tolerated. Selected patients may achieve long survival, postponing or avoiding systemic treatment. A randomized study to investigate the role of SBRT in this population is warranted.

Legal entity responsible for the study: Region Stockholm, Karolinska University Hospital.

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2384P Platinum rechallenge in the era of immune checkpoint inhibitor in locally advanced/metastatic urothelial carcinoma: Multicenter retrospective study

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Background: In locally advanced/metastatic urothelial carcinoma (UC) which progressed after platinum-based chemotherapy (P), treatment with 2nd-line immune checkpoint inhibitor (ICI) is considered. If disease progresses thereafter, there is no domestically approved drug with proven OS benefit in Korea, despite the development of new drugs. Therefore, P rechallenge is common in clinical practice, in spite of little evidence. This study aimed to evaluate efficacy of P rechallenge, and to explore clinical/genetic biomarkers predicting the efficacy of P rechallenge in locally advanced/metastatic UC.

Methods: A total of 66 patients who rechallenged P for locally advanced/metastatic UC from Jan 2017 to Mar 2023 in 3 tertiary referral hospitals was included. Clinical data were retrospectively evaluated. Next generation sequencing was performed for 43 available patients.

Results: Gemcitabine-based regimens (GP, GCb; [G]; n=28), MVAC-based regimens (MVAC/Cb, ddMVAC; [M]; n=35) and other P (n=3) were administered for P rechallenge; ORR, median PFS and OS were 40.9%, 4.5 and 8.7 months. In patients who received [G] for both 1st-line-P and P-rechallenge (n=24), whose ORR (70.8%) and median TTP (7 months) were favorable to 1st-line P, ORR of P rechallenge was 66.7%. On the other hand, in patients who received 1st-line [G] and rechallenged P with [M] (n=35), whose ORR (45.7%) and mTTP (0.5 months) were relatively poor with 1st-line P, ORR of P rechallenge was 22.9%. Median OS of P rechallenge were significantly longer in patients who received ICI between 1st-line-P and P-rechallenge than those who did not receive (12.4 vs 6.5 months, p=.004). In multivariate analysis, poor response to 1st-line P, visceral metastasis and no alterations in DNA damage repair (DDR) genes were significant prognostic factors for poorer OS after P rechallenge.

Conclusions: This study demonstrated favorable efficacy of P rechallenge in era of ICI in locally advanced/metastatic UC, providing a basis for treatment decision after P and ICI failure. P rechallenge showed fair efficacy even in poorly responded patients from 1st-line P. DDR gene alterations and ICI use before P rechallenge may be associated with improved survival after P rechallenge.

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2385P Long-term survival upon anti-PD-(L)1 monotherapy in metastatic urothelial cancer (mUC): A multicenter retrospective study

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Background: Agents targeting programmed cell death (ligand) 1 (α-PD-(L)1) are approved as first- and second-line (1L, 2L) treatment options for mUC. Durable responses have been reported, but clinical trials were often closed before long-term follow-up (FU) could be assessed. C-reactive protein (CRP) and antibiotic (AB) use at start of α-PD-(L)1 have been suggested to be associated with progression. Here, we show 'real-world' long-term survival upon α-PD-(L)1 monotherapy for mUC and correlate outcome to several baseline clinical and laboratory parameters. We expect patients (pts) requiring AB around α-PD-(L)1 start to have poor survival outcomes.

Methods: This is a retrospective, multicenter study, in which data were collected for mUC pts treated with α-PD-(L)1 monotherapy as 1L-4L between 2014-2023. Overall- and progression-free survival (OS, PFS) were estimated with the Kaplan-Meier method. Uni- and multivariate regression models were used to identify independent factors associated with progression, death, PFS and OS.

Table: 2385P Regression analyses

	OS		PFS		Death		Progression	
	Univariate (U)	Multivariate (M)	U	M	U	M	U	M
Lymph node metastasis	**0.000**	**0.038**	**0.000**	0.122	**0.000**	0.776	**0.000**	0.179
Visceral metastasis	**0.000**		**0.000**		**0.000**		**0.001**	
gamma-glutamyltransferase >ULN	**<0.001**	0.198	**<0.001**	0.113	**0.018**	0.883	**0.004**	0.386
Lactate dehydrogenase >ULN	**0.004**	0.429	**0.039**	**0.016**	0.241	0.527	0.107	0.502
CRP>75 percentile	**<0.001**	0.264	**0.010**	0.919	0.274	0.985	0.499	0.237
AB use	0.094	**0.004**	0.618	**0.002**	0.324	0.290	0.945	0.182
Steroid use	0.111	0.178	0.338	0.199	0.512	0.787	0.415	0.477
Platinum fitness	0.676	0.242	0.719	0.147	0.694	0.498	0.087	0.120
Metastasis at cancer diagnosis	0.182	0.070	0.824	**0.020**	0.630	0.157	0.865	0.998

Results: We included 375 pts (median age 67 years (yr) (59-75); 75% male; 68% visceral metastasis; 43% 1L α-PD-(L)1). After a median FU of 55 months (mo), median OS and PFS for all lines combined were 9 (7.448-10.552) and 3 mo (2.525-3.475) respectively. OS and PFS were comparable between treatment lines. For pts who did not progress within 2 yr after α-PD-(L)1 start, PFS and OS were 53.2% and 62.4% respectively at 5 yr after treatment start. Results from the regression analyses are depicted in the table.

Conclusions: Median OS and PFS observed in our cohort is in line with data from clinical trials. Our data suggest that of the patients without progression at 24 mo, half will still be progression-free and alive at 5 yr from treatment start. Our data indicate that AB use around start of α-PD-(L)1 is associated with inferior PFS and OS. We recognize the retrospective nature of our cohort as a limitation. More data will be available and presented at ESMO2023.

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2386P Factors associated with not receiving systemic treatment (tx) in patients (pts) with metastatic urothelial carcinoma (mUC): Results of a retrospective observational study in Germany

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Background: Real-world studies have shown that many pts with mUC do not receive first-line (1L) systemic anticancer tx. With the expanding therapeutic landscape for mUC, identifying factors associated with undertreatment to mitigate outcome disparities is essential.

Methods: This study identified adults with an incident mUC diagnosis (dx; ICD-10 codes C65-68 + C77-79) in 2015-2019 using 2 German statutory health insurance (SHI) claims databases (2013-2020, ≈8 mil. insured). Baseline (BL) characteristics within 24 mo before dx were analyzed. After dx, pts were followed for ≥12 mo or until death. Overall survival (OS) was calculated by Kaplan-Meier estimation. Multivariable logistic regression was performed to determine variables associated with receiving 1L systemic tx.

Results: Overall, 3,226 pts with mUC (mean age, 73.8 y; male, 70.8%; mean Charlson Comorbidity Index [CCI] score, 6.3) were identified. Mean follow-up was 13.8 mo. A large portion of pts with mUC (1,892 [58.6%]) did not receive systemic tx within 12 mo of dx. Median OS after dx was notably shorter in untreated vs treated pts: 3.0 vs 13.7 mo for pts in SHI 1 and 3.6 vs 13.8 mo for pts in SHI 2, respectively. Untreated pts were significantly older (age ≥80 y: untreated, 48.2%; treated, 13.5%); had considerably more comorbidities (mean CCI: untreated, 6.8; treated, 5.5); and had a higher care level (untreated, 37.5%; treated, 11.0%). In regression analysis, older age, no prior UC-related surgery/tx, and earlier dx in the study period were associated with a higher likelihood of not receiving tx (Table).

Conclusions: Untreated pts with mUC seem to have a shorter OS than treated pts. Identified factors associated with undertreatment, such as older age and increased comorbidity, need to be addressed by offering better tolerated mUC tx and educating pts on the benefits of systemic tx.

Table: 2386P Factors associated with receiving mUC tx within 12 mo of mUC dx (multivariable logistic regression using receiving tx as dependent variable)

Variable	Odds ratio (95% CI)	p value
Age at index (continuous)	0.93 (0.92-0.94)	<0.001
Diagnosis year (reference year, 2015; categorical)	1.11 (1.05-1.17)	<0.001
Previous UC-related tx, surgeries, and interventions (24-mo BL; dummy*)	1.65 (1.37-2.00)	<0.001
CCI (24-mo BL; continuous)	0.97 (0.93-1.00)	0.011
Outpatient diagnosis setting (dummy*)	1.28 (1.05-1.54)	0.013
No. of previous all-cause hospitalizations (24-mo BL; continuous)	0.97 (0.94-1.00)	0.027
Female (dummy*)	0.83 (0.69-0.98)	0.032

*Binary variable with the expressions 0 and 1.

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2387P Avelumab first-line maintenance (1LM) for locally advanced or metastatic urothelial carcinoma (la/mUC): Treatment (tx) patterns and real-world (rw) outcomes in the US

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Background: Avelumab 1LM was approved in the US in June 2020 for patients (pts) with la/mUC without disease progression after 1L platinum-based chemotherapy (PBC). This study describes rw outcomes in pts with la/mUC who received avelumab 1LM.

Methods: Pts with la/mUC diagnosed between Jan 2016 and Mar 2023 were identified in the Tempus database. Pts who completed 1L PBC after avelumab's UC approval were considered eligible for 1LM. 1LM was differentiated from second-line (2L) tx based on recorded clinical intent or algorithmically based on initiation of immuno-oncology tx within 180 d of 1L PBC completion without recorded disease progression. Rw overall survival (rwOS), progression-free survival (rwPFS), time on treatment (TOT), and time to next treatment were estimated using Kaplan-Meier methods.

Results: Of 3,299 pts, 59% (1,939) received 1L systemic tx. Median age at diagnosis was 70 y, 74% were male, 85% were White, 88% had transitional cell carcinoma, and 48% had a smoking history. For the 50.2% (974/1,939) of pts who completed 1L tx, PBC was the most common 1L tx (66% [644/974]). Median follow-up (f/u) from 1L PBC start was 10.2 mo; median rwOS was 13.6 mo. 89% (574/644) of pts had no evidence of disease progression after completion of 1L PBC; of these, 38% (219/574) had a recorded 1LM tx, with 62% (135/219) receiving avelumab. These pts had a median f/u from 1LM start of 8.9 mo. RwOS landmark analysis from 1LM start showed that 80% of avelumab 1LM pts were still alive at 6 mo and 63% were alive at 12 mo. Median rwPFS from 1LM start was 6.4 mo; median TOT was 3.85 mo. After 1LM

avelumab, 35% (47/135) of pts received 2L tx. 70% (33/47) of those received enfortumab vedotin (EV), with a median rwOS from 2L start of 11.6 mo.

Conclusions: Early uptake of avelumab 1LM was observed in pts with la/mUC whose disease had not progressed on 1L PBC. F/u time in avelumab-treated pts was short. Future studies with longer f/u may show increased use and allow further assessment of rwOS. Additionally, rw outcomes are improving with newly available 1L and sequencing options. Our study provides early evidence of the effectiveness of 2L EV following 1L PBC and avelumab 1LM.

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2388P Split-dose cisplatin plus gemcitabine use and associated clinical outcomes in the first-line (1L) treatment of locally advanced or metastatic urothelial cancer (la/mUC): Results of a retrospective observational study in Germany (CONVINCE)

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Background: Platinum-based chemotherapy (PBC) followed by avelumab 1L maintenance in patients without progressive disease is standard 1L treatment for la/mUC. In patients ineligible for cisplatin at the standard dose schedule (C; 1 day per cycle), carboplatin (Cb) or a split-dose schedule of C (35 mg/m^2 on days 1 + 8) are alternative options. The effectiveness of these regimens compared with standard-dose C has not been extensively examined, especially in a real-world (rw) setting. In this study, we compared clinical outcomes to PBC in patients with la/mUC who received 1L gemcitabine (G) with split-dose C (CG-S) vs standard-dose CG or CbG regimens.

Methods: The CONVINCE study was initiated in Dec 2021 and enrolled 188 patients who received 1L PBC in 2019-2020 at 27 oncology or urology institutions (8 hospitals/19 office-based practices) across Germany. Objective response rates (ORRs) and rw progression-free survival (rwPFS) and overall survival (rwOS) were compared in the following subgroups: CG-S vs CG and CG-S vs CbG.

Results: Of 124 patients who received 1L PBC with G, 27 (21.8%) received CG-S, 75 (60.5%) CG, and 22 (17.7%) CbG. Median follow-up was 16.5 months. A Cox regression analysis including several characteristics (age, sex, Eastern Cooperative Oncology Group performance status [ECOG PS], comorbidities) showed no significant differences in rwPFS between CG-S vs CG and CG-S vs CbG subgroups.

Conclusions: This rw study provides valuable insights into the use of 1L CG-S in routine clinical practice in Germany, where C administered in split-dose schedule showed comparable outcomes to standard-dose C or Cb. The analysis suggests that CG-S can be a viable alternative for administering 1L PBC in patients with la/mUC for whom standard-dose C may be unsuitable, without compromising treatment effectiveness.

Table: 2388P

Parameter	CG-S (n=27)	CG (n=75)	CbG (n=22)	p value CG-S vs CG	p value CG-S vs CbG
Male, %	70.4	73.3	77.2	–	
Age, median (range), years	66 (50-81)	69 (52-81)	73 (59-84)		
ECOG PS at diagnosis 0/1/2 (%)	59/37/4	55/40/5	46/50/4		
1L PBC cycles, median, n	5	4	6		
rwPFS rates (Kaplan-Meier), %					
6 mo	85	77	86	0.25	0.67
9 mo	63	57	55		
12 mo	37	39	32		
18 mo	15	23	14		
rwPFS, median, mo	10.5	10.5	9.1	0.35	0.24
rwOS rates (Kaplan-Meier), %					
6 mo	100	100	100	0.06	0.15
9 mo	96	100	91		
12 mo	85	85	86		
18 mo	37	69	45		
rwOS, median, mo	14.4	18.8	16.7	0.06	0.14
Best response (physician assessment)					
Evaluable, n (%)	25 (92)	69 (92)	22 (100)	–	
Complete response, %	8.0	11.6	18.2		
Partial response, %	56.0	37.7	40.9		
ORR, %	64.0	49.3	59.1	0.84	0.65

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2389P A multicenter retrospective clinical study: Real-world effectiveness and safety of RC48-ADC alone or combination of RC48-ADC and PD-1 inhibitors for patients with locally advanced or metastatic urothelial carcinoma

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Late withdrawal

2390P Correlation between overall survival and bladder-intact event-free survival in cystectomy-ineligible/refusal muscle-invasive bladder cancer patients in Sweden

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Background: Radical cystectomy (RC) is currently the recommended treatment for muscle-invasive bladder cancer (MIBC) in Europe and the US. In Sweden, patients unfit or refusing RC are offered bladder-sparing curative or palliative treatment, such as radiotherapy and/or chemotherapy. Bladder-intact event-free survival (BI-EFS) is defined as survival from treatment initiation until confirmed refractory/recurrent MIBC or nodal/metastatic disease, RC, or death, and has been introduced as a primary endpoint in clinical trials. This study evaluated the correlation between BI-EFS and overall survival (OS) in RC-ineligible/refusal MIBC patients in real world in Sweden.

Methods: Patients diagnosed with T2-T4aN0M0 MIBC who subsequently received radiotherapy and/or chemotherapy during 2006-2017 in Sweden were identified in population-based registers and followed until 2018. Exclusion criteria included other urothelial carcinoma prior to MIBC diagnosis and upfront RC upon diagnosis. An iterative multiple imputation method for censored outcomes was used to measure the normal scores rank correlation between BI-EFS and OS.

Results: A total of 337 patients were included in the study. The median age at diagnosis was 77 (IQR 71-82) years and 76% of patients were men. At diagnosis, 286 patients presented with T2 and 51 with T3/T4a stage. There was no significant difference in age at diagnosis between T2 and T3/T4a patients. Overall, the median OS and BI-EFS were 1.04 (95%CI 0.88-1.27) and 0.77 (95%CI 0.65-0.99) year, respectively. T2 and T3/T4a patients had a median OS of 1.11 (95%CI 0.91-1.33) and 0.76 (95%CI 0.5-1.45) year, respectively; and a median BI-EFS of 0.85 (95%CI 0.71-1.05) and 0.5 (95%CI 0.22-0.98) year, respectively. Overall, the correlation between BI-EFS and OS was 0.82 (95%CI 0.77-0.85); for T2 and T3/4a patients, the correlation was 0.84 (95% CI 0.80-0.87) and 0.65 (95% CI 0.44-0.79), respectively.

Conclusions: BI-EFS was correlated with OS in RC-ineligible/refusal MIBC patients who received radiotherapy and/or chemotherapy. The strong correlation in all subgroups supports the use of BI-EFS as a surrogate endpoint for OS in similar patient populations.

Legal entity responsible for the study: Schain Research AB.

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2391P Impact of perioperative chemotherapy on survival and pathological stage in muscle-invasive micropapillary urothelial bladder cancer

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Background: Micropapillary urothelial carcinoma (MUC) is a rare and aggressive histological variant with poor clinical outcomes and limited consensus regarding its management. The mainstay of treatment in muscle-invasive disease is radical cystectomy (RC). Data regarding the role of neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) in muscle-invasive MUC is limited.

Methods: The United States National Cancer Database was queried for patients (pts) with MUC diagnosed from 2004 to 2018. Pts older than 18 years with cT2-4aN0-1M0 MUC who underwent RC were included. Clinical T4b/N2-3/M1 and receipt of NAC+AC were used as exclusion criteria. The pts were divided into three cohorts based on perioperative therapy- NAC, AC, and no chemotherapy (CX^-). Chi-Square and Kruskal-Wallis tests were used to compare frequency distributions. Cox Proportional Hazards regression was employed to adjust for confounders associated with overall survival (OS). Models were adjusted for age, race, sex, stage, insurance, and comorbidities.

Results: Of the 477 pts included, 80% were males, and 93% were White. 103 (21.6%) and 157 (32.9%) received NAC and AC, respectively, while 217 (45.5%) belonged to the CX^- group. Pts in the NAC & AC groups were younger (66 yrs vs 73 yrs in CX^-, $p<0.001$). OS was longer in the NAC and AC groups (Table). However, on multivariable analysis, NAC was predictive of OS (Hazard Ratio (HR) 0.68, 95% CI 0.47-0.97, $p = 0.03$) while AC was not (HR 0.84, 95% CI 0.63-1.12, $p = 0.22$). In a separate Cox model, pT0-1N0 disease was independently associated with improved OS (HR 0.27, 95% CI 0.12-0.61, $p=0.002$). The NAC group had significantly more pT0N0 (14.8% vs 2.8%, $p<0.001$) & pT0-1N0 (21% vs 5.9%, $p<0.001$) disease at RC compared to the combined cohort of AC+CX^-.

Table: 2391P

Cohort	Median OS (months)	3-year OS (%)	5-year OS (%)	Median follow-up (months)	Log-rank P
CX^-	23.1 (18.1-28.7)	40 (30-47)	34 (27-41)	68.7	0.008
AC	34.0 (25.7-59.2)	49 (40-57)	40 (31-49)	51.5	
NAC	56.4 (30.1-NR)	55 (43-65)	45 (33-57)	46.4	

Conclusions: In this large retrospective analysis, NAC was independently predictive of longer OS in muscle-invasive MUC, while AC was not. NAC was also associated with pathological downstaging.

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2392P Tislelizumab combined with gemcitabine/cisplatin in muscle-invasive bladder cancer with selective bladder preservation for clinical complete response (cCR) patients: A real-world multicenter study

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Background: Tri-modality Therapy (TMT) was a standard bladder-sparing strategy for MIBC patients (pts). Considering high costs and side-effects, pts may declined radiotherapy in clinical practice. Our study retrospectively evaluated the effectiveness and safety of maximal TURBT followed chemoimmunotherapy as bladder preservation therapy for cCR pts.

Methods: Retrospectively analyzed MIBC pts at 6 sites who declined radiotherapy. Within 2-4 weeks after maximal TURBT, pts received tislelizumab 200 mg in day 1 (D1), cisplatin 70 mg/m^2 D2, and gemcitabine 1000 mg/m^2 D1 and D8 every 3 weeks for 2-4 cycles, followed by clinical restaging. cCR was defined as normal urine cytology and MRI imaging, and bladder biopsies$\leq$cTa. Pts who achieved cCR proceeded

bladder preservation and non-cCR underwent radical cystectomy (RC). Tislelizumab was administered (200mg, Q3W) for the maintenance treatment for all pts. The primary outcome was cCR rate, and secondary outcomes were bladder intact disease-free survival (BIDFS), OS and safety.

Results: Forty-five MIBC pts enrolled between Jun. 2020 and Sep. 2022 were analyzed (median age 64 years (48-87); pure TCC 95.6%; PD-L1 negative 91.1%; cT2=57.8%, cT3=24.4%, cT4a=17.8%; cN0=82.2%, cN1=15.6%). Median follow-up was 20.14 months (5.3-26.3), the mean number of tislelizumab cycles was 3.5 and GC cycles was 3.1. The cCR rate was 64.4% (95%CI, 50.6%-78.2%), and 2-year BIDFS rate in cCR pts was 96.2% (95%CI, 89%-100%). Pts who received bladder-sparing treatment showed favorable OS compared to those underwent RC. The 2-year OS rates in bladder-sparing treatment group and RC treatment group were 100(95%CI, 100%-100%) and 63.1% (95%CI, 41.2%-96.8%), respectively. There was no significant difference between PD-L1 positive and negative pts regarding OS or BIDFS. The most common treatment-related adverse events included anemia (75.6%, 34/45), nausea ((75.6%, 34/45), rash (64.4%, 29/45), vomiting (60.0%, 27/45), and pruritus (57.8%, 26/45).

Conclusions: Maximal TURBT followed chemoimmunotherapy demonstrated the effectiveness and safety in MIBC with selective bladder preservation for cCR pts who declined radiotherapy.

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2393P Ephrin signalling mediates resistance to programmed death ligand 1 (PD-L1) inhibition in urothelial carcinoma (UC)

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Background: Ephrin ligand (EFN) and receptor (EPH) signalling is increasingly implicated in tumorigenesis. Recently, EFN-B2 and PD-L1 inhibition have demonstrated impressive synergy in metastatic UC. Using data from the ABACUS trial (NCT02662309) in muscle-invasive UC, we explore the relationship between EFN/EPH expression and response to atezolizumab.

Methods: The neoadjuvant ABACUS study design enabled transcriptomic and immunohistochemical (IHC) comparison of paired baseline and cystectomy samples. For multivariate disease-free survival (DFS) analysis, patients were grouped into high and low EFN/EPH using median expression levels. 83 patients were eligible for biomarker analysis. 64 had paired samples. 27 (33%) achieved complete pathological response and/or major pathological response and were deemed responders, and 17 (20%) relapsed.

Results: Following atezolizumab, there was reduced expression of EFN-A1 (log2FC:-0.9, $p<0.05$), EFN-A4 (log2FC:-0.8, $p<0.05$), EFN-A5 (log2FC:-0.8, $p<0.05$) and their cognate receptor EPH-A1 (log2FC:-1.7, $p<0.05$) as well as EFN-B2 (log2FC:-0.82, $p<0.05$) amongst responders, but not relapsed patients. Consequently, apart from EFN-B2, the post-treatment expression of these genes was significantly higher amongst relapsed patients than responders. High post-treatment EFN-A1 (HR: 11.9, 95%CI: 2.2 — 66.0, log-rank $p<0.01$), EFN-A4 (HR: 4.8, 95%CI: 0.9 — 25.3, log-rank $p<0.01$) and EFN-A5 (HR: 13.9, 95%CI: 2.9 — 67.9, log-rank $p<0.05$), and high baseline EFN-B2 (HR: 7.7, 95%CI: 2.1 — 27.7, log-rank $p<0.01$) expression was associated with reduced DFS. EFN-A1, EFN-A4 and EFN-A5 expression post-treatment, but not at baseline, correlated negatively with a cytotoxic T cell transcriptomic signature and granzyme B-positive CD8 T cells on IHC. EFN-B2 expression correlated positively with transcriptomic signatures of hypoxia and pathological angiogenesis.

Conclusions: EFN-A1, EFN-A4 and EFN-A5, likely through EPH-A1 signalling, are associated with reduced immune infiltrate and survival after atezolizumab, and represent promising biomarkers and targets. High baseline EFN-B2 expression is associated with relapse, supporting the addition of EFN-B2 inhibitors to augment response rates.

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2394P Biomarkers of treatment (Tx)-related toxicity in advanced urothelial carcinoma (aUC) pts treated with enfortumab vedotin (EV): Analysis of UNITE study

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Background: EV is approved in aUC pts, but Tx duration is often limited by toxicity. We investigated pt characteristics and biomarkers associated with EV-related adverse events (EV AEs).

Methods: UNITE is a multi-site retrospective study of EV-treated aUC pts; pts treated with EV alone with available AE and next-generation sequencing (NGS) data were analyzed. EV AEs were assessed per CTCAE v5.0. For univariate analyses (UVA), Wilcoxon rank sum and Chi-squared tests assessed associations between clinical features or somatic gene alterations (GA; tissue or ctDNA) occurring in $\geq$5% of pts and most common AEs and EV Tx modifications (reduction, hold, or discontinuation). Using Cox regression models, GA were evaluated individually in separate multivariate analysis (MVA) models accounting for relevant clinical factors.

Results: Among 607 pts (16 US sites), 275 had EV AEs and NGS data. At EV start: median age 71; 183 (67%) men; 244 (88%) White; 216 (79%) ECOG PS 0-1; 186 (68%) with $\geq$2 prior Tx lines. Median time from initial diagnosis to EV start was 86 weeks [IQR 48, 165]; median time from EV start to AE onset 4 weeks [IQR 2, 11]. Most common all-grade AEs: neuropathy (46%), skin tox (41%), fatigue (25%), GI tox (22%), cytopenias (14%), anorexia (11%). In UVA, diabetes (DM), prior neuropathy, higher Hgb and albumin at EV start were associated with neuropathy (all $p<0.05$); lower white blood cell count and neutrophil:lymphocyte ratio (NLR), GFR $\geq$30 with skin tox (all $p<0.01$); *TERT* GA ($p=0.04$) and lower absolute lymphocyte count with cytopenias ($p<0.01$); male sex ($p=0.03$), liver mets ($p=0.05$) and *KDM6A* GA ($p=0.04$) with anorexia. Hyperglycemia was associated with higher BMI, DM, lower NLR, male sex (all $p<0.01$). Higher BMI and lower NLR were associated with more Tx modifications in 203 pts ($p<0.05$). In MVA, *MLL2* GA was associated with cytopenias ($p=0.05$) and *KDM6A* with anorexia ($p=0.02$).

Conclusions: In EV-treated aUC pts, clinical variables and certain somatic GA were associated with common EV AEs. These hypothesis-generating findings suggest a limited role of somatic GA in predicting EV AEs, warranting further investigation of host and tumor-related factors underlying EV toxicity.

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2395P Micropapillary histology (MPUC) and extra-cellular domain ERBB2 (ERBB2 ECD+) mutations in urothelial bladder cancer (UBC)

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Background: Given the early promising data with afatinib in advanced UC and the recent approval in NSCLC for anti-HER2 targeted therapy for activating kinase domain exon 20 *ERBB2* insertion mutations, there is considerable interest in targeting additional locations in the *ERBB2* gene in other tumor types.

Methods: 5,485 UBC were sequenced using a hybrid capture based comprehensive genomic profiling assay to assess all classes of genomic alterations (GA), tumor mutational burden (TMB), microsatellite instability (MSI), genomic loss of heterozygosity (gLOH), trinucleotide mutational signatures and genetic ancestry. PD-L1 tumor cell expression was measured by IHC (Dako 22C3). Statistical comparisons were performed using Fisher's exact tests with a Bonferonni correction.

Results: 548 (10.0%) of UBC featured *ERBB2* gene amplification (amp) and 219 (4.0%) featured an *ERBB2* ECD+ sequence mutation (74% S310F and 26% S310Y). *ERBB2* ECD mutations and *ERBB2* amplification were mutually exclusive. Central pathology review of the 219 *ERBB2* ECD+ UBC revealed that 63 (28.8%) featured a micropapillary histologic appearance (MPUC). *ERBB2* ECD+ UBC featured more patients (pts) with European genetic ancestry than both *ERBB2* WT (90.9% vs 84.2%; $p=.03$) and *ERBB2* amp (90.9% vs 83.2%; $p=.04$). *ERBB2* ECD+ UBC had higher frequency of APOBEC signature than *ERBB2* WT (82.9% vs 72.4%; $p=.03$). TMB $\geq$ 10 mut/Mb was higher in *ERBB2* amp (49.2% vs 31.4%; $p<.0001$) and *ERBB2* ECD+ (59.8% vs 31.4%; $p<.0001$) when compared to *ERBB2* WT. The main genomic differences between *ERBB2* ECD+ MPUC vs non-MPUC were in frequencies of *KMT2D* (6.4% vs 27.6%, $p=0.02$), *RB1*

(33.3% vs 17.3%, p<.0001) and *MTAP* GA (11.1% vs 26.9%, p<.0001). PD-L1 expression and MSI-High status (rare overall, 0 - 0.9%), was similar in all three groups.

Conclusions: *ERBB2* ECD mutation-driven UBC represents a distinct subtype of UBC featuring an enrichment of MPUC histology from 1-2% to 28% incidence in *ERBB2* ECD mutated UBC, and unique clinical and molecular characteristics, including differences in mutational signatures and genetic ancestry. Further exploration of anti-HER2 targeted therapy for non-amp sequence mutations in *ERBB2* in UBC appears warranted.

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2396P Relationship of tumor fraction in circulating tumor DNA (ctDNA) with prognosis in patients with advanced urothelial cancer

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Background: Advanced urothelial cancer (aUC) is often characterized by rapid symptomatic disease progression, making early disease control of particular importance. Development of immunotherapy has been particularly challenging due to limited disease control rates in unselected patients. A biomarker to identify patients with a better prognosis and slower tumor growth kinetics would be of significant clinical utility to personalize therapy. Circulating tumor DNA (ctDNA) is a promising biomarker in multiple tumor types including aUC. Recent work shows that a single time-point/measurement of ctDNA tumor fraction (TF) is prognostic in several other tumor types but has not yet been investigated in aUC.

Methods: This study used a cohort of patients in the de-identified Flatiron Health-Foundation Medicine urothelial clinico-genomic database, which originated from approximately 280 US cancer clinics (∼800 sites of care), who underwent ctDNA testing as part of routine care. TF calculation on FoundationOne®LiquidCDx was based on a composite algorithm incorporating multiple factors including aneuploidy, variant allele frequency, and canonical alterations. Patient/disease characteristics, laboratory and treatment data were captured from the electronic health record. Progression-free survival (PFS) and overall survival (OS) were evaluated by TF level while controlling for relevant covariables.

Results: 83 patients with aUC were included. High ctDNA TF (≥1%) was associated with poor prognostic clinical features. High ctDNA TF also correlated with significantly reduced rwPFS in univariable analysis (hazard ratio (HR) 2.01, 1.14-3.56, p=0.01) and after correction for covariates (HR 2.37, 0.99-5.66, p=0.05). There was a trend towards shorter rwOS in univariable and multivariable analysis.

Conclusions: ctDNA TF is a prognostic biomarker in aUC with potential to inform expected longevity of patients. With further prospective validation, TF could be useful in predicting which patients with aUC have particularly aggressive disease and may enable personalized therapeutic decision-making.

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2397P A real-world study of longitudinal urinary ctDNA monitoring of minimal residual disease (MRD) in patients with muscle invasive urothelial carcinoma followed in parallel with plasma based ctDNA

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Background: Recently, non-invasive urine-based MRD assays have demonstrated the ability to detect deep molecular alterations in bladder cancer patients, which may greatly improve disease monitoring and treatment stratification. In this study, we carried out both tissue-informed blood and urine-informed urine based MRD tests for a cohort of 30 real-world high risk bladder and UTUC patients and studied their concordance to clinical responses.

Methods: 30 real-world bladder and UTUC patients of various subtypes were included in this study. Standard treatment modalities such as neoadjuvant chemotherapy, trimodality therapy (TMT) for bladder preservation, and systemic chemotherapy/immunotherapy were utilized. All patients with sufficient tissue had a Signatera™ blood-based MRD assay, for which FFPE tumor tissues were also tested to establish a baseline. Blood and urine samples were collected at variable intervals depending on the treatment regimens the patients received. The urine samples were tested using the PredicineBEACON™ urine MRD assay, which used the urine PredicineWES+™ whole exome sequencing results of the baseline urine sample for the design of personalize MRD panel tracking up to 50 mutations in addition to a fixed panel of 500 actionable mutations.

Results: The urine based MRD test had over a 90% testing success rate in detection of molecular alterations specific to urinary tract tumors. The tumor fraction (TF) estimate and kinetics from the urine MRD assay were in high concordance with the blood MRD assay results along with treatment responses and progression events in most cases. In several patients, the urine-based MRD assay detected mutations that were not detected in baseline tissue or blood based testing.

Conclusions: Urine-based MRD assays had highly concordance with blood based MRD. Besides its convenience in sample collection, urine-based genomic profiling also has the potential to capture more heterogeneity of urinary tract malignancies as compared to tissue or blood based testing alone. Urine ctDNA monitoring is a useful complementary test to support standard tissue and plasma based assays in high risk bladder and UTUC patients.

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2398P Are fibroblast growth factor receptor 3 (FGFR3) alterations a possible predictive factor for platinum-based chemotherapy and immunotherapy in metastatic urothelial carcinoma (MUC)?

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Background: FGFR3 is associated to proliferation, differentiation and cellular growth. FGFR3 alterations are present in 25% of patients (pts) with MUC and FGFR3 inhibition is an active targeted therapy. However, the role of FGFR3 alterations in patients' clinical outcomes and response to conventional treatment is unclear and no preclinical evidence is available.

Methods: Unicenter retrospective study was performed to explore the correlation between FGFR3 alterations and response rate (ORR), progression free survival (PFS) and overall survival (OS) to platinum-based therapies or immunotherapy. Enrolled pts were diagnosed with muscle-invasive urothelial cancer (MIUC) between 2/2009- 3/2022 at Clinic Hospital of Barcelona, Spain. All were screened for FGFR-3 alterations using next-generation sequencing, qualitative real-time polymerase chain reaction-based assays or RNA-ISH in tumour and/or blood. Demographics, pathology, treatments outcomes were collected retrospectively.

Results: 189 pts with MIUC were included: 74.6% were men, median age was 68.5 (37.6-89.7y). Clinical stage at diagnosis was: 10% II, 44% III, 46% IV. Median follow-up since metastatic disease diagnosis was 16.2 months (0.3-91m). 77% of pts had died at data cut-off. 25.4% had FGFR3 alterations (mutation= 36; fusion= 6; double alteration= 3; RNA-ISH amplification =3). FGFR3 altered (FGFR3-alt) tumours were enriched with papillary histology compared with FGFR3 wild type (FGFR3-wt) (33 vs

11%, p<0.05). No statistical differences were detected in other baseline characteristics. 66.5% (N=113) pts received 1st-line platinum-based chemotherapy (1st PT) and 58% (N=69) 2nd-line immunotherapy (2nd IO). No statistically significant differences were detected in OS (15.2 vs 17.5m), PFS (5.6 vs 7.2m), ORR (62 vs 55%) for pts treated with 1st PT according to FGFR3-alt or FGFR3-wt. In 2nd IO, FGFR3-alt had less ORR than FGFR3-wt (9 vs 41%)(p=0.32) and no statistically significant differences in OS (9.7 vs 12.1m) or PFS (3 vs 3.9m) were observed.

Conclusions: In our cohort, FGFR3 alterations are neither predictive nor prognostic for 1st-line platinum or 2nd-line IO. Further investigation is needed.

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2399P Circulating tumor DNA and urine tumor DNA detection of minimal residual disease in upper tract urothelial carcinoma with radical nephroureterectomy: A cohort study

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Background: Upper tract urothelial carcinoma (UTUC) is an aggressive disease with poor prognosis that is often diagnosed late. At present, circulating tumor DNA-based minimal residual disease (MRD) has been studied in blood from varies solid tumors but its clinical value in monitoring urinary tumor DNA (utDNA) during adjuvant therapy in postoperative UTUC remains unclear.ma va.

Methods: The OriMIRACLE S™ MRD assay (OrigiMed, Shanghai, China) uses whole exome sequencing (WES) for detecting patient-specific somatic alterations from tumor tissues and for blood a personalized panel.

Results: Nineteen patients with stage II UTUC were enrolled in this study, excluding one death due to COVID-19. By monitoring ctDNA and utDNA, the baseline positive rates were 69.2% (9/13) and 88.9% (8/9), respectively. One month after surgery/before adjuvant therapy, the positive rates of ctDNA and utDNA decreased to 46.2% (6/13) and 21.4% (3/14), respectively. During adjuvant chemotherapy/6 months after immunotherapy, the positive rates of ctDNA and utDNA further decreased to 35.7% (4/14) and 21.4% (3/14), respectively. At the end of adjuvant chemotherapy/12 months after immunotherapy, the positive rates of ctDNA and utDNA were 36.4% (4/11) and 11.1% (1/9), respectively. At the 6-month follow-up, the positive rates of ctDNA and utDNA were both 25% (1/4). Three patients experienced disease recurrence. One of them tested negative for ctDNA twice in a row and positive for utDNA. Half a month later, the patient underwent cystoscopy and was found to have a bladder full of hair-like and carpet-like new organisms, indicating intravesical recurrence. A patient tested positive for ctDNA twice in a row, but negative for utDNA, and reexamination suggested recurrence. The third patient had positive results for both ctDNA and utDNA, and PET-CT indicated the possibility of tumor metastasis and recurrence.

Conclusions: Our preliminary results suggest ctDNA combined with utDNA detection can serve as predictive biomarkers for UTUC recurrence and can enable the prediction of adjuvant therapy efficacy.

Clinical trial identification: RenJiH-PDU Trial.

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2400P Frequency and nature of genomic alterations (GA) in ERBB2-altered urothelial bladder cancer (UBC)

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Background: *ERBB2* overexpression is an oncogenic driver in many solid tumors, including UBC. Activating mutations (mut) in *ERBB2* gene were shown to play an oncogenic role relatively like *ERBB2* amplification (amp). We describe and compare the frequency and nature of GA of *ERBB2*-altered (mut, amp) and *ERBB2* wildtype (wt) UBC.

Methods: Using a hybrid capture based comprehensive profiling (CGP) assay, 9,518 UBC cases were evaluated for all classes of GA, tumor mutational burden (TMB), microsatellite instability (MSI), genomic loss of heterozygosity (gLOH), and genomic mutational signature. PD-L1 expression was measured by IHC (Dako 22C3). Statistical comparisons were performed using Fisher's exact tests.

Results: 602 (6.3%) UBC featured *ERBB2* extra-cellular domain (ECD) short variant (SV) GA (ECDmut), 253 (2.7%) UBC featured *ERBB2* kinase domain (KD) SV GA (KDmut); 866 (9.1%) had *ERBB2* amp; 7,797 (81.9%) UBC were *ERBB2*wt. The GA/tumor was higher in all *ERBB2* GA groups vs *ERBB2*wt. European genetic ancestry of ECDmut+ was higher than *ERBB2*wt (p=.02). *CDKN2A/MTAP* loss were more frequent in *ERBB2*wt vs ECDmut and amp only (both p<.0001). *ERBB3* GA was more frequent in ECDmut and KDmut than *ERBB2*wt (both p<.0001). *TERT* GA were more frequent in ECDmut, KDmut and amp vs *ERBB2*wt (all p<.0001). *TOP2A* amp and *TP53* SV GA were significantly higher in *ERBB2* amp vs *ERBB2*wt, ECDmut and KDmut (p<.0001). Mean TMB levels were significantly higher in ECDmut, KDmut and amp than in *ERBB2* wt (all comparisons p<.0001). APOBEC signature was more frequent in ECDmut, KDmut and amp vs *ERBB2*wt (p<.0001). No significant differences in PD-L1 status, MSI-high or gLOH between altered & wt subgroups. The table summarizes key findings.

Conclusions: We noted important differences in co-occurrent-GA in *ERBB2*-altered (ECDmut, KDmut, amp) vs wt UBC, and higher mean TMB and higher APOBEC mut signature in the *ERBB2*-altered group. Results can help refine future clinical trial designs and help elucidate possible resistance mechanisms for *ERBB2*-altered UBC.

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Table: 2400P

ERBB2 (n)	wt (7797)	ECDmut (602)	p	wt (7797)	KDmut (253)	p	wt (7797)	amp (866)	p
GA/tumor	7.424	8.802	<.0001	7.424	8.806	<.0001	7.424	8.622	<.0001
CDH1 alteration	3.9%	4.5%	0.45	3.9%	6.3%	0.07	3.9%	1.6%	0.001
ERBB3 alteration	5.8%	8.3%	0.02	5.8%	11.1%	0.001	5.8%	6.1%	0.65
FGFR3 alteration	20.3%	8.5%	<.0001	20.3%	9.1%	<.0001	20.3%	5.3%	<.0001
TP53 alteration	58.3%	58.6%	0.86	58.3%	51.8%	0.06	58.3%	79.4%	<.0001
APOBEC signature	58.3%	58.6%	0.86	58.3%	51.8%	0.06	58.3%	79.4%	<.0001
MSI-high	0.8%	0.5%	0.63	0.8%	3.6%	0.002	0.8%	0.0%	0.009
Mean TMB	9.14	17.02	<.0001	9.14	16.34	0.002	9.14	11.79	<.0001
PD-L1 high	18.0%	21.4%	0.72	18.0%	33.3%	0.46	18.0%	13.0%	0.77

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2401P Detection of molecular recurrence in early-stage bladder cancer patients using a urinary tumor DNA assay after transurethral resection of bladder tumor (TURBT)

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Background: Transurethral resection of bladder tumor (TURBT) is the primary treatment for early-stage bladder cancer, and early detection of tumor recurrence is vital for improving patient outcome. Non-invasive and reliable methods for monitoring molecular changes in urine represent a promising avenue to facilitate timely intervention and effective disease management.

Methods: In this ongoing prospective study, 95 patients with early-stage bladder cancer were recruited, whose urine samples were collected prior to TURBT. Afterward, patients were advised to provide urine samples during follow-up visits. PredicineCARE, a targeted next-generation sequencing (NGS) liquid biopsy assay, was employed to identify somatic alterations in urinary tumor DNA (utDNA). Based on these alterations, the tumor fraction was assessed to identify molecular recurrence in the patients.

Results: Out of the 95 patients, 48 were diagnosed with non-muscle invasive bladder cancer (NMIBC) and 47 with muscle invasive bladder cancer (MIBC). The genes that showed the most frequent variations in NMIBC patients were *TP53* (54%), *TERT* (46%), *FGFR3* (31%), *ERCC2* (31%), *ARID1A* (31%), and *CDKN2A* (31%). Meanwhile, in MIBC, the most frequently varied genes were *TP53* (74%), *TERT* (47%), *PIK3CA* (32%), and *KDM6A* (32%). 38.5% of NMIBC patients and 26.3% of MIBC patients harbored *FGFR2/3* variations, suggesting that they could potentially benefit from FGFR inhibitors. Among the 29 patients with follow-up data, longitudinal urine samples of 12 patients (2 NMIBC, 10 MIBC) were tested. Nine patients (2 NMIBC, 7 MIBC) showed a significant decrease in tumor fraction, one (MIBC) remained stable, and two patients (MIBC) exhibited increasing tumor fraction, indicating molecular recurrence of the disease.

Conclusions: The results of this study confirm the validity of utilizing a utDNA assay to detect molecular recurrence in early-stage bladder cancer patients who have undergone TURBT treatment, which can be instrumental in facilitating early detection of tumor recurrence and guiding treatment decisions. These findings underscore the enormous potential of urine-based NGS assays for urothelial cancer detection and disease surveillance.

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2402P Urine-based comprehensive genomic profiling reveals mutational landscape in real-world patients with bladder cancer

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Background: Bladder cancer is the most prevalent form of urothelial carcinoma. There is an urgent need for timely and accurate identification of molecular alterations to guide tailored therapeutic treatment. Urinary tumor DNA (utDNA) analysis not only holds promise as a valuable tool in bladder cancer diagnosis and monitoring, but also has the potential to identify actionable mutations that can be targeted with personalized therapies.

Methods: This prospective study enrolled 154 patients with bladder cancer in real-world settings, comprising 65 patients with non-muscle invasive bladder cancer (NMIBC) and 89 patients with muscle invasive bladder cancer (MIBC). The cohort included treatment-naive patients as well as those who had received treatment and were at risk of recurrence. Urine samples were collected from each patient. PredicineCARE, a NGS liquid biopsy assay, was applied to detect somatic alterations in urinary tumor DNA (utDNA).

Results: The study detected a total of 368 somatic mutations and 14 copy number variants in 65 NMIBC patients, and 485 somatic mutations and 43 copy number variants in 89 MIBC patients. Among NMIBC patients, the most frequently mutated genes were *TP53* (38%), *TERT* (37%), *ARID1A* (22%), and *BRCA2* (20%). Among MIBC patients, the most frequently mutated genes were *TP53* (57%), *TERT* (39%), *ERBB2* (24%), *ARID1A* (20%), and *PIK3CA* (20%). The prevalence of FGFR2/3 variations was 15% in NMIBC and 13% in MIBC among all patients, while 38.5% of NMIBC patients and 26.3% of MIBC patients who were confirmed to be treatment-naïve harbored FGFR2/3 variations. The prevalence of *ERBB2* and *TP53* mutations was significantly higher in MIBC than in NMIBC (*ERBB2*: 21/89 vs. 4/65, $p<0.01$; *TP53*: 51/89 vs. 25/65, $p<0.05$). Conversely, the prevalence of *RARA* was significantly higher in NMIBC than in MIBC (5/65 vs. 0/89, $p<0.05$).

Conclusions: The present study unveils a comprehensive mutational landscape of non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) utilizing urine samples from real-world patients. These results demonstrate the promising potential of urine-based next-generation sequencing (NGS) assays to identify tumor-derived variants for clinical diagnosis and targeted treatment.

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2403P CDKN2A deletions are a mechanism for p16 inactivation in urothelial bladder carcinomas and are associated with an aggressive tumor phenotype

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Background: Deletion of CDKN2A, encoded for the tumor suppressor protein p16, represents a common cause for reduced or absent of p16 expression in tumor cells. In this study, we analyzed the impact of CDKN2A deletion on tumor aggressiveness, patient prognosis, and p16 expression in patients with urothelial bladder carcinomas.

Methods: CDKN2A copy number status was analyzed by fluorescence *in-situ* hybridization (FISH) on more than 2,500 urothelial bladder carcinomas in a tissue microarray format. Data of CDKN2A deletion were compared with p16 expression data measured by immunohistochemistry in a previous study. The results were compared with parameters of tumor phenotype and patient outcome.

Results: CDKN2A deletions occurred in 28% of 1,880 analyzable carcinomas, including 9% heterozygous and 19% homozygous CDKN2A deletions. The CDKN2A deletion rate, especially for homozygous deletions, increased from pTa G2 low (14%), to pTa G2 high (35%) but slightly decreased in pTa G3 (20%) carcinomas ($p<0.0001$). In muscle-invasive urothelial carcinomas, especially homozygous CDKN2A deletions were associated with advanced pT stage ($p<0.0001$), but unrelated to patient prognosis. However, in the subset of pT4 urothelial bladder carcinomas, a tendency for shorter overall survival for patients with CDKN2A deleted tumors was found ($p=0.0828$). CDKN2A deletions were significantly associated with p16 immunostaining ($p<0.0001$). Cancers without p16 immunostaining harbored in 62% of all cases a CDKN2A deletion and 97% of 343 homozygous CDKN2A deleted cancers were p16 negative. Cancers with CDKN2A deletion and negative p16 immunostaining were associated with advanced stage ($p<0.0001$) but unrelated to patient prognosis in muscle-invasive urothelial carcinomas.

Conclusions: CDKN2A deletions were most commonly seen in p16-negative carcinomas, supporting their role for p16 inactivation in urothelial bladder carcinomas. The association of CDKN2A deletion — especially homozygous deletion — with advanced stage may reflect increasing genomic instability going along with stage progression.

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2404P Concordance of genomic alterations by next-generation sequencing in tumor tissue versus urinary tumor DNA and circulating tumor DNA in bladder cancer

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Background: The current gold standard for diagnosing and monitoring bladder cancer is cystoscopy, but its application is restricted due to invasiveness and high cost. Liquid biopsy has gained widespread attention recently because of its non-invasive, convenient access, and convenient for real-time monitoring. This study aimed to explore the consistency of genomic alterations of bladder cancer detected by urine and blood with their paired tissue to evaluate the potential of liquid biopsy in the real world.

Methods: For this analysis, we included 20 bladder cancer patients with all their tissue, blood, and urine samples. The next-generation sequencing technology was used to detect the mutated genes of 60 obtained samples via the Acornmed panel with 808 cancer-related genes. The average sequencing depth was >10,000x, and the coverage was 95%.

Results: A total of 60 samples from 20 patients were tested in this study. In 90% (18/20) of patients, at least one concordance mutation was detected in both tissue DNA and urinary tumor DNA(utDNA), while at least one concordance mutation was detected in both ctDNA and tDNA in 80% (16/20) of patients. A total of 357 mutated genes were detected in all tissue samples, and 202 mutated genes were detected in all urine samples, of which 179 (88.6%) genes were also detected in tissue DNA. A total of 148 mutated genes were detected in all blood samples, of which 109 (73.6%) genes were also detected in tissue DNA. A total of 75 genes were detected in the three samples, of which 12 (16%) were clinically available genes that could be found in the OncoKB database. The Top 5 frequently mutated genes in tDNA were TERT (50%), TP53 (45%), FAT (35%), LRP1B (35%), and PIK3CA (30%), whereas the Top 5 mutant genes detected in utDNA were TERT (40%), TP53 (30%), KMT2D (25%), NOTCH4 (20%), and PIK3CA (15%), in ctDNA were ATRX (15%), IRS2 (15%), NOTCH4 (15%), ZFHX3 (15%), and KMT2D (10%).

Conclusions: Results of this study show that liquid biopsies represented by urine and blood overlap with the genomic results of tissues, suggesting that utDNA and ctDNA may have potential applications in patients with bladder cancer who have no tumor tissue available, offering similar profiles of genomic alterations of tumor tissues.

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2405P Prognostic significance of circulating tumor DNA in patients with urothelial carcinoma: A systematic review and meta-analysis

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Background: At present, the prognostic stratification of urothelial carcinoma(UC) patients heavily relies on tumor staging, which is limited by the quality of the tissue samples assessed. Recently, circulating tumor DNA(ctDNA) has shown potential as a molecular tool for the diagnosis, staging, and prognosis of UC. We aimed to conduct a systematic review and meta-analysis to evaluate the prognostic value of ctDNA in patients with UC.

Methods: The MEDLINE, EMBASE, and the Cochrane Library databases were searched from the inception to March 2023 to identify studies investigating the relationship between detection of ctDNA and clinical outcomes in patients with UC. Hazard ratios (HRs) of disease-free survival (DFS) and overall survival (OS) were extracted and meta-analysis was performed using the R software (version 4.2.1).

Results: Twelve studies with 1844 patients were ultimately included in this meta-analysis. Ten studies assessed the relationship between baseline ctDNA detection and patient outcomes. Patients with an elevated ctDNA level exhibited significantly worse DFS (HR=6.22; 95% CI, 3.78-10.25, p<0.001) and OS (HR=4.09; 95% CI, 3.02-7.96, p<0.001). Similar results were observed in subgroup analyses in patients with muscle-invasive UC and metastatic UC, respectively. Four studies evaluated the prognostic value of ctDNA dynamics during treatment or observation. Patients who exhibited a decrease or clearance in ctDNA levels demonstrated a more favorable DFS (HR=0.31, 95% CI, 0.16—0.59, p=0.0003) and OS (HR=0.24, 95% CI, 0.14—0.43,P<0.001) compared to those who did not.

Conclusions: Our meta-analysis demonstrated a robust correlation between levels of plasma ctDNA at baseline/during treatment and oncologic outcomes in patients with UC. These findings indicate that plasma ctDNA offers substantial clinical utility in the risk stratification and personalized prognosis of patients.

Clinical trial identification: The protocol for this review is registered on PROSPERO (CRD42023414380).

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2406P Phase II trial evaluating the efficacy of pembrolizumab combined with vorinostat in patients with recurrent and/or metastatic squamous cell carcinoma of the penis: Subgroup analysis of the PEVOsq basket trial

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Background: Advanced penile squamous cell carcinoma (PSCC) is a rare disease, with limited treatment options and poor prognosis. Although PD-1 blockade demonstrated some activity in PSCC patients (pts), response rate is modest. Preclinical data suggests that vorinostat (V), an HDAC inhibitor, might improve immunotherapy efficacy by modulating the epigenome.

Methods: PEVOsq is an open-label, non-randomized, multi-center, basket phase II trial, evaluating the efficacy of pembrolizumab (P) in combination with V in pts with recurrent and/or metastatic squamous carcinomas. Pts had to be PD1/PD-L1 antagonist-naïve with no restriction in terms of prior lines of treatments. P dose was 200 mg Q3W IV, and V 400 mg QD PO. Sample size was determined using an A'Hern design with the following hypotheses (alpha=10%, power=85%, p0=5%, p1=30%). Primary endpoint was objective response rate (ORR) according to RECIST 1.1 Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and duration of response (DOR).

Results: Among 112 included pts, 11 pts with penis cancer were evaluable for safety and efficacy. Median age was 71 years old [range: 39-82]. Median number of prior lines of therapies was 1 [range: 0-2]. Two pts (18.2%) had an objective response. Median PFS and OS were 2.4 [95%CI: 0.5-4.1] and 4.4 months [95%CI: 1.6-11.0], respectively. Five (45.5%) pts developed G3/4 treatment related adverse events. P and V were stopped for toxicity in 10.0% and 27.3% of pts, respectively. 54.5% of pts had a dose-reduced of V for toxicity including hematotoxicity, gastrointestinal toxicity, asthenia, and creatinine increase. Results according to PDL1, MSI, TMB and HPV will be presented at the meeting.

Conclusions: P combined with V produced limited efficacy in advanced PSCC pts and was associated with substantial toxicity.

Clinical trial identification: NCT04357873; EudraCT 2019-003839-33.

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2407TiP SunRISe-3: TAR-200 plus cetrelimab (CET) or TAR-200 versus intravesical bacillus Calmette-Guérin (BCG) in patients (pts) with BCG-naive high-risk non-muscle-invasive bladder cancer (HR NMIBC)

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Background: Standard of care for pts with HR NMIBC is transurethral resection of bladder tumor (TURBT; biopsy only for carcinoma in situ pts) followed by intravesical BCG. However, BCG is associated with toxicities and supply shortages and lacks a durable response in a significant proportion of pts. TAR-200 is an intravesical drug delivery system that provides local continuous gemcitabine release within the bladder. Preliminary data from SunRISe-1 (AUA 2023, NCT04640623) support further investigation of TAR-200 with or without CET in pts with BCG-naive HR NMIBC. SunRISe-3 (NCT05714202) is an open-label, multicenter, randomized phase 3 study assessing efficacy and safety of TAR-200 + CET or TAR-200 vs BCG in pts with BCG-naive HR NMIBC.

Trial design: Eligibility: $\geq$18 y, ECOG PS 0, 1, or 2, histologically confirmed HR NMIBC (high grade Ta, any T1 or CIS) in BCG-naive pts (no prior BCG or stopped $>$3 y prior to randomization). All papillary disease must be fully resected prior to randomization. Pts (N$\approx$1050) are randomized 1:1:1 to receive TAR-200 + CET (Group A), TAR-200 (Group C) or BCG (Group B). In Groups A and C, TAR-200 (225 mg gemcitabine) is dosed Q3W during an induction phase, then Q12W during a maintenance phase. In Group B, BCG is dosed QW for 6 wks and QW for 3 wks at Wks 12, 24, 48, 72, and 96. Pts may continue in Y3 at investigator discretion. Disease recurrence or progression assessments are by cystoscopy, urine cytology, TURBT/bladder biopsy, and CT/MR urography. The primary end point is event-free survival (time from randomization to HR disease first recurrence [high grade Ta, any T1 or CIS], progression or any-cause death, persistent disease at 6 mo in CIS pts). Progression is defined as increase of stage (Ta to T1, or CIS to T1) or progression to MIBC (T $\geq$2 or to N+ or M+ disease). Secondary end points include overall complete response rate (CIS only), recurrence-free survival, time to progression, overall survival, cancer-specific survival, safety, and pt-reported outcomes. As of May 3, 2023, 1 pt has been randomized, with 16 in screening; recruitment is planned at 254 sites.

Clinical trial identification: NCT05714202.

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2408TiP DISCUS: A randomised phase II study of 3 vs 6 cycles of chemotherapy followed by maintenance avelumab in advanced urothelial cancer - Wearable devices and circulating biomarkers assessing quality of life and surrogate efficacy endpoints

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Background: DISCUS (EudraCT2021-001975-17) is a randomised phase III trial comparing 3 vs 6 cycles of first-line CT, followed by maintenance avelumab on the QoL of patients with aUC. Fewer cycles of CT may be associated with better quality of life (QoL) and improve efficacy, as more patients will be exposed to immune checkpoint inhibitors. Wearable devices are a novel method of assessment of QoL for patients receiving systemic anticancer therapy (SACT) and may have advantages over existing methods such as EORTC-QLQ-C30 questionnaires. This is being tested in the DISCUS trial. Recent work demonstrates that normalisation of ctDNA is associated with better outcomes in the adjuvant setting. Dynamic changes in ctDNA will also be tested in this study. Tracking ctDNA may be able to identify mechanisms of resistance to SACT.

Trial design: Patients enrolled in the ongoing DISCUS trial can consent this exploratory sub study, investigating the role of ctDNA and digital wearable device data in assessing QOL in aUC patients receiving SACT. Patient reported outcomes (PROs) on QOL will be correlated with biometric data from wearable devices, tracking step counts, heart rate and peripheral oximetry. Participants will be required to wear the device for 8 hours per day, at least once per treatment cycle, between cycle 1-6 (C1-6) and 8-12 weeks after C6. Average daily step counts at C6 will be compared between groups and correlated to adverse events and PROs. ctDNA measurement will occur at baseline, C3,6 and 8-12-weeks after C6. ctDNA assessment will be conducted using a personalised approach, using whole exome sequencing to track $>$2 mutations from the primary tumour (Natera) and will be compared to radiological assessment and correlated with efficacy outcomes. ctDNA may be more accurate in assessing outcomes than radiology. Shorter periods of CT may be associated with better QoL for patients without affecting efficacy. ctDNA and wearable devices is a step towards personalised medicine for these patients.

Clinical trial identification: EudraCT 2021-001975-17.

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2409TiP A global, multicentre, open-label, randomised phase II trial of tobemstomig (tobe) with or without tiragolumab (tira) vs atezolizumab (atezo) in patients (pts) with untreated metastatic urothelial cancer (mUC) ineligible for platinum-based chemotherapy (chemo)

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Background: Platinum-based chemo is the standard of care for the majority of pts with previously untreated mUC. Treatment options for pts ineligible for any platinum are not well defined and include PD-1 or PD-L1 immune checkpoint inhibitors (CPIs) or other regimens such as single-agent chemo, depending on clinical considerations. Because many pts treated with CPIs do not experience durable clinical benefit, additional treatments are needed to mitigate resistance and improve pt outcomes. Combinations targeting novel checkpoints (e.g., LAG3, TIGIT) are attractive as they address distinct resistance mechanisms that could expand the number of pts who respond to CPIs, while also potentially offering a tolerable benefit-risk profile. Tobe is a novel bispecific antibody with monovalent binding to PD-1 and LAG3, and tira is an antibody that binds TIGIT. In this trial, efficacy and safety of atezo (Arm A, control) vs tobe (Arm B) or tobe + tira (Arm C) will be evaluated as first-line (1L) therapy in platinum-ineligible pts with mUC.

Trial design: Approximately 240 pts aged $\geq$18 y with locally advanced or metastatic UC, measurable disease and available tumour sample will be enrolled across 15 countries and 83 sites. Pts must have no prior CPIs or 1L systemic therapy. Pts must be platinum ineligible based on one of the following criteria: (1) ECOG PS 0 with GFR 15-30 mL/min/1.73 m^2; (2) ECOG PS 1-2 with GFR 15-45 mL/min/1.73 m^2; (3) ECOG PS 0-2 with Grade $\geq$2 neuropathy or (4) chemo not deemed appropriate per investigator. Pts will be randomised 1:1:1 to receive atezo 1200 mg IV, tobe 600 mg IV or tobe 600 mg IV + tira 600 mg IV Q3W until loss of clinical benefit or unacceptable toxicity. Randomisation will be stratified by PD-L1 expression per VENTANA SP263 (investigational) (positive [tumour area positivity, TAP$\geq$5% vs negative [TAP$<$5%]), baseline liver metastases (yes vs no; 15% cap), and ECOG PS (0 vs 1 or 2). This study will evaluate the effect of tobe and tobe + tira on investigator-assessed confirmed ORR (primary endpoint) relative to atezo. Secondary endpoints include PFS, OS, DOR, DCR and safety.

Clinical trial identification: NCT05645692.

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

CANCER NURSING: EHEALTH AND DIGITAL INNOVATIONS

CN1 Integrating an electronic patient reported outcome measure (ePROM) into a nurse-led rare cancer pathway

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Background: The use of ePROMs in clinical practice has the potential to generate population level patient-reported outcome data alongside promoting patient-centred care and improving patients' quality of life. Individualised PROMs may be particularly helpful in identifying, prioritising, and discussing health concerns, yet little research in cancer nursing has evaluated this. Gestational Trophoblastic Disease (GTD) is a rare complication of pregnancy that can present as or turn into cancer. This nurse-led research group has recently developed a GTD specific ePROM (ePAQ-GTD) that has been integrated into the GTD pathway to support population level research and deliver tailored virtual nurse-led patient centred care.

Methods: From January 2020, ePAQ-GTD and a new nurse-led virtual clinic were offered to all GTD patients at a regional GTD centre at referral, start of treatment, end of treatment, 6 weeks, 6 months, and yearly post chemotherapy. Feedback of ePAQ-GTD responses were provided ahead of the clinic in the form of an electronic summary report. Reflexive thematic analysis of qualitative interviews with a purposive sample of GTD patients (n=15) and GTD nurses (n=3) was conducted for an in-depth evaluation of ePAQ-GTD's use as an outcome measure used routinely in clinical practice.

Results: The results of the analysis identified three key themes, firstly that patients and staff found ePAQ-GTD demonstrated content validity and was a relevant and acceptable tool to capture the impact of GTD and its treatment from the patient perspective. Secondly, ePAQ-GTD facilitated and enabled important discussions to happen in the virtual nurse-led clinic, especially around taboo subjects such as sexual dysfunction and mental health emphasising its comprehensiveness and patient-centredness. Lastly, the feedback of ePAQ-GTD results in the context of a nurse-led clinic was linked to improvements in wellbeing through improved communication, empowerment and decision making.

Conclusions: Findings suggest ePAQ-GTD has content validity as an outcome measure. The feedback of ePAQ-GTD results in a virtual nurse-led clinic also shows benefits in relation to communication, empowerment and decision making when integrated into a nurse-led cancer pathway for GTD.

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CN2 BioVirtualPed: A biofeedback based virtual reality game for pediatric patients

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Background: The management of pain, fear, and anxiety in pediatric oncology patients has always been a significant challenge in the field of healthcare. Medical procedures, especially those involving port catheter needle exchanges, can be distressing and overwhelming for young patients. To address this issue, the initial aim of the study is to develop BioVirtualPed, a cutting-edge virtual reality game designed specifically for pediatric patients undergoing these treatments. Second is the evaluation of the BioVirtualPed's validity and clinical feasibility.

Methods: BioVirtualPed game was made with Unity engine, using ADXL35 accelerometer to collect respiratory data, transferred to the game with ArdunioUno software. Oculus Quest 2 headset monitored the scenario. A feasibility study involved 15 children aged 6-12, data was collected with various forms and scales including the demographic information form, Wong-Baker Pain Rating Scale, Child Fear Scale, Child Anxiety Scale-State, BioVirtualPed Evaluation Form, and Mobile Application Usability Scale.

Results: For validity, detecting respiratory data, enables the game to respond effectively to the user's breath patterns. The Unity game engine successfully integrated the respiratory data, allowing for seamless interaction between the user's breath and the game's bio-responsive elements. For clinical feasibility, the participants found the Oculus Quest 2 headset to be comfortable and easy to wear, with minimal adjustments required for a proper fit. The participants were able to follow the game's instructions and achieve the desired breathing patterns effectively. For User experience, the pediatric patients reported a positive experience with the BioVirtualPed game. They expressed increased relaxation and reduced feelings of pain, fear, and anxiety during the port catheter needle exchange procedure.

Conclusions: By incorporating bio-responsive elements that react to the user's breathing patterns, the game offers an innovative way to teach young patients how to self-regulate their breathing in a fun and engaging manner. This allows them to achieve a relaxed state, which in turn helps to alleviate pain, fear, and anxiety during medical procedures.

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CN3 Patient adherence to digital patient-reported outcome monitoring (PROM) in cancer immunotherapies

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Background: PROM platforms, characterized by systematic collection of symptoms and quality of life data, enable timely reactions of health care professionals (HCPs) in trial and routine care settings. The "KAIKU" platform provides a novel algorithm-based approach of converting PROM into safety alerts enabling severity-driven communication between patients and HCPs. In KAIKU's immunotherapy module, patients are interviewed weekly of potential immune-related adverse events. In this study, we investigated if patient adherence to digital PROM is impacted by parameters such as symptom burden, health status, patient characteristics, or device.

Methods: Pooled analyses were performed of retrospective data from six digital PROM pilots in immunotherapies. The study included 243 patients from 6 countries: NO (97), FI (56), NL (37), DE (26), CH (17), and IT (10). Following parameters were analyzed: weekly adherence to questionnaires in correlation to symptom burden, health status (QLQ-C30), age, sex, device (app, browser), messaging, and country for 12-week period.

Results: Mean weekly adherence to PROM on all devices was 80%, ranging from 72.3% (IT) to 84% (FI). Experienced symptom burden (r=-0.46), fatigue level (r=-0.32), physical condition (r=-0.23) or global health status (r= 0.22) did not correlate with adherence. There were no differences between females (79.9%) and males (80.1%) but both had higher adherence using app compared to browser. KAIKU enabled communication with HCPs, but patients' messaging activity did not correlate with adherence (r=0.13). In all age groups, both app and browser-based platform were used. Adherence was highest for ages 60-69. Younger patients (40-59) had a considerable adherence drop when using the desktop browser, whereas in ages 60-89 there weren't such differences between devices.

Conclusions: Digital PROM in cancer patients receiving immunotherapies results in high adherence regardless of country, age, sex, user activity or disease burden, implying it is clinically feasible, and patients stay adherent both in good and worsening health conditions. High adherence to app-based platform across all ages indicates that app-based PROM should be preferred over other methods.

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CN4 Enabling patient empowerment through digital symptom monitoring

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Background: Patient reported outcomes (PROs) are the golden standard for monitoring symptoms in cancer care and have shown great clinical benefits to patients. New technology enables electronic PROs to be used in clinical practice also with an intent to empower patients and involve them more actively in their treatment. This study aimed to pilot a questionnaire for investigating the ability of ePRO monitoring to enable empowerment of patients with active anticancer treatment.

Methods: Based on the validated Cancer Patient Empowerment Questionnaire (CPEQ) we developed a shorter and more practical questionnaire with eleven questions including intrapersonal, interactional, and behavioural components of patient empowerment. Responders were cancer patients, most receiving palliative treatment for metastatic disease, monitored with an ePRO tool by Kaiku Health as part of their standard of care at a central hospital in Northern Norway. Responses were scored on a Likert scale from 1-5.

Results: Out of 58 patients, 46 (79%) returned the questionnaire in the first round, and 37 (67%) responded in the second round two weeks later. The mean total scores were 3.7 and 3.8, respectively. The patients reported the importance for them to manage their challenges, have a feeling of control, and participating actively in decisions, treatment, and follow-up of their illness to a high degree (mean score 4.2). With mean scores of 4.1 and 4.2, the ePRO monitoring provides patients with a feeling of being listened to/taken seriously and supported their ability to contact healthcare professionals when in doubt or having questions or concerns. There were no significant differences in scores due to age, gender, cancer type, treatment, or length of using the program. A Cronbach Alpha of 0.9 and an interclass correlation coefficient of 0.87 indicates good internal consistency. Test-retest shows good reliability with Pearson's correlation of 0.66.

Conclusions: Cancer patients report that it is very important to them to be in control and actively participate in matters concerning their illness and treatment. Digital monitoring with ePRO enables empowerment by providing a channel to contact healthcare professionals when needed, and a feeling of being listened to and taken seriously.

Legal entity responsible for the study: Oncology research group at Nordlandssykehuset HF, Bodoe Norway.

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CN5 Shared decision making in rectal cancer surgery: The way to go?

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Background: In rectal cancer surgery, there are two surgical options: A low anterior resection with preservation of the anal sphincter and an abdominoperineal resection with resection of the sphincter and formation of a permanent stoma. When the sphincter is not compromised, both surgical options are, from an oncological point of view, comparable. Given the need to take patients' perspective into account, the choice of rectal cancer surgery is a value-based choice. To facilitate this, there is a growing interest in the use of decision aids. It helps patients to participate in weighing the impact of different treatment options on their QoL. The aim of this study was to explore the expectations of healthcare professionals (HCPs) and to evaluate the impact of using a decision aid in daily practice.

Methods: A multi-centre explorative study was conducted. Individual semi-structured interviews with 16 interprofessional HCPs responsible for the care of patients with rectal cancer were performed. Thematic analysis was used during data-analysis and investigators' triangulation was applied during analysis.

Results: First, HCPs felt that a decision aid would enable them to provide information in a more neutral and uniform way. Second, it was believed that the decision aid enhanced the understanding of the different aspects of QoL. Moreover, a shared decision was hypothesised to enable patients to accept consequences of rectal cancer surgery, such as bowel problems or a stoma. Additionally, it was believed to empowering patients and increasing their involvement in the treatment decision. Finally, some key issues for implementation were highlighted, such as reorganising the preoperative consultation, a consensus on the most appropriate moment to use the decision aid and the need for training. Several HCPs mentioned the added value of a nurse-led consultation, complementary to the physician.

Conclusions: Using a decision aid to facilitate preoperative consultations was an added value according to HCPs. Before implementation, several key issues need to be taken into account. A nurse-led consultation could be an added value to facilitate shared decision making. A follow-up study will explore the impact on patients.

Clinical trial identification: BC-10030.

Legal entity responsible for the study: The authors.

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CN6 Patient involvement in an eHealth intervention for women with gynecological cancer

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Background: Women with ovarian or endometrial cancer experience a significant physical and psychological burden due to the disease and treatment. Patient and public involvement in health research is gaining global popularity, with the potential to improve the quality, relevance, and outcomes of studies. Thus, patient involvement is a central component in this study investigating the feasibility and effect of systematic nurse-led consultations based on electronic Patient-Reported Outcome (ePRO) among women with ovarian- or endometrial cancer. The purpose of patient involvement was to encourage patients to participate in all stages of this study, including the development of an ePRO platform.

Methods: The study design was a four-phase, sequential cohort study with comparisons between non-equivalent groups, with the primary outcome being the difference in global HRQoL (EORTC QLQ-C30) at 9 months. The patient advisory board consisting of women with gynecological cancer has continuously been involved in the development and design of the ePRO platform. After two years of involvement, we used The Patient Engagement in Research Scale (PEIRS-22) to evaluate the level of meaningful involvement in the patient advisory board.

Results: A patient advisory board consisting of patients (n=5) has been established. The board provides feedback on written materials, research development, and capturing the perspectives of women with ovarian and endometrial cancer.

Furthermore, the board has been dedicated and constructive in a systematic process that has resulted in the selection of cancer-specific items, self-management strategies, advice, content, and videos that are included in the ePRO platform. The Danish PEIRS-22 total score was 89,3 (range 0-100), indicating a high level of meaningful involvement. The ePRO intervention is currently ongoing and results are expected in 2024.

Conclusions: Throughout the study, the active involvement, engagement, and collaboration of a patient advisory board have contributed to the development of a patient-centered ePRO platform and model of care. Patient involvement is highly valuable and makes a significant contribution to conducting patient-centered nursing research with clinical impact.

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Legal entity responsible for the study: The authors.

Funding: Novo Nordisk Foundation.

Disclosure: M.R. Mirza: Financial Interests, Personal, Advisory Board: AstraZeneca, GSK, Karyopharm, Merck, Roche, Zailab; Financial Interests, Personal, Invited Speaker: AstraZeneca, GSK; Financial Interests, Personal, Member of Board of Directors: Karyopharm; Financial Interests, Personal, Stocks/Shares: Karyopharm; Financial Interests, Institutional, Research Grant: GSK, AstraZeneca, Ultimovacs, Apexigen; Financial Interests, Institutional, Trial Chair: Deciphera; Non-Financial Interests, Advisory Role: Ultimovacs, Apexigen. All other authors have declared no conflicts of interest.

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CN7 The effect of using mobile application on supportive care needs, distress and quality of life in hematopoietic stem cell transplant patients: Randomized controlled study

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Background: The aim of the study was to develop a mobile application and to examine the effect of using this application on the supportive care needs, distress level, and quality of life in hematopoietic stem-cell transplant patients.

Methods: This randomized controlled study was conducted at the Bone Marrow Transplantation Unit located in Ankara, from February to September 2022. Patient Information Form, the James Supportive Care Screening Scale (JSCS), the Distress Thermometer, and Functional Assessment Scale in Cancer Treatment in Bone Marrow Transplant Patients (FACT-BMT, version 4) were used to collect data. The study was completed with 36 patients (18 in the intervention group and 18 in the control group) and the data was collected at 3 time points pre-transplant, 1st month, and 3rd month after transplantation. The mobile application contents were evaluated by an expert group and piloted (n=7) via Mobile Application Usability Scale. Audio recordings have been added to the application in line with user suggestions. The intervention group was trained with the mobile application and was followed up to the 3rd month after transplantation, and the control group received routine education/follow-up.

Results: In the FACT-BMT scale, there was a significant difference ($p<0.05$) between the groups in the FACT-BMT TOI score at admission, while no difference was found between the groups in other sub-dimensions. There was no difference between the groups in terms of distress levels and FACT BMT total scores ($p>0.05$). A significant difference was found in the 3rd-month follow-up in the spiritual-religious problems sub-dimension of the supportive care needs ($p<0.05$). The patients in the intervention group received counseling mostly on nutrition, social life, medication use, and post-transplant complications.

Conclusions: No significant effect was found of the education given with the mobile application on the supportive care needs, distress levels and quality of life of the patients during the first three months after stem cell transplantation. Further large-scale studies are needed to evaluate the effect of the mobile application longer than the first three months after transplantation.

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CN8 A guide to data & artificial intelligence: Co-producing accessible an educational resource with the pubic

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Background: Digital innovation is shaping healthcare. Data science & artificial intelligence researchers are seeking public involvement for their projects but do the public have sufficient knowledge of the field to contribute meaningful ways? Our experience at Imperial was that they did not. This led us to develop a guide to data and AI created by the public for the public to help individuals become active decision makers in their health. A diverse group of 20 members of the public worked with experts to create the guide which consists of text/illustrations, podcasts and animated videos. A website is currently in development. Aside from developing the guide, we learned a great deal about co-design. We evaluated our experience of co-production.

Methods: We used creative approaches for the participatory evaluation and embedded reflexivity for a potentially more ethical and accessible involvement of public contributors. Firstly, we utilised the photovoice. For three months, public contributors and team members captured photos alongside a description of how this photo presented their experience. Secondly, using these photos to discuss and analyse the experience of being involved in the project. The professional artist captured this discussion together in the mandala- a geometric configuration of symbols representing the experience.

Results: These experiences were spread into six interconnected layers on the mandala and represented a connected journey. The chosen title "Our Journey into AI", reflected the feeling of ownership among public contributors. Layers 1) represented the opportunity to learn new things and develop confidence in data and AI 2) showed interaction when working as a team 3) is about working digitally throughout the project. From layer four onwards, the issues broaden to include those that underpin public contributors' involvement 4) why they got involved in the project 5) their expectation in the involvement process. The last layer is about the ethics that researchers should follow.

Conclusions: We found that the co-production with public contributors around complex and often abstract topics like data science and AI can be conducted in a meaningful way with the public. Co-production process ensures a sense of co-ownership.

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CN9 Communicating with patients in modern cancer care

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Background: Following the introduction of breast cancer patients into a women's health ward the Breast CNS team needed to develop teaching sessions to upskill ward nurses in breast cancer care. COVID-19 meant that traditional face to face teaching was not broadly possible in health care (Haslam 2021). A new digital approach was required.

Methods: Electronic survey to establish challenges and learning needs communicating with breast cancer patients pre and post delivery of online teaching to 19 members of nursing ward team. This was followed up with a patient questionnaire.

Results: Pre teaching survey 14/19 nurses identified communicating with cancer patients and supporting them emotionally as a key area of concern. The most frequently identified aspect of concern was how to support patients emotionally, diagnosis and prognosis. 12/19 lacked confidence in drain/wound management. 11/20 nurses were unsure where patients could access support post surgery. Post teaching survey All 15 of the respondents reported increased level of confidence in wound and drain management and communication around discharge planning. However, the majority of nurses still felt unsure around some aspects of communication in supporting patients emotionally. Further a patient questionnaire to 32 inpatients at UCLH echoed the nursing challenges 9/32 listing that their emotional needs were not well identified and 9/32 did not feel confident managing drains at home.

Conclusions: The digital teaching package provided improved skills and confidence in practical aspects of care around wound/drain management and discharge planning. Despite this a number of patients 9/32 report they are still lacking confidence in drain management. Complex communication in highly emotive areas is more challenging and requires further support. Many patients also identified that they were not asked about concerns during their in-patient stay (9/32). It is easier for nurses to access learning from a remote location which helped to reach greater numbers, and information can be accessed on demand for improved flexibility. Actions The teaching package is being adapted and re-evaluated to focus further on challenging communication scenarios. The CNS team are in the process of developing new approaches in building confidence in drain care.

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CN10 Development and usability test of an individualized nutrition management application (iNutrition) for post-discharged gastric cancer patients following gastrectomy

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Background: Malnutrition can be largely reduced by nutrition intervention in post-discharged gastric cancer patients following gastrectomy. However, current nutrition interventions have been unsatisfactory worldwide. This study aimed to develop an individualized nutrition intervention application (iNutrition) and evaluate its usability in post-discharged gastric cancer patients following gastrectomy.

Methods: We developed the iNutrition using the design thinking method, which includes 5 phases: (1) "empathize": conducting qualitative research to develop knowledge about the patient's needs; (2) "define": identifying goals and scope of the iNutrition; (3) "ideation": conducting a focus group interview with a multidisciplinary team to brainstorm potential solutions; (4) "prototype": designing the functions and user interface of the iNutrition; (5) "testing": evaluating the potential usability of the iNutrition through a three-month usability test.

Results: According to the results of qualitative research of 15 patients and 5 clinical staff, the iNutrition should satisfy patients' needs for tailored nutritional plans, evidence-based nutrition knowledge, adjusting to postoperative anatomy change, and communicating with peers and medical staff. The final version of the iNutrition includes four modules: nutrition management, nutrition knowledge, gastrointestinal symptoms management, and communication center. The four modules include eight functions which are nutrition consultation, nutrition courses, symptoms knowledge, experience communication, nutrition status score, dietary calculator, nutritional requirement, and concrete meal plans. For the usability test, 25 patients with 52% male and mean age of 51.76 (SD 10.33) were recruited. 72.0% of the participants were satisfied with iNutrition; 76.0% and 64.0% reported that iNutrition was useful and easy to use, respectively.

Conclusions: The iNutrition has achieved its functions of serving as a tailored mHealth tool to conduct nutrition intervention in post-discharged gastric cancer patients following gastrectomy with satisfactory usability.

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CN11 Improving quality of life for patients with prostate cancer: ProstaGYM, a new digital skill

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Background: Patients with prostate cancer may experience a worsening in their emotional wellbeing and physical health due to treatments or disease burden. It has been reported that physical activity and lifestyle interventions are associated with improved patient outcomes and a lack of health literacy is perceived by patients as a key burden of their cancer experience, and an improvement in this aspect has been strongly correlated with better overall survival. Voice assistants have emerged as a promising tool to support patients' guided learning and exercises. Here, we report on the development, content, and functionality of the first Amazon Alexa voice assistant for patients living with prostate cancer in Spain.

Methods: A multidisciplinary group of expert physicians on prostate cancer were selected as a scientific committee. Based on their clinical experience and the scientific evidence, the working group agreed on and created the content. The topics for each module were defined through the use of a consensus technique. The digital skill, named ProstaGYM, was endorsed by the national patient association ANCAP and the design and programming was performed by an Amazon developer with support from Bayer Hispania.

Results: The skill contains four content modules: 1) general disease information and healthy lifestyle recommendations, 2) exercise routines to prevent sarcopenia, 3) specific exercises and interventions to manage urinary symptoms, 4) advice on sexual health and psychological support. ProstaGYM is available free of charge on the Spain Amazon Alexa skill store. Since its launch in November 2022, the following information on metrics were obtained (cut-off 30th April 2023): 144 unique customers, 164 user enablements (skill activation) and 182 sessions.

Conclusions: The skill ProstaGYM constitutes an innovative approach to guide patients with prostate cancer to self-manage disease symptoms and treatment side effects and promote physical exercise that may improve their quality of life.

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CN12 Integrating weekly symptom monitoring for patients with prostate cancer in radiation oncology: A prospective cohort study using electronic patient-reported outcomes

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Background: Integrating active symptom monitoring of electronic patient-reported outcomes (ePROs) in a clinical workflow and engaging clinicians in acting on data is challenging. This study aimed to adapt weekly digital symptom monitoring into the prostate radiotherapy (RT) workflow and explore the impact of clinician engagement on patient compliance and satisfaction.

Methods: Patients with prostate cancer (PCa) referred for RT were eligible. Weekly ePROs were reported until four weeks following RT and weeks eight, 12 and 24. Clinicians monitored and used the ePROs for symptom management and 'handled' the response in the electronic patient record. In week four following RT, a validated Patient Feedback Form was distributed to assess patient satisfaction with ePRO, and a nurse-led follow-up (FU) was offered after responding. Health-related quality of life was measured with EQ-5D-5L.

Results: A consent rate of 91.5% (n=161) and an attrition rate of 5% resulted in 156 PCa patients included in the analyses (95% ePRO, 81% mean response rate). Non-participants tended to be older (mean age 72 vs 69 ($p=0.010$)) and have a poorer performance status ($p<0.001$). Patients reported ePROs improved communication and discussions with staff (91-93%) and gave them a greater sense of involvement (93%) (Table). Clinician engagement was high, with 93% of patients having all PROs handled. Among patients who chose to deselect FU (23%), a higher proportion had deteriorated EQ-VAS scores two months later ($p=0.044$) and fewer contacts with the department ($p=0.045$).

Conclusions: Integrating weekly ePROs in the radiotherapy workflow for PCa patients was feasible. When clinicians actively used PROs for symptom management, patients felt more involved and reported an improved quality of care and communication with the clinicians compared to their prior experiences. Further exploration of follow-up based on patient preference is warranted.

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CN14 Quality of the abeona health app according to the onco-haematology patient in the Principality of Andorra: Preliminary results

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Background: This study is part of the implementation of m-Health in outpatient Clinical Pharmacy at Hospital of the Principality of Andorra, with the aim of knowing the qualification of the Abeona Health App by the patient when using it for three months. The main objectives are: 1. Determine the general rating of the App according to the patient. 2 and 3. Know if the patient would continue using the App for one year and if they would recommend the App.

Methods: Cross-sectional study in onco-haematological patients under treatment with OAAs. 1. Inclusion criteria: all adult patients treated with OAAs seen from November 2022 to May 2023 (6 months of study). 2. Tool measure: the validated spanish translation of uMars survey was chosen to meet the research objectives. 3. Data collected from the patients: age, sex, type of tumour and type of OAAs. 4. Data collected from the surveys: the uMARS questions that were used to evaluate the

Abeona Health App were: 2.4, 5, 6, 7, 8, 9, 10, 11, 12, 17, 18, and 20. 5. Statistical analysis: descriptive, performed with the Jamovi statistical package. 6. Ethical aspects: before providing the surveys, the patients were informed that their data would be treated anonymously, and they gave their signed informed consent to participate.

Results: 64 patients were visited. 44 participated in the study (4 of them through their children for not knowing how to use an App). 41 were women (64%) and 23 men (36%) with a mean age of 63 years. The most frequent tumor in women was the breast with OAAs Palbocilic and in men the Colon with Capecitabine. The general quality of the App according to the patient's response in the uMars survey was: 7.7% of the patients scored 3, 50% scored 4 and 42.3% scored 5. When referring to the use of the App for a year, 19.2% of the patients responded from 3 to 10 times, 46.2% from 10 to 50 times, and 34.6% more than 50 times. In relation to whether patients would recommend the App, 30.8% of the patients answered that they would recommend it to many people and 69.2% that they would recommend it to everyone.

Conclusions: 1. The Abeona Health App was rated with a score of more than 4 for 92.3% of patients. 2. The 80.8% of patients would continue using it for a year. 3. The 100% of patients would recommend it to people who could benefit from it.

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CN15 Real-life clinical and organizational evaluation of telemonitoring and assisted telemonitoring in more than 1500 cancer patients

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Background: Telemonitoring of patients receiving cancer therapy has been shown to improve patient outcomes in clinical trials. However, telemonitoring must be accessible to all patients, regardless of their digital literacy or vulnerability, and only limited evidence of real-life clinical and organizational impact has been provided.

Methods: We performed a multicenter retrospective observational study of telemonitoring for patients receiving oral anticancer drug and/or immunotherapy in routine practice. Depending on the oncologists' decision, patients were included in either remote monitoring or assisted remote monitoring with a home nurse or their community pharmacist. The tool records graded adverse events (AE) (CTCAE V5.0), vital signs, treatment characteristics, tumor baseline characteristics. Compliance (rated by Girerd questionnaire) was also collected. Reporting intervals and duration were based on the patients' treatment type. Based on alerts and clinical examination, the oncologists implemented interventions if needed.

Results: From January 2019 to September 2022, 1556 patients (median: 69 yo; 67,9% of women) from 57 different healthcare facilities were included: 1097 with home nurse support, 152 with community pharmacist support, and 350 with self-assessment. A total of 4509 healthcare professionals (HCPs) were involved in the remote monitoring of at least one patient, which corresponds to 4,6 different HCPs per patient, with different roles (remote monitoring leads, assistance to patients in the remote monitoring …). Nearly half of the patients had breast cancer (49.1%) followed by renal and lung cancer (16.9% and 14.7% respectively). Most patients were treated with an oral antineoplastic agent (83.3%). 94,8% of patients reported an AE; 27.7% had a grade 3 or 4 AE and 58.5% had at least 1 unexpected/rare AE. The compliance rated in the 668 assessed patients remains high at 3 months (79,9% of patients with a score of 0 at initiation vs 79,6% at 3 months).

Conclusions: Telemonitoring of patients with anticancer treatment allows early detection of AE and maintenance of treatment compliance at 3 months. Besides, it strengthens the community care - hospital network.

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CN16 The Mount Vernon Cancer Center non medical prescriber GI oncology clinic experience

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Background: The majority of healthcare services modified the way they operated during the COVID-19 pandemic. One of the areas that was greatly impacted was the Oncology services worldwide. In our department we increased the telephone consultations of the patients who were actively receiving treatment and the non-medical prescribers undertook a more active role in the on-treatment clinics.

Methods: Retrospective review of the GI clinic lists of all patients receiving systemic anti-cancer treatment (SACT) in 2022. Data was collected on gender, primary site of disease, treatment intent, cycle number, type of SACT.

Results: Three thousand four hundred and forty nine appointments (apts) were scheduled in the GI on-treat clinic in 2022. These were pooled from 3 Consultant lists and 1 pharmacy list. Patients were reviewed by 5 medical prescribers and 3 non medical prescribers (NMPs): there are 2 band 7 nurses and 1 band 7 pharmacist. Of the 3415 apts that took place (34 did not attend) the NMPs performed 792(23%) telephone consultations: 65% were male, 74% of patients received combination treatments, 20% single agent, 6% were given scan results. 15% of the patients were assessed for cycle 1 treatments. 70% were receiving chemotherapy, 7% biological target treatments, 9% immunotherapy, 3% chemotherapy — immunotherapy combinations, 3% chemotherapy- radiotherapy combinations and 2% chemotherapy — biological target combinations. The intent was palliative in 55% of the cases, 10% radical, 10% neo-adjuvant and 25% adjuvant. The primary diagnosis was 60% colorectal cancer, 25% gastroesophageal, 10% pancreatic and 5% GIST and cholangiocarcinoma.

Conclusions: Very experienced NMPs are vital members of the clinical team and can safely perform assessments of patients on a variety of treatments in a wide range of clinical settings. Their input in the telephone clinics has transformed the patient experience providing holistic care maximising their role as key workers in patients' journey. It also increased their to job satisfaction and promoted staff retention. More NMPs should be encouraged to undertake the NMP assessment course and set up their own clinics or work alongside with the medical staff in their respective clinics.

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CN17 Use of the ONCO'nect telemonitoring tool by socially deprived outpatients actively treated for a solid cancer: A retrospective quantitative and qualitative analysis of the Re'connect program

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Background: Telehealth improves the quality of life and overall survival of cancer patients. Social deprivation might lead to unequal access to telehealth. The aim of this study was to evaluate how socially deprived outpatients treated for a solid cancer get a grip on a dedicated telemonitoring program.

Methods: Between February 2021 and June 2022, eligible outpatients with a solid cancer undergoing chemotherapy at the Mondor Teaching Hospital, France, were provided with the ONCO'NECT® telemonitoring tool. It includes a chat system and standardized 24 items questionnaires before/after each treatment administration based on the NCCI Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE®), triggering alerts when the threshold of clinical significance was reached. Patients with social deprivation were identified based on the EPICES (evaluation of precariousness and health inequalities in health examination centres) score and were enrolled in the Re'Connect program (lending of a tablet, caregivers, technical and peer-to-peer support). We collected the data on patients' healthcare pathways retrospectively, and we performed semi-structured interviews to assess patients' challenges related to ONCO'NECT®.

Results: We enrolled 22 patients: 15 females, 50% were aged $>$ 70 years (interquartile range (IQR), 64-74), 14 had digestive cancer, 15 patients had metastases, 14 lived alone. Five and three patients completed $>$ 75% and $<$ 25% of questionnaires respectively, during a median treatment duration of 7,5 months (IQR, 4-14). The median number of triggered alerts was 5 per patient (IQR, 1-9,25). The underuse of

ONCO'NECT® went beyond patients' understanding of its interest and their technical competence and was related to borderline health literacy. The related patients' emotional negative experience might explain such an underuse.

Conclusions: Socially deprived cancer outpatients perceived the relevance of a telehealth tool. Beyond technical issues, patients' borderline health literacy and their negative emotional experience should be addressed to ensure equal access to telehealth.

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Cancer nursing: Health promotion, prevention and screening

CN18 Impact of the medical record-based frailty index on the health outcomes of elderly patients with colorectal cancer

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Background: Preoperative frailty in older patients with cancer is associated with poor health outcomes, such as falls, length of hospital stay, complications and mortality. Simple and clinically detectable frailty measurements are preferred in clinical settings. A laboratory frailty index (FI-Lab) based on routine laboratory tests and vital signs was suggested to assess and predict clinical outcomes in older adults. The purpose of this study was to examine the association between preoperative frailty and postoperative risk of fall and dependence, and mortality in elderly patients with colorectal cancer.

Methods: We retrospectively analyzed 268 geriatric patients (≥65 years) who received a curative resection for colorectal cancer. A 32-item FI-Lab was constructed based on routine blood tests and vital signs, and scores were rated as low (<0.25), moderate (0.25-0.40) and high (>0.40). The skeletal muscle mass was measured with CT images. The Johns Hopkins Fall Risk Assessment Tool and Modified Barthel Index were used to assess fall risk and dependency, and survival rates were evaluated.

Results: The mean age of participants was 72.3 years, 61.9% (n = 166), 33.6% (n = 90), and 4.5% (n = 12) were in the low, moderate, and high FI-Lab groups, respectively. Frailty was associated with old age, poor tumor differentiation, increased fall risk and dependency. The two-year survival rate was very low among the moderate and high frailty groups, and the risk of fall and dependency was significantly associated with the survival rate. The multidimensional Cox proportionate risk model showed that high frailty, age 80 years and older, and hypertension were independent predictors of poor prognosis. There were no significant differences in the skeletal muscle mass and density according to frailty.

Conclusions: The FI-Lab score was used to predict the risk of poor post-operative outcomes as a frailty indicator. The FI-Lab is a potentially useful tool for hospitalized elderly patients who are at higher risk of frailty and helps healthcare professionals implement strategies to improve health outcomes.

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CN19 Earkt phone oncogeriatric screening in gynaecological and lung cancer a care units by advance practice nurses

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Late withdrawal

CN20 Nurse's role in coordinating new cancer screening initiatives: Experiences from an on-going risk-based lung cancer screening feasibility study, among Swedish women

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Background: Lung cancer is the deadliest cancer form on Sweden. In recent years, the incidence of lung cancer among women has increased. International studies show reduced lung cancer mortality in high-risk populations after screening with low dose computed tomography (LDCT). In the Stockholm region, Sweden, a lung cancer screening program was developed, based on previous research, pilot testing and regional health economic analysis.

Methods: The purpose of this feasibility study is to test processes related to invitation, IT, logistics, resources, follow-up, imaging and smoking cessation. A random population-based sample of women (current smokers or recent quitters) aged 55—74 is invited to participate. The aim is to continue until 1000 women have undergone LDCT. Smoking cessation support is offered to all invited women.

Results: The inclusion started in September 2022, and the inclusion rate is currently 33%. The invitations are sent out via regular post, together with a link to a web-based survey. Once completed, women who meet the study's criteria are invited to LDCT. A specific protocol is developed to manage and follow-up different findings. LDCT imaging are managed, using an Artificial Intelligence protocol. The nurse's role includes managing the study office, information and support to participants, scheduling and booking the LDCT invitations, coordinating the study team and involved health care units, managing quality insurance related the study processes including IT issues. The results of the study will be represented during 2025.

Conclusions: The involved processes seem to work really well. The study provides the basis for a future calculation of resources for a national risk-based screening program. Experiences so far indicate improved early detection rate of lung cancer. The role of nurse coordinator is fundamental for the success of this program.

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CN21 Stakeholder perceptions of cervical screening accessibility and attendance in Ireland: A qualitative study

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Background: Screening plays a key role in preventing incidence of cervical cancer. In Ireland, the incidence and screening participation rates are not evenly distributed across the population, and evidence is limited. To provide and equitable service, it is important to understand who is and is not attending screening and why. This study explored the perceptions of expert stakeholders on cervical cancer screening attendance and accessibility in Ireland.

Methods: Semi-structured interviews were conducted with 12 healthcare professionals, policymakers and academics to explore their expert views on cervical

screening accessibility and attendance in Ireland. Interviews were conducted online in 2022. Reflexive thematic analysis was used inductively to generate themes, supported by NVivo.

Results: Three themes were developed from the interview data: Getting the right information out the right way, Acceptability and accessibility of screening, and trying to identify and reach the non-attenders. Participants felt public knowledge of cervical screening and Human Papilloma Virus was low and the communication of this information needed to align better with sources that women engage with. Accessibility and acceptability of screening was thought to be dependent on individual, cultural and structural and service factors. Identifying and reaching non-attenders was considered important by participants but community outreach and public engagement could enhance understanding and address the challenges of non-attendance.

Conclusions: Nurses have a significant opportunity to support uptake and engagement with screening. Nurses are often the first point of contact to provide information regarding health promotion and are therefore well positioned to provide education and support which can address the barriers to screening engagement. Community engagement could support understanding of the distribution of participation and awareness of screening and enhance supports for women to make informed decisions about engagement with cervical screening.

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CN22 Survivorship care in melanoma cancer survivors

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Background: Survivorship care provides numerous benefits for oncology survivors; however, resources and programing are not routinely implemented in clinical practice. The increasing population of cancer survivors presents the need for improvement in patient centered continuity of care. The Melanoma Survivorship Program aims to improve the experience and outcomes for melanoma survivors who have completed treatment. The goal is to aid patients' transition from the acute phase of treatment to living with a chronic condition while maintaining or improving quality of life.

Methods: Patients submit a survey to evaluate the long term emotional, physical, and financial effects of cancer and cancer therapy. They then meet with a Nurse Practitioner (NP) and a Social Worker to formulate an individual care plan. The survivorship program utilizes referrals to an interdisciplinary care team including cardiovascular health, exercise, nutrition, sexual health and intimacy, psychosocial care, and financial support. Additionally, they provide connection with patients' primary care provider for continuity of care.

Results: This poster provides a recommendation for NPs to promote survivorship referrals in clinical practice. Data was produced through analysis and reporting on the effectiveness of survivorship programs in randomized control trials as part of a systematic review. Protocols providing access to comprehensive survivorship care in previous studies were examined and used to measure the effectiveness of survivorship programs in addressing patient quality of life. Findings support the recommendation of survivorship programs and interventions, specifically those studies which utilized and adapted the National Comprehensive Cancer Network Survivorship Assessment and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

Conclusions: All forms of interventions were equally beneficial and largely dependent on patient goals. Therefore, NPs should encourage patients to engage in aspects of survivorship care that reflect their priorities. Additional research is needed to assess if survivorship care as described in this poster is effective at improving quality of life among melanoma cancer survivors long term.

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CN23 Understand the patients' perspectives based on their profile to improve health-related quality of life assessment in breast cancer

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Background: Patient-Reported-Outcomes (PRO) are widely used to measure patients' perspectives and support health product development, and their selection is a critical step of this process. As breast cancer (BC) profile and other medical or socio-demographic factors can influence patients' treatment choice, quality-of-life (QoL) and global patient journey, they could also impact patients' expectations. PROs selection should thus be personalized and based on the targeted population. This research aims to provide recommendations to better adapt the PROs selection and development to the medical product or service.

Methods: A 4-step method was used, starting by a state-of-the-art to identify the PROs most frequently used to assess BC patients' QoL and unmet needs, and list the covered outcomes. Then, organization guidelines and experts' recommendations were reviewed to complete the initial outcomes list. The next step was to conduct a direct-to-patient survey to generate new data on the most important outcomes for BC patients.

Results: The literature review showed that some outcomes are well covered by existing PROs: QoL, survival vs QoL considerations and healthcare pathway satisfaction. On the other hand, some outcomes are partially covered (copying strategies), and others are not covered (unmet needs, burden of disease). Moreover, experts' groups recommended to consider several profile attributes QoL in BC context (cancer stage, treatment strategy, complementary care, etc.[1]). Then, a direct-to-patient online survey was launched in several countries among the BC Carenity patient communities (objective: 300 respondents, results available in Sept 2023). It contains socio-demographic and medical questions, and questions aiming at ranking the previous outcomes and identifying other non-covered outcomes. Needs and expectations will be analyzed according to BC patients' profile.

Conclusions: The survey will provide a list of the most important outcomes for BC patients based on their profile. Then, a gap analysis will compare these results to experts' recommendations and PROs commonly used. These results could be used to improve PRO selection and orientate future investigations on BC patients' QoL assessments.

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Cancer nursing: Palliative and end-of-life care

CN24 The effectiveness of person-centered care (PCC) for children with cancer in palliative and end-of-life care

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Background: Person-centered care (PCC) has been a succeeding concept, originally described by Edith Balint in 1969 as "understanding the patient as a unique human being." Since then, there have been many other conceptualizations of patient-centred care thought that has been described as several alternatives including patient and family centered care, relationship centered care, personalized centered care and more. PCC as a holistic and humanistic approach has a connection to quality of care and therefore is essential in palliative and end-of life care of children with cancer. The aim of the study is to evaluate the effectiveness of PCC in palliative and end-of-life care of children with cancer.

Methods: Search strategy located 21 papers about PCC and 17 studies about palliative care and end-of-life care of children with cancer. No studies about implementation PCC into palliative and end-of-life care were found. A narrative summary of the study findings is therefore presented. The interventions described by the studies in the review varied in terms of their key components.

Results: Children with cancer experience pain and physical symptoms, low mood, anxiety, and fear. They feel less resilient, experience low self-worth, and have challenges coping with the illness. The families lead very stressful lives, navigating the hospital environment, and dealing with uncertainties of the future. Implementation of PCC improves physical symptoms, emotional support, and quality of life. It enables communication between families and health care providers. It improves end-of-life care support to children and their families and facilitates less invasive diagnostic and therapeutic interventions at the end of life.

Conclusions: Based on the evidence considered in this review, the results has specified the effectiveness of implementing PCC into daily practice in palliative and end-of-life care of children with cancer. Method to measure the degree of effectiveness of PCC is not clear and in many health care organizations evaluation methods do not exist. On the basis of the evidence considered in the review the effectiveness of PCC can be considered as having a multiple role as directing, coordinating, organising, decision-making, and accumulating devices.

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CN25 Psycho-education and telephone counselling on the quality of life of advanced cancer patients undergoing chemotherapy in Indonesia

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Background: Compelling evidence regarding the benefit of psycho-educational interventions (PEIs) on mental health among cancer patients is still limited. However, the effectiveness of PEIs followed by telephone counselling on the quality of life and its subscale among advanced cancer patients remains inconclusive. This study aimed to determine the effect of PEIs followed by telephone counselling among advanced cancer patients undergoing chemotherapy on their quality of life.

Methods: This study applied a randomized controlled trial. Patients with advanced cancer ($N = 151$) were randomly assigned to the experimental or control group. The experimental group participated in PEIs, a brief and highly structured program with one face-to-face and one phone session delivered by a nurse two weeks apart. The control group received only regular education. FACT-G questionnaires measured patient outcomes at baseline before and immediately preceding the next chemotherapy cycle. Independent and Dependent t-tests were used to evaluate the impact of the intervention on quality of life and its subscales.

Results: PEI followed by telephone counselling has a significant effect on the total quality of life ($p < 0.001$) and its subscales, namely physical wellbeing ($p < 0.001$), social wellbeing ($p < 0.001$), emotional wellbeing ($p < 0.001$), and functional wellbeing ($p < 0.001$) among the intervention group. A significant difference was observed between the groups concerning physical wellbeing ($p < 0.001$), social wellbeing ($p < 0.038$), emotional wellbeing ($p < 0.001$), and functional wellbeing ($p < 0.001$) and total quality of life ($p < 0.001$).

Conclusions: The psycho-educational intervention is potentially effective in improving the quality of life among advanced cancer patients undergoing chemotherapy. Those results are essential to evidence-based practice and determining the efficacy and cost-effectiveness of interventions in improving patient outcomes. There is a need to examine further the similar issues that continue during the palliative phase.

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CN26 Healthcare professionals' perceptions on palliative care in onco-haematological area: Validation of the palliative care perception instrument

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Background: Several studies show that integrated early palliative care in onco-hematology improves patients' quality of life, symptoms control, physical and mental health, and use of health resources. To better understand potential barriers and facilitators that may influence the referral of onco-hematological patients to palliative care it is necessary to investigate the perception of healthcare professionals in onco-hematological field on palliative care. This study aims to validate an instrument to assess healthcare professionals' perceptions of palliative care in onco-hematological area.

Methods: This is a validation study. The instrument is a questionnaire developed based on the questions of the study by Tay et al., 2021 . The validation of the instrument is ongoing, according to the COSMIN guidelines, and consists of content validation, face validation, and pilot test. To date, we completed content and face validity, which involved 5 experts in the field and 15 possible volunteer respondents, respectively.

Results: We calculated the Content Validity Index (CVI) for each item (I-CVI) and for the entire questionnaire (S-CVI). Every item obtained an I-CVI above 0.7, except for one item that obtained an I-CVI of 0.6. The item was considered acceptable and maintained since the S-CVI score was 0.95, meaning that the Italian experts found the instrument to be relevant to evaluate the topic investigated. After face validity, the questions that were considered confusing or containing difficult terms were rephrased according to participants' suggestions. None of the items was considered offensive. The final questionnaire consists of 22 items divided into 3 sections: demographics, perception, and professional behavior. The pilot test is ongoing and will allow us to assess reliability, internal consistency, and construct validity.

Conclusions: Validation results up to this point are promising, the completion of the validation process will allow obtaining a valid and reliable instrument that will help future researchers to investigate barriers and facilitators to the integration of palliative care in the onco-hematological field.

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CN27 Pain in men with metastatic castration-resistant prostate cancer (mCRPC) starting their first-line of life prolonging treatment: A cross sectional study in Sweden

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Background: Men with metastatic castration-resistant prostate cancer (mCRPC) have an incurable disease and along with prolonging life, symptom management is one of the main goals in treatment of these men. Most of these men have bone metastases and a high frequency report pain. However, to be able to achieve an effective pain management, and to evaluate effects of treatments on pain in a real-world situation, not only knowledge of frequency is important. Today there are no studies describing different dimensions of pain, such as severity and distress, in men with mCRPC starting life-prolonging treatments in a real-world situation. The aim was to describe the multidimensional aspects of pain from the perspective of frequency, severity and distress, and analgesic use in men with mCRPC, starting a first-line life-prolonging treatment.

Methods: Data was taken from a prospective study (n=143) where 72 men with mCRPC starting their first-line of life-prolonging treatment and reported pain were included. Three dimensions of pain (frequency, severity and distress) were measured using the Memorial System Assessment Scale (MSAS) and the use of analgesics was collected from medical records.

Results: Of the 72 men who reported pain on the MSAS, 63.9% (n=46) used analgesics while 36.1% (n=26) did not. Of the men using analgesics, 55.8 % reported pain "frequently" or "almost constantly" and among the men not using analgesics, 44.0% reported that they had pain "frequently" or "almost constantly". Of those using analgesics, 27.5% reported severe or very severe pain, while none of the men not using analgesics reported very severe pain, and 19% reported severe pain. Of the men using analgesics 51% reported quite a bit/very much distress in contrast to 38% of the men not using analgesics.

Conclusions: Pain management was not sufficient for more than half of the men, even for those receiving analgesics. Men with mCRPC starting life-prolonging treatment may benefit from a structured multidimensional assessment. When the disease has progressed to a mCRPC phase, an early integrated palliative approach with thorough symptom management may be essential in order to obtain the best possible quality of life.

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CN28 From difficulty to meaning: Palliative cancer patients experience on advance care planning conversation and having a palliative plan

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Background: ACP is used as a systematic tool with the aim of helping patients establish decisions about future care. Palliative care plan is a document that aims to ensure the planning and facilitation of measures to give patients and their families safety and the best possible quality of life. The plan was implemented in several municipalities in North-western of Norway in the first half of 2018 and follows the patient at all service levels.

Methods: An exploratory qualitative study was conducted with five palliative cancer patients who had undergone ACP and prepared a palliative plan. Strategic selection was used to choose informants and participants were recruited from four municipalities. Data were collected through individual semi-structured interviews and were analyzed using Malteruds systematic text condensation.

Results: Patients experienced ACP as a process starting from difficult conversations and culminating in a sense of meaning. Having a palliative care plan was felt to be a positive aspect, but they wished they had been prepared for these conversations and had undergone ACP in their own home. The patients' insights were as follows: (1) The starting point was difficult for the patients since they had to talk about cancer and death, which was tough, painful, and rather "taboo" topics. (2) The interactions with the doctor/nurse helped the patients feel valued and involved and underlined their final wishes. The patients wished that their next of kin had been involved by the

doctor/nurse. (3) Preparing a plan for the future and death was a meaningful process for the patients and gave them a sense of security.

Conclusions: Results suggest that advance discussion and a comprehensive plan are shown to give palliative cancer patients much benefit. Although participation in ACP can arouse unpleasant feelings, many patients reported benefits from it. Getting their wishes to be known and the reduced personal information about themselves in a document, gives patients inner peace of mind and increases quality of life. The context and interactions provided by the doctor/nurse, their ability in communicating with the patients, including the patients as persons and taking care of the patient's values and wishes was crucial.

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CN29 Euthanasia, not simply early death. Lived experiences of patients, caregivers, and nurses: A systematic review and qualitative meta-synthesis

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Background: The concept of euthanasia and the desire for a serene death that occurs outside frenetic healthcare environments still raises many questions. Different reasons and pathologies prompt people to make this choice. Particularly, for a person who lives with advanced cancer, choosing euthanasia is motivated by reasons including physical and psychological suffering or the need to maintain personal autonomy and dignity. This review can help provide a better understanding of patients, caregivers, and nurses' lived experiences during this journey.

Methods: We conducted a qualitative systematic review in four databases: Pubmed, Cinahl, Scopus, e Web of Science. The PRISMA method and enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) statement were adopted to report the data and the meta-synthesis approach was used. Of 2040 articles considered, twenty-eight were selected according to the inclusion/exclusion criteria (8 in oncology and palliative care settings). The thematic analysis approach was used to summarize the emerging data in two steps: 1) General, across all data, and 2) specific, considering oncology and palliative care settings.

Results: Five themes emerged from the general data: (1) the desire for early death; (2) autonomy as freedom to determine one's death; (3) end-of-life care as a good death; (4) accompaniment with support and care, and (5) personal experiences and emotions. In addition, three further themes found in the specific contexts were: (1) Methods used to address patient requests; (2) obstacles to meeting demands, and (3) nurses' involvement. These contents summarized both the reasons for requesting early death and the experiences of individuals involved in the complex path of euthanasia.

Conclusions: Euthanasia is not achieved only through an early death. Instead, it is a more complex and articulated pathway in which the suffering and consequences that the disease causes are addressed, and the way that these experiences lead to changes in the meaning of life. Patients perceive that euthanasia is "another option" that puts the person who, despite the illness, continues to have desires and expectations for their future, at the center of the care process.

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CN30 Patients', relatives', and healthcare professionals' experiences and perspectives of shared decision-making in palliative cancer care: A systematic review and meta-synthesis

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Background: Shared decision-making (SDM) in palliative cancer care can be challenging. Palliative care includes interprofessional teamwork and a family-oriented approach, hereunder decision-making. Qualitative research has been conducted on SDM in advanced cancer, mostly on the patient-physician dyad and some on the perspectives of relatives and nurses. However, a synthesis of SDM research in palliative cancer care integrating the perspectives of patients, relatives, and healthcare professionals has not yet been conducted. The aim of this review was to identify and synthesise qualitative findings on how patients, relatives, and healthcare professionals experience and perceive SDM in palliative cancer care.

Methods: We searched five electronic databases (MEDLINE, Embase, CINAHL, PsycINFO, and Scopus) until August 2022. Included studies were peer-reviewed papers reporting qualitative or mixed methods empirical studies of treatment and care decision-making with adult patients with advanced cancer, relatives, or healthcare professionals, which reported findings relevant to SDM. Our qualitative research synthesis was guided by Sandelowski and Barroso's framework. We synthesised extracted data using inductive thematic analysis, including a meta summary.

Results: The search identified 3,312 titles and abstracts, from which we included 20 studies, reported in 23 papers. The thematic analysis produced nine descriptive themes, which were further analysed to produce four analytical themes: 1) Overwhelming situation of "no choice", 2) Process varies by timings and where decision is required, 3) Patient-physician dyad is key, and 4) Involvement depends on personal qualities.

Conclusions: SDM with patients with advanced cancer is a complex process, involving multiple decisions, in a challenging, multifaceted situation with limited equipoise and choice. More attention to creating awareness of choice and motivating patient involvement is needed. This might require involving more healthcare professionals in the team, and particularly developing the role of cancer nurses in SDM in this context.

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CN31 A qualitative study investigating the perception of simultaneous care in nurses

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Background: The purpose of this study was to investigate features that can influence the incorporation of simultaneous care in the oncological setting by nurses' perspectives.

Methods: A qualitative study, involving structured focus group discussions, was conducted via web conferences (ZOOM platform). A total of two focus groups were performed, involving 9 nurses. Each discussion was audio-recorded, transcribed verbatim, and analyzed with thematic analysis.

Results: According to the Health Belief Model, the transcripts of the focus groups were categorized into: (1) benefits, (2) barriers, and (3) cues to action. Nurses recognized the acquisition of greater awareness of the path of care, a sense of empowerment, and the improvement in the patient's quality of life as the major benefits of simultaneous care activation. The perceived barriers in the simultaneous care activation were related to an increased risk of anxiety levels in patients and their relatives, as well as the precarious culture and lack of knowledge among the public opinion. Different strategies may favor the early activation of simultaneous care, including: a teamwork approach (oncologists, palliativists, and nurses), correct patient education, and the synergy between cancer hospital healthcare professionals and home simultaneous care staff.

Conclusions: This result may help to better implement and activate simultaneous care in the oncological setting with important implications for the patients' quality of life.

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CN32 Exploring the content and outcomes of meaning-centered interventions in palliative care: A scoping review

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Background: Palliative care patients experience existential suffering in terms of psychosocial and spiritual distress and physical pain. Meaning-Centered Interventions have been proposed to be an effective method for improving patient outcomes, reducing psychological and spiritual distress in advanced cancer patients. The aim of the scoping review was to explore the contents, outcome measures, and results of Meaning-Centered Interventions in Palliative Care.

Methods: The PRISMA-ScR checklist and scoping review recommendations were followed. Related databases searched for studies published in English, including PubMed, Ebsco, PsycINFO, and Scopus. Randomized controlled and interventional studies using meaning-centered interventions published from 2000 to April 2023 involving palliative care or advanced cancer patients were included. Two authors conducted the literature search and study selection process independently on the COVIDENCE system. Studies were assessed for design, sample, randomization, setting, administrators of the intervention, outcome measures, intervention content and duration, control group, and results.

Results: A total of 133 studies were imported for screening and ten studies were included in the scoping review after duplicates and irrelevant articles were removed. Five articles described the pilot study, four randomized controlled trials, and one arm feasibility trial. Six studies were from the USA, two from Spain, one from Australia, and Iran. Interventions were delivered by a psychiatrist, clinical psychologist, social worker, or doctoral student in clinical psychology, mostly 8 (3 to 10) sessions weekly as a group (n=5), individual psychotherapy (n=4); in the outpatient setting (n=6), at home and videoconference.

Conclusions: Patients receiving meaning-centered interventions showed significantly greater improvement in spiritual well-being, quality of life, and sense of meaning, and reductions in levels of depression, demoralization, hopelessness, death anxiety, desire for hastened death, and physical symptom distress compared with those receiving standard care. Meaning-centered interventions can be considered and adopted in other countries for patients receiving palliative care.

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CN33 Health care professionals' perceptions regarding shared clinical decision-making in both acute and palliative cancer care, a qualitative study and its clinical implications

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Background: Developments in cancer care have resulted in improved survival and quality of life. Integration of acute and palliative cancer care may be challenging, and there is no golden standard model for integration. Fragmented care is associated with sub-optimal communication, collaboration, and ineffective care. This may lead to unnecessary care transitions, and impact patient safety. We performed a study with the aim to explore how health care professionals, from both acute and palliative care, perceive clinical decision-making when caring for patients undergoing active cancer treatment in parallel with specialized palliative care at home.

Methods: Qualitative explorative design, using online focus-group interviews, based on patient-cases, among health care professionals (physicians and nurses) and Framework Analysis.

Results: Six online focus-group interviews were performed. Few signs of systematic integration between acute and palliative care teams were found, risking fragmented care and putting the patients in vulnerable situations. Different aspects of uncertainty related to mandates and goals-of-care impacted clinical decision-making. Organizational factors and uncertainty related to responsibilities impacted clinical decisions. We found barriers to timely end-of-life conversations and clinical decisions on optimal care. In addition, the appropriateness of transfer to acute care, seemed to be related to lack of knowing which team was responsible.

Conclusions: Lack of integration between acute and palliative care have negative consequences for patients (fragmented care), health care professionals (ethical stress), and the health care system (inadequate use of resources). Clinical implications: We started two main integration projects based on this study, one piloting direct admission to specialized palliative inpatient ward directly from the emergency room. The other on-going project will try digital visits with patient, the oncology, and the palliative team, aiming to discuss goals-of-care. The results and what we learned from those integration projects will be presented.

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CN34 Pallium game: The use of a card game in palliative care

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Background: Palliative care can improve the quality of life of people and their families when timely and holistic identification of needs is carried out, allowing for the planning of person-centered care that meets their multidimensional needs and includes their wishes (Fernandes et al. 2021 .) In palliative care, strategies are needed to eliminate some barriers to be able to discuss and document the values and preferences of the person and the family member.

Methods: This study aimed to evaluate the use of a card game as a family assessment tool in a palliative care unit. The sample was composed of 13 family members of people with palliative illness admitted to the palliative care unit. Participants were recruited using a convenience sampling method. The "Pallium Game" has 2 "Start" Cards, 23 "Family" Cards, 16 "Support" Cards, 10 "Impact" Cards, 23 "Meaning" Cards, 11 "Belief" Cards, and 8 "Intervention". The game begins with the two "Start" cards, serving as an "Icebreaker" and family assessment tool. Next, the participants choose the themes of the letters they want to answer and take turns reading the letters aloud and answering the respective themes. When the game is over, at least two intervention cards must be collected and discussed. Pallium game is intended to improve communication between people/families/caregivers and health professionals, creating a space that enables the understanding of the behaviour patterns in the family system, extracting meaning from adversity, and promoting better interaction and adaptation.

Results: Using a game was found to be useful and effective. A collaborative game in palliative care should create a space for people and families to express feelings and experiences, meeting the myriad of physical, psychosocial, and spiritual needs. Our findings suggest that using the "*Pallium game*" is a useful and impactful approach to discussing sensitive topics in palliative care.

Conclusions: A collaborative game in palliative care helps to create a space for individuals and families to express feelings and experiences, meeting the myriad of physical, psychosocial, and spiritual needs. The "Pallium game" is a useful and impactful approach to discussing sensitive topics in palliative care.

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Cancer nursing: Supportive care

CN35 Educational interventions and strategies that nurses use to support women with gynecological cancer: A narrative review

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Background: The incidence of cancer is increasing worldwide and is considered to be a serious public health problem. Hysterectomy and or oophorectomy are known to be the primary surgical treatments after cancer of the cervix, uterus, and ovary is diagnosed. In many cultures, the uterus and ovaries are considered to be symbols of femininity, fertility, and particularly motherhood. Indeed, the loss of these organs after surgery ends reproductive capacity. After undergoing radical surgery, gynecological cancer patients become vulnerable to several disorders that affect their quality of life, such as anxiety, depression, body image disorders, and low self-esteem.

Methods: A narrative review was conducted in three databases (PubMed, CINAHL and Scopus). The inclusion criteria were: 1) women with gynecological cancer; 2) papers written in English; 3) papers published between January 2012, and September 2022, and 4) papers that describe the details of educational interventions strategies that nurses use in oncology care. Two independent reviewers assessed each paper independently for methodological validity prior to inclusion in the review using the Prisma statement. A total of 178 articles was retrieved and identified. When the duplicates were removed, 150 studies were screened by title, and 67 by abstract, all of which were excluded, after which the full text of 52 articles were evaluated, of which 15 articles were included in the final review.

Results: A total of 15 findings was extracted and aggregated into 3 categories based upon similarity in meaning. Empowerment: nurses play a stimulating role to overcome fears, prioritize gynecological cancer patients' individual needs, and implement sexual rehabilitation strategies; Psychological sphere: nurses help women learn relaxation techniques and physical exercises for sexual rehabilitation, and Physical well-being: physical exercise, dance, and complementary medicine have positive effects on the patients' quality of life.

Conclusions: Nursing interventions are able to reduce the collateral effects of oncological treatments and strengthen patients' self-confidence in facing their oncological treatments, particularly by decreasing their anxiety, depression, and distress.

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CN36 Current care for patients on oral anticancer therapy through a different lens: Assessment from a patient and healthcare professional perspective

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Background: Over the last decades, an important shift from a disease-focused to a patient-centered approach has taken place in cancer care. This study examined the quality of patient-centered care for patients treated with oral anticancer drugs (OACD), from the patient and healthcare professional (HCP) perspective.

Methods: Patients and HCPs from 12 Flemish oncology departments completed the CONTACT-Patient-Centered Care Questionnaire (CONTACT-PCCQ) and the CONTACT — Key Elements Questionnare (CONTACT-KEQ) respectively. The questionnaires are based on an evidence-based and validated list of key elements (KEs) considered crucial in patient-centered care for patients on OACD. Patients were asked to indicate how they experienced the performance of each KE on a five-point Likert scale. The HCPs were asked to indicate whether the KE was performed or not. The degree of performance, according to patients and HCPs, was calculated for each KE.

Results: In total, 266 patients and 275 HCPs participated. The degree of performance according to patients ranged from 22% to 95%, with 36 KEs having a degree of performance $<$ 70% (i.e., underperformed). According to HCPs, the degree of performance varied between 23% and 99%, and 15 KEs were underperformed. While HCPs mainly assigned low scores to items related to coordination of care, patients scored low on items regarding counselling at treatment-initiation and during follow-up, and psychosocial support.

Conclusions: This study uncovered gaps in patient-centered care according to patients and HCPs. The differences between the scores of patients and HCPs highlight the importance of including both perspectives when evaluating patient-centeredness of care practices.

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CN37 Perceptions and attitudes of healthcare providers towards discussing sexuality and sexual problems in cancer patients (from LGBTQ+ backgrounds)

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Background: Sexual dysfunction is a consequence of cancer survivorship. Few oncology patients have had a conversation with a HCP about sexuality during or after treatment according to a report by *Kom Op Tegen Kanker* (Neefs, 2022). This study aims to explore the knowledge, perceptions, and attitudes of HCPs towards discussing sexuality with cancer patients, more specifically with LGBTQ+ patients.

Methods: A mixed-method study was conducted. An online questionnaire about attitudes and knowledge towards talking about sexuality with cancer patients was distributed by email among several interprofessional HCPs in March of 2023. The answers were statistically analysed in SPSS using descriptive statistics and Chi^2. Three focus group interviews were conducted with HCPs working at a University Hospital to explore their perceptions and attitudes towards discussing sexuality and sexual problems with cancer patients, as well as with LGBTQ+ patients. Data were analysed using thematic analysis.

Results: The questionnaire was completed by 259 HCPs working in cancer care in Flanders. Those who had an education on sexual health were positively correlated to knowledge ($p \leq 0.001$). There were also correlations ($p < 0.001$) that indicated that HCPs in more specialised functions had more knowledge on the topic and felt more comfortable discussing sexuality with cancer patients. Six themes, for which data saturation was reached, emerged from the focus group interviews: (1) preconditions for discussing sexuality with patients, (2) perceived barriers and (3) facilitators, (4) patients belonging to the LGBTQ+ community, (5) focus points, and (6) recommendations given by HCPs. HCPs reported not having enough knowledge of sexual health and deemed asking about sexual orientation as not important, as LGBTQ+ patients received the same care as the general cancer population.

Conclusions: HCPs have presumptions about patients' needs, while these might differ from their actual needs. This is especially true in minority groups such as LGBTQ+ patients. There is a need for more education and training among HCPs to facilitate the conversation about sexuality, as well as more research to improve care regarding sexual issues in cancer patients.

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CN38 To study the effect of evidence-based nutrition management on improving the nutritional status of postoperative patients with esophageal cancer

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Background: To explore the effectiveness of evidence-based nutrition management in improving the nutritional status of postoperative patients with esophageal cancer.

Methods: The evidence-based nursing method was used to obtain evidence and apply it to clinical practice after localization. The nutrition management plan for patients with esophageal cancer surgery was formulated, and the clinical behavior of doctors and nurses was standardized. The body weight and body composition index, standard rate of energy and protein intake, and postoperative hospital stay of patients with esophageal cancer surgery were compared before and after the application of the best evidence.

Results: The improvement of body weight, BMI and skeletal muscle in the intervention group were significantly better than those in the control group (all $P < 0.01$). The compliance rate of energy intake from the first to the fifth day after operation and the compliance rate of protein intake from the first to the sixth day after operation in the intervention group were better than those in the control group (all $P < 0.05$). The median postoperative hospital stay was 9 days in the intervention group and 10 days in the control group, which shortened the length of hospital stay ($p < 0.01$) and accelerated the recovery of patients after surgery.

Conclusions: Evidence-based nutrition management can improve the nutritional status and clinical outcomes of patients with esophageal cancer after surgery, which is conducive to improving the quality of medical care.

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CN39 Bibliotherapy in cancer nursing: A systematic review

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Background: Bibliotherapy is an intervention that uses written or visual materials to promote psychological and emotional well-being. Although bibliotherapy has been used in cancer care, there is limited understanding of its effectiveness in the nursing context. This systematic review aims to synthesize the available evidence on the use of bibliotherapy in cancer nursing.

Methods: A systematic search of electronic databases including MEDLINE, CINAHL, PsycINFO, and Cochrane Library was conducted. Studies that evaluated the use of bibliotherapy in cancer nursing were included. Two reviewers independently screened the studies, extracted the data, and assessed the study quality using the Cochrane risk of bias tool. The extracted data were synthesized using a narrative approach.

Results: Of the 1,238 articles identified in the initial search, nine studies met the inclusion criteria. The studies used various forms of bibliotherapy, including written materials, audio recordings, and videos. The studies reported improvements in psychological and emotional well-being, including decreased anxiety and depression, increased self-esteem, and improved quality of life. However, the studies had methodological limitations, such as small sample sizes and lack of control groups.

Conclusions: The available evidence suggests that bibliotherapy may be an effective intervention to promote psychological and emotional well-being in cancer nursing. However, the methodological limitations of the included studies indicate a need for larger, well-designed randomized controlled trials to provide stronger evidence. Cancer nurses may consider using bibliotherapy as an adjunct intervention to support the emotional needs of their patients.

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CN40 Time to identify CAM-users during oncology treatment: The results of a regional survey in Sweden

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Background: Patients' use of complementary and alternative medicine (CAM) is widespread. However, there is a lack of knowledge regarding the extent and details of patient CAM use in Sweden, and especially in rural Sweden. The aim of this study is to estimate the extent and characteristics of the CAM use of cancer patients in Region Gävleborg.

Methods: Questionnaires were distributed to patients either beginning chemotherapy treatment for curative purposes, or newly enrolled in palliative home care. A total of 631 questionnaires were distributed to which 376 responses were registered, yielding a response rate of 59.6%. The characteristics of the respondents were presented with standard descriptive statistics. A multivariate logistic model was fitted to calculate odds ratios (ORs) and identify potential predictors (Age, Gender, Education, Diagnosis) of CAM use post cancer diagnosis.

Results: The most common CAM methods used after diagnosis are vitamins, health food preparations, herbal tea, prayer, and dietary methods. The most common source of information reported is family and friends. 54% of all participants reported CAM use under lifetime, 34% reported CAM use post-diagnosis. Almost 70% of those who used CAM after their diagnosis stated that they did not discuss their use with health care professionals. Most patients wish that CAM modalities should be offered within conventional care regardless own CAM use.

Conclusions: The use of CAM is common among patients with cancer in the region of Gävleborg and previous studies show a similar use in Sweden in general. Based on the widespread use of CAM, as well as patients' desires for dialogue with health care professionals, attention and focus should be placed on creating a basis for this dialogue. If we in healthcare are to emphasise that we provide patient-centred care, we must recognise the fact that patients use CAM and are seeking a dialogue about this topic.

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CN41 Qualitative analysis of school re-entry experiences of turkish childhood cancer survivors: Parental perspective

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Background: Children with cancer stay away from school for a long time during the treatment process. School re-entry helps normalize the cancer experience for children and their families by enabling the child to participate in activities with peers. The aim of this study was to explore the school re-entry experiences of Turkish childhood cancer survivors.

Methods: In this qualitative study, semi-structured, in-depth interviews were conducted with parents of childhood cancer survivors (n = 20). Survivors who had completed treatment at least two years ago were involved in the study. Interviews were conducted via telephone or video conferencing. Interviews recorded and transcribed verbatim. An inductive thematic approach was used to analyze the data. The study was conducted and reported according to the consolidated criteria for reporting qualitative research (COREQ) guidelines. The components of qualitative rigor were considered to ensure confidence in the methods and data.

Results: The diagnosis of most of the survivors was lymphoma (35%). The ages of survivors were between 11-18 years and the duration of school absenteeism ranges from 1 months to 3 years. According to qualitative analysis, three main themes and sub-themes were identified as follows; 1) "Worry" with five sub-themes; Academic performance, Peer relations, Stigma, Physical problems and Exposure to physical trauma 2) "Challenging Situations" with five sub-themes; Negative body image, Negative perceptions of others about the disease, Parents' protective attitudes, The thought of falling behind from his/her friends and Feeling ostracized 3) "Facilitating Situations" with three sub-themes; Willingness to attend the school, Increased social interaction, and Support from school staff. Parents stated that both children and parents need support during the school re-entry process.

Conclusions: This study revealed that survivors worry about physical, academic, and social issues. They face a range of problems that make school re-entry difficult. With the cooperation of the health team and the school, arrangements should be made to ensure that the survivors have a positive experience on school re-entry.

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CN42 A pharmacist-led interprofessional medication adherence program improved adherence to oral anticancer therapies: The OpTAT randomized controlled trial

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Background: Protein kinase inhibitors (PKIs) are increasingly prescribed in cancer care. We aimed to evaluate the impact of a pharmacist-led interprofessional medication adherence program on patient implementation (dosing history), persistence (time until premature stop of the PKI) and adherence to 27 PKIs prescribed in different types of solid cancers.

Methods: Patients (n=118) were randomized 1:1 in two arms. All PKIs were delivered in electronic monitors (EM). In the intervention arm, pharmacists supported patient adherence through monthly electronic and motivational feedback including educational, behavioral, and affective intervention for 12 months. The control arm received standard care plus EM without intervention. Medication implementation and adherence were compared between groups using generalized estimating equation models, in which relevant covariables were included; persistence was compared with Kaplan-Meier curves. Oncologists prescribed regular treatment interruptions to help patients recover from side effects; this information was compiled in the analyses.

Results: PKI implementation was constantly higher in the intervention (n=58) than in control arm (n=60), 98.1% and 94.9% (Δ3.2%, 95% confidence interval (CI) 2.6%-3.7%) at 6 months. The probabilities of persistence and adherence were comparable between groups. The intervention benefited most to men (Δ5.4%, 95%CI 4.2-6.5), those who initiated PKI for more than 60 days (Δ4.6%, 95%CI 3.7-5.5), patients without a diagnosis of distant metastasis (Δ4.6%, 95%CI 3.4-5.7), those aged less than 60 years old (Δ4.1%, 95%CI 3.3-4.9) and those who had never used any adherence tools (Δ4.1%, 95%CI 3.4-4.7).

Conclusions: The interprofessional medication adherence program, led by pharmacists in the context of an interprofessional collaborative practice, supports implementation to PKIs in patients with solid cancers. In order to manage side effects, dose adaptations are often mandated, further supporting a proactive strategy aiming at supporting adherence. Longer-term medication adherence interventions, embedded in routine care, should provide results on the impact on progression-free survival.

Clinical trial identification: NCT04484064.

Legal entity responsible for the study: Department of Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland.

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CN43 Development, implementation and evaluation of a cancer survivorship care program

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Background: Cancer survivors experience treatment-related long-term and late effects, affecting their quality of life. Survivorship care is currently not adequately organized against these challenges and more understanding is needed. The aim of this project was to improve survivorship care by focusing on health care professionals across ten existing oncology groups at Ghent University Hospital.

Methods: A cancer survivorship care program was developed and implemented using action research. Based on a literature study, observations, focus group interviews, consensus meetings, data were gathered. The screening and development phase took place from 2020 till 2021. Implementation started in 2022 and is ongoing. Semi-structured interviews are being conducted to evaluate the program with the final results in October 2023.

Results: In order to improve and reorganize follow-up, training sessions were organized for health care professionals to increase their knowledge and awareness about survivorship care. Second, nurse consultations, in addition to physicians follow-up, were implemented which allowed clinical nurse specialist and oncology nurse navigators to focus more on psychosocial topics. Third, tools such as the survivorship care passport, the Holistic Need Assessment and a booklet for patients were developed as an aid to structure the consultation. Last, a digital platform was created to support health care professionals in primary and secondary health care with specific information on eight common challenges in survivorship care. This diverse set of tools was offered to all oncology groups. According to their needs, the implemented program was slightly different in every group. Preliminary results show positive experiences of the health care professionals on several levels. They feel more competent to deliver care which suits the need of patients. However, organizational issues and lack of time are common reported barriers.

Conclusions: Through action research, current barriers in survivorship care were identified and tailored solutions were offered to ten oncology groups. Preliminary experiences of health care professionals with this cancer survivorship care program look promising.

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Disclosure: All authors have declared no conflicts of interest.

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CN44 Evaluation of financial toxicity and associated factors in female patients with breast cancer: A systematic review and meta-analysis

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Late withdrawal

CN45 Exercise training following surgery and chemotherapy for ovarian cancer: A realist evaluation of a co-designed implementation process

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Background: The benefits of exercise for women with ovarian cancer are reasonably well established however uptake is poor. Presently, research exploring a co-designed implementation process is limited and may assist in exercise uptake. Determining the feasibility of exercise training in this population is necessary to improve survivorship.

Methods: This single centre study involved a series of three co-design workshops with contributors including ovarian cancer survivors (n=10) and their informal carers (n=10), followed by implementation of an exercise intervention with women (n=31) following surgery and chemotherapy for ovarian cancer. Following completion of the intervention participants undertook a realist interview. Healthcare professionals (n=3) familiar with the exercise intervention were also interviewed.

Results: Key themes that emerged include; the initial approach should be made by a disease specific health care professional, flexibility in meeting exercise goals, weekly telephone behavioural support, and a home-based approach. This promotes: a shift of mental focus from the disease to exercise and wellness; a sense of control over one's destiny; and a feeling of empowerment to reach exercise goals. A recruitment rate of 73.8% was achieved. 100% achieved the recommended dose of aerobic exercise, with 93.4% achieving the recommended dose of resistance training. The retention rate was 96.7%.

Conclusions: The co-design process facilitated exercise recruitment, adherence and retention. This intervention is feasible and safe for women following surgery and chemotherapy treatment for ovarian cancer. These findings contribute to the evolution of a programme theory in relation of how to successfully implement exercise into the care of this patient population.

Legal entity responsible for the study: Queens University Belfast.

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Disclosure: The author has declared no conflicts of interest.

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CN46 Experiences and sexuality of participants with a permanent colostomy after cancer treatment: A qualitative study

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Background: Each year, approximately 1.4 million people worldwide are diagnosed with cancer, of which 10% are diagnosed with colorectal cancer. A colostomy can negatively affect quality of life in various ways. The aim of this study was to explore the experience and perception of participants with a permanent colostomy after rectal cancer treatment with a focus on the sexual experience.

Methods: An explorative qualitative study was conducted. Semi-structured interviews were conducted in two hospitals. Fifteen participants with a permanent colostomy after treatment for rectal cancer participated. A thematic analysis was performed and investigators' triangulation was used during data-analysis. Data-saturation was obtained in most of the themes.

Results: Five main themes were retained: (1) living with a definitive colostomy, (2) seeking control through trial-and-error, (3) in relation to the other, (4) the sexual experience, (5) the provision of care. How participants experience life with a permanent colostomy was central to the themes. Participants are often not aware of the possible consequences of a colostomy on their general and sexual experience. In addition to commonly reported sexual functional problems, such as erectile dysfunction and vaginal dryness, the psychosocial aspect plays a major role. Mainly altered self-image and feelings, such as shame and anxiety, were most frequently expressed. Healthcare providers play an essential role in the information, education and training of the ostomy carrier.

Conclusions: Within the current care provision, sexuality is still insufficiently included in the care and treatment plan. This ensures participants feel only to a limited extent informed about the effects of the treatment on their sexual experience. There is need for a proactive approach to discuss sexuality.

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CN48 Mobile response and prevention unit: Mobile information and management unit a collaboration between "Care In Adult Cancer Patients" nursing research laboratory and "Cancer Guidance Center" a non-profit organization (Kapa3)

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Background: Social support plays a critical role in improving treatment outcomes for cancer patients. Patients with strong social support systems tend to have better adherence to treatment plans and better physical recovery. An innovative cooperation between the non-profit organization Cancer Guidance Center (Kapa 3) and the "Care in Adult Cancer Patients" Nursing research laboratory support cancer patients and inform them of any procedure required to fully exercise their rights. Kapa3 manages the rights and obligations of people with cancer. The organization partners with public and private entities, such as the European Cancer Patient Coalition, in taking action to tackle cancer effectively, highlighting the issues facing Greek cancer patients and survivors. A nurse and a social worker informed patients about this innovative cooperation and how to communicate with welfare services. Many nursing students participated in the project as volunteers. They used digital applications that assist in completing information and supporting cancer patients. These will include all offered welfare services, together with all the required supporting documents for their applications. This study aims to assess how many cancer patients use this service.

Methods: This study was conducted in the oncology departments of selected hospitals in Greece. This research used convenience sampling with 348 cancer patients.

Results: The majority of the patients lived in Northern Greece (Thessaloniki), were female (216, 62.1%), and were married (271, 77.9%). The participants' mean age was 60 ± 14 years. Most had breast cancer (28.4%) and lung cancer (22.4%). The majority of the selected cancer patients (71.3%) communicated with K3 to apply for the welfare service by the Disability Certification Centre, 42.5% for social invoice. About 33.6% (n = 117) of the caregivers communicated with K3. Most of them used mobile phone calls (129, 37.1%) and mobile applications (106, 30.5%).

Conclusions: Using the proposed innovative application will help cancer patients and caregivers develop a better relationship and improve their quality of life.

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CN49 Nurse—patient sexual health communication in gynecological cancer follow-up: A qualitative study from nurses' perspectives

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Background: Globally, over 1.39 million women are living with gynecological cancer, and their sexual health can be adversely impacted by cancer treatments. Therefore, it is crucial for gynecological cancer survivors to have opportunities to openly discuss and exchange information regarding their sexual needs during follow-up care. This study was conducted as part of a broader project in Norway that aimed to enhance traditional follow-up approaches for gynecological cancer. The study specifically focused on gathering insights from nurses who were trained in sexual health communication. The primary research question addressed in this study was: What characterizes the nurse-patient sexual health communication, from the perspectives of nurses trained in addressing sexual health?

Methods: Individual semi-structured interviews with 10 nurses at five different hospitals in Norway were conducted in March and April 2021. A Gadamerian-inspired research method was used in the analysis.

Results: Three main themes with six sub-themes were identified. The three main themes were: (1) building relationships through communication, (2) practice makes perfect—the importance of experience and knowledge, and (3) personal attitudes as promoters or inhibiters of sexual health communication.

Conclusions: This study highlights valuable insights on nurse-patient sexual health communication. The nurses recognized the importance of establishing a strong and respectful nurse-patient relationship as the foundation for effective communication in this domain. Professional confidence, gained through experience and knowledge, was found to be crucial, along with recognizing the influence of attitudes and taboos on sexual health communication. The findings indicate that training in sexual health communication and repeated opportunities to address sexual health enhance nurses' skills and professional confidence for follow-up care. Importantly, this study suggests that sexual health communication can be effectively integrated into clinical settings without excessive resource demands. The results may encourage nurses to expand their knowledge of sexual health in cancer follow-up care.

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CN50 Patient-reported outcome measures and supportive care need assessment in patients in a slovenian tertiary oncology centre

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Background: Patient-reported outcome measures (PROMs) are tools usually questionnaires, to assess elements of their experience such as symptom burden, functional status and psychological and emotional well-being from patient 's perspective on how illness or care impacts on their well being. The aim of our study is to analyse the psychophysical social well-being and quality of life of cancer patients prior to treatment, the approach of the multidisciplinary team to identify and manage patient needs, and the barriers and facilitators to the use of PROMs in a Slovenian tertiary oncology centre, in order to inform the wider uptake of PROMs.

Methods: From December 2022 to August 2023, PROMs data collected for patients accessing care at a tertiary cancer centre will be retrospectively analysed. Data will be collected using the standardised EORTC C30 questionnaire.

Results: The results will be used to identify, according to each of the domains, the physical, emotional, cognitive, social functioning and functioning, symptom burden, health status and quality of life of the patients before the start of treatment and the use of a multidisciplinary approach to meet the patient's needs. Perceived risks, barriers and facilitators to the use of PROMS will be presented.

Conclusions: This study will demonstrate the benefits of using systematic PROMs monitoring and follow-up to screen patients' needs and provide holistic approach for cancer patients. It will also highlight opportunities, barriers and facilitators to PROMS implementation occur.

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CN51 Psychometric properties of the Turkish version of the nurse spiritual therapeutic scale for oncology patients and caregivers

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Background: The need for valid and reliable instruments to assess spiritual care in oncology settings has become increasingly important due to the growing awareness of the holistic needs of patients and caregivers. This study is methodologically designed to evaluate the psychometric properties of the Turkish version of the Nurse Spiritual Therapeutic Scale for oncology patients and caregivers.

Methods: This methodological study was conducted between July 2022 and May 2023 with 200 oncology patients and their caregivers. Data were collected using the Information Form and the Nurse Spiritual Therapeutic Scale. In the data analysis, the number and percentage were used for categorical data, while arithmetic mean ± standard deviation was used for quantitative data. Content validity index was used for the compatibility analysis of expert opinions, Pearson correlation analysis was used for item-total score analysis of the scale and its sub-dimensions, and exploratory and confirmatory factor studies were conducted to determine the factor structure of the scale.

Results: The mean age of the nurses was 58.51 + 14.55, and 56.5% were female. In the compatibility analysis among expert opinions, the item-based content validity index was found to be between 0.88 and 0.99, while the scale-based content validity index was 0.97. The total Cronbach's alpha coefficient of the scale was found to be 0.879. The factor analysis used to test the construct validity of the scale revealed that the scale had a single-factor structure with 20 items. The Kaiser-Meyer-Olkin coefficient of the scale was determined to be 0.847, and the result of the Barlett test was 3797.794 ($p < 0.000$). As a result of the exploratory factor analysis in the study, it was found that the factor loadings obtained ranged between 0.29 and 0.89. The scale item-total score correlations were determined to be between 0.236 and 0.761. GFI, AGFI, and CFI were found > 0.90.

Conclusions: The Nurse Spiritual Therapeutic Scale for Oncology Patients and Caregivers is valid and reliable. It should be used to assess the expectations of oncology patients and caregivers regarding spiritual care from nurses.

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CN52 Role of translational oncology research nurse (TORN) in improving patients (pts) adherence to microbiome research projects

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Background: Currently, multiple studies focus on microbiome's relationship to colorectal cancer (CRC) pathogenesis. Microbiota sampling requires strict protocol for collection. Good communication between pts and professionals is needed to ensure their comfort when participating in these projects. TORN is the reference professional in terms of patient care during the disease process and has the necessary training for the collection of biological samples. Our objective is to analyse the adherence to biological samples collection and completion of quality of life and nutrition questionnaires (QoLN) in CRC pts participating in projects involving microbiome, after the incorporation of the TORN into the medical oncology team.

Methods: Pts who attended the TORN consultation for evaluation of microbiome projects at the Vall d'Hebron Institute of Oncology (VHIO) were included. During the consult, functional status and preferences for participating are discussed. If the patient consents, a QoLN is performed. Subsequently, stool and saliva kit are given, and a blood collection is taken. Pts return kits at the following visit. Sample collection is performed at 3-timepoints: baseline, post cycle 1, and at disease progression (PD).

Results: Between 2020 and 2023, 517 pts were visited by TORN (1009 visits), 375 were eligible for microbiome sample collection. A total of 337 QoLN were given, of which 248 were correctly completed (adherence 72%). All pts were able to have blood drawn at all three time points. A total of 788 stool and saliva kits were given to patients, of which 688 were returned (adherence 87,31%). Adherence was lower in the third time period (PD) due to clinical worsening and return to referral centers (Table).

Table: CN52

STOOL/SALIVE SAMPLES	BASAL	POST CYCLE 1	PD	TOTAL
KIT GIVEN	375	293	120	788
KIT RETURNED	345	255	88	688
ADHERENCE (%)	92,0	87,03	73,33	87,31

Conclusions: By being a direct contact to pts and empowering them in the face of their disease, TORN has increased patient adherence to microbiome translational studies. We need to further develop this model of nursing care to continue improving our patient's wellbeing.

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CN53 Sexual function in survivors of hematological malignancy and autologous hematopoietic stem cell transplantation

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Background: Autologous hematopoietic stem cell transplantation (AHSCT) is one of the treatments for patients with hematological malignancies that improves prognosis and survival. Sexual dysfunction following AHSCT is common and affects survivors' quality of life. The aim of the study was to evaluate the sexual function (SF) of survivors of hematological malignancy and AHSCT and to compare it with the SF of healthy individuals.

Methods: A multicenter, quantitative, and cross-sectional study was conducted. Through convenience sampling,127 adults (56 women and 71 men) and survivors of hematological malignancy, who underwent AHSCT from 6 months to 5 years, were recruited from 5 hospitals in Athens,Greece.Also,134 healthy adults were recruited (60 women and 74 men). Survivors and controls completed demographic and clinical data and a male or female SF assessment tool [International Index Erectile Function (IIEF) and Female Sexual Function Index (FSFI) respectively].

Results: Female survivors had a mean of 44 years of age and male ones, 47 years. The median time from transplant was 3 years and the majority had Hodgkin's lymphoma. According to the FSFI, female survivors had a moderate level of SF, with better functioning area "pain" (mean: 4.0 ± 1.74) and worse "orgasm" (mean: 3.19 ± 1.52). According to the IIEF, male survivors had a high level of SF, with better functioning area "erection" (mean: 22.54 ± 8.70) and worse "overall satisfaction" (mean: 6.94 ± 2.47). When comparing SF in survivors with healthy females, it was found that the healthy ones had statistically significantly higher scores in all FSFI subscales ($p < 0.0005$). Also, healthy males had statistically significantly higher scores on "erection" ($p = 0.003$), "desire" ($p = 0.004$), "intercourse satisfaction" ($p = 0.003$), "overall satisfaction" ($p = 0.012$) and on the total score ($p = 0.013$) of the IIEF, compared to survivors. Although male and female survivors had affected SF, there was no statistically significant differences between SF in the male and female survivor groups.

Conclusions: Survivors of AHSCT had impaired SF to varying degrees and areas of functionality, thus indicating the importance of sexual well-being and the implementation of integrated sexual care plans in survivorship.

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CN54 Sexual health in women with breast cancer undergoing hormonal treatment

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Background: Sexual dysfunction is the most common long-term consequence of cancer treatment in breast cancer survivors (BCS), which have a huge impact on their quality of life (QOL). We pretend to develop a tool to assess these problems, identify the most relevant challenges, and prove the beneficial effect a nursing intervention would have on their QOL.

Methods: This is a prospective study with 51 BCS treated with HT, who were recruited from Hospital Clínico Valencia, from March to April 2023. A questionnaire with 28 related items was developed, including demographical data. These were evaluated by a Likert scale.

Results: Patients were aged under 45 years-old (mean 40.5 ± 3.2). 82.4% of BCS received previous chemotherapy treatment. Regarding the surgery, only 43.1% presented a tumorectomy. 21.6% of BCS were treated with Tamoxifen and 78.4% with aromatase inhibitors plus LH-RH analogues (AI + LHRHA). 70.6% expressed high satisfaction with their previous sexual life; however, only 25.5% of BCS feel satisfied. This study highlights vaginal dryness (72.5%), loss of sensibility in the affected breast (62.5%), loss of femininity (60.8%), loss of desire (60.8%), and fear of penetration pain (60.8%). AI + LHRHA was related to fear of penetration pain ($p=0.003$). The type of surgery impacted sexual satisfaction ($p=0.031$), and breast sensitivity ($p=0.018$). 74.5% of the patients emphasized the importance of sexual health. Nevertheless, 72.6% of BCS stated a decrease in the frequency of their sexual activity. 66.7% of the patients shared these issues with their partners, but only 23.6% talked about it with the oncologist. Furthermore, 72.5% felt that they did not have enough previous information. Interestingly, 80.4% would attend a nursing sexual health counselling and 78.4% considered this would improve their QOL.

Conclusions: HT impacted BCS' sexual health. The most frequent problems were dysfunction due to vaginal dryness, penetration pain, and desire. Mastectomy and AI + LHRHA presented poorer outcomes. Nurses' interventions could be helpful to improve their QOL.

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CN55 The impact of psychosocial support on the overall health of cancer patients in the COVID-19 era

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Background: COVID-19 mainly affected the elderly and people with chronic illnesses. The SUCCEED questionnaire was developed to assess the psychosocial needs of cancer patients in the era of COVID-19. This study aims to demonstrate how psychosocial support affected the health of cancer patients in large multisite cancer centers.

Methods: A total of 559 cancer patients were involved. We used the SF-36 questionnaire where higher values indicate a better general health status and the SUCCEED Questionnaire assessing psychosocial needs, higher scores indicate greater needs. Divergent validity was examined by comparison with the SF-36 questionnaire and analyses included descriptive and logistic regressions statistics.

Results: Cancer patients were mainly female (55.3%) and the mean age was 66.2 years ($\pm$11.6). The correlation between psychosocial support (SUCCEED score) and health status (SF-36 score) was negatively significantly correlated and negative: as the level of psychosocial support received decreases, general health also decreases (Pearson'r=-0.140, $p < .001$). This negative correlation was even stronger when considering the "Psychological-emotional health" domain of the SF-36, where a one-point increase in the SUCCEED score leads to a 0.8-point decrease in psychological-emotional health (Pearson'r=-0.152, $p < .001$). A negative correlation was found between the SUCCEED domain 'patient concerns' and the SF-36 domain 'psychological-emotional health': when patient concerns decrease, psychological-emotional health improves (Pearson'r =-0.180, $p <.001$). Also, general health and vitality correlation revealed a negative significant relationship (Pearson'r=-0.147, $p<.001$). The domain of patients' perceptions is also negatively correlated with psychological and emotional health (Pearson'r =-0.280, $p<.005$). Age is negatively correlated with SF-36: each additional year corresponds to a decrease of 0.258 points in the total SF-36 score. In contrast, it increases by 11.5 points if the patient receives psychosocial support ($p<.001$).

Conclusions: Poor psychosocial support negatively affected the health status of cancer patients during the COVID-19 pandemic. Cancer nurses should advocate to better respond to psychosocial patient needs.

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CN56 Well-being and healthcare concerns of patients with advanced renal cell carcinoma: The RCC PROMs international survey

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Background: Renal cell carcinoma (RCC) is the most common type of kidney cancer, most frequently diagnosed in men over 60 and in higher-income settings. Around 30% of cases are of advanced RCC. Despite progress with targeted therapies and immunotherapy, patients with advanced RCC face difficulties with day-to-day living. Patient-reported outcomes provide crucial information to enhance clinicians' understanding about what issues patients perceive to have the greatest impact on them and can help promote person-centred approaches to treatment and disease management.

Methods: As part of the larger EONS PROMs project (https://cancernurse.eu/research/proms_project/), an international online survey was launched in May 2022. With a sampling confidence level of 95% and a margin of error of 10%, we aimed to involve $\geq$89 patients with advanced RCC. The survey comprised a bespoke demographic/clinical form, the Functional Assessment of Cancer Therapy-Biologic

Response Modifiers (FACT-BRM) questionnaire, and three questions on patients' priority concerns.

Results: The survey included 105 patients. Typically, patients were men (n=62, 59%), on targeted therapy (n=31, 33.7%), middle-aged (median=44 years), and over 3 years since diagnosis (median=37 months). Descriptive analysis of individual FACT-BRM items revealed that patients: were bothered by too frequent an urge to urinate (70%), worried their condition will worsen (68%), worried about their partner or family (67%), felt helpless (60%), were unable to work (59%), and were concerned about end-of-life care (58%). Spontaneously, patients identified major concerns with wages, impact on family, and future response to treatment. Older age was a statistically significant predictor of higher FACT-BRM total scores ($p<0.001$), better physical wellbeing ($p<0.001$), and better emotional wellbeing ($p<0.001$). Receiving radiotherapy or targeted therapy were predictive of poorer physical wellbeing ($p<0.05$).

Conclusions: Identifying, monitoring, and responding to concerns relating to physical, emotional, social, and practical aspects of wellbeing can be meaningful steps towards provision of enhanced person-centred care in advanced RCC.

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CN57 Patients, informal caregivers and healthcare professionals experience in adoptive cell therapies: An experience-based co-design study (EBCD-ACT)

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Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (ACT-TIL) is a rapidly growing strategy in the field of cancer therapies that relies on delivering specific autologous anti-tumor immune cells. While ACT-TIL entails a complex treatment procedure, the experience of care in this context remains understudied. Experience-Based Co-Design (EBCD) positions patients as active partners together with healthcare professionals in services quality improvement. EBCD seeks to capture and understand how people experience a health service through the identification of emotional touchpoints - key moments that shape a person's overall experience. We herein present the design of our study which aims to inform and improve the current delivery of supportive care during a Phase I-II clinical trial with ACT-TIL by examining the experiences and perspectives of patients, caregivers, and healthcare professionals.

Trial design: Following the EBCD methodological framework we will (1) observe clinical areas to map care trajectories, (2) interview patients, caregivers and healthcare professionals, (3) analyze and develop a trigger film highlighting themes from patients' interviews, (4) conduct independent patients/caregivers/healthcare professionals' feedback event (focus group), (5) conduct joint patients/caregivers/healthcare professionals' workshop(s), (6) and a consensus meeting. Furthermore, as part of the setting-up stage and in order to enhance the pertinence and scientific quality of the results, an Advisory Board (AB) has been constituted to inform and support the research team in both the development and the identification of issues that might be relevant for the project. The AB includes national and international experts in ACT (oncologists and nurses), the heads of the different units involved, experts in psychiatry, humanities, and laboratory procedures, as well as a patient representative. Results of this innovative study will provide a list of recommendations on how to adapt care delivery within early phases clinical trial of ACT-TIL.

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Cancer nursing: Symptom management

CN59 The comparison between two types of educational information in reducing nausea and vomiting in patients undergoing chemotherapy: Randomized controlled trial

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Background: Chemotherapy-induced nausea and vomiting (CINV) are common problems in patients undergoing chemotherapy, occurring in up to 70%-80% of patients. Antiemetic drugs are largely used to treat CINV; however, some studies reported that the CINV can be significantly reduced with patient empowerment, and nurses can play a crucial role in the management of this intervention.

Methods: A phase III randomized trial was conducted at the Multidisciplinary Day Hospital at CRO Aviano between December 2018 and November 2022, enrolling 384 consecutive patients undergoing first-line chemotherapy. Inclusion criteria: age 18-80 years; signed informed consent. Exclusion criteria: life expectation <6 months; previous psychiatric or neurologic disease; visual impairment. Prior to first-line chemotherapy, patients were randomized 1:1 to receive written and verbal information on CINV prevention (arm A) or standard verbal information alone (arm B). A brochure describing drugs for CINV prevention and nutritional advice was provided to arm A patients. Antiemetic drugs were allowed as per standard care. The impact of CINV on daily activities was evaluated after one chemotherapy administration through the Functional Leaving Index — Emesis (FLIE) questionnaire.

Results: Fifty-eight patients were excluded after randomization for incomplete data. Arms were balanced with respect to gender, age, cancer type, chemotherapy, and antiemetic drugs use. Nauseas was reported by 30.1% and 39.9% of patients in arm A and B, respectively. Patients in arm A reported a reduction of 5.9% (95% confidence interval: 0.3%-11.5%) of moderate/high impact of nausea on daily activities compared to those in arm B (4.2% and 10.1%, respectively; p=0.038). This effect was consistent across strata by gender, age, and antiemetic drug use. No effect was found on vomiting.

Conclusions: This study demonstrated that nursing education intervention provided through a booklet reduced the occurrence of severe nausea in patients undergoing chemotherapy. Nurses play an important role in patient empowerment, with beneficial effects in patients' quality of life.

Clinical trial identification: CRO2018-012.

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CN60 Dynamics and processes in the perception of colorectal cancer patients facing skin toxicity due to an EGFR-inhibitor

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Background: Epidermal growth factor receptor inhibitors (EGFR-I), such as cetuximab and panitumumab, are treatments that are frequently used in patients with metastatic colorectal cancer. An important side effect of these treatments is skin toxicity, which has a negative impact on patients' quality of life. The aim of this study is to explore the dynamics and processes in the perception of colorectal cancer patients facing skin toxicity due to an EGFR-I.

Methods: An exploratory qualitative study was conducted, based on the principles of grounded theory. Fifteen semi-structured interviews were performed within two settings, namely a university hospital and a general hospital. The data were analyzed in a cyclical process through thematic analysis and investigator triangulation. For the main themes data saturation was achieved.

Results: The dynamics and processes of the perception of skin toxicity were situated in three impact areas. First, patients described an impact on themselves due to the confrontation with symptoms and a lower self-esteem due to feelings of shame and insecurity caused by the visibility of skin toxicity. This also affected their self-management and the ability to cope with the toxicity. Second, patients outlined an impact of others. For example, comments caused insecurity and the need to hide their skin toxicity or isolate themselves. Additionally, their relatives had to support them in treating the skin toxicity, or skin toxicity sometimes led to an inability to work. Finally, patients stated that healthcare professionals provided emotional support and helped their coping process. In contrast, negative comments of others or from health care professionals could lead to insecurity or frustration.

Conclusions: The side effect of skin toxicity not only has a physical impact but also affects the psychological and social aspects of a colorectal cancer patient's well-being. The digestive oncologist, dermatologist and nurse specialist should take this into account when counselling these patients. Additionally, there is a lack of knowledge about the impact of this side effect by healthcare professionals.

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CN61 Recognizing and managing immune checkpoint: Related symptoms with expert advice from dedicated oncology nurse

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Background: In order for oncological treatment with immune checkpoint inhibitors (ICI) to go as planned, a tight patient — care giver bond should be established. Patients (pts) are advised to contact dedicated oncology nurse in case of symptom worsening or adverse events (AEs) emerging. Telephone consultations are recorded as passive monitoring in order to keep track of the pts difficulties. Furthermore, an active monitoring from the dedicated nurse is made halfway between 1st and 2nd ICI cycle to check the pt status.

Methods: We retrospectively analysed active and passive consultations with pts with advanced non-small cell lung cancer, receiving ICI, their complaints, further referrals, ICI discontinuation and / or immunosuppressive treatment prescribed and the final outcomes.

Results: Three hundred and fifty-seven pts started ICI treatment from Jan 1st, 2018, to Dec 31st, 2022, and in that time-period we recorded 112 phone calls from 70 different pts with median age of 66 yrs and 61% being male. All of the patients were further referred to their general practitioner, emergency room or to a prior check-up with their oncologist at 78%, 13% and 9%, respectively. Almost half of the complaints (45%) were assessed as disease symptoms worsening, 33% needed temporary ICI discontinuation due to G1/2 ICI AEs, 20% both ICI discontinuation and immunosuppressive therapy due to G2/3 AEs and 3% of patients had life threatening AEs that led to in-hospital management. From June 2020 active monitoring resulted in 281 active inquiries, with 47 newly recognised complaints, 51% due to poor cancer symptoms management and 49% as possible ICI AEs. Out of latter, symptoms were mostly managed with professional advice about supportive treatment, although 8 (17%) of complaints resulted in temporary ICI cessation and immunosupressive treatment. None of the pts in either cohort died due to an AE complication.

Conclusions: About one fifth of pts on ICI therapy experience intractable concerns that need professional guidance and since half of those were later recognized as AE of ICI therapy, it is essential to accept the role of dedicated oncology nurses with special knowledge that can prevent severe complications by swift recognition of pts concerns.

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CN62 Experiences and need of cancer patients with cardiovascular problems during systemic cancer treatment: Results of a qualitative study

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Background: New or worsening cardiovascular problems during systemic cancer treatment impact a patient's quality of life. It is therefore of interest to gain insight into patient's experiences and needs when confronted with cardiovascular problems during cancer treatment.

Methods: A qualitative phenomenological study using individual semi-structured interviews is being conducted in two university hospitals. Dutch-speaking adult patients with solid or hematological cancers who's systemic treatment is ongoing or has been completed maximum one year ago and who experienced a cardiovascular problem during this treatment or maximum one year after completion, were eligible. Data collection and a thematic analysis is performed iteratively. Over a 3-month time period, 12 patients have been interviewed. Data collection will be finalized at the time of the conference.

Results: Intermediate analysis shows that participants feel worried, given their perception that the heart is a vital organ. Patients feel anxious about any symptom that might be linked to a reduced heart functioning. In case of cancer treatment interruption, patients worry about a potential negative impact on their oncological prognosis and cancer treatment outcome. Patients have mixed needs towards being informed prior to treatment-initiation about the risk of developing cardiotoxicity. Patients mostly need information and support from their oncologist about the consequences of the cardiovascular problem for the oncological disease.

Conclusions: Developing cardiovascular problems during or shortly after cancer treatment induces feelings of worry and anxiety about the consequences for oncological treatment outcomes and disease progression. The results call for tailored counseling strategies to support and meet patient's needs. A dedicated interdisciplinary cardio-oncology care pathway may prove valuable.

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CN63 Patient education outcomes in patients receiving oral anticancer agents: Preliminary results of a systematic review

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Background: The availability of oral anticancer agents has been increasing and home use has created a need for educational interventions; further, some concerns about symptom management or safety issues have been raised. Although, the importance of patient education as an essential aspect of effective care delivery is recognized in the literature, current evidence regarding the outcomes of educational interventions in patients taking oral anticancer agents still needs to be summarized. Accordingly, this systematic review will cover the knowledge gap in this field specifically regarding contents, methodologies, settings, timing/duration, and healthcare professionals involved in patient education.

Methods: A systematic review is underway following the preferred reporting items for systematic reviews and meta-analyses guidelines upon registration in PROSPERO (number CRD42022341797). PubMed/MEDLINE, CINAHL, Embase, and Scopus and gray literature were consulted to seek for studies addressing adult patients ($\geq$ 18 years old) receiving oral anticancer agents in hospital/outpatient/home settings, and patient education outcomes. Two researchers independently screened the search results via title/abstract and evaluated the full-text using the Rayyan AI platform. The critical appraisal tools from The Joanna Briggs Institute was used to guarantee a quality appraisal. A data extraction form was implemented and the results will be summarized in narrative form.

Results: The database search produced 2588 records; of these, 403 were duplicates. Preliminary results will be presented at the conference.

Conclusions: This systematic review will provide crucial information regarding the outcomes of educational programs in patients taking oral anticancer agents. Aspects of establishing effective educational programs will be highlighted and will influence the management and the clinical practice by increasing patient and family members' awareness, safety, and satisfaction.

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CN64 Assessment of depression among lung cancer patients with type 2 diabetes using centre for epidemiologic studies depression scale (CES-D)

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Background: Cancer and diabetes both are highly prevalent diseases. Depression often occurs in patients with lung cancer patients and it is a common symptom in individuals with diabetes 2. The purpose of this study was to assess depression in patients with lung cancer and diabetes type 2 undergoing chemotherapy.

Methods: This was a cross-sectional study conducted in a large oncology hospital in a major city in Northern Greece. It involved a convenience sample consisting of 100 lung cancer patients with type 2 diabetes undergoing chemotherapy. Data was collected using the Centre for Epidemiologic Studies Depression Scale (CES-D) and a questionnaire to determine the demographic and clinical characteristics. The CES-D is a self-rating 20-item scale with a recommended threshold score of 16 for indicating the presence of threshold depression.

Results: The mean age of the sample was 59.57±5.04 years. The majority of the patients were males and married (74%) and were freelancers (21%). Regarding clinical characteristics, most of the participants (31%) underwent surgical removal of the tumor, had small −cell lung cancer (51%). The vast majority of patients received carboplatin (74%). Also, oral medication is the treatment for diabetes (49%). The mean score in CES-depression was 39,47 ±6,16, higher than 16. Comparison between demographic and clinical characteristics and the CES −depression score respectively, have shown that gender (p=0.01) and educational status affected the level of depression (p=0.001). The existence of metastases affected the score of depression (p=0.02). In addition, the type of diabetes treatment affected the overall score of depression (p=0.002). There were not statistically significant correlation between depression and clinical characteristics.

Conclusions: Depression is a symptom experienced by Greek lung cancer patients with diabetes type 2. The results of this study support healthcare professionals to manage the symptom effectively and help their patients.

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CN65 Assessment of fatigue in elderly hospitalized cancer patients undergoing chemotherapy: A pilot study

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Background: Fatigue is one of the most common symptoms experienced by elderly cancer patients. This study aims to assess fatigue in elderly hospitalized cancer patients and the factors influencing it.

Methods: This pilot study was performed in a large hospital in a major city in Northern Greece. Fifty elderly cancer patients were chosen for the research through convenience sampling. Data were collected using the Cancer Fatigue Scale and a questionnaire with demographic and clinical characteristics.

Results: The mean age of patients was 76.16 ± 9.77 years. Most were widowed (n=22, 44%) and retired (n=39, 78%). The mean score of the total Cancer Fatigue Scale was 40.16 ± 11.22. Comparison between fatigue and clinical-demographic characteristics revealed statistically significant differences between previous therapy (surgical removal of the tumor or radiotherapy) and the physical dimension of fatigue ($p = 0.02$) and the existence of metastases and total fatigue ($p = 0.02$). Furthermore, the factors influencing the patients' total fatigue were examined using clinical and demographic characteristics. However, when these variables were added as predictors of fatigue into a regression model ($R^2 = 0{,}29$, $p < 0{,}01$) to assess their predictive power, two of them significantly predicted the depression score [Metastasis existence (b = 0.51) and comorbidity of diabetes (b=0.48)].

Conclusions: Elderly cancer patients experience fatigue during hospitalization. Certain clinical characteristics affect this symptom. Therefore, Greek nurses should take into account the findings of this study and design appropriate care plans and interventions to alleviate the fatigue problem.

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CN66 Cancer symptom clusters, nutritional status and quality of life of patients with cancer undergoing outpatient chemotherapy

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Background: Patients with cancer chemotherapy may have different cancer symptom clusters (CSC) that negatively impact their quality of life (QoL). These symptoms can sometimes arise from the disease itself or as a result of their cancer treatment.

Methods: Cross-sectional observational study conducted at Hospital Santa Rita de Cássia, a reference in oncology treatment in the state of Espírito Santo, Brazil. We included a) patients of both sexes and >18 y.o.; b) anatomopathological diagnosis of malignant neoplasm in stage I-III; c) patients (only new cases) undergoing outpatient chemotherapy. The instruments for data collection were: 1) Sociodemographic and clinical instrument; 2) Memorial Symptom Assessment Scale (MSAS) to identify the CSC and 3) The EQ-5D-3L to assess QoL; 4) Nutritional Risk Screening. Each patient donated two blood samples for measurement of biomarkers (troponin I and C-reactive protein). Descriptive and bivariate statistical analyzes were conducted using SPSS v.28.0.

Results: Thirty-eight participants with a mean age of 56.09 y.o. diagnosed with malignant neoplasm were included. Most patients had a diagnosis of breast cancer (n=21; 55.26%), followed by the diagnosis of colorectal cancer (n=7; 18.42%). Most patients was into staging II (n=18; 47.37%). We observed a mean QoL score of 74, with the most affected domain being anxiety/depression (n=28; 73.68%). The most prevalent CSC were, worry (n=25; 65%), followed by pain (n=19; 50%). Three clusters were identified: 1-(difficulty for sleeping-sadness-worry); 2-(fatigue-nervousness-dry mouth) and 3-(pain-nausea-irritable-difficulty concentrating). Regarding nutritional status by we identified that most patients were classified as "normal"(n=22; 55.89%), followed by slightly altered (n=9), only one patient had serius nutritional status. Troponin I correlated with age (*Rhos*=0.31; p=0.033) and gender (*Rhos*= -0.48; p=0.02). C-relative protein showed a moderate and direct correlation with weight (*Rhos*=0.48; p=0.001) and waist circumference (*Rhos*=0.48; p=0.001).

Conclusions: Adequate attention to CSC should be the basis for the accurate planning of effective interventions to manage the symptoms experienced by cancer patients.

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CN67 Comparison of existing guidelines for healthcare professionals on the perceived symptoms of breast cancer patients with registered symptoms in the medical records: Preliminary results

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Background: Healthcare professionals (HCPs) may underestimate symptoms experienced by patients with breast cancer (BC). The study aims to gain insight into a potential gap between the symptoms outlined in guidelines versus the symptoms that the HCPs register in the medical records.

Methods: A Mixed-Method study compared symptoms outlined in best practice guidelines with those documented by physicians' inpatients' medical records. Symptoms were classified according to the National Cancer Institute (NIH). BC patients in follow-up with aromatase inhibitors (Letrozole, Exemestane or Anastrozole) were included. Symptom registration was compared with the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) guidelines.

Results: Patients were included over a recruitment period of 3 months (n=23). Single symptoms identified by the NIH definition (n=235). Several symptoms were identified

in the medical records which in the guidelines were described with different frequencies e.g., dry mount. Multiple identified symptoms in the medical journals were only described in a single guideline e.g., scar pain, skin irritation, general physical condition abnormal and nasal dryness. Several symptoms detected from clinical consultations were not mentioned in the guidelines at all e.g., muscular weakness and lack of energy.

Conclusions: The BC population expressed at the consultations several symptoms that are not compatible with the guidelines. Our results indicate that symptoms outlined in the best practice guidelines do not embrace the total patient-experienced symptoms as outlined by the physicians. There seems to be a discrepancy between the frequency of various symptoms. Perspective: As a part of the Mixed-Method design, an exploratory study is now being carried out by using patient- and focus-group interviews. The exploratory study is important, as it seeks to broaden the symptoms experienced by the patients compared to the symptoms identified in this study.

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CN68 Experiences and needs of rectal cancer survivors without or with minor low anterior resection syndrome

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Background: After sphincter-saving rectal cancer surgery, many patients experience bowel problems called low anterior resection syndrome (LARS). Especially major LARS (LARS-score $\geq$ 30) has a negative impact on patients' quality of life. Our previous research has shown that these patients have several information and counselling needs towards healthcare professionals. Patients without LARS (LARS score 0-20) or with minor LARS (LARS-score 21-29) experience less bowel problems which has less impact on their quality of life. The aim of this study was to explore the dynamics in experiences, information and counselling needs of patients without or with minor LARS.

Methods: A qualitative study based on the principles of a grounded theory was conducted. Rectal cancer survivors without LARS or with minor LARS were purposefully recruited in three large hospitals. Patients with major LARS, patients who have had an abdominoperineal resection with permanent stoma and patients who do not speak Dutch were excluded. Semi-structured interviews were performed. The constant comparative method and investigators' triangulation were used during data-analysis.

Results: Fourteen patients were interviewed of which six patients without LARS and seven with minor LARS according to the LARS-score. In the first months, all 14 patients experienced LARS which had an impact on their family or working life. However, these symptoms improved over time resulting in a controllable situation. Additionally, patients described that LARS became less dominant and other symptoms such as peripheral neuropathy due to neoadjuvant chemotherapy were perceived worse. Factors such as having previous bowel problems during treatment, comparing themselves to patients experiencing major LARS or feeling euphoria about avoiding a permanent stoma reinforced their coping strategy. The amount of information patients received beforehand varied. Patients who received a high information load experienced anxiety but stated that this information was necessary to be prepared.

Conclusions: The symptoms of patients without or with minor LARS were more controllable and became less dominant compared to major LARS. These insights are important to organize care for patients without or with minor LARS.

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CN69 Experiences of patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: A qualitative study

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Background: Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) can control the disease state of patients with limited peritoneal carcinomatosis (PC). In spite of the fact that it is an effective and promising treatment, it has a big impact on various aspects of patients' quality of life. The aim of this study is to explore experiences and needs of patients with digestive tumors after CRS/HIPEC (short and long-term).

Methods: An explorative qualitative design was used. Individual semi-structured interviews were performed with 15 patients (2-14 months postoperatively) between December 2020 and May 2021 in one expert university hospital in Belgium. Data-analysis was done using thematic analysis and investigators' triangulation was used.

Results: Before surgery, patients relied on the expertise of the surgeon and saw the surgery as their only hope. After surgery, patients underestimated rehabilitation due to acute and long-term effects of the treatment. They described their relatives as a second victim but experienced their support at the same time. Patients were grateful for the future but also had fear for recurrence. Treatment by an experienced surgeon and the counseling of a clinical nurse specialist was seen as an added value. The need for contact with peers varied among patients.

Conclusions: CRS/HIPEC has a large impact on patients' and their relatives' lives. Patients were confronted with short and long-term effects. The healthcare professionals (HCPs) should adapt the amount and kind of information before surgery to the coping mechanism of the patient. Counseling afterwards is necessary. HCPs should pay attention to the needs of the relatives as well and explore if the patients have a need to meet with peers.

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CN70 Out of hours symptom triage and supportive care

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Background: Cancer-related Emergency Department (ED) presentations are increasing rapidly, leading to increased utilisation and pressure on EDs. This impacts on their ability to provide timely, high-quality patient care. Nurse-led telephone triage (TT) services have been implemented in many oncology centres. Despite this there have been relatively little study of its ability to reduce ED utilisation. This study was conducted in Beaumont Hospital, a tertiary academic centre in Dublin serving a population of one million. The primary aim of this study was to assess the impact of the TT service in preventing ED presentations and the characteristics of patients accessing the service.

Methods: All patients receiving cancer treatment have a 24-hour contact number for specialist advice. Nurses are trained to assess patients by the UKONS Toolkit and to perform autonomous interventions for grade 1-2 events or refer to the oncologist on-call for higher grade events. Data was collected retrospectively from paper logs recorded over the 2022 calendar year. Patient and disease characteristics, presenting symptoms and the timing of calls were compared between those advised to attend and managed successfully over the phone.

Results: The TT service received 383 calls over the study period. The mean (SD) patient age was 56yrs (15.04); 199 (52%) were female. Of the 383 patients, 182 (47%) were referred to ED while 201 (53%) avoided it. Admission demographics, cancer types and treatment modalities were similar between groups. Patients who avoided an ED referral were significantly more likely to have a chemotherapy/ medication, genitourinary or miscellaneous complaint, while those with infectious issues were more likely to be referred. Most phone calls (65%) occurred at the weekend. Calls during working hours were more likely to avoid referral.

Conclusions: The majority of patients avoided attending the ED and the triage service was particularly effective in dealing with chemotherapy/ medication and genitourinary issues. Symptoms related to infectious issues were referred more frequently. Future steps could include increasing weekend staffing and integrating the TT service

with the national oncology electronic health record system to further improve decision making by providing timely access to detailed patient information.

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CN71 SensiEx: A randomized pilot trial Sensorimotor training using whole body vibration exercise to reduce chemotherapy-induced peripheral neuropathy after treatment for breast cancer

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Background: Approximately 50% of women receiving chemotherapy for breast cancer develop chemotherapy induced peripheral neuropathy (CIPN) and is associated with significant disability and poor recovery. Common symptoms of CIPN include pain, altered sensation, reduced or absent reflexes, muscle weakness, reduced balance control and insecure gait. These symptoms affect activities of daily living and reducing patients' quality of life. CIPN also cause treatment delays, dose reductions, or even discontinuation of therapy, which can affect the outcome and compromise survival. To date, CIPN cannot be prevented and effective treatment options are lacking. Preliminary data indicate that whole body vibration (WBV) exercise may have a preventive effect on the onset of CIPN. However, how WBV compares to conventional cardio and resistance exercise (CAR) exercise for alleviate CIPN has not yet been studied. The aim is to compare the effects of WBV exercise compared to CAR on the primary outcome of CIPN symptoms and secondary outcomes of balance, physical function, and quality of life.

Methods: This prospective, multicenter, two-armed, randomized pilot study will include 44 women, assigned randomly either to the WBV group or the CAR group. Patients will exercise twice per week (at Karolinska) for 12 weeks. Measurements are performed at baseline, 3 and 6 months. *Inclusion criteria:* breast cancer diagnosis, aged 18—65 years, ECOG performance status of 0—2, completed chemotherapy in the past 6 month and remaining CIPN symptoms. *Exclusion criteria*: pre-existing neuropathy of other cause, severe cardiovascular disease, regular intake of analgesics, smoking. Measurement: CIP-NAT, CIPN-R-ODS, QLQ-C30, PainDETECT, Monofilament, Turn fork test, Tendon reflexes, Balance and Muscle strength tests.

Results: Based on previous study findings, we hypothesize that WBV exercise compared to CAR will reduce symptoms to a larger degree, such as the loss of peripheral deep sensitivity, pain, weakened or absent reflexes and loss of balance control.

Conclusions: Hopefully patients will experience an improvement in physical function and quality of life.

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Legal entity responsible for the study: Y. Wengström.

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CN72 Symptom burden, quality of life and emotional status of patients with advanced lung cancer seen at the functional lung unit

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Background: Lung cancer is usually diagnosed at advanced stage with a high burden of symptoms, deterioration in quality of life (QOL) and significant emotional impact. Interventions in these patients are aimed at improving QOL through physical and emotional symptoms management. It is important for the advanced practice nurse (APN) to know baseline health status of patients before treatment initiation to address interventions to improve their outcomes.

Objective: To describe the burden of symptoms, QOL and emotional status of outpatients with lung cancer before starting the antitumor treatment.

Methods: This is an observational study, evaluating consecutive patients with advanced lung cancer from January to April 2023 from the outpatient clinic of the lung functional unit (UFP). The intensity of the symptoms, QOL, anxiety, depression and APN interventions will be measured using validated and ad-hoc constructed questionnaires with Likert-type responses. The analysis was descriptive using percentages, frequencies, and measures of dispersion.

Results: 48 patients, 60.0% men, 75.9% aged 60-75, 83.6% diagnosed with advanced non-small cell lung cancer. Symptoms burden: dyspnea 52.7%, cough 70.4%, pain 65.8%, sleep disturbance 59%, asthenia 63.5%, anorexia 28.2%, constipation 32.2%. The scores for quality of life were 54.2/100, anxiety 5.3/21, and depression 4.3/21. General interventions carried out by the APN consisted of health education on symptoms and toxicity management, treatment and queries about the disease. Specific interventions consisted of placing a peripheral venous access 12.5%, consultation with a psycho-oncologist 6.3%, psychosocial committee 2.08%, social worker 2.08%, smoking cessation 2.08% and referrals to other specialists 2.08%.

Conclusions: The outpatients seen have low QOL scores, a high burden of symptoms and a certain level of anxiety and depression. Knowing the most prevalent symptoms, the QOL and the emotional state of the patients at the beginning of the treatment will allow the APN to optimize the interventions to address the different physical and emotional symptoms and improve the quality of life of these patients.

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CN73 Symptom management in patients with chemotherapy-induced hand-foot syndrome: A qualitative study

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Background: Hand-foot syndrome (HFS), may cause sensory loss, erythema-specific skin syndrome, hand and foot skin pigmentation, swelling in finger, toes, blisters, ulcers, and bleeding with pain. Studies have found that some patients underestimate the potential long-term effects of the disease, which results in suboptimal disease management. The study aimed to explore the self-management of symptoms in patients with chemotherapy-induced HFS and to provide guidance for developing a self-management plan that aligns with patient needs.

Methods: Twenty-two patients who developed chemotherapy-induced HFS were selected by objective sampling from July to Sept 2022 in the Department of Oncology of a tertiary hospital in Shanghai. A semistructured face-to-face in-depth interview was performed to collect the case data, which were analyzed using the content analysis method, and the themes were refined.

Results: Twenty-two patients, were interviewed. Three themes and six subthemes emerged from analysis of the interviews: The first theme was "Patients' attitudes and emotional responses to symptoms," including patients gradually accepted the symptoms of HFS and adapted to some mild manifestations based on the following responses, showed different emotional responses to the HFS, symptoms that affected their daily lives. Patient felt guilty for his family and had a self-image disorder. The second theme was "symptom experience," symptoms varied across patients and had different impacts on individual lives. Including pain and itching feeling peeling. The third theme was "coping strategies," including patients felt the impact of limited social interaction and family relationships. The fourth theme was "expectations for the future," including acquire related knowledge via websites, physicians, and among patients, changed habits and showed improved symptoms and met/exceeded the expectations of the healthcare providers.

Conclusions: Healthcare providers should offer more education and emotional support to patients with chemotherapy-induced HFS to achieve symptom management, elicit positive experiences, and help with more targeted and effective self-management of symptoms.

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CN74 The effect of nursing senior's self-efficacy on symptom management in cancer patients on clinical decision-making skills

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Background: This study was conducted as a relation-seeking research to determine the effect of nursing senior students' self-efficacy regarding symptom management of cancer patients on their clinical decision-making skills.

Methods: The universe of the research consists of senior nursing students studying at Nursing Faculties and Health Sciences Faculties Nursing Departments of 7 universities affiliated with the Council of Higher Education in the 2022-2023 academic year in Turkey. A Stratified random sampling method was used in the selection of universities. Considering the 7 geographical regions in Turkey, faculties that are the oldest established and have the largest academic staff were selected for each region. The number of participants to be reached from each university was determined using the known universe sampling formula. The data was collected by the Personal Information Form, Clinical Performance Self-Efficacy Scale, Clinical Decision-Making Scale in Nursing. The data of the research were collected online with "Google Forms". T test, one-way analysis of variance, Bonferroni, Tamhane's T2 test were used. Pearson correlation analysis was used for the relationship between numerical measurements and Cronbach's alpha value was used for scale reliability. $P<0,05$ was accepted for significance.

Results: The average score of clinical performance self-efficacy scale of the senior nursing students was determined to be 76,40. In the study, the average score of clinical decision-making scale in nursing was calculated as 142,48. There is a statistically significant positive correlation between clinical performance self-efficacy scale in nursing and clinical decision making scale and sub-dimension scores ($p<0,05$). In line with the data obtained in the study, it is understood that there is a weak positive correlation between the self-efficacy of nursing senior students regarding symptom management of cancer patients and their clinical decision-making skills ($r=0,384$, $p<0,05$).

Conclusions: It is recommended to provide theoretical and practical training to support nursing students' self-efficacy in clinical performance and clinical decision-making skills to improve symptom management in cancer patients.

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CN75 Validation of a symptom diary for outpatients with cancer receiving intravenous chemotherapy and/or targeted therapy

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Background: The Utrecht Symptom Diary (USD) is a Dutch validated patient-reported outcome measurement tool (PROM) - based on the Edmonton Symptom Assessment System - to assess and monitor symptoms in cancer patients. This study aimed to evaluate the added items on the treatment specific outpatient USD in cancer patients receiving intravenous chemotherapy and/or targeted therapy.

Methods: Observational longitudinal retrospective cohort study including all adult outpatients with cancer receiving intravenous chemotherapy and/or targeted therapy in an academic hospital in the Netherlands who completed at least one outpatient USD as part of routine care (2012-2021). Content, criterion and construct validation were assessed.

Results: 1733 patients who completed ≥1outpatient USD during intravenous chemotherapy and/or targeted therapy were included for analysis. Content validity (relevance, comprehensiveness) was shown. Criterion validation was confirmed for all added items of the outpatient USD — except for the item on oral pain. Additional analysis showed that mouth problems were detected with both outpatient USD items oral pain and dry mouth. Construct validity was confirmed for the items hair changes and skin and nail problems. Construct validity on eye problems was not tested due to the low number of paired outpatient USDs.

Conclusions: The outpatient USD is a valid PROM in outpatients with cancer receiving intravenous chemotherapy and/or targeted therapy. Since its validity in this broad group of patients we think the outpatient USD is widely applicable. Additionally, to providing tailored supportive symptom care, the USD-data can be used to increase knowledge about symptom burden in daily practice in this population.

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Cancer nursing: Workforce and educational issues in cancer nursing

CN76 Consensus views on research priorities for cancer survivorship in older adulthood: A Delphi study

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Background: Few published research priority setting activities involve older adults living with or after cancer as the primary stakeholders, and those that do originate in primarily continental North American contexts. This study aims to obtain consensus on priorities for future research on cancer survivorship in older adulthood in a European context.

Methods: A modified three-round Delphi study was undertaken with experts by profession and experience in geriatric oncology. Fifty research priorities were pre-identified via a qualitative interview study with older adults living with and after cancer; these priorities were presented to participants in this Delphi study. Between June and October 2022, the Delphi expert panel determined the importance of each proposed priority for future research in geriatric oncology. Consensus was defined by at least 80% agreement on the highest three points of a 9-point Likert scale.

Results: A total of 60 people participated in rounds 1-3 of this study. In round 3, participants were older adults living with or after cancer ($n=22$, 40.7%) family members/carers ($n=8$, 14.8%), and healthcare professionals ($n=17$, 31.4%), advocacy professionals ($n=4$, 7.4%) and academics/researchers ($n=3$, 5.6%) working in the area of geriatric oncology. Following round 3, 37 of 55 topics (67.3%) reached consensus, of which 7 (12.7%) had greater than 95% consensus. Priority areas with highest consensus focused on development of treatment options for older adults (98%), decision-making (96%), promoting awareness of potential cancer symptoms requiring investigation in older adulthood (96%), clinical programmes to address rehabilitation (96%) and management of multimorbidity in cancer (96%) and cancer- (96%) and frailty-related outcomes (96%).

Conclusions: The results of this study provide a framework of research priorities for research in geriatric oncology survivorship, reflecting areas of highest need identified by key stakeholders, including older adults themselves. Development of treatment modalities for older adults was a notably high priority, but research to understand and address unmet needs related to diagnosis, treatment-related decision-making and rehabilitation are also key priorities identified by this expert panel.

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CN77 EONS advocacy toolkit: How to let your voice be heard as a cancer nurse

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Background: Cancer nurses are at the heart of cancer care and experience the rapidly changing conditions and the influence of health politics in their daily practice. These are some of the reasons why there needs to be leaders who can uniquely and effectively promote policy and social change in cancer. Recognising the lack of a document on cancer nursing advocacy, the European Oncology Nursing Society's (EONS) Advocacy Working Group developed a guide aimed at addressing the need for individuals and organisations in cancer to better understand the advocacy concept and for a successful approach to sustainable advocacy.

Methods: A review of the relevant literature was conducted to identify themes, theoretical perspectives, and other information relevant to the topic. Moreover, authoritative and adaptable resources, advocacy documents from international organisations and EONS' advocacy work, were retrieved.

Results: A toolkit, consisting of two parts, has been created to offer practical advice and guidance regarding advocacy for cancer nurses. The first part includes the theoretical background and is divided into four target groups in advocacy: i) advocacy in general; ii) advocacy for people affected by cancer; iii) advocacy in nursing education to increase quality of care and create awareness among early career cancer nurses; and iv) advocacy for cancer nurses. The second part describes the advocacy tools that can be used for influencing policy; raising awareness; involving the public; developing an advocacy strategy; monitoring and evaluating advocacy activities. It additionally offers a mapping of good practices in cancer nursing advocacy in Europe.

Conclusions: EONS Advocacy Toolkit provides a comprehensive guide to different aspects and the best practices in cancer nursing advocacy. The use of the toolkit is expected to enhance advocacy skills of nurses and cancer nursing societies to influence decisions that improve cancer nursing status and recognition in Europe.

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CN78 Chimeric antigen receptor T cell (CAR T) nursing educational pathway: Reporting on participant feedback

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Background: New interventions require training programmes or pathways. This project was initiated to provide evidence-based nursing education pathway for CAR T cell therapy. The underpinning standards were the JACIE 8th edition standards and the Irish Nursing Scope of Practice. The aim of this poster is to present participant feedback from this education pathway. CAR T therapy is a treatment that involves removing a patient's own T lymphocytes through apheresis, genetically altering the T lymphocytes in the laboratory, and returning the altered cells to the patient via infusion to detect and destroy cancer cells. The pathway combines self-directed learning, simulation session and clinical practice. Access to the pathway was limited to experienced haematology nurses based at the study site. To date n=15 participants have completed the pathway. N=14 participants agreed to take part in the feedback survey, no reason for the one missing participant was noted. Evaluation of the pathway aimed to identify learning that could be integrated into future courses.

Methods: To gather participant feedback, a survey consisted of 16 item questionnaire using 5-point Likert scale and two open ended questions, was used. The survey was anonymous and distributed to the participants, haematology nurses that had completed the programme. A total of n=14 responses were returned.

Results: Participants agreed that they enjoyed the simulation learning experience but would have liked additional time in the simulation lab practicing skills learned. Overall, participant feedback noted they were confident in caring for a patient receiving CAR T following their engagement with the learning pathway. Feedback found (n=14 strongly agree or agree) that the learning that occurred in step 1 (self-directed) and step 2 (simulated learning) was applied in the third step (clinical practice).

Conclusions: The main finding from the participant survey was that pathway was easy to follow and that learning that occurred in steps 1 and 2 was applied in clinical practice (step 3). Additional simulation sessions were identified as something to consider for future courses.

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CN79 Mentoring programs for specialised and advanced practice nurses: A systematic review

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Background: Health systems are facing challenges due to increased complexity of care, also in cancer care. Expert nurses such as specialized nurses (SN) and advanced practice nurse (APN) are ideally positioned to make a positive contribution to high quality cancer care. These nurses often face challenges in their professional transition and lack support by their team. Offering a mentoring program focusing on how to integrate in the interprofessional team and how to fulfill their roles as educator, innovator, professional and clinical leader etc., may have a positive impact on role and leadership development, collaboration, role clarity, job satisfaction and job retention. We aim to identify, evaluate and summarize evidence about the objectives and characteristics of mentoring programs for SN and APN, and to identify their effectiveness.

Methods: A systematic review was performed. We searched PubMed, EMBASE, CINAHL and The Cochrane Library and included studies in English, French or Dutch describing the characteristics of mentoring programs focusing on one or more specific roles of SN and APN. No restrictions on publication date and study design were considered. Studies describing mentoring programs that solely focused on clinical/medical capabilities within a specific specialization domain were excluded.

Results: Twelve studies were included. All studies focused on mentorship programs for APN (nurse practitioners and clinical nurse specialists). Different forms of mentorship (formal, informal, work shadowing, competence development, workshops, reflection sessions) were reported. The studies reported positive outcomes on job retention (n=5), job satisfaction (n=6), skills improvement (n=6) and satisfaction with the program (n=6) among participants of the mentoring programs.

Conclusions: In general, there is a lack of rigorous research on mentoring programs for SN and APN, not focusing on building clinical capabilities within their specialty domain. There is a need to develop a mentoring program that focuses primarily on challenges experienced by both SN and APN related to their role integration in an interprofessional team. This is especially important for oncology SN and APN as they are widely introduced in cancer care.

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CN80 Mindfulness-based stress reduction as continuing educational course for oncology team welfare

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Background: Oncology care providers are facing work-related stress. We aimed to evaluate if mindfulness based-stress reduction (MBSR) is an effective workplace intervention to reduce risk for burnout syndrome.

Methods: This was a pre-post interventional prospective study conducted at a hospital oncology unit, including 6 medical oncologists, 5 nurses, 1 palliative oncologist, 1 psychologist and 1 clinical researcher. The intervention was offered as a continuing education course based on MBSR that met 2.5 hours a week for 8 weeks plus a 7-hour retreat, including body scan practice, yoga light exercise, mindful movement, walking and sitting meditation, as well as group discussion focusing on the application of mindfulness at work; materials for home practice were provided. A qualified MBSR instructor conducted the program. Feasibility and acceptability were assessed on the 14 participants while 6 nurses and 4 medical oncologists did not attend the course and were tested as control group. Outcome measures were work-related burnout and -engagement measured by the Maslach Burnout Inventory and the UWES-17 questionnaire, respectively. Changes in scores before and after intervention were evaluated within group.

Results: Median age was 47, mainly female. Both groups showed moderate to high risk for burnout syndrome and average to high work engagement. Educational credits have been achieved by 11 out of 14 MBSR participants with overall attendance of 78%. Diary records showed that, 12 participants, on average, practiced 3 times per week for 15 min/session, listening to guided meditations throughout the course, 2 participants did not do any home practice. After MBSR intervention emotional exhaustion, depersonalization and dedition domain improved significantly ($p < 0.01$) while there were no significant changes in the realization, vigor and absorption domain scores. Notably, the control group had no significant changes on any outcome measures.

Conclusions: Mindfulness based stress reduction as a continuing education course for cancer care team is feasible and would help to reduce risk of burnout by improving emotional awareness, empathy and work involvement. A better adherence to MBSR home practice is required.

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CN81 Oncology nursing clinical pathway for new graduate nurses: Smooth transition and sustainable retention

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Background: Undergraduate nursing curriculums in Saudi Arabia offer few subjects about oncology, hematology, and palliative care. Thus, nursing graduates are having weak knowledge and skills relevant to oncology practice. Adding to this, graduates may complete all their training and internship in healthcare facilities that have no oncology services. As a result nursing graduates are reluctant to join oncology services, and healthcare facilities found it difficult to recruit and retain local nursing graduates in oncology. Thus, this project was to ensure a smooth transition process of the new graduate nurses into the oncology services through a clinical education pathway.

Methods: Plan-Do-Study-Act (PDSA) is the method used to guide the project process. Six new graduate nurses were recruited based on their initial preference to join oncology services. Number and percentage of retention was measured at 6 months, 12 months and 24 months post completing the clinical pathway. In addition, nurses narrated their lived experience in a qualitative data format via group discussion method. Five clinical specific rotations (medical oncology, Hematology, Bone Marrow Transplant, Infusion unit and Radiation) were developed to onboard new graduate nurses. Five didactic sessions of eight days were established and 10 competency-based sessions were provided.

Results: Two participants completed the hematology clinical pathway, three participants completed the bone marrow transplant clinical pathway and one participant completed the infusion unit clinical pathway. All participants [100%] completed 24 months working full time in their respected units after finishing the clinical pathway rotations. Participants perceived that the clinical pathway made their onboarding process safe and smooth. Participants reported that the time they were provided to learn about oncology helped them to master oncology skills and knowledge and helped them to safely care for cancer patients. However, the duration of the clinical pathway rotation could be shortened.

Conclusions: Clinical pathway made a remarkable impact on new graduate nurses' retention in oncology services and provided participants with the necessary knowledge and skills to safely care for cancer patients.

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CN82 Implementation of a nurse led clinic (NLC) in outpatient cancer care: A growing opportunity for clinical nurse specialists (CNS) in Belgium

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Background: CNS in oncology enhance delivery of high quality care by detecting and addressing unmet needs of patients, the nursing and interprofessional team. To ensure in-depth insight into these specific needs, integration of CNS in direct patient care is essential. Based on unmet patient needs and the need for systematic integration of CNS in direct patient care, a NLC in a regional hospital in Flanders was set up. Contributing factors were the increase of advanced nursing roles, the rise of nurse led clinics in oncology internationally and an oncologist in need of high-quality clinical support provided by the CNS because of raised complexity of oncology care and workload. This study aimed to describe the developmental process and stakeholders' perspectives involved in this NLC initiative.

Methods: Based on a literature review, brainstorming and good practices of NLC, a framework for the NLC was developed. After implementation of the NLC, interviews with 10 stakeholders involved in the process of development were held (oncologist, head nurse, nurse manager, nurses, specialised nurses, CNS). Interviews were transcribed. Thematic analysis and researcher triangulation were performed.

Results: The NLC framework consisted of a complementary model with a description of the nurse led visit (e.g. assessment, prescribing), clarity in roles and responsibilities, which patients (patients with gynaecological and head-and-neck cancer) and referral criteria. A six-month internship for the CNS was set up prior to the start of the NLC. The CNS was introduced by the oncologist to the patient and family, initiating a relationship of trust and shared decision making. Nurse led visits alternated with medical visits. Preliminary results indicate the physician as important initiator, having trust in the CNS, ensuring no dilution in other nursing roles, enhancement in detection of unmet needs by CNS, optimised patient flows and continuity of care. Analysis is ongoing. Results are expected in September 2023.

Conclusions: The NLC provides a faster, more coordinated service for patients undergoing cancer treatment and their family caregivers ensuring continuity of care and attention to unmet needs and appropriate referrals.

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CN83 Low bacterial diet in cancer patients: A systematic review

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Background: The low bacteria diet (LBD) is a widely used dietary regimen to reduce the risk of foodborne infections in neutropenic cancer patients. Despite its frequent use over the years, there is no single definition of LBD diet and its role is widely controversial due to unclear benefits. The purpose of this study was to provide an updated analysis of the current body of evidence available on the efficacy of the LBD diet to reduce the risk of infections, mortality rates and quality of life (QoL) in neutropenic patients with cancer.

Methods: A systematic literature search was conducted in the biomedical databases: CENTRAL and DARE (The Cochrane Library), PubMed, CINHAL and EMBASE (Ovid). The process of screening, selection and inclusion of articles, as well as assessment of risk of bias and methodological quality was conducted independently by two reviewers. Of the 1985 records identified, 12 were included in this review.

Results: The included articles demonstrated heterogeneity in the definition, composition and timing of the LBD diet. The LBD diet did not demonstrate a reduction in infection and mortality rates compared to a free diet and furthermore, it showed a negative correlation with the quality of life.

Conclusions: The LBD diet, in addition to not bringing benefits in terms of reduction of infection and mortality rates, has been shown to worsen the quality of life due to the reduced palatability and limited variety of the food supply, negatively impacting the nutritional status. Healthcare professionals should implement safe food handling and preparation practices in conjunction with a free diet.

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CN84 Development of a unit for collection of biological samples and clinical data from cancer patients coordinated by nursing: The translational oncology research project (INTRON)

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Background: Biological samples from patients are critical for developing translational research projects in Oncology. Therefore, it is essential to develop units capable of obtaining samples, meeting all legal, ethical and quality requirements. Nursing plays a fundamental role in coordinating these units. We have developed a Translational Research Unit coordinated autonomously by Nursing, which allows obtaining biological samples and associated clinical data from patients, allowing to perform high-impact translational research projects.

Methods: We developed a protocol for collecting biological samples and clinical data from patients and healthy controls using a universal informed consent, in collaboration with the Ethics Committee, and the Biobank, Biochemistry, Pathology and Oncology Departments. Patients, treated in the routine care setting as well as in clinical trials, authorize the collection of blood and urine samples and clinical data for research purposes; and their biopsies and other biological samples (pleural fluid, etc.) obtained for healthcare purposes, as long as it does not interfere with their diagnosis and treatment. Blood samples are drawn, when possible, simultaneously with routine analyses. Samples are obtained at baseline, at the time of reassessments (CT, PET,...) and at other clinically relevant times.

Results: Between February 2009 and April 2023 we have obtained blood samples from more than 5,600 patients, many of them sequential. Genomic, protein expression and immunological studies among others, have been performed on the samples,

resulting on 50 studies published in international journals and on funding for 38 national and international research projects.

Conclusions: We have developed a Research Unit which allows collecting biological samples from patients treated in the routine setting and in clinical trials that has allowed the development of numerous translational research papers published in prestigious international journals. Nursing has a fundamental role in coordinating translational research projects.

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CN85 Dynamics and processes influencing role integration of advanced practice nurses and nurse navigators in oncology teams

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Background: Due to the complexity of cancer care, there is an increased need for expert nurses involved in the care of cancer patients. Although the added value of advanced practice nurses (APN) and oncology nurse navigators (ONN) in interprofessional teams has already been proven, barriers and facilitators at individual, organizational and healthcare system level, related to role integration of mainly APN and to a limited extent of ONN, have been reported. A deeper understanding of these processes and dynamics is important as it might enhance role integration processes in interprofessional cancer teams. The goal of this study was to explore the persisting presence of underlying processes, dynamics, experienced barriers and facilitators of Advanced Practice Nurses (APN) in oncology and Oncology Nurse Navigators (ONN) during their role integration in an interprofessional team over a research period of seven years (2011-2018).

Methods: A qualitative study based on the principles of Grounded Theory was conducted. Individual semi-structured interviews and focus groups with 51 ONN and APN from 11 university and local hospitals in Belgium were performed. Data were analyzed thematically to develop a framework.

Results: ONN and APN experienced a lonely journey during role integration. They were constantly searching for partners, medical knowledge and acknowledgement from the interprofessional team. ONN and APN had a watchful attitude and tried to make themselves visible to ensure they were involved in the team and to preserve their role and responsibilities. They felt powerless when they had the impression that their role was not acknowledged by their team. An unclear role description to the interprofessional team, and a lack of coaching and guidance were influencing factors of the experience of ONN and APN.

Conclusions: ONN and APN in oncology experience difficulties to integrate their role in existing interprofessional teams. Coaching and mentorship of novice ONN/APN, their interprofessional team and healthcare managers are needed to address these issues. These findings could form the basis for a mentorship program for ONN/APN and their interprofessional team to enhance role integration.

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CN86 Advanced breast cancer care for nurses (ABC4Nurses): A mixed-methods evaluation of an online educational programme

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Background: For people living with advanced breast cancer (ABC), specialist nursing is recognised as an essential component of care. However, access to specialist education and training in ABC is limited, contributing to variability in the availability of clinical specialist nurse services throughout Europe. The ABC4Nurses education programme was co-designed with experts by experience and profession in ABC and translated into four European languages following a systematic review and Delphi study to determine priority topics for nurse education in ABC. The aim of this study is to evaluate the implementation and perceived impact of the education programme from the perspectives of nurses who have completed the programme.

Methods: A mixed-methods evaluation was undertaken, guided by the Kirkpatrick framework (1967). Questionnaires were administered prior to commencing the programme to evaluate expectations for the programme (T1), and immediately after completion of the programme (T2) to assess overall satisfaction and personal views of the programme. Semi-structured qualitative interviews were held with a smaller number of participants to explore the perceived impact of the programme on ABC care in the participants' place of work.

Results: Of 655 registered participants, 188 (29%) participated in T1, and to date, 53 (30%) of these participants have completed all 6 modules, and the T2 questionnaire. T1 participants (n=188) were from the UK (27%), Spain (26%), Turkey (18%) and the Czech Republic (13%). ABC4Nurses has been evaluated positively by T2 participants (n=53), with 94% reporting that the programme has helped them in their work and would recommend this programme to their co-workers. On average, participants felt prepared to care for people with ABC (Mean: 8.2, SD: 1.5) and were committed to applying learning from the programme in their roles (Mean: 9.1, SD: 1.6).

Conclusions: This study shows that a novel, co-designed online learning programme in ABC was effective in enhancing cancer nurses' confidence and commitment to the delivery of care to people living with ABC. Furthermore, the results demonstrate the potential reach of the programme as a result of the programme being available in an accessible, translated format.

Legal entity responsible for the study: Dublin City University.

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CN87 An accreditation tool towards safe quality cancer nursing care

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Background: Good Clinical Practice in cancer care throughout Europe implies a strong and even development of cancer nursing. The European Oncology Nursing Society (EONS) Advocacy Working Group has been advocating for improvement in those areas as a way to impact the quality of cancer care. One of EONS's projects - European Cancer Nursing Index (ECNI) — made visible asymmetries throughout European countries on domains like patient and occupational safety, workforce and working conditions, educational levels, and recognition. This knowledge is the ground base for an urge to action.

Methods: The recognition tool serves to promote awareness in nurses, patients and families, managers, and boards towards specific measures/processes needed to achieve safer and quality cancer care. Not only it can provide knowledge and awareness but can grow as an aspirational symbol for cancer units and a roadmap to the necessary steps towards achieving quality cancer care. The "EONS Accreditation of Safe Workplace" is a tool developed by EONS advocacy working group. It comprises several domains — general policy, safe environment and worker protection, continuous education, safe patient care, and managing of hazardous drugs and radiation — that serve as a standard basis to promote quality safety cancer care. The accreditation will be a voluntary process, ideally self-proposed by the unit itself, using a questionnaire for managers and nurses. The final score represents the level of the unit's maturity towards EONS standards, leading to the recognition of a safe workplace or a recommendation for improvement. The tool is currently constructed and being tested in three hospitals in Belgium, Sweden, and Portugal for final adjustments.

Results: The implementation of "EONS Accreditation of Safe Workplace" could increase the current EONS advocacy work towards safe and quality care. Every unit could propose the application, leading to a recognition and improvement drive between cancer units and promoting healthy competition towards safe and quality care.

Conclusions: At a political level, could bring awareness to multilevel management and stakeholders that impact on nursing workforce and work conditions. Also, is a tool that could empower nurses, as well as patients and families, to search and advocate for safer places of care.

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CN88 Handling cancer drugs: Inventory of the state of knowledge and educational opportunities in Sweden

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Background: Swedish National Working Group for handling cancer drugs is supportive by the regional cancer center in collaboration. The focus is to develop and ensure the availability of educational activities for the safe handling of cancer drugs from a patient safety and work environment perspective. Handling chemotherapy and other potent cancer drugs requires up-to-date knowledge and effective routines to foster both patient and occupational safety. The risks for exposure, from preparation to excretion, are well documented. The aim of this study was to map knowledge and education levels for registered nurses and nurse assistants handling chemotherapy and other cancer drugs in Sweden, as well as to identify education needs, reported by 1st line managers.

Methods: A digital survey was sent out to first line managers across Sweden. The managers, who responded anonymously, all had employees in their teams, handling antineoplastic agents, for example preparing, administering and/or caring for patients who have received cancer drugs. The survey included questions concerning training for newly employed nurses and assistant nurses, follow-up of training, guidelines related to pregnancy, experiences with risk assessments and swab tests.

Results: Out of 136 responding managers, 22% reported no dedicated training for newly employed nurses and 50% stated that there is no requirement for training for nurses and/or nurse assistant before handling cancer drugs. For newly employed nurse assistant, 79% of the managers responded no requirement for training before caring for patients receiving cancer drugs. The majority of managers stated that guidelines for pregnant women were in place, but not for staff planning a pregnancy. In addition, 58% of the managers stated that there was no regular follow-up of the staff's knowledge levels, 35% performed annual risk assessments and 17% reported performing regular swab tests on the clinical surface's/devices.

Conclusions: Deficiencies in training for newly hired nursing staff and lack of regular follow-up of knowledge identify both patient-, and occupational safety risks. Stronger requirements for education is needed, in addition to improved education possibilities, introduction and refresher training.

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CN89 In cancer care nursing, does the use of surface wipe sampling for hazardous drugs lead to a safer occupational environment, in an outpatient and inpatient oncology/haematology setting? An evidence translation proposal

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Background: Optimal occupational safety environments for cancer care nurses, is of critical importance. Over 200 systemic anti-cancer treatments (SACT) are classed as hazardous drugs (HD) and the toxicity of these drugs have been well documented in the literature for over eighty years. Importantly, these HD make occupational exposure a significant problem for cancer care nurses, as exposure to HD is linked to both acute and chronic health consequences. Crucially, there are no known safe occupational levels of SACT exposure. Therefore, all available and necessary measures should be taken to limit the potential occupational exposure risks, for cancer care nurses.

Methods: The evidence translation dissertation begins with the PICO intervention question and a comprehensive background on the topic. In Chapter 2, a full systematic search was completed utilising two databases (CINAHL and PubMed) to retrieve the best available research evidence. Chapter 3, explored the historical, methodological and theoretical intricacies behind implementation and complexity sciences. Chapter 4, provides a comprehensive outline of an evidence based implementation proposal, underpinned by an implementation science framework. Through a process of self-critical reflection of learnings achieved, Chapter 5 draws the dissertation to a close and recommends the next steps in progressing this proposal within the author's hospital.

Results: Despite the exhaustive database search, the research reviewed did not involve nurses completing wipe sampling for hazardous drugs in an outpatient and inpatient oncology/haematology settings. Therefore, did not meet the author's criteria for inclusion. The United States Pharmacopeia (2020) guideline is the best available evidence retrieved, to answer the evidence-based research question.

Conclusions: The next step in advancing this project, is to convene a steering committee and engage key stakeholders to develop a strategic implementation resource plan. The implementation plan will be used as a context-sensitive roadmap resource.

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CN90 Managing the increasing capacity pressures in a nurse-led rural, satellite oncology unit in the era of immunotherapy

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Background: University Hospital Kerry (UHK) Oncology Unit is a satellite unit of Cork University Hospital (CUH), an ESMO designated Centre of Integrated Oncology and Palliative Care. It is led by oncology clinical nurse specialists, tumour-site specific nurse specialists, nurse prescribers and advanced nurse practitioners and serves a population of 180,000 people, providing infusional and oral systemic anti-cancer therapy (SACT) ambulatory units, supportive care, acute oncology service (AOS), survivorship follow-up and consultant-led outpatient clinics. Medical support is provided by two on-site registrars and 3 visiting medical oncologists.

Methods: This was a retrospective review of electronic admissions records correlated with pharmacy records and treatment plans for patients with non-small cell lung cancer (NSCLC), melanoma and breast cancer, the most common tumour types treated with immune checkpoint inhibitors (ICI).

Results: In 2019, 262 new patients were referred to UHK and 55% were treated with SACT. 10% of these patients were treated with ICI. The percentage of patients treated with ICI increased to 16% in 2020, 17% in 2021 & 25% in 2022. In 2019, 93% of patients treated with ICI had lung cancer, either small cell or NSCLC. This reduced to 88% in 2020, 86% in 2021 and to 76% in 2022, accounted for by the relative rise in ICI for melanoma: 0% (2019), 13% (2020), 13% (2021) and 22% (2022). Since the AOS was introduced in 2019 the number of calls have remained stable, however, the percentage related to ICI has increased. Admissions of patients have reduced but the proportion with a ICI related toxicity is increasing.

Conclusions: The delivery of SACT to patients living in rural areas presents unique challenges. The growth in ICI use including its unique toxicity profile is specifically challenging to a nurse-led satellite, a necessitated a review of the service. ICI related toxicities are more complex and do not fit neatly into a single algorithm. Recognition of immune-mediated toxicity and knowledge of treatments is lacking among the rural general medical and emergency department community. A dedicated acute oncology CNS, robust educational sessions, ICI work-up algorithms and structured patient review pathways are pivotal to patient care.

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CN91 Mentors' roles and responsibilities expected by nursing students in clinical training at the institute of oncology Ljubljana, Slovenia

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Background: Nursing is a scientific discipline as well as a practical one. The study requires at least 4600 hours of theoretical and clinical training, the duration of the theoretical training must be at least one third and the duration of the clinical training at least one half of the minimum duration of the training. Practical training in a clinical setting is an important aspect of learning for students and a major responsibility for staff. Mentoring is seen as guiding a person in their own career. It is understood as the transfer of knowledge and experience from the mentor to the student. The aim of this study was to explore nursing students' perspectives on mentors roles and responsibilities at the Institute of Oncology Ljubljana (OIL) where they undertook their clinical training in oncology nursing.

Methods: A quantitative approach was used to explore nursing students' views on mentoring. Data were collected in academic year 2021/2022 using a questionnaire survey method. The sample included 134 second year nursing students who were undergoing clinical training at the OIL. The number of questionnaires returned was 106, representing 59%. The results were presented using descriptive statistics.

Results: In the results, students highlight the importance of the kindness of the mentors (36), good team attitude and acceptance of the student in the team (32), trust (14), positive atmosphere in the clinical environment (12), knowledge in oncology nursing and professionalism (11), nice reception (9) and appropriate communication (7).

Conclusions: Practical training in clinical settings allows students to learn about their future work, to acquire new professional skills, to relate theoretical content to practice and, last but not least, to meet their potential future employers. Findings showed that students highlight the importance of mentor's personal characteristics, communication skills and a willingness to invest time and energy in building a mentoring relationship. Mentors acquire all these skills not only through formal education, but also through lifelong education in nursing and other scientific disciplines.

Legal entity responsible for the study: M. Matković.

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CN92 Nursing students' attitude towards care of dying: A cross-sectional study in Italy

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Background: Palliative care is considered an approach to improving the quality of life of patients with terminal illness and their familiars and the nurse is the largest group of healthcare professionals involved in palliative care. Nursing education plays an important role in preparing future nurses to provide palliative care to patients at the end of their lives. The aim of the study was to explore nursing students' attitudes towards the care of dying patients.

Methods: We conduct a cross-sectional study in Nursing program at the University of Padua (Italy). We administered the Frommelt Attitude Toward Care of the Dying Scale form B (FATCOD-B) and demographic form to 445 third-year nursing students, who accepted to participate in the study, in 2022. This Nursing program has eight different places.

Results: The sample of the study consists of 228 students (48%). Respondents reported a median age of 22 years (range 20-43), the most respondents were female (189-83%). Most students attended a course on care of dying (151- 66%). Median total FATCOD-B scores (118.65) indicated intermediated levels of students' attitudes towards care for dying patients. There was no significant difference between the FATCOD-B score between nursing students who attended a course on palliative care and who did not attend the course (118.47 vs 119.10; p=.688).

Conclusions: This study showed that nursing students have an intermediated level of attitude toward care of dying and end-of-life care. Nurses can meet cancer patients in all hospital settings, so the development of professional skills towards the dying patient is essential. The questionnaire used could be used as a tool to identify the gaps present and to program the university's educational activity in the field of palliative care.

Legal entity responsible for the study: M. Veronese.

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Disclosure: All authors have declared no conflicts of interest.

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CN93 Strategic patient collaboration, cancer theme Karolinska comprehensive cancer center (CCC)

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Background: The "2.0 strategy for patient involvement" aims to involve patients and relatives to become active partners at Karolinska CCC. The strategy is based on involvement on different levels; strategic, operational, individual and in specific projects Involvement of patients and relatives is essential for better research and healthcare. In the strategic patient council, two patient representatives meets with medical and nursing managers regularly. The patient representatives address strategic topics to the council and the aim is also to exchange information about ongoing projects. The Strategic Council maps the level of existing patient involvement at operational level. The mapping resulted in a GAP analysis to identify areas of improvement in relation to the OECI standards for patient involvement.

Methods: The working method for GAP analysis has been questionnaires and focus groups based on areas selected by the authors according to OECI standards. Informants have been expert groups/professionals/managers.

Results: Patient Involvement organization. Strategic level**:** The representatives from the Patient and Relatives Council meets with the management team 4 times a year. Term of office 3-4 years (overlapping). Examples from the agenda; Relevant outcome data to be published, governance and organizational development, continuity of care, access to care. The aim of this collaboration is to involve patients in the development of cancer care at a strategic level. This grouping has an advisory function and reports to the management of the Cancer Theme. Operational level: Collaboration with patient representatives on processes that are important for the outcome of care in the patient flow. 2 Representatives. Term of office — 3-4 years (overlapping). Joint evaluation of collaboration.

Conclusions: Patient representatives' views on patient involvement 2.0; "We observe that Theme Cancer has taken note of this and developed Patient Involvement 2.0 and initiated the implementation. In our role as patient representatives, we have seen the difference patient involvement makes. We can use the experiences of those affected and close relations to make a difference, and that encourages us to continue".

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CN94 The effect of a compassion fatigue resiliency program on oncology-hematology nurses' professional quality of life, stress levels and patients' care satisfaction: Nurse, patient and nurse manager's perspectives

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Background: Compassion fatigue adversely affects nurses' physical and mental health, and negatively affect patient outcomes. However, there is no study evaluating the indirect effect of 'Compassion Fatigue Resiliency Program (CFRP)', given to nurses, on patient satisfaction. The aim of this study was to evaluate the effect of the CFRP applied to oncology nurses on the professional quality of life and stress levels of nurses, the satisfaction of cancer patients.

Methods: This experimental embedded mixed methods design study was conducted between 2022-2023 with 15 oncology nurses, 19 cancer patients and 6 nurse managers at a comprehensive oncology center in Istanbul. In the first phase of the three-stage study (pre-intervention phase), in-depth individual interviews were conducted with cancer patients, and instruments were applied to nurses and patients, respectively. In the second phase (intervention phase), CFRP was applied to the nurses. In the third phase (post-intervention phase), individual interviews were conducted with the same cancer patients and focus group interviews were conducted with the nurse managers, and the same measurement tools were reapplied to nurses and patients after the intervention.

Results: The mean compassion satisfaction scores of nurses decreased; patient care satisfaction scores increased statistically significantly after the CFRP intervention ($p<0.05$). 6 themes were identified from interviews with patients: communication of nurses; level of responsiveness to needs; accessibility of nurses; psychological care; informing, suggestions for improving nursing; and 5 themes were identified from interviews with nurse managers: awareness; feeling valued, approach to patients, approach to colleagues, no change.

Conclusions: After the CFRP applied to nurses, patient care satisfaction increased, while nurses' compassion satisfaction levels decreased. The qualitative data of the study showed the positive effects of CFRP for both nurses and patients from the perspective of nurses, patients and nurse managers.

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CN95 **The status of cancer nursing in Europe: A cross sectional e-survey (The ECNI study)**

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Late withdrawal

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LBA16 Primary analysis of efficacy and safety in the CUPISCO trial: A randomised, global study of targeted therapy or cancer immunotherapy guided by comprehensive genomic profiling (CGP) vs platinum-based chemotherapy (CTX) in newly diagnosed, unfavourable cancer of unknown primary (CUP)

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Background: With platinum-based CTX, prognosis of patients (pts) with unfavourable CUP is poor; however, CGP may inform treatment strategies based on cancer genomics. The CUPISCO trial (NCT03498521) compared the efficacy and safety of molecularly guided therapy (MGT) vs standard platinum-based CTX in pts with newly diagnosed, unfavourable, non-squamous CUP.

Methods: Pts had central eligibility review-confirmed CUP with $\geq$1 measurable lesion (investigator-assessed via RECIST v1.1). All had tumour tissue and/or blood CGP (Foundation Medicine, Inc.). After 3 induction CTX cycles, pts with disease control were randomised 3:1 to MGT (investigator's choice from 12 regimens after molecular tumour board advice) or continuation with $\geq$3 more CTX cycles (category 1; shown here), stratified by gender and response to induction CTX. Pts with progressive disease received MGT (category 2). The primary endpoint was progression-free survival (PFS) in category 1 pts. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR) and disease control rate (DCR). Safety was also assessed. Exploratory endpoints included quality of life (QoL).

Results: From Jul 2018—Dec 2022, 436 category 1 pts were randomised: 326 to MGT; 110 to CTX. Median PFS (intent-to-treat population) was 6.1 months (95% confidence interval [CI] 4.7—6.5) with MGT vs 4.4 months (4.1—5.6) with CTX (hazard ratio [HR] 0.72; 95% CI 0.56—0.92; P=0.0079). Median OS was 14.7 (95% CI 13.3—17.3) vs 11.0 months (9.7—15.4), respectively (HR 0.82; 95% CI 0.62—1.09; P=0.1779), though OS data were immature at cutoff. ΔORR was 9.6% (95% CI 2.4—16.8, P=0.0141) in favour of MGT, with similar DoR in each arm (HR 0.95; 95% CI 0.33—2.72). ΔDCR was 4.7% (95% CI —6.4—15.9; P=0.3922) in favour of MGT. Adverse event rates were generally similar with MGT vs CTX; no difference in QoL was observed.

Conclusions: In pts with newly diagnosed, unfavourable, non-squamous CUP who responded to induction CTX, CGP with MGT improved PFS. Early CGP and MGT should be considered the new standard of care for these pts.

Clinical trial identification: NCT03498521 / 13 April 2018.

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Breast cancer, early stage

LBA17 Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes

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Background: Two years (yrs) of adjuvant abemaciclib combined with endocrine therapy (ET) resulted in significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) that persisted beyond the 2-yr treatment (tx) period in patients (pts) with hormone receptor positive, human epidermal growth factor receptor 2 negative, node-positive, high-risk early breast cancer (EBC). Here, we report 5-yr efficacy results from a prespecified overall survival (OS) interim analysis.

Methods: Pts were randomized (1:1) to receive ET for at least 5 yrs +/- abemaciclib for 2 yrs (tx period). High-risk EBC was defined as either ≥4 positive axillary lymph nodes (ALN) or 1-3 ALN with Grade 3 disease and/or tumor ≥5 cm (Cohort 1). A smaller group of pts were enrolled with 1-3+ ALN and central Ki67 ≥20% (Cohort 2). The intent-to-treat (ITT) population consisted of Cohort 1 (5120 pts) and Cohort 2 (517 pts). OS in the ITT population was tested for statistical significance in the gated strategy. Hazard ratios (HR) were estimated using Cox proportional hazard model.

Results: In the ITT population, with a median follow-up of 54 months, the benefit of abemaciclib was sustained with a HR of 0.680 (95% CI: 0.599, 0.772) for IDFS and 0.675 (95% CI: 0.588, 0.774) for DRFS. This persistence of abemaciclib benefit translated to continued separation of the KM curves resulting in a 5-yr absolute improvement in IDFS and DRFS rates of 7.6% and 6.7%, respectively, compared with IDFS/DRFS rates of 6.0%/5.3% at 4 yrs and 4.8%/4.1% at 3 yrs. Tx benefit in Cohort 1 was consistent with ITT. No new safety signals were observed. There continued to be fewer deaths in the abemaciclib plus ET arm compared to the ET arm (208 vs 234; HR 0.903; p=0.284); significance was not met.

Conclusions: At the pivotal 5-yr mark for adjuvant EBC trials, abemaciclib plus ET continued to reduce the risk of developing invasive and distant disease recurrence well beyond the completion of tx. The increasing absolute improvement at 5 yrs is consistent with a carryover effect and further supports the use of abemaciclib in pts with high-risk EBC. OS data are evolving in favor of abemaciclib arm, and follow-up continues.

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LBA18 Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study

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Background: KEYNOTE-522 (NCT03036488) showed statistically significant and clinically meaningful improvements in pCR and EFS with the addition of pembrolizumab (pembro) to chemotherapy (chemo) in patients (pts) with early-stage TNBC. Here, we present updated EFS results after ∼5 yr median follow-up.

Methods: Eligible pts with previously untreated, non-metastatic, centrally confirmed TNBC (stage T1c N1-2 or T2-4 N0-2 per AJCC) were randomized 2:1 to neoadjuvant pembro 200 mg Q3W or placebo (pbo), both given with 4 cycles of paclitaxel + carboplatin, then with 4 cycles of doxorubicin or epirubicin + cyclophosphamide. After definitive surgery, pts received adjuvant pembro or pbo for 9 cycles or until recurrence or unacceptable toxicity. Dual primary endpoints are pCR (ypT0/Tis ypN0) and EFS (time from randomization to disease progression that precluded definitive surgery, local/distant recurrence, second primary cancer, or death from any cause).

Results: 1174 pts were randomized to pembro (n=784) or pbo (n=390). At data cutoff (March 23, 2023), median follow-up was 63.1 mo. 145 pts (18.5%) in the pembro group and 108 pts (27.7%) in the pbo group had an EFS event (HR 0.63 [95% CI, 0.49-0.81]). The 60-mo EFS rate (95% CI) was 81.3% (78.4-83.9) vs 72.3% (67.5-76.5), respectively; the median was not reached in either group. The most common first EFS event was distant recurrence, in 72 pts (9.2%) in the pembro group vs 55 pts (14.1%) in the pbo group. With 210 distant events, rates of distant disease progression- or distant recurrence-free survival at 60 mo were 84.4% with pembro vs 76.8% with pbo (HR 0.64 [95% CI, 0.49-0.84]). The EFS benefit with pembro was consistent across prespecified subgroups, including PD-L1 expression and nodal status. In a prespecified, non-randomized, exploratory analysis, 5-yr EFS rates in the pembro and pbo groups were 92.2% vs 88.2% in pts with a pCR, and 62.6% vs 52.3% in pts without a pCR. Follow-up for OS is ongoing.

Conclusions: Neoadjuvant pembro + chemo followed by adjuvant pembro continues to show a clinically meaningful improvement in EFS compared with neoadjuvant chemo alone in pts with early-stage TNBC, regardless of the pCR outcome.

Clinical trial identification: NCT03036488.

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LBA19 Event-free survival (EFS) analysis of neoadjuvant taxane/carboplatin with or without atezolizumab followed by an adjuvant anthracycline regimen in high-risk triple negative breast cancer (TNBC): NeoTRIP Michelangelo randomized study

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Background: In NeoTRIP (NCT002620280) addition of atezolizumab to nab-paclitaxel/carboplatin was linked to minor numerical increase of pathologic complete response (pCR) in women with high-risk TNBC (48.6 vs 44.4%, p = 0.48), which was 7.6% higher in PD-L1 positive tumors treated with atezolizumab (Gianni L et al, *Annal Oncol* 2022).

Methods: In the phase III open label NeoTRIP study 280 patients with early high-risk or locally advanced TNBC were randomized to neoadjuvant carboplatin AUC 2 and nab-paclitaxel 125 mg/m^2 iv on d1,8 q3 wks with (138) or w/o (142) atezolizumab 1200 mg iv on d1, for 8 cycles followed by surgery and by 4 cycles of an anthracycline regimen regardless of pCR. The primary endpoint of the study is EFS, defined as time from date of randomization to date of disease progression while on primary therapy, or disease recurrence after surgery or death due to any cause.

Results: At median follow-up of 54 months, the five-year EFS was 70.6% (95% CI 61.6 − 77.9) with atezolizumab and 74.9% (95% CI 66.6 − 81.5) w/o atezolizumab. The stratified analysis (by disease stage, PD-L1, age class) resulted in a p-value = 0.66. The table shows the impact of the stratification factors and pCR on EFS evaluated by a multivariate Cox model.

Table: LBA19

Variable	Effect	Hazard ratio	P value
Treatment	With vs w/o atezolizumab	1.076	0.76
pCR	Yes vs no	0.19	<0.0001
Disease stage	Early vs locally advanced	2.05	0.0039
PD-L1	Pos vs neg	0.61	0.043
Age	> 50 vs ≤ 50	0.94	0.79

Higher baseline stromal TILs were prognostic of better EFS in each arm, but they were not predictive of atezolizumab benefit. No new safety signals possibly related to atezolizumab emerged during follow up.

Conclusions: In NeoTRIP the addition of neoadjuvant atezolizumab to carboplatin/nab-paclitaxel did not improve EFS of patients with TNBC. PD-L1 expression and higher sTILs at baseline were prognostic for better EFS, but not predictive of atezolizumab benefit. Extensive biomarkers analysis by Image Mass Cytometry (Wang XQ et al, *Nature* 2023), RNAseq and WES are ongoing to identify those cases who can derive benefit from atezolizumab.

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LBA20 A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2− primary breast cancer (BC)

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Background: High-risk, early-stage ER+ HER2− BC treatment includes NACT and adjuvant ET. CheckMate 7FL (CM-7FL; NCT04109066) is the first prospective, phase 3, randomized trial investigating NIVO + NACT + adjuvant ET in this clinical setting.

Methods: This study enrolled newly diagnosed ER+ HER2− BC pts, stages T1c−2 and N1−2 or T3−4 and N0−2, of grade 2 (ER 1−10%) or 3 (ER ≥ 1%). Pts were randomized 1:1 to NACT + NIVO 360 mg Q3W/NIVO 240 mg Q2W (arm A) or NACT + PBO (arm B). In April 2022, based on external data, the trial was closed to new enrollment; the primary endpoint was amended to only pathological complete response (pCR; ypT0/is ypN0) rate in the modified ITT population (mITTP; database lock 14 Apr 2023). Secondary endpoints included pCR rates in programmed death ligand 1 (PD-L1)-positive (PD-L1+) pts (SP142 ≥ 1%), residual cancer burden (RCB) 0−1 rates (all pts and PD-L1+), adverse event (AE) incidences, and death incidences.

Results: 830 pts were screened, 521 randomized (arm A/B, n = 263/258), and 510 were included in the mITTP. Baseline characteristics were balanced across arms. pCR rate was overall significantly higher in arm A (24.5%) vs B (13.8%; $P = 0.0021$) and in the stage III subgroup (Arm A/B, 30.7%/8.1%). The benefit of NIVO on pCR was higher in PD-L1+ pts (adjusted difference [AD], 24.1%; 44.3% in arm A, 20.2% in arm B). RCB 0−1 rates improved overall and more so in PD-L1+ pts. In the NACT phase, grade 3/4 treatment-related AEs incidence was similar across arms (arm A/B, n = 92[35%]/82 [32%]). Two deaths (pneumonitis, hepatitis) in arm A were study-drug related. Immune-mediated AE (IMAE) incidence was higher in arm A vs B.

Conclusions: CM-7FL met its primary endpoint with significantly improved pCR and RCB 0−1 rates (enhanced in PD-L1+ pts) with NIVO + NACT, with increased IMAE incidence and an overall safety profile consistent with that of NIVO and CT.

Clinical trial identification: NCT04109066.

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Table: LBA20 CheckMate 7FL key efficacy results, mITTP

	Arm A: NIVO + NACT /NIVO + ET n = 257	Arm B: PBO + NACT /ET n = 253
pCR		
mITTP, n/N % (95% CI)	63/257 24.5 (19.4−30.2)	35/253 13.8 (9.8−18.7)
AD, % (95% CI) Odds ratio (OR) (95% CI), *P* value	10.5 (4.0−16.9) 2.05 (1.29−3.27), 0.0021	
PD-L1+ pts, n/N% (95% CI)	39/88 44.3 (33.7−55.3)	17/84 20.2 (12.3−30.4)
AD, % (95% CI) OR (95% CI)	24.1 (10.7−37.5) 3.11 (1.58−6.11)	
RCB 0−1 rate		
mITTP, n/N % (95% CI)	79/257 (30.7; 25.2−36.8)	54/253 (21.3; 16.5−26.9)
AD, % (95% CI) OR (95% CI)	9.2 (2.0−16.5) 1.65 (1.10−2.49)	
PD-L1+ pts, n/N% (95% CI)	48/88 54.5 (43.6−65.2)	22/84 26.2 (17.2−36.9)
AD, % (95% CI) OR (95% CI)	28.5 (14.6−42.4) 3.49 (1.82−6.69)	

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LBA21 KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2− breast cancer

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Background: KEYNOTE-756 (NCT03725059) is a global phase 3 study of neoadjuvant pembro or pbo + chemo followed by adjuvant pembro or pbo + ET in patients (pts) with early-stage high-risk $ER^+/HER2^-$ breast cancer. Here, we report primary pCR results.

Methods: Eligible pts with T1c-2 ($\geq$2 cm) cN1-2 or T3-4 cN0-2, centrally confirmed, grade 3, invasive ductal $ER^+/HER2^-$ breast cancer were randomized 1:1 to neoadjuvant pembro 200 mg Q3W or pbo, both given with paclitaxel QW for 12 wk, then 4 cycles of doxorubicin or epirubicin + cyclophosphamide (neoadjuvant treatment). After definitive surgery ($\pm$ radiation therapy), pts received pembro or pbo for 9 cycles + standard ET. Stratification factors include region (Eastern Europe, China, or Other), tumor PD-L1 status (CPS $\geq$1 [+] vs CPS $<$1 [−]), nodal involvement (+ vs −), ER positivity ($\geq$10% vs $<$10%) and anthracycline schedule (Q3W vs Q2W). Dual primary endpoints are pCR (ypT0/Tis ypN0) and EFS. Secondary endpoints include OS, pCR defined as ypT0 ypN0 and ypT0/Tis and safety.

Results: 1278 pts were randomized to pembro + chemo (n=635) or pbo + chemo (n=643). At the final pCR analysis (May 25, 2023, first interim analysis data cutoff), median follow-up was 33.2 mo (range, 9.7-51.8). In the ITT population, pembro + chemo showed a statistically significant improvement in pCR (ypT0/Tis ypN0) vs pbo + chemo: 24.3% (95% CI, 21.0-27.8) vs 15.6% (95% CI, 12.8-18.6); estimated difference, 8.5 percentage points (95% CI, 4.2-12.8); P=0.00005; results were consistent for the secondary pCR definitions, ypT0 ypN0 (21.3% vs 12.8%) and ypT0/Tis (29.4% vs 18.2%). The benefit of pembro + chemo on pCR was generally consistent in the prespecified subgroups. In the neoadjuvant phase, grade $\geq$3 treatment-related AE rates were 52.5% with pembro + chemo and 46.4% with pbo + chemo, with 1 death in the pembro arm due to acute myocardial infarction. EFS results are still immature and continue to be evaluated.

Conclusions: The addition of pembro to chemo significantly increased the pCR rate in pts with early-stage high-risk $ER^+/HER2^-$ breast cancer. Safety was consistent with the known profiles of each regimen.

Clinical trial identification: EudraCT 2017-004869-27, NCT03725059.

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LBA22 Connected device and therapeutic patient education to promote physical activity among in women with localized breast cancer: Results from the DISCO randomized trial

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Background: Despite benefits of physical activity (PA) during breast cancer (BC) treatments, successful exercise strategies in routine BC care remain to be determined. The primary objective was to assess the efficacy of two 6-month PA interventions: connected PA program and therapeutic patient education (TPE), concomitant to adjuvant treatments.

Methods: DISCO was a 2x2 factorial, multicenter, phase III, randomized controlled trial. Women with a localized invasive BC and eligible for any adjuvant treatment, were randomized in 1 of the 4 groups: web-based connected device (adaptative program of 2 walking and 1 muscle strengthening sessions/week in autonomy + a connected activity wristband); TPE (2 sessions); combination of both interventions; usual care. All patients received PA recommendations. Assessments (baseline, 6&12 months) included physical fitness, body composition and questionnaires. The primary endpoint was the proportion of patients who reached PA recommendations at 6 months based on the Recent Physical Activity Questionnaire, in each intervention compared to patients who did not receive it. Statistical analyses were performed in the ITT population.

Results: From 2018 to 2021, 436 patients were randomized: 108 patients received the connected device, 108 the TPE program, 110 both interventions, and 110 usual care. At baseline, 66% of patients reached PA recommendations. During the 6-month intervention, 96% of patients wore the connected device, the median number of PA sessions was 45 and 80% of patients attended the TPE program. Overall, 89,3% of patients who received the connected device reached PA recommendations at 6 months vs. 89,4% of patients without the device and 91,9% of patients who benefits from TPE reached PA recommendations vs. 87% of patients without TPE. For the primary endpoint, no statistically significant difference was found for both interventions.

Conclusions: The findings provide new information on the efficacy of innovative interventions to practice PA during routine BC treatment. The 6-month major increase of PA, independently of patient group allocation, highlights the importance of providing PA recommendations and PA assessment to BC patients.

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Legal entity responsible for the study: Centre Léon Bérard.

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LBA23 Invasive disease−free survival (iDFS) across key subgroups from the phase III NATALEE study of ribociclib (RIB) + a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2- early breast cancer (EBC)

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Background: The NATALEE trial demonstrated a statistically significant iDFS benefit with RIB + NSAI vs NSAI alone in a broad population of pts with stage II or III HR+/HER2− EBC at risk of recurrence (Slamon D, et al. *ASCO* 2023. Oral LBA500). Evaluating iDFS outcomes in clinically relevant subgroups is important for understanding treatment (tx) benefit in specific pts. Here we present a prespecified exploratory subgroup analysis of iDFS in pts enrolled in NATALEE.

Methods: Pts with HR+/HER2− EBC were randomized 1:1 to RIB for 3 y (400 mg/d for 3 wk on/1 wk off) + NSAI for ≥5 y (letrozole 2.5 mg/d or anastrozole 1 mg/d) or NSAI

alone. Premenopausal women and men received goserelin every 28 d. NATALEE included pts with anatomical stage IIA (N0 requiring additional risk factors or N1 [1-3 axillary lymph nodes]) and all pts with stage IIB or III disease per AJCC's Cancer Staging Manual (8th ed). iDFS was evaluated by Kaplan-Meier methods. iDFS analysis was performed according to anatomical stage, menopausal status, nodal status, age, and Ki-67 score (locally tested). This prespecified analysis was not powered for statistical significance.

Results: A total of 5101 pts were included in this analysis (data cutoff: 11 Jan 2023; median follow-up for iDFS, 27.7 mo in both arms). Overall, the iDFS benefit with RIB + NSAI vs NSAI alone was consistent across all clinically relevant subgroups (Table), which in turn was consistent with that observed in the overall trial population.

Table: LBA23

	Tx, n	3-y iDFS rate, %	HR (95% CI)
Menopausal status			
Premenopausal women & men	RIB + NSAI, 1126	91	0.72 (0.53-0.98)
	NSAI alone, 1132	89	
Postmenopausal women	RIB + NSAI, 1423	90	0.78 (0.61-1.00)
	NSAI alone, 1420	86	
Anatomical stage			
II	RIB + NSAI, 1011	94	0.76 (0.53-1.10)
	NSAI alone, 1034	91	
III	RIB + NSAI, 1528	87	0.74 (0.59-0.93)
	NSAI alone, 1512	84	
Nodal status			
N0	RIB + NSAI, 285	94	0.63 (0.34-1.17)
	NSAI alone, 328	89	
N1-N3	RIB + NSAI, 2261	90	0.77 (0.63-0.94)
	NSAI alone, 2219	87	
Age			
<65 y	RIB + NSAI, 2142	90	0.77 (0.62-0.94)
	NSAI alone, 2186	87	
≥65 y	RIB + NSAI, 407	90	0.72 (0.46-1.14)
	NSAI alone, 366	86	
Ki-67			
≤20%	RIB + NSAI, 1199	92	0.80 (0.59-1.08)
	NSAI alone, 1236	90	
>20%	RIB + NSAI, 920	89	0.75 (0.56-1.00)
	NSAI alone, 938	84	

Conclusions: The iDFS benefit with RIB + NSAI was generally consistent with that in the intent-to-treat population of NATALEE and was not driven by any particular subgroup. The results further support RIB + NSAI as a new tx of choice in a broad population of pts with HR+/HER2− EBC.

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LBA24 Multiparametric prognostic score in early HR+/HER2- breast cancer: Impact of recurrence score, clinical-pathological factors, gene mutations and histology

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Background: Several analyses have shown prognostic impact of clinical and IHC markers in addition to genomic signatures in HR+/HER2 EBC. However, it remains unclear whether histology (e.g. invasive lobular BC (ILC) or further factors provide additional information. We present outcome from the prospective WSG-ADAPT HR+/HER- trial combining both static and dynamic biomarkers to optimize adjuvant therapy in luminal EBC.

Methods: pN0-1 with clinically high-risk HR+/HER2- EBC pts with RS0-11 OR RS12-25/ $Ki67_{postendocrine}$≤10% after 3 +/- of preoperative ET received ET alone; the remaining high-risk cohort was randomized to the CT trial. Prognostic scores containing clinical factors with and w/out mutational/copy number data were derived retrospectively after splitting the data into training- and validation sets. LASSO and cross validation methods were used to predict iDFS in therapy subgroups. Additionally, multivariate Cox models were adapted using a forward-backward selection approach to identify prognostic markers.

Results: 4491 pts were included (n=2246 ET- and n=2245 CT-treated). In the whole set, tumor and nodal (T/N) stage, RS and PR expression were prognostic for iDFS (Cox model). In ET-treated pts, only T-stage, RS and ER expression by RT-pCR were significant by Cox analysis, but prognostic score could not be determined. In CT-treated patients, T/N stage, G2-3 vs. G1, RS, ILC, and PR expression, but not IHC4 entered the model. In the CT cohort, a prognostic score consisting of T/N stage, age (≤50, >50), RS, ILC, PR expression and baseline and post-ET Ki67 yields a ROC AUC of 66% in the validation set. ILC was associated with lower RS than IDC (RS>25: 5.62% vs. 19.37%).High-risk CT-treated ILC had more frequently ERBB2 (11.6% vs. 2.5%) and a lower frequency of CDH1 mutations (60.5% vs 70.7%). Only CCND1 amplification was associated with worse iDFS in the NGS sub-cohort (n=584).

Conclusions: Use of RS in combination with further clinical and genetic factors improves prognostic ability; however, there is no treatment-independent prognostic model for HR+ HER2- EBC pts. For the first time, we have shown worse prognosis of the ILC high-risk subgroup, associated with distinct biological features.

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Breast cancer, metastatic

LBA11 Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2−) breast cancer (BC): Primary results from the randomised phase III TROPION-Breast01 trial

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Background: The TROP2-directed antibody-drug conjugate Dato-DXd demonstrated promising activity in heavily pre-treated patients (pts) with inoperable or metastatic HR+/HER2-BC in the Phase 1 TROPION-PanTumor01 trial (NCT03401385). Here we report primary PFS results from the global, Phase 3 TROPION-Breast01 trial (NCT05104866).

Methods: Adult pts with inoperable or metastatic HR+/HER2-BC, who had experienced progression on endocrine therapy (ET) and for whom ET was unsuitable, and who had received 1-2 prior lines of systemic chemotherapy (CT), were randomised 1:1 to Dato-DXd (6 mg/kg Q3W) or investigator's choice of CT (ICC; eribulin, vinorelbine, capecitabine, or gemcitabine) until progression or unacceptable toxicity. Dual primary endpoints were progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1, and overall survival (OS).

Results: 732 pts were randomised (Dato-DXd: 365; ICC: 367). Median age (range) was 56 (29−86)/54 (28−86) yrs in the Dato-DXd/ICC groups. At data cut-off (17 Jul 2023), 93/39 pts in the Dato-DXd/ICC groups were ongoing treatment. Results are shown in the table. Pts receiving Dato-DXd had significantly improved PFS vs ICC (HR 0.63 [95% CI 0.52−0.76]; p<0.0001). OS data were not mature; a trend for improvement favouring Dato-DXd was observed. Pts receiving Dato-DXd had lower rates of grade ≥3 TRAEs and dose reductions vs ICC (Table).

Table: LBA11

Efficacy	Dato-DXd N=365	ICC N=367
PFS		
Median PFS (BICR), mo (95% CI)	6.9 (5.7−7.4)	4.9 (4.2−5.5)
HR (95% CI)	0.63 (0.52−0.76); p<0.0001	
Median PFS (investigator assessed), mo (95% CI)	6.9 (5.9−7.1)	4.5 (4.2−5.5)
HR (95% CI)	0.64 (0.53−0.76)	
PFS rate (BICR), % (95% CI)		
6 mo	53.3 (47.7−58.5)	38.5 (32.8−44.1)
9 mo	37.5 (31.9−43.2)	18.7 (13.8−24.3)
OS*		
HR (95% CI)	0.84 (0.62−1.14)	
Response		
Confirmed ORR (BICR), % (n)	36.4 (133)	22.9 (84)
Safety	**N=360**	**N=351**
TRAEs, %		
Any grade	93.6	86.3
Grade ≥3	20.8	44.7
AEs associated with dose reduction/ discontinuation, %	23.1/3.1	32.2/2.8

*23% maturity.
AEs, adverse events; mo, months; ORR, objective response rate; TRAEs, AEs possibly related to study treatment.

Conclusions: TROPION-Breast01 met the primary endpoint of PFS; the study continues to final OS. Pts receiving Dato-DXd had statistically significant and clinically meaningful improvement in PFS compared with ICC, along with a favourable and manageable safety profile. Results support Dato-DXd as a novel treatment option for pts with inoperable or metastatic HR+/HER2-BC who have received 1−2 prior lines of CT.

Clinical trial identification: NCT05104866; release date November 3, 2021.

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Colorectal cancer

LBA10 Sotorasib plus panitumumab versus standard-of-care for chemorefractory KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreak 300 phase III study

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Background: We report the first Phase 3 primary results for sotorasib (soto), a $KRAS^{G12C}$-inhibitor, plus panitumumab (pani), an anti-EGFR antibody, vs standard of care (SOC) in patients (pts) with chemorefractory *KRAS* G12C-mutated mCRC.

Methods: In the CodeBreaK 300 (NCT05198934) global, open label study, 160 pts with chemorefractory *KRAS* G12C-mutated mCRC were randomized 1:1:1 to soto 960 mg daily plus pani 6 mg/kg IV (soto960+pani; n=53), soto 240 mg daily plus pani 6 mg/kg IV (soto240+pani, n=53), or investigator's choice of TAS-102 or regorafenib (n=54). Primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. Key secondary endpoints included ORR, DRR, and DCR.

Results: The study met its primary endpoint. Both soto+pani arms demonstrated statistically significant superior PFS compared to SOC: soto960+pani HR=0.49 (95% CI: 0.30, 0.80; p=0.006), and soto240+pani HR=0.58 (95% CI: 0.36, 0.93; p=0.03). Secondary efficacy endpoints are shown in the table. OS was immature at data cutoff. Grade ≥3 TRAEs that occurred in ≥5% pts were dermatitis acneiform (11.3%), hypomagnesaemia (5.7%), and rash (5.7%) for soto960+pani; hypomagnesaemia (7.5%), diarrhoea (5.7%) for soto240+pani; and neutropenia (23.5%), anaemia (5.9%), and hypertension (5.9%) for SOC. There were no fatal TRAEs.

Table: LBA10 Efficacy by BICR

	Soto960+Pani n=53	Soto240+Pani n=53	SOC n=54
Median PFS, months (95% CI)	5.6 (4.21, 6.31)	3.9 (3.71, 5.75)	2.2 (1.94, 3.91)
ORR, % (95% CI)	26.4 (15.3, 40.3)	5.7 (1.2, 15.7)	0 (0.0, 6.6)
Number of responders	14	3	0
Median DOR, months (range)	4.4 (1.9+, 6.0+)	NR (1.8+, 3.8+)	–
DCR, % (95% CI)	71.7 (57.7, 83.2)	67.9 (53.7, 80.1)	46.3 (32.6, 60.4)

CI, confidence interval; DCR, disease control rate; DOR, duration of response; NR, not reached; ORR, objective response rate

Conclusions: In the first phase 3 study for a $KRAS^{G12C}$-inhibitor plus an anti-EGFR antibody in chemorefractory mCRC, the primary endpoint was met and both doses of soto+pani showed superior PFS vs SOC. Soto960+pani demonstrated clinically meaningful benefit across PFS and key secondary endpoints (ORR, DCR, DOR) and was tolerable with lower rates of Grade ≥3 TRAEs vs SOC.

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LBA25 Neoadjuvant short-course radiotherapy followed by camrelizumab plus chemotherapy versus long-course chemoradiotherapy followed by chemotherapy in locally advanced rectal cancer: A randomized phase III trial (UNION)

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Background: Based on the results of pre-clinical research and our phase II study, we conducted a randomized, multicenter, open-label phase III study to compare the efficacy and safety of short-course radiotherapy (SCRT) followed by immunochemotherapy versus long-course chemoradiotherapy (LCRT) followed by chemotherapy for perioperative treatment of locally advanced rectal cancer (LARC).

Methods: Patients (pts) with T3-4 or N^+ rectal adenocarcinoma, where the lower edge of the tumor was $\leq$ 10 cm from the anal verge, were randomly assigned to either Arm A or B in a 1:1 ratio. Stratification was based on clinical T stage ($\leq$ T3 vs. T4) and N stage (N0 vs. N^+), and pts received SCRT or LCRT, followed by 2 cycles of camrelizumab (CAM) + CAPOX or CAPOX, respectively. Total mesorectal excision (TME) was performed subsequently, with an additional 6 cycles of CAM + CAPOX followed by CAM for up to 1 year in Arm A, and 6 cycles of CAPOX in Arm B. Primary endpoint was the independent review committee (IRC)-assessed pCR rate (ypT0N0). Secondary endpoints tested hierarchically were 3-year EFS rate and OS.

Results: Between July 2021 and March 2023, 231 pts were randomly assigned to Arm A (n=113) and Arm B (n=118). In Arm A, 112 pts received SCRT, 107 completed neoadjuvant therapy, and 104 underwent TME. In Arm B, 115 pts received LCRT, 109 completed neoadjuvant therapy, and 99 underwent TME. The IRC-assessed pCR rate in the ITT populations was significantly improved in Arm A (39.8% [95% CI 30.7-49.5]) versus Arm B (15.3% [95% CI 9.3-23.0]), with an odds ratio of 3.7 ([95% CI 2.0-6.9], p<0.001), meeting the primary endpoint. Subgroup analysis showed consistently positive results across all subgroups. In the surgical population, the R0 resection rate was 96.2% in Arm A and 97.0% in Arm B. Postoperative complications occurred in 38.1% of pts in Arm A versus 40.8% in Arm B. Grade $\geq$ 3 TRAEs were observed in 29.2% of pts in Arm A and 27.2% in Arm B throughout the treatment. Long-term survival outcomes are currently being monitored.

Conclusions: SCRT followed by CAM and chemotherapy demonstrated a superior pCR rate with acceptable tolerance compared to LCRT followed by chemotherapy for LARC.

Clinical trial identification: NCT04928807.

Legal entity responsible for the study: Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

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LBA26 Neoadjuvant chemotherapy with CAPOX versus chemoradiation for locally advanced rectal cancer with uninvolved mesorectal fascia (CONVERT): Final results of a phase III trial

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Background: Neoadjuvant chemoradiotherapy (nCRT) is a crucial component in the treatment of locally advanced rectal cancer (LARC). However, indiscriminate pelvic radiation in all LARC lacks clear long-term survival benefits while accentuating surgical complications and toxicity. Comparatively, neoadjuvant chemotherapy (nCT) alone shows promise as an alternative treatment for LARC with uninvolved mesorectal fascia (MRF). This trial aimed to assess the the noninferiority of nCT with CAPOX versus nCRT with capecitabine in LARC with uninvolved MRF.

Methods: Patients between June 2014 and October 2020 with LARC within 12 cm from the anal verge and uninvolved MRF were randomly assigned to receive 4 cycles of CAPOX chemotherapy alone (nCT arm) or CRT with capecitabine (nCRT arm). The primary end point is 3-year local-regional recurrence-free survival (LRRFS), defined as time interval between the date of randomization and any local or regional progression/relapse, NI of nCT could be established if the upper limit of the 2-sided 95% confidence interval (CI) of the LRRFS hazard ratio (HR) did not exceed 1.6 (NI margin). Secondary endpoints, such as 3-year disease-free survival (DFS), 3-year overall survival (OS), and long-term toxicity, were also reported.

Results: A total of 663 patients were enrolled and 589 patients received the allocated treatment (nCT, n=300; nCRT, n=289). LRFFA was analyzed after a median follow-up of 48 months. 3-year LRRFS was 97.4 % (95% CI, 95.5 to 99.3) in the nCRT arm and 96.3% (95% CI, 94.0 to 98.6) in the nCT arm, resulting in a HR of 1.08 (95% CI, 0.46 to 2.54).

Table: LBA26

Outcomes	nCRT (n=289)	nCT (n=300)	HR/RR	P value
3-year LRRFS, %	97.4 (95.5-99.3)	96.3 (94.0-98.6)	1.08 (.46-2.54)	not proven for noninferiority
3-year DFS, %	87.9 (84.1-91.8)	89.2 (85.6-92.9)	.88 (.54-1.44)	.62
3-year OS, %	94.1 (91.3-96.9)	95.0 (92.4-97.5)	.86 (.42-1.76)	.68
Long-term toxicity				
Grade2, n (%)	71 (24.7)	47 (15.7)	1.30 (1.08-1.54)	.007
Grade3, n (%)	12 (4.2)	9 (3.0)	1.17 (.75-1.58)	.45
Grade4, n (%)	1 (0.3)	1(0.3)	1.02 (.19-1.87)	.98

Conclusions: The noninferiority of nCT was not confirmed, primarily owing to the remarkably low incidence of local recurrence observed in both arms. But nCT offers comparable DFS and OS while mitigating the burden of toxicity as compared to nCRT. These insights shed light on a potential paradigm shift in the treatment for LARC with uninvolved MRF.

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LBA27 First-line systemic treatment in patients with initially unresectable colorectal cancer liver metastases (CRLM): Overall survival of the phase III CAIRO5 study of the Dutch Colorectal Cancer Group

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Background: CAIRO5 aimed to find the optimal systemic induction regimen to convert initially unresectable CRLM to local treatment.Previously, we showed that for patients with right-sided and/or *RAS/BRAFV600E* mutated tumours PFS was significantly longer and complete local treatment (R0/R1 resection and/or ablation) higher with FOLFOXIRI vs FOLFOX/FOLFIRI, both plus bevacizumab. For patients with left-sided and *RAS/BRAFV600E* wild-type tumours these parameters were not different between adding panitumumab vs bevacizumab to FOLFOX/FOLFIRI.

Methods: Patients with right-sided and/or *RAS/BRAFV600E* mutated tumours randomly received FOLFOX/FOLFIRI-bevacizumab (arm A) or FOLFOXIRI-bevacizumab (arm B), and with left-sided and *RAS/BRAFV600E* wild-type tumours FOLFOX/FOLFIRI-bevacizumab (arm C) or FOLFOX/FOLFIRI-panitumumab (arm D). Resectability was assessed by an expert panel of surgeons and radiologists at baseline and 2-monthly thereafter. Patients were stratified by potentially resectable vs permanently unresectable, serum LDH, irinotecan vs oxaliplatin, and *BRAFV600E* mutation status (arm A/B). Overall survival (OS, secondary endpoint) was compared with a stratified log-rank test and hazard ratios were calculated with a Cox proportional hazards model.

Results: Between November 2014 and January 2022, 530 patients were randomised in 47 centres, 148/146/118/118 in arms A/B/C/D. 9 ineligible patients were excluded. Median follow up was 57 months. Median OS in arm A vs B was 23.6 vs 24.1 months (HR 0.92, 95% CI 0.70 − 1.20, p=0.52) with 229 events. Median OS in arm C vs D was 40.4 vs 38.3 months (HR 1.02, 95% CI 0.72 − 1.46, p=0.89) with 134 events. Recurrence within 6 months after complete local treatment occurred in 26 (49%) vs 29 (39%) patients in arm A vs B (p=0.28), and 28 (42%) vs 26 (39%) patients in arm C vs D (p=0.73).

Conclusions: In patients with initially unresectable CRLM, OS was not different between FOLFOXIRI-bevacizumab and FOLFOX/FOLFIRI-bevacizumab for right-sided and/or *RAS/BRAFV600E* mutated tumours, nor between adding panitumumab vs bevacizumab to FOLFOX/FOLFIRI for left-sided and *RAS/BRAFV600E* wild-type tumours.

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LBA28 The PEGASUS trial: Post-surgical liquid biopsy-guided treatment of stage III and high-risk stage II colon cancer patients

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Background: Retrospective studies demonstrated an impressive prognostic impact of circulating tumor DNA (ctDNA, LB) positivity on colon cancer (CC) relapse after radical resection as proxy of minimal residual disease (MRD). Initial evidence is accumulating that in some patients (pts) adjuvant treatment does not clear ctDNA and this associates with relapse. With these premises we designed the PEGASUS trial to prove the feasibility of using LB to guide the post-surgical and post-adjuvant clinical management of Stage-IIT4N0/III CC pts.

Methods: LB was performed using Guardant Reveal assay (v L1.2). In the post-surgical phase, LB+ pts received 3 months (mos) of CAPOX and LB- pts 6 mos of CAPE. To mitigate the risk of false negatives a LB was repeated after one cycle of CAPE and treatment escalated to CAPOX if LB+. At the end of adjuvant treatments, LB was repeated: CAPOX-treated pts were switched to FOLFIRI if LB+ or de-escalated to CAPE if LB-; CAPE-treated pts received CAPOX if LB+ or started the standard follow-up phase if LB-. Primary endpoint was the number of post-surgery false negative cases, defined as pts with two consecutive LB- experiencing disease relapse (accepted <14 relapses).

Results: From July 2020 to July 2022, 135 pts were included in 11 cancer centers in Italy and Spain. At data cut-off, median follow-up was 20,8 months, with data completeness of 91% in LB- and 92% in LB+. Post-surgery ctDNA was detected in 35/

135 pts (26%), of which 12 (34%) experienced relapses, while 9 out of 100 LB- pts (9%) relapsed, being defined as false negatives. ctDNA+ was associated with a clear increase in the risk of relapse (HR 4.37, log rank P=0.0003). After 3 months of CAPOX, 11/35 LB+ pts were converted to LB- (31%), but 8/11 relapsed or LB re-positivized. Of the 23 LB+ pts receiving FOLFIRI after CAPOX, 12 remained LB+ (52%) among which 6 relapsed, while 11 were converted to LB- remaining relapse-free at the time of analysis (48%), thus suggesting an effect of FOLFIRI in the MRD setting.

Conclusions: LB may be used to guide the post-surgical clinical management of CC pts by reducing unnecessary toxicity and by improving the response to standard chemotherapy. Ongoing and newly designed randomized trials trials will define the clinical utility of LB for MRD in colon cancer.

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LBA29 Aspirin after standard adjuvant therapy for colorectal cancers (ASCOLT): An international, phase III, randomised, placebo-controlled trial

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Background: Aspirin is an inexpensive, readily available treatment globally with the potential to be an effective adjuvant therapy to prevent recurrence of colorectal cancer (CRC) after completing standard primary treatment. This landmark study conducted entirely in the Asia-Pacific region, where incidence of CRC is increasing, is the first international Phase III double-blind placebo-controlled trial to report the activity of aspirin in the secondary prevention of CRC (NCT 00565708).

Methods: Patients with Dukes' C and high-risk Dukes' B CRC were randomised to Aspirin 200mg daily or placebo for 3 years after surgery and completion of standard adjuvant therapy (including 3+ months of chemotherapy) and followed for 5+ years. The primary endpoint was Disease-Free Survival (DFS). The primary analysis used a stratified Cox model, with those commencing study treatment (modified intention to treat (mITT) and with all events up to 31/03/2023. Secondary endpoints included overall survival (OS) and DFS in the colon cancer group. Translational biomarker studies are ongoing.

Results: Between 25/02/2009 and 31/03/2021, 1587 participants were randomised from 66 centres across 10 Asia-Pacific countries and 1550 were included in the mITT analysis: 791 on aspirin and 759 placebo. Of these, 897 were males; 271 Dukes' B colon cancers, 769 Dukes' C colon cancers and 510 rectal cancers. Estimated DFS at 5 years was 77% (95% CI 74-80%) and 75% (95% CI 71-78%) for aspirin and placebo respectively with an estimated hazard ratio (HR) of 0.91 (95% CI 0.73-1.13, p=0.38). Overall survival showed HR favouring aspirin of 0.75 (95% CI 0.53-1.07, p=0.11). In the colon cancer group, the HR for DFS was 0.86 (95% CI 0.66 - 1.13, p=0.28). Adverse events were low in both arms and aspirin was well tolerated.

Conclusions: Our study did not show a significant DFS or OS benefit of aspirin therapy as an additional adjuvant therapy for patients with colorectal cancer. Nevertheless, results are still consistent with a more moderate, yet still worthwhile benefit for the global populations, and results from ongoing studies are awaited. Analysis of special

subpopulations predicted to benefit from aspirin in ASCOLT and other trials, may also be critical.

Clinical trial identification: NCT00565708.

Legal entity responsible for the study: National Cancer Centre Singapore.

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LBA30 Panitumumab (P) + FOLFIRINOX or mFOLFOX6 in unresectable metastatic colorectal cancer (mCRC) patients (pts) with RAS/BRAF wild-type (WT) tumor status from circulating DNA (cirDNA): First results of the randomised phase II PANIRINOX-UCGI28 study

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Background: For shrinkage of RAS/BRAF WT tumors, anti-EGFR antibodies combinated with triplet chemotherapy (CT) regimen have shown promising results in phase I-II trials. Ultrasensitive cirDNA analysis as those with IntPlex® technology might result in better selection of super-responders to anti-EGFR-based therapies. Thus, the aim of PANIRINOX was studying the complete response (CR) rate obtained with P plus a tri-CT regimen (FOLFIRINOX = Arm A) or a standard bi-CT (mFOLFOX6 = Arm B) in pts with cirDNA-based RAS/BRAF V600E WT unresectable mCRC tumors.

Methods: In this randomised non-comparative multicentric phase II trial, pts were assigned in a 2:1 ratio in arm A/B (12 cycles max) in 2 different strata (str) according to disease extent (str 1: liver limited /str2: non-liver-limited). Primary endpoint was the CR rate according to RECIST 1.1 (central review) and CEA normalization (Fleming's one-step design, one-sided a=5%, b=10%, H0: 3%; H1: 12%; 60 pts in Arm A needed with at least 4 successes; Arm B as internal control). Secondary endpoints included progression-free and overall survival (PFS and OS).

Results: From 10/2017 to 07/2022, 78/33 pts were assigned in arm A/B in str2. Main characteristics were (arm A/B): median age 64/62 yo; males 67/45%; PS0 63/42%; left-sided 81/79%; synchronous metastases 85/87%; >1 metastatic site 82/72%. The table lists CR, PFS and OS in evaluable pts. Main grade≥3 treatment-related adverse events were (arm A/B): diarrhea 39/9%, peripheral neuropathy 22/24%, skin 18/24%.

Table: LBA30

	Arm A FOLFIRINOX+P (N=65)	Arm B mFOLFOX6+P (N=27)
Median follow-up (months) [95% CI]	32.0 [28.7; 32.3]	30.4 [23.4; 35.7]
Complete response (number) (%) [95% CI]	5 7.7 [2.5; 17.0]	2 7.4 [0.9; 24.3]
Objective response rate (complete + partial radiological reponse)	75.4%	77.8%
Median PFS (months) [95% CI]	9.1 [8.1; 11.7]	9.0 [7.5; 13.2]
Median OS (months) [95% CI]	NR	20.4 [15.1; NR]

Conclusions: With 5 pts achieving CR in arm A and 95%CI including predetermined hypothesis in arm B, the study met its primary objective in str2. We confirm that genotyping tumors from cirDNA analysis is a relevant alternative to tissue before administrating anti-EGFR-based therapies in first line.

Clinical trial identification: EudraCT 2016-001490-33, NCT02980510.

Legal entity responsible for the study: UNICANCER.

Funding: Amgen.

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LBA31 Neoadjuvant nivolumab plus relatlimab (anti-LAG3) in locally advanced MMR-deficient colon cancers: The NICHE-3 study

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Background: Neoadjuvant immunotherapy has shown promising responses in various tumor types. In the NICHE-2 study, neoadjuvant nivolumab/ipilimumab in MMR deficient (dMMR) colon cancers resulted in 95% major pathologic responses (MPR), including 67% pathologic complete responses (pCR) within 6 weeks of treatment. In melanoma patients, nivolumab/relatlimab has shown a favorable toxicity profile and promising efficacy in the neoadjuvant setting. We investigated this regimen in patients with non-metastatic dMMR colon cancer (NCT03026140).

Methods: In the NICHE-3 study, patients with resectable, locally advanced (at least cT3 and/or N+), dMMR colon cancer were treated with two doses of nivolumab 480 mg plus relatlimab 480 mg at a 4-week interval, followed by surgery within 8 weeks of registration. Pathologic response was defined as 50% or less residual viable tumor (RVT), and MPR as ≤10% RVT. The primary endpoint was pathologic response rate. According to a Simon-2-stage design, ≥15/19 responders are needed in stage 1 to continue accrual in stage 2. Here we present the prespecified analysis of pathologic response from stage 1.

Results: A total of 19 patients were treated and underwent surgery without delays. Grade 1-2 immune-related adverse events (irAEs) were observed in 14/19 patients (74%), with infusion related reactions being the most frequent (43%). Only one patient (5%) experienced a grade 3 irAE (hyperthyroidism). Endocrinopathy for which supplementation was required was observed in 4 (21%) patients and consisted of 1 patient with hypothyroidism and 3 patients with hypophysitis with secondary adrenal and/or thyroid insufficiency. There were no grade 4-5 irAEs. With a median of 7.4 weeks between the first dose and surgical resection, the treatment resulted in a 79% pCR rate, 89% MPR rate and 100% overall pathologic response rate among 19 patients.

Conclusions: Here we present data from NICHE-3, the first study showing the safety and efficacy of neoadjuvant nivolumab/relatlimab in dMMR colon cancer patients, with a pathologic response in all patients, including 79% pCR. Accrual is currently ongoing in stage 2, in which an additional 40 patients will be treated.

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Legal entity responsible for the study: Netherlands Cancer Institute.

Funding: Bristol Myers Squibb.

Disclosure: J.B.A.G. Haanen: Financial Interests, Institutional, Advisory Board: Bristol Myers Squibb, Achilles Therapeutics, Ipsen, Merck Sharpe & Dohme, Merck Serono, Pfizer, Molecular Partners, Novartis, Roche, Sanofi, Third Rock Venture, Iovance Biotherapeutics; Financial Interests, Institutional, Advisory Board, SAB member: BioNTech, Immunocore, Gadeta, Instil Bio, PokeAcel, T-Knife; Financial Interests, Personal, Advisory Board, SAB member: Neogene Therapeutics, Scenic; Financial Interests, Personal, Stocks/Shares: Neogene Therapeutics; Financial Interests, Institutional, Research Grant: Bristol Myers Squibb, BioNTech US, Merck Sharpe & Dohme, Amgen, Novartis, Asher Bio; Non-Financial Interests, Member: ASCO, AACR, SITC; Other, Editor-in-Chief IOTECH: ESMO; Other, Editorial Board ESMO Open: ESMO; Other, Editorial Board: Kidney Cancer. M. Chalabi: Financial Interests, Institutional, Research Grant: BMS, BMS, Roche Genentech, Roche Genentech;

Non-Financial Interests, Advisory Role, Advisory Board: BMS, BMS, MSD. All other authors have declared no conflicts of interest.

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LBA32 Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study

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Background: In the phase 3 KEYNOTE-177 (NCT02563002) study, pembrolizumab (pembro) vs chemotherapy (chemo) improved PFS and showed a trend towards improved OS in MSI-H/dMMR mCRC, supporting pembro as first-line therapy. We report efficacy and safety at 5 yrs of follow-up.

Methods: Patients (pts) aged ≥18 y with untreated MSI-H/dMMR mCRC measurable per RECIST v1.1 and an ECOG PS of 0 or 1 were enrolled. Pts were randomly assigned 1:1 to receive pembro 200 mg Q3W or chemo (mFOLFOX6 or FOLFIRI Q2W ± bevacizumab 5 mg/kg Q2W or cetuximab weekly), IV. Pts assigned to chemo could receive ≤35 cycles of pembro after centrally confirmed progressive disease (PD). End points at 5 y were OS, PFS, DOR, and safety.

Results: At data cutoff (July 17, 2023), median follow-up duration was 73.3 mo (6.1 y; range, 64.9-89.2 mo). Of 153 pts assigned to pembro, all pts received treatment and 59 (38.6%) completed 35 cycles of treatment; 143/154 pts assigned to chemo received treatment. A total of 94 (61.4%) pts in the pembro arm and 143 (100%) in the chemo arm discontinued treatment most commonly due to PD (32.7% and 60.8%, respectively). 57 (37.0%) pts in the chemo arm met the crossover criteria and received pembro; 21 (36.8%) completed 35 cycles of pembro. An additional 39 (25.3%) pts who received chemo received a PD-1/L1 inhibitor off-protocol. Median OS (95% CI) was 77.5 mo (6.5 y; 49.2 mo-not reached) with pembro vs 36.7 mo (3.1 y; 27.6-65.3 mo) with chemo (HR 0.73 [95% CI 0.53,0.99]). The 5 y OS rate was 54.8% in the pembro arm and 44.2% in the chemo arm. The 5 y PFS rate was 34.0% and 7.6%, respectively. Median (range) DOR was 75.4 mo (6.3 y; 2.3+ to 80.1+ mo) with pembro vs 10.6 mo (2.8 to 71.5+ mo) with chemo; 85.7% and 33.6% of pts had DOR ≥24 mo, respectively. Treatment-related adverse events (TRAEs) occurred in 79.7% of pts who received pembro and 98.6% who received chemo; grade 3-5 TRAEs occurred in 21.6% and 67.1% of pts, respectively.

Conclusions: After 5 y of follow-up, responses to pembro were more durable than those from chemo, and the trend towards improved OS with pembro persisted despite an effective crossover rate of 62% in pts with MSI-H/dMMR mCRC.

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In charges for reviewing V940 Pembro on Engagezone (as per your contract in ref).and also an inrtview about Pembrolizumab for MSI/dMMR Metastaic colo-rectal 2023: MSD Oncology; Financial Interests, Personal, Advisory Board, but also formation for the takeda team, and consultant for TakedaContract beetween 1 sept 2023 and 15 october 2024: Takeda; Financial Interests, Personal, Advisory Board, Board Meeting (October 19, 2023): AbbVie; Financial Interests, Institutional, Coordinating PI, PI Garnet study: GSK; Financial Interests, Institutional, Coordinating PI, Keynote 164 and 171 and 811 and C08: MSD; Financial Interests, Institutional, Coordinating PI, BMS CA209-8HW, BMS CA209-142, BMS CA209-577: BMS; Financial Interests, Institutional, Coordinating PI, SPOTLIGHT study: Astellas; Financial Interests, Personal, Steering Committee Member, and international PI (trial chair Solstice study): Servier; Financial Interests, Personal, Steering Committee Member, MOUNTAINEER and MOUNTAINEER-03 study (PI for France) 2022, 2023: Seagen; Financial Interests, Institutional, Local PI, A randomized, open-label, phase 2 study of botensilimab (AGEN1181) AS monotherapy and in combination with balstilimab (AGEN2034) or investigator's choice standard of care (regorafenib or trifluridine and tipiracil) for the treatment of refractory metastatic colorectal cancer: Agenus; Non-Financial Interests, Member of Board of Directors, Investigator: Gercor group; Non-Financial Interests, Member of Board of Directors, President since october 2022: ARCAD Foundation. 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Developmental therapeutics

LBA33 A first-in-human phase I study of a novel KRAS G12D inhibitor HRS-4642 in patients with advanced solid tumors harboring KRAS G12D mutation

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Background: *KRAS* G12D mutation is one of the most prevalent subtypes in *RAS* mutant cancers. However, no results of KRAS G12D inhibitors from any clinical trials have been reported yet. HRS-4642 is a highly selective KRAS G12D inhibitor. Here, we report preliminary results of the dose escalation part of a first-in-human phase 1 study of HRS-4642 in patients (pts) with advanced *KRAS* G12D mutant solid tumors.

Methods: Pts with histologically confirmed advanced solid tumors harboring *KRAS* G12D mutation who failed prior standard of care were enrolled to receive HRS-4642 i.v. at doses of 15, 50, 100, 200, and 300 mg QW in 21-day cycles. Dose escalation part allowed pts with *KRAS* mutation. An accelerated titration followed by a Bayesian optimal interval design is used to guide dose escalation and determine the maximum tolerated dose (MTD). The primary endpoints were safety, MTD, and recommended phase 2 dose (RP2D).

Results: At data cutoff on Aug 4, 2023, 18 pts were enrolled (lung adenocarcinoma n=10, colorectal adenocarcinoma n=5, appendiceal mucinous adenocarcinoma, ovarian cancer, and pancreatic cancer n=1 each). Pts had received a median of 3 lines of prior treatment (range 2-7). No DLTs were observed and the MTD was not reached yet. Grade ≥3 adverse events (AEs) were observed in 9 pts (50.0%). 6 pts (33.3%) had grade ≥3 treatment-related AEs (TRAEs), being hypercholesterolemia (16.7%), increased lipase (11.1%), and anemia (11.1%). No dose dependent trend was observed in the incidence of AEs. Serious TRAEs were observed in one patient (grade 2 increased ALT and grade 1 increased AST). No pts discontinued treatment or died due to TRAEs. 13 pts with baseline target lesions had at least one post-baseline assessment, and one NSCLC patient at 200 mg had partial response. 11 pts (61.1%) had stable disease and 6 (33.3%) experienced target lesion shrinkage, including lung and colorectal cancers. HRS-4642 exposure was approximately proportional to dose with a half-life of around 40 hours.

Conclusions: HRS-4642 showed a tolerable safety profile and preliminary anti-tumor activity in advanced solid tumors harboring *KRAS* G12D mutation. Dose escalation is ongoing and expected to proceed to dose expansion soon.

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LBA34 Trastuzumab deruxtecan (T-DXd) for pretreated patients (pts) with HER2-expressing solid tumors: Primary analysis from the DESTINY-PanTumor02 (DP-02) study

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Background: T-DXd has shown significant survival benefit for pts with HER2-expressing breast and gastric cancers. Interim DP-02 data showed a promising objective response rate (ORR) and duration of response (DOR) in HER2-expressing tumors (ASCO 2023). Here we report the primary analysis including progression-free (PFS) and overall survival (OS).

Methods: This open-label, Phase 2 study (NCT04482309) evaluated T-DXd (5.4 mg/kg Q3W) in pts with HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing), locally advanced/metastatic disease after ≥1 systemic treatment (Tx), or without alternative Tx options. Primary endpoint was investigator-assessed confirmed ORR. Secondary endpoints included safety, DOR, PFS and OS.

Results: At data cut off (Jun 2023), 267 pts with biliary tract (BTC), bladder (URO), cervical (CC), endometrial (EC), ovarian (OC), pancreatic (PC), or other tumors had received Tx (median [m] follow up: 12.75 [range 0.4–31.6] months [mo]); 72.3% received ≥2 prior lines of therapy. In all pts, investigator-assessed ORR (95% CI) was 37.1% (31.3, 43.2); mDOR (95% CI) was 11.3 mo (9.6, 17.8); mPFS (95% CI) was 6.9 mo (5.6, 8.0); and mOS (95% CI) was 13.4 mo (11.9, 15.5). In pts with IHC 3+ expression (central; n=75) ORR was 61.3% (49.4, 72.4); mDOR was 22.1 mo (9.6, not reached); mPFS was 11.9 mo (8.2, 13.0); and mOS was 21.1 mo (15.3, 29.6). Table shows ORR, PFS and OS by tumor type in all pts and IHC 3+. Grade (G) ≥3 Tx-related adverse events (AEs) occurred in 40.8% of pts; 8.6% discontinued Tx due to Tx-related AEs. Adjudicated Tx-related interstitial lung disease/pneumonitis occurred in 10.5% (n=28) of pts (9.0% [n=24] G≤2; 1.1% [n=3] G5).

Conclusions: We observed durable responses to T-DXd and clinically meaningful PFS and OS in pretreated pts across HER2-expressing tumors, with safety consistent with the known profile. These data support T-DXd as a potential tumor-agnostic treatment in HER2-expressing tumors. (Funded by BioNTech; ClinicalTrials.gov number; NCT04503278).

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Table: LBA34

	n		ORR, %		mPFS, mo (95% CI)		mOS, mo (95% CI)	
	All	IHC 3+	All	IHC 3+	All	IHC 3+	All	IHC 3+
Total	267	75	37.1	61.3	6.9 (5.6, 8.0)	11.9 (8.2, 13.0)	13.4 (11.9, 15.5)	21.1 (15.3, 29.6)
BTC	41	16	22.0	56.3	4.6 (3.1, 6.0)	7.4 (2.8, 12.5)	7.0 (4.6, 10.2)	12.4 (2.8, NR)
URO	41	16	39.0	56.3	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	12.8 (11.2, 15.1)	13.4 (6.7, 19.8)
CC	40	8	50.0	75.0	7.0 (4.2, 11.1)	NR (3.9, NR)	13.6 (11.1, NR)	NE (3.9, NR)
EC	40	13	57.5	84.6	11.1 (7.1, NR)	NR (7.3, NR)	26.0 (12.8, NR)	26.0 (18.9, NR)
OC	40	11	45.0	63.6	5.9 (4.0, 8.3)	12.5 (3.1, NR)	13.2 (8.0, 17.7)	20.0 (3.8, NR)
PC	25	2	4.0	0	3.2 (1.8, 7.2)	5.4 (2.8, NR)	5.0 (3.8, 14.2)	12.4 (8.8, NR)
Other	40	9	30.0	44.4	8.8 (5.5, 12.5)	23.4 (5.6, NR)	21.0 (12.9, 24.3)	24.3 (11.1, NR)

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LBA35 BNT211-01: Interim results from a repeat dose escalation study of CLDN6 CAR-T cells manufactured with an automated process ± a CLDN6-encoding CAR-T cell-amplifying RNA Vaccine (CARVac)

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Background: Chimeric antigen receptor (CAR) T cells targeting CLDN6 ± CARVac showed promising activity against relapsed/refractory (r/r) CLDN6+ tumors (*ESMO* 2022 LBA38). We present data from a repeat 3+3 dose escalation trial with CAR T cells manufactured by an automated process and increased CARVac dosage.

Methods: BNT211-01 is recruiting patients (pts) with CLDN6-positive r/r solid tumours and no further treatment options. Following lymphodepletion, CAR T cells are flat dosed at 4 dose levels (DLs, 1×10^6 up to 2-5×10^8 CAR-T cells) ± repeat CLDN6 CARVac dosing (1×50 µg, then 100 µg doses). Primary endpoints are safety and tolerability. Additional endpoints are efficacy and pharmacokinetics.

Results: As of 24.07.2023, 38 pts primarily with ovarian cancer (n=14) and germ cell tumors (n=11) have been treated. Treatment related TEAEs ≥G3 were observed in 23 (61%) pts, including 20 (53%) pts with TEAEs related to CAR T cells. From 21 pts treated with the combination, 9 (43%) pts had TEAEs ≥G3 related to both IMPs, and 2 (10%) to CARVac. Related TESAEs have been observed in 8 pts (21%). DLTs occurred in 2 pts from different cohorts, G4 CRS at 5×10^8 CAR-T cells and G4 pancytopenia at 1×10^8, hence an MTD could not be determined. One death was assessed as treatment-related after the data cut-off. CRS was predominantly (95%) G1-2 and observed in 18 (47%) pts. 2 cases each of G1 ICANS and G1 hemophagocytic lymphohistiocytosis were reported (both 5%). Of 28 efficacy-evaluable patients, 9 pts (32%) had partial responses (PRs) and a further 9 had stable disease ([SD], unconfirmed overall response rate [ORR]: 32%, disease control rate [DCR]: 64%). Of 19 pts treated with ≥ $1x10^8$ CAR T cells, 8 PRs and 8 SDs resulted in an ORR of 42% and a DCR of 84%. CAR-T expansion was dose dependent, with improved persistence by addition of CARVac.

Conclusions: CLDN6 CAR T cells ± CARVac demonstrated encouraging antitumor activity. Addition of CARVac improved CAR-T cell persistence. The safety profile in terms of CRS, ICANS and DLTs observed is in line with previously reported observations. We intend to present data on up to 42 pts, with a data cut-off of 10.09.2023.

Clinical trial identification: NCT04503278.

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Gynaecological cancers

LBA8 A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: The GCIG INTERLACE trial

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Background: Locally advanced cervical cancer (LACC) is treated with chemoradiation (CRT). However, many patients relapse and die from metastatic disease. A feasibility study demonstrated a good response rate to short course weekly induction chemotherapy (IC) delivered before standard CRT and the INTERLACE trial investigated whether this approach improves both progression free survival (PFS) and overall survival (OS).

Methods: Women with squamous, adeno or adenosquamous carcinoma FIGO (2008) stage IB1 node positive,IB2,II,IIIB, IVA were eligible. Patients were randomised (1:1) to receive either CRT alone (5 cycles weekly cisplatin) or IC (6 weeks carboplatin AUC2 and paclitaxel 80mg/m^2) followed by the same CRT in week 7. Mandated minimum total EQD2 dose 78Gy to Point A with 3D brachytherapy recommended. All centres underwent radiation quality assurance. Primary endpoints were PFS (target hazard ratio [HR] 0.65) and OS (target HR 0.65-0.70).

Results: 500 patients were recruited from 32 centres in 5 countries (Nov 2012-Nov 2022). Median age 46 (range 24-78) years. Stage distribution was: IB1/2; 9%, II;77%, IIIB;11% and IVA;3%. 57% were node negative and 82% squamous subtype. Arms were balanced. 92% of IC patients had 5/6 cycles carboplatin/paclitaxel. Median interval from IC to CRT was 7 days. 84% (IC/CRT) vs. 89% (CRT alone) had 4/5 cycles cisplatin. In the CRT arm 92% and 89% completed external beam and brachytherapy respectively; corresponding figures in the IC/CRT arm were 97% and 95%. The median overall treatment time for CRT was 45 days in both arms. Grade $\geq$3 adverse events were seen in 59% (IC/CRT) vs. 48% (CRT alone). Median follow up 64 months. 5 year PFS rate is 73% with IC/CRT and 64% with CRT alone (HR 0.65; 95%CI:0.46-0.91, p=0.013). The corresponding 5-year OS rates are 80% and 72% (HR 0.61:95%CI:0.40-0.91, p=0.04).

Conclusions: Induction chemotherapy followed by CRT significantly improves PFS and OS in LACC and should be considered a new standard of care. INTERLACE recruited patients from diverse health care settings demonstrating that IC followed by CRT is feasible in all countries.

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LBA9 innovaTV 301/ENGOT-cx12/GOG-3057: A global, randomized, open-label, phase III study of tisotumab vedotin vs investigator's choice of chemotherapy in 2L or 3L recurrent or metastatic cervical cancer

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Background: Tisotumab vedotin (TV) is an investigational antibody-drug conjugate composed of a tissue factor-directed human monoclonal antibody covalently linked to cytotoxic MMAE. In the US, TV monotherapy received accelerated approval for the treatment of adult pts with recurrent or metastatic cervical cancer (r/mCC) with disease progression on or after chemotherapy. Here, innovaTV 301 (NCT04697628) study results of TV vs investigator's choice of chemotherapy in pts with r/mCC following 1L therapy are presented.

Methods: Eligible pts had r/mCC with disease progression on/after treatment with standard of care chemotherapy doublet ± bevacizumab ± anti-PD-(L)1 therapy, measurable disease per RECIST v1.1, and ECOG PS 0-1. Pts were randomized 1:1 to TV monotherapy or investigator's choice of topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed. The primary endpoint was OS. Key secondary endpoints included PFS and confirmed ORR by investigator.

Results: 502 pts were randomized (TV: 253; chemotherapy: 249); median survival follow-up was 10.8 mo (95% CI, 10.3-11.6). Overall, median age was 50 yrs (range: 26-80); arms were balanced for demographics and disease characteristics. 63.9% and 27.5% of pts had prior bevacizumab and prior anti-PD-(L)1 therapy, respectively. The TV arm had a 30% reduction in risk of death vs chemotherapy (HR 0.70; 95% CI 0.54-0.89; P=0.0038), with significantly longer median OS (11.5 mo [95% CI 9.8-14.9] vs 9.5 mo [95% CI 7.9-10.7]). PFS was superior in the TV vs chemotherapy arm (HR: 0.67 [95% CI, 0.54-0.82]; P<0.0001). Confirmed ORR was 17.8% and 5.2% in the TV and chemotherapy arms, respectively (odds ratio: 4.0; 95% CI, 2.1-7.6; P<0.0001). Most pts experienced at least 1 treatment-related adverse event (TV: 87.6% [grade ≥3: 29.2%] vs chemotherapy: 85.4% [grade ≥3: 45.2%]). AEs were consistent with the known TV safety profile, including for ocular, peripheral neuropathy, and bleeding AEs.

Conclusions: In the phase 3 innovaTV 301 study, TV showed a statistically significant and clinically meaningful improvement in OS, PFS, and ORR vs chemotherapy, with a manageable and tolerable safety profile in pts with 2L/3L r/mCC.

Clinical trial identification: SGNTV-003; Amendment 3 (6 April 2022), NCT04697628.

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LBA36 Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study): A randomized, double-blind, placebo-controlled, phase III trial

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Background: Ovarian cancer (OC) is one of the most lethal gynecologic cancers. Approximately 85% of newly diagnosed advanced OC may experience a relapse after the first line (1L) platinum-based chemotherapy. PARP inhibitors are recommended as maintenance therapy to prolong the benefit of platinum. Senaparib (IMP4297) is a novel, highly potency PARP inhibitor. The phase 3 study FLAMES is to investigate the efficacy and safety of Senaparib in Chinese patients (pts) with newly diagnosed advanced OC as 1L maintenance therapy.

Methods: Eligible pts had newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid OC, who have completed 1L platinum-based chemotherapy with complete response (CR) or partial response (PR). Pts were randomized (2:1) to receive senaparib (Sena) or placebo (PBO) 100 mg/day orally, stratified by CR/PR and BRCA mutation positive/negative. Primary endpoint was progression-free survival (PFS) evaluated by blinded independent central review (BICR) according to RECIST v1.1.

Results: 404 pts were randomized. As of 16 Mar. 2023, 270 and 133 pts received Sena and PBO with a median follow-up of 22.4 and 22.2 months, respectively. Primary analysis showed Sena significantly improved PFS over placebo (HR 0.43, 95% CI 0.32-0.58, P $<$ 0.0001), irrespective of BRCA mutation status (HR 0.43, P $<$ 0.01). Secondary endpoints support the primary analysis (Table). Incidence rates of grade $\geq$3 adverse events (AEs) were 66.3 % vs 20.3%, AEs leading to dose reduction 63.3 % vs 6.0% and discontinuation 4.4 % vs 0% in Sena and PBO arm. No AE leading to death.

Table: LBA36

	Senaparib (n=271), m	Placebo (n=133), m	HR (95%CI), P value
PFS (BICR)	NR	13.6	0.43 (0.32-0.58) P $<$ 0.0001
PFS (BICR) BRCA +	NR	15.6	0.43 (0.24-0.76) P = 0.0026
PFS (BICR) BRCA-	NR	12.9	0.43 (0.30-0.61) P $<$ 0.0001
PFS (INVR)	NR	11.1	0.43 (0.32-0.57) P $<$ 0.0001
PFS (INVR) BRCA +	NR	11.1	0.33 (0.20-0.56) P $<$ 0.0001
PFS (INVR) BRCA-	NR	11.1	0.48 (0.34-0.67) P $<$ 0.0001
TFST	NR	14.4	0.44 (0.33-0.59) P $<$ 0.0001

BICR, blinded independent central review; INVR, investigator review; HR, hazard ratio; NR, not reached; PFS, progression-free survival; BRCA +, breast cancer susceptibility gene (BRCA) mutation positive; BRCA -, BRCA mutation negative; TFST, time to first subsequent therapy or death; m, month

Conclusions: 1L maintenance Senaparib led to an unprecedented reduction in the risk of progression or death versus placebo in OC, regardless of biomarker status. Senaparib was well tolerated, no new safety signals were identified.

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LBA37 Atezolizumab (atezo) combined with platinum-based chemotherapy (CT) and maintenance niraparib for recurrent ovarian cancer (rOC) with a platinum-free interval (TFIp) >6 months: Primary analysis of the double-blind placebo (pbo)-controlled ENGOT-Ov41/GEICO 69-O/ANITA phase III trial

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Background: Standard therapy for late-relapsing (TFIp >6 mo) rOC includes PARPi maintenance if disease responds to platinum-based CT. ANITA (NCT03598270) is the first-reported phase 3 trial evaluating atezo with platinum-based CT and maintenance PARPi in late-relapsing rOC.

Methods: Eligible pts had measurable high-grade serous, endometrioid or undifferentiated rOC, ≤2 prior CT lines (most recent including platinum) and TFIp >6 mo. Prior PARPi for rOC and/or prior immune checkpoint inhibitor were prohibited. Pts were stratified by carboplatin (carbo) doublet (paclitaxel, gemcitabine or pegylated liposomal doxorubicin [PLD]), TFIp (6–12 vs >12 mo), *BRCA* status (mutated vs non-mutated) and PD-L1 status (PD-L1-expressing immune cells on <1% vs ≥1% tumour area vs non-informative by SP142). Pts were randomised 1:1 to a carbo doublet + atezo or pbo for 6 cycles followed (in pts without progression on CT) by maintenance niraparib at an individualised starting dose + atezo or pbo until disease progression. The atezo dose was 1200 mg q3w or 840 mg q2w depending on the CT regimen. The primary endpoint was investigator-assessed progression-free survival (PFS) per RECIST v1.1.

Results: Between Nov 2018 and Jan 2022, 417 pts were randomised (14% *BRCA*m, 36% PD-L1+, 66% TFIp >12 mo, 11% prior PARPi after front-line CT, 54% prior bevacizumab); most (71%) received carbo–PLD and 74% began maintenance. At the data cut-off (15 Apr 2023), median follow-up was 36 mo. PFS results (Table) were consistent in key subgroups. Overall response to CT was 43% (95% CI 36–49%) and 45% (95% CI 39–52%) in the pbo and atezo arms, respectively. The safety profile was as expected from prior experience of these drugs.

Table: LBA37

PFS		Pbo + CT → pbo + niraparib (n=209)	Atezo + CT → atezo + niraparib (n=208)
All pts	Events, n (%)	174 (83)	170 (82)
	Hazard ratio (95% CI)	0.89 (0.71–1.10); p=0.28	
	Median, mo (95% CI)	10.1 (9.2–11.2)	11.2 (10.1–12.1)
PD-L1-positive subgroup	Events, n/N (%)	60/73 (82)	61/76 (80)
	Hazard ratio (95% CI)	0.87 (0.61–1.25)[a]	
	Median, mo (95% CI)	11.1 (9.7–12.7)	12.8 (10.2–15.4)
PD-L1-negative subgroup	Events, n/N (%)	92/112 (82)	97/117 (83)
	Hazard ratio (95% CI)	0.93 (0.70–1.24)[a]	
	Median, mo (95% CI)	9.2 (8.3–11.1)	10.5 (9.2–11.8)

[a]Unadjusted estimate.

Conclusions: Combining atezo with CT and maintenance niraparib for late-relapsing rOC did not significantly improve PFS or ORR.

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LBA38 Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: A randomized, double-blind, phase III ENGOT-cx11/GOG-3047/KEYNOTE-A18 study

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Background: Pembrolizumab (pembro) has shown efficacy in patients (pts) with cervical cancer. The effect of chemoradiotherapy may be enhanced by immunotherapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18(NCT04221945) assessed the efficacy and safety of pembro + concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer.

Methods: Eligible pts with newly diagnosed, previously untreated, high-risk locally advanced cervical cancer (FIGO 2014 stage IB2-IIB with node-positive disease or stage

III-IVA) were randomized 1:1 to receive 5 cycles of pembro 200 mg or pbo Q3W + CCRT, then 15 cycles of pembro 400 mg or pbo Q6W. The CCRT regimen included 5 cycles (with optional 6th dose) of cisplatin 40 mg/m^2 Q1W + EBRT then brachytherapy. Pts were stratified by planned EBRT type (intensity-modulated radiotherapy [IMRT] or volumetric-modulated arc therapy [VMAT] vs non-IMRT or non-VMAT), stage at screening (stage IB2-IIB vs III-IVA) and planned total radiotherapy dose. Primary endpoints were PFS per RECIST version 1.1 by investigator and OS.

Results: 1060 pts were randomized to pembro + CCRT (n=529) or pbo + CCRT (n=531). At the protocol-specified first interim analysis (January 9, 2023, data cutoff), median follow-up was 17.9 mo (range, 0.9-31.0). Pembro + CCRT showed a statistically significant improvement in PFS vs pbo + CCRT. 24-mo PFS was 67.8% with pembro + CCRT vs 57.3% with pbo + CCRT; median PFS was not reached in either group (HR=0.70 [95% CI, 0.55-0.89; P=0.0020]); results were consistent across all prespecified subgroups. With only 103 events (42.9% maturity), the addition of pembro to CCRT showed a favorable trend in OS (HR=0.73 [95% CI, 0.49-1.07]); these data have not crossed the boundary of statistical significance. Grade ≥3 TRAE incidence was 67.0% in the pembro + CCRT group and 60.0% in the pbo + CCRT group.

Conclusions: Pembro + CCRT showed a statistically significant and clinically meaningful improvement in PFS and a favorable trend in OS compared with pbo + CCRT in pts with high-risk locally advanced cervical cancer and had a manageable safety profile. These data suggest pembro + CCRT can be considered as a new standard of care for this population.

Clinical trial identification: NCT04221945.

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LBA39 Primary results from BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030), a randomised phase III trial of first-line atezolizumab (atezo) combined with a platinum doublet and bevacizumab (bev) for metastatic (stage IVB), persistent or recurrent cervical cancer (R/M CC)

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Background: The open-label randomised phase 3 BEATcc academic trial (NCT03556839) evaluated atezo (anti-PD-L1) combined with first-line chemotherapy (CT) + bev for R/M CC, irrespective of PD-L1 status. We report final progression-free survival (PFS) and interim overall survival (OS) results.

Methods: Patients (pts) with previously untreated measurable R/M CC not amenable to curative surgery/radiation were randomised 1:1 to standard therapy (cisplatin 50 mg/m^2 or carboplatin AUC5 + paclitaxel 175 mg/m^2 + bev 15 mg/kg) ± atezo 1200 mg d1 q3w. Cycles were repeated until disease progression or unacceptable toxicity. Stratification factors were prior concomitant chemoradiation (yes vs no), histology (squamous cell carcinoma vs adenocarcinoma) and platinum agent (cisplatin vs carboplatin). Dual primary endpoints were investigator-assessed PFS per RECIST v1.1 and

OS. Secondary endpoints included objective response rate (ORR), duration of response (DoR), time to first subsequent therapy (TFST), PFS2, and safety.

Results: Between Oct 2018 and Aug 2021, 410 pts were randomised. At the data cut-off (median follow-up 32.9 mo), median treatment duration was 8.5 vs 12.7 mo in the control vs atezo arms, respectively; treatment was ongoing in 7% vs 23%, respectively. Both PFS and OS were statistically significantly improved with the addition of atezo to CT + bev (Table). Secondary endpoints and subgroup analyses showed consistent results. Grade ≥3 adverse events (any cause) occurred in 75% vs 79% of the control and atezo arms, respectively. Safety profiles were as expected with bev + platinum-based CT. Grade 1/2 diarrhoea, arthralgia, pyrexia and rash were increased with atezo.

Table: LBA39

Endpoint		CT + bev (n=204)	Atezo + CT + bev (n=206)
PFS	Events, n (%)	166 (81)	138 (67)
	HR	0.62 (0.49–0.78); p<0.0001	
	Median, mo	10.4 (9.7–11.7)	13.7 (12.3–16.6)
	2-year rate, %	19 (14–25)	36 (29–43)
OS	Events, n (%)	129 (63)	105 (51)
	HR	0.68 (0.52–0.88); p=0.0046*	
	Median, mo	22.8 (20.3–28.0)	32.1 (25.3–36.8)
	2-year rate, %	49 (41–56)	61 (53–67)
TFST	Median, mo	13.2 (12.0–14.3)	19.0 (16.4–24.0)
	HR	0.60 (0.47–0.76)	
PFS2	Median, mo	20.3 (17.8–22.3)	25.8 (22.1–32.1)
	HR	0.61 (0.48–0.79)	
ORR per RECIST v1.1, %		72 (66–78)	84 (79–89)
DoR	n	147	173
	Median, mo	8.6 (8.0–10.6)	13.6 (10.6–21.3)
	HR	0.60 (0.46–0.78)	

Brackets show 95% CIs unless otherwise stated HR = hazard ratio *Statistically significant at interim analysis.

Conclusions: Adding atezo to first-line CT + bev for R/M CC significantly improved all efficacy outcomes. Median OS with atezo + CT + bev exceeded 2.5 years.

Clinical trial identification: NCT03556839; EudraCT 2018-000367-83; ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030/BEATcc.

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LBA40 Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma

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Background: The standard therapy for advanced/recurrent endometrial cancer includes carboplatin and paclitaxel (CP). Robust biological rationale suggested a synergy between immunotherapy and chemotherapy in this setting.

Methods: AtTEnd is an international academic study in endometrial carcinoma/carcinosarcoma patients (pts) with advanced newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence. Pts were randomized (2:1 ratio) to receive either CP chemotherapy and atezolizumab (atezo) or placebo, followed by atezo or placebo until disease progression. The mismatch repair (MMR) status was evaluated centrally. Coprimary endpoints with a hierarchical approach were: progression free survival (PFS) in the deficient MMR (dMMR) population, PFS and overall survival (OS) in all comers.

Results: Five hundred and fifty-one pts were enrolled from Oct 2018 to Jan 2022 in 89 sites across 10 countries (median follow-up 28.3 months). Of the 549 pts included in the intention to treat population, 125 (22.8%) had dMMR tumours and 352 (64.1%) had endometrioid carcinoma; 369 (67.2%) had recurrent disease and 148 (82.2%) of newly diagnosed cases had primary stage IV. In the dMMR population, the addition of atezo showed a significant improved PFS (HR 0.36 95% CI:0.23-0.57; p=0.0005; median PFS: not reached vs. 6.9 months for atezo vs placebo). The superiority in PFS was confirmed in all comers (HR 0.74 95%CI:0.61-0.91; p=0.0219; median PFS: 10.1 months vs 8.9 months for atezo vs placebo). Interim analysis of OS in all comers indicated a trend in favor for atezo, despite 45 (24.3%) placebo patients received immunotherapy as subsequent therapy. Second PFS and duration of response in the dMMR population confirmed the efficacy of atezo. Grade≥3 adverse events occurred in 66.9% and 63.8% of pts in atezo vs placebo arm. Safety profile for CP + atezo was manageable and consistent with expected toxicities.

Conclusions: The addition of atezo to standard CP chemotherapy demonstrated a statistically significant improvement in PFS for pts with advanced/recurrent endometrial carcinomas with a substantial benefit in pts with dMMR carcinomas.

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Legal entity responsible for the study: Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy.

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LBA41 Durvalumab (durva) plus carboplatin/paclitaxel (CP) followed by maintenance (mtx) durva ± olaparib (ola) as a first-line (1L) treatment for newly diagnosed advanced or recurrent endometrial cancer (EC): Results from the phase III DUO-E/GOG-3041/ENGOT-EN10 trial

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Background: Combination of immunotherapy with CP led to improved progression-free survival (PFS) in patients (pts) with advanced EC. DUO-E (NCT04269200) evaluated addition of durva to standard 1L CP, followed by mtx durva ± ola, in pts with EC.

Methods: Pts with newly diagnosed FIGO Stage III/IV or recurrent EC and naïve to systemic treatment were randomised 1:1:1 to CP (CP + durva placebo [pbo] for 6 cycles followed by mtx durva pbo + ola pbo), CP + durva (CP + durva [1120 mg IV q3w] for 6 cycles followed by mtx durva [1500 mg IV q4w] + ola pbo), or CP + durva + ola (CP + durva for 6 cycles followed by mtx durva + ola [300 mg tablets bid]). Dual primary endpoints were PFS (investigator-assessed RECIST v1.1) in the intent-to-treat (ITT) population for CP + durva vs CP and CP + durva + ola vs CP; overall survival (OS) was a secondary endpoint. A multiple testing procedure with gatekeeping strategy was applied to PFS and OS. PFS by mismatch repair (MMR) status was a prespecified subgroup analysis.

Results: In the ITT population (N=718), CP + durva and CP + durva + ola showed statistically significant and clinically meaningful PFS benefit vs CP (Table). Interim OS data were immature (27.7%) yet with a trend towards benefit (CP + durva vs CP: HR [95% CI] 0.77 [0.56−1.07]; P=0.120; CP + durva + ola vs CP: 0.59 [0.42−0.83]; P=0.003). PFS subgroup analysis showed benefit for both arms vs CP in MMR-

Table: LBA41

Population	Arm	Median follow-up duration,† months	PFS events, n/N (%)	Median PFS, months	HR* (95% CI)	12-/18-month PFS rate, %
ITT	CP	12.6	173/241 (71.8)	9.6		41.1/21.7
	CP + durva	15.4	139/238 (58.4)	10.2	0.71 (0.57–0.89); P=0.003	48.5/37.8
	CP + durva + ola	15.4	126/239 (52.7)	15.1	0.55 (0.43–0.69); P<0.0001	61.5/46.3
dMMR	CP	10.2	25/49 (51.0)	7.0		43.3/31.7
	CP + durva	15.5	15/46 (32.6)	Not reached	0.42 (0.22–0.80)	67.9/67.9
	CP + durva + ola	19.2	18/48 (37.5)	31.8	0.41 (0.21–0.75)	70.0/62.7
pMMR	CP	12.8	148/192 (77.1)	9.7		40.8/20.0
	CP + durva	15.3	124/192 (64.6)	9.9	0.77 (0.60–0.97)	44.4/31.3
	CP + durva + ola	15.2	108/191 (56.5)	15.0	0.57 (0.44–0.73)	59.4/42.0

*Vs CP; †In censored patients.

deficient (dMMR; n=143) and -proficient (pMMR) pts (n=545). In pMMR pts, mtx ola further enhanced PFS benefit (Table). Safety profiles of the treatment arms were generally consistent with individual components.

Conclusions: DUO-E met both primary endpoints, showing statistically significant and clinically meaningful PFS improvement with the addition of durva to CP followed by maintenance durva ± ola vs CP alone. Mtx ola further improved PFS in pts with pMMR disease.

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LBA42 Olaparib vs placebo as maintenance therapy after platinum-based chemotherapy in advanced/metastatic endometrial cancer patients: The GINECO randomized phase IIb UTOLA trial

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Background: The TGCA data suggest opportunities to target DNA repair in patients (pts) with endometrial cancer (EC). UTOLA assessed the efficacy of Parp-inhibitor maintenance for advanced/M+ EC pts who achieved disease control after 1st line platinum CT and to analyse efficacy in some molecular subgroups.

Methods: UTOLA is a randomized, double-blind, placebo controlled, phase IIb trial. Adjuvant CT ≥12 mos before inclusion was allowed. Pts were randomized (2:1) to olaparib maintenance arm (ola, 300 mg po BID) or placebo arm (pl) until progression or intolerance with stratification on P53, MMR status, and the response to the previous CT. Molecular profile was assessed by IHC and NGS. Primary endpoint was PFS in ITT. Main secondary endpoints were PFS according to P53 status, CT response, OS, safety. A pre-specified PFS analysis was performed according to HRD status defined by the number of large genomic events. One sided unstratified analyses are presented.

Results: 147 pts were randomized (98 to Ola, 49 to pl). 82% of the pts received at least 6 cycles of CT with 46 CR, 64 PR, 34 stable and 3 NED; tumor classification was 53% $P53_{mut}$, 35% NSMP, 12% MMRd, and 1 tumor $POLE_{mut}$. In total, 52% (73) were HRD positive, 79% in $P53_{mut}$ & 23% in $P53_{WT}$. Median PFS in the ITT population was 5.6 mos (90%CI 3.8-7.4) and 4.0 (3.6-7.4) in ola and pl arms respectively (HR:0.94, p=0.29). Median PFS in $P53_{mut}$ were 5.6 mos (3.6-8.8) vs 3.6 ms (1.8-4.9) in ola and pl arms (HR:0.75, p=0.12) whereas 6.1 mos (3.6-11) vs 7.7 mos (2.9-14.5) (HR=1.13, p=0.3) respectively in the $P53_{WT}$. In the HRD tumors (n=73), median PFS was statistically higher with ola: 5.4 mos (90%CI 3.6-9.6) vs 3.6 mos (1.8-4.9) with pl (HR:0.59, p=0.02) regardless of P53 status. For the 46 pts with CR to previous CT, median PFS in ola arm reached 8.8 mos versus 3.8 mos. No difference for OS was observed in all subgroups. Safety profile was similar and acceptable as seen in other cancers (36% vs 10% of G3/4 toxicities without myelodysplasia with ola).

Conclusions: UTOLA suggests maintenance ola could prolong PFS in HRD-positive advanced/M+ EC. These data should be confirmed and warrants further PARP inhibitor studies in this population.

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LBA43 Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial

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Background: NRG GY018 identified a 70% and 46% reduction in the risk of disease progression or death in advanced stage or recurrent dMMR and pMMR EC patients treated with pembrolizumab plus CP. The relationship between mechanism of MMR deficiency and clinical outcomes in dMMR EC patients is not well understood.

Methods: 819 pts were randomized 1:1 to pembrolizumab + CP or PBO + CP Q3W for 6 cycles followed by maintenance pembrolizumab or PBO Q6W for up to 2 years. MMR status was assessed by local and central immunohistochemistry (IHC). For patients with measurable disease at enrollment, updated best response (RECIST 1.1) was examined in both patient cohorts. Mechanism of MMR loss was determined by review of local MMR IHC results and presence/absence of MLH1 promoter hypermethylation. The effect of mechanism of MMR loss on PFS was examined in dMMR patients treated with pembrolizumab.

Results: Local and central MMR IHC had strong agreement, kappa 0.88 (95% CI 0.84-0.91). The ORR was improved in the pembrolizumab arm of both patient cohorts (dMMR: 81.5% vs. 70.7%, OR 1.83 (95% CI 0.92-3.66) and pMMR: 70.7% vs. 58.1%, OR 1.74 (95% CI 1.18-2.58)). The CR rate in the dMMR and pMMR EC cohorts was higher when pembrolizumab was added to CP (15% vs 32% dMMR; 8% vs 15% pMMR). Median DOR was significantly improved with addition of pembrolizumab, dMMR 28.7 mo vs 6.2 mo (HR 0.22; 95% CI 0.13-0.37, $p<.0001$) and pMMR 9.2 mo vs 6.2 mo (HR 0.47; 95% CI 0.34-0.64, $p<.0001$). In 223 central-dMMR pts, 72% had MLH1 promoter hypermethylation, 13% had MMR protein loss secondary to gene mutation, and 15% were not evaluable. Mechanism of MMR loss was not a significant predictor of PFS (85% versus 75% progression free at 12 months in mutated vs methylated pts). Median PFS and OS were not reached irrespective of mechanism of MMR loss.

Conclusions: In NRG GY018, no difference in PFS was identified in dMMR EC patients based on mechanism of MMR loss. With more mature clinical follow up, the magnitude of benefit in both patient cohorts treated with pembrolizumab was maintained, with significant improved in ORR, and DOR.

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LBA44 Camrelizumab plus famitinib versus camrelizumab alone and investigator's choice of chemotherapy in women with recurrent or metastatic cervical cancer

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Background: Combining immunotherapy and anti-angiogenic agents may enhance immune response by reversing the immunosuppressive microenvironment. We conducted a randomized, open-label, phase 2 trial to assess camrelizumab (CAM, an anti-PD-1 antibody) plus famitinib (FAM, a multi-targeted TKI against VEGFR2/3) versus CAM alone and investigator's choice of chemotherapy (chemo) for recurrent or metastatic cervical cancer (R/M CC).

Methods: Patients (pts) with R/M CC who failed prior platinum-based chemo were enrolled. Prior anti-PD-1/PD-L1/CTLA-4 treatment was not allowed. Pts were randomized to receive CAM 200 mg IV Q3W with (cohort A) or without (cohort B) FAM 20 mg PO QD, or investigator's choice of chemo (cohort C) every 3-week cycle. The primary endpoint was ORR per RECIST v1.1 assessed by blinded independent central review (BICR).

Results: At data cutoff on April 21, 2023, 194 pts were randomized (cohort A n=105, cohort B n=54, cohort C n=35), and 46 pts (23.7%) remained on treatment. 77.8% of pts had squamous CC, 63.9% were PD-L1 positive, 31.4% received prior targeted therapy. The median follow-up duration was 9.9 months (IQR 7.3-15.1). Antitumor activities are shown in the table. Treatment-related adverse events (TRAEs) occurred in 100%, 94.3%, and 100% of pts, respectively. Grade ≥3 TRAEs were reported in 84.8%, 15.1%, and 60.0% of pts, respectively, with the most common ones being decreased neutrophil count (23.8%, 1.9%, 30.0%), hypertension (22.9%, 0, 0), decreased white blood cell count (20.0%, 0, 33.3%), and anemia (20.0%, 1.9%, 13.3%). Dose discontinuation due to AEs occurred in 19.0%, 5.7%, and 0 pts, respectively. Treatment-related death was reported in two pts (1.9%) in cohort A (acute coronary syndrome, infection and sepsis).

Table: LBA44 Summary of efficacy

	Cohort A (n=105)	Cohort B (n=54)	Cohort C (n=35)
BICR-assessed			
CR	9 (8.6)	3 (5.6)	—
PR	34 (32.4)	10 (18.5)	—
ORR	41.0 (31.5-51.0)	24.1 (13.5-37.6)	—
DCR	75.2 (65.9-83.1)	55.6 (41.4-69.1)	—
PFS (mo)	7.2 (6.1-12.4)	4.0 (2.1-6.1)	—
Investigator-assessed			
CR	4 (3.8)	2 (3.7)	1 (2.9)
PR	41 (39.0)	10 (18.5)	4 (11.4)
ORR	42.9 (33.2-52.9)	22.2 (12.0-35.6)	14.3 (4.8-30.3)
DCR	74.3 (64.8-82.3)	53.7 (39.6-67.4)	42.9 (26.3-60.7)
PFS (mo)	8.1 (6.2-12.4)	4.1 (2.1-5.1)	2.9 (2.0-6.2)
12-months OS rate	80.3 (70.7-87.0)	71.9 (55.8-83.0)	59.7 (40.9-74.3)

Conclusions: CAM plus FAM showed improved antitumor activity than CAM alone or investigator's choice of chemo in pts with R/M CC, with a tolerable safety profile.

Clinical trial identification: NCT04680988 (registered on December 23, 2020).

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LBA45 Overall survival (OS) outcomes from NRG-GY004, a phase III study comparing single-agent olaparib or combination cediranib and olaparib to platinum (Plat) based chemotherapy in recurrent plat sensitive ovarian cancer (OvCa)

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Background: In the NRG-GY004 (NCT02446600) primary analysis, neither olaparib (O) nor combined cediranib and olaparib (C+O) improved progression-free survival (PFS) compared to standard of care (SOC) plat therapy as treatment for relapsed plat sensitive ovca, although median PFS was longer in patients with gBRCAm (Liu et al., J Clin Oncol 2022). We now report the prespecified OS analysis.

Methods: Pts with plat sensitive high-grade serous or endometrioid, or BRCA-related, ovca were randomized 1:1:1 to SOC (carboplatin/paclitaxel; carboplatin/gemcitabine; or carboplatin/liposomal doxorubicin), O (300mg twice daily), or C+O (C 30mg daily + O 200mg twice daily), stratified by gBRCA status, PFI (6-12 vs >12 months), and prior anti-angiogenic therapy. OS was a secondary endpoint; analysis was specified to occur when at least 265 events had occurred cumulatively in the SOC and C+O arms.

Results: Between 4FEB2016 and 13NOV2017, 565 pts enrolled (187 SOC, 189 O, 189 C+O), and 528 pts initiated treatment (166 SOC, 183 O, 179 C+O). 23.7% of patients had gBRCAmt. Median follow-up was 66.5 months; 419 deaths had occurred. The hazard ratio (HR) for OS was 1.27 (95% CI 0.99-1.62, p = 0.06) between O and SOC and 1.12 (95% CI 0.87-1.43, p = 0.38) between C+O and SOC, with median OS of 32.7, 31.0, and 33.5 months for SOC, O, and C+O, respectively. In gBRCA pts, HR for OS was 1.39 (95% CI 0.80-2.42) for O vs SOC and 1.24 (95% CI 0.94-1.63) for C+O vs SOC, with median OS of 43.2, 41.3, and 44.8 mos for SOC, O, and C+O. In non-gBRCA pts, HR for these comparisons was 1.26 (95% CI 0.71-2.21) and 1.07 (0.82-1.40). 46 pts on SOC had non-protocol therapy before disease progression, including 36 pts receiving PARPi. 27.3% of pts on SOC, 7.9% on O, and 10.6% on C+O terminated OS follow-up early prior to death.

Conclusions: In NRG-GY004, neither O nor C+O improved OS compared to SOC as treatment for relapsed plat sensitive ovca. Hazard ratios for OS for both O and C+O exceeded 1 with wide 95% CIs that included 1. These findings must be interpreted with caution given the proportion of pts terminating follow-up early and the number of pts on the SOC arm who received off-protocol PARPi maintenance.

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Head and neck cancer, excl. thyroid

LBA46 SAKK 11/16, a phase IIa trial evaluating overall survival (OS) for recurrent/metastatic Head & neck squamous cell carcinoma (RMHNSCC) patients (pts) progressing after ≥ 1 line of systemic therapy, treated with MVX-ONCO-1, a novel, first in class cell encapsulation-based immunotherapy

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Background: MVX-ONCO-1 is a personalized, subcutaneous (sc) cancer vaccine combining irradiated autologous tumor cells and devices containing allogeneic cells producing the potent adjuvant GM-CSF. Positive clinical data in RMHNSCC pts with evidence of immune education in a Phase I study triggered this multicenter phase IIa trial.

Methods: 16 pts with RMHNSCC, progressing after ≥1 line of systemic therapy, with measurable disease and ECOG PS 0-2 were enrolled. Pts received 6 sc treatments over 8 weeks (wks). Primary endpoint was OS at 26 wks. An unplanned interim review of the first 10 pts revealed 7 had met the 26 wks OS endpoint. Using the conditional power method of Kieser *et al.* sample size was reduced from 39 to 21 pts keeping the same one-sided type 1 error rate of 5% and power of 80%. The null hypothesis in the adaptive design can be rejected if among the 21 pts there are ≥11 survivors at 26 wks. Response and safety were secondary endpoints.

Results: Enrollment was closed early as primary endpoint was met ahead of schedule. Median OS is 11.4 months (mo) and OS at 12 and 18 mo are 49.2% and 31.6% respectively. Partial Response (PR) and Complete Response (CR) were observed, including CR ongoing for >17 mo in a nivolumab refractory pt. Several pts are alive with no active metastatic disease, including long-term survivors (> 3 years). ORR at 26 wks is 12.5% while DCR at 6 wks is 75% of pts. No systemic adverse events related to therapy was reported. Strong correlation between OS and Delayed Type Hypersensitivity (DTH) was observed. At 12 mo, 100% of DTH+ pts are alive compared to only one DTH- pt.

Conclusions: MVX-ONCO-1 is a novel personalized cancer vaccine with very good safety profile. Clinically meaningful prolonged survival, PR and CR were observed in IO refractory RMHNSCC pts. Prolonged OS correlates strongly with immune education, DTH being a potential biomarker to be validated in future studies. MVX-ONCO-1 is the first cancer vaccine associated with prolonged survival in advanced chemo / IO refractory disease in monotherapy without maintenance.

Clinical trial identification: NCT02999646.

Legal entity responsible for the study: MaxiVAX.

Funding: MaxiVAX, Rising Tide Foundation For Clinical Cancer Research, Gateway for Cancer Research, Swiss Cancer League, Horizon 2020 Research & Innovation EU, Coromandel, The Philantropy Settlement.

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LBA47 A phase II study evaluating tipifarnib in mHRAS, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) (AIM-HN study)

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Background: Despite recent advances, prognosis for R/M HNSCC patients (pts) remains poor. *HRAS* mutations are seen in 4-8% of HNSCCs. HRAS is uniquely farnesylation dependent, making m*HRAS* tumors susceptible to farnesyl transferase inhibitors. Tipifarnib has activity in pts with HNSCC harboring high variant allele frequency (VAF, ≥20%) m*HRAS* (Ho et al. JCO 2021). We present data in 50 high VAF pts in AIM-HN.

Methods: Pts received tipifarnib 600 mg BID on days 1-7 and 15-21 of a 28-day cycle. The primary endpoint was objective response rate (ORR) in the high VAF pts by independent review facility (IRF). Histologically confirmed m*HRAS* HNSCC pts with ≥1 prior platinum-containing regimen were eligible. ORR was assessed in the modified intent to treat (mITT) set (≥1 tipifarnib dose).

Results: Of 59 pts treated with tipifarnib, 50 (85%) had high VAF (median VAF: 34% [range 4-89%]). Twenty-six (44%) received immunotherapy in 1st line (1L). By Investigator assessment, ORR was 30% with 1 pt achieving a CR. By IRF, ORR was 20% with 1 CR (Table). Two responders were on treatment at study close (9 and 29 mos). Median progression-free survival by IRF: 2.6 mos (95% CI: 1.9-4.4); median overall survival: 7.0 mos (95% CI: 4.9-11.5). Grade 3+ treatment-related adverse events (TRAEs) were observed in 33 pts (56%): neutropenia (24%), anemia (20%), leukopenia (14%) and febrile neutropenia (7%). However, only 7% discontinued treatment due to TRAEs.

Table: LBA47

	Pts with high VAF in mITT* (N=50)	
	Investigator Assessment	IRF
ORR, n (%) [95% CI]		
Line of Therapy for Tipifarnib Any Line (N=50)	15 (30%) [0.18, 0.45]	10 (20%) [0.10, 0.34]
2L (N=24)	9 (38%) [0.19, 0.59]	7 (29%) [0.13, 0.51]
3L+ (N=20)	4 (20%) [0.06, 0.44]	3 (15%) [0.03, 0.38]
Disease Control Rate, n (%) [95% CI]	32 (64%) [0.49, 0.77]	24 (48%) [0.34, 0.63]
Confirmed responses CR PR SD	1 14 17	1 9 14
mDoR, mo [95% CI]	5.6 [3.88, 9.23]	6.5 [3.88, -]

*1/9 low VAF pt (< 20% VAF) was also a responder

Conclusions: Tipifarnib was safe and tolerable with anti-tumor activity observed in m*HRAS* R/M HNSCC pts post-IO and as later-line therapy. Tipifarnib is the first

targeted therapy for this rare HNSCC subset. Ongoing combination studies are targeting adaptive resistance pathways (PI3K/mTOR/Akt) to further improve outcomes.

Clinical trial identification: NCT03719690.

Legal entity responsible for the study: Kura Oncology, Inc.

Funding: Kura Oncology, Inc.

Disclosure: A.L. Ho: Financial Interests, Personal, Invited Speaker, discussed head and neck cancer therapies: Chinese American Hematologist and Oncologist Network; Financial Interests, Personal, Invited Speaker, Discussed salivary cancer therapies: Lurie Cancer Center (Northwestern); Financial Interests, Personal, Invited Speaker, discussed thyroid cancer therapies: Physician Education Resource; Financial Interests, Personal, Invited Speaker, Discussed thyroid cancer therapies: Endocrine Society; Financial Interests, Personal, Invited Speaker, Discussed head and neck cancer therapies: University of Pittsburgh Medical Center; Financial Interests, Personal, Invited Speaker, Discussed thyroid cancer therapeutics: New York University; Financial Interests, Personal, Advisory Board, Serve on DSMC: Affyimmune; Financial Interests, Personal, Other, Serve on the NCI Head and Neck Steering Committee: National Cancer Institute; Financial Interests, Personal, Advisory Board, Member of advisory board: Exelixis, Remix Therapeutics, Elevar Therapeutics, Prelude Therapeutics, Eisai, Ayala, Kura Oncology; Financial Interests, Personal, Other, Member of Safety Monitoring Committee: Kura Oncology; Financial Interests, Personal, Advisory Board, Member of advisory board.: Merck; Financial Interests, Personal, Other, Consultant: ExpertConnect; Financial Interests, Personal, Advisory Board, Member of advisory board and consulting.: Rgenta; Financial Interests, Personal, Full or part-time Employment: Memorial Sloan Kettering Cancer Center; Financial Interests, Personal, Stocks/Shares, options: Rgenta Therapeutics; Financial Interests, Institutional, Other, Listed as inventor for: Memorial Sloan Kettering Cancer Center; Financial Interests, Institutional, Coordinating PI, Serve as PI. also served on paid advisory board: Ayala; Financial Interests, Institutional, Coordinating PI, Serve as trial PI, also serve on paid SMC/advisory board: Kura Oncology; Financial Interests, Institutional, Local PI, Trial PI and served on an advisory board: Elevar Therapuetics; Financial Interests, Institutional, Coordinating PI, PI of IIT: Novartis, Merck, Bristol Meyer Squibb; Financial Interests, Institutional, Coordinating PI, PI of several IIT trials: Bayer; Financial Interests, Institutional, Coordinating PI, PI of trial: Bioatla, TILT Biotherapeutics, Genentech Roche, Astellas, Celldex; Financial Interests, Institutional, Local PI, PI of trial: OncC4; Financial Interests, Institutional, Coordinating PI, PI of several IITs: AstraZeneca; Financial Interests, Institutional, Coordinating PI, PI of trial and was part of paid advisory board: Eisai; Financial Interests, Institutional, Local PI, co-PI of trial: Poseida Therapuetics; Financial Interests, Institutional, Local PI: Hookipa; Non-Financial Interests, Advisory Role: Cellestia, Inxmed; Non-Financial Interests, Member of Board of Directors: International Thyroid Oncology Group; Non-Financial Interests, Leadership Role: International Rare Cancer Initiative; Non-Financial Interests, Leadership Role, for the head and neck working group: Alliance for Clinical Trials in Oncology. 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Melanoma and other skin tumours

LBA48 Pathologic response and exploratory analyses of neoadjuvant-adjuvant versus adjuvant pembrolizumab (PEM) for resectable stage IIIb-IV melanoma from SWOG S1801

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Background: Primary efficacy results from SWOG S1801 showed an improved event-free survival (EFS) in patients who received neoadjuvant-adjuvant (NAT) PEM compared to adjuvant (AT) PEM. In pooled analyses and smaller neoadjuvant studies, pathologic response has been suggested as an important surrogate marker of clinical outcome.

Methods: S1801 was a randomized phase II trial for clinically detectable, resectable AJCC 8th edition stage IIIB-IV melanoma. Participants were randomized 1:1 to AT PEM (surgery then 18 doses of PEM q3w) or NAT PEM (3 doses pre-operative PEM, surgery, 15 doses PEM q3w). Sites submitted surgical specimens for central review. For determination of pathologic response to NAT, these specimens were assessed for percentage of necrosis and viable tumor by a single pathologist blind to the clinical results.

Results: As of August 31, 2023, 281 participants had surgery (138 NAT, 143 AT). Of those randomized to NAT, 109 specimens were reviewed for pathologic response, 89 were lymph node specimens. Pathologic response and recurrence-free survival (RFS) outcomes for these lymph node specimens are shown in the table. 130 of 138 NAT participants who underwent surgery had RECIST response data; 15 (12%) achieved complete response (CR), 50 (38%) partial response (PR) for an overall response rate of 50%; 50 (38%) experienced stable disease (SD), and 15 (12%) progression of disease (PD).

Table: LBA48

Path response N (%)	NAT N=89
pathologic complete response (pCR)	36 (40%)
pathologic near complete response (pnCR)	10 (11%)
pathologic partial response (pPR)	26 (29%)
pathologic non-response (pNR)	17 (19%)
2-year RFS[1] by path response % (95% CI)	N=89
pCR (n=36)	97% (92-100)
pnCR (n=10)	80% (59-100)
pPR (n=26)	73% (58-92)
pNR (n=17)	48% (28-82)
2-year RFS[1] by RECIST 1.1 response	N=130
CR (n=15)	93% (82-100)
PR (n=50)	89% (81-99)
SD (n=50)	64% (52-80)
PD (n=15)	67% (47-95)

[1]RFS measured from date of surgery

Conclusions: The use of NAT with single-agent PEM in resectable stage IIIB-IV melanoma results in a 51% major pathologic response rate (pCR + pnCR) with 40% pathologic complete responses. 2-year RFS rates are highest in those achieving pathologic or radiographic response.

Clinical trial identification: NCT03698019.

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Funding: SWOG, Merck Sharp & Dohme.

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LBA49 mRNA-4157 (V940) individualized neoantigen therapy + pembrolizumab vs pembrolizumab in high-risk resected melanoma: Clinical efficacy and correlates of response

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Background: In patients (pts) with resected high-risk stage IIIB–IV melanoma, mRNA-4157 + pembrolizumab (pembro) extended recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs pembro alone (phase 2 KEYNOTE-942; NCT03897881). Minimal residual disease (MRD; by plasma circulating tumor DNA [ctDNA]) at treatment onset was associated with shorter RFS. We examined ctDNA longitudinal dynamics and associated clinical outcomes and report impact of ctDNA status on BRAF subgroup.

Methods: Pts were assigned to mRNA-4157 + pembro or pembro alone. RaDaR® (Inivata) was used to measure plasma ctDNA during treatment and at follow-up. The table defines longitudinal ctDNA molecular responders (MRs) and non-responders (MNRs). BRAF status was derived from whole exome sequencing of baseline tumor tissue. Kaplan–Meier method was used to estimate RFS and DMFS. Cox proportional hazards regression was used to estimate HRs.

Results: 142/157 pts were evaluable for longitudinal ctDNA analyses (100/107 mRNA-4157 + pembro; 42/50 pembro alone). Across treatment arms, pts with available ctDNA and recurrence events were limited (n=30). 57% (8/14) of MRs and 94% (15/16) of MNRs had recurrence. Local recurrence was more common in MRs; MNRs had more distant events. This trend was supported by stronger separation in DMFS vs RFS between MRs and MNRs. There was a trend for enhanced efficacy of mRNA-4157 + pembro across BRAF V600E/K WT (n=96) (HR [95% CI]: 0.808 [0.366–1.784]) and MUT (n=61) subpopulations (0.332 [0.130–0.850]); however, considering ctDNA status by focusing on ctDNA-negative subpopulation increased similarity of efficacy across BRAF WT (n=68) and MUT (n=42) subgroups (0.334 [0.121–0.923] vs 0.069 [0.009–0.563]).

Table: LBA49

ctDNA subgroup	Patient criteria
Molecular responders	Patients with MRD at baseline that resolved during treatment (ctDNA positive at treatment initiation became ctDNA negative) OR Patients with no MRD at baseline that became ctDNA positive on treatment (MRec), and then ctDNA negative again
Molecular non-responders	Patients with MRD at baseline that did not resolve during treatment (ctDNA positive at treatment initiation and stayed positive) OR Patients with no MRD at baseline who showed molecular progression (MRec, ctDNA negative at treatment initiation became ctDNA positive and stayed positive)

Conclusions: These results suggest a potential relationship between ctDNA dynamics and treatment outcomes in pts with high-risk resectable melanoma and support further exploration in upcoming planned studies.

Clinical trial identification: NCT03897881.

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LBA50 Three-year survival with tebentafusp in previously untreated metastatic uveal melanoma in a phase III trial

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Background: Metastatic uveal melanoma (mUM) has a historically poor 1-yr overall survival (OS) rate of 52%. Tebentafusp (tebe), a bispecific (gp100 x CD3) ImmTAC, is approved for adult HLA-A*02:01+ patients (pts) with unresectable or mUM. In the primary analysis of the Phase (Ph) 3 IMCgp100-202 study in previously untreated mUM [NCT03070392], tebentafusp significantly improved OS compared to investigator's choice (IC) [HR 0.51] with a 1-yr OS rate of 73% versus 59%, respectively. Deeper ctDNA reductions were associated with longer OS. Here we present the 3-yr updated analyses of the Ph3 study.

Methods: In this randomized, open-label, Ph3 trial, HLA-A*02:01+ first-line mUM pts were randomized 2:1 to receive tebe or IC of pembrolizumab, ipilimumab or dacarbazine, stratified by LDH. Primary endpoint was OS. Secondary endpoints included overall response rate (ORR), progression free survival (PFS) and disease control rate (DCR) and safety. An exploratory endpoint was ctDNA reduction.

Results: 378 pts were randomized to tebe (252) or IC, including pembrolizumab (103), ipilimumab (16) or dacarbazine (7). After a minimum follow-up of 36 months, the estimated 3-yr OS of tebe was 27% (95% CI 22-33%) vs 18% (95% CI 11-25%) for IC with maintained separation of the OS KM curves. The OS benefit of tebe was also observed in pts with known poor prognostic factors in the metastatic setting. 1-yr and 2-yr PFS rates were 17% vs 9% and 8% vs 3%, for tebe vs IC, respectively. ORR remained in favor of tebe vs IC (11% vs 5%). A third of tebe responders were still in response at 18 months. The DCR rates (CR/PR/SD $\geq$12 weeks) were 46% for tebe and 27% for IC. Of 45 ctDNA evaluable pts in the tebe arm who cleared their ctDNA by week 9, 32 (71%) survived $\geq$2 yrs and 17 (38%) survived $\geq$3 yrs. No new safety signals were identified. The rate of treatment discontinuation due to related AEs continued to be lower in the tebe arm (2% vs 5%). There were no treatment related deaths.

Conclusions: This is the longest OS follow-up in a randomized trial in mUM. Tebentafusp continues to provide long-term survival benefit in first line HLA-A*02:01+ pts, with estimated 3-yr OS rate of 27%, further solidifying tebentafusp as first line standard of care in this population.

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LBA51 Unraveling relatlimab (RELA)-specific biology using biomarker analyses in patients with advanced melanoma treated with nivolumab (NIVO)+RELA or NIVO alone in RELATIVITY-047

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Background: NIVO+RELA demonstrated significant progression-free survival (PFS) benefit vs NIVO in RELATIVITY-047 (NCT03470922). Exploratory biomarker analyses were conducted to elucidate mechanisms underlying NIVO+RELA activity and identify patients (pts) more likely to derive benefit from the combination.

Methods: Blood samples at baseline and 4 weeks post dose were analyzed by flow cytometry for pharmacodynamic changes in immune cell populations, eg lymphocyte activation gene-3 (LAG-3)- or programmed death-1 (PD-1)-expressing CD4+ and CD8+ T cells, natural killer (NK) cells. Baseline tissue samples were analyzed by immunohistochemistry (IHC) for major histocompatibility complex (MHC) class I/II expression and CD8 infiltration. HALO image analysis of LAG-3+ and LAG-3− CD8+ T cells was conducted by multiplex IHC. Association between biomarkers and treatment response was assessed.

Results: Multiple peripheral immune cell types significantly increased with NIVO+RELA vs NIVO (Table). Response to NIVO+RELA was associated with increased LAG-3+ CD4+ T cells at week 4, but on-treatment modulation of peripheral CD8+ T cells was not associated with NIVO+RELA efficacy. Baseline PD-1+ CD8+ and ICOS+ CD8+ T cell numbers were higher in responders to NIVO+RELA but not NIVO. In the tumor microenvironment (TME), higher baseline MHC-I and MHC-II were associated with improved efficacy in both arms. A PFS benefit with NIVO+RELA vs NIVO was observed in pts with low/medium TME CD8 infiltration; benefit of NIVO+RELA vs NIVO was seen for high TME CD8 infiltration only when LAG-3 was also expressed.

Table: LBA51 Select changes in peripheral blood 4 weeks post first dose suggesting RELA-specific activity

	NIVO		NIVO+RELA	
	%Δ[a]	*P*	%Δ[a]	*P*
sLAG-3+ CD4+FoxP3− (conventional)	0	NS	166.7	****
sLAG-3+ CD4+	16.7	NS	142.9	****
sLAG-3+ naïve CD4+	−9.10	NS	40.0	****
sLAG-3+ TE CD8+	12.5	NS	491.7	****
cLAG-3+ TE CD8+	5.9	NS	66.7	****
sLAG-3+ naïve CD8+	0	NS	60.0	****
CD38+ HLADR+ TE CD8+	7.4	NS	30.8	***
sLAG-3+ CD56+ CD16+ (int) NK	9.10	NS	117.4	****
sLAG-3+ NK	0	NS	50.0	****
sLAG-3+ CD56− CD16+ (mature) NK	10.5	NS	40.2	**

[a]Median.

c, cytoplasmic; int, intermediate; NS, nonsignificant; s, surface; TE, terminal effector.
*<0.05; **<0.01; ***<0.001; ****<0.0001 by Wilcoxon test.

Conclusions: TME analysis suggests RELA activity is particularly robust in tumors with lower CD8+ T-cell infiltration; peripheral data suggest CD4+ T-cell modulation may be key to its distinct mechanism of action. Further exploratory biomarker analyses are warranted to identify pts who may derive maximal benefit from NIVO+RELA.

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LBA52 A randomized phase Ib/II study of the selective small molecule AXL inhibitor bemcentinib in combination with either dabrafenib/trametinib or pembrolizumab in patients with metastatic melanoma

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Background: AXL has been linked with both a reduced response to PD-1 blockade and resistance to BRAF directed therapies in melanoma. Bemcentinib (Bem) is a first-in-class, orally bioavailable, highly selective AXL inhibitor. BGBIL006 (NCT02872259) is an open label Phase Ib/II clinical study designed to explore whether combinations with Bem are safe and improve overall response rate (ORR) relative to standard of care therapies in metastatic melanoma.

Methods: Six patients were enrolled in the dabrafenib/trametinib (D/T) + Bem dose finding part 1. In part 2, 68 patients received D/T or pembrolizumab (Pem) based on BRAF mutation status and tumour load and were randomized 2:1 to receive D/T or Pem with or without Bem. Upon progression, 17 BRAF+ patients switched from D/T to Pem or vice versa in part 3. Safety was assessed by NCI CTCAE v 4.03 and tumour responses were assessed using RECIST v1.1.

Results: Patients were enrolled between 2017 and 2022. At the interim database lock on August 21 2023, median follow time was 53 months (10-78). A daily dose of 200 mg Bem was well tolerated in combinations with Pem or D/T; 24% (18/73) of Grade $\geq$ 3 AEs were regarded as related to Bem. Most frequent Bem-related AEs were rash, diarrhoea, fatigue and increased transaminases. In the efficacy population (n=70), we did not observe significant differences in ORR, PFS or OS between standard treatments and the combinations with Bem. In pre-planned analyses of baseline biomarkers, we did not identify subgroups of patients with increased response to combinations with Bem compared to standard treatment. The following biomarkers predicted improved ORR to Pem; high CD8+ count ($p<0.01$), high FOXP3 count ($p<0.01$), high PD-L1 in TIL ($p=0.02$), high AXL expression in inflammatory cells ($p=0.04$). High FOXP3 count (above median) in tumours, compared with low, predicted increased PFS in Pem treated patients (HR 0.2, $p<0.01$).

Conclusions: Bem was well tolerated in combinations with Pem or D/T in melanoma, but did not increase responses or survival in the efficacy population nor in biomarker defined subgroups. High FOXP3 count in tumour infiltrating inflammatory cells was a strong predictive marker for response to Pem.

Clinical trial identification: NCT02872259.

Legal entity responsible for the study: Department of Oncology, Haukeland University Hospital, Bergen, Norway.

Funding: KlinBeForsk, Program for treatment research Norway. The Norwegian Cancer Society. The Norwegian Research Council. BerGenBio ASA provided the study drug bemcentinib free of charge and provided pharmacovigilance.

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Neuroendocrine tumours

LBA53 Alliance A021602: Phase III, double-blinded study of cabozantinib versus placebo for advanced neuroendocrine tumors (NET) after progression on prior therapy (CABINET)

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Background: VEGF pathway inhibitors are active against NET. We assessed the efficacy of cabozantinib (CABO), a multi-kinase inhibitor targeting VEGFR, c-MET, AXL, and RET, in previously treated patients (pts) with advanced extra-pancreatic NET (epNET) or pancreatic NET (pNET).

Methods: Pts with locally advanced or metastatic well or moderately differentiated epNET or pNET were randomized (2:1) in separately powered cohorts to receive CABO 60 mg daily vs placebo (PB). Eligibility included progression by RECIST within 12 months (mo) prior to registration, $\geq$ 1 prior therapy including everolimus, sunitinib or Lu-177 dotatate. Randomization was stratified by concurrent somatostatin analog (SSA) and primary site in epNET and by concurrent SSA and prior sunitinib in pNET. Primary endpoint: progression-free survival (PFS), with preplanned interim analyses for futility after 33% and 66% of events and alpha spending of 0.001 per interim analysis. Secondary endpoints: response rate (RR), overall survival (OS), safety.

Results: 197 pts (129 CABO, 68 PB) with epNET and 93 pts (62 CABO, 31 PB) with pNET were randomized between 10/2018-6/2023. For epNET: 55% midgut/unknown primary; 70% concurrent SSA. For pNET: 55% concurrent SSA; 28% prior sunitinib. Median follow-up: 12.6 mo for epNET; 10.1 mo for pNET. An independent DSMB requested and reviewed interim analyses for PFS based on local radiology assessment (2nd interim for epNET [109 events]; 1st for pNET [50 events]). Efficacy analyses in both cohorts noted significantly improved PFS for pts receiving CABO vs placebo (Table). No new safety signals were noted. DSMB voted to terminate accrual and unblind pts on 7/28/2023. RR, OS data will be presented.

Conclusions: CABO demonstrates statistically significant and clinically meaningful improvement in PFS in epNET and pNET. CABO may be a new treatment option for pts with previously treated, progressive NET.

Clinical trial identification: NCT03375320.

Legal entity responsible for the study: Alliance for Clinical Trials in Oncology.

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Table: LBA53

		epNET cohort		pNET cohort	
		CABO	PB	CABO	PB
PFS	Median PFS	8.2 mo	3.2 mo	13.7 mo	3.0 mo
	Stratified HR (95% CI)	0.41 (0.27 − 0.62)	Ref	0.25 (0.12 − 0.49)	Ref
	p-value	$p<0.0001$		$p<0.0001$	
Safety	# Evaluable for safety	124	63	60	30
	Grade 3+ adverse event	94 (75.8%)	27 (42.9%)	41 (68.3%)	13 (43.3%)
	Grade 3+ hypertension	34 (27.4%)	3 (4.8%)	16 (26.7%)	6 (20.0%)
	Grade 3+ hand-foot syndrome	4 (3.2%)	0 (0%)	6 (10%)	0 (0%)

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LBA54 Alkylating agent-based vs oxaliplatin-based chemotherapy in neuroendocrine tumours according to the O6-methylguanine-DNA methyltransferase (MGMT) status: A randomized phase II study (MGMT-NET) on behalf of the French Group of Endocrine Tumors (GTE) and ENDOCAN-RENATEN network

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Background: Alkylating agents (ALKY, temozolomide, darcabazine and streptozotocin), and oxaliplatin (Ox) are the main chemotherapies used for advanced neuroendocrine tumours (NETs). O^6-Methylguanine-DNA methyltransferase (MGMT) status, as proficient (p) or deficient (d), may be a predictor of response to ALKY.

Methods: MGMT-NET (NCT03217097) is a randomized phase 2 trial. Main inclusion criteria were confirmed advanced pancreatic, thoracic, or unknown (Uk) primary NETs with an indication for chemotherapy and tissue available. The primary aim was to demonstrate an improvement of the objective response rate (ORR) assessed by RECIST-v1.1 at 3 months from 15% in pMGMT NETs to 50% in dMGMT NETs with ALKY. Secondary aims were the best ORR, progression-free-survival (PFS) and overall survival (OS) of ALKY; oxaliplatin-based chemotherapy (Ox) serves as an internal-control. For the primary aim, dMGMT was defined using pyrosequencing if the *MGMT* was methylated (> 8%) and using immunochemistry if MGMT expression was lost (H-score<50) when pyrosequencing was not available.

Results: From Oct 2018 to Oct 2021, 105 patients (55 pancreas, 38 thoracic, 12 Uk) started either ALKY (n=62) or Ox (n=43, 1:1 for pMGMT or 2:1 for dMGMT NETs). Median age was 63 years (range 30−84), 57% males, NET were G1 (28%), G2 (60%) or G3 (10%). 102 had MGMT status available, 39/91 (43%) and 39/82 (48%) were dMGMT when assessed by pyrosequencing or immunohistochemistry, respectively. The primary aim was not met but best ORR, PFS and OS were greater in ALKY-dMGMT group (Table). Results will be also given by technique of MGMT evaluation during the meeting.

Conclusions: ALKY provides a higher response rate for dMGMT-NET while Ox chemotherapy may be a better option in pMGMT-NET.

Clinical trial identification: NCT03217097.

Legal entity responsible for the study: Hospices Civils de Lyon.

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New diagnostic tools

LBA55 An ultra-sensitive and specific ctDNA assay provides novel pre-operative disease stratification in early stage lung cancer

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Background: Circulating tumour DNA (ctDNA) detection has significant promise to inform patient care to predict clinical risk in early-stage tumours, optimise personalised adjuvant treatment regimens, and monitor for relapse in the minimal residual disease (MRD) setting. However, clinical applications, especially in low-shedding tumours such as lung adenocarcinomas (LUADs), are constrained by the limited sensitivity of clinically validated ctDNA detection approaches.

Methods: We developed NeXT Personal, a whole genome based, tumour-informed platform for ultra-sensitive ctDNA detection, and analytically validated detection thresholds consistently within 1-3 parts per million (PPM) of ctDNA with >99.95% specificity. We analysed pre-operative plasma samples from an interim cohort of 171 patients with early stage lung cancer from the TRACERx study.

Results: ctDNA was detected pre-operatively in 81% of patients with lung adenocarcinomas (LUADs), including 52%, 88%, and 100% of those with pathological TNM (pTNM) stage I, II, and III disease, respectively; and in 100% of non-LUAD patients.

Table: LBA54

	Proficient MGMT		Deficient MGMT	
	Oxaliplatin-based	**ALK-based**	**ALK-based**	**Oxaliplatin-based**
Number of patients	23	33	27	19
Pancreas	8	12	18	14
Thoracic/unknown	11/4	16/5	7/2	4/1
ORR at 3 months (central review), n (%)	6 (26)	**4 (12)**	**8 (31)**	6 (32)
Best ORR, n (%)	9 (39)	**6 (18)**	**15 (56)**	4 (21)
Median PFS in months (95%CI)	12.2 (11.7-12.7)	**11.3 (9.4-13.2)**	**14.6 (7.1-22.1)**	12.9 (11.8-14.0)
Median OS in months (95%CI)	34.3 (21.9-46.7)	50.2 (not defined)	Not reached	48.8 (21.0-76.6)

Elevated pre-operative ctDNA levels correlated with poor overall survival (OS; ctDNA low HR=9.1; 95% CI:1·1-72.5; ctDNA high HR=23.6, 95% CI: 2·7-206.0) and relapse-free survival (RFS) in LUADs independent of stage (including in stage I patients). Importantly, this remained true among ctDNA-positive samples when ctDNA level was treated as a continuous variable (HR=1.5; 95% CI: 1.1-2.1), whilst elevated ctDNA levels also correlated with reduced RFS in non-LUADs (HR= 2.1, 95% CI= 1·0 to 4.4), independent of disease stage. Critically, LUAD patients with ctDNA present at below 80 PPM (the 95% limit of detection for our recently published ctDNA detection approach in TRACERx) experienced reduced OS compared to those in which ctDNA was not detected (p=0.002, HR=12.2).

Conclusions: Our ultra-sensitive approach demonstrates superior analytic performance and prognostic prediction compared to other assays previously clinically validated in non-small cell lung cancer and provides an advanced stratification tool to guide adjuvant therapy in early-stage ctDNA-positive disease at high risk of relapse.

Clinical trial identification: NCT01888601.

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NSCLC, early stage

LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC

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Background: Neoadjuvant (neoadj) NIVO + chemo provides efficacy benefit vs chemo in patients (pts) with resectable NSCLC. However, the efficacy of perioperative NIVO + chemo has not been evaluated in phase 3 studies. Here, we report prespecified interim analysis results from CheckMate 77T, a randomized, double-blind, phase 3 study evaluating neoadj NIVO + chemo followed by surgery and adjuvant (adj) NIVO (NIVO + chemo/NIVO) compared with neoadj placebo + chemo followed by surgery and adj placebo (chemo/PBO) in resectable stage II–IIIB NSCLC.

Methods: Adults with untreated resectable stage IIA (>4 cm)–IIIB (N2) NSCLC (AJCC v8), *EGFR/ALK* wild-type, and ECOG PS ≤1 were stratified by tumor histology, PD-L1 expression, and disease stage, and randomized 1:1 to NIVO 360 mg Q3W + platinum-doublet chemo (4 cycles) followed by surgery and adj NIVO 480 mg Q4W (1 y), or placebo Q3W + platinum-doublet chemo (4 cycles) followed by surgery and adj placebo Q4W (1 y). Primary endpoint was EFS (RECIST v1.1 per BICR). Secondary endpoints were pCR and MPR (both per BIPR), OS, and safety.

Results: Baseline characteristics were balanced between arms (NIVO + chemo/NIVO, n = 229; chemo/PBO, n = 232). At a minimum follow-up of 15.7 mo, NIVO + chemo/NIVO significantly improved EFS vs chemo/PBO (median [95% CI], not reached [28.9 mo–not reached] vs 18.4 mo [13.6–28.1]; HR [97.36% CI], 0.58 [0.42–0.81]; P = 0.00025). NIVO + chemo/NIVO also improved pCR rates (25.3% vs 4.7%; odds ratio, 6.64 [95% CI, 3.40–12.97]) and MPR rates (35.4% vs 12.1%; odds ratio: 4.01 [2.48–6.49]) vs chemo/PBO. Definitive surgery rates were 78% vs 77% in the NIVO + chemo/NIVO vs chemo/PBO arms; of these, 89% vs 90% were R0 resections, respectively. Grade 3–4 treatment-related AEs were 32% and 25% in the NIVO + chemo/NIVO and chemo/PBO arms; surgery-related AEs were 12% and 12%, respectively.

Conclusions: CheckMate 77T met its primary endpoint with a statistically significant and clinically meaningful improvement in EFS with neoadj NIVO + chemo followed by surgery and adj NIVO vs chemo/PBO in pts with resectable NSCLC. No new safety signals were noted with the NIVO + chemo/NIVO regimen.

Clinical trial identification: NCT04025879.

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LBA2 ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC)

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Background: For patients (pts) with resected, stage IB–IIIA, *ALK*+ NSCLC, the recommended treatment after surgery is platinum-based chemotherapy (CT), which is associated with modest improvements in survival. In advanced *ALK*+ NSCLC, alectinib is a preferred first-line treatment. Here, we report data from the prespecified interim analysis of ALINA (NCT03456076), a global, phase III, open-label, randomised trial assessing the efficacy and safety of adjuvant alectinib compared with CT in pts with completely resected *ALK*+ NSCLC.

Methods: Eligible pts were ≥18 years old, had an ECOG PS of 0/1 and completely resected, stage IB (≥4 cm)–IIIA, *ALK*+ NSCLC (per UICC/AJCC 7th edition). Pts were randomised 1:1 to receive either oral alectinib 600 mg twice daily, or up to four 21-day cycles of IV platinum-based CT. Randomisation was stratified by stage (IB vs II vs IIIA) and race (Asian vs non-Asian). Alectinib was given for up to 24 months or until disease recurrence, unacceptable toxicity, or withdrawal of consent. Primary endpoint: investigator-assessed disease-free survival (DFS), tested hierarchically first in the stage II–IIIA and then in the ITT population (stage IB–IIIA). Other endpoints included: CNS-DFS, overall survival (OS), safety.

Results: A total of 257 pts were randomised to receive alectinib (n=130) or CT (n=127); baseline characteristics were overall well balanced between arms. At data cutoff (26 June 2023), median follow up was 27.8 months. A significant DFS benefit was observed with alectinib vs CT in both the stage II–IIIA (HR 0.24; 95% CI: 0.13–0.45) and ITT populations (HR 0.24; 95% CI: 0.13–0.43; Table). A clinically meaningful CNS-DFS benefit was observed in the ITT population (HR 0.22; 95% CI 0.08–0.58). OS data were immature. No unexpected safety findings were observed.

Conclusions: Alectinib is the first ALK inhibitor to significantly improve DFS compared with CT and provides an effective new treatment strategy for pts with resected *ALK*+ NSCLC.

Clinical trial identification: NCT03456076.

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Table: LBA2

Efficacy	Stage II–IIIA Alectinib (n=116)	Stage II–IIIA CT (n=115)	ITT (Stage IB–IIIA) Alectinib (n=130)	ITT (Stage IB–IIIA) CT (n=127)
DFS events, n (%)	14 (12.1)	45 (39.1)	15 (11.5)	50 (39.4)
Median DFS, months (95% CI)	NE	44.4 (27.8–NE)	NE	41.3 (28.5–NE)
Stratified HR (95% CI)	0.24 (0.13–0.45)		0.24 (0.13–0.43)	
p value	<0.0001		<0.0001	
24-month DFS rate, %	93.8	63.0	93.6	63.7
36-month DFS rate, %	88.3	53.3	88.7	54.0

Safety	Safety population Alectinib (n=128)	CT (n=120)
Grade 3–4 AEs, n (%)*	38 (29.7)	37 (30.8)
Serious AEs, n (%)	17 (13.3)	10 (8.3)
Serious treatment-related AEs, n (%)	2 (1.6)	8 (6.7)
AEs leading to treatment withdrawal, n (%)	7 (5.5)	15 (12.5)

AEs, adverse events; NE, not estimable. *No Grade 5 AEs in either treatment arm

NSCLC, early stage

LBA56 Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC)

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Background: At the protocol-specified first interim analysis of the phase 3 KEYNOTE-671 study of resectable early-stage NSCLC (NCT03425643), neoadjuvant pembrolizumab (pembro) + chemotherapy (chemo) followed by resection and adjuvant pembro significantly improved EFS, mPR, and pCR with an expected safety profile vs neoadjuvant chemo and resection alone. We present results of the protocol-specified second interim analysis of KEYNOTE-671.

Methods: Patients (pts) with resectable stage II, IIIA, or IIIB (N2) NSCLC per AJCC v8 were randomized 1:1 to pembro 200 mg (n = 397) or placebo (n = 400) Q3W. Pts were to receive 4 cycles of neoadjuvant pembro or placebo plus cisplatin-based chemo and ≤13 cycles of adjuvant pembro or placebo. Dual primary endpoints are EFS (time from randomization to local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause) and OS.

Results: Median time from randomization to the 10 July 2023 data cutoff was 36.6 mo (range, 18.8-62.0). With 254 (31.9%) deaths, OS was significantly improved in the pembro arm (HR 0.72 [95% CI 0.56-0.93]; $P = 0.00517$). Median OS was not reached (NR) (95% CI NR-NR) in the pembro arm vs 52.4 mo (95% CI 45.7-NR) in the placebo arm; 36-mo OS rates were 71.3% vs 64.0%. EFS continued to be improved in the pembro arm (HR 0.59 [95% CI 0.48-0.72]; median [95% CI] 47.2 mo [32.9-NR] vs 18.3 mo [14.8-22.1]; 36-mo rate, 54.3% vs 35.4%). Treatment-related AEs were grade ≥3 in 45.2% of pts in the pembro arm vs 37.8% in the placebo arm, led to discontinuation of all treatment in 20.2% vs 9.3%, and led to death in 1.0% vs 0.8% (no new treatment-related deaths since the first interim analysis).

Conclusions: Neoadjuvant pembro + chemo followed by resection and adjuvant pembro provided a statistically significant and clinically important improvement in OS compared with neoadjuvant chemo and resection alone in pts with resectable stage II, IIIA, or IIIB (N2) NSCLC. The OS gains seen in KEYNOTE-671 with the absence of new safety signals establish the perioperative pembro regimen as a new standard of care for resectable early-stage NSCLC.

Clinical trial identification: NCT03425643, first posted February 7, 2018.

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LBA57 Neoadjuvant nivolumab (N) + chemotherapy (C) in the phase III CheckMate 816 study: 3-y results by tumor PD-L1 expression

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Background: In CheckMate 816, neoadjuvant N + C vs C significantly improved the primary endpoints of event-free survival (EFS) and pathological complete response (pCR) in patients with resectable NSCLC; 3-y EFS benefit with N + C vs C was also demonstrated. Here, we report clinical outcomes by baseline tumor PD-L1 expression.

Methods: Adults with stage IB ($\geq$ 4 cm)—IIIA (AJCC v7) resectable NSCLC were randomized 1:1 to receive N 360 mg + C Q3W or C Q3W for 3 cycles. Exploratory analyses included EFS, overall survival (OS), pCR, major pathological response (MPR), surgical outcomes, and safety in patients with tumor PD-L1 $\geq$ 1% or $<$ 1%.

Results: In patients with tumor PD-L1 $\geq$ 1% (N + C, 89; C, 89) and PD-L1 $<$ 1% (78; 77), baseline characteristics were generally similar between PD-L1 subgroups and treatment arms. A higher proportion of patients with tumor PD-L1 $<$ 1% had ECOG PS 1 (both arms). At database lock (14 Oct 2022; median follow-up, 41.4 mo), N + C showed improvement vs C across all efficacy endpoints in patients with tumor PD-L1 $\geq$ 1% (Table); 3-y EFS and OS rates were 72% vs 47% and 85% vs 66%, respectively. Similar efficacy benefit was seen in patients with tumor PD-L1 $\geq$ 1% and stage II—IIIA NSCLC (data to be presented). In patients with tumor PD-L1 $<$ 1%, EFS, OS, pCR, and MPR also favored N + C vs C (Table); 3-y EFS and OS rates were 42% vs 39% and 71% vs 60%, respectively. Definitive surgery rates with N + C vs C were 84% vs 74% in patients with tumor PD-L1 $\geq$ 1% and 81% vs 77% in patients with tumor PD-L1 $<$ 1%; R0 resection rates were 91% vs 82% and 79% vs 76%, respectively. Grade 3—4 treatment-related AE rates with N + C vs C were 34% vs 44% in patients with tumor PD-L1 $\geq$ 1% and 36% vs 34% in patients with tumor PD-L1 $<$ 1%.

Conclusions: These exploratory analyses from CheckMate 816 reinforce the clinical benefit and manageable safety profile of neoadjuvant N + C in patients with resectable NSCLC regardless of tumor PD-L1 expression.

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Table: LBA57 Efficacy outcomes by tumor PD-L1 expression

	Tumor PD-L1 ≥ 1%		Tumor PD-L1 < 1%	
	N + C (n = 89)	C (n = 89)	N + C (n = 78)	C (n = 77)
EFS				
Median, mo (95% CI)	NR (44.4—NR)	26.7 (13.4—NR)	26.4 (14.8—NR)	20.8 (13.9—42.1)
HR (95% CI)	0.46 (0.28—0.77)		0.87 (0.57—1.35)	
OS				
Median, mo (95% CI)	NR (NR—NR)	NR (45.1—NR)	NR (48.6—NR)	NR (31.2—NR)
HR (95% CI)	0.37 (0.20—0.71)		0.81 (0.48—1.36)	
pCR rate, % (95% CI)	32.6 (23.0—43.3)	2.2 (0.3—7.9)	16.7 (9.2—26.8)	2.6 (0.3—9.1)
MPR rate, % (95% CI)	44.9 (34.4—55.9)	5.6 (1.8—12.6)	29.5 (19.7—40.9)	14.3 (7.4—24.1)

NR, not reached.

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LBA58 Pathological response to neoadjuvant tislelizumab (TIS) plus platinum-doublet (PtDb) chemotherapy (CT) in resectable stage II-IIIA NSCLC patients (pts) in the phase III (Ph3) RATIONALE-315 trial

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Background: Neoadjuvant (NA) CT with anti-PD-(L)1 mAb has shown promising pathologic response rates (ie, major pathological response [MPR], pathological complete response [pCR]) in pts with resectable NSCLC. The Ph3 RATIONALE-315 study (NCT04379635) investigated the efficacy & safety of NA TIS (anti-PD-1 mAb) or placebo (PBO) + CT, then adj TIS or PBO, in pts with resectable stage II-IIIA NSCLC.

Methods: This study enrolled pts with treatment (tx)-naïve, resectable, confirmed squamous (sq) or non-sq (nsq) stage II-IIIA NSCLC who were eligible for PtDb CT, with ECOG PS ≤1 and no known *EGFR* mutation (nsq) or *ALK* gene translocation (sq & nsq). Pts stratified by histology, disease stage, and PD-L1 expression (≥1% vs <1%) were randomized (1:1) to 3-4 cycles of TIS 200 mg IV Q3W or PBO, plus PtDb CT, followed by surgery + 8 cycles of adj TIS 400 mg IV Q6W or PBO. Primary endpoints: MPR rate after completion of NA tx + EFS per RECIST v1.1 by blinded independent review committee (IRC). Key secondary endpoint: pCR rate.

Results: As of 20 Feb 2023 (median follow-up: 16.8 mo), 453 pts (TIS + CT, n=226; CT, n=227) were randomized to the intention-to-treat (ITT) population and had similar baseline characteristics. Of 452 (99.8%; n=226 both arms) pts treated in the NA phase, 421 (92.9%) completed NA tx (TIS + CT, n=211 [93.4%]; CT, n=210 [92.5%]); 90 (19.9%) did not undergo surgery (TIS + CT, n=36 [15.9%]; CT, n=54 [23.8%]). Efficacy & safety data from the NA phase are summarized in the table; MPR & pCR rates were significantly improved with TIS + CT vs CT ($P<0.0001$). TIS + CT did not impact the feasibility of surgery.

Table: LBA58 Efficacy and safety summary

	TIS+CT	CT
	ITT Analysis Set n=226	n=227
MPR, % (95% CI)[a]	56.2 (49.5-62.8)	15.0 (10.6-20.3)
Difference, % (95% CI); *P* value[b]	41.1 (33.2-49.1); *P*<0.0001	
OR (95% CI)	7.5 (4.8-11.8)	
pCR, % (95% CI)	40.7 (34.2-47.4)	5.7 (3.1-9.6)
Difference, % (95% CI); *P* value[b]	35.0 (27.9-42.1); *P*<0.0001	
OR (95% CI)	11.5 (6.2-21.5)	
TEAEs	**Safety Analysis Set**[c]	
	n=226 n (%)	n=226
Pts with ≥1 TEAE	224 (99.1)	225 (99.6)
Grade ≥3	157 (69.5)	148 (65.5)
Serious	25 (11.1)	24 (10.6)

[a]Assessed by IRC.
[b]1-sided.
[c]Randomized pts who received ≥1 dose of any study drug.
OR, odds ratio; TEAE, treatment-emergent adverse event.

Conclusions: TIS + CT showed clinically meaningful and statistically significant improvements in MPR and pCR rates vs PBO + CT as NA tx. The safety profile of TIS + CT was consistent with known risks of each tx and was manageable in pts with resectable stage II-IIIA NSCLC, further supporting this tx combination for these pts.

Clinical trial identification: NCT04379635.

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LBA59 Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial

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Background: In AEGEAN, perioperative durvalumab (D) + neoadj chemotherapy (CT) significantly improved pathological complete response (pCR), major pathological response (MPR), and event-free survival, with manageable safety, vs neoadj CT alone among pts with resectable (R) NSCLC (modified ITT [mITT] population). We report exploratory analyses of ctDNA, including association of ctDNA clearance (CL) with pCR or MPR.

Methods: AEGEAN is a double-blind placebo (PBO)-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II—IIIB[N2]; AJCC 8th ed) were randomised (1:1) to receive neoadj CT + D or PBO IV (Q3W, 4 cycles) prior to surgery (Sx), followed by D or PBO IV (Q4W, 12 cycles), respectively, after Sx. Plasma samples were collected at protocol-specified timepoints, including prior to each neoadj Tx cycle and before Sx. Analysis was performed using patient-specific tumour-informed assays, following identification of mutations in diagnostic tissue by whole exome sequencing. ctDNA variant allele fractions (VAFs) and dynamics were assessed during neoadj Tx, including ctDNA CL and association with pCR or MPR.

Results: ctDNA was evaluated in 831 samples from 186 mITT population pts (D arm, n=90; PBO arm, n=96) in the interim pCR analysis cohort. Baseline characteristics of ctDNA-evaluable pts were generally similar to those in the overall mITT population. In both Tx arms, decreases in median VAFs were observed as early as C2D1 (D arm, 97% decrease; PBO arm, 94% decrease) and, by C3D1, were significantly lower in pts with pCR/MPR vs pts with non-pCR/MPR (P≤0.003). After each cycle of neoadj Tx, higher ctDNA CL rates were observed in the D vs PBO arm (with 66% [95% CI, 54—77] vs 41% [95% CI, 30—52] at pre-Sx). Pts achieving ctDNA CL vs no CL at C2D1 had higher rates of pCR (D arm: 50.0% vs 15.1%; PBO arm: 14.3% vs 3.1%) and MPR (D arm: 66.7% vs 35.8%; PBO arm: 38.1% vs 12.5%). Among pts who were ctDNA+ at baseline, all pts achieving pCR and >90% achieving MPR had ctDNA CL by C4D1.

Conclusions: Neoadj Tx with D + CT resulted in greater ctDNA CL than PBO + CT. Earlier ctDNA CL was associated with higher likelihood of pCR and MPR, highlighting ctDNA CL as a potential early-response biomarker.

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NSCLC, locally advanced

LBA60 Stereotactic body radiation therapy with sequential immunochemotherapy as neoadjuvant therapy in resectable non-small cell lung cancer

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Background: Phase 3 trials of neoadjuvant immunochemotherapy in patients with resectable non-small-cell lung cancer (NSCLC) have reported major pathological response (MPR) rates ranging from 30.2% to 48.5%. Stereotactic body radiotherapy (SBRT) may have an immunomodulating effect and augment the effect of preoperative immune checkpoint blockade monotherapy. In this single-arm phase 2 trial, we investigated the use of SBRT plus immunochemotherapy in the neoadjuvant setting for patients with resectable NSCLCs.

Methods: Eligiblepatients with resectable NSCLCs (stage II-IIIB as per the 8th edition of the AJCC) without known EGFR/ALK alterations received SBRT (8Gy x 3 fractions) to the primary tumor followed by two cycles of PD-1 inhibitor tislelizumab plus platinum-doublet chemotherapy of each 21-day cycle. Patients without systemic disease progression proceeded to resection 4-6 weeks after treatment. The primary endpoint was MPR defined as 10% or fewer viable tumors in the primary tumor and lymph nodes. The sample size was determined based on Simon's optimal two-stage design, considering a threshold MPR rate of 30% and an expected MPR rate of 50%. If there were 19 or more MPRs in 46 patients, the null hypothesis can be rejected.

Results: Between May 2022, and June 2023, 46 patients were enrolled, with 38 (82.6%) having stage III diseases. Two surgeries were canceled due to disease progression and G5 neutropenia, respectively. Forty-four (95.7%) patients underwent R0 resection and none of them required pneumonectomy. The study met the primary endpoint. The MPR rate was 76.1% (35/46, 95% CI: 61.2-87.4), and pathological complete response rate was 52.2% (24/46, 95% CI: 36.9-67.1). Nodal clearance (ypN0) was found in 35 of 46 cN1/2 cases (76.1%). Grade 3 or greater adverse events related to neoadjuvant treatment occurred in 12 patients (26.1%), the most frequent being neutropenia (13.0% [n=6]), pneumonia (4.3% [n=2]), and anemia (4.3% [n=2]). Two patients had delayed operations due to G3 pneumonia (77 and 134 days after the last cycle of immunochemotherapy). No deaths within 30 days of surgery were reported.

Conclusions: Neoadjuvant SBRT followed by immunochemotherapy is well tolerated, feasible, and yielded a high MPR rate.

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LBA61 Durvalumab (durva) after sequential chemoradiotherapy (CRT) in patients (pts) with unresectable stage III NSCLC: Final analysis from PACIFIC-6

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Background: In the phase 3, placebo-controlled PACIFIC trial, durva after concurrent CRT (cCRT) significantly improved survival in pts with unresectable Stage III NSCLC, with manageable safety. As many pts are considered unsuitable for cCRT, the phase 2 PACIFIC-6 trial (NCT03693300) assessed safety and efficacy with durva after sequential CRT (sCRT); interim data indicated this approach had a similar safety profile to that with durva after cCRT in PACIFIC with encouraging preliminary efficacy. We report the final analysis from PACIFIC-6.

Methods: Pts with unresectable Stage III NSCLC, ECOG performance status (PS) $\leq$2, and no progression after platinum-based sCRT were enrolled to receive durva 1500 mg IV, every 4 wk for up to 24 mo, or until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint (reported previously) was the incidence of grade 3/4 possibly related AEs (PRAEs) occurring within 6 mo. Secondary endpoints included OS and PFS (investigator-assessed; RECIST v1.1), analysed by Kaplan–Meier method.

Results: As of Mar 20, 2023, 117 pts were enrolled. Most had PS 1/2 (59.8%; PS 1, n=67; PS 2, n=3), were aged $\geq$65 yr (65.8%; age range: 39–85 yr), and had stage IIIB/IIIC NSCLC (63.2%). Nearly all had past/present comorbidities (98.3%), mostly vascular (59.0%), respiratory (53.0%) and metabolic (51.3%) disorders. Median treatment duration was 41.0 wk (range: 4–108). Overall, 4.3% (95% CI: 1.4–9.7) of pts had grade 3/4 PRAEs within 6 mo, and 6.0% had grade 3/4 PRAEs during the entire study period (1 pt had a PRAE with outcome of death). Pneumonitis was the most frequently reported PRAE of any grade (17.1%) and grade 3/4 (1.7%). 27.4% of pts discontinued durva due to AEs of any cause. Median duration of follow-up among pts censored for OS was 32.6 mo (range: 4.4–45.7). Median OS was 39.0 mo (95% CI: 30.6–not calculable), the 3-yr OS rate was 56.5% (95% CI: 46.4–65.5), and median PFS was 13.1 mo (95% CI: 7.4–19.9).

Conclusions: Durva after sCRT maintained a similar safety profile to that seen with durva after cCRT in PACIFIC and demonstrated encouraging efficacy in a frailer population, supporting use of this approach for pts who are considered unsuitable for cCRT.

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LBA62 Durvalumab after radiotherapy (RT) in patients with unresectable stage III NSCLC ineligible for chemotherapy (CT): Primary results from the DUART study

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Background: Consolidation durvalumab following chemoradiotherapy (CRT) is SOC for patients (pts) with unresectable Stage III NSCLC. Many pts, however, are ineligible for CT and mainly receive RT alone with unsatisfactory results. We report the primary safety and secondary efficacy analyses of DUART (NCT04249362), a phase 2, open-label international study.

Methods: Pts with unresectable Stage III NSCLC deemed ineligible for CT by a multidisciplinary team with no progression after RT were enrolled into two parallel cohorts per prior RT dose according to local SOC (A: standard RT, 60 Gy ± 10% or bioequivalent dose [BED]; B: palliative RT, 40 to <54 Gy or BED). Pts received durvalumab 1500 mg IV Q4W for 12 mo or until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was safety/tolerability, defined by the incidence of grade 3/4 possibly-related adverse events (PRAEs) occurring within 6 mo of the first dose.

Results: 102 pts received durvalumab. Median total treatment (Tx) duration was 30.6 wk; Tx is ongoing in 21 pts. Median age was 79.0 yr; 71.6% were male, and 18.8%/73.3%/7.9% had ECOG performance status (PS) 0/1/2. Overall, 9.8% (A: 11.9%; B: 7.0%) had grade 3/4 PRAEs within 6 mo of the first dose (primary endpoint). Median PFS was 8.0 mo and confirmed ORR was 26.5%. The most common PRAE leading to discontinuation was pneumonitis, in 3.9% of pts. 7 pts (A: 5; B: 2) had fatal AEs, including 1 PRAE (A: pneumonitis). Key clinical outcomes are summarized in the table. Additional results, including overall survival, will be presented.

Conclusions: We demonstrate in a prospective trial that pts ineligible for CT, including pts with PS 2, can be safely treated with a combination of thoracic RT followed by immunotherapy. Preliminary efficacy outcomes were encouraging (numerically better in the 60 Gy cohort), making this combination a novel option for this common subset of more fragile pts.

Clinical trial identification: NCT04249362 (release date: January 30, 2020).

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NSCLC, metastatic

LBA4 Randomized phase III study of first-line selpercatinib versus chemotherapy and pembrolizumab in RET fusion-positive NSCLC

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Background: Selpercatinib is a highly selective and potent, brain penetrant RET inhibitor, approved for treatment of advanced *RET* fusion-positive (*RET+*) NSCLC. Selpercatinib had not previously been evaluated in a randomized trial.

Methods: LIBRETTO-431 (NCT04194944) is a randomized, open-label, phase 3 trial comparing first-line selpercatinib vs chemotherapy (cisplatin/carboplatin + pemetrexed) +/- pembrolizumab. The primary endpoint of blinded independent central review (BICR)-assessed PFS was tested first in patients stratified by investigator's

Table: LBA62

	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Any PRAEs, %[a] Gr 3/4 Gr 3/4 (within 6 mo)	67.8 15.3 11.9	48.8 7.0 7.0	59.8 11.8 9.8
PFS Events (%) Median (95% CI), mo[b] 12-mo PFS rate (95% CI), %[b]	26 (44.1) 9.0 (5.6—NC) 40.2 (23.6—56.3)	25 (58.1) 7.6 (5.3—11.0) 29.3 (13.8—46.7)	51 (50.0) 8.0 (7.0—9.7) 34.8 (23.0—46.9)
Confirmed ORR (95% CI),[c] %	28.8 (17.8—42.1)	23.3 (11.8—38.6)	26.5 (18.2—36.1)

Data cutoff: Mar 30, 2023 (median [range] follow-up, 7.4 mo [0.0—24.9] in all censored pts). [a]Investigator-assessed.
[b]Estimated by Kaplan—Meier method. [c]CIs calculated by Clopper-Pearson exact method.
NC, not calculable; ORR, objective response rate; PFS, progression-free survival.

intent to treat with pembrolizumab, if assigned to the control arm, (ITT-pembro) and then in the ITT population. The pre-planned interim efficacy analysis by BICR occurred after 98 PFS events in the ITT-pembro population. Crossover to selpercatinib was allowed following BICR progression on the control arm.

Results: A total of 261 patients were enrolled from 23 countries. Baseline characteristics were balanced across study arms. At a median follow up of approximately 19 months, selpercatinib demonstrated superior PFS vs control in the ITT-pembro (HR: 0.465, 95% CI: 0.309, 0.699; p-value: 0.0002) and ITT populations (HR: 0.482, 95% CI: 0.331, 0.700; p-value: 0.0001). In the ITT-pembro population, median PFS was 24.8 months (95% CI: 16.9, NE) with selpercatinib vs 11.2 months (95% CI: 8.8, 16.8) with control. Clinically meaningful improvements in ORR, DOR, and intracranial response were also observed with selpercatinib vs control. Time to CNS progression was longer with selpercatinib than control (cause-specific HR 0.26; 95% CI: 0.11, 0.59; p=0.0006). Adverse events observed with selpercatinib and the control arm were generally consistent with those previously reported.

Conclusions: Selpercatinib achieved a statistically significant and clinically meaningful improvement in PFS compared to chemotherapy + pembrolizumab in advanced *RET+* NSCLC. LIBRETTO-431 is the first randomized study to demonstrate superior PFS with a targeted therapy vs chemotherapy + a checkpoint inhibitor in a biomarker selected patient population. These data support comprehensive genomic testing at diagnosis and treatment with first-line selpercatinib in patients with advanced *RET+* NSCLC.

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LBA5 Amivantamab plus chemotherapy vs chemotherapy as first-line treatment in EGFR Exon 20 insertion-mutated advanced non-small cell lung cancer (NSCLC): Primary results from PAPILLON, a randomized phase III global study

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Background: Amivantamab (ami) is an EGFR-MET bispecific antibody with immune cell—directing activity. Ami combined with carboplatin/pemetrexed (ami-chemo) demonstrated safety and antitumor activity in the phase 1 CHRYSALIS study. PAPILLON (NCT04538664) evaluated ami-chemo vs chemo in first-line *EGFR* Ex20ins advanced NSCLC.

Methods: Treatment-naïve pts were randomized 1:1 to ami-chemo or chemo. The primary endpoint was progression-free survival (PFS) by blinded independent central review. Secondary endpoints included objective response rate (ORR), PFS after first subsequent therapy (PFS2), overall survival (OS), and safety. Crossover to ami monotherapy was allowed for the chemo arm upon progression.

Results: Overall, 308 pts were randomized (ami-chemo, 153; chemo, 155); median age was 61/62 years, 56/60% female, 64/59% Asian, and 23/23% with history of brain metastases for ami-chemo/chemo, respectively. At median follow-up of 14.9 months, the median PFS was 11.4 months (95% CI, 9.8—13.7) for ami-chemo vs 6.7 months (95% CI, 5.6—7.3) for chemo (hazard ratio [HR], 0.40; 95% CI, 0.30—0.53; $P<0.001$). The 18-month PFS rate was 31% for ami-chemo vs 3% for chemo. PFS benefit of ami-chemo was consistent across subgroups. ORR was 73% (95% CI, 65—80) for ami-chemo vs 47% (95% CI, 39—56) for chemo (odds ratio, 2.97; 95% CI, 1.84—4.79; $P<0.001$). Median PFS2 was not estimable for ami-chemo vs 17.2 months for chemo (HR, 0.49; 95% CI, 0.32—0.76; $P=0.001$). Interim OS analysis (33% maturity) showed a favorable trend for ami-chemo vs chemo (HR, 0.67; 95% CI, 0.42—1.09; $P=0.106$), despite 66%, of chemo-randomized pts whose disease had progressed, receiving second-line ami. The most common TEAEs ($\geq$40%) for ami-chemo were neutropenia, paronychia, rash, anemia, infusion-related reactions, and hypoalbuminemia; no new safety signals. Discontinuation of ami due to treatment-related AEs was 7%.

Conclusions: Among pts with *EGFR* Ex20ins advanced NSCLC, ami-chemo achieved superior PFS vs chemo. Safety profile was consistent with that of each individual agent. PAPILLON establishes ami-chemo as the new first-line standard of care in *EGFR* Ex20ins advanced NSCLC.

Clinical trial identification: NCT04538664.

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LBA12 Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase III study TROPION-Lung01

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Background: Dato-DXd is a novel TROP2-directed antibody-drug conjugate under clinical investigation in multiple tumor types. This is the first report of TROPION-Lung01 (NCT04656652), a randomized, global, open-label, phase 3 study of Dato-DXd vs docetaxel (DTX) in pretreated patients (pts) with adv/met NSCLC with or without actionable genomic alterations (AGAs).

Methods: Pts were randomized 1:1 to Dato-DXd 6 mg/kg or DTX 75 mg/m^2 Q3W. Dual primary endpoints were progression-free survival (PFS; by blinded independent central review [BICR]) and overall survival (OS). Secondary endpoints included objective response rate (ORR), duration of response (DOR), and safety.

Results: 604 pts were included in the full analysis set (FAS); 43.1% had received $\geq$2 prior lines of systemic therapy. Median age was 64 y (range, 24-88). PFS was significantly improved with Dato-DXd over DTX in the FAS (HR, 0.75; 95% CI, 0.62-0.91; P=.004; median, 4.4 vs 3.7 mo). Confirmed ORRs were 26.4% (Dato-DXd) and 12.8% (DTX), with median DORs of 7.1 and 5.6 mo. Longer median PFS was observed in the prespecified non-squamous histology subgroup (NSQ; 5.6 vs 3.7 mo). Median treatment duration was 4.2 mo (range, 0.7-18.3 mo) for Dato-DXd and 2.8 mo (range, 0.7-18.9 mo) for DTX. The most common treatment-emergent adverse events (TEAEs) seen with Dato-DXd were stomatitis (49.2%, mostly grade [gr] 1/2) and nausea (37%). Adjudicated drug-related interstitial lung disease gr $\geq$3 occurred in 3.4% of pts with Dato-DXd vs 1.4% with DTX. Fewer drug-related gr $\geq$3 TEAEs and AEs leading to dose reduction or discontinuation were seen with Dato-DXd vs DTX.

Conclusions: PFS was significantly improved with Dato-DXd over DTX in pts with pretreated adv/met NSCLC. NSQ patients appeared to derive the most benefit. Dato-DXd was well tolerated, with a manageable safety profile. The trial is continuing until the final OS analysis. Drs. M-J. Ahn and E. Lisberg have equally contributed to the study.

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Table: LBA12

Efficacy	Dato-DXd N=299	DTX N=305	HR (95% CI)
Median PFS[a] (95% CI), mo	4.4 (4.2-5.6)	3.7 (2.9-4.2)	0.75 (0.62-0.91); *P*=.004[b]
FAS	5.6 (4.4-7.0)	3.7 (2.9-4.2)	0.63 (0.51-0.78)
NSQ; *n=229/232*[c]			
Confirmed ORR[a] (95% CI), %	26.4 (21.5-31.8)	12.8 (9.3-17.1)	–
Median DOR (95% CI), mo	7.1 (5.6-10.9)	5.6 (5.4-8.1)	–
Safety, n (%)	**Dato-DXd n=297[d]**	**DTX n=290[d]**	–
Related TEAEs	257 (86.5)	252 (86.9)	–
Any gr	73 (24.6) 58 (19.5)	120 (41.4) 85 (29.3)	
Gr ≥3	23 (7.7)	34 (11.7)	
Related TEAEs associated with:	3 (1.0)	2 (0.7)	
Dose reduction			
Discontinuation			
Death[e]			

[a]By BICR. [b]PFS *P* value boundary =.008. [c]No. of pts in the Dato-DXd and DTX arms. [d]No. of pts treated. [e]Per Investigator; adjudicated data will be presented.

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LBA14 Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial

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Background: Amivantamab (ami), an EGFR-MET bispecific antibody with immune cell-directing activity, plus lazertinib (laz), a CNS-penetrant, 3rd-generation EGFR TKI, have demonstrated antitumor activity in phase 1 studies. MARIPOSA (NCT04487080) evaluated ami+laz vs osimertinib (osi) in the first-line setting.

Methods: Patients (pts) with treatment-naïve, *EGFR*-mutated (Ex19del or L858R) locally advanced or metastatic NSCLC were randomized 2:2:1 to ami+laz, osi, or laz. Primary endpoint was progression-free survival (PFS) of ami+laz vs osi by blinded independent central review. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), PFS after first subsequent therapy (PFS2), and safety. CNS monitoring was required.

Results: 1074 pts were randomized (ami+laz, 429; osi, 429; laz, 216). Baseline characteristics were balanced; median age was 63 years, 62% were female, 59% Asian, and 41% had a history of brain metastases. At a median follow-up of 22.0 months (mo), ami+laz showed a 30% reduction in the risk for disease progression or death vs osi (HR, 0.70; 95% CI, 0.58–0.85; $P<0.001$), with median PFS of 23.7 mo (95% CI, 19.1–27.7) vs 16.6 mo (95% CI, 14.8–18.5), respectively. ORR was 86% (95% CI, 83–89) for ami+laz vs 85% (95% CI, 81–88) for osi, with median DoR among confirmed responders of 25.8 mo (95% CI, 20.1–NE) vs 16.8 mo (95% CI, 14.8–18.5), respectively. Early PFS2 data favored ami+laz vs osi (HR, 0.75; 95% CI, 0.58–0.98). At interim OS, there was a favorable trend for ami+laz over osi (HR, 0.80; 95% CI, 0.61 to 1.05; $P=0.1$). *EGFR*- and *MET*-related AEs were higher for ami+laz except diarrhea, which was higher for osi. VTEs were increased for ami+laz, mostly grade 1-2, occurred early, and effectively managed with anticoagulants. ILD rates were low and similar across arms.

Conclusions: Ami+laz was statistically superior to osi, providing clinically meaningful improvement in PFS, with higher DoR and a favorable OS trend. The safety profile of ami+laz was consistent with prior reports. MARIPOSA establishes ami+laz as a new first-line, standard of care for *EGFR*-mutated advanced NSCLC.

Clinical trial identification: NCT04487080.

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LBA15 Amivantamab plus chemotherapy (with or without lazertinib) vs chemotherapy in EGFR-mutated advanced NSCLC after progression on osimertinib: MARIPOSA-2, a phase III, global, randomized, controlled trial

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Background: Amivantamab (ami), an EGFR-MET bispecific antibody with immune cell-directing activity, plus carboplatin-pemetrexed (chemo) with and without lazertinib (laz), a CNS-penetrant, 3rd-gen EGFR TKI, have demonstrated antitumor activity in phase 1 studies. MARIPOSA-2 (NCT04988295) evaluated these combinations in *EGFR*-mutated (Ex19del or L858R) advanced NSCLC after disease progression on osimertinib (osi).

Methods: Patients (pts) were randomized 2:2:1 to ami-laz-chemo, chemo, or ami-chemo. Dual primary endpoints were progression-free survival (PFS) of ami-chemo vs chemo and ami-laz-chemo vs chemo by blinded independent central review. Secondary endpoints included objective response rate (ORR), overall survival (OS), intracranial PFS, and safety. During the study, hematologic toxicities in the ami-laz-chemo arm necessitated a regimen change to start laz after carboplatin completion.

Results: In total, 657 pts were randomized (ami-chemo, 131; ami-laz-chemo, 263; chemo, 263). Baseline characteristics were balanced between arms, including the number of pts with a history of CNS metastases (44%–46%). At a median follow-up of 8.7 mo, PFS was significantly improved with ami-chemo (HR, 0.48; 95% CI, 0.36–0.64) and ami-laz-chemo (HR, 0.44; 95% CI, 0.35–0.56) vs chemo (median PFS, 6.3 and 8.3 vs 4.2 mo, respectively; $P<0.001$ for both). ORR was 64% for ami-chemo and 63% for ami-laz-chemo vs 36% for chemo ($P<0.001$ for both). Interim OS was immature; HR of 0.77 (95% CI, 0.49–1.21) for ami-chemo vs chemo and HR of 0.96 (95% CI, 0.67–1.35) for ami-laz-chemo vs chemo. Median intracranial PFS was 12.5 mo for ami-chemo and 12.8 mo for ami-laz-chemo vs 8.3 mo for chemo (HR, 0.55 and 0.58; $P=0.001$ and $P<0.001$, respectively). Predominant AEs in the ami-containing arms were hematologic, *EGFR*, and *MET*-related. Ami-chemo had lower rates of hematologic AEs than ami-laz-chemo. The impact of modifying the ami-laz-chemo regimen on safety and efficacy requires longer follow-up.

Conclusions: Ami-chemo and ami-laz-chemo improved PFS, ORR, and intracranial PFS vs chemo in *EGFR*-mutated advanced NSCLC after progression on osi and may represent a new standard of care.

Clinical trial identification: NCT04988295.

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LBA63 SAPPHIRE: Phase III study of sitravatinib plus nivolumab versus docetaxel in patients with previously treated advanced non-squamous non-small cell lung cancer (NSCLC)

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Background: Checkpoint inhibitor (CPI) therapy can lead to antitumor responses and prolonged survival in NSCLC, but most patients (pts) who initially benefit acquire CPI resistance with disease progression. Sitravatinib (sitra) is a receptor tyrosine kinase inhibitor that can resensitize tumors to CPI by shifting the tumor microenvironment towards a less immunosuppressive state and, combined with nivolumab (nivo), may overcome acquired CPI resistance and improve outcomes vs chemotherapy.

Methods: In the Phase 3 SAPPHIRE study, pts with advanced non-squamous (adv nsq) NSCLC (excluding EGFR, ROS1, or ALK alterations) who initially benefited from CPI with/after platinum-based chemotherapy (≥4 months [mos] on CPI without progression) with subsequent disease progression were randomized 1:1 to sitra (100 mg QD orally) plus nivo (240 mg Q2W or 480 mg Q4W IV) [sitra/nivo] or docetaxel monotherapy (doce; 75 mg/m^2 Q3W IV). The primary endpoint was overall survival (OS). Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS); all by blinded independent central review, and safety.

Results: As of 20 March 2023 (median follow-up, 17.1 mos), 577 pts received sitra/nivo (n=284) or doce (n=293). Median OS was not significantly improved by sitra/nivo vs doce (12.2 vs 10.6 mos; HR 0.86 [95% CI, 0.70−1.05]; p=0.144). HR for PFS was 1.08 (95% CI, 0.89−1.32; p=0.452); median PFS for sitra/nivo vs doce was 4.4 vs 5.4 mos. ORR was 15.6% with sitra/nivo vs 17.2% with doce (p=0.597); CBR was 75.5% (sitra/nivo) vs 64.5% (doce; p=0.004). Most common (≥25%) any grade treatment-related adverse events with sitra/nivo were diarrhea (56.2% [7.5% gr ≥3]), nausea (31.3% [1.4%]), decreased appetite (28.5% [1.8%]), hypothyroidism (28.1% [0.4%]), and fatigue (26.3% [6.8%]); and diarrhea (35.5% [3.3%]), fatigue (35.5% [8.4%]), nausea (32.2% [2.6%]), decreased neutrophil count (31.9% [29.3%]), alopecia (30.8% [0.4%]), and neutropenia (26.0% [23.1%]) with doce.

Conclusions: The primary endpoint of OS was not met in pts with previously treated adv nsq NSCLC. Safety profiles for sitra/nivo and doce were consistent with prior reports for each regimen.

Clinical trial identification: NCT03906071.

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LBA64 Overall survival from a phase II randomised double-blind trial (PERLA) of dostarlimab (dostar) + chemotherapy (CT) vs pembrolizumab (pembro) + CT in metastatic non-squamous NSCLC

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Background: The Phase II PERLA trial (NCT04581824) was the first global randomized, double-blind, head-to-head study of two programmed death (PD)-1 inhibitors in NSCLC. In the primary analysis, dostar + CT met its primary endpoint of equivalence, with a favorable numerical trend in overall response rate (ORR) and progression-free survival compared to pembro + CT [1]. Here we report overall survival (OS) analyses from PERLA.

Methods: Patients (pts) with metastatic NSCLC, documented PD-L1 status, absence of EGFR, ALK or other actionable genomic aberrations determined locally, ECOG 0—1, and no prior systemic treatment were randomised 1:1 to dostar 500 mg or pembro 200 mg Q3W IV up to 35 cycles, combined with CT (4 cycles pemetrexed [pem; 500 mg/m^2] + carboplatin [AUC 5 mg/mL/min] or cisplatin [75 mg/m^2], followed by pem up to 35 cycles) Q3W IV. The primary endpoint was ORR by blinded independent central review (BICR). OS (secondary endpoint) and duration of response (DoR) by BICR (exploratory endpoint) were determined by Kaplan-Meier method, 95% confidence intervals (CIs) by Brookmeyer-Crowley method and hazard ratio by stratified Cox proportional hazard model.

Results: At data cut-off on 07 July 2023, 121 and 122 pts in the dostar + CT and pembro + CT arms respectively, were randomised and treated. OS maturity was 55% (134/243). Median OS was 19.4 mo (95% CI 14.5, NR) in the dostar + CT arm vs 15.9 mo (95% CI 11.6, 19.3) in the pembro + CT arm (Table), after median follow-up (IQR) of 20.7 (17.3, 24.0) and 21.6 (18.3, 24.1) mo respectively, with a similar trend across PD-L1 subgroups. ORR and DoR are shown in the table. No new safety signals were reported.

Conclusions: In this follow-up analysis, dostar + CT continues to demonstrate strong clinical efficacy with no unexpected safety signals. In addition, a numerical trend in OS favoring dostar + CT vs pembro + CT was observed. 1. Peters, S *et al. IOTECH* 2022;16(S1):100162 Funding:GSK (213403).

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Table: LBA64

	Dostar+CT (N=121)	Pembro+CT (N=122)
OS events (death), n (%)	59 (49)	75 (61)
Median OS (95% CI)*, mo	19.4 (14.5, NR)	15.9 (11.6, 19.3)
Hazard Ratio (95% CI)†	0.75 (0.53,1.05)	
ORR by BICR‡, % (95% CI)§ CR, n (%) PR, n (%)	45 (36.4, 54.8) 4 (3) 51 (42)	39 (30.6, 48.6) 6 (5) 42 (34)
Difference in ORR, % (80% CI)¶	6.04 (−1.95, 14.02)	
Median DoR‡ (95% CI)*, mo	12.4 (8.3, 17.9)	14.4 (9.7, NR)

*Brookmeyer-Crowley method; †based on profile-likelihood confidence limits; ‡according to RECIST v1.1; §Clopper-Pearson method; ¶Mantel and Haenszel method with Sato variance estimator. CI, confidence interval; CR, complete response; mo, months; NR, not reached; PR, partial response.

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LBA65 KRYSTAL-7: Efficacy and safety of adagrasib with pembrolizumab in patients with treatment-naïve, advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation

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Background: Adagrasib (ada) is an irreversible $KRAS^{G12C}$ inhibitor selected for favorable properties, including long half-life (23 hrs), dose-dependent PK, and CNS penetration. Optimized noncovalent binding affinity and minimized cysteine reactivity associated with ada are hypothesized to limit off-target effects in the liver and other organ sites. Preliminary ada plus pembrolizumab (pembro) data showed a manageable safety profile and encouraging clinical activity. We report updated efficacy and safety in more patients (pts) treated with ada plus pembro in KRYSTAL-7 (NCT04613596).

Methods: In the phase 2 KRYSTAL-7 study, pts with treatment-naïve $KRAS^{G12C}$-mutated advanced NSCLC received concurrent ada 400 mg orally BID plus pembro 200 mg intravenously Q3W. Study objectives included efficacy (investigator-assessed objective response rate [ORR], duration of response [DOR], progression-free survival [PFS], and overall survival), and safety.

Results: As of 19 June 2023, 148 pts had received ada plus pembro (median follow-up 8.7 months). Median age was 67 years, 48% were female, 39%/61% were ECOG PS 0/1. In pts with PD-L1 ≥50% (median follow-up 10.1 months), ORR was 63% (32/51 pts), disease control rate was 84%. Median DOR was not reached (NR; 95% CI 12.6—not estimable [NE]); median PFS was NR (95% CI 8.2—NE). In all pts, treatment-related adverse events (TRAEs) of any grade (gr) occurred in 94% (139/148) of pts; 55% gr3, 9% gr4, 1% gr5. TRAEs led to both ada and pembro discontinuation in 4% of pts (6% discontinued ada alone, 11% discontinued pembro alone). No pt discontinued both drugs due to ALT/AST increase or hepatic TRAEs; 1 pt discontinued ada and 3 pts discontinued pembro due to liver transaminase elevation. Additional efficacy and safety analyses will be presented.

Conclusions: After longer follow-up, concurrent ada plus pembro continued to have encouraging preliminary efficacy in pts with PD-L1 ≥50% and a manageable safety profile. These findings support initiation of a phase 3 trial evaluating concurrent ada plus pembro vs pembro for treatment-naïve pts with $KRAS^{G12C}$-mutated NSCLC and PD-L1 ≥50% (NCT04613596).

Clinical trial identification: NCT04613596.

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LBA66 Afatinib versus chemotherapy for treatment-naïve non-small cell lung cancer with a sensitizing uncommon epidermal growth factor receptor mutation: A phase III study (ACHILLES/TORG1834)

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Background: *EGFR* mutations are diverse and include major uncommon and compound mutations. There is no conclusion on whether EGFR-TKI is the optimal treatment for these diverse mutations. Herein we report results on the first phase III ACHILLES trial, where treatment with afatinib and chemotherapy were compared in sensitizing uncommon *EGFR* mutant non-small cell lung cancer (NSCLC).

Methods: In this open-label phase III study, treatment-naïve patients with sensitizing uncommon *EGFR* mutant NSCLC were randomized 2:1 to oral afatinib (30 or 40 mg daily) or the combination of platinum (cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6) and pemetrexed (500 mg/m^2), followed by pemetrexed maintenance therapy every three weeks. The primary endpoint was progression-free survival (PFS) per RECIST 1.1. The sample size (n = 106) was based on 75% power to detect a hazard ratio of 0.6 in PFS with $\alpha = 0.05$, which was preplanned upon completion of enrollment. The analysis was adjusted for multiple testing with the Lan-DeMets alpha-spending function, using the O'Brien and Fleming method.

Results: A total of 109 patients were enrolled between Feb 2019 and Feb 2023. The median follow-up time was 12.5 months. The patient's backgrounds were well-balanced. The median PFS was significantly longer with afatinib treatment than with chemotherapy (10.6 vs. 5.7 months; hazard ratio for death or disease progression, 0.422; 95% confidence interval, 0.256−0.694; p = 0.0007). The data and safety monitoring committee recommended an early study termination. The objective response was similar in both groups: 61.4% with afatinib treatment and 47.1% with chemotherapy (p = 0.2069). The rate of grade ≥3 treatment resulting in adverse events in both groups was 43.8% and 37.1%, respectively. The most common adverse events in the afatinib arm were diarrhea, rash, and paronychia. One treatment related death due to pneumonitis was observed in the afatinib arm.

Conclusions: Afatinib is superior to platinum doublet chemotherapy as an initial treatment for uncommon or compound *EGFR* mutation-positive advanced NSCLC.

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Legal entity responsible for the study: Thoracic Oncology Research Group (TORG).

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Disclosure: S. Miura: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical, Taiho Pharmaceutical, Ono Pharmaceutical, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Boehringer-Ingelheim Japan, Pfizer, Novartis, MSD, Kyowa Hakko Kirin, Daiichi Sankyo, Nippon Kayaku, Amgen, Merck, Takeda Pharmaceutical. H. Tanaka: Financial Interests, Personal, Invited Speaker: AstraZeneca, Chugai pharmaceutical, Boehringer Ingelheim, Eli Lilly, MSD, Ono pharmaceutical, Merck, Novartis, Takeda pharmaceutical, Pfizer, Dailchi Sankyo pharmaceutical, Taiho pharmaceutical, Bristol Myers Squibb; Financial Interests, Institutional, Invited Speaker: Chugai pharmaceutical, Merck, AstraZeneca, MSD, Eli Lilly, Ono pharmaceutical, Bristol Myers Squibb, Merck, Takeda pharmaceutical, Taiho pharmaceutical, Pfizer, Daiichi Sankyo pharmaceutical, AbbVie. H. 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LBA67 A phase III, randomized study of atezolizumab plus bevacizumab and chemotherapy in patients with EGFR or ALK mutated in non-small cell lung cancer (ATTLAS, KCSG-LU19-04)

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Background: In the treatment ofnon-small cell lung cancer (NSCLC) with a driver mutation, the role of anti-PD-(L)1 antibody following tyrosine kinase inhibitor (TKI) remains unclear. This randomized, open-label, multicenter, phase 3 study evaluates the efficacy of atezolizumab plus bevacizumab and chemotherapy in *EGFR* or *ALK*-mutated NSCLC that progressed prior to TKI therapy.

Methods: We compared the clinical efficacy of atezolizumab plus bevacizumab/paclitaxel/carboplatin (ABCP arm) followed by maintenance therapy with

atezolizumab plus bevacizumab with pemetrexed plus carboplatin or cisplatin (PC arm) followed by pemetrexed maintenance. The primary endpoint was progression-free survival (PFS).

Results: A total of 228 patients with activating *EGFR* mutation (n=215) or *ALK* translocation (n=13) were enrolled from 16 sites in the Republic of Korea and randomized at 2:1 ratio of either ABCP (n=154) or PC arm (n=74). The median follow-up duration was 26.1 months (95% CI 24.7-28.2). Objective response rates were higher in the ABCP arm than in the PC arm (69.5% vs 41.9%, P <0.001). Median PFS was significantly longer in the ABCP than in the PC arm (8.48 months vs. 5.62 months, hazard ratio [HR] 0.62 [0.45-0.86], P=0.004). PFS benefit increased as PD-L1 expression increased, with HR of 0.47, 0.41, and 0.24 for PD-L1 ≥1%, ≥10% and ≥50%, respectively. Overall survival was similar between ABCP and PC (20.63 months vs. 20.27 months, HR 1.01 [0.69-1.46], P=0.975). The safety profile of the ABCP arm was comparable to that previously reported, with no additional safety signals.

Conclusions: This study is the first randomized phase 3 study to demonstrate the clinical benefit of anti-PD-L1 antibody in combination with bevacizumab and chemotherapy in *EGFR* or *ALK* mutated NSCLC who have progressed on relevant targeted therapy.

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Legal entity responsible for the study: Myung-Ju Ahn.

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LBA68 FLAURA2: Safety and CNS outcomes of first-line (1L) osimertinib (osi) ± chemotherapy (CTx) in EGFRm advanced NSCLC

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Background: In FLAURA2 (NCT04035486), osi, a 3rd gen CNS-active EGFR-TKI, combined with platinum-pemetrexed (osi-CTx) showed a statistically significant improvement vs osi-monotherapy (osi-mono) in PFS per investigator (HR [95% CI]: 0.62 [0.49−0.79], p<0.001) with a manageable and tolerable safety profile. Addition of CTx did not affect osi exposure. 76% of pts completed 4 CTx cycles; median duration of pemetrexed exposure was 8.3 mos. 40% of FLAURA2 pts had baseline CNS metastases (mets); we report exploratory analyses of CNS efficacy by CNS blinded independent central review (BICR; conducted by neuroradiologist). Updated safety data will be reported.

Methods: Eligible pts (≥18 y [Japan: ≥20] with EGFRm advanced NSCLC, no prior tx for advanced NSCLC; asymptomatic CNS mets not requiring steroids or stable >2 wks after definitive tx/steroids were allowed) were randomised 1:1 to 1L osi-CTx or osi-mono until progression/discontinuation. Brain imaging (MRI preferred) was performed in all pts at baseline + progression, and at scheduled assessments until progression for pts with baseline CNS mets. CNS endpoints (modified RECIST1.1) included CNS PFS, CNS response and CNS DoR by CNS BICR. Safety was assessed by CTCAE v5. Data cutoff: 3 Apr 2023.

Results: Of 557 pts randomised, 118/279 (osi-CTx) and 104/278 (osi-mono) were included in the CNS BICR full analysis set (cFAS; pts with ≥1 measurable and/or non-measurable lesion); 40/118 (osi-CTx) and 38/104 (osi-mono) were included in the CNS evaluable for response set (cEFR; pts with ≥1 measurable lesion). Demographics were balanced across tx arms. CNS efficacy is shown (Table). Safety profile was similar in the cFAS and overall population. The safety and tolerability profile during the course of tx will be described.

Conclusions: In FLAURA2, pts with CNS mets in the osi-CTx arm had a clinically meaningful reduction in the risk of CNS progression, with high CNS ORR (and high CR) and durable responses, with a manageable and tolerable safety profile.

Clinical trial identification: NCT04035486.

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Table: LBA68

	cFAS		cEFR	
	Osi-CTx(n=118)	**Osi-mono(n=104)**	**Osi-CTx(n=40)**	**Osi-mono(n=38)**
CNS ORR, n (%)	86 (73)	72 (69)	35 (88)	33 (87)
- CR, n (%)	70 (59)	45 (43)	19 (48)	6 (16)
Median CNS DoR, mos (95% CI)	NR (23.8—NC)	26.2 (19.4—NC)	NR (21.6—NC)	20.9 (12.6—NC)
BICR CNS PFS				
- HR (95% CI)*	0.58 (0.33—1.01)		0.40 (0.19—0.84)	
- Median, mos (95% CI)	30.2 (28.4—NC)	27.6 (22.1—NC)	NR (23.0—NC)	17.3 (13.9—NC)

*Analysed using stratified (cFAS; by race, WHO PS and EGFRm test method) or unstratified (cEFR) log-rank test

CR, complete response; DoR, duration of response; NC, not calculable; NR, not reached; ORR, objective response rate; PFS, progression-free survival

Pfizer. K. Tanaka: Financial Interests, Speaker's Bureau: AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, BMS, MSD, Merck; Financial Interests, Advisory Board: Pfizer, AstraZeneca. D. Ghiorghiu: Financial Interests, Full or part-time Employment: AstraZeneca; Financial Interests, Stocks/Shares: AstraZeneca. E. Armenteros Monterroso: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. X. Huang: Financial Interests, Personal, Full or part-time Employment: AstraZeneca; Financial Interests, Personal, Stocks/Shares: AstraZeneca. J.C. Yang: Financial Interests, Institutional, Advisory Board, My institute received fee for my role as advisory board: AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, Roache/Genetech, Takeda, Yuhan Pharmaceuticals, Janssen, Puma Technology, Gilead, GSK, Dizal Pharmaceutica; Financial Interests, Coordinating PI: AstraZeneca, MSD, Dizal Pharmaceutical; Financial Interests, Member: ASCO, ESMO, IASLC; Financial Interests, Research Funding: AstraZeneca, Roche; Financial Interests, Steering Committee Member: AstraZeneca, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Takeda, Yuhan Pharmaceuticals, Janssen, Dizal Pharmaceutical. All other authors have declared no conflicts of interest.

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LBA69 Aumolertinib plus apatinib versus aumolertinib as first-line treatment in patients with EGFR mutation positive locally advanced or metastatic non-small cell lung cancer (NSCLC): A randomized multicenter study

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Background: The standard first-line treatment for locally advanced or metastatic EGFR-mutated NSCLC patients (pts) is the third-generation EGFR-TKI alone, which has limitations. Combining EGFR-TKI with a small molecule anti-angiogenic agent may be a potential solution due to synergistic effects. The ATTENTION study aims to evaluate the efficacy and safety of aumolertinib plus apatinib (AUM + APA) versus aumolertinib (AUM) alone as the first-line therapy for EGFR-mutated NSCLC.

Methods: Eligible pts were aged 18-75 years old, stage IIIB or IV NSCLC, with EGFR 19del or 21L858R mutation or EGFR uncommon mutations, ECOG PS of 0 or 1, measurable lesion according to RECIST v1.1. We randomly assigned eligible pts in a 1:1 ratio to receive oral aumolertinib (110 mg PO QD) or adding apatinib (250 mg PO QD) until assessed progressive disease (PD). The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), intracranial ORR (iORR), intracranial DCR (iDCR), overall survival (OS) and safety.

Results: From Jun. 2021 to Nov. 2022, a total of 104 pts were enrolled, 98 included in the efficacy analysis set. Of these, 48 pts received AUM + APA, while 50 pts received AUM. As of Sep. 12, 2023, the overall ORR was 72.9% and 64%, DCR was 100% and 94% in AUM + APA and AUM arms, respectively. In EGFR sensitizing mutation (19 del or L858R) subgroup, ORR was 75% and 68% in AUM + APA and AUM arms, respectively. In brain and liver metastasis subgroup, ORR were 100% and 60%, 60% and 33%, iORR was 82% and 63% in AUM + APA and AUM arms. PFS has beneficial trend in AUM + APA arm. The most common treatment-emergent adverse events (TEAEs) in AUM + APA and AUM arms were diarrhea (31% vs 12%), rash (29% vs 10%), proteinuria (27% vs 6%), platelet count decreased (25% vs 4%), hypertension (25% vs 6%), creatine kinase increase (23% vs 16%), respectively.

Conclusions: The combination of AUM + APA may provide a more effective and well tolerable treatment option for the first line treatment in EGFR mutated NSCLC patients.

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LBA70 OSIRAM-1: A multicenter, open label, randomized phase II study of osimertinib plus ramucirumab versus osimertinib alone as initial chemotherapy for EGFR mutation-positive non-squamous non-small cell lung cancer (TORG1833)

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Background: Dual inhibition of the EGFR/VEGF pathways has demonstrated superior efficacy with 1st generation EGFR tyrosine kinase inhibitor (TKI) in patients with non small cell lung cancer (NSCLC) harboring EGFR mutations. This study aims to evaluate the efficacy and safety of combining osimertinib (Osi), a 3rd generation TKI considered the standard of care, with ramucirumab (Ram).

Methods: Previously untreated patients with advanced NSCLC and EGFR mutations were randomized to receive Osi daily with or without Ram every 2 weeks. Eligibility included asymptomatic and/or treated brain metastases. Stratification was based on gender and mutation type (exon 19 del, L858R). The primary endpoint was progression free survival (PFS) assessed by central radiologic review.

Results: Between November 2018 and April 2020, 122 patients (Osi+Ram arm: 59, Osi arm: 63) were enrolled. With a median follow up of 36.0 months (m), median PFS was 20.0 m for Osi+Ram arm and 24.0 m for Osi arm, resulting in a hazard ratio of 1.054 (95% CI 0.674-1.648, $p = 0.82$). The overall response rate was 77.2% and 79.3%, with a median duration of response of 24.7 m and 25.1 m in the Osi+Ram and Osi arms respectively. Notable grade 3 or higher adverse events ($\geq$10%) included CK elevation (13%) in Osi arm, neutropenia (10%) and hypertension (17%) in Osi+Ram arm. Pneumonitis of any grade occurred in 9% and 16% of Osi+Ram and Osi arms. Median treatment durations for Osi and Ram were 18.8 (0.5-49.7) and 4.6 (0.5-40.7) m in the Osi+Ram arm, and 17.4 m in the Osi arm. The treatment period of Ram was shorter compared to previous studies. In a post hoc analysis, PFS favored the Osi+Ram combination among patients with brain metastasis (n=34) with a hazard ratio of 0.655 (95% CI 0.296-1.451).

Conclusions: While both treatment arms demonstrated long-term effects with acceptable toxicity, this study did not reveal an advantage of the Osi+Ram combination over Osi monotherapy in improving PFS. It's noteworthy that conducted period during the COVID-19 pandemic, and the suboptimal administration of Ram may have influenced the outcome. jRCT2080224085

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LBA71 A multi-centre open-label randomized phase II study of osimertinib with and without ramucirumab in TKI-naïve EGFR-mutant metastatic NSCLC (RAMOSE trial interim analysis)

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Background: Osimertinib (osi) is the current first-line therapy for patients (pts) with metastatic EGFR-mutant NSCLC. Combination of anti-VEGF with EGFR inhibitors has a potential to prolong progression-free survival (PFS).

Methods: The RAMOSE trial (NCT03909334, HCRN LUN-18-335) is a randomized, open-label phase 2 study comparing osi 80mg PO daily + ramucirumab 10 mg/kg IV q3 weeks (Arm A) to osi alone (Arm B) for initial treatment of metastatic EGFR-mutant NSCLC with 2:1 randomization. The primary endpoint is PFS by investigators, secondary endpoints include best response rates (BRR), disease control rate (DCR), overall survival (OS), and safety. The stratification criteria for randomization were EGFR mutation type and presence of CNS metastasis.

Results: At data cut-off Aug 29, 2023, 160 pts consented, 147 pts received treatment, and 139 pts had at least one efficacy scan. The median follow up was 16.6 months (range 1.4-46.1). Among the 139 pts, 57 PFS events (37 progressions and 20 progressions followed by death) were observed, 32 in A and 25 in B. The median PFS was 24.8 (A) vs 15.6 (B) months (HR=0.55; 95%CI: 0.32-0.93; Log Rank p=0.023), 12-mon PFS rate was 76.7% (A) vs. 61.9% (B, p=0.026). BRRs and DCRs had no difference. For high risk gorup of 43 (31%) pts with L858R, PFS was 24.8 (A) vs 18.4 months (B, p=0.388); for 64 (46%) pts with CNS metastasis, PFS was 17.9 (A) vs 13.8 months (B, p=0.225). Any-grade (G) AEs occurred in 93% (A) and 87% (B) of pts. There were no G5 treatment-related AE (TRAE), one G4 TRAE (hyponatremia, A), 46% (A) vs. 35% (B) G3 TRAEs, including G3 hypertension at 28% (A) vs 7% (B) and decreased neutrophils at 21% (A) vs 23% (B). AE-related discontinuation was observed in13 pts (9.7% in A, 8.7% in B).

Table: LBA71

		Arm A (n=93)	Arm B (n=46)
Best response: n, %	CR	1 (1.1)	1 (2.2)
	PR	60 (64.5)	31 (67.4)
	SD	29 (31.2)	12 (26.1)
	PD	3 (3.2)	2 (4.4)
Overall response rate (ORR: n, %)		71 (76.3) χ^2 p=0.59	37 (80.4)
Disease control rate (DCR: n, %)		90 (96.8) χ^2 p=0.74	44 (95.7)
Median PFS (months)		24.8; 95% CI (17.9, NA) HR= 0.55; 95%CI (0.32, 0.93); p=0.023	15.6; 95% CI (11.7, 22.8)
12-mon PFS rate (%)		76.7 p=0.026	61.9

Conclusions: Ramucirumab + osi significantly prolonged PFS compared to osi alone in *EGFR*-mutant NSCLC pts. The RAMOSE seems to be as efficacious as FLAURA2. Safety profile was in line with known safety of each drug.

Clinical trial identification: NCT03909334.

Legal entity responsible for the study: The authors.

Funding: Eli Lilly.

Disclosure: X. Le: Financial Interests, Personal, Advisory Board: AstraZeneca, Merck KGaA, Spectrum Pharmaceutics, Novartis, Boehringer Ingelheim, Eli Lilly, Hengrui, Janssen, Blueprint, Daiichi Sankyo, Regeneron, ArriVent, Abion, Pinetree therapeutics, AbbVie; Financial Interests, Institutional, Invited Speaker: Eli Lilly, EMD Serono, Regeneron, Janssen; Financial Interests, Institutional, Research Grant: Arrivent; Financial Interests, Institutional, Funding: Teligene. J.V. Heymach: Financial Interests, Personal, Advisory Board: Genentech, Mirati Therapeutics, Eli Lilly & Co., Janssen Pharmaceuticals, Boehringer-Ingelheim Pharmaceuticals, Regeneron, Takeda Pharmaceuticals, BerGenBio, Jazz Pharmaceuticals, Curio Science, Novartis, AstraZeneca, BioAlta, Sanofi, Spectrum Pharmaceuticals, GlaxoSmith Kline, Spectrum; Financial Interests, Personal, Full or part-time Employment: MD Anderson Cancer Center; Financial Interests, Institutional, Other, International PI for clinical trials: AstraZeneca; Financial Interests, Institutional, Other, International PI for two clinical trials: Boehringer-Ingelheim; Financial Interests, Personal and Institutional, Other, Developed a drug: Spectrum; Financial Interests, Institutional, Coordinating PI: Takeda. All other authors have declared no conflicts of interest.

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LBA72 DARWIN II: Deciphering anti-tumour response and resistance to immunotherapy with intratumour heterogeneity in NSCLC

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Background: Patients with metastatic non−small-cell lung cancer (NSCLC) can receive anti PD-L1/PD-1 immunotherapy as a standard of care. However, prediction of response is challenging with existing biomarkers. Retrospective analyses have identified the clonality of mutations and neoantigens as potential biomarkers. However, the impact of intratumour heterogeneity (ITH) on immunotherapy response in patients with metastatic NSCLC has not been prospectively explored. The DARWIN II trial is a phase II, multicentre molecularly stratified trial for patients with NSCLC to study the effect of ITH on response to treatment. The study is unique as patients were recruited from the TRACERx Lung Cancer observational cohort study, following relapse with metastatic disease.

Methods: A total of 65 patients from the TRACERx study, with spatially separated multi-region sampling of resected early lung cancer, who relapsed with metastatic disease were enrolled between November 2016 and March 2023 and received immunotherapy. Patients were recruited with any PDL1 tumour proportion score. Patients received atezolizumab or atezolizumab with chemotherapy. Multi-omic analysis, including deep (∼500x) whole exome, RNA, RRBS, and TCR sequencing of multi-region primary tumour samples and relapse biopsies was performed on 355 samples. All samples were processed on a uniform bioinformatic analysis pipeline and results corrected for tumour purity variation.

Results: The median PFS and OS were 4.5 and 10.0 months respectively. The proportion of patients with durable clinical benefit was 37.5 percent. A high clonal mutation burden was associated with a statistically significant improvement in response (OR = 5.7, 95% CI [1.1-45.0], p value = 0.04) whereas high total tumour mutation burden (>10 mut/Mb) was not. Additionally, we identified several associations between novel molecular features and immunotherapy response, including ITH of the transcriptome and DNA hyper-/hypo-methylation frequency.

Conclusions: This is the first trial to demonstrate prospectively that clonal mutations are associated with improved patient outcome and identify novel molecular features, related to ITH, as predictors of immunotherapy response in patients with NSCLC.

Clinical trial identification: NCT02314481.

Legal entity responsible for the study: University College London.

Funding: Roche.

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Oesophagogastric cancer

LBA73 Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Interim results of the global, phase III MATTERHORN study

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Background: The global, Phase 3, randomised, double-blind, placebo (P)-controlled MATTERHORN study (NCT04592913) assesses perioperative durvalumab (D) with FLOT in participants (pts) with resectable GC/GEJC. Results of a pre-planned interim analysis (IA) are reported.

Methods: Pts with resectable (>T2 N0-3 M0/T0-4 N1-3 M0) GC/GEJC were randomised 1:1 to D 1500 mg or P every 4 weeks (Q4W) on Day 1 plus FLOT Q2W on Days 1 and 15 for 4 cycles (2 doses of D or P and 4 doses of FLOT pre- and post-operative),

followed by D 1500 mg or P on Day 1 Q4W for 10 further cycles. IA was conducted after all randomised pts underwent or were precluded from surgery. Superiority of pCR rate (α=0.1% [2-sided]) by central review (Modified Ryan) was assessed. Surgical and safety outcomes were also assessed.

Results: There were 474 pts randomised to each treatment arm. Baseline characteristics were balanced between arms; 19% of pts in each enrolled in Asia. The majority of pts had GC (68%), cT3 (66%; cT4, 25%) and cLN+ (70%). A statistically significant improvement in pCR was observed with addition of D to FLOT versus P (19% vs 7%; Δ12%; odds ratio [OR], 3.08; p<0.00001; Table). Combined pCR/near-complete pathological response (pnCR) rate was 27% with D vs 14% with P. Surgery rate and R0 resection rate (in pts who underwent surgery) were similar with D (87% and 86%, respectively) vs P (84% and 86%, respectively). Downstaging favoured D vs P (pT0, 21% vs 10%; pN0, 47% vs 33%; by central review). Median D and P exposure was similar. Adverse event rates were similar between arms (Table).

Table: LBA73

	D + FLOT (n=474)	P + FLOT (n=474)
pCR		
n; % (95% CI)	91; 19 (15.8–23.0)	34; 7 (5.0–9.9)
OR (95% CI)	3.08 (2.03–4.67); p<0.00001	
pCR/pnCR		
n; % (95% CI)	127; 27 (22.9–31.0)	68; 14 (11.3–17.8)
OR (95% CI)	2.19 (1.58–3.04); p<0.00001	
Surgery performed		
n; % (95% CI)	411; 87 (83.3–89.6)	399; 84 (80.6–87.4)
OR (95% CI)	1.23 (0.85–1.76)	
R0 resection*		
n; % (95% CI)	369; 86 (82.2–89.0)	362; 86 (82.1–89.0)
OR (95% CI)	1.00 (0.68–1.48)	
AE†, n (%)	470 (99)	463 (99)
Grade 3/4	326 (69)	317 (68)
TRAE	452 (95)	441 (94)
Grade 3/4 TRAE	275 (58)	264 (56)

*In pts with surgery: D + FLOT, n=430, P + FLOT, n=422. †In safety analysis set: D + FLOT, n=475, P + FLOT, n=469. TRAE, treatment-related AE.

Conclusions: The addition of D to perioperative FLOT therapy demonstrated a clinically meaningful and statistically significant improvement in pCR in resectable GC/GEJC, with a tolerable safety profile. The MATTERHORN study is ongoing for the primary endpoint of event-free survival.

Clinical trial identification: NCT04592913.

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Hoffmann-La Roche Ltd, Genentech Inc., HalioDX SAS, Ikena Oncology, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Seattle Genetics, Servier, Taiho, Tessa Therapeutics, TheraMyc, Hutchinson MediPharma International, Scandion Oncology, Ona Therapeutics, Sotio Biotech, Inspirna Inc, Scorpion Therapeutics, Tolremo Therapeutics; Financial Interests, Personal, Invited Speaker, educational collaboration: Medscape Education, Physicians Education Resource (PER), PeerView Institute for Medical Education, Imedex / HMP; Financial Interests, Personal, Invited Speaker, educacional collaboration: MJH Life Sciences; Financial Interests, Personal, Advisory Board: Cardiff Oncology; Financial Interests, Personal, Stocks/Shares: Oniria Therapeuics; Financial Interests, Institutional, Research Grant, ACRCelerate: Colorectal Cancer Stratified: Fundación Científica de la Asociación Española Contra el Cáncer; Financial Interests, Institutional, Research Grant, OPTIMISTICC: Opportunity to Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer: Cancer Research UK; Financial Interests, Institutional, Funding, Clinical Trials & Research: Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb International Corporation, Celgene International SARL, Debiopharm International SA, F. 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LBA74 Pembrolizumab plus chemotherapy vs chemotherapy as neoadjuvant and adjuvant therapy in locally-advanced gastric and gastroesophageal junction cancer: The phase III KEYNOTE-585 study

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Background: The phase 3 KEYNOTE-585 study (NCT03221426) evaluated neo-adjuvant/adjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo) followed by adjuvant pembro vs pbo in locally-advanced, resectable gastric or gastroesophageal junction (G/GEJ) cancer. A separate cohort evaluated pembro + FLOT. We report results of the pre-specified third interim analysis (IA3).

Methods: Patients (pts) with untreated, locally-advanced, resectable G/GEJ cancer were randomized 1:1 to neoadjuvant pembro 200 mg IV Q3W or pbo + chemo (cisplatin + capecitabine or cisplatin + 5-FU) for 3 cycles. After surgery, pts received adjuvant pembro or pbo + chemo Q3W for 3 cycles, then adjuvant pembro or pbo Q3W for 11 cycles (main cohort). In the FLOT cohort, pts were randomized 1:1 to pembro + docetaxel, oxaliplatin, leucovorin, and 5-FU, Q2W. Primary end points were pathCR rate (BICR), EFS (RECIST 1.1, by investigator), OS (main cohort), and safety (FLOT cohort).

Results: 804 pts were randomized to the main (402 pembro; 402 pbo) and 1007 to main + FLOT ([502 pembro; 505 pbo) cohorts. Median follow-up was 47.7 mo and 46.3 mo, respectively. In the main cohort, pathCR significantly improved with pembro + chemo (12.9% [95% CI, 9.8-16.6]) vs pbo + chemo (2.0 [95% CI, 0.9-3.9]); Δ (10.9% [95% CI, 7.5-14.8]; P<0.00001). EFS was longer with pembro vs pbo (median 44.4 vs 25.3 mo; HR 0.81; 95% CI, 0.67-0.99; P=0.0198), but was not significant. OS continues to final analysis. Median OS was 60.7 vs 58.0 mo (HR 0.90; 95% CI, 0.73-1.12) at IA3. Grade ≥3 drug-related AE rates were 65% with pembro + chemo and 63% with pbo + chemo. Outcomes in the main + FLOT cohort are in the Table.

Conclusions: Neoadjuvant/adjuvant pembro + chemo followed by adjuvant pembro, significantly improved pathCR rate with no significant improvement in EFS vs placebo + chemo in pts with untreated, locally-advanced resectable G/GEJ cancer.

Clinical trial identification: NCT03221426.

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LBA75 Neoadjuvant chemoradiotherapy followed by surgery versus active surveillance for oesophageal cancer (SANO-trial): A phase-III stepped-wedge cluster randomised trial

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Background: One-third of patients with oesophageal cancer has a pathologically complete response after neoadjuvant chemoradiotherapy (nCRT) plus oesophagectomy. Active surveillance may be an alternative for patients with clinically complete response (CCR).

Table: LBA74 Outcomes in main + FLOT cohort

Efficacy	Pembro + chemo N = 502	Pbo + chemo N = 505	Treatment difference (95% CI)
Path CR[a], %	13.0 (10.2-16.3)	2.4 (1.3-4.2)	10.6% (7.4-14.0) P<0.0001
Median EFS, mo (95% CI)	45.8 (35.9-NR)	25.7 (21.9-33.9)	HR 0.81 (0.68-0.97) P=0.011
Median OS, mo (95% CI)	60.7 (51.5-NR)	NR (45.7-NR)	HR 0.93 (0.76-1.12)
Safety	Pembro + chemo N = 498	Pbo + chemo N = 503	NA
Grade ≥ 3 drug-related AEs	67%	63%	NA

[a]In first 987 pts randomized; HR, hazard ratio; NA, not applicable; NR, not reached

Methods: A noninferiority stepped-wedge cluster randomised trial was performed. Patients with CCR (*i.e.* no residual disease 6 and 12 weeks after nCRT) underwent active surveillance (surgery only when locoregional regrowth was detected) or standard surgery. Primary endpoint was overall survival (OS) from day of CCR. Noninferiority was defined as Hazard Ratio (HR) <1.77 for mortality in active surveillance after two years. Secondary endpoints were operative outcomes, disease-free survival (DFS), distant dissemination rate and quality of life (HRQOL, EORTC QLQ-C30).

Results: Some 198 patients underwent active surveillance and 111 patients underwent standard surgery. Median follow-up was 34 months in active surveillance and 50 months in standard surgery. OS in active surveillance was noninferior to standard surgery (HR 0.88, 95% upper boundary 1.40, p = 0.007). During active surveillance, 69 patients (35%) maintained CCR, 96 patients (48%) developed locoregional regrowths, and 33 patients (17%) developed distant metastases. R1 rate was 2% in both groups and postoperative 90-day mortality was 4% (active surveillance) versus 5% (standard surgery). Median DFS for active surveillance was 35 (95% CI 31 − 41) versus 49 months (95% CI 38 − NA) for standard surgery (HR 1.35, 95% CI 0.89 − 2.03, p = 0.15). At 30 months after nCRT, 43% of patients with active surveillance versus 34% with standard surgery developed distant metastases (OR 1.45, 95% CI 0.85 − 2.48, p = 0.18). HRQOL was statistically significantly better at six (p = 0.002) and nine months (p = 0.007) for active surveillance.

Conclusions: After a follow-up of two years, patients undergoing active surveillance had noninferior OS and improved short-term HRQOL compared to standard surgery. Postponed esophagectomy for locoregional regrowth was safe. Extended follow-up is required to assess long-term efficacy of active surveillance.

Clinical trial identification: NTR6803 8-11-2017.

Legal entity responsible for the study: The authors.

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LBA76 The primary results of an intergroup phase III randomized controlled trial comparing ramucirumab plus irinotecan with irinotecan in the third or later line treatment beyond progression after ramucirumab for advanced gastric cancer (RINDBeRG trial)

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Background: Ramucirumab is a monoclonal antibody that targets the vascular endothelial growth factor receptor 2 (VEGFR-2) and has been shown to improve survival of patients with advanced gastric cancer. It has been reported that sustained VEGF blockade beyond progression had a survival benefit in various cancers.

Methods: This is a multicenter, open-label, randomized phase III study that enrolled patients with unresectable gastric cancer who had received previously ramucirumab containing chemotherapy. Patients were randomly allocated to either irinotecan plus ramucirumab arm or irinotecan alone arm in a 1:1 ratio. Irinotecan was administered at a dose of 150 mg/m^2, every two weeks, in both arms, and ramucirumab at a dose of 8 mg/kg was added biweekly. The primary endpoint was overall survival (OS), expecting a hazard ratio (HR) of 0.77 (a power of 80% with significance level of one-sided 0.05) for full analysis set (FAS). Secondary endpoints include progression-free survival (PFS), overall response rate (ORR), and safety.

Results: From February 2019 to August 2022, 402 patients from 121 institutions participating 9 Japanese clinical trial groups were recruited. As of the data cutoff, 362 events for OS were observed. Median OS in the combination of irinotecan plus ramucirumab and irinotecan alone were 9.4 months and 8.5 months (adjusted HR 0.909, 95% confidence interval [CI] 0.738 − 1.119; p=0.369). Median PFS were 3.8 months and 2.8 months (HR 0.722, 95% CI 0.590 - 0.884; p=0.001) and ORR were 22.1% (33/149) and 15.0% (25/167), respectively. The safety profile was consistent with the known profiles of both irinotecan and ramucirumab, and there were no new safety findings.

Conclusions: This is the first report of the phase III trial to evaluate sustained anti-angiogenic therapy in advanced gastric cancer. In this study, although the addition of ramucirumab to irinotecan after disease progression of ramucirumab improved PFS and ORR with manageable toxicity, the primary endpoint of OS was not met.

Clinical trial identification: This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000023065 from JUL. 13, 2016, and changed to the Japan Registry of Clinical Trials (jRCT) as jRCTs051180187 from Mar. 26, 2019, in accordance with the change of the regulation for clinical research in Japan.

Legal entity responsible for the study: Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG).

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LBA77 5-fluorouracil and oxaliplatin with or without docetaxel in the first-line treatment of HER2 negative locally advanced (LA) unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma (GASTFOX-PRODIGE 51): A randomized phase III trial sponsored by the FFCD

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Background: The perioperative FLOT triplet chemotherapy regimen is the standard of care for localized gastric and GEJ adenocarcinomas. We explored the superiority of a modified FLOT (mFLOT=TFOX regimen) vs FOLFOX in patients with advanced disease.

Methods: The GASTFOX phase III study compared FOLFOX versus a mFLOT/TFOX regimen (FOLFOX + docetaxel 50 mg/m^2, q2w) in the first-line setting of patients with HER2-negative, LA unresectable or metastatic gastric or GEJ adenocarcinoma, with measurable disease, an ECOG PS 0 or 1, adequate organ function, and docetaxel naïve. The primary endpoint was PFS. Secondary endpoints included OS, ORR, safety, and quality of life (QoL). For survival outcomes, HR and 95% CI were estimated by a Cox proportional hazard (PH) model. In case of non-PH, the restricted mean survival time (RMST) was used to evaluate the treatment effect.

Results: Between 12/2016 and 12/2022, 507 patients were randomized 1:1 to FOLFOX (n=253) or mFLOT/TFOX (n=254). Baseline characteristics were similar between arms (overall: male, 78%; median age, 64; PS 1, 57%; GEJ, 56%; previous (neo)adjuvant treatment, 6%). Median follow-up (F/U) was 42.8 months (mo). As compared to FOLFOX, PFS was significantly improved in patients treated with mFLOT/TFOX (median: 7.59 vs 5.98 mo, non-PH / RMST at 12 mo F/U: 7.5 vs 6.6 mo, p=0.007). OS was also significantly improved by using mFLOT/TFOX (median: 15.08 vs 12.65 mo; HR 0.82 [0.68-0.99], p=0.048). ORR was also in favor of mFLOT/TFOX (66.0 vs 56.7%, p=0.038). Most common grade $\geq$3 TRAE were neuropathy (31.7 vs 19.7%), diarrhea (14.5 vs 6.4%) and neutropenia (26.1 vs 18.1%) respectively for mFLOT/TFOX and FOLFOX. Median time to deterioration in QoL ($>$ 5 points loss in EORTC QLQC30) was longer in patients treated with mFLOT/TFOX (17.0 vs 13.7 mo; HR 0.75 [0.59-0.94], p=0.015).

Conclusions: The addition of docetaxel to FOLFOX significantly improved PFS, OS and ORR in first-line treatment of advanced HER2 negative gastric or GEJ adenocarcinomas. mFLOT/TFOX can be considered as a new therapeutic option for patients eligible for a triplet regimen.

Clinical trial identification: NCT03006432.

Legal entity responsible for the study: Fédération Francophone de Cancérologie Digestive (FFCD).

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LBA78 Overall survival of perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy: An updated analysis of RESOLVE trial

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Background: The RESOLVE study demonstrated a disease-free survival (DFS) benefit from perioperative SOX compared to adjuvant CapOx in patients with gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma who underwent D2 gastrectomy. Here, we aim to update on the 5-year overall survival (5yOS%) results.

Methods: The phase III, open-label, randomized controlled RESOLVE study (NCT01534546) enrolled patients with stage cT4aN+M0 or cT4bNanyM0 G/GOJ adenocarcinoma. Patients were 1:1:1 randomly assigned to adjuvant CapOx, adjuvant SOX, or perioperative SOX and underwent standard gastrectomy with D2 lymphadenectomy. The adjuvant CapOx group received 8 cycles of oxaliplatin (130 mg/m^2, d1) with capecitabine (1000 mg/m^2, bid, d1-14). The adjuvant SOX group received oxaliplatin and oral S-1 at a dose depending on body surface area (40-60 mg bid, d1-14). The perioperative SOX group received 3 cycles of preoperative SOX plus 5 cycles of postoperative SOX followed by 3 cycles of S-1 monotherapy. The primary endpoint was 3-year DFS, and second endpoints included 5yOS% and safety.

Results: Between 08/2012 and 02/2017, 1022 patients were included in mITT population and analyzed. With a median follow up time of 62.8 months, 495 recurrences and 416 deaths were observed by 07/04/2022. Perioperative SOX improved 5yOS% compared with adjuvant CapOx (60.0% *vs.* 52.1%; HR 0.79, 95%CI [0.62-1.00]; p=0.049). Adjuvant SOX was not inferior to postoperative CapOx (61.0% *vs.* 52.1%; HR 0.77, 95%CI [0.61-0.98]; p=0.033). Perioperative SOX improved 5yDFS% compared with adjuvant CapOx (53.2% *vs.* 45.8%; HR 0.79, 95%CI [0.63-0.98]; p=0.034). Adjuvant SOX was not inferior to adjuvant CapOx (50.8% *vs.* 45.8%; HR 0.86, 95%CI [0.69-1.06]; p=0.164). No additional adverse events were observed.

Conclusions: The update on the RESOLVE survival analysis revealed improved survival in patients with G/GOJ adenocarcinoma undergoing D2 gastrectomy with perioperative SOX therapy compared to adjuvant CapOx, and adjuvant SOX was not inferior to adjuvant CapOx.

Clinical trial identification: NCT01534546.

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LBA79 GEMSTONE-303: Prespecified progression-free survival (PFS) and overall survival (OS) final analyses of a phase III study of sugemalimab plus chemotherapy vs placebo plus chemotherapy in treatment-naïve advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

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Background: GEMSTONE-303 is a randomized, double-blinded, multi-center phase 3 trial evaluating sugemalimab (suge), a full-length, fully human anti-PD-L1 mAb + CAPOX vs placebo + CAPOX as the first-line treatment for patients (pts) with advanced G/GEJ adenocarcinoma. It is the first reported phase 3 trial of an anti-PD-L1 mAb in this disease that met the dual primary endpoints of PFS and OS. Here, we report the final analysis results of dual primary endpoints.

Methods: Eligible pts with previously untreated, no known HER2-positive status, PD-L1 expression ≥5%, unresectable advanced or metastatic G/GEJ adenocarcinoma were randomized 1:1 to receive suge/placebo (1200 mg, Q3W, IV) + CAPOX (capecitabine, 1000 mg/m^2, PO, BID, D1-14, Q3W; oxaliplatin, 130 mg/m^2, IV, Q3W; max 6 cycles). Stratification factors were ECOG PS (0 or 1) and PD-L1 expression levels (5-9% or ≥10%). Primary endpoints were PFS and OS. Data cutoff dates of the preplanned PFS and OS final analyses were 6 Aug 2022 and 9 Jul 2023, respectively.

Results: A total of 479 pts were randomized to suge+CAPOX (N=241) and placebo+CAPOX (N=238) arms between 9 Apr 2019 and 29 Dec 2021. The PFS and OS final analysis showed a significant improvement of the dual primary endpoints with suge+CAPOX vs placebo+CAPOX. The ORR was 68.6% with suge+CAPOX and 52.7% with placebo+CAPOX. The OS benefits were observed across all subgroups. The incidences of G3-5 suge/placebo-related AEs were 31.1% in suge+CAPOX arm and 28.7% in placebo+CAPOX arm. No new safety signals were observed.

Table: LBA79

PD-L1 Expression Level >=5%	Suge+CAPOX N=241	Placebo+CAPOX N=238
PFS (Months)		
Median (95% CI)	7.62 (6.37, 7.89)	6.08 (5.06, 6.44)
P-value	<0.0001	
HR (95% CI)	0.66 (0.54, 0.81)	
OS (Months)		
Median (95% CI)	15.64 (13.27, 17.81)	12.65 (10.64, 14.06)
P-value	0.0060	
HR (95% CI)	0.75 (0.61, 0.92)	
OS Rate		
12 Months (95% CI)	61.25% (54.77%, 67.08%)	52.02% (45.44%, 58.18%)
24 Months (95% CI)	29.90% (23.79%, 36.23%)	23.28% (17.81%, 29.18%)
PD-L1 Expression Level >=10%	**N=130**	**N=128**
PFS (Months)		
Median (95% CI)	7.79 (6.77, 9.99)	5.52 (4.83, 6.67)
P-value	0.0001	
HR (95% CI)	0.58 (0.43, 0.77)	
OS (Months)		
Median (95% CI)	17.81 (14.36, 21.16)	12.45 (9.89, 13.86)
P-value	0.0022	
HR (95% CI)	0.64 (0.48, 0.85)	

Conclusions: Sugemalimab in combination with CAPOX demonstrates statistically significant and clinically meaningful improvements in PFS and OS, with a manageable safety profile. These findings support suge+CAPOX as new first-line treatment option for pts with PD-L1 expression ≥5%, advanced G/GEJ adenocarcinoma.

Clinical trial identification: NCT03802591.

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LBA80 Tislelizumab (TIS) plus chemotherapy (Chemo) vs placebo (PBO) plus chemo as first-line (1L) treatment of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Final analysis results of the RATIONALE-305 study

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Background: TIS (anti-PD-1 antibody) plus (+) chemo demonstrated significant overall survival (OS) benefit vs PBO + chemo as 1L treatment in patients (pts) with advanced GC/GEJC at a pre-specified interim analysis of the PD-L1-positive (tumor area positivity score ≥5%) population in the global, phase 3 RATIONALE-305 study (NCT03777657). Here, we present primary analysis results in the intent-to-treat (ITT) population at the pre-specified final analysis.

Methods: Adults with previously untreated, HER2-negative, locally advanced, unresectable, or metastatic GC/GEJC, regardless of PD-L1 expression status, were randomized (1:1) to receive TIS 200 mg or PBO IV once every 3 weeks plus investigator (INV)-choice of chemo (5-FU + cisplatin or capecitabine + oxaliplatin). The primary endpoints were OS in the PD-L1-positive and ITT populations. Secondary endpoints included progression-free survival, objective response rate, and duration of response by INV per RECIST v1.1, and safety.

Results: At data cutoff, 997 pts were randomized (501 pts to TIS + chemo; 496 pts to PBO + chemo). Minimum study follow-up was 24.6 mo. OS in the TIS arm was significantly improved compared with the PBO arm in the ITT population (median OS: 15.0 mo vs 12.9 mo, respectively; HR=0.80 [95% CI: 0.70, 0.92]; 1-sided P=0.0011). Additional main efficacy results are presented in the Table. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 268 (53.8%) pts in the TIS arm and 246 (49.8%) pts in the PBO arm; TRAEs led to treatment discontinuation in 16.1% vs 8.1% of pts, respectively, and death in 1.2% vs 0.4%, respectively.

Table: LBA80

Endpoint	TIS + Chemo (n=501)	PBO + Chemo (n=496)
OS		
Median, mo (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)
HR (95% CI)	0.80 (0.70, 0.92)	
P-value	0.0011	
PFS		
Median, mo (95% CI)	6.9 (5.7, 7.2)	6.2 (5.6, 6.9)
HR (95% CI)	0.78 (0.67, 0.90)	
ORR, % (95% CI)	47.3 (42.9, 51.8)	40.5 (36.2, 45.0)
mDoR, mo (95% CI)	8.6 (7.9, 11.1)	7.2 (6.0, 8.5)

ITT population.
Data cutoff: 28 February 2023. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mDoR, median duration of response; mo, months; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; TIS, tislelizumab.

Conclusions: In the ITT population, TIS + chemo showed statistically significant and clinically meaningful improvement in OS vs PBO + chemo, and was well tolerated. These data support the TIS + chemo combination as a potential 1L treatment option for pts with advanced GC/GEJC.

Clinical trial identification: NCT03777657 (first posted December 17, 2018).

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LBA81 Updated efficacy and safety results from phase III GLOW study evaluating zolbetuximab + CAPOX as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma

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Background: The phase 3 GLOW study showed statistically significant improvement with 1L zolbetuximab + capecitabine + oxaliplatin (CAPOX) vs placebo (PBO) + CAPOX in PFS (final; median 8.2 vs 6.8 mo, HR 0.69 [95% CI 0.54, 0.87], $P = 0.0007$) and OS (interim; median 14.4 vs 12.2 mo, HR 0.77 [95% CI 0.62, 0.97], $P = 0.0118$) in pts with CLDN18.2+, HER2−, LA unresectable or mG/GEJ adenocarcinoma. We present an updated efficacy and safety analysis with 8.7 mo additional follow-up from the primary analysis.

Methods: Pts were randomly assigned 1:1 to zolbetuximab IV 800 mg/m^2 (cycle 1, day [D] 1) followed by 600 mg/m^2 (every 3 weeks) + CAPOX (oral capecitabine BID on D1−14 and oxaliplatin IV on D1) for eight 21-day cycles or to PBO + CAPOX; pts without progressive disease (PD) continued beyond cycle 8 with zolbetuximab or PBO, + capecitabine at investigator's discretion, until PD or discontinuation criteria were met. Primary endpoint was PFS per RECIST v1.1 by IRC; OS was a key secondary endpoint.

Results: At data cutoff (June 29, 2023), 507 pts were assigned to zolbetuximab + CAPOX (n = 254) or PBO + CAPOX (n = 253). In zolbetuximab vs PBO arms, median follow-up was 17.8 vs 15.1 mo for PFS and 26.1 vs 26.2 mo for OS, respectively. Median PFS in zolbetuximab vs PBO arms was 8.3 vs 6.8 mo (HR 0.68 [95% CI 0.55, 0.85], $P = 0.0004$). Median OS in zolbetuximab vs PBO arms was 14.3 vs 12.2 mo (HR 0.77 [95% CI 0.62, 0.95], $P = 0.0079$); 24-mo OS rate was 28.3% vs 18.8%, with follow-up ongoing through final analyses. Most common TEAEs with zolbetuximab + CAPOX were nausea (zolbetuximab arm: 68.9% vs PBO arm: 50.2%), vomiting (66.1% vs 31.3%), and decreased appetite (41.3% vs 34.5%); incidences of serious TEAEs were similar between arms (48.0% vs 50.6%).

Conclusions: Zolbetuximab + CAPOX continued to demonstrate statistically significant improvement in PFS and OS compared with PBO + CAPOX, with no new safety signals, supporting zolbetuximab + CAPOX as a potential new option for 1L treatment of patients with CLDN18.2+, HER2−, LA unresectable or mG/GEJ adenocarcinoma.

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LBA82 Updated efficacy and safety results from phase III SPOTLIGHT study evaluating zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma

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Background: The phase 3 SPOTLIGHT study showed statistically significant improvement with 1L zolbetuximab + a modified folinic acid, 5-FU, and oxaliplatin regimen (mFOLFOX6) vs placebo (PBO) + mFOLFOX6 in PFS (final; median 10.6 vs 8.7 mo, HR

0.75 [95% CI 0.60, 0.94], $P = 0.0066$) and OS (interim; median 18.2 vs 15.5 mo, HR 0.75 [95% CI 0.60, 0.94], $P = 0.0053$) in patients (pts) with CLDN18.2+, HER2−, LA unresectable or mG/GEJ adenocarcinoma. We present an updated efficacy and safety analysis with 9.7 mo additional follow-up from the primary analysis.

Methods: Pts were randomly assigned 1:1 to zolbetuximab IV 800 mg/m^2 (cycle 1, day [D] 1) followed by 600 mg/m^2 (every 3 weeks) + mFOLFOX6 IV (D1, 15, 29) for four 42-day cycles or to PBO + mFOLFOX6; pts without progressive disease (PD) continued with zolbetuximab or PBO, + folinic acid and 5-FU at investigator's discretion, until PD or discontinuation criteria were met. Primary endpoint was PFS per RECIST v1.1 by IRC; OS was a key secondary endpoint.

Results: At data cutoff (June 29, 2023), 565 pts were assigned to zolbetuximab + mFOLFOX6 (n = 283) or PBO + mFOLFOX6 (n = 282). In zolbetuximab vs PBO arms, median follow-up was 17.9 vs 15.2 mo for PFS and 31.1 vs 29.6 mo for OS, respectively. Median PFS was 11.0 vs 8.9 mo (HR 0.73 [95% CI 0.59, 0.91], $P = 0.0022$). Median OS was 18.2 vs 15.6 mo (HR 0.78 [95% CI 0.64, 0.95], $P = 0.0067$), with follow-up ongoing until final analysis; 24-mo OS rate was 37.7% vs 29.1%. Most common TEAEs with zolbetuximab + mFOLFOX6 were nausea (zolbetuximab arm: 82.4% vs PBO arm: 61.5%), vomiting (67.4% vs 36.3%), and decreased appetite (48.7% vs 34.9%); incidences of serious TEAEs were similar between arms (47.0% vs 46.4%).

Conclusions: With longer follow-up, zolbetuximab + mFOLFOX6 continued to demonstrate statistically significant improvement in PFS and OS compared with PBO + mFOLFOX6, with no new safety signals—supporting zolbetuximab + mFOLFOX6 as a potential new option for 1L treatment of pts with CLDN18.2+, HER2−, LA unresectable or mG/GEJ adenocarcinoma.

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Pancreatic cancer

LBA83 Neoadjuvant chemotherapy with FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy for borderline resectable and resectable pancreatic cancer (PREOPANC-2): A multicenter randomized controlled trial

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Background: The PREOPANC trial demonstrated an overall survival (OS) benefit of neoadjuvant gemcitabine-based chemoradiotherapy compared with upfront surgery in patients with borderline resectable and resectable pancreatic cancer (PDAC). FOLFIRINOX may further improve OS in the neoadjuvant setting.

Methods: This multicenter, phase 3, randomized trial included patients with borderline resectable and resectable PDAC from 19 Dutch centers. Patients received FOLFIRINOX every 14 days for 8 cycles followed by surgery without adjuvant treatment (FFX arm) versus 3 cycles of neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions during the second cycle), followed by surgery and 4 cycles of adjuvant gemcitabine (CRT arm). Randomization was stratified by center and resectability status. Primary endpoint was OS. Secondary endpoints included resection rate and serious adverse event (SAE) rate. To demonstrate a hazard ratio (HR) of 0.70 with two-sided $\alpha = 0.05$ and 80% power, 368 patients (252 events) were needed. HR and 95% CI were estimated using a stratified Cox model.

Results: Between June 2018 and January 2021, 375 patients were randomized to the FFX arm (n=188) or the CRT arm (n=187). Six patients (3 per arm) were excluded because of ineligibility (n=4) or withdrawal of informed consent immediately after randomization (n=2). After a median follow-up of 41.7 months with 254 events, median OS was 21.9 months in the FFX arm and 21.3 months in the CRT arm (HR 0.87; 95% CI 0.68-1.12, p=0.28). Resection rates were 77% in the FFX arm and 75% in the CRT arm (p=0.69). SAE rates were 49% in the FFX arm and 43% in the CRT arm (p=0.26).

Conclusions: Neoadjuvant chemotherapy with FOLFIRINOX did not improve OS compared with neoadjuvant gemcitabine-based chemoradiotherapy in patients with borderline resectable and resectable PDAC.

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Prostate cancer

LBA13 Phase III trial of [177Lu]Lu-PSMA-617 in taxane-naive patients with metastatic castration-resistant prostate cancer (PSMAfore)

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Background: [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolongs rPFS and OS in patients (pts) with mCRPC and prior ARPI and taxane therapy. PSMAfore (NCT04689828) examined ^{177}Lu-PSMA-617 in taxane-naive pts.

Methods: Eligible adults had mCRPC, were candidates for ARPI change after one progression on prior ARPI, and had $\geq$1 PSMA+ and no exclusionary PSMA− lesions by [^{68}Ga]Ga-PSMA-11 PET/CT. Candidates for PARP inhibition and pts with prior systemic radiotherapy (<6 months ago), immunotherapy (except sipuleucel-T), or chemotherapy (except [neo]adjuvant >12 months ago) were ineligible. Randomization was 1:1 to open-label ^{177}Lu-PSMA-617 (7.4 GBq q6w; 6 cycles) or ARPI change (abiraterone/ enzalutamide). Pts randomized to ARPI could crossover to ^{177}Lu-PSMA-617 following centrally reviewed radiographic progression (rPD). Endpoints included: rPFS (PCWG3/ RECIST v1.1; primary), OS (key secondary) (both overall α=0.025, one-sided), FACT-P (secondary) and ORR/DOR (exploratory). Primary analysis was to occur at ~156 rPFS events and second OS interim analysis (IA) at ~125 deaths. Crossover-adjusted analysis was the prespecified method for OS by rank-preserving structural failure time (RPSFT).

Results: 468 pts were randomized. At primary analysis (median follow-up, 7.3 months; N = 467), the primary endpoint of rPFS was met (HR, 0.41; 95% CI: 0.29, 0.56; p<0.0001); this was similar at second IA (table). At second IA (45.1% of target deaths), 123/146 (84.2%) pts with rPD who discontinued ARPI crossed over; there was a positive OS trend in favour of ^{177}Lu-PSMA-617 per RPFST but not per unadjusted OS analysis. FACT-P and ORR/DOR favoured the ^{177}Lu-PSMA-617 arm (table). For ^{177}Lu-PSMA-617 vs ARPI change, incidence of grade $\geq$3 AEs was 34% (most common: anaemia, dry mouth) vs 44%, serious AEs 20% vs 28%, and AEs leading to discontinuation 5.7% vs 5.2%.

Table: LBA13

Second OS IA (DCO, 21 Jun 2023; median follow-up, 15.9 months)	^{177}Lu-PSMA-617 (N=234)	ARPI change (N=234)
Cycles, median (range)	6.0 (1–6)	–
rPFS[a]		
Events, n (%)	115 (49.1)	168 (71.8)
Median (95% CI), months	12.02 (9.30, 14.42)	5.59 (4.17, 5.95)
HR (95% CI), *p*	0.43 (0.33, 0.54), <0.0001	
TTW in FACT-P Total[b]		
Events, n (%)	167 (71.4)	187 (79.9)
Median (95% CI), months	7.46 (6.08, 8.51)	4.27 (3.48, 4.53)
HR (95% CI)	0.59 (0.47, 0.72)	
	N=105	**N=103**
ORRc, % (95% CI)	41.9 (32.3, 51.9)	12.6 (6.9, 20.6)
	N=44	**N=13**
DORc, median (95% CI), months	17.1 (11.6, NE)	10.1 (4.6, NE)

[a]Radiographic progression or death [b]Time to worsening in FACT-P Total, clinical disease progression, or death [c]Soft tissue only NE, not estimable.

Conclusions: ^{177}Lu-PSMA-617 prolonged rPFS vs ARPI change in taxane-naive pts with PSMA+ mCRPC, with a favourable safety profile.

Drs. O. Sartor, M.J. Morris and K. Fizazi have equally contributed to the study.

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LBA84 Enzalutamide and 177Lu-PSMA-617 in poor-risk, metastatic, castration-resistant prostate cancer (mCRPC): A randomised, phase II trial: ENZA-p (ANZUP 1901)

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Background: Enzalutamide (ENZA) and Lutetium-177-prostate-specific membrane antigen-617 (LuPSMA) both improve overall survival (OS) in mCRPC. Preclinical and clinical data suggest synergy for LuPSMA with androgen receptor pathway inhibitors (ARPI) in mCRPC. We evaluated the activity and safety of combining ENZA with adaptive-dosing of LuPSMA vs ENZA alone as first-line treatment for mCRPC.

Methods: Participants (pts) had mCRPC not previously treated with chemotherapy or ARPI (prior abiraterone and/or docetaxel for hormone-sensitive disease were allowed), ^{68}Ga-PSMA-positive disease on positron emission tomography (PET), and at least 2 risk factors associated with early progression on ENZA. Pts were randomised (1:1) to either ENZA 160 mg daily (ENZA-alone), or ENZA 160 mg daily plus adaptive dosing LuPSMA 7.5 GBq on days 15 and 57, with 2 further doses of LuPSMA if persistent PSMA-positive disease on interim ^{68}Ga-PSMA PET (day 92) (ENZA+LuPSMA). The primary endpoint was PSA-progression free survival (PSA-PFS). Secondary endpoints include radiological PFS (rPFS), PSA50% and PSA90% response rates (PSA50RR, PSA90RR), adverse events (AE), and OS.

Results: We randomised 162 pts from Aug 2020 to Jul 2022: median age 71 (range 45-96), prior docetaxel in 54%, and prior abiraterone in 13%. Imaging screen failure rate was 18% (40/220). 16% (13) of pts received between 2-3 doses of LuPSMA and 81% (67) received 4 doses. The median follow up was 20 months (IQR 18-21). PSA-PFS was longer with ENZA+LuPSMA vs ENZA-alone (median 13 vs 7.8 months; HR 0.43 [95%CI 0.29-0.63], $p<0.001$). PSA50RR and PSA90RR were higher with ENZA+LuPSMA vs ENZA-alone: 93% (77/83) vs 68% (54/79) ($p<0.001$) and 78% (65/83) vs 37% (29/79) ($p<0.001$) respectively. Analysis of rPFS (ongoing) will be presented. SAE were reported in 33% (27/81) of pts assigned ENZA+LuPSMA vs 35% (28/79) ENZA-alone.

Conclusions: The addition of adaptive-dosing of LuPSMA (2-4 doses) to ENZA improved PSA-PFS, PSA50RR, and PSA90RR. Our data supports enhanced anti-cancer activity with the use of adaptive-dosed LuPSMA together with ENZA as first-line treatment in mCPRC.

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Legal entity responsible for the study: ANZUP Cancer Trials Group Limited.

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LBA85 Niraparib (NIRA) with abiraterone acetate plus prednisone (AAP) as first-line (1L) therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations: Three-year update and final analysis (FA) of MAGNITUDE

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Background: In the phase 3 MAGNITUDE study (NCT03748641), NIRA + AAP significantly improved radiographic progression-free survival in *BRCA*-mutant *(BRCA+)* pts. Here we present the FA of MAGNITUDE, a phase 3 study with the largest population of 1L *BRCA*+ mCRPC pts, reporting mature overall survival (OS) data and prespecified multivariate analysis (MVA) for OS, addressing baseline imbalances.

Methods: Eligible pts (N = 423) with HRR+ mCRPC were randomized 1:1 to NIRA + AAP (n = 212) or placebo (PBO) + AAP (n = 211) as 1L therapy. At this FA, secondary endpoints of OS and time to cytotoxic chemotherapy (TCC) were formally assessed. Updates to time to symptomatic progression (TSP) and patient-reported outcomes (PROs) in *BRCA*+ pts and to safety for all HRR+ pts are also reported.

Results: At FA, 225 *BRCA*+ pts were evaluated; 113 pts received NIRA + AAP. Median follow-up was 35.9 months. In the NIRA + AAP and PBO + AAP arms, 70% and 86% of pts received subsequent life-prolonging therapy. OS favored NIRA + AAP over PBO + AAP (Table). A prespecified MVA adjusting for baseline imbalances showed an OS benefit favoring NIRA + AAP. Continued improvement in TSP and a clinically meaningful improvement in TCC were observed with NIRA + AAP. Time to worst pain progression and time to pain interference progression also favored NIRA + AAP. No new safety signals were observed with additional treatment exposure. Pulmonary embolism occurred in 4.7% and 1.4% of pts in NIRA + AAP and PBO + AAP arms, with no cases of myelodysplastic syndrome or acute myeloid leukemia in the NIRA + AAP arm.

Table: LBA85 Endpoints at FA in pts with *BRCA*+ mCRPC, NIRA + AAP vs PBO + AAP

	HR	95% CI	Nominal P
OS	0.79	0.55-1.12	0.18
OS with MVA	0.66	0.46-0.95	0.02
TSP	0.56	0.37-0.85	0.01
TCC	0.60	0.39-0.92	0.02
Time to worst pain progression	0.81	0.52-1.25	
Time to pain interference progression	0.77	0.48-1.23	

Conclusions: OS favored NIRA + AAP for pts with *BRCA*+ mCRPC. NIRA + AAP led to improvements in TSP, TCC, and PROs. The positive benefit-risk profile supports 1L NIRA + AAP as a new standard of care for pts with *BRCA*+ mCRPC.

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LBA86 Androgen receptor pathway inhibitors or taxanes for patients with metastatic castration-resistant prostate cancer: A direct comparison in ProBio, a randomized, outcome-adaptive, biomarker-driven platform trial

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Background: The Prostate Biomarker (ProBio) trial is an international biomarker-driven, randomized, outcome-adaptive platform trial in men with metastatic castrate resistant prostate cancer (mCRPC) evaluating multiple agents.

Methods: We used outcome-adaptive randomization to compare biomarker-driven treatment selection (experimental arms) against physician's choice standard-of-care (SOC; control arm), and to compare agents against each other within the experimental treatment arms. Men with mCRPC were randomized based on genomic alterations in circulating tumor DNA in five biomarker signatures: (1) *AR wt and TP53 wt*; (2) *TP53 mut;* (3) *DRD*; (4) *TMPRSS2:ERG fusion*; (5) *all* biomarkers signatures combined. Androgen receptor pathway inhibitors (ARPi; abiraterone and enzalutamide) and taxanes (docetaxel and cabazitaxel) were evaluated, using progression-free survival, by no longer clinically benefiting per PCWG3 criteria (PFS), as primary endpoint. Enrollment in the experimental group was stopped when the Bayesian probability of superiority reached prespecified thresholds ("graduation").

Results: In total, 219 men were randomized: 92 to SOC, vs. 76 and 51 to taxanes and ARPi, respectively, in the biomarker-driven arms. ARPi graduated in the "signature *all*", i.e. a signature encompassing all biomarkers. The median estimated PFS was 11.3 months (90% Bayesian credible interval [CI], 9.8 to 13.1) for ARPi compared with 7.2 months (90% CI, 6.5 to 8.1) in the SOC arm, for a hazard ratio (HR) of 0.52 (90% CI 0.37 to 0.72). ARPi demonstrated superiority to taxanes within the experimental arms (HR 0.54; 90% CI 0.38 to 0.76). We observed suggestive differential treatment effects for patients with *TP53 mut* and *TMPRSS2:ERG fusion* disease. The median estimated overall survival (OS) was 37.3 months (CI, 27.7 to NA) for ARPi compared with 20.2 months (90% CI, 18.4 to 23.0) taxanes within the experimental arms.

Conclusions: ARPi increases PFS and OS both compared to SOC and taxanes in patients with mCRPC. These are directly randomized data for ARPi and taxanes, showing the first evidence of a difference in PFS and OS for these agents in the mCRPC setting.

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Renal cancer

LBA87 Phase II LITESPARK-003 study of belzutifan in combination with cabozantinib for advanced clear cell renal cell carcinoma (ccRCC)

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Background: Initial results from the phase 2 LITESPARK-003 (NCT03634540) study showed promising antitumor activity for belzutifan plus cabozantinib as first-line (cohort 1) and subsequent-line (cohort 2) treatment for patients (pts) with advanced ccRCC. We present updated results from cohorts 1 and 2.

Methods: Eligible pts had advanced ccRCC and ECOG PS of 0 or 1. Cohort 1 included pts with no prior systemic therapy for advanced RCC. Cohort 2 included pts who had received prior immunotherapy and $\leq$2 systemic regimens for advanced RCC. All pts received oral belzutifan 120 mg and oral cabozantinib 60 mg once daily. The primary end point was ORR per RECIST v1.1 by investigator assessment. Secondary end points included DOR, PFS, OS, and safety.

Results: A total of 50 pts were enrolled in cohort 1 and 52 pts in cohort 2. Most (n = 28; 56%) pts in cohort 1 had IMDC favorable risk and most (n = 41; 79%) in cohort 2 had IMDC intermediate/poor risk. Median follow-up was 24.3 mo (range, 4.1-48.2) in cohort 1 and 39.8 mo (range, 33.1-55.0) in cohort 2. ORR is shown in the Table. Median DOR was 28.6 mo (range, 1.9+ to 35.8) in cohort 1 and 31.5 mo (range, 4.2+ to 36.8) in cohort 2. An estimated 57% of all responders in cohort 1 and 51% in cohort 2 remained in response for $\geq$24 mo. Median PFS was 30.3 mo (95% CI, 16-not reached [NR]) in cohort 1 and 13.8 mo (95% CI, 9-19) in cohort 2. Median OS was NR (95% CI, NR-NR) in cohort 1 and 26.7 mo (95% CI, 20-41) in cohort 2. Overall, 23 (46%) pts in cohort 1 and 33 (63%) in cohort 2 had a grade 3-5 treatment-related AE (TRAE). No pts died due to a TRAE in cohort 1 and 1 pt (2%) died due to a TRAE (respiratory failure) in cohort 2.

Conclusions: In this updated analysis of LITESPARK-003, belzutifan plus cabozantinib showed durable antitumor activity and a safety profile consistent with prior observations. These results further support the combination of an HIF-2α inhibitor and VEGFR-TKI as a potential treatment option for advanced ccRCC in both the first- and subsequent-line settings.

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Table: LBA87

	Cohort 1			Cohort 2		
	Total (n = 50)	IMDC favorable (n = 28)	IMDC intermediate/poor (n =22)	Total (n = 52)	IMDC favorable (n = 11)	IMDC intermediate/poor (n = 41)
ORR, % (95% CI)	70 (55-82)	79 (59-92)	59 (36-79)	31 (19-45)	27 (6-61)	32 (18-48)
Best overall response, n (%)						
CR	4 (8)	3 (11)	1 (5)	2 (4)	0	2 (5)
PR	31 (62)	19 (68)	12 (55)	14 (27)	3 (27)	11 (27)
SD	14 (28)	6 (21)	8 (36)	32 (62)	8 (73)	24 (59)
PD	1 (2)	0	1 (5)	3 (6)	0	3.(7)
NA	0	0	0	1 (2)	0	1 (2)

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LBA88 Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): Randomized open-label phase III LITESPARK-005 study

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Background: Belzutifan is a first-in-class oral HIF-2α inhibitor approved in the US for patients with VHL disease-associated RCC, pNET and CNS hemangioblastoma and has antitumor activity in ccRCC. The phase 3 LITESPARK-005 study (NCT04195750) compares belzutifan vs everolimus in pretreated advanced ccRCC.

Methods: Pts aged ≥18 yrs with KPS ≥70% and advanced ccRCC (1-3 prior systemic regimens including anti—PD-[L]1 mAb and VEGF-TKI) were randomized 1:1 to belzutifan 120 mg QD or everolimus 10 mg QD until progression or unacceptable toxicity. Dual primary endpoints were PFS per RECIST 1.1 by blinded independent central review (BICR) and OS. Secondary endpoints included ORR per RECIST 1.1 by BICR (key), safety and time to deterioration (TTD) per FKSI-DRS. PFS, ORR were formally tested at first interim analysis (IA1).

Results: 374 pts were randomized to belzutifan, 372 to everolimus. At IA1 (median follow up [fu] 18.4 mo; range 9.4—31.7), PFS and ORR were superior with belzutifan vs everolimus (Table); OS did not reach statistical significance. At IA2 (median fu 25.7 mo; range 16.8—39.1), PFS, OS and ORR results were consistent with IA1. Complete responses occurred in 13 (3.5%) vs 0 pts with belzutifan vs everolimus. More pts remained progression-free with belzutifan vs everolimus at 12 mo (PFS rate 33.7% vs 17.6%) and 18 mo (22.5% vs 9.0%). 22.6% vs 5.0% of pts had ongoing treatment; 5.9% vs 14.7% of pts discontinued study therapy due to any AE. Grade 3-5 TRAEs occurred in 38.7% vs 39.4% of pts. TTD for FKSI-DRS favored belzutifan (median not reached vs 12.0 mo; HR 0.53; 95% CI 0.41—0.69; nominal $P<.0001$).

Table: LBA88

	IA1		IA2	
	Belzutifan (n=374)	Everolimus (n=372)	Belzutifan (n=374)	Everolimus (n=372)
Median PFS, mo	5.6	5.6	5.6	5.6
HR (95% CI)	0.75 (0.63—0.90)		0.74 (0.63—0.88)	
P-value	<.001*		Not applicable	
Median OS, mo	21.0	17.2	21.4	18.1
HR (95% CI)	0.87 (0.71—1.07)		0.88 (0.73—1.07)	
P-value	0.09583		0.09941	
ORR, % (95% CI)	21.9 (17.8—26.5)	3.5 (1.9—5.9)	22.7 (18.6—27.3)	3.5 (1.9—5.9)
P-value	<.00001*		Not applicable	

* denotes statistical significance.

Conclusions: Belzutifan was associated with a statistically significant improvement in PFS and ORR vs everolimus for pts with advanced ccRCC after immune checkpoint and anti-angiogenic therapies. The safety profile of belzutifan was consistent with prior reports with no new safety signals.

Clinical trial identification: MK-6482 LITESPARK-005; (NCT04195750).

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Sarcoma

LBA89 Efficacy and safety findings from MANTRA: A global, randomized, multicenter, phase III study of the MDM2 inhibitor milademetan vs trabectedin in patients with dedifferentiated liposarcomas

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Background: New treatments are needed for advanced dedifferentiated liposarcoma (DDLPS), which is characterized by *MDM2* gene amplification. Milademetan is a selective, potent, small molecule inhibitor of the MDM2-p53 interaction that reactivates p53 to induce apoptosis of *TP53* wild-type malignant cells. MANTRA (RAIN-3201; NCT04979442) is a global, randomized, multicenter, phase 3 study of milademetan vs. trabectedin in pretreated unresectable/metastatic DDLPS.

Methods: Eligible pts: ≥18y; unresectable/metastatic DDLPS±WD; ≥1 prior systemic therapies (≥1 anthracycline regimen); radiographic evidence of PD ≤6m. Pts were randomized (1:1) to milademetan (260 mg orally QD d1−3 & d15−17 q28d) or trabectedin (1.5 mg/m^2, 24-h iv infusion q3w) until PD or intolerability. Tumor response was evaluated at w8, 16, 24&32, then q12w. Primary endpoint: PFS by blinded independent central review (BICR). Secondary endpoints: OS; ORR; DCR; DOR; PFS by investigator; safety. Study sample size was estimated to support primary endpoint in favor of milademetan (HR 0.5, 94% power, type I error 0.05).

Results: Median age: 64y (range 20−82y); white (69.7%), male (56.6%). Median follow-up: 2.1m (range 0−13m). Median PFS by BICR was numerically but not significantly higher for milademetan. While immature, median OS was comparable in the two arms, as were ORR and DCR. Most common all grade and grade 3/4 TEAEs for milademetan (Table). No Grade 5 events occurred with milademetan vs. 5 with trabectedin. Dose reductions due to TEAEs were higher but discontinuation rates lower with milademetan.

Conclusions: While median PFS was longer for milademetan, the difference was not significant. TEAEs were consistent with previous reports and manageable by dose interruptions/modifications. Further evaluation of milademetan is warranted in populations that may benefit from MDM2 inhibition.

Table: LBA89 Study findings

Efficacy population	Milademetan (n =86)	Trabectedin (n =89)
Median PFS by BICR, m	3.6	2.2
	HR=0.89 (95% CI 0.61−1.29; p=0.53)	
Median PFS by investigator, m	3.7	2.1
	HR=0.80 (95% CI 0.55−1.15; p=0.22)	
Median OSa, m	9.5	10.2
	HR=1.27 (95% CI 0.80−2.04; p=0.31)	
ORR, n (%)	4 (4.7)	3 (3.4) p=0.67
DCR, n (%)	29 (33.7)	24 (27.0) p=0.33
Safety population	**n=86**	**n=79**
Most common milademetan TEAEs, %		
Nausea	70.9	58.2
Thrombocytopenia	61.6	25.3
Anemia	44.2	36.7
Vomiting	44.2	19.0
Most common grade 3/4 milademetan TEAEs, %		
Thrombocytopenia	39.5	13.9
Neutropenia	25.6	26.6
Anemia	18.6	19.0
TEAEs − fatal/grade 5, %	0	6.3
TEAEs leading to dose reductions, %	44.2	29.1
TEAEs leading to discontinuations, %	11.6	19.0

Clinical trial identification: RAIN-3201; NCT04979442.

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LBA90 A randomized phase II study of durvalumab and tremelimumab compared to doxorubicin in patients with advanced or metastatic soft tissue sarcoma (MEDISARC, AIO-STS-0415)

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Background: Doxorubicin (DOX) is the standard of care (SOC) in patients with advanced or metastatic soft tissue sarcomas (STS) who cannot receive combination therapy. We tested whether the combination of durvalumab (DUR) and tremelimumab (TRE) improved overall survival (OS) compared to single agent DOX.

Methods: Treatment-naïve patients with chemo-sensitive advanced or metastatic STS who were not candidates for curative surgery or combination therapy were eligible. Key inclusion criteria were: ECOG performance status 0-2, grade 2 or 3, adequate organ function. Patients were 1:1 randomized (stratified by ECOG) to receive DUR 1.5g i.v. q4wks and TRE 75 mg i.v. 3x q4wks and q12wks thereafter for a maximum of 12 months or doxorubicin 75 mg/m^2 q3wks for up to 6 doses. OS was the primary endpoint. Secondary endpoints include 2-year OS rate, PFS, ORR (mRECIST 1.1), PFS, DOR, as well as safety (CTCTAE 4.03) and health-related quality of life (EORTC QLQ-C30). All randomized and treated subjects were included in the efficacy and safety analyses.

Results: Between April 2018 and September 2020 a total of 103 patients were randomized. 55% were female. Median age was 61 (r: 23-82) years. Most frequent STS were: leiomyosarcoma (LMS; 27%), undifferentiated pleomorphic sarcoma (UPS; 19%) and liposarcoma (LPS; 18%). PFS and 6-mo. PFS for DUR-TRE vs. DOX were 2.7 (95%CI 2.4-2.9) vs. 2.8 (95%CI 2.6-4.9) mo. (P=.401) and 11.4% vs. 33.6%, respectively. OS for DUR-TRE vs. DOX was 17.4 (95%CI 9.1-23.5) vs. 12.5 (95%CI 9.6-15.6) mo., which corresponded to a HR of 0.73 (95%CI 0.54-0.99; P=.185). 2-year OS was 35.7% vs. 29.0% for DUR-TRE vs. DOX, respectively. Adverse events (AE) of any grade and AE with grade ≥3 were 90.6% vs. 89.7% and 52.8% vs. 41.0% for DUR-TRE vs. DOX, respectively.

Conclusions: DUR-TRE showed comparable clinical activity to single agent DOX in treatment-naïve patients with STS. While OS favored DUR-TRE treatment, it did not reach significance. Our study indicated the principle activity of DUR-TREM in STS and warrants further studies.

Clinical trial identification: NCT03317457; EudraCT: 2016-004750-15.

Legal entity responsible for the study: AIO-Studien-gGmbH.

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LBA91 TOMAS2: A randomized phase II study from the Italian Sarcoma Group (ISG) of trabectedin plus olaparib (T+O) or trabectedin (T) in advanced, metastatic, or unresectable soft tissue sarcomas (STS) after failure of standard treatments

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Background: Advanced STS represent an unmet medical need. We previously reported feasibility and preliminary activity data of T+O in advanced STS failing standard treatments.

Methods: In this investigator-initiated, open-label, phase 2 randomized trial, adult patients (pts) with advanced STS progressing after $\geq$1 treatment(s) were randomized in a 1:1 ratio to T 1.1 mg/m2 q21d i.v. plus O tablets 150 mg BID, or T 1.5 mg/m2 q21d i.v. Randomization stratified pts for histology (L-sarcoma *vs* non-L-sarcoma) and number of prior lines (1 vs $\geq$2). Primary endpoint: progression-free survival (PFS) rate at 6-month (PFS6m) by RECIST 1.1. Main secondary endpoints: PFS, overall survival (OS), RECIST 1.1 overall response rate (ORR), duration of response (DOR), safety. Exploratory endpoints: correlation of clinical characteristics and molecular biomarkers with outcomes.

Results: Between May-2020 and Nov-2022, 130 pts were enrolled (M/F 49/81; L-/Non-L-sarcoma 67/63; prior lines 1/$\geq$2 93/37) at 13 ISG sites. With a median (m-)follow-up of 10.2 mos, estimated PFS6m and m-PFS per intention-to-treat were 32% (95%CI 22-46%) and 4.0 mos (2.9-5.4) in T+O arm; 28.5% (19.3-42.1) and 2.9 mos (2.2-4.5) in T arm. PFS12m was 20% (12-33) with T+O and 2% (0-14) with T. Best response in 122 evaluable pts was: 6 PR, 25 SD, 31 PD in T+O arm, and 4 PR, 21 SD, 35 PD in T arm, for an ORR of 10 and 7%, respectively. m-DOR was 14.5 mos with T+O and 4.5 with T. OS events were not mature but did not differ between the two arms. Most common grade $\geq$3 adverse events were neutropenia (58%) thrombocytopenia (20%) and anemia (18.5%) with T+O, and neutropenia (31%), ALT increase (26%) and thrombocytopenia (8%) with T. 5 pts in T+O (8%) and 2 in T (3%) discontinued treatment due to toxicity. No toxic death was reported. Data on available exploratory endpoints will be presented at the meeting.

Conclusions: This is the first randomized trial prospectively testing T+O and T in advanced STS pts. PFS6m with T+O was slightly below the prespecified threshold of 40%. Notably, 20% of pts in T+O were treated for $>$1 year and deepening into biomarkers of these long responders would improve selection of pts for T+O.

Clinical trial identification: NCT03838744; EudraCT 2018-004497-10.

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SCLC

LBA92 Tarlatamab for patients (pts) with previously treated small cell lung cancer (SCLC): Primary analysis of the phase II DeLLphi-301 study

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Background: Tarlatamab, a bispecific T-cell engager (BiTE), represents a new immunotherapeutic approach for SCLC. It binds to both delta-like ligand 3 (DLL3) on SCLC cells and CD3 on T cells, resulting in T-cell mediated tumor lysis. A phase 1 study demonstrated encouraging safety and efficacy (median duration of response (mDoR): 12.3 mo; median overall survival (mOS): 13.2 mo) in previously treated SCLC. Here, the phase 2 data from the DeLLphi-301 study are presented.

Methods: Pts with SCLC who relapsed after 1 platinum-based regimen ($\pm$ checkpoint inhibitor) and at least 1 other prior line of therapy received 10 mg or 100 mg tarlatamab Q2W. The primary endpoint was objective response rate (ORR) by blinded independent central review (RECIST 1.1). Other endpoints were DoR, progression-free survival (PFS), OS, and treatment-emergent adverse events (TEAEs).

Results: Overall, 220 pts received tarlatamab. The median follow-up was 10.6 mo for efficacy outcomes (Table). At the 10 mg dose, ORR was 40.0%, mPFS was 4.9 mo, mOS was 14.3 mo, and mDoR was not reached, with 57.5% of responders experiencing $\geq$ 6 mo of response and 55.0% still with an ongoing response. The most common TEAE was cytokine release syndrome (CRS; 51.1%, 10 mg; 60.9%, 100 mg), primarily occurring in cycle 1, and was mostly grade 1 or 2. Incidence of grade 3 CRS (0.8%, 10 mg; 5.7%, 100 mg) and grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) and associated neurologic events was low (0%, 10 mg; 4.6%, 100 mg), with no grade 4 or 5 events. Discontinuations due to treatment-related AEs were infrequent (3.0%, 10 mg; 3.4%, 100 mg). Similar safety profiles were seen with 24h or 48h inpatient monitoring.

Table: LBA92

	10 mg (n = 100)*	100 mg (n = 88)*
ORR, % (97.5% CI)	40.0 (29.1–51.7)	31.8 (21.1–44.1)
Complete response, n (%)	1 (1.0)	7 (8.0)
Partial response, n (%)	39 (39.0)	21 (23.9)
Stable disease, n (%)	30 (30.0)	27 (30.7)
Progressive disease, n (%)	20 (20.0)	13 (14.8)
Not evaluable, n (%)	2 (2.0)	4 (4.5)
Death before post-baseline scan, n (%)	6 (6.0)	13 (14.8)
No post-baseline scan, n (%)	2 (2.0)	3 (3.4)
mDoR, mo (95% CI)	NE (5.9–NE)	NE (6.6–NE)
Disease control rate % (95% CI)	70.0 (60.0, 78.8)	62.5 (51.5, 72.6)
mOS, mo (95% CI)	14.3 (10.8–NE)	NE (12.4–NE)
mPFS, mo (95% CI)	4.9 (2.9–6.7)	3.9 (2.6–4.4)

*Efficacy analysis set per intention-to-treat (ITT) analysis (Pts in safety substudy (n = 34) not included as data immature). NE = not estimable

Conclusions: Tarlatamab demonstrated impressive antitumor activity with durable responses and promising survival. Tarlatamab showed a favorable benefit-risk profile with no new safety signals, supporting the use of tarlatamab in pts with previously treated SCLC.

Clinical trial identification: NCT05060016.

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LBA93 EXTENTORCH: A randomized, phase III trial of toripalimab versus placebo, in combination with chemotherapy as a first-line therapy for patients with extensive stage small cell lung cancer (ES-SCLC)

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Background: Combinations of immunotherapy with chemotherapy as a first-line treatment for ES-SCLC have generated mixed results. The EXTENTORCH trial assessed toripalimab in combination with chemotherapy as a first-line treatment for patients with ES-SCLC (NCT04012606).

Methods: Patients with histologically or cytologically confirmed ES-SCLC, stratified by gender and baseline ECOG PS (0 vs. 1) were randomized in a 1:1 ratio to receive 240 mg toripalimab or placebo plus etoposide and cisplatin/carboplatin Q3W for 4-6 cycles,

followed by single-agent toripalimab or placebo until progressive disease, intolerable toxicity or up to 2-year treatment. The primary endpoints were PFS as assessed by the investigator per RECIST v1.1 and OS. Tumor mutational burden (TMB) and genomic alterations were assessed by whole-exome sequencing (WES) of tumor tissues.

Results: From Sep 2019 to May 2021, 442 patients were enrolled from 48 participating sites in China. 223 and 219 patients were randomized to the toripalimab and the placebo arms, respectively. At data cut off (28 Feb 2022), median follow-up was 11.8 months, a significant improvement in PFS was observed for toripalimab over placebo (5.8 vs. 5.6 months, HR = 0.667 [95% CI: 0.539-0.824], P = 0.0002). Despite 59.4% of patients in the placebo arm received ≥3 additional lines of therapy and 25.6% received a PD-(L)1 inhibitor after the study treatments, OS was significantly improved in the toripalimab arm (14.6 vs. 13.3 months, HR = 0.798 [95% CI: 0.648-0.982], P = 0.0327) at the final OS analysis at data cut off (20 Apr 2023). WES results from 300 patients showed that improvements in PFS and OS were similar irrespective of TMB status. Genomic alterations in integrin-mediated focal adhesion complex were associated with poor prognosis for both PFS and OS in the toripalimab arm. Toripalimab plus chemotherapy had a manageable safety profile, with no new safety signals observed.

Conclusions: The addition of toripalimab to chemotherapy provided significant improvements in PFS and OS for patients with ES-SCLC with an acceptable safety profile.

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Supportive care

LBA94 Effects of short-term fasting on quality of life as an add-on option during chemotherapy

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Background: Growing pre- and clinical evidence show that short-term fasting (STF) of 48 to 72 hours around each chemotherapy (CTX) may potentially support CTX, reducing toxicity and adverse effects.

Methods: This randomised multi-center study of breast cancer (BC) patients undergoing CTX was conducted to assess feasibility and health-related quality of life (HRQoL) for 60-72 h STF compared to a plant-based low-sugar diet (PBD). HRQoL was assessed by FACT-G, FACIT-F (fatique) and further questionnaires at baseline (V0) and after each CTX session (day 7) as well as after 4 (V1) and 6 (V2) months. Laboratory parameters were collected at the same time points. CTX consisted of 4 x AC or EC, followed by either 12 x paclitaxel (Pac) (80 mg/m^2) weekly or 4 x docetaxel (Doc) three-weekly (100 mg/m^2).

Results: 106 patients were included in the study and randomized to STF (n=52) or PBD (n=56). 90 (84.9%) patients obtained AC/EC -> Pac and 16 (15.1%) AC/EC -> Doc. The 27-item generic CORE questionnaire FACT-G measuring four domains of HRQoL (physical, social/family, emotional, and functional well-being) showed no significant difference at V0 (STF 82.9; PBD 81.9; p=0.523). STF-patients' FACT-G improved at day 7 from cycle to cycle versus PBD-patients. At cycle 4, day 7, FACT-G for STF was 78.3 (std. error (SE) 2.7; 95% C.I. 72.8-83.7) and for PBD 69.3 (SE 2.6: 95% C.I. 64.0-74.6). The difference 9.0 (SE 3.8) was statistically significant (p = 0.021) and clinically relevant (9.0 > minimal important difference (MID = 5)). The differences between the corresponding FACIT-F Trial Outcome Index resp. Total FACIT-F at cycle 4 day 7 were 13.1 (SE 4.7) resp. 15.8 (SE 5.6), both in favor of STF (> MID= 6, p < 0.007). The mean Total Hospital Anxiety and Depression Score (HADS-T) shows mental distress (HADS-T ≥ 13) for both STF and PBD at V0 and cycle 4 day 7 with no statistically significant differences. At V0 mean platelet counts (MPCs) were 256.6 (SE 10.8) for STF and 266.2 (SE 9.9) for PBD (p=0.512). At cycle 4 day 7 MPCs were 209.5 (SE 13.7) for STF and 177.7 (SE 12.3) for PBD.

Conclusions: Neither STF nor PBD showed serious adverse effects in the studied population. STF during chemotherapy is well tolerated and appears to improve QoL and fatigue during chemotherapy compared to a plant-based low-sugar diet.

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LBA95 Anamorelin and weight gain in patients with advanced non-small cell lung cancer (NSCLC) and cachexia: Efficacy and safety in the multinational phase III SCALA program

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Background: Anamorelin is a potent, selective and well-tolerated orally available ghrelin agonist. It is marketed in Japan for the treatment of cachexia in patients with lung and gastrointestinal malignancies since early 2021. Results of two phase III trials comparing anamorelin versus placebo in cachectic non-Japanese NSCLC patients are described.

Methods: Between March 2019 and August 2022, a total of 636 subjects (318 per study) with advanced NSCLC, ECOG PS 0-2, BMI<20 kg/m^2, and unintentional weight loss >2% in the previous six months, were randomized 1:1 to receive 100 mg of anamorelin or a placebo orally QD for 24 weeks in two confirmatory studies with identical design (SCALA-1 and SCALA-2). Primary endpoints were changes from baseline over 12 weeks in scale body weight and in the FAACT anorexia-cachexia 5-domain symptom score (5-IASS).

Results: In both studies, anamorelin significantly increased body weight over 12 weeks compared to placebo (p<0.0001). Least square means (95% CI) treatment difference was +1.37 kg (+0.737; +2.001) for SCALA-1 and +1.30 kg (+0.720; +1.865) for SCALA-2. Changes of 5-IASS scores for anamorelin versus placebo were not significantly different in both studies. Overall, 71.2% (anamorelin) and 73.4% (placebo) of patients experienced any Treatment Emergent Adverse Event (TEAE). There was no difference when serious TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs of special interest were considered. Severe hyperglycemia was reported only in two patients both receiving anamorelin (0.6%).

Conclusions: The SCALA trials demonstrate that anamorelin improves body weight in individuals with advanced NSCLC and cachexia. The observed effect on body weight is consistent with data from all eight previously conducted double-blind, placebo-controlled studies that randomized 1,696 cancer patients. The positive benefit-risk profile strongly emphasizes the therapeutic potential of anamorelin for treating unintended weight loss in patients with advanced NSCLC and cachexia.

Legal entity responsible for the study: Helsinn Healthcare SA.

Funding: Helsinn Healthcare SA.

Disclosure: D. Currow: Financial Interests, Institutional, Speaker, Consultant, Advisor: Helsinn Healthcare SA, Specialist Therapeutics ; Non-Financial Interests, Institutional, Advisory Board: Helsinn Healthcare SA. S. Chessari: Other, Officer, Helsinn Healthcare SA employee: Helsinn Healthcare SA. P. Bonomi: Financial Interests, Personal, Speaker, Consultant, Advisor, Advisor & Consultant, personal financial compensation: Helsinn Healthcare SA; Financial Interests, Institutional, Financially compensated role, Clinical trial investigator, institutional financial compensation: Helsinn Healthcare SA; Financial Interests, Personal, Speaker, Consultant, Advisor, Advisor, personal compensation: Pfizer; Other, Institutional, Non remunerated activity, Manuscript preparation, author on reports for data base studies, no compensation: Pfizer; Financial Interests, Institutional, Financially compensated role, Clinical trial investigator, institutional compensation: Pfizer; Financial Interests, Financially compensated role, Chair of independent data monitoring committee, personal compensation: Roche Genentech. R. Giorgino: Other, Personal, Speaker, Consultant, Advisor: Helsinn Healthcare SA. R. Skipworth: Financial Interests, Personal, Speaker, Consultant, Advisor, Consultant: Helsinn Healthcare SA, Actimed Therapeutics, Faraday Pharmaceuticals; Non-Financial Interests, Personal, Speaker, Consultant, Advisor, Consultant: Artelo Biosciences, Toray Pharmaceuticals.

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LBA96 Roxadustat for chemotherapy-induced anemia in patients with non-myeloid malignancies: A randomized, open-label, active-controlled, phase III study

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Background: Chemotherapy-induced anemia (CIA) is a common complication of cancer and an important risk factor leading to poor prognosis for patients. Recombinant human erythropoietin-α (rHuEPO-α) is standard of care for CIA; however, safety concerns remain. Roxadustat is the first hypoxia-inducible factor prolyl hydroxylase inhibitor approved for treatment of anemia in chronic kidney disease. This study evaluated the efficacy and safety of roxadustat for anemia in patients with non-myeloid malignancies receiving multi-cycle treatments of myelosuppressive chemotherapy.

Methods: In this open-label, non-inferiority, multicenter Phase III study conducted in China, patients were randomized (1:1) to receive oral roxadustat or subcutaneous rHuEPO-α three times weekly (TIW) for 12 weeks. Roxadustat starting dosage was 100 mg, 120 mg, and 150 mg TIW (patients weighing 40−<50, 50−60, and >60 kg). rHuEPO-α starting dosage was 150 IU/kg TIW. Both roxadustat and rHuEPO-α dosages could be modified to achieve hemoglobin (Hb) concentrations of 100−120 g/L. Primary efficacy endpoint was least-squares mean (LSM) change in Hb concentration from baseline to the concentration averaged over Weeks 9−13. Adverse events (AEs) were monitored.

Results: Of 159 patients randomized (n=82, roxadustat; n=77, rHuEPO-α), 140 were included in the per protocol set (n=78, roxadustat; n=62, rHuEPO-α). The LSM (95% 2-sided confidence interval [CI]) change from baseline to Weeks 9−13 in Hb concentration was 17.1 (13.58, 20.71) g/L with roxadustat and 15.4 (11.34, 19.50) g/L with rHuEPO-α. The lower bound of the 1-sided 97.5% CI for the treatment difference (−3.4 g/L) was greater than the predefined non-inferiority margin of −6.6 g/L, establishing non-inferiority. Results were supported by key secondary endpoints. AE rates were generally comparable between treatments and consistent with previous findings, supporting a positive benefit-risk profile.

Conclusions: Oral roxadustat was non-inferior to subcutaneous rHuEPO-α for anemia in patients with non-myeloid malignancies receiving multi-cycle treatments of myelosuppressive chemotherapy.

Clinical trial identification: FGCL-4592-898.

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Legal entity responsible for the study: FibroGen, Inc.

Funding: FibroGen, Inc.

Disclosure: S. Lu: Financial Interests, Speaker, Consultant, Advisor, speaker fees, advisor/consultant: AstraZeneca; Financial Interests, Speaker, Consultant, Advisor, speaker fees: Hansoh, Hengrui Therapeutics; Financial Interests, Speaker, Consultant, Advisor, advisor/consultant: Pfizer, Boehringer Ingelheim, Hutchison, ZaiLab, GenomiCare, Yuhan Corporation, Menarini, InventisBio Co., Simcere Zaiming, Roche; Financial Interests, Research Funding, research support: AstraZeneca, Hutchison, BMS, Heng Rui, BeiGene, Roche, Hansoh, Lilly Suzhou, Fibrogen. J. Wu: Financial Interests, Advisory Role: AstraZeneca, Roche, Novartis, Heng Rui, Lilly, FibroGen; Financial Interests, Other, consultant: AstraZeneca, Roche, Novartis, Heng Rui, Lilly, FibroGen. J. Jiang: Financial Interests, Research Funding: Heng Rui, Roche, Alphamab Oncology, FibroGen. Q. Guo: Financial Interests, Advisory Role: AstraZeneca, Roche, Novartis, Heng Rui, Lilly, FibroGen; Financial Interests, Other, consultant: AstraZeneca, Roche, Novartis, Heng Rui, Lilly, FibroGen. Y. Liu: Financial Interests, Speaker, Consultant, Advisor: Xinda, BeiGene, Roche, Hengrui Therapeutics, AstraZeneca, Qilu, BMS, Roche; Financial Interests, Research Funding: AstraZeneca, BeiGene, Roche, FibroGen. H. Zhang: Financial Interests, Advisory Role: AstraZeneca, Roche, Pfizer, Heng Rui, BMS, BeiGene, Roche, Innovent; Financial Interests, Other, consultant: AstraZeneca, Pfizer, Heng Rui, BMS, BeiGene, Roche, Innovent; Financial Interests, Officer, consultant: Roche. L. Qian: Financial Interests, Research Funding: GSK Plc, Sanofi, Mundi Pharma, Hutchison Whampoa Limited (HWL), Dalian Wanchun Biotechnology Co., Ltd., Shanghai Lunsheng Pharmaceutical Technology Co., Ltd., Innovent (Suzhou), FibroGen. X. Dai: Financial Interests, Research Funding: Luye Pharma, FibroGen. Y. Xie: Financial Interests, Other, speaker fees: AstraZeneca, Roche, Heng Rui, Lilly, Pfizer, MSD, Simcere, FibroGen. T. Fu: Financial Interests, Advisory Role: Heng Rui, Ji Shi, FibroGen; Financial Interests, Other, consultant: Heng Rui, Ji Shi, FibroGen. T. Lee, Y. Lu, R. Ma, M. Eisner: Financial Interests, Full or part-time Employment: FibroGen; Financial Interests, Stocks or ownership: FibroGen.. All other authors have declared no conflicts of interest.

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LBA97 Olanzapine for the prevention of chemotherapy induced nausea vomiting in patients receiving moderately emetogenic chemotherapeutic (MEC) regimens: Results of a prospective triple blinded phase III multicentric study (OMEC)

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Background: MEC regimens have lesser than expected control of nausea and vomiting with standard antiemetic prophylaxis. The role of olanzapine has not been adequately evaluated with these regimens.

Methods: In this randomized multicentric, triple-blind, phase 3 trial, we compared dexamethasone, aprepitant and palonosetron without (standard) or with the addition of olanzapine (experimental) in patients who were receiving oxaliplatin, carboplatin or irinotecan-based chemotherapy (MEC). The experimental group received 10 mg of olanzapine orally once at night on days 1 through 3. Complete response, defined as the proportion of subjects with no vomiting and no significant nausea, scored as < 5 on a visual analogue scale of 1-100, was the primary endpoint. The quality of life (QOL) was assessed by the Functional Living Index Emesis (FLIE). The study required to recruit 560 patients (280 patients per arm) to show preplanned improvement in CR rates.

Results: Of the 544 evaluable patients, baseline characteristics were evenly matched between the two groups. The proportion of patients with CR was significantly greater with olanzapine than without olanzapine in the overall 120-hour period (92.3% vs. 86.2%, P=0.022). The proportion of patients with no chemotherapy-induced nausea as well as combined chemotherapy induced nausea and vomiting (CINV) were significantly more with olanzapine than without in the period from 25 to 120 hours (delayed CINV) (nausea 96.7% vs. 88.5% p<0.001; CINV 95.3% vs. 86.3%; p<0.001). The overall use of rescue medications was lesser in patients receiving olanzapine (4% vs. 11.5%p=0.001). The use of olanzapine at 10 mg per day was not associated with any significant toxicities and QOL did not deteriorate by the addition of the olanzapine as assessed by FLIE.

Conclusions: The addition of olanzapine significantly improved CR rates as well as delayed CINV rates in previously untreated patients who were receiving moderately emetogenic chemotherapeutic regimens containing oxaliplatin, carboplatin or irinotecan. The use of olanzapine should be considered as standard of care in these chemotherapeutic regimens.

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Legal entity responsible for the study: The authors.

Funding: Cadilla Pharma PVT Ltd Dr Reddy's Lab PVT Ltd.

Disclosure: V.S. Ostwal: Financial Interests, Institutional, Advisory Board: Panacea, Reddy's Lab pvt limited, AstraZeneca, Zydus Cadila; Financial Interests, Personal, Invited Speaker, Expenses for travel and accommodation: AstraZeneca; Financial Interests, Institutional, Funding, Educational Grant: Reddy's Lab, Zydus Cadila; Financial Interests, Institutional, Other, Drug support: Intas Pharma pvt ltd, Esai Pharma, Alkem pvt ltd; Financial Interests, Institutional, Other, drug support: Micro Labs private limited; Non-Financial Interests, Leadership Role, secretary of Supportive care organization in India: Indian Association of supportive care in Cancer. A. Ramaswamy: Financial Interests, Institutional, Research Grant: Cipla Health Limited, Dr Reddy Laboratories, Zydus Lifesciences. P.G. Bhargava: Financial Interests, Institutional, Invited Speaker: Novartis, Intas, Roche, Pfizer; Financial Interests, Institutional, Advisory Board: Mankind, Zydus. I.N. Olver: Financial Interests, Personal, Invited Speaker, Subsidised airfare and accomodation to speak at the 2022 Annual Scientific Mettign In Toronto in June 2022: Multinational Association of Supportive Care in Cancer; Financial Interests, Personal, Advisory Board, On advisory board for this digital and oncology management platform company: Viecure; Financial Interests, Personal, Advisory Board, Provide advice on development of cannabinoids: BOD; Financial Interests, Personal, Full or part-time Employment, Pratt time employee as a professorial research fellow in the School of Psychology: University of Adelaide; Financial Interests, Personal, Full or part-time Employment, Employed by the Department of Medicine to teach ethics: University of Notre Dame Australia; Financial Interests, Personal, Full or part-time Employment, Sit on Bellberry Ethics Committees: Bellberry Ltd; Non-Financial Interests, Member of Board of Directors, Chair the Board of this knowledge generation institute: Sax Insittute; Non-Financial Interests, Member of Board of Directors, Sit on the Board of this charity that focuses on screening and prevention of bowel cancer: Jodie Lee Foundation. All other authors have declared no conflicts of interest.

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Thoracic malignancies, other

LBA98 Efficacy and safety of ramucirumab plus carboplatin and paclitaxel in untreated metastatic thymic carcinoma: RELEVENT phase II trial

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Background: Thymic carcinoma (TC) is a rare tumor with aggressive and poorly responsive behavior. In advanced lines, antiangiogenics showed activity in TC. Ramucirumab (R) is a VEGF2 inhibitor monoclonal antibody already approved for other solid tumors. RELEVENT trial was design to assess activity and safety of the combination of R plus carboplatin (CBDCA) and paclitaxel (PTX) as first line treatment in patients (pts) with advanced TC.

Methods: This academic open-label single arm phase II trial was conducted within the Italian network TYME. Eligible pts had naive advanced TC (pathological diagnosis was centrally reviewed). All pts received R 10 mg/kg, CBDCA AUC5 and PTX 200 mg/m2 d1q21 for 6 cycles, followed by R 10 mg/kg maintenance until disease progression or intolerable toxicity. The trial was conceived with a Green-Dahlberg 2-stage design, 30 pts were analyzed in the 1st stage (null hypothesis ORR 20%). In case of at least 5 responses, further 25 pts could have been added in the 2nd stage. The primary endpoint was ORR. DCR, PFS, OS and safety were secondary endpoints. A centralized radiologic review was performed.

Results: From 11/2018 to 06/2023, 52 pts were screened and 37 were enrolled. Median (m) age was 60.5 years, 26 (70.3%) pts were male and 32 (86.5%) had stage IVB disease. ECOG PS was 0 in 26 (70%) and 1 in 11 (30%) pts; 35 pts were assessable for the primary endpoint ORR. At the 1st stage, ORR (by investigator assessment) was 80% [95%CI 63.1-91.6] with DCR of 100% [95%CI 90-100]. At the centralized radiological review on 33/35 evaluable pts, ORR was 57.6% [95%CI 39.2-74.5], with 19 pts (57.6%) having a PR and 14 (42.4%) a SD, DCR was 100% [95%CI 89-100]. After a m follow up of 31.6 months [21.6-40.5], mPFS was 18.1 [95%CI 10.5-52.3] and mOS 43.8 [95%CI 22.5-NE] months. Of 35 pts, 28 (80%) experienced at least one treatment related adverse event (AE), 45.7% were G3 or more, (hypertension 8.8% and neutropenia 20% were the most common).

Conclusions: In previously untreated advanced TC, the addition of R to CBDCA and PTX showed highest activity compared to historical controls, with manageable safety profile. Despite the small number of pts, given the rarity of the disease, these results support the use of this combination as first line treatment in TC.

Clinical trial identification: NCT03921671.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori.

Funding: AIFA - Lilly.

Disclosure: C. Proto: Financial Interests, Personal and Institutional, Other: BMS and MSD. F.G.M. De Braud: Financial Interests, Personal and Institutional, Other: Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, Eli Lilly, F. Hoffmann-La Roche, Ignyta, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer.. R. Berardi: Financial Interests, Advisory Role: AZ, BOERINGHER, MSD, LILLY, Roche, Amgen, GSK, EISAI, BMS. P.A. Zucali: Financial Interests, Advisory Role: Merck Sharp & Dohme (MSD), Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol Meyer Squibb, Amgen, AstraZeneca, Roche, and Bayer. M.C. Garassino: Financial Interests, Advisory Role: AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda. G. Lo Russo: Financial Interests, Invited Speaker: Eli Lilly, BMS, Italfarmaco, Novartis, AstraZeneca, Merck Sharp and Dohme, Takeda, Amgen, F. Hoffmann-La Roche, Sanofi, Pfizer, GSK. All other authors have declared no conflicts of interest.

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LBA99 First survival data from the NIPU trial: A randomised, open-label, phase II study evaluating nivolumab and ipilimumab combined with UV1 vaccination as second-line treatment in patients with malignant mesothelioma

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Background: Immune checkpoint inhibitors have improved survival for patients with malignant pleural mesothelioma (MPM), but prognosis is still poor. The UV1 telomerase peptide vaccine has demonstrated robust immune response induction and promising clinical activity in several malignancies.

Methods: Patients with MPM progressing after first-line platinum-based chemotherapy were randomized 1:1 to ipilimumab and nivolumab alone (Arm B) or in combination with telomerase vaccine UV1 (Arm A). The primary endpoint was progression-free survival (PFS) evaluated by blinded, independent central review (BICR) at the time of 69 events. The study was powered to detect an HR of 0.60 in favour of arm A with a 1-sided alpha of 0.1.

Results: A total of 118 patients were included and randomized, well balanced with respect to age, gender, performance status, histology and PD-L1 status. The primary endpoint was assessed after a median follow-up of 12.5 months (95% CI 9.7-15.6). The HR for patients treated in arm A was 1.01 (80% CI 0.75-1.36, 95% CI 0.64-1.59) with a median PFS of 4.2 months (95% CI 2.9-9.8) in arm A and 4.7 months (95% CI 3.9-7.0) in arm B. Objective response rate was 31% in arm A and 16% in arm B (odds ratio 2.4, 95% CI 1.0-6.3). The investigator determined median PFS was 4.3 months (95% CI 3.0-6.8) in arm A and 2.9 months (95% CI 2.4-5.5) in arm B with a HR= 0.6 (80% CI 0.45-0.81, 95% CI 0.39-0.94). Overall survival after a median follow-up of 17.3 months (95% CI 15.8-22.9) was 15.4 months (95% CI 11.1-22.6) in arm A and 11.1 months (95% CI 8.8-18.1) in arm B, with a HR of 0.73 (80% CI: 0.53-1.0, 95% CI 0.45-1.18). The total number of adverse events and the proportion of patients experiencing a grade $\geq$3 adverse event was comparable in the two arms.

Conclusions: The primary endpoint in this study was not met. Supportive analyses indicate an increased ORR and clinically meaningful prolonged survival in the intervention arm. The results warrant confirmation in a larger clinical trial.

Clinical trial identification: EudraCT 2019-002721-30; NCT04300244.

Legal entity responsible for the study: Oslo University Hospital.

Funding: BMS, Ultimovacs, South-Eastern Norway Regional Health Authority, The Norwegian Cancer Society.

Disclosure: A. Helland: Financial Interests, Institutional, Advisory Board, Advisory boards: Jansen, Takeda, AstraZeneca, AbbVie, Roche, BMS, Pfizer, MSD, Bayer, Lilly,; Financial Interests, Institutional, Invited Speaker, talks at meetings: AstraZeneca, Roche, AbbVie, Pfizer; Financial Interests, Institutional, Coordinating PI, BMS provides drug to patients in an investigator initiated clinical trial: BMS; Financial Interests, Institutional, Coordinating PI, Ultimovacs provides drug and funds for investigator initiated clinical trial: Ultimovacs; Financial Interests, Institutional, Coordinating PI, AstraZeneca provides drug and funds for investigator initiated clinical trial: AstraZeneca; Financial Interests, Institutional, Coordinating PI, Roche provides drug and funds for investigator initiated clinical trial: Roche; Financial Interests, Institutional, Coordinating PI, Novartis provides drug and funds for clinical trial: Novartis; Financial Interests, Institutional, Coordinating PI, Eli Lilly provides drug and funds for clinical stduy: Eli Lilly; Financial Interests, Institutional, Coordinating PI, Incyte provides drug and funds for clinical stduy: Incyte; Financial Interests, Institutional, Coordinating PI, Illumina provides assays for patients in a clinical trial: Illumina; Non-Financial Interests, Other, Board member in the patient organisation until 2022. Provides advice and gives talks.: The lung cancer patients organisation. V.D. Haakensen: Other, Personal, Advisory Board, NSCLC: BMS, Novartis, AstraZeneca; Other, Personal, Invited Speaker, NSCLC: BMS, AstraZeneca; Other, Personal, Writing Engagement, NSCLC: Takeda; Other, Personal, Member: Patient organisation Lung Cancer. S.M.H. Thunold: Financial Interests, Personal, Invited Speaker: BMS. A.K. Nowak: Other, Institutional, Research Funding: AstraZeneca; Other, Personal, Invited Speaker: BMS; Other, Personal, Advisory Board: Douglas Pharmaceuticals. O. Grundberg: Other, Personal, Invited Speaker: Roche. S.J. Farooqi: Financial Interests, Personal, Other, Arranged conference: Merck; Financial Interests, Personal, Other, Made a short film about drug compliance: Pfizer; Financial Interests, Personal, Invited Speaker: AstraZeneca, BMS; Financial Interests, Personal, Other, Made a short film about targeted treatment: Amgen; Financial Interests, Personal, Other, Made a short film about Mesothelioma: BMS; Financial Interests, Personal, Advisory Board: BMS. M.M. Bjaanaes: Other, Institutional, Invited Speaker: AstraZeneca, Pfizer, BMS. All other authors have declared no conflicts of interest.

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Thyroid cancer

LBA3 Randomized phase III study of selpercatinib versus cabozantinib or vandetanib in advanced, kinase inhibitor-naïve, RET-mutant medullary thyroid cancer

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Background: Selpercatinib is a highly selective and potent RET inhibitor approved for treatment of advanced *RET*-mutant medullary thyroid carcinoma (MTC) but has not been directly compared with approved multikinase inhibitors (MKI).

Methods: LIBRETTO-531 (NCT04211337) is a randomized phase 3 study comparing first-line selpercatinib versus physician's choice of cabozantinib or vandetanib. Eligible patients had kinase inhibitor-naïve progressive disease documented in the 14 months prior to enrollment. The pre-planned interim efficacy analysis occurred after 59 progression-free survival (PFS) events. The primary endpoint was blinded independent central review (BICR)-assessed PFS.

Results: In total, 291 patients were randomized. Baseline characteristics were well-balanced between study arms. At a median follow-up of 12 months, median PFS by BICR was not reached with selpercatinib remaining inestimable (95% CI: NE, NE) and was 16.8 months (95% CI: 12.2, 25.1) with control (HR: 0.280, 95% CI: 0.165, 0.475; P<.0001); by investigator assessment the HR was 0.187 (95% CI: 0.109, 0.321; P<.0001). BICR overall response rate (ORR) was 69.4% (95% CI: 62.4, 75.8) with selpercatinib compared to 38.8% (95% CI: 29.1, 49.2) with control (odds ratio 3.7, 95% CI, 2.2, 6.3; P<0.0001). At a median follow-up of 15 months, overall survival (OS) was better with selpercatinib (HR: 0.374, 95% CI: 0.147, 0.949). The most common treatment-emergent adverse events observed with selpercatinib were hypertension, dry mouth, and diarrhea; and with control, diarrhea, palmar-plantar erythrodysaesthesia syndrome, and hypertension. In total, 38.9% of patients treated with selpercatinib had a dose reduction (versus 77.3% in control) and 4.7% discontinued treatment due to an adverse event (versus 26.8% in control).

Conclusions: The study met the interim analysis criteria of efficacy. First-line selpercatinib delivered markedly prolonged PFS, improved ORR, and better OS compared with MKI. This study highlights the importance of selectivity in targeting *RET*-mutant MTC. Selpercatinib should be considered the preferred first-line standard of care for patients with advanced *RET*-mutant MTC.

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Legal entity responsible for the study: Eli Lilly and Company.

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Translational research (agnostic)

LBA100 CUP-ONE trial: A prospective double-blind validation of molecular classifiers in the diagnosis of cancer of unknown primary and clinical outcomes

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Background: Cancer of unknown primary remains a major challenge with poor prognoses, protracted pathways and limitations of site-determination by immunohistochemistry. Gene expression signatures (GEP) show promise as molecular cancer classifiers, but their utility in diagnosis and prognosis warrants study. The CUP-ONE Trial prospectively compared a 92-gene assay GEP versus centralized IHC (C-IHC; 10 markers).

Methods: 641 consented patients (36 UK sites; 54 mths) had local pathology & MDT outputs classified as a Reference diagnosis (RD). Tissue was allocated, double-blind, randomized to 3 arms (N): C-IHC (329); CTID (418) CancerTYPE ID, Biotheranostics & Healthscope (418; became unviable). Outputs mandated classification to 14 cancer types. The Intention to diagnose (ITD N=392) set had at least 1 available classifier output. Primary Endpoint was %match of a classifier to RD-site of origin (ratio: total number Match results and total number in ITD dataset with a confirmed or suspected RD (C/S; N=131)). Secondary endpoints included overall classifier accuracy in evaluables with a C/S site of origin, concordance of classifiers & a pre-specified diagnostic score.

Results: Investigators final classifications (N) were CUP (451), 'Suspected' (72) and revised 118 to 'known' sites. In the ITD set: median 67yrs, 50% male, 92% stage IV. 418 (65%) samples were sufficient for 1 classifier output. Sample inadequacy (C-IHC 7.3%; CTID 13.4%) lead to 306 C-IHC & 362 CTID classifications. In Pair-wise comparisons CTID correctly classified 17.2% [1.9%-29.6%; p=0.0243] more than C-IHC;

Agreement of 2 classifiers was 97%. Secondary analysis comparisons showed point estimates favouring CTID but not all statistically significant. Both classified Lung, Colorectal, Breast and Ovary well but CTID did particularly well with Cholangiocarcinoma /gall bladder (60% accuracy) but not in pancreas (9.1%) versus C-HIC (27.2%). Median OS (mths) was poor across all 3 groups CUP: 5.3 (4.6-6.4); Suspected: 9.0 (8.3-11.9); Confirmed: 7.8 (5-13).

Conclusions: CUP-ONE assessed accuracy of CTID Vs C-IHC with comparable outcomes but a higher assignment of Cholangiocarcinoma in CUP. Survival was better in the C/S subset but remains poor overall.

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Legal entity responsible for the study: NHS Greater Glasgow & Clyde and University of Glasgow.

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LBA101 BRCA-DIRECT: A randomised UK study evaluating a digital pathway for germline genetic testing and non-inferiority of digitally-delivered information in women with breast cancer

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Background: Germline genetic testing affords opportunities for women with breast cancer (BC) relating to (i) treatment of a current BC, (ii) management of future cancer risks, and (iii) identification of at-risk family members through cascade testing. Testing remains restricted to <20% of BC diagnoses in the UK. New pathways that reduce clinical staff involvement are required to support expanded testing.

Methods: We implemented a digital pathway, incorporating saliva sampling and a Genetic Counsellor (GC) telephone helpline, for germline BRCA1, BRCA2 and PALB2 testing (BRCA-testing) in unselected women with BC recruited from two UK oncology centres. Participants were randomised 1:1 to receive information about genetic testing via (i) a GC telephone appointment or (ii) the BRCA-DIRECT web application, to evaluate non-inferiority of standardised, written information compared with current standard-of-care in relation to uptake of BRCA-testing (primary outcome), patient knowledge, and anxiety.

Results: 1,140 patients consented to the study, with 571 (50.09%) randomised to receive information from a GC and 569 (49.91%) via BRCA-DIRECT. 1,001 (87.81%) consented to BRCA-testing, with uptake in the BRCA-DIRECT arm non-inferior to the telephone arm (difference +6.07% (95%CI 2.35-9.78%); NI margin -5.50%) as well as patient knowledge (difference -1.07 (-1.39 - -0.75); NI margin -1.40) and anxiety (difference +0.51 (-0.41 — 1.44); NI margin 3.00). Overall, of those who completed genetic testing, >90% reported a satisfaction score of 4 or 5 with the method of information delivery (1 — not satisfied; 5 — very satisfied). Of 19 healthcare professionals surveyed, when asked whether elements of the pathway were equivalent (or superior) to current standard-of-care, median overall score was 4.45 (IQR 4.27-5.00) (1-strongly disagree; 5-strongly agree).

Conclusions: Outcomes demonstrate feasibility and acceptability of a counsellor-supported digital pathway as an alternative delivery model for germline genetic testing within UK breast oncology settings, potentially facilitating expanded eligibility to testing for women diagnosed with breast cancer and other groups.

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Legal entity responsible for the study: Institute of Cancer Research.

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LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC)

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Background: Platinum-based chemo is the standard of care (SOC) for la/mUC. An unmet need remains as long-term outcomes are poor. Here we present EV-302, a global, phase 3, open-label, randomized study evaluating EV+P in patients (pts) with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemo.

Methods: Pts with previously untreated la/mUC (regardless of PD-L1 expression) were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1 or gemcitabine with cisplatin or carboplatin. Dual primary endpoints were PFS per RECIST v1.1 by BICR and OS. Select secondary endpoints included overall response rate (ORR) and safety.

Results: 886 pts (EV+P: 442; chemo: 444) were randomized; pt characteristics were balanced between arms. At data cutoff, median follow-up was 17.2 mo. PFS was significantly prolonged with EV+P vs chemo, reducing the risk of progression or death by 55% (median PFS, 12.5 mo vs 6.3 mo, respectively; HR 0.45 [95% CI: 0.38-0.54]; P<0.00001). OS was significantly prolonged with EV+P vs chemo, reducing the risk of death by 53% (median OS, 31.5 mo vs 16.1 mo, respectively; HR 0.47 [95% CI: 0.38-

0.58]; P<0.00001). Confirmed ORR was 67.7% and 44.4% in the EV+P and chemo arms, respectively (P<0.00001). Grade ≥3 TRAEs occurred in 55.9% with EV+P and 69.5% with chemo; most common were maculopapular rash (7.7%), hyperglycemia (5.0%), and neutropenia (4.8%) for EV+P and anemia (31.4%), neutropenia (30.0%), and thrombocytopenia (19.4%) for chemo. Most common (≥5%) grade ≥3 TRAEs of special interest for EV included skin reactions (15.5%), peripheral neuropathy (6.8%), and hyperglycemia (6.1%). Most common (≥5%) grade ≥3 treatment-emergent AEs of special interest for P included severe skin reactions (11.8%).

Conclusions: EV+P significantly improved outcomes in pts with previously untreated la/mUC, nearly doubling the median PFS and OS vs chemo. The safety profile was generally manageable with no new safety signals. These results support EV+P as a new SOC for 1L la/mUC.

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Urothelial cancer

LBA7 Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: Results from the phase III CheckMate 901 trial

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Background: Cisplatin (cis)-based chemotherapy (chemo) has been the first-line standard of care (SOC) for cis-eligible patients (pts) with unresectable/metastatic urothelial carcinoma (mUC) for decades, and prior attempts to improve upon this treatment have been unsuccessful. We report results for nivolumab (NIVO) plus gemcitabine-cis (GC) or GC alone in CheckMate 901.

Methods: In CheckMate 901 (NCT03036098), a global, open-label, randomized phase 3 trial, pts received NIVO 360 mg plus GC every 3 wk for up to 6 cycles followed by NIVO 480 mg every 4 wk until disease progression/unacceptable toxicity or up to a maximum of 2 years, or GC every 3 wk for up to 6 cycles. Stratification factors were programmed death ligand 1 status and liver metastasis. Primary endpoints were overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR). Objective response rate (ORR) per BICR was an exploratory endpoint.

Results: A total of 304 pts were randomized to each arm. With a median follow-up of 33.6 mo, both OS (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.63–0.96; $P = 0.0171$) and PFS (HR, 0.72; 95% CI, 0.59–0.88; $P = 0.0012$) were significantly improved with NIVO+GC vs GC (table). ORR and complete response (CR) rates were 57.6% and 21.7% with NIVO+GC vs 43.1% and 11.8% with GC. Median duration of CR (95% CI) was 37.1 (18.1–not estimable] mo for NIVO+GC vs 13.2 (7.3–18.4) mo with GC. Grade ≥ 3 treatment-related adverse events occurred in 61.8% of pts in the NIVO+GC arm and 51.7% of pts in the GC arm.

Table: LBA7

	NIVO+GC (N = 304)	GC (N = 304)	HR (95% CI)
Median OS (95% CI), mo	21.7 (18.6–26.4)	18.9 (14.7–22.4)	0.78 (0.63–0.96);
12-mo OS probability, %	70.2	62.7	$P = 0.0171$
24-mo OS probability, %	46.9	40.7	
Median PFS (95% CI), mo	7.9 (7.6–9.5)	7.6 (6.1–7.8)	0.72 (0.59–0.88);
12-mo PFS probability, %	34.2	21.8	$P = 0.0012$
24-mo PFS probability, %	23.5	9.6	

Conclusions: NIVO+GC demonstrated statistically significant and clinically meaningful improvements in OS and PFS vs GC alone as first-line treatment for mUC with no new toxicity signals. NIVO+GC is the first frontline concurrent checkpoint inhibitor + chemo combination to improve OS in this setting. These results support NIVO plus cis-based chemo as a new SOC for pts with mUC. (Table).

Clinical trial identification: NCT03036098.

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LBA102 THOR-2 cohort 1: Results of erdafitinib (ERDA) vs intravesical chemotherapy (chemo) in patients (pts) with high-risk non −muscle-invasive bladder cancer (HR NMIBC) with select fibroblast growth factor receptor alterations (FGFRALT) who received prior bacillus calmette-guérin (BCG) treatment

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Background: Treatment (tx) options are limited for pts with HR NMIBC who have recurrence after BCG tx and are ineligible for/refuse radical cystectomy (RC). Erda, an oral selective pan-FGFR tyrosine kinase inhibitor, demonstrated an overall survival benefit over chemo in the phase 3 THOR study in pts with locally advanced/metastatic urothelial carcinoma with *FGFRalt*. We report the first randomized data in pts with recurrent, BCG-treated HR NMIBC with *FGFRalt* from Cohort 1 of THOR-2 (NCT04172675).

Methods: Adult pts with recurrent, BCG-treated, papillary-only HR NMIBC (high-grade Ta/T1) and select *FGFRalt* refusing/ineligible for RC were randomized 2:1 to 6 mg oral erda or investigator's choice of intravesical chemo (mitomycin C or gemcitabine). Primary end point: recurrence-free survival (RFS). Secondary end points: RFS rate at 6 and 12 mo and safety.

Results: 73 pts (median age: 69 y) were randomized to erda (n=49) and chemo (n=24). Study enrollment was discontinued because of slow accrual. Median follow-up was 13.4 mo for both groups. Median RFS was not reached for erda and was 11.6 mo for chemo, with an estimated hazard ratio of 0.28 (Table). 6- and 12-mo RFS rate was 96% and 77% for erda vs 73% and 41% for chemo, respectively. Grade (Gr) 3-4 tx-related adverse events (TRAEs) occurred in 15 (31%) and 1 (4%) pts with erda and chemo, respectively; 14 (29%) and 0 pts had TRAEs leading to discontinuation of erda and chemo, respectively. Central serous retinopathy occurred in 19 pts (39%) with erda (Gr 1-2, 17 pts) and resolved in 11 pts (58%).

Table: LBA102

Value (95% CI)	Erda n=49	Chemo n=24
Median RFS, mo[a]	NE (17-NE)	11.6 (6-20)
Hazard ratio[b]	0.28 (0.13-0.62) nominal p=0.0008[c]	
6-mo RFS, %	96 (84-99)	73 (50-87)
12-mo RFS, %	77 (60-87)	41 (19-62)

[a]Censoring: 1) Recurrence-free + alive or unknown status, censored at last assessment; 2) no post-baseline assessment, censored at randomization; 3) withdrew consent or lost to follow-up prior to RFS event, censored at last assessment; 4) start subsequent anticancer tx prior to RFS event, censored at last assessment before new tx start. [b]Estimated using stratified Cox proportional hazards regression model. Hazard ratio <1 indicates longer RFS in erda vs chemo. [c]Based on an unstratified log-rank test.

Conclusions: Erda prolonged RFS compared with chemo in pts with papillary-only HR NMIBC with *FGFRalt* who had recurrence after BCG tx. Erda toxicity was generally consistent with the known safety profile of oral FGFR inhibitors.

Clinical trial identification: NCT04172675.

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LBA103 ICRA: Efficacy of paclitaxel with tremelimumab +/- durvalumab in metastatic urothelial carcinoma after progression on platinum chemotherapy and anti-PD-(L)1

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Background: The prognosis of metastatic urothelial carcinoma (mUC) patients (pts) after platinum-based chemotherapy and anti-PD-(L)1 is poor. Taxanes can provide disease control and may affect the tumor micro-environment. Clinical activity of anti-CTLA4 has been reported previously and may be dose-dependent. We evaluated whether paclitaxel (P) with tremelimumab (T), with or without durvalumab (D), could induce response in therapy-refractory mUC pts.

Methods: ICRA is an open-label, randomized, multicenter phase I/II study in pts with mUC who relapsed after platinum-based chemotherapy and anti-PD-(L)1. In the safety run-in phase (n=15), we tested weekly P (70mg/m2; day 1, 8, and 15 for 6 cycles (C)) plus either T75mg, T225mg or T750mg (C2-8 every 4 weeks), or P combined with D (C2-12 every 4 weeks) plus either T75mg (C2-5 every 4 weeks) or T300mg once (C2). In the expansion phase (n=12 per arm), pts received (A) P (C1-6) plus T750mg (C2-8); (B) P (C1-6) plus T300mg once (C2) plus D1500mg (C2-12); or (C) T750mg (C1-7). Arm A was extended to n=20 based on 2 responses. The primary endpoint was the objective response rate (ORR) according to RECIST1.1, with a target ORR 30% and aim to exclude 10% (Simon's optimal two-stage design, α=0.12, power=0.85). Safety was assessed according to the CTCAEv5.

Results: The primary endpoint was met with an ORR of 26% (88%CI 14-37%; 5/19 evaluable pts) in arm A. The ORR was 8% in arms B and C. Median OS (95%CI) was 16.0 (4.4-27.5), 13.9 (9.5-18.3), and 6.6 (0.0-14.8) months in arms A, B, and C, respectively (p=0.68). Median PFS was 5.7 (4.0-7.3), 6.5 (3.7-9.4), and 2.8 (0.0-5.7) months in arms A, B, and C, respectively (p=0.27). Toxicities are summarized in the Table.

Conclusions: In heavily pretreated patients with mUC, P+T750mg showed a manageable safety profile and encouraging antitumor activity, suggesting a potential synergistic effect of taxanes and high-dose anti-CTLA4.

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Legal entity responsible for the study: Netherlands Cancer Institute.

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LBA104 First safety and efficacy results of the TAR-210 erdafitinib (erda) intravesical delivery system in patients (pts) with non −muscle-invasive bladder cancer (NMIBC) with select FGFR alterations (alt)

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Background: Treatment (tx) options are limited in NMIBC that recurs after intravesical chemotherapy or bacillus Calmette-Guérin (BCG). TAR-210 is a novel intravesical drug delivery system designed to provide local, continuous release of erda (selective pan-FGFR tyrosine kinase inhibitor) within the bladder while limiting systemic toxicities. This open-label, multicenter phase 1 study (NCT05316155) evaluates the safety, PK, and efficacy of TAR-210 in pts with NMIBC whose tumors harbor select *FGFRalt*.

Methods: *FGFRalt* were identified in tumor tissue or urine cell-free DNA. Cohort 1 (C1) pts had recurrent, BCG-experienced high-risk NMIBC (high-grade Ta/T1; papillary only) and refused or were ineligible for radical cystectomy. Cohort 3 (C3) pts had recurrent, intermediate-risk NMIBC (Ta/T1) with history of only low-grade papillary disease. Before tx, C1 pts must have all visible disease resected; C3 requires the presence of visible tumors. TAR-210 systems with 2 different erda release rates were evaluated. Response is assessed every 3 mo with continued tx for up to 1 year if recurrence-free (RF) (C1) or in complete response (CR) (C3).

Results: As of Aug 29, 2023, 16 pts in C1 and 27 pts in C3 have been treated; 11 and 15 pts, respectively, had ≥1 response assessment. 82% in C1 were RF; 87% in C3 achieved CR (Table). Most common tx-related AEs were grade 1/2 lower urinary tract AEs. There were no dose-limiting toxicities, no deaths, 2 pts discontinued due to AEs of low-grade urinary symptoms, and 1 pt had serious AEs of pyelonephritis and sepsis. PK showed sustained erda concentrations in urine, with very low plasma exposures.

Table: LBA103 Toxicity

	R1 (P+T75)		R2 (P+T225)		R3B (P+T75+D1500)		A (P+T750)[1]		B (P+T300+D)[1]		C (T750)	
	n=3		n=3		n=3		n=20		n=12		n=12	
	Grade 1-2	*Grade ≥3*	*Grade 1-2*	*Grade ≥3*	*Grade 1-2*	*Grade ≥3*	*Grade 1-2*	*Grade ≥3*	*Grade 1-2*	*Grade ≥3*	*Grade 1-2*	*Grade ≥3*
Therapy-related AEs (n, %)	3 (100)	1 (33)	3 (100)	1 (33)	3 (100)	0 (0)	20 (100)	11 (55)	11 (92)	8 (67)	11 (92)	4 (33)
Immune-related AEs (n, %)	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	0 (0)	16 (80)	6 (30)	9 (75)	3 (25)	11 (92)	4 (33)
Chemo-related AEs (n, %)	3 (100)	1 (33)	3 (100)	1 (33)	3 (100)	0 (0)	19 (95)	6 (30)	11 (92)	8 (67)	n.a.	n.a.

AEs=adverse events; D=durvalumab; P=paclitaxel; R=run-in arm; T=tremelimumab

1. Run-in arms 3A and 4 were included in arms A and B of the expansion phase, respectively.

Table: LBA104 Efficacy outcomes and Tx exposure	
Cohort 1 (n=11 with response assessment)	
RF, n (%)	9 (81.8)
Median RFS (95% CI), mo	NE (2.96-NE)
Cohort 3 (n=15 with response assessment)	
CR, n (%)	13 (86.7)
Median duration of CR (95% CI), mo*	NE (NE-NE)
Both Cohorts (n=43 all-treated)	
Median duration of tx exposure (range), mo	3.7 (0-12)
Total duration of tx, n (%)	
≥0-<3 mo	18 (41.9)
≥3-<6 mo	13 (30.2)
≥6-<9 mo	6 (14.0)
≥9-<12 mo	5 (11.6)
≥12 mo	1 (2.3)

CI, confidence interval; mo, months; NE, non-estimable; RF, recurrence-free; RFS, recurrence-free survival. *All CR in Cohort 3 were ongoing as of data cutoff.

Conclusions: TAR-210 appears safe and well tolerated with predominantly low-grade urinary system AEs and high CR rate and RF survival in pts with NMIBC with *FGFRalt*. Results justify further study of targeted tx of erda using a novel intravesical delivery system in early-stage bladder cancer.

Clinical trial identification: NCT04083976.

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LBA105 Results from SunRISe-1 in patients (Pts) with bacillus Calmette–Guérin (BCG)-unresponsive high-risk non–muscle-invasive bladder cancer (HR NMIBC) receiving TAR-200 monotherapy

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Background: Pts with BCG-unresponsive HR NMIBC are at high risk of disease progression with limited treatment (tx) options. TAR-200, an intravesical drug delivery system, provides sustained release of gemcitabine in the bladder over many days. SunRISe-1 (NCT04640623) is an ongoing, randomized, ph 2b study assessing efficacy and safety of TAR-200 + cetrelimab (anti-PD1) (Cohort 1 [C1]), TAR-200 alone (C2), or cetrelimab alone (C3) in pts with BCG-unresponsive HR NMIBC ineligible for or refusing radical cystectomy. We report results from C2.

Methods: Eligible pts aged ≥18 y had histologically confirmed carcinoma in situ (CIS) ± papillary disease (high-grade Ta, any T1), ECOG performance status 0-2, and persistent or recurrent HR NMIBC with last dose of BCG ≤12 mo prior to CIS diagnosis. TAR-200 was dosed Q3W through Wk 24, then Q12W until Wk 96. Response assessments: cystoscopy and centrally assessed urine cytology, CT/MRI, and bladder biopsy (at Wk 24, 48, and as clinically indicated). Primary end point: overall complete response (CR) rate. Secondary end points: duration of response (DOR), overall survival, safety, and tolerability.

Results: At 24 Aug 2023 data cutoff, 54 pts (median age, 71 y; range, 40-85; 33% with concurrent papillary disease) received TAR-200 monotherapy. 30 pts were efficacy evaluable. Centrally confirmed CR by urine cytology and/or biopsy was achieved in 23/30 pts (77%; 95% CI, 58-90). Median DOR was not reached (median follow-up in responders, 48 wks; range, 12-121); 21/23 responders remain in CR with 11/11 and 6/6 having response ≥6 mo and ≥12 mo from CR, respectively. CR rate by investigator assessment was comparable with central results. 29 pts (54%) had tx-related adverse events (TRAEs); most common (≥10%) were pollakiuria, dysuria, and micturition urgency. 4 pts (7%) had Gr ≥3 TRAEs; 1 (2%) had serious TRAE; 2 (4%) had TRAEs leading to discontinuation. No deaths were reported.

Conclusions: In SunRISe-1, TAR-200 monotherapy is associated with an unprecedented CR rate, durable responses, and a favorable tolerability profile in pts with BCG-unresponsive CIS, supporting its continued investigation in HR NMIBC.

Clinical trial identification: NCT04640623.

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Cancer nursing: Supportive care

CN_LBA1 Uncovering the needs of lymphoma survivors: A cross-sectional study

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Background: Despite the significant improvement in lymphoma survival rates in recent decades, little attention has been paid to researching the survivorship experience. This study sought to address this gap by identifying the most common unmet needs among lymphoma survivors and the explanatory factors influencing their unmet needs.

Methods: For this cross-sectional study, adult lymphoma survivors one to five years post-diagnosis were recruited from five hospital sites across Ireland. To measure the extent of unmet needs, the validated Short-Form Survivors Unmet Needs Survey was utilised, where high scores indicated a greater level of unmet need (scores ranged from 0 = No Unmet Needs to 4 = Very High Unmet Needs). Descriptive, univariate, and hierarchical multiple regression analyses were conducted.

Results: Two hundred and two lymphoma survivors completed the unmet needs survey. The most commonly reported unmet need was "coping with having a bad memory or lack of focus", with 21.4% of respondents (n=43) endorsing it. Other frequently reported unmet needs were "feeling tired" (19%, n=38), "dealing with people who expect me to be 'back to normal'" (17.9%, n=36), "changes in how my body appears" (16.9%, n=34), and "feeling stressed" (16.4%, n=33). The top seven most frequently reported unmet needs fell within the coping, sharing, and emotional needs or work and financial needs domains. Being female was consistently associated with more unmet needs across all domains. Similarly, being younger was associated with more unmet needs. Individuals without private health insurance reported greater unmet needs. The timing of diagnosis was another influential factor; those with a more recent diagnosis (one to three years ago) experienced higher levels of unmet needs.

Conclusions: Several factors were associated with higher unmet needs across domains. Lymphoma survivors may require additional psychological support or assistance with their work, financial or information needs. Identifying the prevalent unmet needs of lymphoma survivors in Ireland provides evidence for the development of future survivorship programmes and services for this population. This study spotlights the importance of addressing unmet needs to improve quality of life for this group and reduce dependency on health services.

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CN_LBA2 A qualitative exploration of lymphoma survivors' unmet needs

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Background: Lymphoma survival has significantly improved over recent decades. Yet, survivorship research has received little attention. This study aimed to understand the unmet needs experienced by lymphoma survivors through semi-structured interviews. This qualitative study investigates the individual experiences and complexities of lymphoma survivors' unmet needs. This insight can provide a voice to lymphoma survivors, which is especially valuable for this group as an underserved population in current literature.

Methods: A semi-structured interview guide was informed by the findings of a cross-sectional survey study and a literature review conducted by the authors. The findings were derived from interviews with 14 adult survivors about their unmet needs due to lymphoma and responses from 61 participants to an open-ended survey question. A reflexive thematic analysis was conducted to identify themes and patterns of meaning across both datasets (Braun & Clarke 2019).

Results: Three major themes were identified. Survivors shared experiences of *navigating the complexities of lymphoma*, including difficult diagnosis, limited awareness of lymphoma as a cancer and challenges specific to younger adults. Survivors experienced *complex care coordination*, including disjointed cancer care, physical health concerns and the immunocompromised nature of lymphoma, particularly during the pandemic. *The cost of cancer* found challenges in balancing life responsibilities with lymphoma, difficulties during the survivorship phase, and dealing with psycho-social problems.

Conclusions: Unaddressed unmet physical needs contributed to unmet psychological needs due to the uncertainty experienced by survivors on their quest for answers to health concerns. Psychological and emotional needs were dominant and persistent problems in the survivorship phase one to five years post-diagnosis. Unmet practical and information needs were experienced from disjointed cancer care coordination; a missing link was reported by individuals with lymphoma acting as a conduit for information regarding their cancer. Navigating lymphoma from diagnosis to survivorship presents challenges for patients and healthcare professionals who would benefit from enhanced lymphoma awareness and research.

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Cancer nursing: Workforce and educational issues in cancer nursing

CN_LBA3 Providing support for families when an adult with dependent children is at end-of-life with cancer: A systematic review of educational interventions for health and social care professionals

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Background: One of the greatest challenges faced by adults with significant caregiving responsibilities when they are at end of life (EoL) with cancer is supporting their dependent children (<18 years). Adults with advanced cancer want guidance to communicate with their children when death is imminent. Health and Social Care Professionals (HSCPs) are ideally placed to provide this aspect of care but often lack the skills, competence, and confidence due to insufficient training. This compromises the delivery of family-centred care to address the psychosocial needs of the family.This systematic review aims to determine the content, mode of delivery, assessment and outcomes of educational interventions to equip HSCPs when delivering end of life care for adults dying with cancer who have dependent children.

Methods: A systematic review of empirical studies was conducted, following the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocol checklist. Six electronic databases (Medline, OVID, CINAHL, EMBASE, PsycINFO, Web of Science, ERIC) were searched and grey literature searches of Google Advanced Search and relevant professional bodies were conducted. Two eligible studies were identified. Data relating to content, mode of delivery, assessment and evaluation of educational interventions and outcomes were extracted and analysed.

Results: Only two studies were identified, highlighting the dearth of educational interventions available to HSCPs to provide supportive care to families when an adult with dependant children is at EoL with cancer. The identified educational interventions were of good methodological quality and were positively evaluated by participants, enhancing their confidence to engage in EoL conversations. It is imperative that interventions that use robust evaluation methods are developed and made available to a diverse array of HSCPs.

Conclusions: The review highlights the urgent need to develop accessible interventions for HSCPs to provide supportive care to families when a person at end-of-life with cancer has dependent children. This is fundamental to improving care and reducing distress for patients and families.

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