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Original article

1st International consensus guidelines for advanced breast cancer (ABC 1)

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A B S T R A C T

The 1st international Consensus Conference for Advanced Breast Cancer (ABC 1) took place on November 2011, in Lisbon. Consensus guidelines for the management of this disease were developed. This manuscript summarizes these international consensus guidelines.

Introduction

Women and men diagnosed with advanced breast cancer (ABC) face the double burden of an illness associated with significant

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symptoms and the knowledge that metastatic breast cancer (MBC) is ultimately incurable, although treatable. Feelings of abandonment and isolation are also frequent since these patients are too often forgotten by those involved in the fight against breast cancer, including health professionals, patient groups and the media.[1] ABC is a disease that challenges the knowledge, competence, creativity and emotions of every oncology provider.

In contrast to early stage disease, for which level 1 evidence exists for the majority of treatment options, there are few recognized therapeutic standards for ABC, particularly after 1st line treatment. While important advances have been made, the pace of change has been slow and the median overall survival for patients with MBC is still only 2–3 years, although the range is wide. For HER-2-positive ABC the development of anti-HER-2 agents has effectively led to a change in the natural history of this disease with a substantial improvement in survival. However, for triple negative ABC no significant improvement in survival has yet been achieved, and for ER-positive ABC, the most frequent subtype, overall survival has remained stable since the early nineties.[2–5] Additionally, each new therapeutic advance has led to a series of new questions, many of which unfortunately remain unanswered in the rush to move new therapies to the early disease setting.

Several international and national guidelines for early stage breast cancer exist and are widely used.[6–9] Implementation of these guidelines has been associated with a significant improvement in survival.[10–12] The landscape is markedly different for ABC and particularly MBC, where only national efforts have been made and no international consensus guidelines exist. Acknowledging the urgent need for an international accord in this field, the European School of Oncology (ESO) created an ABC Task Force in 2005, aiming to develop international consensus guidelines for the management of ABC that can be applied worldwide and also to identify areas where research/clinical trials are urgently needed. This task force has held public and interactive sessions during three consecutive European Breast Cancer Conferences, followed by the publication of manuscripts reviewing the available data and issuing the task force's recommendations on several issues.[13–15] This work also led to the establishment of the 1st International Consensus Guidelines Conference on ABC (ABC 1), held in November 2011.

The present manuscript summarizes the guidelines developed at ABC 1, providing the level of evidence and supporting references for each, and highlighting areas where research efforts are urgently needed. It is important to emphasize that the ABC 1 guidelines are intended to be management recommendations that can be applied internationally, albeit with the necessary adjustments for each country, based on the underlying principles of modern oncology, namely a multidisciplinary and individualized approach that respects the specificities of the advanced setting and each patient's preferences.

Methodology

Prior to the ABC 1 Conference, a set of preliminary recommendation statements on the treatment of ABC were prepared, building on the previous work of the ESO-ABC Task Force and subsequent clinical data, and in a coordinated effort with the ESMO guidelines methodology. These recommendations were circulated to all panel members by email for comments and corrections on content and wording. A final set of statements was presented, discussed and voted upon during the consensus session of ABC 1. 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., because it is not an area of expertise) instructed to "abstain" from voting. Additional changes in the wording of statements were made during the session. The available literature supporting each statement is provided as references.

Of note, ABC 1 focused primarily on metastatic breast cancer (MBC) while locally advanced breast cancer, the other component of advanced breast cancer (ABC) will be discussed in detail at ABC 2. Some of the recommendation statements apply to both locally advanced and metastatic breast cancer, while others are specific to the metastatic setting (Table 1).

Supplementary Table 1 lists all members of the ABC 1 consensus panel and their disclosure of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

General guidelines (Table 2)

The central role of a multidisciplinary approach to cancer treatment,[17,18] which developed towards the end of the 20th century, is one of the major achievements in oncology. The recognition that active cooperation amongst all health professionals involved in patient care leads to better treatment selection for each

Table 1
Levels of evidence grading system.[16]

Grade of Recommendation/ Description	Benefit vs. 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 2
General guideline.

Guideline statement	LoE	Consensus
1) 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, gynaecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.	Expert opinion	100% Yes (29 voters)
2) 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% Yes (30 voters)
3) 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 women 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.	Expert opinion	97% (29) Yes 3% (1) Abstain (30 voters)
4) 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% Yes (30 voters)
5) There are few proven standards of care in ABC management. After appropriate informed consent, inclusion of patients in well-designed, prospective, randomized trials must be a priority whenever such trials are available and the patient is willing to participate.	Expert opinion	100% Yes (30 voters)
6) 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 patient's preference should always guide decisions.	Expert opinion	100% Yes (32 voters)
7) Validated patient reported outcome measures provide useful information about symptom severity and the burden and the impact of these symptoms on overall quality of life. Systematic collection of such data should be integrated with other clinical assessments and form part of the decision-making about treatment and care.	Expert opinion	94% (30) Yes 3% (1) Abstain (32 voters)

Legend: MBC: metastatic breast cancer; LoE: available level of evidence; Consensus: percentage of panel members in agreement with the statement.

individual patient necessitated a change in mindset and required a reorganization of health services. A step forward has been the definition and establishment of specialized breast units.[19] These two milestones in breast care (multidisciplinary approach and breast units) although now routinely applied in the early breast cancer setting, are very often forgotten in the advanced setting. Patients with ABC, and even more so patients with MBC, are often treated outside of a multimodality program and may not have access to some of the specialized services that may be available for treatment of specific metastatic sites (e.g., bone).

In the past decades many new therapies have been developed and incorporated in the treatment of ABC and help to improve the overall outcome of this disease. However, very few have provided a survival benefit, particularly beyond the 1st line setting.[20,21] Although an overall survival (OS) benefit is undoubtedly the most desired outcome, this endpoint requires long follow-up and is potentially confounded by the effects of subsequent therapy. Progression free survival (PFS) has been the most widely used endpoint. However it cannot be considered a good surrogate for OS benefit in many circumstances.[22,23] In fact, no optimal surrogate for overall survival has yet been identified. The discussion regarding the merits of OS or PFS as the most adequate endpoint for the advanced setting is ongoing, along with the incorporation of validated quality of life measurements and patient-reported outcomes.[24–26] Composite endpoints, involving efficacy and toxicity measurements, seem to be a promising solution but additional research is still needed, particularly with regard to a clinically adequate assessment of toxicity and quality of life.

Assessment guidelines (Table 3)

A minimal staging workup for MBC should always include a thorough history and physical examination and haematology and biochemistry tests including liver function tests, renal function, electrolytes, calcium, total proteins and albumin. The panel also agreed that tumour markers (if initially elevated) are a useful aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease. While there was consensus that

Table 3
Assessment guidelines.

Guideline statement	LoE	Consensus
8) Minimal staging workup for MBC includes a history and physical examination, haematology and biochemistry tests, and imaging of chest, abdomen and bone.	2 C	67% (20) Yes 3% (1) Abstain (30 voters)
9) 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% (30) Yes (32 voters)
10) The clinical value of tumour 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 tumour markers alone should not be used to initiate a change in treatment.	2 C	89% (24) Yes 4% (1) Abstain (27 voters)
11) Evaluation of response to therapy should generally occur every 2–4 months for ET or after 2-4 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 symptoms appear. Thorough history and physical examination must always be performed.	Expert opinion	81% (25) Yes 10% (3) Abstain (31 voters)
12) 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.	2 C	96% (27) Yes (28 voters)
13) Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible.	2 C	90% (26) Yes 7% (2) Abstain (29 voters)
14) 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.	Expert opinion	87% (27) Yes 3% (1) Abstain (31 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; TNBC: triple negative breast cancer; PD: progressive disease; ET: endocrine therapy; HR: hormone receptors.

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this minimal staging should also include imaging of chest, abdomen and bone, there was greater disagreement regarding the optimal imaging modality. In many cases a chest X-ray, an abdominal ultrasound and a bone scan are sufficient. The level of evidence for these recommendations is only 2-C, since most studies have focused on the accuracy of imaging for detection of disease rather than evaluating whether inclusion of imaging as part of staging affects clinical outcomes.[27–30]

There was consensus that a PET-scan (Positron emission tomography scan) should not be part of the minimal staging workup but should be reserved for specific situations; for example when a relapse is suspected but not confirmed by the initial tests or to confirm possible oligo-metastatic disease.[31]

Importantly, there was strong consensus that routine brain imaging should not be performed in asymptomatic patients, even in patients with HER-2-positive or triple negative MBC, the two subtypes with the highest incidence of brain metastases. However, particularly among patients with HER-2-positive or triple negative MBC, careful evaluation of signs and symptoms is needed since clinical manifestations of brain metastases may sometimes be quite subtle. In the setting of suggestive signs or symptoms, a lower threshold to image such patients should be considered given the higher pre-test probability for CNS involvement.

Treatment general guidelines (Table 4)

A recent update of the recommendations of the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA)[32] summarizes available data and emphasizes the importance of not using age alone as a reason to withhold effective therapy.

Guidelines statements 17 and 18 were initially discussed during an interactive session at EBCC-6. At that meeting, available data were extensively reviewed and later published in one of the ESO-ABC Task Force recommendation papers.[15] All but one study published after this 2010 manuscript support the surgical removal of the primary tumour in patients with stage IV disease,[33–37] reinforcing the importance of the ongoing prospective trials evaluating this approach since existent data come almost exclusively from retrospective studies.

Treatment guidelines: ER-positive HER-2-negative ABC (Table 5)

There is strong evidence[38] and unanimous consensus among panellists that endocrine therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease requiring a fast response.

The Breast Health Global Initiative (BHGI) notes that many countries around the world still lack adequate pathology services and that ER is not routinely determined. The panel strongly agrees with the BHGI recommendation that ER determination by immunohistochemistry should be available even in low income countries for optimization of treatment selection.[39]

The panel also agreed that tamoxifen is an acceptable option for the first line treatment of postmenopausal women. This option is recommended for low- and middle- income countries.[40]

Table 4
Treatment general guidelines.

Guideline statement	LoE	Consensus
15) Treatment choice should take into account at least these factors: HR & HER-2 status; previous therapies and their toxicities; disease-free interval; tumour burden (defined as number and site of metastases); physiologic 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% Yes (30 voters)
16) The age of the patient should not be a reason to withhold effective therapy.	1 B	94% (28) Yes 3% (1) Abstain (30 voters)
17) A small but very important subset of patients with MBC, for example those with oligo-metastatic disease, can achieve complete remission and a long survival. A multimodal approach should be considered for these selected patients. A prospective clinical trial addressing this specific situation is needed.	Expert opinion	96% (25) Yes (26 voters)
18) The true value of the removal of the primary tumour in patients with stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease. Prospective clinical trials to confirm the value of this approach, the best candidates and timing are currently ongoing.	2 B	100% Yes (29 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; ET: endocrine therapy; HR: hormone receptors.

Table 5
ER +/HER-2 negative ABC.

Guideline statement	LoE	Consensus
19) Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, *even in the presence of visceral* disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response.	1 A	100% Yes (29 voters)
20) For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice.	1 A	97% (29) Yes (30 voters)
21) The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proven. An AI is also a viable option, but absolutely mandates the use of ovarian suppression/ablation.	1 B	97% (29) Yes (30 voters)
22) The preferred 1st line ET for postmenopausal patients is an aromatase inhibitor; however, tamoxifen remains a viable option in selected patients. Type and duration of adjuvant ET must be taken into account.	1 A	94% (29) Yes 6% (2) Abstain (32 voters)
23) Optimal post-aromatase inhibitor treatment is uncertain. Available options include, but are not limited to, tamoxifen, another AI (with a different mechanism of action), fulvestrant, and megestrol acetate.	1 A	97% (30) Yes 3% (1) Abstain (30 voters)
24) The addition of everolimus to an AI has shown favourable results in patients with acquired endocrine resistance when added to a non-steroidal AI. However, the majority of the panel believes that additional data/studies are needed before this strategy can be recommended as standard of care. At this time, everolimus is not approved for use in this setting by any regulatory authority.	Expert opinion	48% (15) Yes 13% (4) Abstain (31 voters)
25) Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been assessed in randomized trials	1 C	88% (28) Yes 9% (3) Abstain (32 voters)
26) Concomitant CT + ET has not shown a survival benefit and should not be performed outside a clinical trial.	1 B	100% Yes (30 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; ET: endocrine therapy; CT: chemotherapy; HR: hormone receptors; AI: aromatase inhibitor.

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Much discussion arose regarding the recommendation about the use of everolimus combined with an AI in clinical practice, following the very promising results of three trials presented during 2011.[41–43] 77% of the panel does not believe this combination should now be recommended for patients whose tumour has acquired resistance to non-steroidal AIs and 53% of panel members felt the combination should not be considered outside a clinical trial. The panel agreed that this statement can be revised once more mature PFS data and OS data become available from the above mentioned trials, and/or the drug gets marketing authorisation for use in this patient group. Importantly, taking into account the added toxicity, even in the event of marketing authorisation, this combination should be considered an option and not the only standard of care.

Treatment guidelines: HER-2-positive ABC (Table 6)

HER-2-positive MBC is probably the biological subtype for which highest level of evidence exists for the largest number of management issues. The recommendations for early administration of an anti-HER-2 agent to all patients with HER-2-positive ABC except in the presence of contra-indications,[44–47] for the combination of endocrine therapy and anti-HER-2 therapy for ER+/HER-2+ disease,[48,49] and for continuing blockade of the HER-2 pathway even upon progression on an anti-HER-2 agent,[50,51] are all supported by level 1 evidence.

Notwithstanding these advances, some questions remain open including the optimal duration of anti-HER-2 therapy (indefinitely?)[52] and the best treatment option at the time of progression on trastuzumab plus a cytotoxic agent (should only the cytotoxic drug be changed or both the cytotoxic and the anti-HER-2 agent?).

The role of the dual blockade with and without chemotherapy is a field of intense research with several options being evaluated. In the case of progression on trastuzumab, the combination of trastuzumab plus lapatinib has shown a survival benefit in heavily pretreated patients with MBC[53] and interesting efficacy has been seen in the neoadjuvant setting.[54] It is thus a reasonable treatment option for patients with MBC, although the relative efficacy of adding lapatinib or a different chemotherapeutic agent to trastuzumab has not been confirmed.

Newer agents are showing efficacy in phase III trials and will need to find their optimal place in the treatment paradigm. In the future, additional statements regarding specific anti-HER-2 therapies will be included as these agents are approved for treatment (e.g., pertuzumab, trastuzumab emtansine, etc).

Treatment guidelines: chemotherapy and biological therapy (other than anti-HER-2 agents) (Table 7)

Most available trials of cytotoxic agents for MBC were conducted in "all-comers", i.e., without a biologically-based patient selection. Additionally, almost all available data comes from an era when adjuvant taxane use was not yet standard and even anthracycline-based regimens were not always used. For these reasons, older trials are not readily applicable to the patient population seen in 2012. Despite these pitfalls, many important lessons were learned from these "older" studies. Furthermore, adjuvant therapy is not consistent everywhere in the world, and there are 1st line MBC patients not pre-treated with taxanes and, less commonly, neither taxanes nor anthracyclines. For these patients the conclusions from previous trials and meta-analyses are more applicable.

Randomized trials and meta-analyses have shown that: a) for taxane-naive and anthracycline-naive/minimally exposed patients, single agent anthracycline or single agent taxane yield similar results; b) for taxane-naive and anthracycline-resistant/refractory patients, single agent taxane leads to better outcomes than single agent anthracycline; c) combinations of anthracyclines and taxanes in the metastatic setting consistently lead to higher response rates (RR), sometimes higher time-to progression (TTP) or PFS, higher toxicity, but very rarely to better OS. Caution must be used when evaluating these studies since many lack sufficient power to draw definite conclusions and most did not have a planned crossover, which renders the application of results to clinical practice difficult. Importantly, a meta-analysis of individual patient data[55] provides sufficient power to conclude that, for patients with ABC not previously exposed to adjuvant taxanes, these agents do not improve survival when compared with anthracyclines, either as single agents or in anthracycline combinations, and that combinations of taxanes with anthracyclines modestly improve RR and PFS but not OS. Additionally, patient preferences must always be

Table 6
HER-2-positive ABC.

Guideline statement	LoE	Consensus
27) Anti-HER-2 therapy should be offered early to all patients with HER-2+ MBC, except in the presence of contra-indications to the use of such therapy.	1 A	91% (30) Yes 3% (1) Abstain (33 voters)
28) For patients with ER+/HER-2+ MBC for whom ET was chosen over CT, anti-HER-2 therapy + ET should be considered with the initiation of endocrine therapy (provided that further anti-HER-2 therapy is available) since anti-HER-2 therapy (either trastuzumab or lapatinib) in combination with ET has shown substantial PFS benefit (i.e., "time without CT") compared to ET alone. The addition of anti-HER2 therapy in this setting has not led to a survival benefit.	1 A	90% (27) Yes 10% (3) Abstain (30 voters)
29) 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	97% (29) Yes (30 voters)
30) It is currently unknown if the best option for patients progressing after receiving one line of trastuzumab + cytotoxic agent is to continue trastuzumab in conjunction with another cytotoxic agent or to change to lapatinib in combination with capecitabine. Therefore, both options are viable.	1 A	90% (26) Yes 10% (3) Abstain (29 voters)
31) In patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy, the best option remains unclear, but all such patients should be considered for further anti-HER-2 therapy. The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy that was administered, and the relapse free interval.	1 B	85% (23) Yes 15% (4) Abstain (27 voters)
32) Patients who have received any type of (neo)adjuvant anti-HER-2 therapy should not be excluded from clinical trials for HER-2+ MBC.	1 B	100% Yes (27 voters)
33) In case of progression on trastuzumab, the combination trastuzumab + lapatinib is a reasonable treatment option.	1 B	83% (24) Yes 10% (3) Abstain (29 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; ET: endocrine therapy; CT: chemotherapy; HR: hormone receptors.

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Table 7
Chemotherapy and biological therapy.

Guideline statement	LoE	Consensus
34) 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% (25) Yes 4% (1) Abstain (26 voters)
35) In the absence of medical contra-indications 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 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% (17) Yes 4% (1) Abstain (24 voters)
36) In patients with taxane-naive and anthracycline-resistant MBC or with anthracycline 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% (14) Yes 8% (2) Abstain (24 voters)
37) In patients pre-treated with anthracycline and taxanes (in the adjuvant or metastatic setting) and who do not need combination CT, capecitabine single agent is the preferred choice.	1 B	56% (15) Yes 11% (3) Abstain (27 voters)
38) 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.	1 A	92% (22) Yes 8% (1) Abstain (24 voters)
39) Duration of each regimen and number of regimens should be tailored to each individual patient.	Expert opinion	96% (26) Yes (27 voters)
40) Usually each regimen should be given until progression of disease or unacceptable toxicity (unacceptable should be defined together with the patient).	1 B	72% (21) Yes 7% (2) Abstain (29 voters)
41) Bevacizumab combined with a taxane as 1st 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 and it is a research priority. Bevacizumab can only therefore be considered as an option in selected cases.	1 A	74% (17) Yes 17% (4) Abstain (23 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; CT: chemotherapy; OS: overall survival; PFS: progression-free survival.

taken into account since other options are available and effective such as capecitabine[56] and vinorelbine, particularly when avoiding alopecia is a priority for the patient.

In the current era, a new type of 1st line MBC population is emerging – taxane pretreated but anthracycline-naive/minimally exposed, for whom thoughtfully designed randomized trials with pre-planned crossover are needed. For patients pretreated with both anthracyclines and taxanes, the most consistent data concerns capecitabine use. Vinorelbine has been compared head-to-head with docetaxel, both in association with trastuzumab in HER-2-positive breast cancer, and yielded similar efficacy and significantly less toxicity.[57] There are data supporting the re-challenge with taxanes as 1st line therapy, when the disease-free interval has been at least one year. However, given the wealth of other available options and toxicity concerns, this is a less appealing option. Re-challenge has also been shown to be valuable with other cytotoxic drugs.

The important issue of the use of combinations of cytotoxic agents versus their sequential use as monotherapy (guideline statement 34) was discussed during an interactive session at EBCC-6, extensively reviewed and published in one of the ESO-ABC Task Force recommendation papers,[14] and supported by a recent Cochrane review update.[58]

There are no data to support an optimal sequence of therapies and very few agents as monotherapy[56,59] have demonstrated an OS benefit in the metastatic setting. The duration of each regimen and number of regimens should be tailored to each individual patient, as well as the decision of when to stop active anti-cancer therapy.[21,60–63] A meta-analysis of published trials[64] concluded that longer 1st line chemotherapy duration is associated with a marginally longer OS and a substantially longer PFS, and proposes that this therapy is prescribed until progression or unacceptable toxicity. A strong and unanimous recommendation from the panel is that every agent and regimen used does not necessarily need regulatory approval but must be evidence-based, with proven efficacy and acceptable toxicity, the latter evaluated from the patient (and not only the physician) perspective.

The extent of the benefits seen in the initial trials of bevacizumab in combination with a taxane were not confirmed in other trials.[65–67] All of these results taken together and a recent meta-analysis[68] led to the conclusion that the benefits of bevacizumab in ABC are moderate and limited to PFS, with no benefits in overall survival. These data have been interpreted differently on either side of the Atlantic, with the FDA withdrawing its earlier "accelerated approval" for bevacizumab as a treatment for MBC whilst EMA has so far retained approval for bevacizumab in combination with a taxane, as 1st line therapy for MBC and even extended the indication to include the combination with capecitabine in this setting. These contradictory decisions, on the basis of the same data, are a source of confusion both for clinicians and patients, and could be avoided through better coordination between regulatory agencies, in collaboration with breast cancer experts. The identification of validated predictive biomarkers to select the patients who derive a significant benefit from this agent is therefore a research priority.

Treatment guidelines: bone and brain metastases (Table 8)

The routine use of a bone modifying agent (bisphosphonate or denosumab) in combination with other systemic therapy in patients with MBC and bone metastases is supported by level 1-A evidence and included in other international recommendations[69–72] and by the ABC 1 panellists. Usually these agents should be started early, if possible before the onset of any bone symptoms, and in principle should be continued even in the presence of overall disease progression. In the situation of an isolated bone lesion the optimal timing and duration of bone modifying agent treatment is less clear.

The panel recognises the difficulty in evaluating bone metastases and particularly of measuring response/progression in some patients with bone only disease.[27,29,73–80]

While there is level 1 evidence for the radiotherapeutic treatment of choice for painful bone metastases[81] and for the management of spinal cord compression,[82,83] better evidence is needed regarding the optimal management of bone metastases in long bones, especially when there is radiological evidence of a fracture.[84,85] A multi-disciplinary discussion including pain control experts, radiation oncologists, medical oncologists, surgeons specialized in bone treatment and radiologists with expertise in vertebroplasty/kyphoplasty, is crucial to establish the best therapeutic approach for each individual patient.

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Table 8
Bone and brain metastases.

Guideline statement	LoE	Consensus
42) 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	96% (26) Yes 4% (1) Abstain (27 voters)
43) 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% (23) Yes 4% (1) Abstain (24 voters)
44) 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 (neurosurgery or orthopaedic surgery) opinion may be required for surgical decompression. If no decompression/stabilization is feasible, emergency radiotherapy is the treatment of choice.	1 B	100% Yes (24 voters)
45) 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.	1 B	92% (22) Yes 4% (1) Abstain (24 voters)
46) 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% (18) Yes 16% (4) Abstain (25 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; RT: radiotherapy.

Brain metastases are a relatively frequent event in patients with HER-2-positive and triple negative ABC[86]. However, the outcome for these patients is quite different according to the biological subtype. In patients with triple negative MBC, brain metastases usually occur earlier in the course of the disease and are associated with a dismal outcome, also due to the lack of control of extracranial disease. Typically, in patients with HER-2-positive MBC, brain metastases appear later in the course of the disease. Patients who respond to anti-HER-2-based therapy and have controlled extracranial disease, can live several years after the diagnosis and treatment of brain metastases.

In recent years, with the development of several radiosurgical techniques, less toxic treatment approaches can be provided to selected patients. Patients with a single or a small number of potentially resectable brain metastases should be treated with surgery or radiosurgery.[87–92] Radiosurgery is a feasible option in some patients with unresectable metastases. If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control with the risk of neurocognitive effects.[93–96]

For all cases where a more localized therapy approach is not possible, whole brain radiotherapy is the treatment of choice.

A multi-disciplinary discussion including neurosurgeons, radiation oncologists and medical oncologists is indispensable in determining the optimal treatment for each patient. The treatment plan can also be a combination of these three available therapeutic approaches.

Supportive and palliative care guidelines (Table 9)

The role of supportive and expert palliative care, particularly symptom control, in the treatment of advanced cancer is crucial and supported by extensive evidence.[97–100] Of major concern is the access to an effective pain treatment including adequate access to morphine, which is not occurring in several countries, particularly those with low and middle income levels.[101,102] Pain treatment agents, including morphine and its derivates, are very cost-effective and crucial for the management of this major cancer related symptom. A lack of access to these medications is considered unethical.

Guidelines for metastatic male breast cancer (Table 10)

Male breast cancer is a rare disease accounting for about 1% of all breast cancers and 1% of all cancers in men. Male breast cancer may be disproportionately associated with germline BRCA mutations.[103,104] Advanced male breast cancer is an even rarer entity.

Table 9
Supportive and palliative care.

Guideline statement	LoE	Consensus
47) Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.	1 A	100% Yes (26 voters)
48) Expert palliative care, including effective control of pain and other symptoms, should be a priority.	1 A	100% Yes (26 voters)
49) Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.	1 A	100% yes (27 voters)
50) 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% (25) Yes 4% (1) Abstain (26 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; RT: radiotherapy.

Table 10
Metastatic male breast cancer.

Guideline statement	LoE	Consensus
51) 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% Yes (25 voters)
52) For ER + Male MBC tamoxifen is the preferred option.	Expert opinion	83% (15) Yes 6% (1) Abstain (18 voters)
53) For Male patients with MBC needing to receive an AI a concomitant LHRH agonist or orchiectomy is necessary.	Expert opinion	58% (14) Yes 29% (7) Abstain (24 voters)

Legend: MBC: metastatic breast cancer; LoE: Available level of evidence; Consensus: Percentage of panel members in agreement with the statement; ET: endocrine therapy.

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There are no randomized clinical trials for this disease, with almost all data coming from retrospective series of patients. Treatment strategies are extrapolated from female breast cancer, without the full knowledge whether they are the most appropriate.[105,106] A greater awareness about this disease has been raised in recent years, among the patient advocacy groups and general population as well as within the scientific community. Some studies seem to indicate the existence of important differences in the biology of male and female breast cancer. The International Male Breast Cancer Program has been created to better understand the biology of this disease and determine the best therapeutic approaches.[105] This project, together with other important initiatives such as the Male Breast Cancer Consortium,[107] will hopefully generate the needed higher level of evidence for management recommendations for male breast cancer.

One of the most controversial issues relates to the use of AIs in male patients with breast cancer. Animal models and studies in healthy male volunteers have shown that aromatase inhibition in men induces a lower reduction of oestrogen levels than in women (50–70% depending on the agent used vs. 98% in women) while also significantly increasing circulating levels of follicle-stimulating hormone and testosterone.[108–111] Importantly, about 20% of circulating oestrogen in men is produced by the testis and is not influenced by the use of AIs. Although there are some reports of responses with AIs alone in advanced male breast cancer,[112] the majority of the panel believes that when AIs are used in male patients with breast cancer they should be combined with an LHRH agonist since the increase in testosterone seen after aromatase inhibition may overcome oestrogen blockade. This combination can be effective even in cases refractory to AIs.[113]

Conclusions

The treatment of MBC is complex and must take into account multiple, disease-related factors, both clinical and biological, as well as patient-related factors. It is also deeply influenced by the lack of high-level evidence in many situations and by the incurable nature of the disease in virtually all cases. To complicate matters further, MBC is a "moving target," for several reasons. Adjuvant breast cancer therapy has changed substantially over the last decades leading to changes in the MBC population with regard to previous treatments and related resistance mechanisms, which frequently make even fairly recent trial results difficult to apply to all patients.

A strong commitment on the part of all involved parties, (academia, the pharmaceutical industry, independent funding sources, advocacy groups) is urgently needed to develop well designed, high quality trials in the advanced setting to address the many unanswered questions, both strategy-related and optimal drug use-related (including best dose, schedule, and predictive markers). This is important even after a new therapy has moved to the adjuvant setting. Only then will the elusive high level of evidence be obtained for ABC management issues.

Notwithstanding what still needs to be investigated, if research efforts are not matched by educational efforts, improvement in the outcome of patients with ABC will continue to be too slow, lagging behind what has been achieved in the early setting. Optimal implementation of available knowledge will undoubtedly lead to improved overall survival and quality of life for these patients. The development of the ABC international consensus guidelines has been a major step forward but will only bear fruit if these recommendations are correctly implemented in clinical practice. It is now the responsibility of clinicians to use them and we call on patient advocates and patients to demand their widespread use.

Appendix. Supplementary Table 1: Panellists' disclosure of relationships with pharmaceutical industry

Matti Aapro – Division of Oncology, Institut Multidisciplinaire d'Oncologie, Genolier, CH. Abraxis, Amgen, AstraZeneca, Bayer Schering, Bristol Myers, Celgene, Cephalon, GSK, Helsinn, Hospira, Johnson and Johnson, Ortho Biotech, Merck, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, Sandoz, Schering, Sanofi-Aventis, Vifor: speakers bureau, consultant, research support.

Jonas Bergh – Department of Oncology-Pathology, Karolinska Institute, Stockholm, SE. Affibodies, Amgen, AstraZeneca, 13 Innovus, GSK, Onyx, Pfizer, Sanofi-Aventis, Tapestry: consultant or advisory role. All payments made to Asklepios Medicine (none to Prof. J. Bergh). Sanofi-Aventis, Amgen, Merck: research support. All payments made to Karolinska University Hospital (none to Prof. J. Bergh).

#David A. Cameron – University of Edinburgh and NHS Lothian, Western General Hospital, Edinburgh, UK. Roche, GSK, Pfizer: consultant or advisory board member and travel support. Roche: speakers bureau, consultancy, travel support and research support. Pfizer: research support. Sanofi-Aventis: consultant or advisory board member. Amgen: research support and consultant.

#Fatima Cardoso – Breast Cancer Unit, Champalimaud Cancer Center, Lisbon, PT. GSK: speakers bureau, consultant, travel support. Roche: speakers bureau, consultant, research support, travel support. Eisai: speakers bureau, consultant, travel support. Pfizer: speakers bureau, consultant, travel support. Novartis: speakers bureau, consultant, research support, travel support. AstraZeneca: speakers bureau consultant, research support, travel support. Johnson and Johnson: consultant, research support, travel support. Sanofi-Aventis: speakers bureau, consultant, travel support. Wilex: consultant. Bristol–Myers-Squibb: consultant, travel support. Abraxis/Celgene: consultant.

#Alberto Costa – Director, European School of Oncology, Milan, IT and Bellinzona, CH. No significant relationships.

#Tanja Cufer – University Clinic Golnik, SL. No significant relationships.

Angelo Di Leo – Ospedale Misericordia e Dolce, Prato, IT. AstraZeneca, GSK, Pfizer, Roche, Sanofi-Aventisi, Cephalon: consultant, honoraria. AstraZeneca, GSK: research support.

Nagi El Saghir – NK Basile Cancer Institute Breast Center of Excellence, American University of Beirut Medical Center, Beirut, LB: Roche, GSK: speakers bureau, research support, travel support. Novartis: research support, travel support. Sanofi-Aventis: research support.

#Lesley Fallowfield – Brighton & Sussex Medical School, University of Sussex, Falmer, UK. No significant relationships.

#Prudence Francis – Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, AU. Amgen, Sanofi-Aventis: travel support. Roche: honorarium.

Patricia A. Ganz – Division of Cancer Prevention & Control Research, Jonsson Comprehensive Cancer Center, Los Angeles, US. No significant relationships.

Karen Gelmon – BC Cancer Agency, Vancouver, CA. Roche: consultant. GSK: research support: AstraZeneca: consultant. Amgen: consultant.

#Joseph Gligorov – CancerEst APHP Tenon, University Paris VI, Francilian Breast Intergroup Paris, FR. Roche, Sanofi-Aventis and Eisai: Consultant or advisory board member. Roche and Novartis: Research support. Roche and Novartis: speaker's bureau. GSK, Sanofi, Roche: travel support.

Aron Goldhirsch – Department of Medicine, European Institute of Oncology, Milan IT. Novartis, GSK: speakers bureau. Pfizer: travel support.

Nadia Harbeck – Breast Center, University of Cologne, Cologne, DE. Roche: speakers bureau, consultant, research support. Sanofi-Aventis: speakers bureau, consultant. Amgen, Novartis, GSK: speakers bureau. AstraZeneca, Eisai: consultant.

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Nehmat Houssami – Screening and Test Evaluation Program, School of Public Health, Sydney Medical School, University of Sydney, Sydney, AU. No significant relationships.

Clifford A. Hudis – Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York US. No significant relationships.

Bella Kaufman – Sheba Medical Center, Tel Hashomer, Israel, IL. Roche: speakers bureau, GSK: Consultant or advisory board member, Janssen-Cilag: Travel support

Ian E. Krop – Breast Oncology Center, Dana-Farber Cancer Institute, Boston, US. Genentech/Roche: Research support, Novartis: Consultant or advisory board member

#Stella Kyriakides – Europa Donna Cyprus, Nicosia, CY. No significant relationships.

Maria Leadbeater – Breast Cancer Care, London, UK. No significant relationships.

#Nancy U. Lin – Breast Oncology Center, Dana-Farber Cancer Institute, Boston, US. Genentech, GSK, Boehringer Ingelheim, Bayer: research support

Musa Mayer – AdvancedBC.org, New York, US. No significant relationships.

Larry Norton – Breast Cancer Programs, Memorial Sloan-Kettering Cancer Centre, New York, US. No significant relationships.

#Olivia Pagani – Oncology Institute of Southern Switzerland and Breast Unit of Southern Switzerland, Bellinzona, CH. No significant relationships.

Alan Rodger – Radiotherapy Specialty Editor, The Breast, UK. No significant relationships.

Hope S. Rugo – Department of Medicine, Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, US. Genomic: consultant. Genentech/Roche, Merck, Novartis, BMS, Celgene, Sanofi/Bipar, Lilly/Imclone: research support to UCSF.

Virgilio Sacchini – Breast Service, Memorial Sloan-Kettering Cancer Center, New York, US. No significant relationships.

#Elzbieta Senkus-Konefka -Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, PL. Roche: travel support. Glaxo SmithKline: speakers bureau, travel support. AstraZeneca: advisory board member, speakers bureau. Sanofi Aventis: speakers bureau, travel support. Pfizer: travel support.

George W. Sledge – Indiana University Medical CTR, Indianapolis, US. No significant relationships.

#Christoph Thomssen – Clinic for Gynaecology, Martin-Luther-Universität, Klinikum Kröllwitz, Halle (Saale), DE. Amgen, AstraZeneca and Pfizer: speakers bureau, consultant or advisory board member, travel support. Celgene: consultant or advisory board member and travel support. Eisai: consultant or advisory board member. Glaxo (GSK), Roche: speakers bureau and consultant or advisory board member. Novartis, Sanofi: speakers bureau, consultant or advisory board member and research support.

Laura van't Veer – Breast Oncology Program, University of California – Helen Diller Family Comprehensive Cancer Center, San Francisco, US. Agendia NV: Stock royalty or equity ownership and employment.

Giuseppe Viale – Department of Pathology and Laboratory Medicine, European Institute of Oncology, Milan IT. No significant relationships.

#Eric P. Winer – Breast Oncology Center, Dana-Farber Cancer Institute, Boston, US. Novartis: honorarium for one meeting.

Legend: # = Members of the ESO-ABC Task Force

Conflict of interest statement

See Supplementary Table 1.

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