International Consensus Guidelines for Advanced Breast Cancer
ABC GUIDELINES

INTRODUCTION/INSTRUCTIONS

- **All panel members voted in all questions (yes/no/abstain). Voting was MANDATORY.**
- **Members of the panel who had a conflict of interest OR who did not feel comfortable answering the question (e.g. not area of expertise) were instructed to vote "abstain".**
- ABC 1-2-3-4-5-6 statements that were not re-voted (not updated or with only minor changes) will be published in the manuscript
- As in previous editions, where the Guidelines state "preferred option" or "standard of care", they assume availability of the agent. All guidelines that are related to a certain treatment depend, obviously, on the availability of that treatment. It is possible to discuss adaptation of the ABC Guidelines to different environments, but that is a separate project, outside the scope of the main guidelines.

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LEVELS OF EVIDENCE GRADING SYSTEM

LEVELS OF EVIDENCE

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity.
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.
III	Prospective cohort studies.
IV	Retrospective cohort studies or case–control studies.
V	Studies without control group, case reports, experts' opinions.

GRADES OF RECOMMENDATION

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional.
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended.
E	Strong evidence against efficacy or for adverse outcome, never recommended.

Adapted by permission from the Infectious Diseases Society of America-United States Public Health Service Grading System; Dykewicz et al, 2001

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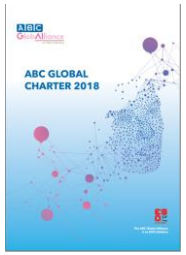
ABC Global Charter

10 goals for 10 years

Through the kind support of the Alliance members the Charter has been translated in 17 languages.
Files available at on the Alliance website



COMPREHENSIVE NEEDS ASSESSMENT
DEFINES MOST URGENT AND ACTIONABLE GOALS
Developed with members of the ABC Global Alliance, including (almost) all different stakeholders involved in ABC

1. HELP PATIENTS WITH ABC LIVE LONGER BY DOUBLING ABC MEDIAN OVERALL SURVIVAL BY 2025
2. ENHANCE OUR UNDERSTANDING ABOUT ABC BY INCREASING THE COLLECTION OF HIGH QUALITY DATA
3. IMPROVE THE QUALITY OF LIFE (QOL) OF PATIENTS WITH ABC
4. ENSURE THAT ALL PATIENTS WITH ABC RECEIVE THE BEST POSSIBLE TREATMENTAND CARE BY INCREASING AVAILABILITY OF ACCESS TO CARE FROM A MULTIDISCIPLINARY TEAM
5. IMPROVE COMMUNICATION BETWEEN HEALTHCARE PROFESSIONALS (HCP) AND PATIENTS WITH ABC THROUGH THE PROVISION OF COMMUNICATION SKILLS TRAINING FOR HCPS
6. MEET THE INFORMATIONAL NEEDS OF PATIENTS WITH ABC BY USING EASY TO UNDERSTAND, ACCURATE AND UP-TO-DATE INFORMATION MATERIALS AND RESOURCES
7. ENSURE THAT PATIENTS WITH ABC ARE MADE AWARE OF AND ARE REFERRED TO NON-CLINICAL SUPPORT SERVICES
8. COUNTERACT THE STIGMA AND ISOLATION ASSOCIATED WITH LIVING WITH ABC BY INCREASING PUBLIC UNDERSTANDING OF THE CONDITION
9. ENSURE THAT PATIENTS WITH ABC HAVE ACCESS TO TREATMENT REGARDLESS OF THEIR ABILITY TO PAY
10. HELP PATIENTS WITH ABC CONTINUE TO WORK BY IMPLEMENTING LEGISLATION THAT PROTECTS THEIR RIGHTS TO WORK AND ENSURE FLEXIBLE AND ACCOMMODATING WORKPLACE ENVIRONMENTS

ABC GlobAlliance

ABC DEFINITIONS

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VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.

Examples:
***Liver visceral crisis*: rapidly increasing bilirubin >1.5x ULN, in the absence of Gilbert's Syndrome or biliary tract obstruction**
***Lung visceral crisis*: rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion**

(LoE/GoR: Expert opinion/NA) (97%)

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ENDOCRINE SENSIVITY/RESISTANCE

NEW/MODIFIED

ET NAÏVE: unknown if there is sensitivity or resistance to endocrine therapy (ET) since has never received ET

PRIMARY ENDOCRINE RESISTANCE is defined as:

Relapse while on the first 2 years of adjuvant ET, or
PD within first 6 months of 1st line ET-based therapy for ABC
(note: this definition is the same regardless of whether therapy included a CDK4/6i or not)

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

All other clinical situations of endocrine-resistance
(examples include: 1) Relapse while receiving adjuvant ET but after at least 2 years; 2) PD after at least 6 months of 1st line ET-based therapy for ABC; 3) PD after any duration of 2nd+ line ET-based therapy for ABC; 4) Known ESR1 mutation)
(note: definition unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs)

ENDOCRINE INSENSITIVITY is defined as:

PD within 2 months of later-line ET-based therapy for ABC and no additional ET-based approaches likely to result in clinically meaningful benefit

(LoE: Expert opinion/NA) (95%)

Note: resistance is a continuum, and these definitions help clinical trials but do not necessarily dictate clinical practice

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PATIENTS WITH MULTIPLE CHRONIC CONDITIONS (MCCs) are defined as patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease), which may decrease tolerance to treatment and impact outcomes and the incidence of toxicities. This limits the ability to extrapolate existing data and make evidence-based recommendations for care.

(LoE: Expert opinion/NA) (100%)

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ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF ABC

Adequate OFS for ABC premenopausal patients can be obtained through bilateral oophorectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is the least preferred option). (LoE/GoR: I/A) (85%)
If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. (LoE/GoR: II/B) (85%)

Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered. (LoE/GoR: Expert Opinion/B) (85%)

As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression and cost.

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MAINTENANCE THERAPY

In the context of ABC Guidelines, maintenance therapy refers to the continuation of anti-HER2 therapy, immunotherapy and/or endocrine therapy after discontinuation of chemotherapy.

(LoE: Expert Opinion/NA) (100%)

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INTEGRATIVE MEDICINE

Complementary and Integrative Medicine (CIM) represents the use of complementary treatments side by side with conventional approaches in a proper therapeutic environment.

(LoE: Expert Opinion/NA) (100%)

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OLIGO-METASTATIC DISEASE

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OLIGO-METASTATIC DISEASE - Definition

NEW/MODIFIED

OLIGO-METASTATIC DISEASE is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.

Note: Oligometastatic sites need to be solid; excludes pleural effusion, ascites, leptomeningeal disease.

The definition of oligometastatic disease is highly dependent on the imaging method used. Trials are necessary to compare different imaging techniques specifically in breast cancer and to evaluate the exact benefit of local treatments.

(LoE/GoR: Expert opinion/NA) (87%)

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NEW/MODIFIED

OLIGO-METASTATIC DISEASE in CONTRALATERAL AXILLA

Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage IV metastatic breast cancer.

However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach.

(LoE/GoR: Expert opinion/NA) (85%)

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OLIGO-METASTATIC DISEASE - Management

NEW/MODIFIED

A randomized phase 2 trial (NRG-BR002) in patients (n=125) with oligometastatic breast cancer (≤ 4 extra-cranial sites) evaluated use of SBRT and/or Surgical Resection to all oligometastatic sites, in context of ≤ 12 months of first-line systemic therapy without progression. Most enrolled pts had oligometastatic recurrence (78%) and ER+/HER2-negative breast cancer (80%). The results showed no difference in median PFS and 3-yr OS, no difference in rate of metastases outside index area, and the trial did not proceed to phase 3.

A small randomized phase 2 trial (SABR-COMET) in patients with different types of advanced cancers including breast (18 patients only), evaluated the use of SBRT to all sites of oligometastatic disease, in the context of a controlled primary tumour, and showed a significant OS benefit.

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OLIGO-METASTATIC DISEASE - Management

NEW/MODIFIED

Based on available data, routine ablation of extra-cranial asymptomatic oligometastatic sites is not recommended, outside a clinical trial, until further data is available.
(LoE/GoR: II/D) (98%)

It may however be discussed on an exceptional basis in a multidisciplinary tumor board and the patient should be informed about the uncertainty about impact on OS seen so far.

Systemic therapy should be the 1st treatment initiated and decision about possible loco-regional treatments should be taken based on disease response.
(LoE/GoR: II/B) (98%)

Results of additional ongoing trials are awaited. Further data specific to patients with de novo oligometastatic breast cancer is needed, as well as a better characterization of the subset of patients likely to benefit from a local-regional approach.

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GENERAL STATEMENTS

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The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.

(LoE/GoR: Expert opinion/A) (100%)

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From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalized to meet the needs of the individual patient.

(LoE: Expert opinion/A) (100%)

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Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances).

This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.

(LoE/GoR: Expert opinion/A) (97%)

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All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy to understand information about their disease and its management.

(LoE/GoR: I/A) (97%)

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Patients (and their families, caregivers or support network, if the patient agrees) should be invited to participate in the decision-making process at all times.
When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network).

(LoE/GoR: Expert opinion/A) (100%)

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Every ABC patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient centered care, as defined by:

- **Open communication between patients and their cancer care teams as a primary goal.**
- **Educating patients about treatment options and supportive care, through development and dissemination of evidence-based information in a clear, culturally appropriate form.**
- **Encouraging patients to be proactive in their care and to share decision-making with their health care providers.**
- **Empowering patients to develop the capability of improving their own quality of life within their cancer experience.**
- **Always taking into account patient preferences, values and needs as essential to optimal cancer care.**
- **Patients should have easy access to well designed clinical studies, since these are crucial for further improvement in the management of ABC.**

(LoE/GoR: Expert opinion/A) (100%)

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Every ABC patient should:

- **Have access to the most up-to-date treatments and to innovative therapies at accessible Breast Units/Centers. (LoE/GoR: Expert opinion/A) (100%)**
- **Be treated in Specialist Breast Units/Centers/Services (SBU) by a specialized multidisciplinary team including specialized side effects management and a nurse experienced in the treatment of ABC. (LoE/GoR: I/A) (100%)**
- **Survivorship issues and palliative care should be addressed and offered at an early stage. (LoE/GoR: Expert opinion/A) (100%)**
- **A Quality Assurance Program covering the entire breast cancer pathway from screening and diagnosis to treatment, rehabilitation, follow up and palliative care including services and support for ABC patients and their caregivers, should be implemented by SBUs. (LoE/GoR: Expert opinion/B) (100%)**

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GENERAL STATEMENTS - QoL

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PROs, e-PROs and QUALITY OF LIFE ASSESSMENTS

NEW/MODIFIED

Strong consideration, as part of routine clinical care, should be given to the integration of patients' reports of symptoms of disease and side effects of treatment.

Several remote measurement systems exist but these must be evidence-based and shown to be simple enough for use in clinical practice, in particular employ user-friendly collection platforms e.g. tablets or smartphones appropriate for different patient groups.

Such regular systematic monitoring may facilitate communication between patients and their treatment teams about the toxicities of anticancer therapies.

Reporting does not have to be tied to regular follow-up visits so that it may permit earlier introduction of ameliorative interventions and supportive care services.

(LoE/GoR: I/B) (100%)

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PROs, e-PROs and QUALITY OF LIFE ASSESSMENTS

NEW/MODIFIED

Trials evaluating QoL in ABC should employ standardized PROMs and not focus exclusively on reporting CTCAE symptom grades. If generic measures are used, then appropriate symptom and treatment specific modules or subscales that exist within the EORTC and FACT systems should be incorporated.

Additionally, attention must be paid to collection methods, timing of assessments and handling of missing data.

More sophisticated statistics should also be employed to ensure that clinicians have better, reliable data to help patients choosing between treatment options.

(LoE/GoR: Expert opinion/A) (98%)

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GENERAL STATEMENTS- CLINICAL TRIALS

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After appropriate informed consent, inclusion of patients in well-designed, prospective, independent trials must be a priority, whenever such trials are available, and the patient is willing to participate.

(LoE/GoR: Expert opinion/A) (100%)

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The ABC community strongly calls for clinical trials addressing important unanswered clinical questions in this setting, and not just for regulatory purposes.
Clinical trials should continue to be performed, even after approval of a new treatment, to provide real world data on its performance, effectiveness and toxicity.

(LoE/GoR: Expert opinion/A) (100%)

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NEW/MODIFIED

MAXIMUM TOLERATED DOSE vs. MINIMAL EFFECTIVE DOSE

In the treatment of human breast cancer, the biology of dose-response relationship curves for newer targeted medicines and even older chemotherapy drugs does not support the requirement that these agents always be employed at maximum tolerated dose, a concept that originated in the study of murine leukemia.
This insight is amplified by considerations of feasibility, as well as quality of life and goals of care.
From this perspective, finding and utilizing the optimal dose level and the best schedule should be an important part of the clinical development of any anticancer agent.

(LoE/GoR: Expert Opinion/NA) (96%)

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GENERAL STATEMENTS - AFFORDABILITY/COST-EFFECTIVENESS

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The ABC community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients' well being, length of life and preferences should always guide decisions.

(LoE/GoR: Expert opinion/A) (100%)

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We strongly recommend the use of objective scales, such as the ESMO Magnitude of Clinical Benefit Scale or the ASCO Value Framework, to evaluate the real magnitude of benefit provided by a new treatment and help prioritize funding, particularly in countries with limited resources.

(LoE/GoR: Expert opinion/A) (88%)

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BIOSIMILARS

The ABC community strongly supports the use of biosimilars both for treatment of breast cancer (i.e. trastuzumab) and for supportive care (i.e. growth factors).
To be used, the biosimilar must be approved after passing the stringent development and validation processes required by EMA or FDA or other similarly strict authority.

(LoE/GoR: I/A) (90%)

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GENERAL STATEMENTS-SURVIVORSHIP ISSUES

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SURVIVORSHIP ISSUES

As survival is improving in many patients with ABC, consideration of survivorship issues should be part of the routine care of these patients.

Health professionals should therefore be ready to change and adapt treatment strategies to disease status, treatment adverse effects and QoL, patients' priorities and life plans.

Attention to chronic needs for home and family care, job and social requirements, should be incorporated in the treatment planning and periodically updated.

(LoE/GoR: Expert opinion/A) (95%)

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SURVIVORSHIP ISSUES

ABC patients who desire to work or need to work for financial reasons should have the opportunity to do so, with needed and reasonable flexibility in their working schedules to accommodate continuous treatment and hospital visits.

(LoE/GoR: Expert opinion/A) (100%)

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SURVIVORSHIP ISSUES

ABC patients with stable disease, being treated as a “chronic condition”, should have the option to undergo breast reconstruction, if clinically appropriate.

(LoE/GoR: Expert opinion/B) (82%)

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SURVIVORSHIP ISSUES

In ABC patients with long-standing stable disease or complete remission, breast imaging is an option.

(LoE/GoR: Expert opinion/C) (83%)

Note: systemic work up imaging doesn't give good imaging of breast

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SURVIVORSHIP ISSUES

Breast imaging should also be performed when there is a suspicion of loco-regional progression.

(LoE/GoR: I/A) (100%)

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GENERAL STATEMENTS - OTHER

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RELEVANT DRUG INTERACTIONS

NEW/MODIFIED

Special attention should be given to potential interactions between targeted agents and common medications for comorbidities, due to the risk of interference with efficacy and/or safety.

Examples:

- **Tamoxifen and ribociclib – increased risk of QTC prolongation**
- **PPI and ribociclib/palbociclib/abemaciclib – likely decreased efficacy**
- **Corticosteroids and checkpoint inhibitors – possible decreased efficacy due to competing mechanisms of action (i.e. immunosuppression)**
- **Antibiotics and checkpoint inhibitors – decreased efficacy due to possible interference with microbiota**

(LoE/GoR: III/A) (82%)

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Specialized oncology nurses (if possible specialized breast nurses) should be part of the multidisciplinary team managing ABC patients.
In some countries this role may be played by a physician assistant or another trained and specialized health care practitioner.

(LoE/GoR: Expert opinion/A) (92%)

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The use of telemedicine in oncology to help management of patients with ABC living in remote places is an important option to consider when geographic distances are a problem and provided that issues of connectivity are solved.

(LoE/GoR: Expert opinion/B) (93%)

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SUPPORT FOR CAREGIVERS

NEW/MODIFIED

The wellbeing of all informal and formal carergivers of patients with ABC is frequently ignored and their pivotal role in supporting patients underestimated and undervalued. They too often need appropriate psychological and practical support. Working carers require protection from discrimination in the workplace (current and future).

With the patient's agreement, culturally sensitive, up-to-date, and easy to understand information about their loved one's disease and its management throughout the whole trajectory from diagnosis to end-of-life should be provided by the healthcare team and needs to be congruent with that given to patients.

Identification of formal and informal carers' needs and referral to appropriate resources should be available for all patients with ABC.
For working carers, entitlement to continued employment and requests for reasonable adjustments, such as flexible working, to accommodate their caring responsibilities should be addressed.

Country-specific political mediation may be required.

(LoE: Expert opinion/NA) (100%)

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NEWMODIFIED

CARING FOR PATIENTS WITH ABC DURING WAR AND CONFLICT

War and conflict can cause major disruption to delivery of care for patients with cancer.

If access to medical care is disrupted or erratic, when possible, consider treatment with oral regimens and treatment regimens requiring minimal routine monitoring and blood work.

Telemedicine should be utilized to ensure continuity of care and contact with patients.

All efforts should be made to ensure access to pain medications and integrate in humanitarian packages.

Providing online support for colleagues in regions of conflict, who may themselves be at risk but who are essential workers trying to ensure best delivery of oncology care under difficult circumstances, is meaningful and important.

(LoE/GoR: Expert Opinion/B) (100%)

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CARING FOR PATIENTS WITH ABC AND PRE-EXISTING SERIOUS MENTAL HEALTH ILLNESS

NEW/MODIFIED

Individuals diagnosed with **serious mental illness (SMI)** (including but not limited to major depression, bipolar disorder and schizophrenia) are more likely to be diagnosed with advanced stage cancer and to have poorer outcomes than individuals without SMI.

Attention needs to be given to the special needs of patients with ABC and SMI and there should be no discrimination against them. The oncology team should endeavor to work together with the patient's psychiatrist and mental illness care team and endeavor to engage carers in order to ensure optimization, compliance and continuity of oncology care.

Special attention needs to be given to drug-drug interactions between psychiatric medication and oncological therapies.

Under certain circumstances steroid and medicinal cannabis use should be minimized to avoid triggering episodes of mania and psychosis.
(LoE/GoR: IV/B) (95%)

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ACCESS OF PATIENTS WITH ABC TO ICU

NEW/MODIFIED

Patients with ABC should receive patient-centered communications regarding their prognosis and treatment options and have the right to forego treatment as well as to pursue treatments to the degree they desire, where available and appropriate for the disease setting.
They should not be denied access to ICU (intensive care units) based solely on their ABC diagnosis, in particular in cases of potentially reversible serious adverse events or complications of comorbidities other than ABC.

(LoE/GoR: Expert Opinion/B) (100%)

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IMAGE AND DISEASE ASSESSMENT GUIDELINES

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Minimal staging workup for ABC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone.

(LoE/GoR: II/A) (67%)

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The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. An increase in tumor markers alone should not be used to initiate a change in treatment.

(LoE/GoR: II/C) (89%)

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Evaluation of response to therapy should generally occur every 2 to 4 months for ET-based therapy or after 2 to 4 cycles for CT, depending on the dynamics of the disease, the location and extent of metastatic involvement, and type of treatment.

Imaging of a target lesion may be sufficient in many patients.

In certain patients, such as those with indolent disease, less frequent monitoring is acceptable.

Additional testing should be performed in a timely manner, irrespective of the planned intervals, if PD is suspected or new symptoms appear. Thorough history and physical examination must always be performed.

(LoE/GoR: Expert opinion/B) (81%)

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BIOPSY OF METASTATIC LESION(S)

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BIOPSY OF METASTATIC LESION

A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.

(LoE/GoR: I/B) (98%)

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BIOPSY OF METASTATIC LESION

NEW/MODIFIED

Biological markers (especially ER and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible.

(LoE/GoR: I/A) (98%)

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BIOPSY OF METASTATIC LESION

NEW/MODIFIED

The value of PR in the metastatic setting is limited and reserved only for confirmation of triple negative status. In the very rare cases of ER-/HER2-/PR+ ABC, approved therapies for triple negative ABC can be used.
(LoE/GoR: Expert Opinion/B) (82%)

Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist and the interventional radiologist.

The quality of IHC assessments is crucial to ensure adequate treatment decisions.

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NEW/MODIFIED

BIOPSY OF METASTATIC LESION

If the results of ER and HER2 in the metastatic lesion differ from the primary tumor, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of endocrine therapy or anti-HER2 therapy, respectively, when ER or HER2 are positive in at least one biopsy, regardless of timing.

(LoE/GoR: Expert opinion/B) (71%)

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NEW/MODIFIED

BIOPSY OF METASTATIC LESION

For tumors with confirmed triple negative histology in the primary tumor, if the results of any receptor status in the metastatic lesion differ, it is currently unknown which result should be used for treatment decision making. Since a clinical trial addressing this issue is difficult to undertake, the use of therapies specifically approved for triple negative, ER+/HER2 negative or HER2+ ABC should be discussed on a case-by-case basis.

(LoE/GoR: Expert opinion/B) (96%)

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LOCAL-REGIONAL TREATMENT GENERAL GUIDELINES

SURGERY OF THE PRIMARY

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SURGERY OF THE PRIMARY

NEW/MODIFIED

To date, the removal of the primary tumor in patients with de novo stage IV breast cancer has not been associated with prolongation of survival.
However, it can be considered in selected patients, particularly to improve quality of life, always taking into account the patient's preferences, after a multidisciplinary discussion.
(LoE/GoR: I/C) (98%)

Examples of situations where surgery of the primary may be considered include:

- **Symptomatic primary site (for control of symptoms)**
- **Progression of the primary tumor when distant disease is controlled**
- **No evidence of disease except in the primary tumor**

Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (i.e. complete removal of the disease) as in patients with early stage disease.
(LoE/GoR: II/B) (98%)

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SYSTEMIC TREATMENT GENERAL GUIDELINES

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Treatment choice should take at least these factors into account :

ER and HER-2 status

BRCA status in HER-2 negative ABC, *PIK3CA* in ER+ and PD-L1 in TNBC, if targeted therapies are accessible

Previous therapies and their toxicities, disease-free interval,

Tumor burden (defined as number and site of metastases),

Biological age, performance status, co-morbidities (including organ dysfunctions),

Menopausal status (for ET),

Need for a rapid disease/symptom control,

Socio-economic and psychological factors,

Available therapies in the patient's country

Patient's preference.

(LoE/GoR: Expert opinion/A) (95%)

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The age of the patient should not be the sole reason to withhold effective therapy (in older patients) nor to overtreat (in young patients).
Age alone should not determine the intensity of treatment.

(LoE/GoR: I/E) (100%)

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TREATMENT HOLIDAYS

NEW/MODIFIED

Planned treatment holidays, with careful supervision, are an acceptable option in the case of long-term responders with controlled disease.

(LoE/GoR: IV/B) (98%)

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TREATMENT HOLIDAYS

NEW/MODIFIED

Stopping treatment in patients with long-term complete remissions has not been adequately studied but should be considered on a case-by-case basis, after extensive discussion with the patient.
It is crucial that resuming the treatment if progression of disease occurs, is allowed in all countries.

(LoE/GoR: Expert Opinion/B) (98%)

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CHEMOTHERAPY GENERAL GUIDELINES

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Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for ABC. Combination CT should be reserved for patients with rapid clinical progression, visceral crisis, or need for rapid symptom and/or disease control.

(LoE/GoR: I/A) (96%)

F. Cardoso et al, The Breast 2024

HER-2 NEGATIVE MBC

In the absence of medical contraindications or patient concerns, anthracycline or taxane based regimens, preferably as single agents, would usually be considered as first line CT for HER-2 negative ABC, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom chemotherapy is appropriate. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

(LoE/GoR: I/A) (71%)

F. Cardoso et al, The Breast 2024

HER-2 NEGATIVE MBC

In patients with taxane-naive and anthracycline-resistant ABC or with anthracycline maximum cumulative dose or toxicity (i.e. cardiac) who are being considered for further CT, taxane-based therapy, preferably as single agent, would usually be considered as treatment of choice. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

(LoE/GoR: I/A) (59%)

F. Cardoso et al, The Breast 2024

HER-2 NEGATIVE MBC

In patients pre-treated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, single agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, a different taxane, and liposomal anthracyclines. The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

(LoE/GoR: I/A) (77%)

F. Cardoso et al, The Breast 2024

HER-2 NEGATIVE MBC

If given in the adjuvant setting, a taxane can be re-used as 1st line therapy, particularly if there has been at least one year of disease-free survival.

(LoE/GoR: I/B) (92%)

F. Cardoso et al, The Breast 2024

HER-2 NEGATIVE MBC

If given in the adjuvant setting, provided that maximum cumulative dose has not been achieved and that there are no cardiac contra-indications, anthracyclines can be re-used in ABC, particularly if there has been at least one year of disease-free survival.

(LoE/GoR: I/B) (93%)

F. Cardoso et al, The Breast 2024

Metronomic chemotherapy is a treatment option for patients not requiring rapid tumor response.

Available regimens are CM (low dose oral cyclophosphamide and methotrexate), capecitabine or oral vinorelbine based regimens.

Randomized trials are needed and underway to accurately compare metronomic CT with standard dosing regimens.

(LoE/GoR: I/B) (98%)

F. Cardoso et al, The Breast 2024

Duration of each regimen and number of regimens should be tailored to each individual patient.

(LoE/GoR: Expert opinion/A) (96%)

F. Cardoso et al, The Breast 2024

Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.

(LoE/GoR: I/B) (72%)

F. Cardoso et al, The Breast 2024

OTHER AGENTS

F. Cardoso et al, The Breast 2024

Bevacizumab combined with CT as 1st line therapy for MBC provides a moderate benefit in PFS and no benefit in OS. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases and only in the 1st line setting.

(LoE/GoR: I/C) (No consensus: Yes: 42%, No: 53%, Abstain: 5%)

ESMO-MCBS: 2

In manuscript: explanation for lack of consensus

F. Cardoso et al, The Breast 2024

ER POSITIVE/HER-2 NEGATIVE ABC

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Endocrine-based therapy is the preferred option for ER-positive disease, even in the presence of visceral disease, unless there is visceral crisis.

(LoE/GoR: I/A) (93%)

for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Many trials in ER+ ABC have not included pre-menopausal women.
Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.
(LoE/GoR: Expert Opinion/A) (95%)

Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women, and men.
(LoE/GoR: Expert Opinion/A) (92%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

For pre-menopausal women, for whom endocrine therapy was decided, ovarian suppression/ablation combined with additional endocrine-based therapy is the preferred choice.

(LoE/GoR: I/A) (93%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Ovarian ablation by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids potential initial tumor flare with LHRH agonist, and may increase eligibility for clinical trials.
Patients should be informed on the options for OFS/OFA and decision should be made on a case-by-case basis.

(LoE/GoR: Expert Opinion/C) (91%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Single agent Tamoxifen is the only available endocrine option for pre-menopausal women who decline ovarian suppression or ablation (OFS/OFA) but the panel believes it is a less effective option.

(LoE/GoR: I/D) (92%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

The preferred 1st line endocrine agent depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant.

(LoE/GoR: I/A) (84%)

for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC
CDK4/6 INHIBITORS

A CDK4/6 inhibitor combined with endocrine therapy is the standard of care for patients with ER+/HER-2 neg ABC, since it very substantially increases OS, as well as PFS and either maintains or improves QoL.

The CDK4/6 inhibitor can be combined with an AI or with fulvestrant (tamoxifen can not be combined with ribociclib but can be combined with abemaciclib or palbociclib), in de novo or recurrent ABC, in 1st or 2nd line, and in cases of primary or secondary resistance (as defined per ABC guidelines).

This recommendation applies to post-menopausal women, to premenopausal women in combination with an LHRH agonist, and to men preferably in combination with an LHRH agonist.

(LoE/GoR : I/A) (97%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC: CDK4/6 INHIBITORS

The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with endocrine therapy for ABC patients vary according to the setting and drug.
They are the following, with the current available data and FU:

- **RIBOCICLIB + ET 1st line Pre-menopausal: ESMO-MCBS : 5**
- **RIBOCICLIB + AI 1st line Post-menopausal: ESMO-MCBS : 4**
- **PALBOCICLIB + AI 1st line: ESMO-MCBS = 3**
- **ABEMACICLIB + AI 1st line: ESMO-MCBS = 3**
- **PALBOCICLIB + Fulvestrant 2nd line: ESMO-MCBS : 4**
- **RIBOCICLIB + Fulvestrant (1st , 2nd line): ESMO-MCBS = 4**
- **ABEMACICLIB + Fulvestrant 2nd line: ESMO-MCBS = 4**

(LoE/GoR : I/A) (89%)

Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial.

MCBS scores are updated when new data is published

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC
CDK4/6 INHIBITORS

NEW/MODIFIED

The SONIA trial attempted to answer the question whether a CDK4/6 inhibitor (90% palbociclib) combined with endocrine therapy should be given as 1st or 2nd line therapy for ER+/HER-2 neg ABC. No statistically significant differences were seen in PFS 2 (primary endpoint) nor OS nor QoL, at 37 ms follow-up.

It is currently unknown if the results would be the same with ribociclib or abemaciclib.

In view of the totality of data (OS benefit and different 2nd line options), the panel still considers the use of a CDK4/6i + ET as the standard 1st line therapy for the majority of patients with ER+/HER-2 neg ABC.

However, based on the SONIA trial results, it is an acceptable option to use ET alone as 1st line therapy for selected patients (e.g. low volume of disease, long DFI, patient preferences, accessibility constraints) with this ABC subtype.
(LoE/GoR : I/A) (93%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC
CDK4/6 INHIBITORS

NEW/MODIFIED

There are no data comparing a combination of CDK4/6 inhibitor and ET vs. ET alone as maintenance therapy after chemotherapy.
Both options are acceptable.

(LoE/GoR: Expert Opinion/B) (75%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

The use of a CDK4/6 inhibitor + ET after disease progression on a CDK4/6 inhibitor (i.e. beyond progression) has been evaluated in small phase 2 trials, with conflicting results and is not recommended for routine clinical practice, outside a clinical trial.

(LoE/GoR : Expert Opinion/D) (91%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

Trials comparing the different combinations of endocrine + targeted agents with single agent CT, in the 1st and later lines settings, are ongoing and some have been reported.

In the PEARL trial, despite several trial limitations, ET + Palbociclib and Capecitabine yielded similar efficacy, while toxicity profiles were different.
In Young-PEARL, for premenopausal women, ET + Palbociclib was superior to capecitabine in terms of PFS.

In view of the substantial survival benefit seen with ET + CDK4/6 inhibitors in 1st line, never seen before with chemotherapy, this combination should be considered the standard of care for 1st line therapy of ER+/HER2 negative ABC.

(LoE/GoR : I/A) (96%)

For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

In the RIGHT Choice trial, the combination of ribociclib + aromatase inhibitor (+ LHRH agonist in pre-menopausal women) was compared to combination chemotherapy (docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine) as 1st line therapy for pre/peri-menopausal women with ER+/HER2 neg ABC with "clinically aggressive disease" defined as: symptomatic visceral metastases, rapid disease progression or impending visceral compromise, markedly symptomatic non-visceral disease, but with bilirubin <1.5x ULN (therefore not in liver visceral crisis as defined by the ABC guidelines).
The ET + CDK4/6i arm yielded 12-month benefit in PFS, with similar ORR and similar time to onset of response in both arms, but substantially better toxicity profile.

These results reinforce the place of ET + CDK4/6 inhibitors as standard of care for 1st line therapy for the majority of patients with ER+/HER2 negative ABC, including those with "clinically aggressive disease".
(LoE/GoR : I/A) (95%)

Although the trial was performed only in pre/peri-menopausal women, the panel believes the results also apply to post-menopausal women and men with the same disease characteristics.
(LoE/GoR: Expert opinion/B) (95%)

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ER POSITIVE / HER-2 NEGATIVE MBC

The addition of everolimus to an AI is a valid option for some patients previously exposed to or naïve of (in case CDK4/6 inhibitors are not available) endocrine therapy, since it significantly prolongs PFS, albeit without evidence of significant OS benefit.

ESMO-MCBS : 2

(LoE/GoR : I/B) (88%)

Tamoxifen or fulvestrant can also be combined with everolimus.
(LoE/GoR : II/B) (80%)

Adequate prevention with steroids mouthwashes, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the Bolero-2 trial. (LoE/GoR : I/B) (97%)

for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Everolimus should not be used after disease progression on that agent (i.e. beyond progression), outside a clinical trial.

(LoE/GoR : NA/E) (74%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC: ALPELISIB

NEW/MODIFIED

ALPELISIB with fulvestrant is a treatment option for patients with PIK3CA-mutant tumors (in exons 9 or 20), previously exposed to an AI and with appropriate HbA1C levels, since it provided about 5 months benefit in median PFS, without statistically significant OS benefit. The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the Solar-1 study (i.e: pre-existing diabetes & baseline HbA1c), as well as the toxicity profile of alpelisib.

(LoE/GoR: I/A) (96%)

ESMO-MCBS: 2

For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC: ALPELISIB

NEW/MODIFIED

Few patients previously treated with a CDK4/6 inhibitor were included in the Solar-1. However, a non- randomized cohort study (ByLieve) seems to indicate that alpelisib retains its efficacy if used after a CDK4/6 inhibitor.

In view of the magnitude of OS benefit seen with ET + CDK4/6i, this approach is considered the standard of care for 1st line therapy and ET (fulvestrant or AI) + alpelisib should be reserved for the 2nd line setting, in cases of PIK3CA-mutant tumors.

(LoE/GoR: I/B) (93%)

For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Patients receiving ALPELISIB in combination with endocrine therapy for PIK3CA mutated ABC should be instructed to take non-sedating antihistamines daily to prevent rash at start of therapy.
Antihistamines can be discontinued after 4 weeks, as the risk for rash is primarily in the first 2 weeks of therapy.

(LoE/GoR: I/B) (93%)

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ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

Elacestrant, an oral SERD, has been approved as 2nd/3rd line therapy for patients with ER+/HER2 negative ABC with an ESR1 mutation, based on a randomized phase III trial demonstrating a 1.9 months median PFS advantage (HR: 0.546). This advantage was most notable in patients who were previously treated with a CDK4/6 inhibitor for more than 6 months.

Where available, single agent Elacestrant is an option for patients in 2nd/3rd line setting with an ESR1 mutation.

(LoE/GoR: I/C) (81%)

Data only available in post-menopausal women and men

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

Capivasertib, an AKT inhibitor, combined with fulvestrant was compared to placebo plus fulvestrant, in patients with ER+/HER2 negative ABC, with 1 or 2 lines of previous ET and none or 1 line of chemotherapy for metastatic disease; recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC was required; about 70% of pts received prior CDK4/6i.
The results showed a 3.6 ms benefit in median PFS (HR: 0.60) in the overall population and a 4.2 ms median PFS benefit (HR: 0.50) in the AKT pathway-altered population (i.e. PIK3CA and/or PTEN and /or AKT1 alteration). OS results are still immature. GI side effects, mainly diarrhea (72%), were seen.

Based on these results, where approved, capivasertib added to fulvestrant may be used as a treatment option in endocrine resistant ER+/HER2 neg ABC with an AKT pathway-altered (i.e. PIK3CA and/or PTEN and /or AKT1 alteration). **(LoE/GoR: I/B) (95%)** **ESMO-MCBS: 3**

It is unknown what is the efficacy of capivasertib after an ADC such as T-DXd or sacituzumab govitecan or how it compares with everolimus or alpelisib.

for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

Sacituzumab govitecan was compared with chemotherapy of physician's choice, in patients with ER+/HER2 negative ABC, previously treated with at least 1 line of ET, taxane, and CDK4/6 inhibitor in any setting and at least 2, but no more than 4, lines of CT for metastatic disease (60% of pts have received 3 or more lines of CT). Results showed a 1.5 months improvement in median PFS and 3.2 months median OS, both in HER2 low and HER2 zero.
No new safety signals were seen. Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, remain important.

The OS benefit seen in this heavily pretreated population makes sacituzumab govitecan a treatment option for this patient population.

(LoE/GoR: I/B) (95%)

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

Datopotamab deruxtecan (Dato-DXd) was compared with chemotherapy of physician's choice (mostly eribulin), in patients with ER+/HER2 negative ABC, previously treated with 1–2 lines of chemotherapy in the inoperable or metastatic settings and experienced progression on ET and for whom ET was unsuitable, and led to a 2 months improvement in median PFS (HR: 0.63). Results from the dual primary endpoint OS are still awaited. Stomatitis, ocular events (mostly dry eye), nausea, vomiting and fatigue were the most common side effects. ILD/pneumonitis was uncommon. Education and preventive measures (i.e. mouthwashes, anti-emetics) are recommended.

In view of the modest PFS difference, absence of OS data for the moment, side effect profile and availability of other treatment options, Dato-DXd can not yet be recommended for routine clinical practice use.

(LoE/GoR: I/D) (66%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 LOW ABC

NEW/MODIFIED

Trastuzumab Deruxtecan (T-DXd) was compared to chemotherapy of physician's choice, in patients with HER2 low ABC, treated with 1-2 lines of chemotherapy in the metastatic setting and ER+ disease considered endocrine refractory, and yielded a 6.3 months benefit in median OS and 5.8 months in median PFS, **making it a preferred treatment option in this setting.**

Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.

(LoE/GoR: I/A) (100%)

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 LOW ABC

NEW/MODIFIED

There are very few data regarding the best sequence of administration of ADCs for ER+/HER2 low ABC.

In view of the populations treated and results of the trials of T-DXd and sacituzumab govitecan, the panel believes that T-DXd should be used earlier than sacituzumab govitecan.

(LoE/GoR: Expert opinion/B) (95%)

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ER POSITIVE / HER-2 NEGATIVE MBC

The **combination of a nonsteroidal AI and fulvestrant** as first-line therapy for post-menopausal patients resulted in significant improvement in both PFS and OS compared to AI alone in one phase III trial and no benefit in a second trial with a similar design. Notably, a sub-optimal dose of Fulvestrant was used in the study that demonstrated benefit.
Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen).

Based on these data, combination ET may be offered to some patients with ABC without prior exposure to adjuvant ET, when CDK4/6 inhibitors will not be given.
Comparative data between this combination and a CDK4/6 inhibitor with ET, are not available.

(LoE/GoR: II/D) (Yes: 38%; No: 60%; Abstain: 2%)

ESMO-MCBS: 2

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ER POSITIVE / HER-2 NEGATIVE MBC

NEW/MODIFIED

The optimal sequence of endocrine-based therapy is uncertain.
It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), duration of response to those agents, burden of the disease, patients' preference and availability.

(LoE/GoR : I/A) (100%)

for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Options for treatment of ER positive disease in later lines include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megesterol acetate, low dose estrogen). Single agent abemaciclib is also a potential option.
Challenging a patient with an agent on which the disease previously progressed, after an initial response, is occasionally considered, but there are no robust data to support this approach.

(LoE/GoR : II/B) (98%)

for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Concomitant CT + ET has not shown a survival benefit and should not be performed outside a clinical trial.

(LoE/GoR: II/D) (100%)

F. Cardoso et al, The Breast 2024

ER POSITIVE / HER-2 NEGATIVE MBC

Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been properly assessed in randomized trials.

(LoE/GoR: III/B) (88%)

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HER-2 POSITIVE ABC

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

Anti-HER2 therapy should be offered *early* (as 1st line) to all patients with HER2+ ABC, except in the presence of contra-indications to the use of such therapy.

(LoE/GoR: I/A) (98%)

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HER-2 POSITIVE MBC

Patients with disease progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway.

(LoE/GoR: I/A) (91%)

The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered, and the relapse free interval. The optimal sequence of all available anti-HER2 therapies is currently unknown.

The optimal duration of anti-HER2 therapy for MBC (i.e. when to stop these agents) is currently unknown.

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HER-2 POSITIVE MBC

In patients whose tumors achieve a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.

(LoE/GoR: Expert Opinion/C) (93%)

F. Cardoso et al, The Breast 2024

ER + / HER-2+ MBC

For highly selected patients* with ER+/HER-2+ ABC, for whom ET + anti-HER2 therapy was chosen as 1st line therapy, dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) can be used since it provides a benefit in PFS.
This decision must be balanced against the higher side effects, higher costs and lack of OS benefit so far, as compared to ET + anti-HER2 monotherapy.

(LoE/GoR : I/B) (80%)

*** Defined in the manuscript**

F. Cardoso et al, The Breast 2024

ER + / HER-2+ MBC

For patients with ER+/HER-2+ ABC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied in randomized trials.
Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request, and needs to be evaluated in clinical trials.
(LoE/GoR: NA/B) (80%)

There are no data to decide between single agent anti-HER2 or dual blockade, to combine with maintenance ET after stopping CT, in ER+/HER2+ ABC.

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

In the 1st line setting, for HER2+ ABC previously treated (in the adjuvant setting with DFI >12 ms) or untreated with trastuzumab, combinations of chemotherapy + trastuzumab are superior to combinations of chemotherapy + lapatinib in terms of PFS and OS.

(LoE/GoR: I/A) (95%)

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC: 1st line

The standard 1st line therapy for patients previously untreated with anti-HER2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population.

(LoE/GoR: I/A) (86%)

ESMO-MCBS: 4

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HER-2 POSITIVE MBC: 1st line

For patients previously treated (in the (neo)adjuvant setting) with anti-HER2 therapy, the combination of chemotherapy + trastuzumab and pertuzumab is the preferred option for 1st line therapy.
(LoE/GoR: I/A) (76%)

Few (88) of these pts were treated in the Cleopatra trial and all with trastuzumab-free interval > 12 months.

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and CT beyond progression and therefore dual-blockade should not be given beyond progression outside clinical trials.

(LoE: I/E) (86%)

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

In a HER2+ ABC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1st line.

(LoE/GoR: II/B) (76%)

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

NEW/MODIFIED

Trastuzumab Deruxtecan (T-DXd) showed a 22 ms benefit in median PFS and a 7,5% difference in 24-month survival when compared to T-DM1, in pretreated patients with HER2+ ABC. About 50% of patients received the treatment as 1st or 2nd line and the other 50% in later lines.
Where approved, trastuzumab deruxtecan (T-Dxd) is one of the preferred treatment options in the 2nd line setting, after exposure to trastuzumab and pertuzumab.

Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.

ESMO-MCBS: 4

(LoE/GoR: I/A) (89%)

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

NEW/MODIFIED

For patients without access to or with contra-indications for T-DXd, T-DM1 remains the preferred 2nd line therapy, since it has proven superior efficacy (in terms of OS) relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice).

(LoE/GoR: I/A) (89%)

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

NEW/MODIFIED

If not used in the 2nd line setting, trastuzumab deruxtecan (T-DXd) is the preferred treatment option in later lines of therapy, including in heavily pretreated patients with HER2+ ABC, since it provided a 11 ms benefit in median PFS and a 12.7 ms benefit in median OS, when compared to capecitabine + trastuzumab or lapatinib.

Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.

(LoE/GoR: I/A) (85%)

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

NEW/MODIFIED

Dual blockade with tucatinib + trastuzumab + capecitabine showed a benefit in median PFS (2.7 ms) and median OS (5.5 ms), over trastuzumab + capecitabine, in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with stable or active brain metastases.
Where approved, it is a treatment option in this setting.
Toxicity needs education and early intervention (i.e. diarrhea).

(LoE/GoR: I/A) (91%)

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients.
(LoE/GoR: I/B) (84%)

There are however, no randomized data on the use of this combination after progression on pertuzumab, T-DM1, tucatinib or T-DXd.

ESMO-MCBS: 4

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

The combination of neratinib + capecitabine was compared to lapatinib + capecitabine, as 3rd line or beyond therapy for HER2+ ABC, showing a marginal benefit in PFS, and with no significant difference in the co-primary endpoint of OS.
There was no comparator arm with trastuzumab + capecitabine, which had previously been demonstrated to give superior OS to lapatinib + capecitabine.
Therefore, the combination of neratinib + capecitabine is not recommended for routine clinical practice.

(LoE/GoR: I/D) (90%)

Additional studies are needed to clearly establish the potential role of this combination in the treatment of brain metastases, as well as the role of neratinib for ABC.

ESMO-MCBS: 1

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE ABC: 2nd line and beyond

Margetuximab + chemotherapy showed only a small PFS benefit (1 month) and no OS benefit when compared with trastuzumab + chemotherapy, for patients pretreated with pertuzumab and T-DM1, and cannot therefore be recommended for routine clinical practice.
(LoE/GoR: I/D) (95%)

The role of CD16A genotype as a predictor of anti-HER2 antibody efficacy and selection of anti-HER2 agent should be further explored.

ESMO-MCBS: 2

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

Regarding the CT component of HER2 positive ABC treatment:

When pertuzumab is not given, 1st line regimens for HER2+ ABC can include trastuzumab combined with vinorelbine or a taxane.
(LoE/GoR: I/A) (88%)

Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision.
Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred.

Single agent vinorelbine in association with anti-HER-2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.

F. Cardoso et al, The Breast 2024

HER-2 POSITIVE MBC

For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), taxanes (if not given in 1st line), capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM.
(LoE/GoR: II/A) (91%)

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

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HER-2 POSITIVE MBC

CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel (LoE/GoR: I/A) or paclitaxel (LoE/GoR: I/B).
Also possible are vinorelbine (LoE/GoR: II/A), nab-paclitaxel (LoE/GoR: II/B) and capecitabine (LoE/GoR: I/A).

(Consensus: 86%)

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TRIPLE NEGATIVE ABC

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TRIPLE NEGATIVE ABC

In patients with triple negative ABC (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option.

(LoE/GoR: I/A) (91%)

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TRIPLE NEGATIVE ABC

For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations, besides platinum. Therefore, all CT recommendations for HER2 negative disease also apply for triple negative ABC.

(LoE/GoR: I/A) (98%)

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TRIPLE NEGATIVE AR+ ABC

The androgen receptor (AR) is a potential target in triple negative ABC. There are however no standardized methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide.

At this time, these agents should not be used in routine clinical practice.

(LoE/GoR: II/D) (85%)

More definitive trials are needed and research efforts must continue to optimize and standardize the determination of AR.

F. Cardoso et al, The Breast 2024

IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC

NEW/MODIFIED

Checkpoint inhibitors + chemotherapy (pembrolizumab + taxane or carboplatin/gemcitabine) is the preferred treatment option for 1st line therapy for most patients with PD-L1+* triple negative ABC, either de novo or diagnosed at least 6 months from (neo)adjuvant chemotherapy.

(LoE/GoR: I/A) (91%)

ESMO-MCBS: 4

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IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC

NEW/MODIFIED

In countries where atezolizumab is available, its combination with nab-paclitaxel may be an option for 1st line therapy of patients with PD-L1+* triple negative ABC.

(LoE/GoR: II/B) (81%)

ESMO-MCBS: 3

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IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC

Checkpoint inhibitor monotherapy in later lines for triple negative ABC is <u>not recommended</u>, due to low response rates.

(LoE/GoR: I/E) (89%)

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IMMUNOTHERAPY FOR OTHER ABC SUBTYPES

Several ongoing trials are evaluating the role of this type of treatment in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials.

(LoE/GoR: NA/E) (98%)

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SACITUZUMAB GOVITECAN FOR TRIPLE NEGATIVE ABC

NEW/MODIFIED

Sacituzumab govitecan is the preferred treatment option for patients with triple negative ABC, treated with ≥ 2 lines (at least one of them in the metastatic setting), since it demonstrated a 4.9 months benefit in OS and a 3.1 months benefit in PFS.
Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, are important.

(LoE/GoR: I/A) (96%)

ESMO-MCBS: 4

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TRIPLE NEGATIVE/HER2 LOW ABC

NEW/MODIFIED

Trastuzumab deruxtecan (T-DXd) was compared to treatment of physician's choice, in 58 patients with triple negative/HER2 low ABC, treated with 1-2 lines of chemotherapy in the metastatic setting. In this small population the results in terms of PFS and OS were similar to the overall study population and **T-DXd may therefore be considered a treatment option for patients with the same characteristics of those enrolled in the DB04 trial.**

ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.

(LoE/GoR: I/B) (89%)

ESMO-MCBS: 4

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TRIPLE NEGATIVE/HER2 LOW ABC

NEW/MODIFIED

There are very few data regarding the best sequence of administration of ADCs for ER negative/HER2 low ABC.

In view of the results of the trials of T-DXd and sacituzumab govitecan in this patient population, the panel believes that sacituzumab govitecan should be used earlier than T-DXd.

(LoE/GoR: II/A) (90%)

F. Cardoso et al, The Breast 2024

HEREDITARY ABC

F. Cardoso et al, The Breast 2024

GERMLINE GENETIC TESTING

For ABC patients, results from germline genetic testing have therapeutic implications and should therefore be performed as early as possible.

Appropriate counselling should be provided, to patients and their families, if a pathogenic germline mutation is found.

(LoE/GoR: I/A) (88%)

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HEREDITARY ABC GENETIC TESTING

NEW/MODIFIED

At present, only germline mutations in BRCA 1/2 have robust data for clinical utility and therapeutic impact.
(LoE/GoR: I/A) (93%)

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HEREDITARY ABC GENETIC TESTING

NEW/MODIFIED

Testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, in particular because it may have implications for family members. However, it must be clarified to the patient that at present, a mutation in most other moderate-high penetrance genes has no direct clinical implications, for the patients themselves, in the setting of ABC, , apart from germline PALB2 mutation for olaparib use.

(LoE/GoR: Expert Opinion/C) (89%)

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BRCA-associated ABC

In patients with gBRCA-associated triple negative or endocrine-resistant HER2 negative ABC, previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred chemotherapy option, if not previously administered.

(LoE/GoR: I/A) (100%)

All other chemotherapy recommendations are similar to those for sporadic ABC.

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HEREDITARY ABC
PARP INHIBITORS

NEW/MODIFIED

For patients with a gBRCA mutation, single agent PARP inhibitor (olaparib or talazoparib) is one of the preferred treatment options for those with triple negative or ER+/HER2 negative ABC, since they are associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

(LoE/GoR: I/A) (94%)

ESMO-MCBS: 4

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HEREDITARY ABC
PARP INHIBITORS

NEW/MODIFIED

Data from a small phase 2 trial demonstrated a benefit from Olaparib for individuals with a somatic BRCA1/2 mutation or a germline PALB2 mutation. It is acceptable to offer this treatment to these patients, acknowledging the limitation of data, since it is unlikely that large trials will be run.

(LoE/GoR: II/B) (93%)

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It is unknown how single agent olaparib or talazoparib compare with platinum compounds in this setting, as well as to the optimal use with platinum (combined or sequential), and their efficacy in tumors progressing after platinum.

(LoE/GoR: II/B) (89%)

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HEREDITARY ABC: PARP INHIBITORS
Sequence of treatments

NEW/MODIFIED

In ER+ gBRCA-associated ABC, the optimal sequence between PARP inhibitor and ET+ CDK4/6 inhibitor was not formally tested. However, given the OS benefit seen with CDK4/6 inhibitor, the panel considers them the standard of care for 1st line therapy and recommends their use before a PARP inhibitor.

(LoE/GoR: Expert Opinion/A) (94%)

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HEREDITARY ABC: PARP INHIBITORS
Sequence of treatments

NEW/MODIFIED

In triple negative PD-L1+ and gBRCA-associated ABC, the optimal sequence between PARP inhibitors and CT + pembrolizumab was not formally tested. However, given the OS benefit seen with CT + pembrolizumab, the panel considers it the preferred option for 1st line therapy, for the majority of the patients.
(LoE/GoR: Expert Opinion/B) (91%)

More research is needed to answer questions related to treatment sequencing and other disease subtypes, i.e., HER2+ disease in the context of BRCA1/2 mutations.

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HEREDITARY ABC: PARPi VELIPARIB

BROCADE3 was the first phase 3 trial testing a PARP inhibitor (Veliparib) in gBRCA ABC that included platinum. Initial presentation of results showed a small benefit in PFS (1.9 ms). However, durable PFS at 3 years was seen in a significant minority (1/4 patients) during veliparib maintenance, which could provide patients lacking other maintenance treatment options, with chemotherapy-free time.

Mature OS data are needed before this regimen can be recommended for routine clinical practice.

(LoE/GoR: I/D) (98%)

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PRECISION MEDICINE

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PRECISION MEDICINE

MULTIGENE PANELS, such as those obtained using next generation sequencing (NGS) or other technology on tumor DNA have not yet proven beneficial in clinical trials for ABC, their impact on outcome remains undefined and should not be used in routine clinical practice.

For patients who are suitable to participate in clinical trials of novel therapies and readily able/motivated to attend a centre with relevant clinical trials, NGS testing may be used in the context of prospective molecular triage programs to select patients for therapeutic trials.

Specific tests (as distinguished from broad mutation profiles) are useful and discussed in separate statements; others may play a role in the future as the medicines they are linked with, achieve regulatory approval.

(LoE/GoR: I/D) (83%)

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PRECISION MEDICINE

Circulating tumour DNA (ctDNA) assessment is not recommended for demonstration of disease progression.
(LoE/GoR: I/D) (97%)

Circulating tumour DNA (ctDNA) assessment is an option for the detection of *PIK3CA* mutations, for selection of patients eligible for PIK3CA inhibitors.
(LoE/GoR: II/A) (93%)

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ER POSITIVE / HER-2 NEGATIVE MBC

At present, no validated predictive biomarkers other than hormone receptor status exist to identify patients who will/will not benefit from the addition of a CDK4/6 inhibitor or an mTOR inhibitor to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.
(LoE/GoR: I/E) (95%)

Alpelisib should only be used in cases of PIK3CA-mutant tumors.
(LoE/GoR: I/A) (95%)

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PIK3CA MUTATION STATUS

If treatment with PIK3CA inhibitor alpelisib is available, patients should be tested for *PIK3CA* mutation (in exon 9 and 20) in a tissue (metastasis or primary) and/or in ctDNA testing in blood.

Patients who do not have an available archival tissue sample and have an uninformative result using the liquid biopsy test could consider undergoing a tumor biopsy for PIK3CA mutation testing.

(LoE/GoR: I/B) (100%)

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ESR1 MUTATION STATUS

NEW/MODIFIED

Where ESR1 mutation status is available, in the presence of an ESR1 mutation, treatment with an aromatase inhibitor is not the optimal strategy.
In case of disease progression under treatment with an AI +/- a targeted agent (i.e. CDK4/6 inhibitor), acquired ESR1 mutations are common. In the next line of therapy, a non-AI-based option may therefore be a better option.

(LoE/GoR: II/B) (84%)

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ESR1 MUTATION STATUS

NEW/MODIFIED

Treatment should not be changed based on ESR1 mutation status alone and confirmation of disease progression is mandatory. Availability of ESR1 mutation status is not mandatory for the adequate management of ER+/HER2 negative ABC.

(LoE/GoR: II/D) (85%)

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PD-L1 STATUS FOR ABC

NEW/MODIFIED

PD-L1 status should be tested in cases of 1st line triple negative ABC, if treatment with immune checkpoint inhibitors is available, preferably in a metastatic tumor sample.

(LoE/GoR: I/A) (96%)

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PD-L1 STATUS FOR ABC

NEW/MODIFIED

PD-L1 status is the companion test for the use of the combination of pembrolizumab and chemotherapy, as 1st line therapy for triple negative ABC, using PD-L1 IHC with a Combined Positive Score or CPS ≥ 10 (CPS score : number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100) .

(LoE/GoR: I/A) (89%)

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PD-L1 STATUS FOR ABC

NEW/MODIFIED

PD-L1 status is the companion test for the use of the combination of atezolizumab and nab-paclitaxel, as 1st line therapy for triple negative ABC, using IHC with the SP142 antibody (Ventana), and a cut-off of 1% of positive staining on immune cells.

(LoE/GoR: I/A) (87%)

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LOW ER ABC

Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC should not be considered for endocrine therapy exclusively.

Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC can be considered as patients with triple negative ABC, for clinical trials.

(LoE/GoR: III/B) (95%)

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HER2 LOW

To be eligible for treatment with trastuzumab-deruxtecan, the presence of HER2-low status on one sample is sufficient, regardless of the stage of the disease at which it was assessed (primary tumor or metastatic lesion).
It is therefore advisable to systematically reassess HER2 status during the course of the disease if the initial HER2 status is zero.

(LoE/GoR: I/A) (95%)

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HER2 LOW

NEW/MODIFIED

The pathology report must detail the HER2 score according to ASCO/CAP 2023 recommendations [0, 1+, 2+ (amplified or not amplified) or 3+]. It is desirable to report the percentage of labeled cells.
It is recommended to detail in the conclusion: HER2 zero, HER2 low (1+ or 2+ non-amplified), HER2 positive (HER2 3+ or ISH amplified).

(LoE/GoR: Expert opinion/A) (98%)

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PRECISION MEDICINE

If a patient with ABC presents with a tumor with MSI-H/MMR deficiency, treatment with an anti-PD1 agent is a possible consideration. (LoE/GoR: Expert opinion/C) (Y: 41%; Abstain: 10%; Insufficient data: 49%)

If a patient ABC presents with a tumor with a NTRK fusion, treatment with TRK inhibitor is a possible consideration. (LoE/GoR: I/B) (Y: 29%; Abstain: 24%; Insufficient data: 47%)

Patients must be informed about the amount of data available for ABC specifically. Research on the best companion diagnosis tools and techniques is needed. Prospective registries should be created to collect data from all patients treated with these innovative approaches, after proper consent.

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HOW TO TREAT TOUGH ISSUES IN ABC

NOTE:
These guidelines statement were produced during the working webinars from the web-series "Tough issues in ABC", with experts in these specific topics.

NEW/MODIFIED

Webinar 2:

Optimal Management of a Patient with Inflammatory Locally Advanced/Metastatic Breast Cancer

15 DECEMBER 2022

For the purpose of these recommendations, LABC means INOPERABLE, NON-METASTATIC LOCALLY ADVANCED BC

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INFLAMMATORY BC (IBC): Definition

NEW/MODIFIED

IBC is a clinicopathological diagnosis that requires an interprofessional approach for diagnosis.
IBC is designated as T4d or stage IV in case of metastatic disease at presentation.
All of the following criteria must be met for a diagnosis of IBC:

a) rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass;
b) duration of history no more than six months;
c) erythema occupying at least one-third of the breast;
d) pathologic confirmation of invasive carcinoma.

A skin punch biopsy may help in the diagnosis, but it is not indispensable.
Skin ulcerations are rare in IBC and more common in non-inflammatory LABC.

(LoE/GoR: I/A) (95%)

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INOPERABLE LABC or IBC and METASTATIC IBC

NEW/MODIFIED

BEFORE starting any therapy, at least one core biopsy providing histological type, grade and biomarker expression is indispensable to guide treatment decisions.

Biomarkers include:
a) For inoperable LABC and inoperable IBC : ER, PR, HER2, Ki67

b) For metastatic IBC: ER, HER2, PD-L1 if TNBC and PIK3CA if ER+/HER2 negative ABC

For a) and b), patients should also have germline BRCA1, BRCA2 and PALB2 testing, but this result is not necessary prior to starting treatment. If germline testing is negative, BRCA1/2 somatic testing can be done as it may impact treatment.

(LoE/GoR: I/A) (89%)

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NEW/MODIFIED

LABC and IBC

Since patients with LABC and IBC have a substantial risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen and bone, before initiation of systemic therapy is highly recommended.

(LoE/GoR: I/A) (100%)

For non-lobular invasive breast cancers PET-CT, if available, is preferred instead of and not in addition to CT-scans and bone scans.
For most invasive lobular breast cancers CT-scans and bone scans or whole-body MRI are preferred.

(LoE/GoR: II/A) (95%)

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LOCALLY ADVANCED INOPERABLE BC (LABC)

Systemic therapy (not surgery or radiotherapy) should be the initial treatment.
(LoE/GoR: III/A) (100%)

If LABC remains inoperable after systemic therapy and eventual radiation, "palliative" mastectomy should not be done, unless the surgery is likely to result in an overall improvement in quality of life.
(LoE/GoR: Expert opinion/D) (100%)

A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and radiotherapy) is strongly indicated in the vast majority of cases.
(LoE/GoR: I/A) (100%)

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INOPERABLE LABC HR+

Options for HR+ inoperable LABC include an anthracycline- and taxane-based primary chemotherapy regimen, or endocrine-based therapy (i.e. ET + CDK4/6 inhibitor).

(LoE/GoR: I/A) (96%)

The choice of chemotherapy versus ET + CDK4/6 inhibitor, as initial treatment, depends on tumor characteristics (grade, biomarker expression, burden of disease,) and patient considerations (performance status, associated symptoms, comorbidities, preferences).

(LoE/GoR: Expert Opinion/A) (89%)

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If chemotherapy is chosen, an anthracycline- and taxane-based primary chemotherapy regimen is recommended, followed by an endocrine-based therapy (ET + CDK4/6 inhibitor) post-operatively.

(LoE/GoR: I/A) (95%)

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NEW/MODIFIED

INOPERABLE LABC or metastatic IBC TNBC

Anthracycline- and taxane + platinum-based primary chemotherapy is recommended as initial treatment.

(LoE/GoR: I/A) (83%)

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INOPERABLE LABC or metastatic IBC TNBC

NEW/MODIFIED

Pembrolizumab should also be added, independently of PD-L1 status if non-metastatic disease and in PD-L1+ metastatic disease.

(LoE/GoR: I/A) (93%)

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LOCALLY ADVANCED INOPERABLE HER2+

NEW/MODIFIED

Concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR. The optimal anti-HER2 therapy is dual blockade with trastuzumab and pertuzumab.

(LoE/GoR: I/A) (96%)

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NEW/MODIFIED

INOPERABLE LABC and IBC HER2+

Anthracycline-based primary chemotherapy should be incorporated in the treatment regimen.

(LoE/GoR: I/B) (63%)

When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.

(LoE/GoR: I/A) (87%)

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LOCALLY ADVANCED INOPERABLE BC (LABC) HER-2+

NEW/MODIFIED

For patients with HER-2+ LABC (Inflammatory or non-inflammatory), without distant metastases, who are in complete remission after appropriate preoperative systemic therapy and appropriate loco-regional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 1 year of anti-HER2 therapy should be used.
The optimal anti-HER2 therapy is double blockade with trastuzumab and pertuzumab.

(LoE/GoR: I/A) (91%)

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LOCALLY ADVANCED INOPERABLE BC (LABC) HER-2+

NEW/MODIFIED

For patients with HER-2+ LABC (Inflammatory or non-inflammatory), without distant metastases, who are not in complete remission after appropriate preoperative systemic therapy and appropriate loco-regional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 14 courses of T-DM1 is recommended.

(LoE/GoR: I/A) (87%)

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NEW/MODIFIED

INOPERABLE LABC and IBC *gBRCAmut*

Olaparib Olaparib should be given for 1 year, after CTh and local treatments, for IBC or initially inoperable LABC in *gBRCAmut* as this is a potentially curable situation and fits with the results from the OLYMPIA study. .
(LoE/GoR: I/A) (100%)

It is currently unknown how to optimally integrate the use of Olaparib with post-operative capecitabine or pembrolizumab, in *gBRCA mut* triple negative initially inoperable LABC or IBC, with residual disease after surgery. However, there are safety data allowing for the concomitant use of olaparib and pembrolizumab, and the panel prefers this option to the combination of capecitabine + pembrolizumab for these patients.

(LoE/GoR: III/B) (80%)

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INOPERABLE LABC and IBC *gBRCAmut*

NEW/MODIFIED

It is also currently unknown how to optimally integrate the use of Olaparib with post-operative abemaciclib, in *gBRCA mut* ER+/HER2 neg initially inoperable LABC or IBC. It is not possible to administer concomitantly olaparib and a CDK4/6 inhibitor (safety concerns); since there are data allowing for a later start of abemaciclib in the post-operative setting, it can be envisioned to administer olaparib first and then abemaciclib.

(LoE/GoR: III/B) (68%)

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Loco-regional management of LABC

Following effective preoperative systemic therapy with or without radiotherapy, surgery will be possible in many patients.
This will consist of mastectomy with axillary dissection in the vast majority of cases, but in selected patients with a good response, breast conserving surgery may be possible.

(LoE/GoR: II/A) (98%)

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Loco-regional management of LABC

In patients with axillary low burden of disease at presentation (previously cN0-cN1) with complete response after systemic treatment (ycN0), sentinel lymph node biopsy can be an option, provided all the recommendations for sentinel node after primary systemic treatment are followed (i.e. dual tracer, clipping/marking positive nodes, minimum of three sentinel nodes).

(LoE/GoR: III/B) (62%)

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Loco-regional management of IBC

Mastectomy with axillary dissection is recommended in almost all cases, even when there is good response to primary systemic therapy.
(LoE/GoR: I/A) (95%)

Immediate reconstruction is generally not recommended in patients with IBC.
(LoE/GoR: IV/E) (95%)

Loco-regional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy.
(LoE/GoR: I/A) (98%)

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SPECIFIC POPULATIONS

F. Cardoso et al, The Breast 2024

Advanced breast cancer in MALE patients

F. Cardoso et al, The Breast 2024

NEW/MODIFIED

TREATMENT OF ABC in MALE PATIENTS

Male patients with ABC should be offered genetic counselling and testing.

(LoE/GoR: II/A) (100%)

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TREATMENT OF ABC in MALE PATIENTS

For ER+ Male ABC, which represents the majority of the cases, endocrine-based therapy is the preferred option, even in the presence of visceral disease, unless there is visceral crisis.

(LoE/GoR: III/A) (100%)

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TREATMENT OF ABC in MALE PATIENTS

For ER+ Male ABC previously untreated or with a DFI longer than 12 months, tamoxifen is the preferred option.

(LoE/GoR: IV/B) (83%)

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TREATMENT OF ABC in MALE PATIENTS

For male patients with ABC who need to receive an AI, a concomitant LHRH agonist or orchidectomy is the preferred option.
AI without LHRH agonist may also be considered, with close monitoring of response.
(LoE/GoR: IV/B) (86%)

Clinical trials are needed in this patient population.

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TREATMENT OF ABC in MALE PATIENTS

NEW/MODIFIED

Male patients with ER+ ABC should be treated with the same options as female patients, including access to targeted agents such as CDK4/6, mTOR and Pi3KCA inhibitors.

(LoE/GoR: II/A) (96%)

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Webinar 1:

Management of Metastatic Breast Cancer in a Pregnant Patient

13 October 2022

F. Cardoso et al, The Breast 2024

ABC, CONTRACEPTION and PREGNANCY

NEW/MODIFIED

All persons of reproductive age with ABC should be counselled about use of non-hormonal contraception (independent of the tumor subtype) and the risks of conceiving while receiving treatment for ABC.

LoE/GoR: II/A (93%)

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ABC, CONTRACEPTION and PREGNANCY

NEW/MODIFIED

Special attention should be given to persons of reproductive age with ABC being treated without OFS/OFA since several therapies used for ABC have a low gonadotoxic effect and will not induce menopause.

LoE/GoR: II/A (100%)

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ABC and PREGNANCY

NEW/MODIFIED

Management of a pregnant patient with ABC is a complex and delicate situation that requires multidisciplinary discussion and experienced care.
(LoE/GoR: Expert opinion/A) (98%)

Advice should be sought from experts in the field such as the International Advisory Board of CIP (Cancer In Pregnancy) (www.ab-cip.org)

The preferences of the patient and of whomever the patient wishes to be involved must always be taken into account, after appropriate and transparent sharing of information about all management options and their potential impact on the patient's survival, fetal health and the future of the child.

(LoE/GoR: Expert opinion/A) (98%)

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ABC and PREGNANCY

NEW/MODIFIED

The preferred imaging method to stage a pregnant patient with breast cancer is whole-body MRI including diffusion weighted imaging, where available.

(LoE/GoR: Expert opinion/B) (77%)

F. Cardoso et al, The Breast 2024

ABC and PREGNANCY

NEW/MODIFIED

Among all available systemic therapies, only chemotherapy can be safely administered during pregnancy and only in the 2nd and 3rd trimesters.
LoE/GoR: II/A (95%)

The most complex situation relates to HER2+ disease diagnosed in the 1st and 2nd trimesters, because anti-HER2 therapy is critical for optimal disease control but can not be administered during the entire pregnancy.
LoE/GoR: Expert opinion/A (95%)

F. Cardoso et al, The Breast 2024

ABC and PREGNANCY

NEW/MODIFIED

Termination of pregnancy is a major consideration in some circumstances and should be available for patients who decide in favor of it, within the first 12 weeks of pregnancy.

LoE/GoR: Expert opinion/A (95%)

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NEW/MODIFIED

Webinar 4:

Managing a patient with advanced/metastatic breast cancer and HIV

20 April 2023

F. Cardoso et al, The Breast 2024

MANAGEMENT OF A PATIENT WITH ABC AND HIV

NEW/MODIFIED

- Prevalence of HIV comorbidity in ABC patients depends on HIV endemicity (varies 6 - 26%).
- Patients living with HIV who develop breast cancer have consistently worse survival, both in early and metastatic settings.
- HIV+ breast cancer patients have worse toxicity, especially myelotoxicity and infections.
- Data on how to manage ABC in a patient living with HIV are scarce, especially concerning new anticancer agents.

- **Breast cancer in patients living with HIV should be co-managed by an oncologist and HIV specialist working in a multidisciplinary way.** **(LoE/GoR: Expert Opinion/A) (100%)**
- **HIV positivity, if under treatment and controlled (undetectable viral load), should no longer be an exclusion criteria in most clinical trials.** **(LoE/GoR: Expert Opinion/A) (100%)**
- **People living with HIV have a higher incidence of other diseases such as tuberculosis and hepatitis. Before starting anticancer treatment, these diseases should be looked for and if diagnosed, treatment should be initiated.** **(LoE/GoR: Expert Opinion/B) (100%)**

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MANAGEMENT OF A PATIENT WITH ABC AND HIV

NEW/MODIFIED

- **In general, the same ABC guidelines apply to HIV+ and HIV neg patients with ABC. (LoE/GoR: Expert Opinion/A) (95%)**
- **However, careful consideration should be given to dose reductions and/or increased intervals (G-CSF recommended for myelotoxic chemotherapy agents). (LoE/GoR: Expert Opinion/A) (95%)**
- **Data suggest safety of immune-checkpoint inhibitors (LoE/GoR: IV/B) (95%) and there are no data regarding the use of CDK4/6 inhibitors (research need). (LoE/GoR: Expert Opinion/NA) (95%)**

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MANAGEMENT OF A PATIENT WITH ABC AND HIV

NEW/MODIFIED

- **Most cytotoxic agents can be safely initiated if viral load is undetectable and CD4+T-count is at least 200 under modern anti-retroviral therapy regimens. (LoE/GoR: Expert Opinion/B) (93%)**

- **HIV therapy should be initiated or continued during cancer therapy. (LoE/GoR: Expert Opinion/A) (93%)**

- **In anti-retroviral naïve patients, it is recommended to initiate anti-retroviral therapy and wait for about 2 weeks before starting anticancer therapies, if clinically possible. (LoE/GoR: Expert Opinion/B) (93%)**

- **Potential drug-drug interactions must always be checked. If interactions are a concern, it is recommended to check the viral load more often. For drugs that cause lymphopenia, CD4+ T-cell counts should be monitored more frequently. (LoE/GoR: Expert Opinion/B) (93%)**

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NEW/MODIFIED

Webinar 5:

Optimal management of an older frail patient with advanced/metastatic breast cancer

15 June 2023

F. Cardoso et al, The Breast 2024

When no specific note is made, all ABC guidelines are to be implemented independently of the age of the patient.

(LoE/GoR: Expert opinion/A) (100%)

Independent of age, all patients should be involved in the treatment decision making process if they wish to do so, and their preferences should be taken into account.

(LoE/GoR: Expert opinion/A) (100%)

Independent of age, all eligible patients should be informed about potential clinical trials and provided with the adequate information and informed consent to be able to decide if they wish to participate.

(LoE/GoR: Expert opinion/A) (100%)

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The age of the patient should not be the sole reason to withhold effective therapy (in older patients) nor to overtreat (in young patients).
Age alone should not determine the intensity of treatment. (LoE/GoR: I/E) (100%)

NEW/MODIFIED

What determines the possibility to use a specific anticancer agent is not age by itself but the existence of co-morbidities with associated impact in adequate organ function such as liver, renal, cardiac and/or neurological functions, as well as bone marrow reserve.

(LoE/GoR: I/A) (95%)

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NEW/MODIFIED

For treatment decision making, careful evaluation of co-morbidities, performance status and geriatric assessment are crucial and more relevant than chronological age.
G8 assessment should be used initially, and a full geriatric assessment is needed if low G8 scores are found.

(LoE/GoR: I/A) (90%)

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Special attention should be given to potential drug interactions, in view of the common use of comedication/polypharmacy by older patients.

(LoE/GoR: I/A) (100%)

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The ABC Guidelines endorse the EUSOMA-SIOG guidelines for the management of older patient with breast cancer, namely the following statement:

Regarding systemic treatment for metastatic disease, different treatment schedules, dose reductions, or stepwise dose-escalation before reaching standard recommended dose might be required in older patients to reduce the risk of adverse outcomes.
(LoE/GoR: Expert opinion/A) (77%)

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ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

In view of the substantial survival benefit seen with ET + CDK4/6 inhibitors, this combination is considered the standard of care for 1st line therapy for the majority of patients with ER+/HER2 negative ABC, independently of the patient's age. (LoE/GoR: II/A) (93%)

Real world-data suggest that ET+CDK4/6 inhibitors can be beneficial also in unfit older patients. (LoE/GoR: III/B) (93%)

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ER POSITIVE / HER-2 NEGATIVE ABC

NEW/MODIFIED

In unfit patients, testing a reduced starting dose of the CDK4/6 inhibitor, is a reasonable but not sufficiently studied strategy.

(LoE/GoR: Expert opinion/B) (91%)

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HER-2 POSITIVE ABC

NEW/MODIFIED

If no absolute cardiac contra-indications exist, older patients with HER2 positive ABC should have access to anti-HER2 agents. (LoE/GoR: I/A) (100%)

Certain anti-HER2 agents such as TKIs and ADCs, which are usually associated with more side effects, may need a lower starting dose, careful monitoring and dose adjustments according to toxicity in older frail patients.

(LoE/GoR: Expert opinion/A) (84%)

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NEW/MODIFIED

Webinar 3:

How to optimally treat a patient with Advanced/Metastatic Breast Cancer in Visceral Crisis

9 FEBRUARY 2023

F. Cardoso et al, The Breast 2024

MANAGEMENT OF VISCERAL CRISIS

NEW/MODIFIED

Therapeutic options for patients with visceral crisis are limited and evidence is scarce since these patients are almost always excluded from clinical trials.

In ER+/HER2 negative ABC with visceral crisis, ET + CDK4/6 inhibitor are not contraindicated and may be a better option than chemotherapy. (LoE/GoR: II/B) (95%)

In HER2+ ABC with visceral crisis, the use of anti-HER2 agents is crucial and feasible. (LoE/GoR: II/A) (95%)

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MANAGEMENT OF VISCERAL CRISIS

NEW/MODIFIED

In situations of liver visceral crisis, options are further limited by the severe liver function impairment.
Weekly regimens and lower doses are recommended. (LoE/GoR: IV/B) (93%)

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MANAGEMENT OF VISCERAL CRISIS

NEW/MODIFIED

For bone marrow infiltration, weekly reduced dose paclitaxel or capecitabine or ET + CDK4/6i (in case of ER+/HER2 neg disease) are among the best options.
(LoE/GoR: IV/B)(86%)

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MANAGEMENT OF VISCERAL CRISIS

NEW/MODIFIED

In some situations, urgent surgery and/or radiation therapy and/or other interventional techniques (i.e. laser therapy for bronchial obstruction) may be needed.
(LoE/GoR: IV/B) (98%)

Admission to ICU should not be denied if there is a possibility of reversing the clinical situation, after careful discussion with the patient and family, and always respecting the patient's wishes.
(LoE/GoR: Expert Opinion/NA) (98%)

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- **SPECIFIC SITES OF METASTASES**
  Bone
  Brain
  Liver
  Pleural Effusion
  Chest wall recurrences
  Peritoneal metastases and ascites

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- **SPECIFIC SITES OF METASTASES**
  Bone

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BONE METASTASES

Radiological assessments are required in patients with persistent and localized pain due to bone metastases to determine whether there are impending or actual pathological fractures.
If a fracture of a long bone or vertebrae is likely or has occurred, an orthopaedic assessment is required as the treatment of choice may be surgical stabilization which is generally followed by radiotherapy.
In the absence of a clear fracture risk, radiotherapy is the treatment of choice.

(LoE/GoR: I/A) (96%)

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BONE METASTASES

Neurological symptoms and signs which suggest the possibility of spinal cord compression must be investigated as a matter of urgency. This requires a full radiological assessment of potentially affected area as well as adjacent areas of the spine. MRI is the method of choice. An emergency surgical opinion (neurosurgical or orthopaedic) may be required for surgical decompression.
If no decompression/stabilization is feasible and indicated, emergency radiotherapy is the treatment of choice and vertebroplasty is also an option.

(LoE/GoR: I/B) (100%)

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BONE METASTASES

Regarding the use of bone targeted agents (bisphosphonate, denosumab), the ABC panel endorses the ESMO Guidelines related to this subject. (LoE/GoR: Expert Opinion/A) (100%)

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- **SPECIFIC SITES OF METASTASES**
  Brain

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BRAIN IMAGING

NEW/MODIFIED

Brain imaging should not be routinely performed in asymptomatic patients.
This approach is applicable to all patients with ABC including those with HER-2+ and/or TNBC ABC.

(LoE/GoR: II/D) (85%)

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BRAIN METASTASES

Patients with a single or a small number of potentially resectable brain metastasis should be treated with surgery or radiosurgery.
Radiosurgery is also an option for some unresectable brain metastases.

(LoE/GoR: I/B) (92%)

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BRAIN METASTASES

If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy, but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects.

(LoE/GoR: I/C) (72%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

Because patients with HER2+ ABC and brain metastases can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. stereotactic radiotherapy) should be preferred to whole brain radiotherapy, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

(LoE/GoR: I/A) (89%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

In patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, for whom stereotactic radiotherapy is feasible and accessible, systemic therapy should not be changed.

(LoE/GoR: I/D) (89%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

For patients with HER2 positive ABC where brain metastases are the only site of recurrence and for whom stereotactic radiotherapy is feasible and accessible, the addition of chemotherapy to local therapy is not known to alter the course of the disease and is not recommended.

(LoE/GoR: I/D) (83%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.

(LoE/GoR: II/B) (87%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

A possible alternative is the usage of Tucatinib + Trastuzumab + Capecitabine, although this option may also be reserved for progression of the disease after local therapy.

(LoE/GoR: I/A) (91%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

TDM-1 has also shown activity against active HER2+ brain metastases in one prospective single arm study (KAMILLA) and is therefore a treatment option.

(LoE/GoR: II/A) (80%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

For patients with HER2 positive ABC with progressive brain metastases as the predominant site of disease burden and no local therapy option available, treatment with Tucatinib + Trastuzumab + Capecitabine is the best available option.

(LoE/GoR: I/A) (91%)

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HER-2 POSITIVE ABC & BRAIN METASTASES

NEW/MODIFIED

If this treatment is not accessible and/or if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option.

(LoE/GoR: II/B) (93%)

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BRAIN METASTASES from HER2+ ABC

NEW/MODIFIED

Trastuzumab Deruxtecan (T-Dxd) has shown activity against brain metastases from HER2+ ABC, previously treated or untreated with local therapy, and can be considered a treatment option.

(LoE/GoR: II/B) (98%)

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BRAIN METASTASES

Radio-necrosis after stereotactic radiotherapy for brain metastases is an uncommon complication that may occur especially with longer survival and follow-up, and in particular in cases of re-irradiation.
Differential diagnosis with tumor progression is often difficult.
Treatment of symptomatic patients with a course of high dose steroids is the first treatment of choice.
If no response, bevacizumab may be used, as an option to decrease the surrounding edema, usually at a dose of 7.5 mg/kg every 2 weeks, for a median of four cycles.
Prospective randomized trials are needed to validate further this option.

(LoE/GoR: III/B) (61%)

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Webinar 6:

Managing a patient with advanced/metastatic breast cancer with leptomeningeal disease

7 September 2023

F. Cardoso et al, The Breast 2024

LEPTOMENINGEAL DISEASE (LMD)

NEW/MODIFIED

There is no accepted standard of care for breast cancer LMD. **It is crucial that patients with LMD are included in clinical trials, namely in trials evaluating therapies for CNS disease. (LoE/GoR: Expert Opinion/A) (100%)**

The choice of treatment (radiotherapy, intra-CSF therapy, systemic therapy, supportive care) should consider prognostic evaluation, multidisciplinary discussion and always an in-depth discussion with the patient and the caregivers. (LoE/GoR: Expert Opinion/A) (100%)

Staging of patients with LMD should include full spine imaging with MRI with gadolinium to assess the full extent of the disease. (LoE/GoR: Expert Opinion/A) (100%)

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LEPTOMENINGEAL DISEASE (LMD)

NEW/MODIFIED

- **Focal radiotherapy (brain or cranio-spinal) should be considered for circumscribed, particularly symptomatic lesions. (LoE/GoR: III/B) (98%)**

- **WBRT can be considered for extensive nodular or symptomatic linear LMD. (LoE/GoR: III/B) (98%)**

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LEPTOMENINGEAL DISEASE (LMD)

NEW/MODIFIED

- **A ventriculoperitoneal shunt may be placed to palliate symptoms of increased intracranial pressure or symptomatic hydrocephalus. (LoE/GoR: Expert Opinion/B) (100%)**

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LEPTOMENINGEAL DISEASE (LMD)

NEW/MODIFIED

- **Intra-CSF chemotherapy has not been proven to improve OS nor QoL but may palliate symptoms in some cases, although significant toxicity may also occur. It can be considered in select cases, if systemic disease is stable. (LoE/GoR: III/C) (95%)**

- **Intra-CSF trastuzumab has been evaluated in small studies and has shown some efficacy relatively to historical control data. It may be used in some patients with HER2+ LMD. (LoE/GoR: III/B) (95%)**

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LEPTOMENINGEAL DISEASE (LMD)

NEW/MODIFIED

- **The choice of systemic therapy for LMD should take into account the breast cancer subtype and previous treatments. (LoE/GoR: II/A) (100%)**

- **Albeit in very small case series, there are some efficacy data in LMD for capecitabine monotherapy, the combination capecitabine + trastuzumab + tucatinib, and for T-Dxd. (LoE/GoR: V/B) (100%)**

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- **SPECIFIC SITES OF METASTASES**
  Liver

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LIVER METASTASES

Prospective randomized clinical trials of local therapy for breast cancer liver metastases are urgently needed, since available evidence comes only from series in highly selected patients.

Since there are no randomized data supporting the effect of local therapy on survival, every patient must be informed of this when discussing a potential local therapy technique.

Local therapy should only be proposed in very selected cases of good performance status, with limited liver involvement, no extra-hepatic lesions, after adequate systemic therapy has demonstrated control of the disease.

Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic RT, intra-hepatic CT…).

(LoE/GoR: Expert opinion/C) (83%)

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- **SPECIFIC SITES OF METASTASES**
  Pleural Effusion

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MALIGNANT PLEURAL EFFUSIONS

Malignant pleural effusions require systemic treatment with/without local management.
(LoE/GoR: III/A) (86%)

Thoracentesis for diagnosis should be performed if it is likely that this will change clinical management. False negative results are common.
(LoE/GoR: III/B) (86%)

Drainage is recommended in patients with symptomatic, clinically significant pleural effusion.
(LoE/GoR: III/A) (86%)

Use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful.
(LoE/GoR: III/B) (86%)

Clinical trials evaluating the best technique are needed.

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- **SPECIFIC SITES OF METASTASES**
  Chest wall recurrences

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CHEST WALL AND REGIONAL (NODAL) RECURRENCES

Due to the high risk of concomitant distant metastases, patients with chest wall or regional (nodal) recurrence should undergo full restaging, including assessment of chest, abdomen and bone.

(LoE/GoR: Expert opinion/A) (100%)

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CHEST WALL AND REGIONAL (NODAL) RECURRENCES

Chest wall and regional recurrences should be treated with surgical excision when feasible with limited risk of morbidity.
(LoE/GoR: II/A) (97%)

Locoregional radiotherapy is indicated for patients not previously irradiated.
(LoE/GoR: II/A) (97%)

For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.
(LoE/GoR: Expert opinion/C) (97%)

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CHEST WALL AND REGIONAL (NODAL) RECURRENCES

In addition to local therapy (surgery and/or RT), in the absence of distant metastases, the use of systemic therapy (CT, ET and/or anti-HER2 therapy) should be considered.
(LoE/GoR: I/B) (95%)

CT after first local or regional recurrence improves long term outcomes in ER negative disease, and can be used.
(LoE/GoR: I/B) (95%)

ET in this setting improves long term outcomes for ER positive disease and should be used.
(LoE/GoR: I/B) (95%)

The choice of systemic treatment depends on tumor biology, previous treatments, length of disease free interval, and patient-related factors (co-morbidities, preferences, etc). (LoE/GoR: Expert Opinion/A) (95%)

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CHEST WALL AND REGIONAL (NODAL) RECURRENCES

In patients with disease not amenable to radical local treatment, the choice of palliative systemic therapy should be made according to principles previously defined for metastatic disease.
These patients may still be considered for palliative local therapy.

(LoE/GoR: Expert opinion/B) (97%)

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- **SPECIFIC SITES OF METASTASES**
  Peritoneal metastases and ascites

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PERITONEAL CARCINOMATOSIS AND ASCITES (1)

NEW/MODIFIED

- Are more common in case of infiltrating lobular carcinoma.
- Confer poor prognosis and have a negative impact on QoL, requiring early active palliative measures.
- Early involvement of palliative care team is crucial. (LoE/GoR: I/A) (96%)
- Diagnosis is clinical, radiological and cytological (via paracentesis). Peritoneal carcinomatosis is often difficult to visualize radiologically and needs to be suspected clinically and actively sought for.
- Symptoms include abdominal pain, nausea, anorexia, cachexia, distension, constipation, fatigue.
- Attention must be given to cachexia and fatigue. The panel endorses the ESMO guidelines for management of these symptoms, emphasizing the importance of nutrition supplements. (LoE/GoR: Expert Opinion/A) (96%)

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PERITONEAL CARCINOMATOSIS AND ASCITES (2)

NEW/MODIFIED

- **Anti-emetics include metoclopramide, serotonin 5-HT3 receptor antagonists, neuroleptics; octreotide (somatostatin analogue) helps reduce nausea; steroids reduce nausea and alleviate obstructive symptoms.**

  (LoE/GoR: I/A) (89%)

- **Treatment of underlying ABC disease with systemic therapy, according to the guidelines is recommended. (LoE/GoR: Expert Opinion/A) (100%)**

- **More invasive interventions may include nasogastric tube for vomiting, surgery for GI obstructions and adhesions. (LoE/GoR: II/A) (91%)**

- **Ascites management options include low sodium diet, diuretics, paracentesis, intraperitoneal catheters, intraperitoneal port, peritoneal-venous shunt. (LoE/GoR: I/A) (96%)**

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SUPPORTIVE and PALLIATIVE CARE

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SUPPORTIVE and PALLIATIVE CARE

Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.

(LoE/GoR: I/A) (100%)

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SUPPORTIVE and PALLIATIVE CARE

Early introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.

(LoE/GoR: I/A) (100%)

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SUPPORTIVE and PALLIATIVE CARE

Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.

(LoE/GoR: I/A) (100%)

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SUPPORTIVE and PALLIATIVE CARE

The ABC community is aware of the limitations that are being imposed worldwide, as a consequence of the opioid use disorders in certain areas of the world.
The ABC community is united in insisting that cancer patients should not have restrictions placed that will limit their access to adequate pain control.

(LoE/GoR: Expert Opinion/NA) (100%)

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SUPPORTIVE and PALLIATIVE CARE

The panel encourages research on the potential role of cannabis to assist with pain and symptom control but strongly stresses that it can not replace proven medicines such as morphine, for adequate pain control.

(LoE/GoR: I/C) (97%)

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SUPPORTIVE and PALLIATIVE CARE

Optimally, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. However, when active treatment no longer is able to control widespread and life-threatening disease, and the toxicities of remaining options outweigh the benefits, physicians and other members of the healthcare team should initiate discussions with the patient (and family members/friends, if the patient agrees) about end-of-life care.

(LoE/GoR: Expert opinion/A) (96%)

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Management of CANCER RELATED FATIGUE
Older patients

NEW/MODIFIED

Cancer related fatigue is frequently experienced by patients with ABC, exerts a deleterious impact on QoL and limits physical, functional, psychological, and social well-being.
The etiology of this fatigue is complex, therefore effective management needs to be multidimensional (LoE/GoR: Expert opinion/A, 100%).

It is important to assess cancer related fatigue using appropriate PRO measures before implementing various non-pharmacological (such as exercise (LoE/GoR: I/A, 100%) and if needed pharmacological interventions* (LoE/GoR: II/B, 100%).

Fatigue is particularly frequent and relevant in the older population and often underestimated. A close monitoring of fatigue, a very common adverse event induced by systemic therapies in older ABC patients, is recommended due to its impact on function (LoE/GoR: I/A, 100%).

* Details in manuscript

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Management of CDK4/6 INHIBITOR INDUCED NEUTROPENIA

Neutropenia is the most common toxicity associated with CDK 4/6 inhibition and is not generally associated with febrile neutropenia, although an increase in infections has been reported.

Treatment should be delayed until neutrophils have recovered to at least 1000/ul; dose reduction can also be considered.

(LoE/GoR: II/A) (100%)

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Management of INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS DUE TO OTHER AGENTS THAN T-DXD

NEW/MODIFIED

ILD (also known as pneumonitis) is an uncommon complication of many cancer agents, including some chemotherapy agents, antibody drug conjugates, mTOR and Pi3KCA inhibitors, immunotherapy, radiation and rarely, CDK4/6 inhibitors.

Differential diagnosis with carcinomatosis lymphangitis is sometimes difficult. Patient and provider education is critical to ensure early reporting and timely management.

For symptomatic ILD grade 2 or higher, treatment interruption and systemic steroids are indicated, followed by a dose reduced rechallenge after resolution of symptoms.

For ILD grade 3 or higher, treatment should be discontinued.

(LoE/GoR: I/A) (84%)

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Management of INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS DUE TO TRASTUZUMAB-DERUXTECAN (T-DXd)

NEW/MODIFIED

For ILD/pneumonitis related to trastuzumab-deruxtecan, special precautions are necessary to prevent progression to life-threatening symptoms.

For asymptomatic radiographic changes (ground glass opacities), T-DXd should be held, and systemic steroids (≥ 0.5 mg/kg prednisone or equivalent) should be considered. Treatment may be restarted at full dose if changes resolve within 28 days. For delayed recovery, T-DXd should be reduced by one dose level.

For ILD grade 2 or higher, prompt steroid treatment is required (≥ 1 mg/kg prednisone or equivalent) and T-DXd should be permanently discontinued. It is also important to taper the steroids slowly for at least 4 weeks.

(LoE/GoR: I/A) (84%)

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Management of DYSPNEA

- Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anemia, drug toxicity must be ruled out. (LoE/GoR: I/A) (100%)
- Patient support is essential. (LoE/GoR: I/A) (100%)
- Oxygen is of no use in non-hypoxic patients. (LoE/GoR: I/A) (100%)

- Opioids are the drug of choice in the palliation of dyspnea.
(LoE/GoR: I/A) (100%)

- Benzodiazepines can be used in patients experiencing anxiety.
(LoE/GoR: II/A) (100%)

- Steroids can be effective in dyspnea caused by lymphangitis carcinomatosis, radiation or drug-induced pneumonitis, superior vena cava syndrome, an inflammatory component, or in (cancer-induced) obstruction of the airways (in which case laser/stent is to be considered).
(LoE/GoR: Expert opinion/B) (100%)

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Management of NAUSEA & VOMITING

ESMO/MASCC guidelines are available for management of chemotherapy-induced and morphine-induced nausea and vomiting, and these are endorsed by ABC.
(LoE/GoR: Expert Opinion/A) (100%)

There is a need to study nausea and vomiting related to chronic use of anticancer drugs.
(LoE/GoR: Expert opinion/A) (100%)

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Management of ENDOCRINE TOXICITIES of mTOR or PI3KCA inhibition

Hyperglycemia and hyperlipidemia are common sub-acute complications of mTOR or Pi3KCA inhibition. Evaluation of preexisting diabetes or hyperglycemia at baseline is essential. Regular careful monitoring of glycemia and lipid panel is needed to identify these toxicities.

Management of grade 1 and 2 hyperglycemia includes treatment with oral antidiabetics and basal insulin, in accordance with international recommendation for diabetes mellitus treatment. Statins are indicated to treat grade 2 and 3 hypercholesterolemia, and fibrates should be introduced if triglyceride level >500mg/dl (with attention to possible drug-drug interaction between everolimus and fibrates).

Treatment interruption and dose reduction are generally effective for grade 2 and 3 toxicity. Treatment should be discontinued for grade 4 toxicity.
(LoE/GoR: II/A) (100%)

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Management of MUCOSITIS/STOMATITIS

Steroid mouthwash should be used for prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5mg/5ml dexamethasone, 10 ml to swish x 2 minutes then spit out qid). (LoE/GoR: I/B) (100%)

Early intervention is recommended. (LoE/GoR: Expert opinion/A) (100%).

For grade > 2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended. (LoE/GoR: Expert opinion/A) (100%).

Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis. (LoE/GoR: Expert opinion/B) (100%).

Consider adding steroid dental paste to treat developing ulcerations. (LoE/GoR: Expert opinion/B) (100%).

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Management of CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)

Chemotherapy induced peripheral neuropathy (CIPN) is frequent and potentially dose-limiting. Risk factors for neuropathy and preexisting neuropathy need to be identified.

No medical prevention can currently be recommended (LoE/GoR: II/C) (100%).
Drug-related factors (dosing, timing, route) can lower the risk of CIPN.
The use of tight gloves and socks during CT may help reduce the incidence and severity of CIPN (LoE/GoR: I/C) (100%).

There are limited evidence-based treatments for CIPN, with tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, duloxetine, pregabalin, and gabapentin being most often used (LoE/GoR: II/B) (100%).

Limited data exists supporting use of acupuncture for risk reduction and alleviation of CIPN.

High quality studies are needed to evaluate strategies for prevention and management of CIPN.

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Management of HAND AND FOOT SYNDROME (HFS)

Hand and Foot syndrome (HFS) is also described as palmar-plantar erythrodysesthesia syndrome. Most frequent causes are capecitabine, pegylated liposomal doxorubicin, multikinase inhibitors.

Patients should be instructed about early recognition of HFS.

Drug-related factors (dosing, timing, route) can lower the risk of HFS.

Treatment of hyperkeratoses / fungal infections, comfortable shoes, avoidance of friction and heat are recommended (LoE/GoR: Expert opinion/A) (100%).

Intensive skin care of hands and feet (urea cream/ointment) is recommended (LoE/GoR: II/A) (100%).

High quality studies are needed to evaluate strategies for prevention and management of HFS.

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Management of POSTMENOPAUSAL SYMPTOMS

Systemic hormone therapy is generally not recommended to treat postmenopausal symptoms in ABC patients, particularly not in ER+ disease. The final decision belongs to the woman, after correct information, since in some cases these symptoms are highly impacting on QoL. (LoE/GoR: I/D) (100%)

Valid alternatives are:

- **For postmenopausal symptoms in general: Mind-body interventions, physical training, and cognitive behavioral therapy are effective non-pharmacological treatment options. (LoE/GoR: I/B) (100%)**
- **For hot flushes: Venlafaxine, oxybutynin, gabapentin, clonidine, megace 40mg, and acupuncture are available options. (LoE/GoR: I/B) (100%)**
- **For sleep disturbances: Melatonin (LoE/GoR: II/C) (100%)**

There is no convincing evidence that phytotherapeutic drugs improve postmenopausal symptoms. Possible drug interactions must be considered. (LoE/GoR: I/D) (100%)

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SEXUAL HEALTH

Sexuality is an experience on many levels and is not confined to the act of intercourse. Sexuality and physical intimacy remain important for many patients with ABC.
These patients frequently experience impaired sexual health and need specific attention. Openly addressing misconceptions and sexual challenges after treatment, as well as educating patients, have shown to improve quality of life.
When life expectancy is limited, physical contact, affection, emotional communication and comfort are particularly important.
Standardized instruments (questionnaires) may help assess grade of impairment.

(LoE/GoR: Expert opinion /NA) (100%)

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Management of DYSPAREUNIA

Dyspareunia is often caused by vaginal dryness.

The 1st choice for treating vaginal dryness and soreness are hormone-free lubricants and moisturizers (e.g. water-based gel, hyaluronic acid gel). (LoE/GoR: II/B) (100%)

If hormone-free measures are not effective, low-dose estrogen-containing vaginal medication can be used. (LoE/GoR: II/B) (100%)

The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.

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CANCER AND TREATMENT-RELATED COGNITIVE IMPAIRMENT (CRCI), aka “ONCO-BRAIN”

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CANCER AND TREATMENT-RELATED COGNITIVE IMPAIRMENT (CRCI), aka "ONCO-BRAIN"

NEW/MODIFIED

- **Cognitive dysfunction associated with cancer diagnosis and treatment has been increasingly reported by breast cancer patients, in the early and advanced settings, who did not have localized treatment to the brain nor other cognitive disorders.**
- **Poor performance in neuropsychological tests and structural changes in brain imaging (e.g. volume reduction in grey matter, less connectivity and activation) are findings of this effect. However, self reports of cognitive dysfunction are more prevalent than objective findings, probably due to the multidimensionality of this complaint.**
- **Imaging studies should only be used to rule out CNS disease.**
- **The exact mechanisms of CRCI are not clear, probably multifactorial and is frequently associated with other cancer related symptoms such as fatigue, anxiety, depression, pain, distress and sleep disorders.**

(LoE/GoR: III/NA) (98%)

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Management of CANCER AND TREATMENT-RELATED COGNITIVE IMPAIRMENT (CRCI), aka “ONCO-BRAIN”

NEW/MODIFIED

- **Perform routine assessment of clinical symptoms of cognitive dysfunction and awareness/education.**

  (LoE: II/A) (91%)

- **Routine physical activity is recommended (weekly: 150–300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity) in view of its association with neurogenesis in brain areas related to memory.**

  (LoE: II/A) (89%)

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Management of CANCER AND TREATMENT-RELATED COGNITIVE IMPAIRMENT (CRCI), aka “ONCO-BRAIN”

NEW/MODIFIED

- **Screening for potential reversible factors and corrective measures when possible. Such factors include: medications and their side effects, emotional distress, depression/anxiety, symptom burden (specially pain, fatigue and sleep disturbance), comorbidities, use of alcohol and other agents that may alter cognition, new-onset vitamin deficiencies and endocrinopathies (e.g. TSH, B12).**

  (LoE: II/A) (100%)

- **If important impact on self-reported QoL: Refer to neuropsychological assessment and cognitive rehabilitation.**

  (LoE: III/A) (96%)

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INTEGRATIVE MEDICINE

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INTEGRATIVE MEDICINE

Alternative therapies (i.e. therapies used instead of scientifically based medicines) are not recommended in any phase or stage of cancer treatment.

(LoE/GoR: NA/E) (100%)

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INTEGRATIVE MEDICINE

Breast Cancer Centers/Units/Departments should be aware that the majority of their patients would like to be informed about Complementary and Integrative Medicine and that many of them are using it.

Physicians should actively ask for information about its use, in view of the potential deleterious interactions with specific anti-cancer therapies.

If complementary therapies are not available at the centre, certified contacts should be available to promote referral to practitioners qualified in the therapies people are interested in receiving.

(LoE/GoR: Expert opinion/C) (100%)

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INTEGRATIVE MEDICINE

Some Complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and therefore improve the QoL of patients with ABC.
(LoE/GoR: Expert opinion/C) (100%)

Evidence suggests <u>beneficial effects</u> of the following methods, which can therefore be used:

- **Physical exercise / sport (equivalent to 3–5 hours of moderate walking per week) improves QoL, cardio-respiratory fitness, physical performance and fatigue, and it may also improve PFS and OS.**
- **MBSR (Mindfulness-based stress reduction) programs, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side effects of anti-cancer therapies.**
- **Acupuncture may help against chemotherapy-induced nausea and vomiting, fatigue and hot flashes.**

(LoE/GoR: I/B) (100%)

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INTEGRATIVE MEDICINE

Methods with no or unfavorable effects.

The following methods of Alternative Medicine are not recommended in ABC since available evidence shows no effect at best, or even association with worse outcome:

- **Antioxidant supplements**
- **Drugs outside the approved indication (e.g. methadone)**
- **Herbs including Chinese herbal medicine**
- **Orthomolecular substances (Selenium, Zinc...)**
- **Oxygen and ozone therapy**
- **Proteolytic enzymes, thymic peptides**
- **Phytoestrogens (soy-food, isoflavones)**
- **High dose vitamins (vitamin C, D, E, carotenoids, etc)**
- **L-carnitine, laetrile.**

(LoE/GoR: II/E) (100%)

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