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Original article

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3)

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Introduction

Advanced Breast Cancer (ABC) comprises both locally advanced (LABC) and metastatic breast cancer (MBC) [1]. Although treatable, it is remains an incurable disease with a median overall survival of ~2–3 years and a 5-year survival of only ~25% [2–4]. Some more recent series seem to indicate an improvement in median overall survival [5,6].

A recent comprehensive report [2] of the advances in this field in the last decade shows that progress has been slow in terms of improved outcomes, quality of life, awareness and information regarding ABC.

The level of evidence used to base many recommendations remains low, and more and better designed trials are needed to address clinically important questions. An improved understanding of the biology of ABC, its heterogeneity, and of the mechanisms of resistance to the different types of therapies is being acquired and it is anticipated that the application of new technologies, such as next generation sequencing, patient xenographs, systems biology, and computer modelling, among others, will accelerate advances.

Aiming at providing clinically oriented guidelines on how to best manage ABC, the 3rd International Consensus Conference for Advanced Breast Cancer (ABC 3) took place in Lisbon, Portugal on November 5th–7th, 2015, bringing together over 1100 participants from 84 countries, including health professionals, patient advocates and journalists.

The ABC guidelines are developed as a joint effort from ESO (European School of Oncology) and ESMO (European Society of Medical Oncology), and are endorsed by EUSOMA (European Society of Breast Cancer Specialists), ESTRO (European Society of Radiation Oncology), UICC (Union for International Cancer Control), SIS (Senologic International Society) and FLAM (Federatión LatinoAmericana de Mastologia). There was also official representation of ASCO (American Society of Clinical Oncology) in the consensus panel. The ABC Conference was also organized under the auspices of OECI (Organization of European Cancer Institutes), and with the support of the BCRF (Breast Cancer Research Foundation) and the Susan G Komen for the Cure.

The present article summarizes the guidelines developed at ABC3 and is supported with the level of evidence, the percentage of consensus reached at the Conference, and supporting references.

Methodology

Prior to the ABC 3 Conference, a set of preliminary recommendation statements on the management of ABC were prepared, based on available published data and following the ESMO guidelines methodology. These recommendations were circulated to all 44 panel members by email for comments and corrections on content and wording. A final set of recommendations was presented, discussed and voted upon during the consensus session of ABC 3. All panel members were instructed to vote on all questions, with members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field) instructed to vote 'abstain'. Additional changes in the wording of statements were made during the session. The statements related to management of side effects and difficult symptoms, included under the Supportive and Palliative care section, were not voted on during the consensus session, but discussed and unanimously agreed by email, and are considered to have 100% agreement.

Supplementary Table S1, available at *Annals of Oncology* online, lists all members of the ABC 3 consensus panel and their disclosures of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

Table 1
Grading system [7].

Grade of recommendation/description	Benefit versus risk and burdens	Methodological quality of supporting evidence	Implications
1A/strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

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Table 1 describes the grading system used [7]. ABC1 [10] and ABC2 [1] statements with only minor updates or with no updates are listed in Table 2.

General recommendations

The continuous increase in cancer care costs has inevitably led to inequalities in access both between countries and within each

Section 1: General recommendations.

Guideline statement	LoE	Consensus
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, providing real world performance of the therapy.	Expert opinion	Voters: 43 Yes: 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.	Expert opinion	Voters: 44 Yes: 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.	Expert opinion	Voters: 40 Yes: 87.5% (35) Abstain: 5% (2)
The use of telemedicine 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.	Expert opinion	Voters: 42 Yes: 92.8% (39) Abstain: 4.7% (2)
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 quality of life	1 C	Voters: 39 Yes: 87.1% (34) Abstain: 5.1% (2)
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 quality of life, 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.	Expert opinion	Voters: 40 Yes: 95% (38) Abstain: 5% (2)
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.	Expert opinion	Voters: 42 Yes: 100%
ABC patients with stable disease, being treated as a 'chronic condition', should have the option to undergo breast reconstruction.	Expert opinion	Voters: 39 Yes: 82% (32) Abstain: 7.6% (3)
In ABC patients with long-standing stable disease, screening breast imaging should be an option.	Expert opinion	Voters: 40 Yes: 52.5% (21) N: 47.5% (19)
Breast imaging should also be performed when there is a suspicion of loco-regional progression.	Expert opinion	Voters: 40 Yes: 100%
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.	1 B	Voters: 43 Yes: 98% (42)
Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible. Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.	1 B	Voters: 44 Yes: 98% (43)
If the results of tumour biology in the metastatic lesion differ from the primary tumor, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing.	Expert opinion	87%
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. 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. Additional prospective clinical trials evaluating the value of this approach, the best candidates and best timing are currently ongoing	2 B	Voters: 44 Yes: 70.4% (31)
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.	Expert opinion	Voters: 43 Yes: 91% (39)

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement.

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country. Cost, value and access are now central discussion points and important factors in treatment-decision making. Both ESMO and ASCO have put considerable effort into the development of validated objective scales aiming at evaluating the real magnitude of benefit provided by each new treatment, including efficacy measures (e.g. impact on DFS, OS or PFS) and toxicity/quality of life measures. The ESMO Magnitude of Clinical Benefit Scale [8] and the ASCO Value Framework [9] are user-friendly tools that can greatly assist decision-makers at the country and/or hospital level in the difficult decisions regarding approval and reimbursement.

The ABC3 experts also emphasize the responsibility of the academic and medical communities to advance the knowledge on breast cancer and other relevant unanswered issues, by involvement in clinical research aimed at addressing important clinical questions, and not only in studies conducted for regulatory purposes.

The importance of providing patients with full information in appropriate, understandable and culturally sensitive way, as well as involving them in sharing the decision-making regarding all aspects of their management has been repeatedly stressed in all ABC guidelines [1,10]. A high standard of patient centred care includes the following elements: appropriate information, good communication with health professionals, patient education, proactive advocacy, sensitivity to the patient's preferences, values and needs, and providing patients with the capabilities to improve their own quality of life [11].

Although the overall survival of ABC has remained stable, for some subtypes, and in particular HER-2-positive metastatic breast cancer, prolonged survival, well beyond the median 2–3 years, has become a frequent reality. For these long-term survivors, survivorship issues which are specific for advanced cancer patients, have emerged and need appropriate attention, research and management. Work-related issues are central and solutions not easy to implement. A recently published survey [12], found that approximately half of the women in employment had to change their work situation due to ABC and that 37% of them had to give up work temporarily or permanently. Due to these income problems and those related to the cost of care, the same survey found that 56% of ABC patients experienced a decline in household income as a result of their disease. The ABC community strongly advocates for the right of ABC patients to return or maintain their work, since a substantial proportion of these patients are in their most productive years. Furthermore, in some countries, health coverage is dependent on being employed. For that to occur, we need flexibility of working schedules, new communication technologies and home-based work which the ABC community supports. In many countries this may imply a change in the current labour-related laws.

Survivorship issues also include the potential discussion of breast reconstruction, in those cases where the metastatic disease is either in complete remission or in a durable stable situation. No consensus could be reached regarding the use of breast imaging to follow-up the unaffected breast, but the experts agreed that imaging should be performed in case of suspicion of disease progression in the breast.

Regarding the need to biopsy metastatic disease and re-evaluate the common biomarkers, the ABC recommendations had only minor changes. There are situations where the need for a biopsy in the metastatic setting is very clear, such as single lesions, history of two or more malignancies, suspicion of benign histology or doubt between progression or post-treatment necrosis. There is also consensus regarding the importance of such biopsy in situations where when a change in biomarkers would impact the treatment choice, which would mainly occur when biomarkers were negative in the primary tumor. There is some controversy about the benefits of a biopsy in situations where there is no doubt about the nature of the lesion(s) and where all receptors were positive in the primary tumor, since the clinical implementation of new technologies such as next generation sequencing for management decision-making is not yet validated. However, the exact nature of a lesion is hard to ascertain without the confirmation by a biopsy as shown in some retrospective and prospective studies [13–15]. There is also an undisputable importance of collection of material for research purposes, both ongoing and future.

Technical issues should be discussed with the breast pathologist, in particular in case of bone biopsies with the inherent decalcification problems, which may interfere with the biomarker analysis [16,17], as experienced in Safir01/UNICANCER trial [18]. For that reason, decalcification using EDTA is recommended for bone biopsies, when it is the only metastatic site [17]. Adding to the complexity of this issue is the fact that negative biomarker results may limit the eligibility for reimbursement of therapies dedicated to specific subtypes, in some countries.

A number of prospective randomized trials have assessed or are assessing the role of removing the primary tumor in patients with *de novo* metastatic disease. So far only two small studies have been published/presented [19,20]. A subgroup analysis of the Turkish study suggested a potential benefit in patients with ER/PgR+, HER-2 negative, solitary bone metastasis, who are younger than 55 years of age, while patients with multiple pulmonary and liver metastasis did worse with an overall 3-year survival of 31% in the surgery group versus 67% for the systemic therapy group [20]. In the Indian trial, a decrease in distant progression-free survival was observed in patients allocated to surgery. Results of larger, prospective studies are awaited. Until then, the recommendation is to discuss surgery on a case-by-case basis and importantly, only consider surgery if it can be performed with a high quality procedure [21].

The definition of oligometastatic disease (see next section) has been enlarged to encompass low volume metastatic disease, i.e. limited number and size of metastatic lesions (up to five and not necessarily in the same organ) and potentially amenable for local treatment which is aimed at achieving a complete remission. The development of minimally invasive surgical techniques and highly conformal ablative radiotherapy allow for safe and effective ablation of metastatic lesions in most locations. Although some retrospective studies have suggested that achieving a sustained complete remission seems to be associated with a longer survival [22], the true impact of these local-regional therapies on long-term outcome remains unknown, and prospective and if possible randomized trials are needed.

Section 2: ABC important definitions.

Guideline statement	LoE	Consensus
Oligo-metastatic disease is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to five and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.	Expert opinion	• Voters: 36 • Yes: 78% (28) • Abstain: 6% (2)
Patients with multiple chronic conditions are defined as patients with additional comorbidities (e.g. 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.	Expert opinion	• Voters: 42 • Yes:100%

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement.

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Table 2
Other ABC1 [10] and ABC2 [1] statements with only minor updates or with no updates.

Recommendations	LoE	% Consensus
ABC important 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.	Expert opinion	95
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 MBC, while on ET.	Expert opinion	67
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 $\geq$ 6 months after initiating ET for MBC, while on ET.		
Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice		
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.	Expert opinion	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.	Expert opinion	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).	Expert opinion	97
This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.		
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).	Expert opinion	100
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.	Expert opinion	100
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.	Expert opinion	100
Specialized oncology nurses (if possible specialized breast nurses) should be part of the multidisciplinary team managing ABC pts. In some countries this role may be played by a physician assistant or another trained and specialized health care practitioner.	Expert opinion	92
All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy to understand information about their disease and its management.	1 B	97
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.	1 B	100
Assessment guidelines		
Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone.	2 C	67
Brain imaging should not be routinely performed in asymptomatic patients. This approach is applicable to all patients with MBC including those patients with HER-2+ and/or TNBC MBC.	Expert opinion	94
The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy, but their use is reasonable (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease. A change in tumor markers alone should not be used to initiate a change in treatment.	2 C	89
Evaluation of response to therapy should generally occur every 2–4 months for ET or after two to four cycles for CT, depending on the dynamics of the disease, the location and extent of metastatic involvement, and type of treatment.	Expert opinion	81
Imaging of target lesions 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.		
Treatment general guidelines		
Treatment choice should take into account at least these factors: HR and HER-2 status, previous therapies and toxicities, disease-free interval, tumour 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 preference.	Expert opinion	100
ER+/HER-2 negative ABC		
Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, although this approach has not been assessed in randomized trials.	1 C	88
Concomitant CT + ET has not shown a survival benefit and should not be performed outside of a clinical trial.	1 B	100
Chemotherapy and biological therapy		
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	1 B	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.	1 A	71

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Table 2 (*continued*)

Recommendations	LoE	% Consensus
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 agents, 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.	1 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.	1 B	77
If given in the adjuvant setting, a taxane can be re-used as 1st line therapy, particularly if there has been at least 1 year of disease-free survival.	1 A	92
Duration of each regimen and the number of regimens should be tailored to each individual patient.	Expert opinion	96
Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity.	1 B	72
What is considered unacceptable should be defined together with the patient.		
Other agents		
Bevacizumab combined with a chemotherapy 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.	1 A	74
Specific populations: treatment of metastatic male MBC		
For ER+ Male MBC, 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.	Expert opinion	100
For ER+ Male MBC tamoxifen is the preferred option.	Expert opinion	83
For male patients with MBC 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.	Expert opinion	86
Clinical trials are needed in this patient population.		
Specific sites of metastases		
Bone metastases		
Radiological assessments are required in patients with persistent and localized pain due to bone metastases to determine whether there are impending or actual pathological fractures. If a fracture of a long bone is likely or has occurred, an orthopaedic assessment is required as the treatment of choice may be surgical stabilization, which is generally followed by RT. In the absence of a clear fracture risk, RT is the treatment of choice.	1 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.	1 B	100
Brain metastases		
Patients with a single or small number of potentially resectable brain metastases should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases.	1 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.	1 B	72
Because patients with HER2+ve MBC and brain metastases can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to whole brain RT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).	1 C	89
Liver metastases		
Prospective randomized clinical trials of local therapy for BC 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…).	Expert opinion	83
Malignant pleural effusions		
Malignant pleural effusions require systemic treatment with/without local management. Thoracentesis for diagnosis should be performed if it is likely that this will change clinical management. False negative results are common. Drainage is recommended in patients with symptomatic, clinically significant pleural effusion. Use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful. Clinical trials evaluating the best technique are needed.	2 B	86
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.	Expert opinion	100
Chest wall and regional recurrences should be treated with surgical excision when feasible with limited risk of morbidity.	1 B	97
Locoregional radiotherapy is indicated for patients not previously irradiated.	1 B	97
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion	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-HER-2 therapy) should be considered.	1 B	95
CT after first local or regional recurrence improves long-term outcomes primarily in ER negative disease. ET in this setting improves long-term outcomes for ER positive disease.		

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Table 2 (*continued*)

Recommendations	LoE	% Consensus
The choice of systemic treatment depends on tumor biology, previous treatments, length of disease free interval, and patient-related factors (co-morbidities and preferences).		
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 BC.	Expert opinion	97
These patients may still be considered for palliative local therapy.		
Supportive and palliative care		
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.	1 A	100
Early introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.	1 A	100
Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.	1 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.	Expert opinion	96
ABC statements for LABC *(Note: For the purpose of these recommendations, LABC means inoperable, non-metastatic locally advanced breast cancer)*		
Before starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER-2, proliferation/grade) expression is indispensable to guide treatment decisions.	1 B	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 CT) and bone, prior to initiation of systemic therapy is highly recommended.	1 B	100
PET-CT, if available, may be used (instead of and not on top of CTs and bone scan).	2 B	100
Systemic therapy (not surgery or RT) should be the initial treatment.	Expert opinion	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.		
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and radiotherapy) is strongly indicated in the vast majority of cases.	1 A	100
For **Triple Negative LABC**, Anthracycline- and-taxane-based chemotherapy is recommended as initial treatment.	1 A	85
For **HER-2 + LABC**, concurrent taxane and anti-HER-2 therapy is recommended since it increases the rate of pCR.	1 A	92
For **HER-2 + LABC**, anthracycline-based chemotherapy should be incorporated in the treatment regimen.	1 A	72
When an anthracycline is given, it should be administered sequentially with the anti-HER-2 therapy.	1 A	87
Options for **HR + LABC** include an anthracycline- and taxane-based chemotherapy regimen, or endocrine therapy.	1 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.	Expert opinion	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.	2 B	98
Inflammatory LABC		
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment.	1 B	93
Mastectomy with axillary dissection is recommended in almost all cases, even when there is good response to primary systemic therapy.	I B	95
Immediate reconstruction is generally not recommended in patients with inflammatory LABC.	Expert opinion	95
Loco-regional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy.	1 B	98

ABC important definitions

Most clinical situations occur as a continuum and dividing them into categories of stage, grade, risk group, or other factors is always artificial and based on oversimplification of thresholds. Such a categorization is, however, useful to guide treatment choices, to help assure adherence to guidelines and recommendations, and to facilitate clinical research. Following the effort of previous editions, ABC provides two additional definitions: 'oligometastatic disease' discussed above and the complex clinical situation of 'multiple chronic conditions'. The latter is becoming increasingly important and more frequent in view of the aging of the population in general and of cancer patients in particular. Managing advanced cancer, the consequences of the disease and of the rapidly increasing number and type of pharmacologic and non-pharmacologic interventions in patients with several coexisting conditions is a major challenge. Furthermore, these patients are systematically excluded from clinical trials and hence available data, in particular regarding the use of new agents in these situations, are scarce and eagerly needed.

Section 3: HER-2 positive ABC.

Guideline statement	LoE	Consensus
Anti-HER-2 therapy should be offered early (as 1st line) to all patients with HER-2+ ABC, except in the presence of contra-indications to the use of such therapy	1 A	Voters: 43 Yes: 98% (42)
For highly selected patients* with ER+/HER-2+ MBC, for whom ET is chosen over CT, ET should be given in combination with anti-HER-2 therapy (either trastuzumab or lapatinib) since the combination provides PFS benefit (i.e. 'time without CT') compared to ET alone. The addition of anti-HER-2 therapy to ET in the 1st line setting has not led to a survival benefit but long-term follow-up was not collected in the available trials. In addition, this strategy is currently being directly compared with CT + anti-HER2 therapy. (*see definition in text)	1 A	Voters: 43 Yes: 72% (31) Abstain: 9% (4)

(*continued on next page*)

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(*continued*)

Guideline statement	LoE	Consensus
For patients with ER+/HER-2+ MBC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied in randomized trials.	1 C	Voters: 39 Yes: 79% (31) Abstain: 10% (4)
Patients progressing on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway. The optimal duration of anti-HER-2 therapy for MBC (i.e. when to stop these agents) is currently unknown.	1 B	Voters: 43 Yes: 91% (39) Abstain: 7% (3)
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.	Expert opinion	Voters: 42 Yes: 93% (39) No: 7% (3)
Patients who have received any type of (neo)adjuvant anti-HER-2 therapy should not be excluded from clinical trials for HER-2+ MBC. These patients remain candidates for anti-HER-2 therapies.	1 B	Voters: 40 Yes: 100%
In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting with DFI >12 months) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS.	1 A	Voters: 44 Yes: 95% (42) Abstain: 5% (2)
The standard 1st line therapy for patients previously untreated with anti-HER-2 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.	1 A	Voters: 42 Yes: 86% (36) Abstain: 12% (5)
For patients previously treated (in the (neo)adjuvant setting) with anti-HER-2 therapy, the combination of CT + trastuzumab and pertuzumab is an important option for 1st line therapy. Few (88) of these patients were treated in the Cleopatra trial and all with trastuzumab-free interval >12 months.	1 A	Voters: 41 Yes: 76% (31) Abstain: 22% (9)
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.	1 A (against its use)	Voters: 43 Yes: 86% (37) Abstain: 9% (4)
In a HER-2+ MBC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1st line.	Expert opinion	Voters: 37 Yes: 76% (28) Abstain: 16% (6)
After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd line (versus lapatinib + capecitabine) and beyond (versus treatment of physician's choice).	1 A	Voters: 42 Yes: 88% (37) Abstain: 129% (5)
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.		
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. There are however, no data on the use of this combination after progression on pertuzumab or T-DM1.	1 B	Voters: 43 Yes: 84% (36) Abstain: 12% (5)
All patients with HER-2+ MBC who relapse after adjuvant or any line metastatic anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications. The choice of the anti-HER-2 agent will depend on country-specific availability, the specific anti-HER-2 therapy previously administered, and the relapse free interval. The optimal sequence of all available anti-HER-2 therapies is currently unknown.	1 B	Voters: 40 Yes: 86% (36) Abstain: 12.5% (5)
Regarding the CT component of HER-2 positive MBC treatment:	1 A	Voters: 41 Yes: 88% (36) Abstain: 10% (4)
When pertuzumab is not given, 1st line regimens for HER-2 MBC can include trastuzumab combined with vinorelbine or a taxane. 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.		
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. The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.	2 A	Voters: 43 Yes: 91% (39) Abstain: 9% (4)
CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel (LoE: 1A) or paclitaxel (LoE: 1B). Also possible are vinorelbine (LoE: 2 A), nab-paclitaxel (LoE: 2B) and capecitabine (LoE: 2A).	See in statement	Voters: 43 Yes: 86% (37) Abstain: 11.6% (5)
HER-2 + ABC and brain metastases		
In patients with HER-2-positive ABC with brain metastases and stable extracranial disease, systemic therapy should not be changed.	1 C	Voters: 42 Yes: 95% (40) Abstain: 5% (2)
For patients with HER-2-positive cancers 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. It is recommended to re-start the anti-HER-2 therapy (trastuzumab) if this had been stopped.	1 C	Voters: 42 Y: 83% (35) A: 7% (3)

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement; ET, endocrine therapy; CT, chemotherapy; DFI, disease-free interval, CM, cyclophosphamide + methotrexate.

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HER-2 positive ABC

Among all breast cancer subtypes, HER2-positive ABC has had the largest progress over the last decade. The introduction of new anti-HER2 therapies, such as pertuzumab and T-DM1 [23–27], was a significant step forward but also created a number of new uncertainties related to optimal combination/sequence of all available treatments.

In view of the overall survival (OS) results obtained with most combinations of chemotherapy plus anti-HER-2 agents, the role of endocrine therapy plus anti-HER-2 agents for the subgroup of patients with ER+/HER-2+ disease has been questioned. Although published studies have not demonstrated an OS benefit of this combination, long-term data were not collected in these trials. Of note, the OS analysis of the TAnDEM trial, excluding patients who crossed over to trastuzumab, demonstrated a borderline OS benefit for the combination arm [28]. In the absence of valuable biomarkers, this approach should be reserved for highly selected patients, including those with contraindications to chemotherapy, patient's with a strong preference against chemotherapy or those with a long disease-free interval, minimal disease burden, in particular in terms of visceral involvement, and/or strong ER/PgR expression. Trials directly comparing chemotherapy plus anti-HER2 therapy versus endocrine therapy plus anti-HER2 therapy are currently ongoing (Detect V/CHEVENDO (NCT02344472), SYSUCC-002 (NCT01950182) and PERNETTA trials) and their results will allow for better recommendations. In addition, in several countries anti-HER2 therapy, namely trastuzumab, can only be used once in the metastatic setting since its use beyond progression is either not approved or not reimbursed; in those cases, preference should be given to a combination of chemotherapy plus anti-HER-2 therapy.

The combination of endocrine therapy plus anti-HER2 therapy is particularly useful as maintenance therapy for ER+/HER2+ ABC, after initial cycles of chemotherapy plus anti-HER-2 therapy. Despite the absence of randomized trials, clinical experience and low toxicity (in particular if trastuzumab is used), makes this a reasonable option, most probably delaying disease progression and the consequent need for chemotherapy.

The issue of duration of anti-HER-2 therapy in the metastatic setting is of crucial importance, in view of the potential benefits as well as the substantial costs associated with these agents. There are sufficient data [29,30] to recommend continuing trastuzumab beyond progression, but the optimal duration of this treatment and how many lines beyond progression should it be used is currently unknown. Data are very scarce related to the use beyond progression of other anti-HER2 agents and no data exist supporting the use of dual blockade beyond progression.

A particularly difficult situation, albeit also a fortunate one, relates to the optimal duration of trastuzumab therapy in patients achieving long-term complete remission. This needs to be balanced against toxicity, logistical burden and cost. Currently no data exist to support therapeutic decisions in this setting, and the panel supported a cautious statement approving consideration of stopping trastuzumab in these circumstances in some patients, particularly if treatment re-challenge is available in case of progression, which is not the case in all countries.

Dual blockade with trastuzumab and pertuzumab in combination with chemotherapy as 1st line therapy, provides substantial benefit in terms of OS and PFS [23]. It is therefore considered by the panel as the standard of care for patients previously untreated with trastuzumab, in the (neo)adjuvant setting, and an important treatment option for patients previously treated with trastuzumab. The difference in the strength of recommendation is due to the fact that very few patients (only 88) who were previously treated with trastuzumab were enrolled in the Cleopatra trial. In addition, in the Marianne trial [26] the dual blockade strategy did not prove to be superior to chemotherapy and trastuzumab, albeit with a different combination of agents—T-DM1 and Pertuzumab. The reasons for this lack of benefit are currently unknown and could be related to the different patient populations enrolled in both trials (more (30%) patients in Marianne had been previously treated with trastuzumab), the choice of agents with the presence or absence of synergistic effects, the absence of standard chemotherapy agents (DM1 being a cytotoxic agent not used as single agent) or other factors.

After the discussion and voting during ABC3, the Pherexa [27] study was presented, evaluating the role of dual blockade with trastuzumab + pertuzumab + capecitabine for patients previously treated with a taxane and trastuzumab in the metastatic setting. Surprisingly, a non-significant benefit of only 2 months was seen in the primary endpoint PFS, while an 8-month benefit was observed in OS albeit non-statistically significant (in view of the lack of significant PFS benefit).

Many questions remain unanswered in the management of HER-2 + ABC. We have no data on the role of dual blockade for patients relapsing during and within 12 months of adjuvant trastuzumab, since these patients have been excluded from clinical trials. This aggressive situation is a clear unmet need for which data must be generated. Following the approval, both by FDA and EMA, of pertuzumab use in the neoadjuvant setting, there is an urgent need to evaluate the best treatment options for the patients who relapse after receiving chemotherapy +trastuzumab+pertuzumab in the early setting. It is also currently unknown how trastuzumab + pertuzumab + chemotherapy compares to T-DM1, as 1st or later lines of therapy. We also have no data on the best treatment option after progression on dual blockade with pertuzumab+trastuzumab, namely how T-DM1 performs in this setting.

While trastuzumab + lapatinib (without chemotherapy) is a valuable option for some patients, after progression on chemotherapy + trastuzumab, there are no data on the use of this combination after progression on pertuzumab or T-DM1.

All these unanswered questions and the definition of the best sequence of therapies for the individual patient may prove difficult to evaluate in prospective, randomized trials, with the absence of specific biomarkers. In this scenario, registry studies, such as the SystHERs Registry Study [31] and registHER, as well as collection of treatment and outcome data beyond progression in all HER-2-positive ABC clinical trials, are of great importance.

In ABC3, the optimal chemotherapy component for the treatment of HER-2+ disease was discussed. The panel has stressed the importance of treatment decisions that are based not only on efficacy, but also on toxicity profile, and patients' preferences.

For 1st line therapy, when trastuzumab is used as sole anti-Her2 agent, the preferred agents are vinorelbine or a taxane. Importantly, single agent vinorelbine in association with trastuzumab has shown superior or equal efficacy compared to either paclitaxel or docetaxel, in the TRAVIOTA and HERNATA trials, and has a better tolerability [32,33]. For later lines of therapy, trastuzumab can be administered with almost all chemotherapy 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 (low dose, oral, cyclophosphamide and methotrexate). The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability. Combinations of other anti-HER2 agents, namely TKIs, with chemotherapy are more limited due to toxicity. There are currently no data to decide on the best sequence for each individual patient.

When dual blockade with trastuzumab and pertuzumab is used, possible agents to combine are docetaxel [23], weekly paclitaxel [34], vinorelbine [35] and nab-paclitaxel [36]. After the voting that took place in ABC3, the Pherexa trial [27], presented at ASCO 2016,

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provided some evidence regarding the combination of dual blockade with capecitabine.

new class of agents, the CDK4/6 inhibitors, in combination with an endocrine agent.

Section 4: ER positive/HER-2 negative (luminal) ABC.

Guideline statement	LoE	Consensus
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.	1 A	Voters: 41 Yes: 93% (38) Abstain: 7% (3)
The preferred 1st line ET for postmenopausal patients 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.	1 A	Voters: 44 Yes: 84% (37) Abstain: 7% (3)
The combination of a nonsteroidal AI and fulvestrant as first-line therapy for postmenopausal 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.	2 B	Voters: 43 Yes: 33% (14) No: 53% (23) Abstain: 14% (6)
The addition of everolimus to an AI is a valid option for some postmenopausal patients with disease progression after a non-steroidal AI, since it significantly prolongs PFS, albeit without OS benefit. The decision to treat must take into account the individual relevant toxicities associated with this combination and should be made on a case by case basis.	1 B	Voters: 40 Yes: 84% (34) Abstain: 13% (5)
Tamoxifen can also be combined with everolimus.	2 B	
The addition of the CDK4/6 inhibitor palbociclib to an aromatase inhibitor, as 1st line therapy, for postmenopausal patients (except patients relapsing <12 months from the end of adjuvant AI), provided a significant improvement in PFS (10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options, where available. OS results are still awaited.	1 A	Voters: 37 Yes: 92% (34) Abstain: 3% (1)
ESMO MCBS: 3*		
The addition of CDK4/6 inhibitor palbociclib to Fulvestrant, beyond 1st line therapy, for pre/peri/postmenopausal patients, provided significant improvement in PFS (~5 months) as well as improvement of QoL, and is a treatment option. OS results are awaited.	1 A	Voters: 42 Yes: 86% (36) Abstain: 10% (4)
For pre/peri-menopausal pts, an LHRH-agonist must also be used.		
At present, no predictive biomarker other than hormone receptor status exists to identify patients who will benefit from these type of agents and research efforts must continue.		
ESMO MCBS: 4*		
The optimal sequence of endocrine agents after 1st line ET is uncertain. It depends on which agents were used in the (neo)adjuvant and 1st line ABC settings. Available options include AI, tamoxifen, fulvestrant + palbociclib, AI + everolimus, tamoxifen + everolimus, fulvestrant, megestrol acetate and estradiol.	1 A	Voters: 40 Yes: 93% (37) Abstain: 5% (2)
It is currently unknown how the different combinations of endocrine + biological agents compare with each other, and with single agent CT. Several trials are ongoing.		
For pre-menopausal women, for whom ET was decided, ovarian suppression/ablation combined with additional endocrine therapy is the preferred choice.	1 B	Voters: 43 Yes: 93% (40) Abstain: 5% (2)
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.	Expert opinion	Voters: 43 Yes: 91% (39)
Patients should be informed on the options of OS/OA and decision should be made on a case by case.		Abstain: 7% (3)
For pre-menopausal women, the additional endocrine agent can be AI or tamoxifen, according to type and duration of prior adjuvant endocrine therapy but AI absolutely mandates the use of ovarian suppression/ablation.	1 B	Voters: 42 Y: 95% (40)
Fulvestrant is also a valuable option, but for the moment also mandates the use of ovarian suppression/ablation.	1 C	Abstain: 5% (2)

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement; ET, endocrine therapy; CT, chemotherapy; QoL, quality-of-life. ESMO MBCS = ESMO Magnitude of Clinical Benefit Scale; OS/OA, ovarian suppression/ovarian ablation; * = **very important explanation in text**.

ER positive/HER-2 negative (Luminal) ABC

One of the most important recommendations relates to the preferred treatment for luminal ABC, which should be endocrine therapy in the majority of cases, excluding those with visceral crisis and concern or proof of endocrine resistance. All breast cancer guidelines concur with this recommendation but unfortunately real life data studies show that most of these patients still receive chemotherapy as their first treatment, despite the lower efficacy [37].

Visceral crisis and endocrine resistance have been defined during ABC 2 and published [1]. However, better predictive factors are urgently needed to clearly identify those patients whose tumors have primary endocrine resistance and are responsible for the early and rapid progression seen in ~20–25% of luminal ABC patients treated with endocrine therapy [38]. Possible reasons may include ER loss [39] or ER mutations [40].

The most important advance in the management of luminal ABC over the last 2 years has undoubtedly been the introduction of a

The value of the CDK4/6 inhibitor palbociclib, combined with an aromatase inhibitor as 1st line therapy was evaluated initially in a randomized phase II study, the PALOMA 1 trial [41], which showed a substantial 10-month benefit in progression-free-survival (PFS) coupled with a favorable toxicity profile (main toxicity being neutropenia). Based on these results, FDA granted accelerated approval, which resulted in the drug being commercially available in USA. At the 2016 ASCO meeting, the phase III PALOMA 2 trial was presented and confirmed the 10-month benefit in PFS, with the main toxicities being hematological (mainly neutropenia) and fatigue [41]. OS results are still awaited. In view of these results, the initial statement developed at ABC3 was modified and re-voted by email and considers this option as one of the preferred treatment options, where available. Very recently (September 2016) EMA also started the approval process of Palbociclib. However, its approval/reimbursement in all individual countries is still pending and the issue of cost is of crucial importance for its implementation in clinical practice, as it is for many targeted agents namely anti-HER-2 agents.

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Beyond 1st line endocrine therapy, addition of palbociclib to fulvestrant resulted in significant albeit lower 5-month PFS prolongation in the PALOMA 3 phase III trial [42]. The quality of life substudy has shown both an overall improvement and a delayed deterioration of this important endpoint, with greater improvement in baseline pain, in the palbociclib arm [43]. Importantly, the PALOMA-3 study accrued both postmenopausal and pre/perimenopausal (in combination with ovarian function suppression) patients, allowing for assessment of the drug efficacy in a breast cancer population usually excluded from ABC endocrine therapy trials. OS results are still awaited. In view of available results, the ABC panel considers this as a treatment option, where available.

The ESMO Magnitude of Clinical Benefit Scale (MCBS) was calculated for the recently approved Palbociclib, for use in 1st line and in 2nd line. As a reminder, the MCBS scores a given treatment in a given setting, and based on published trials. At the time of publishing the ABC3 guidelines, PALOMA 2 main results and the accompanying quality of life substudy have been presented but not yet published. For this reason, the MCBS for the use of palbociclib in 1st line was calculated using the PALOMA 1 trial efficacy data, which scores a 3 for efficacy. Once the PALOMA 2 data is published the MCBS will be updated with an e-update made available through the ESMO guidelines website. For the use of palbociclib as 2nd line therapy, data from PALOMA 3, both efficacy and quality of life, were used. The MCBS was 3 for efficacy, and due to the improvement in quality of life upgraded to 4, which is the final score for this setting.

Another possible therapy is the combination of endocrine therapy with the mTOR inhibitor, everolimus. This combination has shown a PFS benefit of ~6 months, without a significant OS benefit, and with significant toxicity [44,45]. However, as with many agents, as more experience is gained regarding the use of everolimus and the management of its toxicities, its clinical use becomes easier. In addition, patient education is fundamental for prevention and early management of associated side effects. Of particular attention is the possibility of an excess mortality of this combination in elderly patients (>70 years of age) [44,46].

Currently, and in spite of intensive research, no predictive biomarker, other than hormone receptor status, exists to identify patients who will benefit the most from either m-TOR or CDK4-6 inhibitors and research efforts must continue.

The panel did not support (53.4% against) the 1st line combination of non-steroidal aromatase inhibitor and fulvestrant based on the results of the SWOG S0226 trial [47]. There may be a benefit for the minority of postmenopausal patients who are endocrine-naïve.

The definition of the best 1st line approach for postmenopausal patients will soon have additional data through the phase III FALCON data that will be presented this year.

The optimal sequence of single endocrine agents and combinations with targeted agents is currently unknown and is a research priority. It is crucial to collect data from clinical trials beyond progression to better understand the efficacy of each class of agent when given after the other (e.g. CDK4-6 inhibitors after m-TOR inhibitors and vice-versa).

Section 5: triple negative ABC.

Guideline statement	LoE	Consensus
For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations. Therefore, all CT recommendations for HER-2 negative disease also apply for triple negative ABC.	1 A	Voters: 44 Yes: 98% (43) Abstain: 2% (1)
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.	1 A	Voters: 43 Yes: 91% (39) Abstain: 5% (2)

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement; CT, chemotherapy.

Triple negative ABC

The treatment of triple-negative breast cancer (TN-ABC) still remains the largest unmet need within ABC. In spite of extensive research, no treatments apart from chemotherapy have so far proven to be effective for this population. For this reason, no specific recommendations can be made for this ABC subtype, with the possible exception of platinum compounds for BRCA-mutated patients.

Probably the largest achievement of the last 2 years was the TNT study, comparing 'standard' docetaxel to carboplatin in unselected TNBC patients (with pre-specified subgroup analysis of BRCA-mutation carriers). The superiority of carboplatin was demonstrated only among BRCA-positive patients, while in the unselected TN-ABC population docetaxel and carboplatin seem to have a similar efficacy [48], although the study was not designed as a non-inferiority study. Of note, in this study, 15% of patients had no prior adjuvant chemotherapy and only 35% had received (neo)adjuvant taxanes. Importantly, due to the significantly better toxicity profile of carboplatin, it remains an attractive treatment choice even for unselected TN-ABC patients. Unfortunately, other putative predictive factors of increased sensitivity to platinum, such as homologous recombination deficit (HRD) and the basal-like Prosigna PAM50 signature were not proven of value for making treatment decisions in this setting.

The future of TN-ABC treatment seems to lie in a better biological characterization of this breast cancer subtype into further subgroups, followed by the development of specific therapies for each of the subgroups. An example is the Luminal AR subtype, characterized by the expression of the androgen receptor; anti-androgens have recently demonstrated some activity and are being further evaluated, and where a potential predictive marker, the Predict AR assay, is also being tested [49,50].

Section 6: other recommendations.

Guideline statement	LoE	Consensus
Chemotherapy other		
Metronomic chemotherapy is a reasonable treatment option, for patients not requiring rapid tumor response. 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.	1 B	Voters: 43 Yes: 88% (38) Abstain: 5% (2)

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Guideline statement	LoE	Consensus
Even if given in the adjuvant setting, provided that 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 1 year of disease-free survival.	1 C	Voters: 44 Yes: 93% (41) Abstain: 5% (2)
BRCA-associated ABC		
In patients with **BRCA-associated** triple negative or endocrine-resistant MBC 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.	1 A	Voters: 44 Yes: 86% (38) Abstain: 9% (4)
In patients with TN or Luminal MBC, **genetic counseling and possibly BRCA testing** should be discussed with the patient, if the results can impact on treatment decisions and/or on clinical trials entry.	Expert opinion	Voters: 43 Yes: 91% (39) Abstain: 7% (3)
Bone metastases		
A **bone modifying agent** (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with MBC and bone metastases.	1 A	Voters: 44 Yes: 95% (42)
Three-monthly zolendronic acid seems to be not inferior to standard monthly schedule.	1 B	Abstain: 5% (2)
Supplementation of calcium and vitamin D3 is mandatory, unless contraindications exist.	1 C	
Other—biomarkers		
Multigene panels, such as those obtained using next generation sequencing (NGS) or other technology, regarding evolving molecular changes in ABC tumors has not yet proven beneficial in clinical trials, their impact on outcome remains undefined and should only be considered investigational.	1 C	Voters: 44 Yes: 95% (42) Abstain: 5% (2)

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement; MBC, metastatic breast cancer.

Other recommendations

Several options exist for chemotherapy both for first and subsequent lines of therapy. The ABC panel maintains that for patients pretreated with anthracyclines and taxanes the preferred agents, based on their efficacy and toxicity profile, are capecitabine, vinorelbine and eribulin. The latter is one of the few agents to provide a survival gain, albeit small (2.5 months) in a heavily pretreated population of ABC patients [51]. In a head-to-head comparison between eribulin and capecitabine, as first or second line therapy, there were no major differences between the drugs in efficacy but a different toxicity profile [52].

It is also possible to re-challenge with anthracyclines, particularly if there has been at least 1 year of disease-free survival, and if the cumulative dose has not been reached, a common situation nowadays because of the lower doses of anthracyclines used in the adjuvant setting. Re-challenge with taxanes is also possible, provided that there has been at least 1 year of disease-free survival.

Another very attractive option is the use of metronomic chemotherapy, defined as the use of low doses and short intervals, which has been evaluated in the advanced setting with interesting efficacy results and an excellent toxicity profile [53]. The best evaluated regimen is oral cyclophosphamide and oral methotrexate but other agents are being studied such as vinorelbine and capecitabine.

In view of the lack of substantial efficacy differences among the different available options, their toxicity profile must be discussed with the patient and her/his preferences taken into account.

ABC3 also further endorsed the use of bone-modifying agents (bisphosphonate, denosumab) in combination with calcium + vitamin D3 supplementation as a routine component of management of patients with bone metastases. Denosumab has demonstrated slightly better efficacy and better tolerability, compared to zoledronic acid [54], having the advantage of a subcutaneous route of administration and the disadvantage of a substantially higher cost in most countries; where available, it can be considered a preferred option. Currently available data support replacing routine 4 weekly administration of intravenous bisphosphonates by 3-monthly zoledronic acid after an initial period of monthly use [55,56]. Early 3-monthly use seems associated with increased need for major surgeries [57], so a reasonable compromise may be to start with the monthly schedule for the first year and then change to 3-monthly regimen. No data exist on the optimal overall treatment duration of bone modifying agents, and their efficacy must be weighed against long-term toxicity (such as osteonecrosis of the jaw and atypical fractures).

When a bone modifying agent is given, supplements of calcium and vitamin D are mandatory, except in the presence of contra-indications.

Unfortunately, no multigene testing technology has been proven to be beneficial in supporting treatment choices in ABC patients [18] and the panel strongly discourages their use in clinical practice. They should continue to be considered investigational.

Section 7: Supportive and palliative care.

Guideline statement	LoE	Consensus
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 etiology of this fatigue is complex so 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: 1 A) and if needed pharmacological interventions (LoE: 2 B).	As in the text	100%
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/il; dose reduction can also be considered.	2 A	100%
Management of Non-Infectious Pneumonitis (NIP) 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.	2 A	100%

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Guideline statement	LoE	Consensus
Management of MUCOSITIS/STOMATITIS		100%
Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis. Early intervention is recommended. For grade 2 or higher stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended. Consider adding steroid dental paste to treat developing ulcerations.	Expert opinion	
Steroid mouthwash can be used for prevention of stomatitis (suggested schedule: 0.5 mg/5 ml dexamethasone, 10 ml to swish × 2 min then spit out qid).	1 B	
Management of DYSPNEA	As in the text	100%
Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anemia or 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: 1 A). Benzodiazepines can be used in patients experiencing anxiety (LoE: 2A). 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).		
Management of NAUSEA and VOMITING	Expert opinion	100%
ESMO/MASCC GUIDELINES are available for management of chemotherapy-induced and morphine-induced nausea and vomiting, and these are endorsed by ABC3.		
There is a need to study nausea and vomiting related to chronic use of anticancer drugs.		
Management of endocrine toxicities of mTOR inhibition	2 A	100%
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 >500 mg/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. Treatment should be discontinued for grade 4 toxicity.		

LoE, available level of evidence; consensus, percentage of panel members in agreement with the statement; QoL, quality of life.
Note: The statements of this section were not voted during the ABC Consensus panel but were developed and agreed upon by email, by all panel members.

Supportive and palliative care

The ABC panel decided to dedicate several recommendations to the management of disease and treatment-related symptoms, a problem faced daily by patients and every practicing oncologist, that can significantly affect a patient's quality of life.

Unfortunately, little high-quality data exist in many areas of symptom management, probably due to difficulties in conducting research in this field, including the lack of well-defined endpoints, of patient-reported symptoms and side effects, and of optimal tools to evaluate impact on quality of life for advanced cancer patients. New classes of drugs introduced into breast cancer management have brought into the clinical practice new toxicities, poorly understood in the beginning and unfamiliar to most oncologists. Undoubtedly this is an area of unmet need, which should be a research priority.

The ABC3 guidelines provide guidance on the management of drug-induced pneumonitis, mucositis [58,59], endocrine and metabolic disorders and CDK4/6 inhibitor-related neutropenia. For nausea and vomiting ABC fully endorses the guidelines developed by ESMO/MASCC [60].

The ABC panel continues to discuss and provide guidance on the management of frequent and difficult to manage cancer-associated symptoms. In this edition, dyspnea and fatigue were discussed. Cancer related fatigue is frequently experienced by advanced cancer patients, exerts a deleterious impact on their quality of life and limits physical, functional, psychological and social well-being. Its etiology is complex and therefore effective management needs to be multidimensional [61–63]. It is important to assess cancer related fatigue using appropriate patient-reported outcome measures before implementing various pharmacological and non-pharmacological interventions. Randomized studies have suggested improvement of fatigue by various types of exercise quite convincingly [64], and meditation and some pharmacologic interventions are under evaluation. The use of good evidence-based algorithms for management of cancer related fatigue can also be helpful [65].

Conclusions

Since the ABC3 Conference two important initiatives have already been initiated.

The ESMO Magnitude of Clinical Benefit Scale (MCBS) [8] has been published and is being applied to all new anticancer treatments approved by EMA. The latest drug for which EMA started the approval process was Palbociclib in September 2016 and its MCBS evaluation is included in the present article. Should another agent be approved before the next ABC Consensus Conference, the ESMO Committees will apply the MCBS and the result will be made available as an e-update to the present guidelines.

Following on the success of the ABC Consensus Conference, the ABC community has come together to create the ABC Global Alliance. This Alliance will function as a platform where all involved partners (advocacy groups, pharma, cooperative groups, societies, individuals) will be able to work together, in projects designed to improve the lives of ABC patients. The Global Status of ABC Decade Report [2] has highlighted several areas of unmet needs. Based on these findings, a global Call-To-Action is being developed, with tangible objectives that need to be achieved within the next decade to meaningfully impact the outcomes of ABC patients.

Conflicts of interest statement

Faculty members were asked to disclose any potential conflict of interest in relation to their participation in the conference. Potential conflicts of interest are considered any of the following:

- Any financial interest in or arrangement with a company whose products or services are discussed in the lecture or that might be considered as part of the consensus process.
- Any financial interest in or arrangement with a competing company.
- Any other financial relationship, direct or indirect, or other situations that might raise the question of bias in the work

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presented or in the participation in the consensus process, including pertinent commercial or other sources of funding for the speaker or panellist or for the associated department or organisation, personal relationships or direct academic competition.

The full list of disclosures is published as an Appendix to this Consensus Statement.

Appendix. Supplementary Table S1. ABC3 panellists' disclosure of relationships with pharmaceutical industry.

Matti Aapro: Consultant for Abraxis, Amgen, BMS, Caris LifeSciences, Celgene, Eisai, Genomic Health, GSK, Helsinn, Hospira, Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Teva, Vifor and has received honoraria for lectures at symposia f Amgen, Astellas, Bayer Schering, Cephalon, Eisai, Ferring, Genomic Health, GSK, Helsinn, Hospira, Ispen, JnJ OrthoBiotech, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Teva, Vifor.

Fabrice Andre: No significant relationships.

Carlos H. Barrios: Receipt of grants/research supports: Amgen, Astra Zeneca, Boehringer-Ingelheim, GSK, Novrtis, Pfizer, Roche/Genentech, Eisai, Lilly, Sanofi-Aventis, Celgene and has received honoraria or consultation fees from: Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech.

Jonas Bergh: Receipt of grants/research supports paid to Karolinska Institute and University Hospital: Roche, Bayer, Sanofi-Aventis, Astra Zeneca, Pfizer, Merck, Amgen.

Gouri Shankar Bhattacharyya: No significant relationships.

Laura Biganzoli: No significant relationships.

Fatima Cardoso: Consultant for: Astellas/Medivation, Astra Zeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GSK, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre , Roche, Sanofi, Teva.

Maria-João Cardoso: No significant relationships.

Dian "CJ" M. Corneliussen-James: Receipt of honoraria for work for ABC.

Alberto Costa: No significant relationships.

Giuseppe Curigliano: No significant relationships.

Véronique Dieras: Receipt of honoraria or consultation fees: Roche, Genentech, Novartis, Eisai, Pfizer. Participation in a sponsored speakers' bureau: Roche, Pfizer.

Nagi S. El Saghir: Receipt of grants/research supports: GSK, Novartis, Roche. Receipt of honoraria or consultation fees: Lecture honoraria: Novartis, Roche, MSD, AstraZeneca, Celgene.

Alexandru Eniu: Receipt of grants/research supports: Astra Zeneca, Roche, Celltrion, Pfizer, Mylan.

Lesley Fallowfield: No significant relationships.

Doris Fenech: No significant relationships.

Patrick Flamen: Receipt of grants/research supports: Sirtex/Bayer, receipt of honoraria or consultation fees: Sirtex/Bayer.

Prudence A. Francis: Conference travel support from Roche and Amgen.

Karen Gelmon: Receipt of honoraria or consultation fees: Roche, Genetech, Astra Zeneca, Pfizer, Nanostring, Novartis.

Alessandra Gennari: Receipt of grants/research supports: Celgene/Teva, receipt of honoraria or consultation fees: Celgene, Teva, Eisai, Pierre Fabre, participation in a sponsored speakers' bureau: Celgene, Teva, Eisai.

Nadia Harbeck: Receipt of honoraria or consultation fees: Amgen, Astra Zeneca, Celgene, Novartis, Pfizer, Roche.

Clifford Hudis: No significant relationships.

Bella Kaufman: Receipt of honoraria: AstraZeneca, Novartis, Pfizer and Roche.

Ian E. Krop: Receipt of grants/research supports: Genentech/ Roche.

Musa Mayer: No significant relationships.

(*continued*)

Hanneke Meijer: No significant relationships.

Shirley A. Mertz: Receipt of honoraria or consultation fees: Pfizer.

Larry Norton: No significant relationships.

Shinji Ohno: No significant relationships.

Olivia Pagani: Participation in a sponsored speakers' bureau: Novartis, Celgene.

Evi Papadopoulos: No significant relationships.

Fedro A. Peccatori: No significant relationships.

Frédérique Penault-Llorca: No significant relationships.

Martine J. Piccart: Board Member: Radius; Consultant (honoraria): AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Crescendo Biologics, Roche, Periphagen, Huya, Debiopharm, PharmaMar, Radius. Research grants to my Institute: most of the companies cited above. Speakers bureau/stock ownership: none.

Jean-Yves Pierga: Receipt of grants/research supports: Roche, Jansen Diagnostics; receipt of honoraria or consultation fees: Roche, GSK, Novartis, Genomic Health, Astra-Zeneca; participation in a sponsored speakers' bureau: Roche, Novartis.

Hope S. Rugo: receipt of grants/research supports: GSK, Genentech/Roche, Novartis, Merck, Pfizer, Eisai, Macrogenics, Amgen, Biomarin, Plexxikon.

Elzbieta Senkus-Konefka: Receipt of honoraria or consultation fees: AstraZeneca, Pfizer, Pierre Fabre, Roche; travel expenses: AstraZeneca, Egis, Novartis, Pfizer, Roche.

Lille D. Shockney: No significant relationships.

George W. Sledge Jr.: Member Board of Directors: Syndax; member SAB: Symphogen.

Sandra Swain: Receipts of grants/research support to institution: Genentech/ Roche, Pfizer, PUMA, Lilly, Merrimack, BCRF. Receipt of honoraria or consultation fees: Genentech/Roche, Clinigen, AstraZeneca, Pfizer, Lilly, Pieris; non promotional speaking Genentech/Roche; spouse and self travel: Genentech/Roche.

Christoph Thomssen: Receipt of honoraria or consultation fees: Amgen, Astra Zeneca, Celgene, Janssen, Nanostring, Novartis, Pfizer, Roche, TEVA.

Andrew Tutt: Receipt of grants/research supports: Vertex, Astra Zeneca, Myriad Genetics, Roche; receipt of honoraria or consultation fees: Verte, Eisai; named on patent (King's College London) Genome Instability; rewards to Inventors Scheme Institute of Cancer Research ARP inhibitors BRCA1/2 Associated Cancers.

Daniel A. Vorobiof: No significant relationships.

Eric Winer: Receipt of grants/research supports: Genentech/Roche.

Binghe Xu: No significant relationships.

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