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

ESO-ESMO ABC RECOMMENDATIONS
### 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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<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>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<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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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.”

• At ABC4, a new possible answer was included in 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 statements that will not be re-voted (not updated or with only minor changes) will be published in the manuscript.
In the manuscript it will be explained that 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 visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

*(LoE: Expert opinion/NA) (95%)*
PRIMARY ENDOCRINE RESISTANCE is defined as:
Relapse while on the first 2 years of adjuvant ET, or
PD within first 6 months of 1\textsuperscript{st} line ET for MBC, 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 MBC, 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, specially 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 along period of time, 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: 1/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 advanced breast cancer 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 advanced breast cancer 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 MBC 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 specific 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
There are few proven standards of care in ABC management. 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, screening breast imaging should be an option.

(LoE/GoR: Expert opinion/C) (Y: 53%; N: 47%)
Breast imaging should also be performed when there is a suspicion of loco-regional progression.

(LoE/GoR: I/A) (100%)
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 MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone.

(LoE/GoR: II/A) (67%)
Brain imaging should not be routinely performed in asymptomatic patients. This approach is applicable to all patients with MBC including those with HER-2+ and/or TNBC MBC.

(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. A change 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.
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, 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 into account at least these factors:

- HR & HER-2 status,
- 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 and patient’s preference.

(LoE/GoR: Expert opinion/A) (100%)
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 MBC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, 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 MBC, 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%)
In patients with taxane-naive and anthracycline-resistant MBC 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%)
In patients pre-treated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, and who do not need combination CT, single agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, 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%)
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%)
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 MBC, particularly if there has been at least one year of disease-free survival.

(LoE/GoR: I/B) (93%)
Metronomic chemotherapy is a reasonable treatment option for patients not requiring rapid tumor response. 
(LoE/GoR: I/B) (88%)

The better studied regimen is CM (low dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine).

Randomized trials are needed to accurately compare metronomic CT with standard dosing regimens.
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 1st or 2nd line therapy for MBC provides only 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 in these settings and is not recommended after 1st/2nd line.

(LoE/GoR: I/C) (74%)
• ER POSITIVE/HER-2 NEGATIVE ABC
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.

(LoE/GoR: I/A) (93%)
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 ET was decided, ovarian suppression/ablation combined with additional endocrine therapy is the preferred choice. (LoE/GoR: I/A) (93%)
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.

(LoE/GoR: Expert Opinion/C) (91%)
Tamoxifen single agent 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 ET 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
The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

OS results are still awaited. QoL was comparable to that with ET alone.

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

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
The addition of a CDK4/6 inhibitor to Fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6 to 7 months) as well as improvement of QoL, and is one of the preferred treatment options, if a CDK4/6 inhibitor was not previously used.

OS results are awaited.

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

* For pre and peri with OFS/OFA, and post-menopausal women and men
ER POSITIVE / HER-2 NEGATIVE MBC

The addition of everolimus to an AI is a valid option for some patients previously exposed to 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%)

ESMO-MCBS: 2

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), the burden of the disease, patients’ preference, costs and availability.

Available options include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and estradiol, as well as repetition of previously used agents, may be used.

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

It is currently unknown how the different combinations of endocrine + targeted agents compare with each other, and with single agent CT. Trials are ongoing.

* for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women
Everolimus and CDK4/6 inhibitors should NOT be used after disease progression on that specific agent (i.e. beyond progression).

(LoE/GoR : NA/E) (74%)
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 targeted agent (i.e. CDK4/6 inhibitor, 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%)
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.

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 MBC without prior exposure to adjuvant ET.

(LoE/GoR: II/C) (No consensus: Y: 33%, N: 53%, Abstain: 14%)
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 assessed in randomized trials.

(LoE/GoR: III/B) (88%)
• HER-2 POSITIVE ABC
Anti-HER2 therapy should be offered *early* (as 1st 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+ MBC. 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 1<sup>st</sup> 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
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)
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%)
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%)
For patients previously treated (in the (neo)adjuvant setting) with anti-HER2 therapy, the combination of CT + trastuzumab and pertuzumab is an important 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.
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 this 3 drug regimen should not be given beyond progression outside clinical trials.

(LoE: Expert Opinion/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 1\textsuperscript{st} line.

(LoE/GoR: II/B) (76%)
After 1\textsuperscript{st} line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2\textsuperscript{nd} 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%)

However, there are no data on the use of T-DM1 after dual blockade with trastuzumab + pertuzumab.
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 data on the use of this combination after progression on pertuzumab or T-DM1.
Regarding the CT component of HER2 positive ABC treatment:

When pertuzumab is not given, 1<sup>st</sup> 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
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: II/A).

(Consensus: 86%)
• TRIPLE NEGATIVE ABC
For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations. Therefore, all CT recommendations for HER2 negative disease also apply for triple negative ABC.

(LoE/GoR: I/A) (98%)
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%)
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.
• HEREDITARY ABC
In the setting of ABC, results from genetic testing may have therapeutic implications and should therefore be considered as early as possible.

(LoE/GoR: Expert Opinion/B) (100%)
Genes to be tested for depend on personal and family history, however 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. 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 BRCA-associated triple negative or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option, if not previously administered and no suitable clinical trial is available.

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

All other treatment recommendations are similar to sporadic ABC.
A PARP inhibitor (olaparib or talozaparib) is a reasonable treatment option for patients with BRCA-associated triple negative or luminal (previously exposed to endocrine therapy) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favorable toxicity profile.

OS results are awaited. It is unknown how PARP inhibitors compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumors.

(LoE/GoR: I/B) (80%)
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) 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 ready for routine clinical practice use and is not recommended, either for demonstration of disease progression or selection of targeted therapies.

(LoE/GoR: I/D) (74%)
In case an ABC patient was tested in the context of a clinical trial and the information is available:

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: Expert opinion/C) (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.
Immunotherapy, with a checkpoint inhibitor, for any biological subtype of ABC should not be used in routine clinical practice, outside clinical trials.

Several ongoing trials are evaluating the role of this type of treatment in all ABC subtypes.

(LoE/GoR: III/D) (85%)
• 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 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, emergency radiotherapy is the treatment of choice and vertebroplasty is also an option.

(LoE/GoR: I/B) (100%)
A bone modifying agent (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with ABC and bone metastases. *(LoE/GoR: I/A) (95%)*

Three-monthly zolendronic acid seems to be not inferior to standard monthly schedule. *(LoE/GoR: I/B) (95%)*

Supplementation of calcium and vitamin D3 is mandatory, unless contraindications exist. *(LoE/GoR: I/A) (95%)*

Notes in manuscript:  
a) When available Denosumab is preferred in view of better efficacy and tolerability; 
b) Denosumab is also being studied q3 ms; 
c) q3 ms schedule was associated with more major surgeries, therefore a good compromise may be to start monthly for the 1st year and then change to q3ms; 
d) no data on when to stop
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%)
For patients with HER2 positive ABC with progressive brain metastases as the predominant cause 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%)
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.
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%)
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 primarily 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 breast cancer. These patients may still be considered for palliative local therapy.

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

CHEST WALL AND REGIONAL (NODAL) RECURRENTS
• 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 concern or proof of endocrine resistance 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%)
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, prior to initiation of systemic therapy is highly recommended. (LoE/GoR: I/A) (100%)

PET-CT, if available, may be used (instead of and not on top of CT-scans and bone scan). (LoE/GoR: II/B) (100%)
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%)
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-inflammatory), without distant metastases, who are in complete remission after appropriate neoadjuvant 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 neoadjuvant 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%)
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%)
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment. *(LoE/GoR: I/A) (93%)*

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 inflammatory LABC. *(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%)*
• SUPPORTIVE & 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%)
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 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%)
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 it 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
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%)
NIP is an uncommon complication of mTOR 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%)
ESMO/MASCC GUIDELINES are available for management of chemotherapy-induced and morphine-induced nausea and vomiting, and 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 inhibition

Hyperglycemia and hyperlipidemia are common sub-acute complications of mTOR 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)

Early intervention is recommended. (LoE/GoR: Expert opinion/A). 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). Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis. (LoE/GoR: Expert opinion/B). Consider adding steroid dental paste to treat developing ulcerations. (LoE/GoR: Expert opinion/B).
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.\(^{(\text{LoE/GoR: II/C})}\) 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.\(^{(\text{LoE/GoR: Expert Opinion/C})}\)

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

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)

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

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

(LoE/GoR: Expert opinion/C)
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)

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)
Advanced Breast Cancer

Fifth International Consensus Conference

14-16 November 2019
Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT

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Eric P. Winer, US (Chair & ESO-ABC Task Force)  
Alberto Costa, CH/IT (Chair & ESO-ABC Task Force)  
Larry Norton, US (Chair) (absent from voting)  
Maria Leadbeater, UK (Nurse)  
Musa Mayer, US (Advocate)  
Stella Kyriakides, CY (Advocate & ESO-ABC Task Force)  
Olivia Pagani, CH (ESO-ABC Task Force)  
David A. Cameron, UK (ESO-ABC Task Force)  
Tanja Cufer, SL (ESO-ABC Task Force)  
Lesley Fallowfield, UK (ESO-ABC Task Force)  
Prudence Francis, AU (ESO-ABC Task Force)  
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Laura van’t Veer, US  
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Musa Mayer, US (Advocate)
Olivia Pagani, CH
Tanja Cufer, SL
Lesley Fallowfield, UK
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Joseph Gligorov, FR
Elzbieta Senkus, PL
Christoph Thomssen, DE
Nancy U. Lin, US
Nehmat Houssami, AU
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Jonas Bergh, SE
Nagi El Saghir, LB
Karen Gelmon, CA
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Larry Norton, US (Chair)
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Musa Mayer, US (Advocate)
Shirley A. Mertz, US (Advocate)
Dian C.J. Corneliussen-James, US (Adv)
Evi Papadopoulos, CY (Advocate)
Lillie D. Shockney, US (Nurse)
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Olivia Pagani, CH
Lesley Fallowfield, UK
Prudence Francis, AU
Christoph Thomssen, DE
Gouri S. Bhattacharyya, IN
Matti Aapro, CH
Jonas Bergh, SE
Nagi El Saghir, LB
Karen Gelmon, CA
Nadia Harbeck, DE
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