

ESMO management and treatment adapted recommendations in the COVID-19 era: Breast cancer

These recommendations aim to develop guidance to mitigate the negative effects of the COVID-19 pandemic on the diagnosis and treatment of breast cancer patients. The situation is evolving, and pragmatic actions may be required to deal with the challenges of treating patients, while ensuring their rights, safety and wellbeing. The points mentioned below are intended to provide guidance for all physicians involved in cancer care during this time. Due to the urgency and the rapidly evolving situation, further updates to this guidance are possible and likely. Also, we recognise that there might be specific national legislation and guidance in place, which can be taken into account to complement this guidance, or, with respect to particular matters, may take priority over these recommendations. This document is however seeking to include most of the current guidance with the aim to serve as a set of recommendations.

Cancer patient prioritisation

The tiered approach of ESMO in delivering a guidance for cancer patients during the COVID-19 pandemic is designed across three levels of priorities, namely: tier 1 (high priority intervention), 2 (medium priority) and 3 (low priority) – defined according to the criteria of the Cancer Care Ontario, Huntsman Cancer Institute and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS), incorporating the information on the value-based prioritisation and clinical cogency of the interventions

- **High priority:** Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]);
- **Medium priority:** Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority;
- **Low priority:** Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain with no change nor reduced QoL).

Priorities for breast cancer patients

Outpatient visit priorities

High Priority
• Post-operative unstable clinical scenario (e.g. haematoma, infection) • Breast cancer diagnosis during pregnancy
High/Medium Priority
• New diagnosis of invasive breast cancer (for multidisciplinary tumour board discussion: biology and stage will drive priority) • On-treatment patients with new symptoms or side effects (depending on severity of symptoms/side effects, burden of progression, etc.). <i>Convert as many visits as possible to telemedicine visits. Intensify safety monitoring for those patients on oral chemotherapy or endocrine therapy plus biological agents</i>
Medium Priority
• New diagnosis of non-invasive cancer. <i>Convert as many visits as possible to telemedicine visits</i> • Post-operative visits in patients with no complications

Low Priority

- Established patients with no new issues: *refer to telemedicine*
- Survivorship follow-up: *refer to telemedicine*
- Follow-up for patients at high risk of breast cancer (BRCA carriers, etc...) or patients at high risk of relapse
- Psychological support visits (*convert to telemedicine*)

Priorities for Breast Disease: Diagnostics and imaging

High Priority

- Self-diagnosis of breast lump or other symptoms suggestive of malignancy
- Clinical evidence of locoregional relapse with surgical radical approach feasible (according to stage, histology and biological features of the disease)
- Pathology assessment (histopathology or cytopathology) for abnormal mammograms or breast symptoms or a symptomatic metastatic relapse
- Further diagnostic imaging for BIRADS 5 screening mammogram in asymptomatic subjects

Medium Priority

- Further diagnostic imaging for BIRADS 4 screening mammogram in asymptomatic subjects
- Image-guided or clinically guided biopsy to ascertain a suspicion of metastatic relapse
- Initial metastatic work-up (according to stage and biological features) in patients with early stage invasive breast cancer
- Echocardiograms in patients with early stage invasive breast cancer requiring indication to anthracycline-based or anti-HER2 treatment

Low Priority

- Mammography-based population screening and risk-adapted breast screening programmes for asymptomatic subjects (e.g. MRI or US)
- Patients with abnormal findings at screening mammograms who can go to 6-month interval imaging (BIRADS 3)
- In patients with early stage breast cancer, follow-up imaging, restaging studies, echocardiograms, ECGs and bone density scans can be delayed if clinically asymptomatic
- In patients with metastatic breast cancer, we recommend symptom-oriented follow-up. Imaging, restaging studies, echocardiograms and ECGs can be delayed or done at lengthened intervals. *Implement telemedicine follow-up*

Priorities for Breast Disease: Surgical Oncology

High Priority

- Breast cancer surgery complication with bleeding or indication to incision and drainage of a breast abscess and/or haematoma
- Complications of reconstructing surgery (e.g. ischaemia)
- Surgery in patients who have completed neoadjuvant chemotherapy-based treatment (or, in exceptional cases, with progression of disease during neoadjuvant treatment)
- Surgery in patients with invasive cancer for whom a multidisciplinary tumour board may decide, case by case, to proceed with upfront surgery
- Breast cancer surgery during pregnancy (multidisciplinary treatment should be individualised according to stage and biology)

High/Medium Priority

- Excision of malignant recurrence (depending on phenotype and extent)

Medium Priority
- Clinically low-risk primary breast cancer (e.g. stage I/II ER-positive/PR-positive/HER2-negative, low grade/low proliferative index tumours). <i>After multidisciplinary tumour board discussion consider starting neoadjuvant/preoperative endocrine therapy according to menopausal status and delay surgery</i> - Discordant biopsies likely to be malignant
Low Priority
- Excision of benign lesions and duct excision (fibroadenomas, atypia, papillomas) - Surgery of non-invasive breast cancer (in situ) except for extended high-grade DCIS - Discordant biopsies likely to be benign - Breast reconstruction with autologous tissue and/or implants - Prophylactic surgery for asymptomatic high-risk patients

Priorities for Breast Cancer: Radiation Oncology

High Priority
- Palliative treatment of bleeding/painful inoperable breast mass, when control of symptoms cannot be achieved pharmacologically - Patients already on radiation treatment - Acute spinal cord compression, symptomatic brain metastases or any urgent palliative radiotherapy - Adjuvant post-operative radiotherapy for high-risk breast cancer patients (inflammatory disease at diagnosis, node-positive disease, TNBC or HER2-positive breast cancer, residual disease at surgery post neoadjuvant therapy, young age (<40))
Medium Priority
Adjuvant post-operative radiotherapy for low-/intermediate-risk breast cancer patients (age <65y and stage I/II luminal cancer, ER-positive regardless of nodal status or positive margins). <i>Use of hypofractionated regimens should be considered to reduce hospital visits. Endocrine therapy can be started during the waiting interval</i>
Low Priority
- Elderly patients with low-risk breast cancer (age >70y, with low-risk stage I ER-positive/HER2-negative breast cancer): <i>Starting adjuvant endocrine therapy is recommended while postponing radiotherapy</i> - Carcinoma <i>in situ</i>

Priorities for Breast Cancer: Medical Oncology - Early Breast Cancer

High Priority
• Neoadjuvant and adjuvant chemotherapy for TNBC patients • Neoadjuvant and adjuvant chemotherapy in combination with targeted therapy for HER2-positive breast cancer patients • Neoadjuvant and adjuvant endocrine therapy +/- chemotherapy for high-risk ER-positive/HER2-negative breast cancer as defined by current guidelines • Completion of neoadjuvant chemotherapy (with or without anti-HER2 therapy) that has already been initiated • Continuation of adjuvant capecitabine treatment in high-risk TNBC patients, and T-DM1 in high-risk HER2-positive breast cancer patients (in the post-neoadjuvant setting) • Continuation of treatment in the context of a clinical trial, provided patient benefits outweigh risks, with possible adaptation of procedures without affecting patient safety and study conduct. <i>Regulatory agencies and sponsors may provide guidance on rules on study conduct during pandemics</i>
Medium Priority
• For postmenopausal women with stage I cancers, with low-intermediate-grade tumours, lobular breast cancers, endocrine therapy may be started first while surgery can be delayed • For patients with low-risk genomic signatures/score, prefer endocrine therapy alone • Ongoing adjuvant trastuzumab alone may be postponed by 6-8 weeks in patients at high risk of complicated COVID-19 infection
Low Priority
• Follow-up imaging, restaging studies, echocardiograms, ECGs and bone density scans can be delayed if patient clinically asymptomatic or clinical signs of response in the neoadjuvant setting

Specific recommendations

- Continuation of standard adjuvant endocrine therapy in pre and postmenopausal setting. *Use telemedicine to manage potential toxicity reported by patients*
- Neoadjuvant endocrine therapy is an option for patients with ER-positive/HER2-negative breast cancer to enable deferral of surgery by 6 to 12 months in clinical stage I or II breast cancers
- For selected HER2-positive breast cancer, low-risk or elderly patients with cardiovascular or other comorbidities, adjuvant anti-HER2 therapy may reasonably be discontinued after 6 months instead of 12 months of treatment according to data from prospective randomised trials
- If chemotherapy is considered for a patient with ER-positive/HER2-negative breast cancer, then it can be administered in the neoadjuvant setting
- Chemotherapy schedules may be modified to reduce accesses to hospital (for instance, using 2- or 3-weekly dosing instead of weekly dosing for selected agents when appropriate). Patients should receive G-CSF growth factor and, eventually, antibiotics support to minimise neutropaenia, while dexamethasone use should be limited, as appropriate, to reduce immunosuppression
- Following a case-by-case discussion according to the logistics of the patient, LHRH analogue may be given with long acting, every 3 months dosing, to reduce patient visits or alternatively, home administration of LHRH analogue by the patient or visiting nurse may be considered. Monthly home administration of LHRH analogue by the patient or visiting nurse is the preferred recommendation
- If possible, schedule imaging exams and blood tests near home
- Implement telemedicine safety monitoring whenever possible

Priorities for Breast Cancer: Medical Oncology - Metastatic Breast Cancer

High Priority
• Early-line chemotherapy, endocrine therapy, targeted agents or immune-checkpoint inhibitors likely to improve outcomes in metastatic disease (high priority to pertuzumab/trastuzumab plus chemotherapy in HER2-positive breast cancer). Consider also discussing case by case in a multidisciplinary tumour board, endocrine therapy with CDK 4-6 inhibitors in ER-positive/HER2-negative breast cancer, chemotherapy plus atezolizumab in PD-L1-positive TNBC • Visceral crisis • Continuation of treatment in the context of a clinical trial, provided patient benefits outweigh risks, with possible adaptation of procedures without affecting patient safety and study conduct. <i>Regulatory agencies and sponsors may provide guidance on rules on study conduct during the pandemics</i>
Medium Priority
• Second-, third-, beyond third-line treatment when therapy may provide clinical benefit and impact on outcome • Consider avoiding or delaying the addition of mTOR or PIK3CA inhibitors (still not approved in European Union) to endocrine therapy, particularly in elderly patients with comorbidities • Consider, discussing case by case, inclusion in a clinical trial, provided patient benefits outweigh risks, with possible adaptation of procedures without affecting patient safety and study conduct
Low Priority
• Bone agent therapy (zoledronic acid, denosumab) not urgently needed for hypercalcaemia, or not needed for pain control and in patients who are otherwise not in need of coming to the hospital (i.e. receiving oral chemotherapy or endocrine therapy). Bone agents can be administered every 3 months • If clinically asymptomatic, follow-up imaging, restaging studies, echocardiograms and ECGs can be delayed or done at lengthened intervals

Specific recommendations

- When chemotherapy is recommended, prefer oral treatments in order to reduce access to hospital
- Chemotherapy schedules may be modified to reduce clinical visits (for instance, using 3-weekly dosing instead of weekly dosing for selected agents when appropriate). Patients should receive G-CSF growth factor support to minimise neutropaenia, while dexamethasone use should be limited, as appropriate, to reduce immunosuppression
- LHRH analogue may be given with long acting, every 3 months dosing, to reduce patient visits or alternatively, home administration of LHRH analogue by the patient or visiting nurse may be considered. Monthly home administration of LHRH analogue by the patient or visiting nurse is the preferred recommendation
- Endocrine therapies: oral agents used widely in adjuvant or metastatic setting (e.g. tamoxifen, aromatase inhibitors) should have no effect on immune function and can be safely continued. Fulvestrant should have no effect on immune function but requires monthly i.m. administration
- Implement telemedicine safety monitoring whenever possible
- All patients must be assured with the best home-based supportive care and enhanced symptoms control via telemedicine
- Bone agents for patients with bone metastases should be delivered at minimal hospital access

- The incorporation of CDK4/6 inhibitors to endocrine treatments should align with ongoing recommendations, the local practice and resource availability. The risk associated with neutropaenia has not been clearly defined and demands research implementation - close monitoring for symptoms of infection is recommended, to promptly withdraw the treatment and possibly refer to COVID-19 diagnostic pathway
- The choice of postponing the incorporation of a CDK4/6 inhibitor in the first line, for patients presenting with special patterns of disease (e.g. bone only, low-burden, de novo metastatic disease) could be an option, especially in the elderly population
- For patients with advanced-metastatic TNBC, the first-line treatment can be defined based on biomarkers, according to the local practice and resource availability. For patients with PD-L1-positive TNBC, an indication for immunotherapy could be considered. The risk associated with immunotherapy in the onset and progression of COVID-19 has not been clearly described and demands research implementation - close monitoring for specific symptoms, pneumonitis or infection is recommended, to promptly withdraw the treatment and possibly refer to COVID-19 diagnostic pathway
- Oral chemotherapy agents should be prioritised, whenever possible, prescribed for multiple courses and managed via telemedicine, for the predictable and manageable toxicities
- The addition of mTOR or PI3KCA inhibitors is not of immediate priority and should be avoided. The induced immune-suppression (everolimus), risk of diabetes (alpelisib), risk for pulmonary side effects demanding CT scan and other healthcare services overlapping with the COVID-19 algorithm could be a reason to postpone the incorporation of these agents in later lines (e.g. in frailer patients with multiple COVID-19 risk-increasing comorbidities)
- In the metastatic setting, following multidisciplinary tumour board discussion and according to patient preference, in later lines may discuss drug holidays, best supportive care and delayed regimens or de-escalated maintenance regimens, wherever appropriate

List of abbreviations: BIRADS, Breast Imaging-Reporting and Data System; COVID-19, severe acute respiratory syndrome coronavirus 2-related disease; CT, computed tomography; DCIS, ductal carcinoma in situ; ECG, electrocardiogram; ER, oestrogen receptor; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; i.m., intramuscular; LHRH, luteinising hormone releasing hormone; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; PD-L1, programmed death-ligand 1; PR, progesterone receptor; TDM1, trastuzumab emtansine; TNBC, triple-negative breast cancer; US, ultrasonography.

Note: Cancer care prioritisation and cancer care intensity should be adapted to the pandemic scenario [from 1 to 4 according to the European Centre for Disease Prevention and Control (ECDC)], to local R0 index and to health facilities and resources. With a pandemic scenario 1 or 2, we recommend to be compliant to guidelines and to avoid any deviation from standard of care.

Essential bibliography

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