ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer – ABC

ESO-ESMO ABC RECOMMENDATIONS
ABC Global Charter
10 goals for the next 10 years

COMPREHENSIVE NEEDS ASSESSMENT DEFINES MOST URGENT AND ACTIONABLE GOALS
Done with (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 TREATMENT AND 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
# LEVELS OF EVIDENCE GRADED SYSTEM

## LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>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.</td>
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<tr>
<td>II</td>
<td>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.</td>
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<tr>
<td>III</td>
<td>Prospective cohort studies.</td>
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<td>IV</td>
<td>Retrospective cohort studies or case–control studies.</td>
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<td>V</td>
<td>Studies without control group, case reports, experts’ opinions.</td>
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## GRADES OF RECOMMENDATION

<table>
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<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.</td>
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<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.</td>
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<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional.</td>
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<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended.</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended.</td>
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*Adapted by permission from the Infectious Diseases Society of America-United States Public Health Service Grading System; Dykewicz et al, 2001*
INTRODUCTION

• All panel members (including the chairs) must vote in all questions.

• Members of the panel who have a conflict of interest OR who do not feel comfortable answering the question (e.g. not area of expertise) should vote “abstain”.

• There is an additional possible answer for the Precision Medicine statements: “Insufficient data”, which should be selected if the panel member believes the existent data is not enough to vote “yes” or “no”, highlighting an area where research is needed.

• ABC 1-2-3-4 statements that will not be re-voted (not updated or with only minor changes) will be published in the manuscript.
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.
• ABC DEFINITIONS
**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: Expert opinion/NA) (97%)

To be discussed in manuscript: “impending visceral crisis”, clinical situation very difficult to objectively define
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 for ABC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:
Relapse while on adjuvant ET but after the first 2 years, or
Relapse within 12 months of completing adjuvant ET, or
PD ≥ 6 months after initiating ET for ABC, while on ET

(LoE: Expert opinion/NA) (67%)

Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice
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.

(LoE: Expert opinion/NA) (78%)
PATIENTS WITH MULTIPLE CHRONIC CONDITIONS (MCCs) are defined as patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease) making it difficult to account for all of the possible extrapolations to develop specific recommendations for care.

(LoE: Expert opinion/NA) (100%)
ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF ABC

Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is not always effective and therefore 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)

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

(LoE: Expert Opinion/NA) (100%)
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%)
• GENERAL STATEMENTS
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%)*
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%)
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%)*
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%)
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%)
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%)*
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%)*
• GENERAL STATEMENTS - QoL
Strong consideration should be given to the use of validated PROMs (patient-reported outcome measures) for patients to record the symptoms of disease and side effects of treatment experienced as a regular part of clinical care.

These PROMs should be simple and user-friendly to facilitate their use in clinical practice and thought needs to be given to the easiest collection platform e.g. tablets or smartphones.

Systematic monitoring would facilitate communication between patients and their treatment teams by better characterizing the toxicities of all anticancer therapies. This would permit early intervention of supportive care services enhancing QoL.

(LoE/GoR: I/C) (87%)
Specific tools for evaluation of QoL in ABC patients should be developed.
Until then, trials evaluating QoL in this setting should use standardized PROs (instead of focusing exclusively on CTCAE) and incorporate site and treatment specific modules or subscales that exist both in the EORTC and FACT systems.

Additionally, attention needs to 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 when choosing between treatment options.

(LoE/GoR: Expert opinion/A) (100%)
• GENERAL STATEMENTS- CLINICAL TRIALS
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%)
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, efficacy and toxicity.

(LoE/GoR: Expert opinion/A) (100%)
• GENERAL STATEMENTS - AFFORDABILITY/COST-EFFECTIVENESS
The medical 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%)
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%)
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%)
• GENERAL STATEMENTS-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%)
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%)
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%)
In ABC patients with long-standing stable disease or complete remission, breast imaging is an option.

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

To be discussed in manuscript: explain why and that systemic work up imaging doesn’t give good imaging of breast
Breast imaging should also be performed when there is a suspicion of loco-regional progression.

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

The impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).

(LoE/GoR: Expert Opinion/B) (100%)
• GENERAL STATEMENTS - OTHER
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%)
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%)
• IMAGE AND DISEASE ASSESSMENT GUIDELINES
Minimal staging workup for ABC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bones.

(LoE/GoR: II/A) (67%)
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) (94%)
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%)
Evaluation of response to therapy should generally occur every 2 to 4 months for ET 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%)
• BIOPSY OF METASTATIC LESION(S)
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%)
Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible. (LoE/GoR: I/B) (98%)

Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.
BIOPSY OF METASTATIC LESION

If the results of tumour biology in the metastatic lesion differ from the primary tumour, 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 targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing.

(LoE/GoR: Expert opinion/B) (87%)
• LOCAL-REGIONAL TREATMENT GENERAL GUIDELINES
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, with the possible exception of the subset of patients with bone only disease. However, it can be considered in selected patients, with controlled systemic disease, particularly to improve quality of life, always taking into account the patient’s preferences. (LoE/GoR: I/C) (70%)

Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. complete removal of the disease) as in patients with early stage disease. (LoE/GoR: II/B) (70%)

Additional prospective clinical trials evaluating the value of this approach, the best candidates and best timing are currently ongoing.
A small but very important subset of patients with ABC, for example those with oligo-metastatic disease or low volume metastatic disease that is highly sensitive to systemic therapy, can achieve complete remission and a long survival. A multimodal approach, including local-regional treatments with curative intent, should be considered for these selected patients.

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

A prospective clinical trial addressing this specific situation is needed.
• SYSTEMIC TREATMENT GENERAL GUIDELINES
Treatment choice should take at least these factors into account:

- HR & HER-2 status and germline BRCA status
- PIK3CA in HR+ 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%)
The **age** of the patient should not be the sole reason to withhold effective therapy (in elderly patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment.

(LoE/GoR: 1/E) (100%)
• CHEMOTHERAPY GENERAL GUIDELINES
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%)
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%)
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%)
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%)
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 interval.

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

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

In manuscript: define metronomic CT, including suggestions for dosages
Duration of each regimen and number of regimens should be tailored to each individual patient.

(LoE/GoR: Expert opinion/A) (96%)
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%)
• OTHER AGENTS
Bevacizumab combined with CT as 1\textsuperscript{st} 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 1\textsuperscript{st} line setting.

(LoE/GoR: I/C) (No consensus: Yes: 42%, No: 53%, Abstain: 5%)
• ER POSITIVE/HER-2 NEGATIVE ABC
Endocrine-based therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis. 
(LoE/GoR: I/A) (93%)

ER POSITIVE / HER-2 NEGATIVE MBC

* for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
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%)
**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%)*
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 of OFS/OFA and decision should be made on a case by case basis.

(LoE/GoR: Expert Opinion/C) (91%)
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%)
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
A CDK4/6 inhibitor combined with endocrine therapy is the standard of care for patients with ER+/HER-2 neg ABC, since it achieves substantial PFS benefit, significantly increases OS and either maintains or improves QoL.

The CDK4/6 inhibitor can be combined with an AI or with Fulvestrant, 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%)
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:

- PALBOCICLIB + AI 1\(^{st}\) line: Efficacy score: 3 (PFS); No improved QoL; ESMO-MCBS = 3
- ABEMACICLIB + AI 1\(^{st}\) line: Efficacy score: 3 (PFS); No QoL reported; ESMO-MCBS = 3
- RIBOCICLIB + AI 1\(^{st}\) line Post-menopausal: Efficacy score: 3 (PFS); No improved QoL; ESMO-MCBS = 3
- RIBOCICLIB + ET 1\(^{st}\) line Pre-menopausal: Efficacy score: 4 (PFS&OS); Improved QoL; ESMO-MCBS = 5
- PALBOCICLIB + Fulvestrant 2\(^{nd}\) line: Efficacy score: 3 (PFS&OS); Improved QoL; ESMO-MCBS = 4
- RIBOCICLIB + Fulvestrant (1\(^{st}\), 2\(^{nd}\) line): Efficacy score: 4 (PFS&OS); No improvement in QoL; ESMO-MCBS = 4
- ABEMACICLIB + Fulvestrant 2\(^{nd}\) line: Efficacy score: 4 (PFS&OS); No QoL benefit; ESMO-MCBS = 4

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

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

In manuscript: MCBS scores will be updated when new data is available
It remains unclear if CDK4/6 inhibitors should be preferably administered in the 1st or in the 2nd line setting. However, the majority of panelists preferred giving a CDK4/6 inhibitor in the 1st line setting for the majority of their patients.

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

In manuscript: The panel acknowledges that there is a small group of patients, those with limited burden of metastatic disease and features of less aggressive biology (i.e. very long DFI), who can be treated with ET alone. There are currently no biomarkers that allow an accurate identification of these patients.
There are no data supporting the use of a combination of CDK4/6 inhibitor and ET as maintenance therapy after chemotherapy. (LoE/GoR: NA/D) (66%)

Maintenance therapy, in this situation, should be performed with ET alone.
The addition of everolimus to an AI is a valid option for some patients previously exposed to or naïve of (in case CDK4/6i are not available) endocrine therapy, since it significantly prolongs PFS, albeit without evidence of OS benefit. The decision to treat must take into account the toxicities associated with this combination, lack of statistical significant OS benefit, cost and availability. (LoE/GoR : I/B) (88%)

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

Adequate prevention, 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
ER POSITIVE / HER-2 NEGATIVE MBC

Everolimus and CDK4/6 inhibitors should NOT be used after disease progression on that specific agent (i.e. beyond progression), outside a clinical trial.

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

The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the study Solar-1 (i.e: pre-existing diabetes & baseline HbA1c), as well as the toxicity profile of alpelisib.

Its efficacy after exposure to CDK4/6 inhibitors is unknown, since only 7% of patients in the Solar-1 trial had been previously treated with those agents.

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

ESMO-MCBS: 3

Note: For PIK3CA mutation testing, see Precision Medicine statements

In manuscript: Need to elaborate about inclusion/exclusion criteria in study and how this should guide which patients should/shouldn’t receive drug
Patients receiving ALPELISIB in combination with endocrine therapy for PIK3CA mutated ABC should be instructed to take non-sedating antihistamines 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%)
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%)
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, in cases where a CDK4/6 inhibitor 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%)
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.

Available options for 1st and 2nd line include AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus, fulvestrant + alpelisib (for PIK3CA mut), AI, tamoxifen, fulvestrant.

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

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
Options for treatment of ER positive disease beyond second line include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megestrol 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
Trials comparing the different combinations of endocrine + targeted agents with single agent CT are ongoing. Initial results from phase 2 & 3 randomized trials comparing combinations of endocrine + targeted agents to single agent CT, do not show significant differences in terms of efficacy, and the former compares favorably in terms of safety. 

(LoE/GoR : II/B) (not voted – discuss in manuscript once trials are published)

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
Concomitant CT + ET has not shown a survival benefit and should not be performed outside a clinical trial.

(LoE/GoR: II/D) (100%)
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%)
• HER-2 POSITIVE ABC
Anti-HER2 therapy should be offered *early* (as 1<sup>st</sup> line) to all patients with HER2+ ABC, except in the presence of contraindications to the use of such therapy.

*(LoE/GoR: I/A) (98%)*
Patients 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.
In patients achieving 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%)
Patients who have received any type of (neo)adjuvant anti-HER2 therapy should not be excluded from clinical trials for HER-2+ ABC. These patients remain candidates for anti-HER2 therapies.

(LoE/GoR: I/B) (100%)
For the 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%)
For patients with ER+/HER-2+ ABC, for whom CT + anti-HER2 therapy was chosen as 1\textsuperscript{st} 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.

Note in manuscript: in Cleopatra, maintenance was done with dual blockade alone (without ET)
HER-2 POSITIVE MBC

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

(LoE/GoR: I/A) (95%)
HER-2 POSITIVE MBC: 1\textsuperscript{st} line

The \textit{standard 1\textsuperscript{st} line therapy} for patients \textit{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.

\textit{(LoE/GoR: I/A) (86%)}
HER-2 POSITIVE MBC: 1\textsuperscript{st} line

For patients \textit{previously treated} (in the (neo)adjuvant setting) with anti-HER2 therapy, the combination of CT + trastuzumab and pertuzumab is an \textit{important option for 1\textsuperscript{st} 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.
HER-2 POSITIVE MBC

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

(LoE: I /E) (86%)

Note in manuscript: there are no data on how to treat patients who have a relapse after receiving CT + trastuzumab + pertuzumab in the early setting.
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%)
HER-2 POSITIVE MBC: 2nd line and beyond

After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician’s choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.

(LoE/GoR: I/A) (88%)
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 or T-DM1.
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.
Trastuzumab Deruxtecan (DS-8201) showed important activity in a phase 2 study, in heavily pretreated patients with HER2+ ABC (median lines of therapy: 6), and is a treatment option in this setting, where approved. Pulmonary toxicity (ILD*/Pneumonitis) can be fatal and requires active surveillance and proper management.

(LoE/GoR: II/B) (98%)
Dual blockade with **tucatinib + trastuzumab + capecitabine** showed a small benefit in median PFS (2 ms) and median OS (4 ms), over trastuzumab + capecitabine, in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with brain metastases, at the expenses of higher toxicity (i.e. diarrhea). If approved, it can be considered a treatment option in this setting.

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

**MCBS: 3**

In manuscript: there are no comparative data between the 3 new anti-HER2 agents (Trastuzumab Deruxtecan, Tucatinib and Margetuximab)
Margetuximab + chemotherapy showed only a small PFS benefit (1 month) 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.

MCBS: waiting for publication

In manuscript: there are no comparative data between the 3 new anti-HER2 agents (Trastuzumab Deruxtecan, Tucatinib and Margetuximab)
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.

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

In manuscript: Data to decide on best sequence are lacking
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), capecitabine (LoE/GoR: I/A), and metronomic CT in older patients (LoE/GoR: II/B).

(Consensus: 86%)
• TRIPLE NEGATIVE ABC
In triple negative ABC patients (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%)
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%)
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.
IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC

Atezolizumab + nab-paclitaxel is an option for 1st line therapy for PD-L1+* triple negative ABC, either de novo or at least 12 months since (neo)adjuvant chemotherapy.

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

MCBS: 3

* For PD-L1 testing, see Precision Medicine statements
Checkpont inhibitor monotherapy in later lines for triple negative ABC is not recommended, due to low response rates.

(LoE/GoR: I/E) (89%)
Several ongoing trials are evaluating the role of immunotherapy in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials.

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

* For PD-L1 testing, see Precision Medicine statements
• HEREDITARY ABC
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%)
At present only germline mutations in BRCA 1/2 have proven clinical utility and therapeutic impact.  
(LoE/GoR: I/A) (100%)

Testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, in particular because they may have implications for family members. However it must be clarified to the patient that at present, a mutation in another moderate-high penetrance gene has no direct clinical implications, for the patients themselves, in the setting of ABC.  
(LoE/GoR: Expert Opinion/C) (100%)
The therapeutic implications of somatic BRCA 1/2 mutations in breast tumors need to be further explored within a research setting and should not be used for decision making in routine clinical practice.

(LoE/GoR: NA/E) (83%)
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.
For patients with a gBRCA mutation single agent PARP inhibitor (olaparib or talazoparib) is a preferred treatment option for those with triple negative ABC.

(LoE/GoR: I/A) (78%)

In ER+ gBRCA-associated ABC, the optimal sequence between PARPi and ET with or without CDK4/6i is unknown. Given the OS benefit seen with CDK4/6i, the panel recommends their use before a PARPi.

(LoE/GoR: Expert Opinion/B) (78%)

Single agent PARP inhibitors (olaparib or talozaparib) are associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

Results suggest that any benefit in OS may be limited to the 1st line setting.
It is unknown how PARP inhibitors (olaparib or talazoparib) compare with platinum compounds in this setting, the optimal use with platinum (combined or sequential), and their efficacy in tumors progressing after platinum.

More research is needed to answer questions related to treatment sequencing.

(LoE/GoR: Expert Opinion/NA) (90%)
BROCADE3 was the first phase 3 trial testing a PARP inhibitor (Veliparib) in gBRCA MBC 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%)
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%)
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 Alpelisib. (LoE/GoR: II/A) (93%)

Modified statement
If treatment with Pi3k 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%)*

In manuscript: The test can be performed on either metastatic tissue biopsy or if not available on primary tumor specimen. The technology used, either multiplex qualitative real-time PCR assays for the detection of specific mutations in the PIK3CA gene or NGS, has to cover the most frequent mutations (hot spots) on exons 7, 9, and 20) which include mutations common in patients with HR+ breast cancer. If the tissue is exhausted or inaccessible, liquid biopsy either multiplex qualitative real-time PCR assays or NGS is a reliable option. Patients who are negative by the liquid biopsy test, should undergo tumor biopsy for PIK3CA mutation testing.
**ESR1 mutation status** assessment is not ready for routine clinical practice use and is **not recommended**, either for demonstration of disease progression or selection of endocrine treatment (such as switch from AI to fulvestrant).

(LoE/GoR: I/D) (90%)
PD-L1 status should be tested in cases of 1\textsuperscript{st} line triple negative ABC, if treatment with immune checkpoint inhibitors is available. 
(LoE/GoR: I/A) (97%)

PD-L1 status is the companion test for the use of the combination of atezolizumab and taxane, for 1\textsuperscript{st} line therapy for triple negative ABC, using immunohistochemistry with the SP142 antibody (Ventana), and a cut-off of 1\% of positive staining on immune cells. 
(LoE/GoR: I/A) (97%)
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%)
If an ABC patient 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 an ABC patient 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.
SPECIFIC SITES OF METASTASES

Bone
Brain
Liver
Pleural Effusion
Chest wall recurrences
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%)
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%)
Regarding the use of bone targeted agents (bisphosphonate, denosumab), the ABC panel endorses the ESMO Guidelines related to this subject.
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%)
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%)
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%)
In patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.

(LoE/GoR: I/D) (95%)
For patients with HER2 positive ABC where brain metastases are the only site of recurrence, the addition of CT to local therapy is not known to alter the course of the disease and is not recommended. (LoE/GoR: I/D) (83%)

It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped. (LoE/GoR: I/B) (83%)
HER-2 POSITIVE ABC & BRAIN METASTASES

For patients with HER2 positive ABC with progressive brain metastases as the predominant site of disease burden, if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option, preferably in clinical trials.

(LoE/GoR: III/A) (85%)
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%)
LEPTOMENINGEAL DISEASE (LMD)

- There is no accepted standard of care for breast cancer LMD.
- The choice of treatment (radiotherapy, intra-CSF therapy, systemic therapy, supportive care) should consider prognostic evaluation and multidisciplinary discussion. *(LoE/GoR: Expert Opinion) (95%)*
- Focal RT should be considered for circumscribed, notably symptomatic lesions. *(LoE/GoR: Expert Opinion) (95%)*
- WBRT can be considered for extensive nodular or symptomatic linear LMD. *(LoE/GoR: Expert Opinion) (95%)*
- Addition of intra-thecal to systemic therapy has no OS and QoL advantage and no clinically meaningful effect on CSF-progression. *(LoE/GoR: II/D) (95%)*
- Intra-thecal therapy can be considered if systemic disease is stable and there is normal CSF flow, when there is evidence of malignant cells in the CSF (Type I LMD). Significant toxicity may occur. *(LoE/GoR: Expert Opinion) (95%)*
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%)
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.
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%)
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%)
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%)
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%)*
• SPECIFIC POPULATIONS
Advanced MALE breast cancer
For ER+ Male ABC, which represents the majority of the cases, ET is the preferred option, unless there is visceral crisis or rapidly progressive disease needing a fast response.

(LoE/GoR: III/A) (100%)
For ER+ Male ABC tamoxifen is the preferred option.

(LoE/GoR: IV/B) (83%)
TREATMENT OF MALE ABC

For male patients with ABC who need to receive an AI, a concomitant LHRH agonist or orchidectomy is the preferred option. AI monotherapy may also be considered, with close monitoring of response. Clinical trials are needed in this patient population.

(LoE/GoR: IV/B) (86%)
For the purpose of these recommendations, LABC means INOPERABLE, NON-METASTATIC LOCALLY ADVANCED BC
BEFORE starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER2, proliferation/grade) expression is indispensable to guide treatment decisions.

(LoE/GoR: I/A) (97%)
Since LABC patients have a significant risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen (preferably with CT-scan) and bone, before initiation of systemic therapy is highly recommended. 
(LoE/GoR: I/A) (100%)

PET-CT, if available, may be used (instead of and not in addition to CT-scans and bone scan). 
(LoE/GoR: II/B) (100%)

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%)
Options for HR+ LABC include an anthracycline- and taxane-based chemotherapy regimen, or endocrine therapy.  
(LoE/GoR: I/A) (85%)

The choice of CT versus ET, as initial treatment, will depend on tumor (grade, biomarker expression) and patient (menopausal status, performance status, comorbidities, preference) considerations.  
(LoE/GoR: Expert Opinion/A) (85%)
Anthracycline- and-taxane-based chemotherapy is recommended as initial treatment.

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

Platinum can be combined with the taxane.
Concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR.  
(LoE/GoR: I/A) (92%)

Anthracycline-based chemotherapy should be incorporated in the treatment regimen.  
(LoE/GoR: I/A) (72%)

When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.  
(LoE/GoR: I/A) (87%)
For patients with HER-2+ LABC (Inflammatory or non-inflamatory), 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.

(LoE/GoR: I/A) (85%)
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%)
LOCALLY ADVANCED INOPERABLE BC (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%)
INFLAMMATORY LABC

For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment. \((\text{LoE}/\text{GoR}: \text{I/A}) (93\%)\)

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

Immediate reconstruction is generally not recommended in patients with inflammatory LABC. \((\text{LoE}/\text{GoR}: \text{IV/E}) (95\%)\)

Loco-regional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy. \((\text{LoE}/\text{GoR}: \text{I/A}) (98\%)\)
• 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%)
Early introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.

(LoE/GoR: I/A) (100%)
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%)
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%)
The panel encourages research on the potential role of cannabis to assist with pain and symptom control but strongly stresses that it cannot replace proven medicines such as morphine, for adequate pain control.

(LoE/GoR: I/C) (97%)
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%)
Management of CANCER RELATED FATIGUE

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 aetiology of this fatigue is complex, therefore effective management needs to be multidimensional. 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%).

* Details in manuscript
Management of CDK 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%)
Management of Non-Infectious Pneumonitis (NIP)

NIP is an uncommon complication of mTOR or CDK4/6 inhibition. Patient education is critical to ensure early reporting of respiratory symptoms.

Treatment interruption and dose reduction are generally effective for grade 2 symptomatic NIP with use of systemic steroids and treatment discontinuation for grade 3 or greater toxicity.

(LoE/GoR: II/A) (100%)
Management of DYSPNEA

• Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anemia, drug toxicity must be ruled out.
• Patient support is essential.
• Oxygen is of no use in non-hypoxic patients.

• Opioids are the drugs 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%)
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: NA)

There is a need to study nausea and vomiting related to chronic use of anticancer drugs.

(LoE/GoR: Expert opinion/A) (100%)
Management of endocrine toxicities of mTOR or PI3KCA inhibition

Hyperglycemia and hyperlipidemia are common sub-acute complications of mTOR or Pi3K 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 include 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%)
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%).
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%).

High quality studies are needed to evaluate strategies for prevention and management of CIPN.
Management of HAND AND FOOT SYNDROME

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.
Systemic hormone therapy is generally **not recommended** to treat postmenopausal symptoms in ABC patients, particularly not in ER+ disease*. (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 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%)

* Discussed in manuscript that the final decision belongs to the woman, after correct information, since in some cases these symptoms are highly impacting on QoL
Sexuality is an experience on many levels and is not confined to the act of intercourse. Sexuality remains important for many ABC patients. ABC 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%)
Dyspareunia is often caused by vaginal dryness.

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

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

The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.
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%)
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%)
Some Complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and therefore improve the QoL of ABC patients.

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

Evidence suggests beneficial effects of the following methods, which can therefore be used:

- Physical exercise / sport (equivalent to 3–5 hrs of moderate walking per week) improves QoL, cardio-respiratory fitness, physical performance and fatigue, and it may also improve DFS 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 CT-induced nausea and vomiting, fatigue and hot flashes.

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