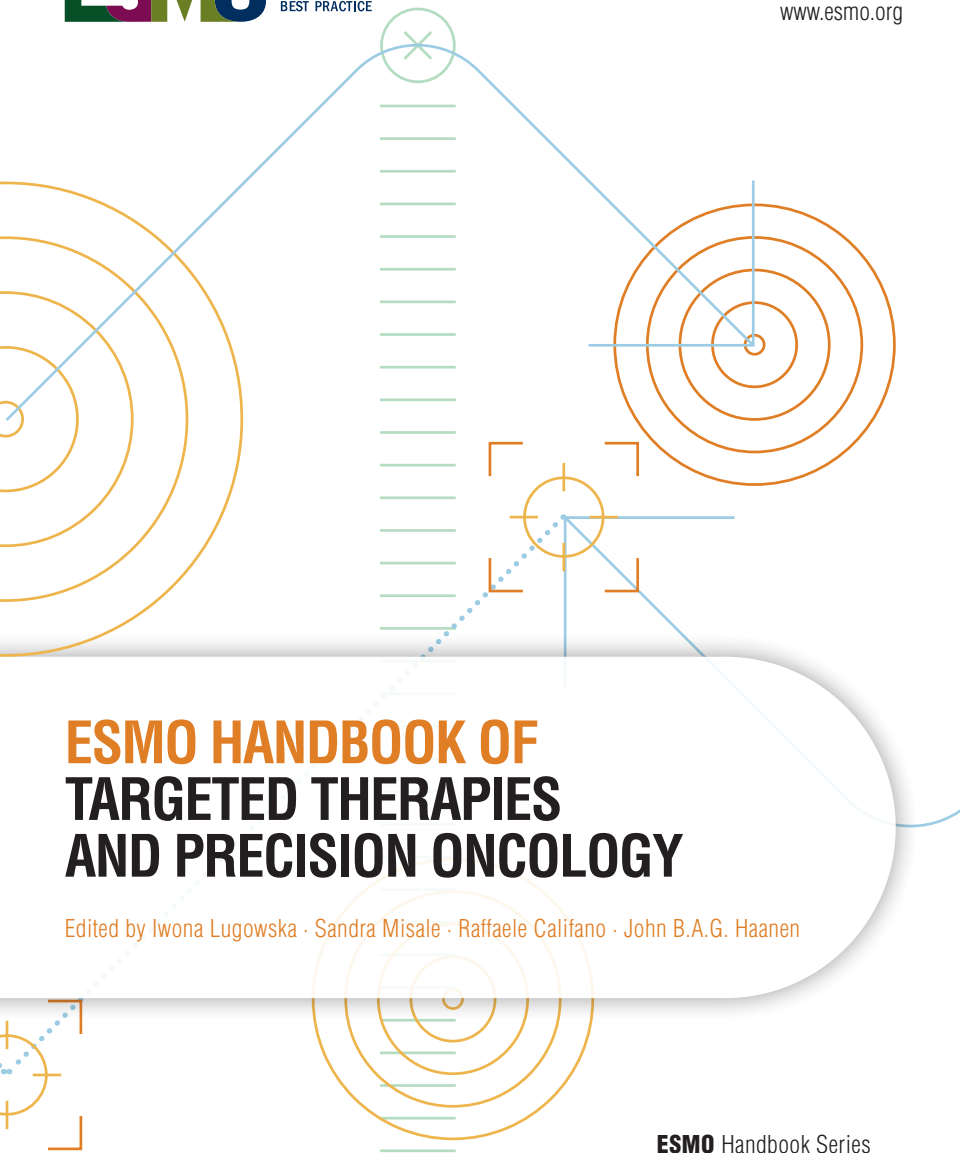




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ESMO HANDBOOK OF TARGETED THERAPIES AND PRECISION ONCOLOGY

Edited by Iwona Lugowska · Sandra Misale · Raffaele Califano · John B.A.G. Haanen

ESMO Handbook Series



ESMO HANDBOOK OF TARGETED THERAPIES AND PRECISION ONCOLOGY



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Edited by

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Abbreviations

2HG	R-2-hydroxyglutarate
5-HT ₃	5-hydroxytryptamine
ACEi	Angiotensin-converting enzyme inhibitor
ACMG	American College of Medical Genetics and Genomics
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AI	Aromatase inhibitor
ALK	Anaplastic lymphoma kinase
ALT	Alternative lengthening of telomere
AML	Acute myeloid leukaemia
AP-1	Activator protein 1
APL	Acute promyelocytic leukaemia
AR	Androgen receptor
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
ATP	Adenosine triphosphate
ATR	Ataxia telangiectasia and Rad3-related protein
ATRA	All-trans-retinoic acid
ATRi	ATR inhibitor
BB	Beta-blocker
BCC	Basal cell carcinoma
BCL2	B-cell lymphoma 2
BCMA	B-cell maturation antigen
BCR	B-cell receptor
bd	<i>bis in die</i> (twice a day)
BER	Base excision repair
BiTE	Bispecific T-cell engager
BNP	B-type natriuretic peptide
BP	Blood pressure
BRAF _i	BRAF inhibitor

Breg	Regulatory B cell
BS	Bone sarcoma
BTk	Bruton's tyrosine kinase
CAF	Cancer-associated fibroblast
CAR	Chimeric antigen receptor
CC	Cervical cancer
ccRCC	Clear cell renal cell cancer
CDK	Cyclin-dependent kinase
CDK 4/6	Cyclin-dependent kinase 4/6
CDKi	Cyclin-dependent kinase inhibitor
cDNA	Complementary DNA
CEA	Carcinoembryonic antigen
CHIP	Clonal haematopoiesis of indeterminate potential
CHK1	Checkpoint kinase 1
CHMP	EMA Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CI	Confidence interval
CISH	Chromogenic <i>in situ</i> hybridisation
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNA	Copy number alteration
CNS	Central nervous system
COL1A1	Collagen type I alpha 1 chain
COL6A3	Collagen type VI alpha 3 chain
CPK	Creatine phosphokinase
CPS	Combined positive score
CR	Complete response
CRC	Colorectal cancer
CRISPR	Clustered regularly interspaced short palindromic repeats
CRPC	Castration-resistant prostate cancer
CRS	Cytokine release syndrome
CS	Chondrosarcoma
CSF-1	Colony-stimulating factor 1
CSF-1R	CSF-1 receptor
CT	Computed tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA

CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
DCR	Disease control rate
DCS	Dedifferentiated chondrosarcoma
DDLPS	Dedifferentiated liposarcoma
ddPCR	Droplet digital polymerase chain reaction
DDR	DNA damage response
DDRi	DNA damage response inhibitor
DFSP	Dermatofibrosarcoma protuberans
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
dMMR	Deficient mismatch repair
DNA-PK	DNA-protein kinase
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
DoR	Duration of response
DR5	Death receptor 5
DSB	Double-strand break
E1	Oestrone
E2	Oestradiol
E3	Oestriol
EBC	Early breast cancer
EBV	Epstein-Barr virus
EC	Endometrial cancer
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRi	EGFR inhibitor
EMA	European Medicines Agency
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
EPC	Endothelial progenitor cell
ER	Oestrogen receptor
ERE	Oestrogen-responsive element
ERK	Extracellular signal-regulated kinase
ES	Ewing sarcoma
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets
ESMO	European Society for Medical Oncology
ESR1	Oestrogen receptor 1
ET	Endocrine therapy

EWSR1	Ewing sarcoma breakpoint region 1
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FGFRi	FGFR inhibitor
FISH	Fluorescent <i>in situ</i> hybridisation
FL	Follicular lymphoma
FRα	Folate receptor alpha
ft4	Free thyroxine
FTI	Farnesyltransferase inhibitor
GABA	Gamma aminobutyric acid
GAP	GTPase-activating protein
gBRCAm	Germline <i>BRCA</i> -mutated
GC	Gastric cancer
GCTB	Giant cell tumour of bone
GDP	Guanosine diphosphate
GEF	Guanine nucleotide exchange factor
GH	Growth hormone
GIS	Genomic instability score
GIST	Gastrointestinal stromal tumour
GLS	Global longitudinal strain
gp100	Glycoprotein 100
GPCR	G-protein coupled receptor
GTP	Guanosine triphosphate
GU	Genitourinary
HA-1	Histocompatibility antigen 1
HCC	Hepatocellular carcinoma
HER	Human epidermal growth factor receptor
HF	Heart failure
HFSR	Hand-foot skin reaction
HGF	Hepatocyte growth factor
HGFR	Hepatocyte growth factor receptor
HGSOC	High-grade serous ovarian cancer
Hh	Hedgehog
HIF	Hypoxia-inducible factor
HIF-1α	Hypoxia-inducible factor-1 alpha
HLA	Human leukocyte antigen

HNPCC	Hereditary non-polyposis colorectal cancer
HNSCC	Head and neck squamous cell carcinoma
HP	Trastuzumab/pertuzumab
HPV	Human papillomavirus
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
IAP	Inhibitor of apoptosis proteins
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICC	Immunocytochemistry
ICI	Immune checkpoint inhibitor
IDFS	Invasive disease-free survival
IDH	Isocitrate dehydrogenase
IDH1-vac	IDH1(R132H) peptide vaccine
IF	Immunofluorescent
IFN-α	Interferon- α
IGF	Insulin-like growth factor
IGFR	IGF receptor
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
ImmTAC	Immune-mobilising monoclonal T-cell receptor against cancer
IMT	Inflammatory myofibroblastic tumour
INI1	Integrase interactor 1
INSR	Insulin receptor gene
IR	Insulin receptor
IRS	IR substrate
JAK	Janus kinase
JNK	C-Jun N-terminal kinase
LA	Locally advanced
LDH	Lactate dehydrogenase
LGSOC	Low-grade serous ovarian cancer
LH	Luteinising hormone
LOH	Loss of heterozygosity
LTK	Leukocyte receptor tyrosine kinase
LVEF	Left ventricular ejection fraction

LVSD	Left ventricular systolic dysfunction
MA	Molecular alteration
mAb	Monoclonal antibody
MAGE	Melanoma antigen gene
MAP2K1	Mitogen-activated protein kinase kinase 1
MAPK	Mitogen-activated protein kinase
MAPKK	MAPK kinase
MBC	Metastatic breast cancer
mCRC	Metastatic colorectal cancer
mCRPC	Metastatic CRPC
MCS	Mesenchymal chondrosarcoma
MDSC	Myeloid-derived suppressor cell
MEKi	MEK inhibitor
MHC-I	Major histocompatibility complex class I
MIBC	Muscle-invasive bladder cancer
MiHA	Minor histocompatibility antigen
MKI	Multikinase inhibitor
MKP	MAPK phosphatase
MLH1	MutL homologue 1
MM	Multiple myeloma
MMR	Mismatch repair
mOS	Median overall survival
mPFS	Median progression-free survival
mRCC	Metastatic renal cell cancer
MRD	Minimal residual disease
mRNA	Messenger RNA
MSH2	MutS homologue 2
MSH6	MutS homologue 6
MSI	Microsatellite instability
MSI-H	MSI-high
MTB	Molecular tumour board
mTOR	Mammalian target of rapamycin
mTORC2	Mammalian target of rapamycin complex 2
mTORi	mTOR inhibitor
mUC	Metastatic urothelial cancer
N+	Node-positive
NAC	N-acetyl cysteine
NF1	Neurofibromin 1

NF-κB	Nuclear factor-kappa B
NGS	Next-generation sequencing
NHEJ	Non-homologous end joining
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NK1	Neurokinin 1
NMIBC	Non-muscle invasive bladder cancer
NR	Nuclear receptor
NRG1	Neuregulin-1 gene
NSCLC	Non-small cell lung cancer
NT-proBNP	N-terminal (NT) pro-hormone BNP (B-type natriuretic peptide)
NTRK	Neurotrophic tyrosine receptor kinase
NY-ESO-1	New York oesophageal squamous cell carcinoma-1
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
PARP	Poly(ADP-ribose) polymerase
PARPi	PARP inhibitor
PC	Prostate cancer
pCR	Pathological complete response
PCT	Physician's choice of therapy
PD	Progressive disease
PD-1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor
PDGFB	Platelet-derived growth factor beta chain
PDGFR	PDGF receptor
PD-L1	Programmed death-ligand 1
PDX	Patient-derived xenograft
PEComa	Perivascular epithelioid cell tumour
PET	Positron emission tomography
PFS	Progression-free survival
PGM	Personal Genome Machine
PgR	Progesterone receptor
PI3K	Phosphoinositide 3-kinase
pMMR	Proficient MMR
PMS2	Post-meiotic segregation increased 2

POLE	Polymerase epsilon catalytic subunit
PP2A	Protein phosphatase 2A
PR	Partial response
PRAME	Preferentially expressed antigen in melanoma
PRCC	Papillary renal cell cancer
PRE	Progesterone response element
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PTC	Papillary thyroid cancer
PTCH1	Patched 1
PTEN	Phosphatase and tensin homologue
pVHL	von Hippel Lindau protein
PVN	Pigmented villonodular synovitis
qd	Once a day
qPCR	Quantitative polymerase chain reaction
QTc	Corrected QT
R/M	Recurrent/metastatic
R/R	Relapsed/refractory
RA	Retinoic acid
RANK	Receptor activator of nuclear factor-kappa B
RANKL	RANK ligand
RAR	Retinoic acid receptor
RB	Retinoblastoma
RB1	Retinoblastoma 1
RCC	Renal cell cancer
R-CHOP	CHOP with rituximab
RCS	Round cell sarcoma
RE	Responsive element
RECIST	Response Evaluation Criteria In Solid Tumours
RETi	RET inhibitor
RFS	Relapse-free survival
rPFS	Radiographic PFS
RR	Response rate
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcriptase polymerase chain reaction
SASP	Senescence-associated secretory phenotype
SCLC	Small cell lung cancer
SD	Stable disease

SEER	Surveillance, Epidemiology, and End Results
SH2	Src homology 2
SHP2	Src homology region 2 domain-containing phosphatase 2
SINE	Selective inhibitor of nuclear export
SLL	Small lymphocytic lymphoma
SMO	Smoothened homologue
SNP	Single nucleotide polymorphism
SoC	Standard of care
SPRY	Sprouty
SSB	Single-strand break
SSQ	Sanger sequencing
STS	Soft tissue sarcoma
SWI/SNF	SWItch/Sucrose-Non-Fermentable
T3	Triiodothyronine
T4	Tetraiodothyronine
TCR	T cell receptor
T-DM1	Trastuzumab emtansine
T-DXD	Trastuzumab deruxtecan
TE	Thromboembolic event
TERT	Telomerase
TF	Tissue factor
TGCT	Tenosynovial giant cell tumour
TGF-β	Transforming growth factor-beta
TH	Thyroid hormone
TIL	Tumour-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TMB	Tumour mutational burden
TMB-H	TMB-high
TME	Tumour microenvironment
TNBC	Triple-negative breast cancer
TNM	Tumour, Node, Metastasis
TPS	Tumour proportion score
TR	Thyroid hormone receptor
Treg	Regulatory T cell
TRH	Thyrotropin-releasing hormone
TRK	Tyrosine receptor kinase
Trop-2	Trophoblast cell-surface antigen 2
TSC1/TSC2	Tuberous sclerosis complex subunit 1/2

TSH	Thyroid-stimulating hormone
TT	Targeted therapy
TTE	Transthoracic echocardiography
TTP	Time to progression
UC	Urothelial cancer
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VHL	Von Hippel-Lindau
WHO	World Health Organization
XPO1	Exportin 1

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Professor Iwona Lugowska, on behalf of all the Editors

Preface

Precision oncology is a term used to describe novel treatments with much more specific modes of action compared to classic chemotherapy. Starting with imatinib as a breakthrough for the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia, this field, also described as targeted therapy, has evolved enormously.

Developments in genomic testing and of targeted therapies go hand-in-hand. Treatments may consist of small molecule inhibitors targeting receptor tyrosine kinases, or even transcription factors, antibodies, antibody-drug conjugates and cell therapies. Currently, cancers can be classified according to their genomic alterations (translocations, amplifications, mutations, etc), allowing drugs developed for a specific cancer to be ‘repurposed’ and used to treat other cancers sharing the same or a similar alteration. An example is targeting ErbB2 (or human epidermal growth factor receptor 2 [HER2]) overexpression, which was originally found to be an important target in breast cancer. Genomic testing has unveiled *HER2* gene amplifications and activating mutations are also present in many other cancers including gastric, colon, lung and bladder cancer, where some of these HER2-targeting drugs appear highly efficacious as well.

This handbook brings together specialists in the field of precision medicine, who have shared their knowledge and insights on this broad topic, providing you with a solid base to understand this field from basic science to clinical application. This book cannot be missing from the desk of any medical professional working in the field of cancer care!

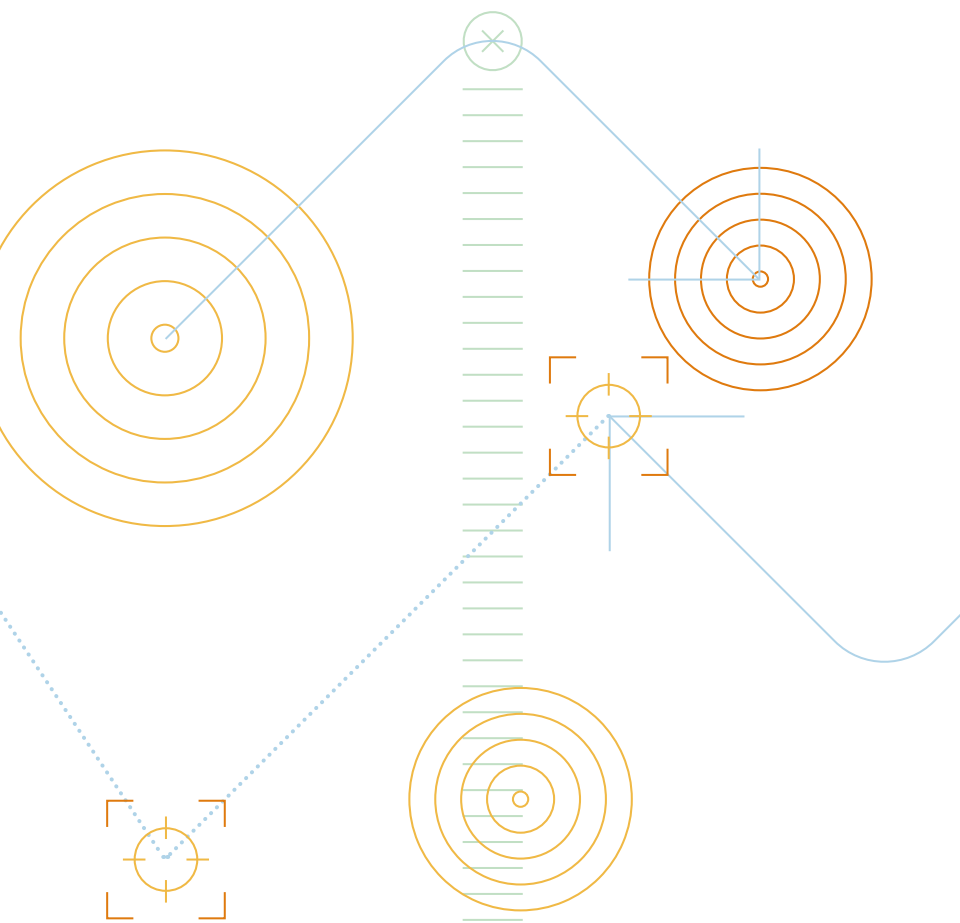
Professor John B.A.G. Haanen, on behalf of the editors

Dedication



This Handbook is dedicated to José Baselga, physician, scientist and former ESMO President who was truly committed to the development of molecularly targeted therapies. His work significantly changed the landscape of cancer treatment. His passion and dedication to cancer research will be remembered by all, and he will continue to be an inspiration to researchers and oncologists for generations to come.

Section I: Molecular Targets



Introduction

1

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Precision oncology is quickly becoming mainstream in clinical practice and research, dedicated to high-technology diagnostics and innovative drug development. The identification of targetable molecular alterations and thus therapy adjustment enables treatment individualisation and increases efficacy.

The first Food and Drug Administration (FDA)-approved targeted therapy leading to clinical remissions was imatinib for the treatment of *BCR-ABL* rearrangement in chronic myeloid leukaemia in 2001. Today, the number of targeted therapies approved for use continues to grow.

Advances in precision oncology are usually implemented in highly specialised cancer research centres, which have access to clinical trials and advanced diagnostic technologies. To define molecular alterations and tailor therapy accordingly, a tissue sample is needed, which is delivered to a high-quality laboratory equipped with next-generation sequencing (NGS) technology. However, even smaller institutions without laboratories can take advantage of commercially available testing platforms to analyse paraffin-embedded tissue samples or plasma samples. Since

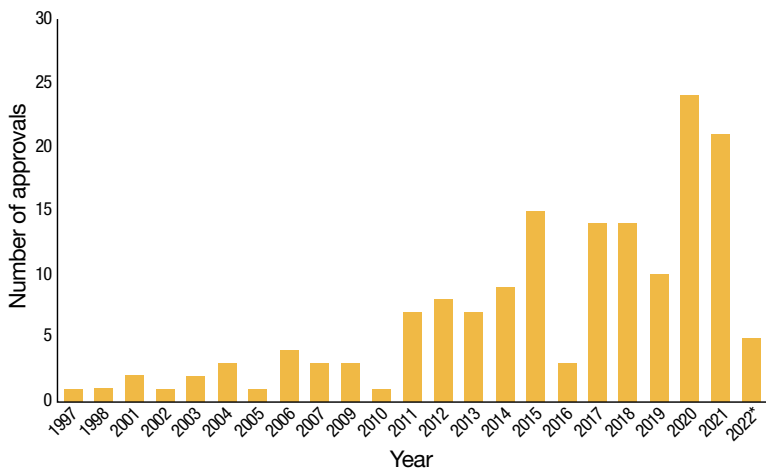


Figure 1 FDA approvals of targeted therapies in oncology.

*Approvals to end May 2022.

Abbreviation: FDA, Food and Drug Administration.

there is a risk of underutilisation of targeted therapies with confirmed benefits, or overutilisation when the drug-target combination has not yet been confirmed, appropriate identification of actionable mutations and assessment of available therapeutic options must be established by molecular tumour boards (MTBs). MTBs, comprised of a multi-disciplinary team of specialists from the fields of molecular biology, pathology, oncology and research, enable interdisciplinary knowledge transfer in the highly complex field of cancer biology and research/clinical care. The MTBs need appropriate organisation (regular multidisciplinary meetings) and implementation of IT platforms capable of searching new scientific evidence in the context of available therapeutic options, as well as gathering real-world evidence. The emerging concept is to build a national/international network of MTBs to share knowledge about MTB recommendations as well as encouraging the active participation of healthcare professionals from peripheral hospitals, thereby providing access to precision oncology for all patients with cancer.

Non-small cell lung cancer (NSCLC) is recognised as a prototype disease for molecularly-driven targeted oncology. This approach is also now part of clinical practice in melanoma and colorectal cancer. As techniques evolve and become more cost effective, the use of molecular testing and molecularly guided drugs may be addressed to a larger number of patients. Therefore, the major implication for patients and healthcare systems is to build optimal therapeutic pathways based on pathological diagnosis, molecular testing, recommended therapies and access to clinical trials. The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group provides recommendations on precision oncology in daily practice, which are available here: <https://oncologypro.esmo.org/oncology-in-practice/personalised-medicine/esmo-recommendations-in-precision-medicine>.

Biomarker-driven therapies have an impact on clinical trial methodology and drug approval processes. Their novel designs enable the investigation of multiple hypotheses. The most widely used are protocols with multiple treatments (umbrella trials), multiple populations (basket trials) or those enabling the addition or removal of trial arms (platform trials). In recent years, the FDA and the European Medicines Agency (EMA) have approved an increasing number of precision oncology drugs targeting molecular biomarkers based on early-stage non-randomised clinical trials. This increase in the availability of novel treatments has contributed to a rise in global oncology spending: \$185 billion in 2021 and predicted to exceed \$300 billion by 2026¹. From the perspective of patients and healthcare systems, monitoring the impact of new registrations on survival, quality of life and cost in the post-approval period is mandatory.

In conclusion, medical reality driven by precision oncology needs optimisation of resources used for patient diagnostics and care by applying the recommendations, gathering real-world evidence for research purposes and monitoring cost-effectiveness, and knowledge-sharing about the agnostic approach in research and clinical practices. With all these advances, it is critical to concentrate on community medical education to empower the implementation of precision oncology in clinical practice.

¹ IQVIA Institute. Global Oncology Trends 2022: Outlook to 2026. Published May 2022. <https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2022> (date last accessed, 19 August 2022).

The idea behind the *ESMO Handbook of Targeted Therapies and Precision Oncology* was to provide comprehensive and practical information for clinicians, who should be familiar with the technology used to determine the types of genomic alterations, correctly interpret the molecular results and implement personalised management in cancer care.

Table 1 FDA Approvals of Targeted Therapies in Oncology.

Year	Drug	Target(s)
1997	Rituximab	CD20
1998	Trastuzumab	HER2
2001	Imatinib Alemtuzumab	BCR-ABL/PDGFR/KIT CD52
2002	Ibritumomab tiuxetan	CD20
2003	Gefitinib Bortezomib	EGFR Proteasome
2004	Erlotinib Cetuximab Bevacizumab	EGFR EGFR VEGF
2005	Sorafenib	VEGFR/KIT/FLT3/PDGFR
2006	Sunitinib Dasatinib Vorinostat Panitumumab	PDGFR/VEGFR/FLT3/KIT/RET BCR-ABL/Src/KIT/LCK/PDGFR HDAC EGFR
2007	Nilotinib Lapatinib Temozolimus	BCR-ABL HER2/EGFR mTOR
2009	Pazopanib Everolimus Ofatumumab	PDGFR/VEGFR/KIT/FGFR/ITK mTOR CD20
2010	Romidepsin	HDAC
2011	Icotinib Crizotinib Vandetanib Ruxolitinib Vemurafenib Ipilimumab Brentuximab vedotin	EGFR ALK/ROS/c-MET EGFR/VEGFR/RET JAK1/JAK2 RAF CTLA-4 CD30
2012	Axitinib Radotinib Bosutinib Vismodegib Carfilzomib Regorafenib Pertuzumab Ado-trastuzumab emtansine	VEGFR BCR-ABL Abl1/Src SMO Proteasome VEGFR/PDGFR/FGFR/RAF/RET/KIT HER2 HER2

Table 1 FDA Approvals of Targeted Therapies in Oncology. (Continued)

Year	Drug	Target(s)
2013	Cabozantinib Ponatinib Afatinib Ibrutinib Trametinib Dabrafenib Obinutuzumab	VEGFR/ROS/TIE2/MET/KIT/TRK2/RET BCR-ABL/PDGFR/FGFR/Src/FLT3/KIT EGFR/HER2/HER4 BTK MEK1/MEK2 RAF CD20
2014	Ceritinib Apatinib Belinostat Olaparib Idelalisib Ramucirumab Nivolumab Pembrolizumab Blinatumomab	ALK/ROS VEGFR2 HDAC PARP PI3Kδ VEGFR2 PD-1 PD-1 CD19/CD3
2015	Alectinib Cobimetinib Palbociclib Osimertinib Sonidegib Sunitinib Panobinostat Tucidinosat Ixazomib Lenvatinib Nintedanib Necitumumab Dinutuximab Daratumumab Elotuzumab	ALK MEK1/2 CDK4/CDK6 EGFR SMO mTOR HDAC HDAC Proteasome PDGFR/VEGFR/FGFR/KIT/RET VEGFR/PDGFR/FGFR/MDR1/BCRP EGFR GD2 CD38 SLAMF7
2016	Venetoclax Rucaparib Atezolizumab	BCL-2 PARP PD-L1
2017	Brigatinib Tivozanib Acalabrutinib Ribociclib Abemaciclib Neratinib Midostaurin Enasidenib Niraparib Copanlisib Inotuzumab ozogamicin Avelumab Durvalumab Gemtuzumab ozogamicin	ALK/EGFR/IGF1R/FLT3/ROS PDGFR/VEGFR/FGFR/KIT/RET BTK CDK4/CDK6 CDK4/CDK6 HER2/EGFR FLT3/KIT IDH2 PARP PI3K CD22 PD-L1 PD-L1 CD33

Table 1 FDA Approvals of Targeted Therapies in Oncology. (Continued)

Year	Drug	Target(s)
2018	Anlotinib	VEGFR/PDGFR/FGFR
	Lorlatinib	ALK
	Fruquintinib	VEGFR
	Binimetinib	MEK1/2
	Encorafenib	RAF
	Dacomitinib	EGFR
	Gilteritinib	FLT3
	Glasdegib	SMO
	Ivosidenib	IDH1
	Larotrectinib	TRK
	Talazoparib	PARP
	Duvelisib	PI3K δ /PI3K γ
	Cemiplimab	PD-1
	Moxetumomab pasudotox	CD22
2019	Pexidartinib	CSF1R/KIT/FLT3
	Zanubrutinib	BTk
	Entrectinib	TRK
	Erdafitinib	FGFR
	Quizartinib	FLT3
	Fedratinib	JAK2
	Alpelisib	PI3K α
	Polatuzumab vedotin	CD79B
	Enfortumab vedotin	Nectin-4
	Trastuzumab deruxtecan	HER2
2020	Pemigatinib	FGFR
	Avapritinib	KIT/PDGFR
	Ripretinib	KIT/PDGFR
	Selumetinib	MEK 1/2
	Capmatinib	MET
	Tepotinib	MET
	Tucatinib	HER2
	Almonertinib	EGFR
	Tazemetostat	EZH2
	Selpercatinib	RET
	Pralsetinib	RET
	Neratinib	HER2
	Brexucabtagene autoleucel	CD19
	Brigatinib	ALK
	Olaparib	HRR/BRCA
	Rucaparib	BRCA
	Erlotinib	EGFR
	Encorafenib	BRAF V600E
	Isatuximab	CD38
	Belantamab mafodotin	BCMA
	Sacituzumab govitecan	TROP-2
	Tafasitamab	CD19
	Naxitamab	GD2
	Margetuximab	HER2

Table 1 FDA Approvals of Targeted Therapies in Oncology. (Continued)

Year	Drug	Target(s)
2021	Tivozanib Lorlatinib Umbrelisib Tepotinib Crizotinib Carfilzomib Asciminib Abemaciclib Ruxolitinib Cabozantinib Mabocertinib Zanubrutinib Ivosidenib Leventanib Avapritinib Infigratinib Sotorasib Dostarlimab Amivantamab Loncastuximab tesirine Tisotumab vedotin	VEGFR1/2/3 ALK PI3Kδ/CK1γ MET ALK/ROS 1 Proteasome ABL/BCR-ABL1 HER2 JAK1/2 VEGFR/MET/KIT/RET/AXL/FLT3 EGFR exon 20 BTK IDH1 VEGFR/FGFR/PDGFR/RET/KIT KIT/PDGFR FGFR2 KRAS G12C PD-1 EGFR/cMET CD19 TF
2022*	Alpelisib Olaparib Pacritinib Tebentafusp Relatlimab	PIK3CA PARP JAK2/FLT3 gp100/CD3 LAG-3

*Approvals to end May 2022.

A list of FDA-approved targeted therapies by tumour type is available here: <https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/approved-drug-list> (date last accessed, 19 August 2022).

Abbreviations: ALK, anaplastic lymphoma kinase; BCL-2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; BCRP, breast cancer resistance protein; BTK, Bruton's tyrosine kinase; CDK 4/6, cyclin-dependent kinase 4/6; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; EGFR, epidermal growth factor receptor; FDA, food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; HER2/4, human epidermal growth factor receptor 2/4; HRR, homologous recombination repair; IDH1/2, isocitrate dehydrogenase 1/2; IGFRI, insulin-like growth factor receptor 1; ITK, interleukin-2 receptor T-cell kinase; JAK1/2, Janus kinase 1/2; MDRI, multidrug resistance 1; mTOR, mammalian target of rapamycin; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; SMO, smoothened homologue; TF, tissue factor; TRK, tropomyosin receptor kinase; VEGFR, vascular endothelial growth factor receptor.

Declaration of Interest:

Professor Lugowska has received personal honoraria for writing engagements from Roche, Novartis and BMS; institutional research grants from Roche and Agenus. She has received personal and institutional honoraria for her work as a Coordinating Principal Investigator from Roche, BMS, Janssen, Novartis, AstraZeneca, Incyte, Boehringer Ingelheim, Agenus, MacroGenics, Checkpoint Therapeutics, Pfizer, Lilly Oncology, MSD and Debiopharm.

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