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ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

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introduction

Advanced breast cancer (ABC) is a treatable but still generally incurable disease. The goals of care are to optimize both length and quality of life. Due to continuous research, several advances have been made, particularly for the human epidermal growth factor receptor 2 (HER-2)-positive and for luminal-like subtypes. Notwithstanding these advances, median overall survival of patients with ABC is still only 2–3 years, although the range is wide [1–5], and survival may be longer for patients treated in specialized institutions [6]. Implementation of current knowledge is highly variable among countries and within each country.

The use of treatment guidelines has been associated with a significant improvement in survival [7–9]. This has been achieved mainly in early breast cancer. For ABC, and particularly metastatic breast cancer (MBC), less level 1 evidence exists and only recently has international consensus guidelines been developed (ABC1) [10]. The ABC Consensus Conference was created by the European School of Oncology (ESO) with the ambitious goal of improving outcomes for all patients with ABC. Backed by strong political advocacy, ABC guidelines are seeking to improve standards of care, to raise awareness about how to best meet to the needs of this underserved group of patients, and to identify research priorities, so that clinical research is focused on the most important areas of unmet need.

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Following the work of the ESO-ABC Task Force [11–14], created in 2005, and the successful undertaking of the 1st International Consensus Guidelines Conference on ABC (ABC1), held in November 2011, the 2nd International Consensus Conference for Advanced Breast Cancer (ABC2) took place in Lisbon, Portugal, on 7–9 November 2013. The conference brought together about 1100 participants from 71 countries, including health professionals, patient advocates, and journalists. A series of guidelines were discussed and agreed upon, based on the most up-to-date evidence, and can be used to guide treatment decision-making in diverse health-care settings globally. These guidelines are developed as a joint effort from ESO and ESMO (European Society of Medical Oncology), are endorsed by EUSOMA (European Society of Breast Cancer Specialists), SIS (Senologic International Society), and Flam (Federación Latino Americana de Mastologia), and organized under the auspices of UICC (Union Internationale Contre Le Cancer), OECI (Organization of European Cancer Institutes), and the BCRF (Breast Cancer Research Foundation).

The present study summarizes the guidelines developed at ABC2. The guidelines include the level of evidence, the percentage of panel members who agreed with the consensus statements, and the supporting references for each recommendation. Importantly, the ABC guidelines are developed as clinical management recommendations potentially applicable worldwide, albeit with the necessary adjustments for each country, depending on access to therapies. The guidelines are based on the underlying principles of modern oncology, emphasizing the crucial role of a multidisciplinary and individualized approach that respects the specificities of the advanced setting and the preferences of each patient. The manuscript also clearly highlights areas where research efforts are urgently needed.

methodology

Prior to the ABC2 Conference, a set of preliminary recommendation statements on the treatment of ABC were prepared, based on available published data and following the ESMO guidelines methodology. These recommendations were circulated to all 43 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 ABC2. 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 their area of expertise) instructed to 'abstain' from voting. Additional changes in the wording of statements were made during the session. The statement on everolimus was updated after the presentation of the overall survival results of the BOLERO-2 trial and re-voted by email by all panel members.

Supplementary Table S1, available at *Annals of Oncology* online, lists all members of the ABC2 consensus panel and their disclosure of any relationships that could be perceived as a potential conflict of interest.

Table 1 describes the grading system used [15].

Three main issues were discussed at ABC2: inoperable locally advanced breast cancer (LABC), both inflammatory and non-inflammatory; MBC; and specific definitions for which a consensus was deemed important.

For clarification, ABC comprises both LABC and MBC or stage IV. Some of the ABC guidelines apply to both LABC and MBC, while others are specific to each of the settings.

Table 1. Levels of evidence grading system [15]

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	randomized clinical trials (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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I. general guidelines

Guideline statement	LoE	Consensus
All ABC patients should be offered comprehensive, culturally sensitive, up-to-date, and easy to understand information about their disease and its management.	IB	97.2% (36) yes 0% (0) abstain (37 voters)
Specialized oncology nurses (if possible specialized breast nurses) should be part of the multidisciplinary team managing ABC patients. In some countries, this role may be played by a physician assistant or other trained and specialized health-care practitioner.	Expert opinion	92.1% (35) yes 7.8% (3) abstain (38 voters)
Strong consideration should be given to the use of validated instruments for patients to report the symptoms of disease and side-effects of treatment they experience as a regular part of their clinical care. These patient-reported outcome (PRO) instruments should be simple and user-friendly to facilitate their use in clinical practice. This systematic monitoring will serve to facilitate communication between patients and their treatment teams, allow optimal quality of life, and may better characterize the toxicities of all anticancer therapies.	IC	89.4% (34) yes 5.2% (2) abstain (38 voters)
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 type and intensity of treatment.	IB	100% (38) yes 0% (0) abstain (38 voters)

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

ABC1 guidelines had already emphasized the importance of including the patient in all steps of the decision-making process [10]. For active and informed participation, patients must have access to comprehensive, culturally sensitive, up-to-date, and easy to understand information about their disease and its management.

A 'patient navigator' can help the patient going through all phases of the cancer journey [16–20]. This is particularly relevant for advanced cancer patients who are often overwhelmed with difficult decisions to make, through complex information and available treatment options, and are frequently co-managed by the breast cancer and the palliative care teams. This role is best taken by a specialized breast nurse, or at least a specialized oncology nurse, who should be part of the multidisciplinary team managing ABC patients. In some countries, however, this role may be played by a physician assistant or another trained and specialized health-care practitioner. It is also recognized that, in many centres, it is not yet possible for each patient to have a navigator due to the lack of human resources.

There is an implicit assumption that the recording of adverse events by clinicians reliably documents patients' side-effects and symptoms. However, there is an accumulating body of evidence suggesting that the frequency and severity of many symptoms that impact on an individual patient's quality of life go under-reported, under-recognized, and consequently under-treated [21]. Since quality of life is one of the main aims of ABC treatment, this poses an important problem. It is also potentially dangerous from a drug safety point of view. The inability of traditional methods for capturing adverse events has led to renewed interest in incorporating patient-reported outcomes (PROs/PROMs) with Common Terminology Criteria for Adverse Events (CTC-AEs) in clinical trials, as well as utilizing PROs outside a clinical trial setting to reflect and monitor more accurately the harms and benefits of patient experience. This may be particularly important for drugs approved based solely on progression-free survival (PFS) benefits or only modest overall survival (OS) benefits, for which the balance between efficacy and toxicity may be more difficult to accurately determine. Many standardized, well-validated instruments or PRO measures are available with translations into most languages. The most frequently used are the generic EORTC-QLQ-C3 (http://groups.eortc.be/qol/eortc-qlq-c30) and the FACT (http://www.facit.org/FACITOrg/Questionnaires). Both have breast cancer-specific modules/subscales (EORTC QLQ-BR23 and FACT-B) and the FACT, in particular, has several other specific subscales covering, for example, treatment with epidermal growth factor receptor (EGFR) inhibitors, taxanes, anti-angiogenesis drugs, endocrine agents, and monoclonal antibodies. Recently, the FDA and EMA have published guidance for industry on how to utilize PROs in applications for drug labelling claims. There has also been an important initiative, funded by the NCI, to produce a PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which is suggested for use in NCI-sponsored trials (http://outcomes.cancer.gov/tools/pro-ctcae.html).

Although age is an important factor to consider in decision-making for ABC, it must not be the sole factor to determine the intensity and type of treatment. There is a tendency to withhold therapy in some elderly patients because of fear of toxicity or concern about co-morbidity. In some cases, however, such therapies may be highly effective and could improve both survival and quality of life. At the same time, younger patients are often overtreated or treated somewhat inappropriately. Age may influence breast cancer treatment, but it should not be the guiding force [10, 22–24].

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'Survivorship' in ABC

The complex needs of patients living with ABC, at times for many years, as well as their caregivers, should be addressed not only in terms of supportive and palliative care but also regarding 'survivorship' concerns. The multidisciplinary approach of ABC should encompass early in the history of the disease not only physical, but also functional, social, psychological, and spiritual, domains [25–27].

It is important to clearly define the disease context with patients and families, addressing the concept of uncertainty and tailoring the treatment strategy according to individual priorities and disease status [28]. Specific psychosocial needs of young and elderly patients should also be recognized and supported, i.e. social security, job flexibility, rehabilitation, body image (including sexuality), home, and child care.

II. important ABC-related definitions

Guideline statements	LoE	Consensus
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	95.0% (38) yes 5.0% (2) abstain (40 voters)
Primary endocrine resistance is defined as: a relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of first-line ET for MBC, while on ET ***Secondary (acquired) endocrine resistance*** is defined as: a relapse while on adjuvant ET but after the first 2 years, or a relapse within 12 months of completing adjuvant ET, or PD ≥6 months after initiating ET for MBC, while on ET.	Expert opinion	66.6% (22) Yes 21.2% (7) abstain (33 voters)

LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; ET: endocrine therapy; PD: progressive disease; MBC: metastatic breast cancer.

Current terminology uses several ill-defined terms that often have different meanings, leading to confusion and difficulty in adapting clinical trial findings to current practice populations.

The ABC2 panel tried to define two of these important terms, aiming at standardization of their use.

Regarding endocrine resistance, an attempt was made to be consistent with a definition reached by a number of investigators involved in breast cancer clinical trials, at a meeting sponsored by NCI held in May 2012 and later approved by the North American Breast Cancer Groups (NABCGs).

It is also important to note that endocrine resistance is a continuum, and that strict definitions are mainly helpful for the clinical trial setting and not necessarily for routine clinical practice.

III. inoperable locally advanced, non-inflammatory, breast cancer

Guideline statements	LoE	Consensus
Before starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER-2, and proliferation/grade) expression is indispensable to guide treatment decisions.	IB	97.2% (36) yes 2.7% (1) abstain (37 voters)
Since LABC patients have a significant risk of metastatic disease, a full staging workup, including a complete history, physical examination, laboratory tests, and imaging of chest and abdomen (preferably CT scans) and bone, prior to initiation of systemic therapy, is highly recommended.	IB	100% (37) yes 0% (0) abstain (37 voters)
PET–CT, if available, may be used (instead of and not on top of CT scans and bone scan).	IIB	100% (37) yes 0% (0) abstain (37 voters)
Systemic therapy (not surgery or radiotherapy) should be the initial treatment. 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.	Expert opinion	100% (40) yes 0% (0) abstain (40 voters)
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery, and radiotherapy) is strongly	IA	100% (39) yes 0% (0) abstain (39 voters)

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Guideline statements	LoE	Consensus
indicated in the vast majority of cases.		
For *triple-negative LABC*, anthracycline- and taxane-based chemotherapy is recommended as an initial treatment.	IA	85.3% (35) yes 9.7% (4) abstain (41 voters)
For *HER-2-positive LABC*, concurrent taxane and anti-HER-2 therapy is recommended since it increases the rate of pathological complete response (pCR).	IA	91.8% (34) yes 5.4% (2) abstain (37 voters)
For *HER-2-positive LABC*, anthracycline-based chemotherapy should be incorporated into the treatment regimen.	IA	71.7% (28) yes 12.8% (5) abstain (39 voters)
In *HER-2-positive LABC*, when an anthracycline is given, it should be administered sequentially with the anti-HER-2 therapy.	IA	86.8% (33) yes 10.5% (4) abstain (38 voters)
Options for *hormonal receptor-positive LABC* include an anthracycline- and taxane-based chemotherapy regimen, or endocrine therapy. The choice of chemotherapy versus endocrine therapy, as an initial treatment, will depend on tumour (grade, biomarker expression) and patient (menopausal status, performance status, comorbidities, preference) considerations.	IA	85.3% (35) yes 9.7% (4) abstain (41 voters)
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.	IIB	97.5% (39) yes 0% abstain (40 voters)

LABC: locally advanced breast cancer; LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy.

IV. inoperable, locally advanced inflammatory, breast cancer

Guideline statements	LoE	Consensus
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as a first treatment.	IB	92.6% (38) yes 4.8% (2) abstain (41 voters)
Mastectomy with axillary dissection is recommended in almost all cases, even when there is a good response to primary systemic therapy.	IB	95.1% (39) yes 4.8% (2) abstain (41 voters)
Immediate reconstruction is generally not recommended in patients with inflammatory LABC.	Expert opinion	94.7% (36) yes 2.6% (1) abstain (38 voters)
Locoregional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy.	IB	97.5% (39) yes 2.5% (1) abstain (40 voters)

MBC: metastatic breast cancer; LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; pCR: pathological complete remission.

LABC occurs at first presentation in about one-fifth of breast cancer patients worldwide, with lower incidence in countries with established screening programmes but as high as 60% in some other countries [29]. Usually, the definition of LABC includes large operable primary breast tumours (stage IIB, IIIA) and/or those involving the skin or chest wall and/or those with extensive lymphadenopathies (stage IIIB, IIIC) [30]. For the purpose of ABC guidelines, we define LABC as inoperable locally advanced disease that has not yet spread to distant sites.

Inoperable LABC is a heterogeneous designation encompassing a range of clinical situations from neglected low-grade ER-positive breast cancers to rapidly progressing usually ER-negative disease [30–33].

A more homogenous form of LABC is inflammatory breast cancer (IBC), a distinct clinic–pathologic entity. IBC has a greater association with younger age at diagnosis, higher tumour grade, and negative estrogen receptor (ER) status.

The first steps in the management of this disease are a core biopsy to provide histology and biomarker assessment (including ER, PR, HER-2, and proliferation/grade), and a full staging workup. Due to a relatively high risk of distant metastases [34], thoracic and abdominal CT scans are preferred to thorax X-ray

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and liver ultrasound, and a PET–CT is also an acceptable option [34].

A multimodality approach is key for locoregional control and survival, including systemic therapies, surgery, and radiation.

The type of systemic therapy is similar to the one used in the (neo)adjuvant setting, with anthracycline and taxanes as the backbone of the chemotherapy regimes. For HER-2-positive LABC, anthracyclines should not be administered concurrently with trastuzumab since this approach does not increase the pCR rate, and it could increase the risk of cardiac toxicity, based largely on studies in the metastatic setting [35, 36].

For luminal-like LABC, initial treatment options include chemotherapy (with sequential anthracyclines and taxanes) and endocrine therapy, depending on tumour (grade, biomarker expression) and patient characteristics (menopausal status, performance status, comorbidities) and preferences. A number of studies have demonstrated significant activity of endocrine therapy, particularly in luminal A-like disease [37–40]. Data presented after ABC2 strongly suggest that this subset of breast cancer, especially lobular histology, is less sensitive to chemotherapy (at least in terms of pCR rate) [41]. Very few data exist on primary endocrine therapy in premenopausal women [42] and, therefore, it cannot be recommended outside of clinical trials.

Primary systemic therapy in inoperable LABC allows breast-conserving surgery in variable percentages depending on tumour/patient characteristics [43]. Mastectomy remains the only option before or after radiotherapy for those patients not amenable to breast conservation and for all patients with IBC [44]. For the time being, axillary dissection is still standard of care in inoperable LABC [45].

As for all other stages of breast cancer, decision-making at a multidisciplinary tumour board is highly recommended.

V. specific ABC populations

Guideline statements	LoE	Consensus
In patients with ***BRCA-associated triple-negative or endocrine-resistant MBC*** previously treated with an anthracycline and a taxane (in the adjuvant or metastatic setting), a platinum regimen may be considered, if the patient is not included in a clinical trial. All other treatment recommendations are similar to sporadic MBC.	IC	82.5% (33) yes 12.5% (5) abstain (40 voters)
For ***male patients with ABC*** who need to receive an aromatase inhibitor, a concomitant LHRH agonist or orchiectomy is the preferred option. Aromatase inhibitor monotherapy may also be considered, with close monitoring of response. Clinical trials are needed in this patient population.	Expert opinion	86.1% (31) yes 11.1% (4) abstain (36 voters)

Continued

MBC: metastatic breast cancer; LHRH: luteinizing-hormone–releasing hormone; LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement.

As predicted by their DNA-damaging mechanism of action, platinum compounds are expected to be particularly active in tumours deficient of mechanisms responsible for DNA damage repair, e.g. those without active BRCA1/2 proteins. Due to rarity of such patients, little evidence exists on the clinical activity of these drugs in BRCA1/2 mutation carriers in the metastatic setting. However, available data suggest their promising activity mostly in the neoadjuvant setting [46, 47], and to a lesser degree in advanced disease [48].

In triple-negative breast cancer (TNBC), another putatively BRCA-deficient population, a relatively large amount of data from prospective studies, recently summarized in a meta-analysis, demonstrated improved pCR rates in patients whose neoadjuvant treatment included a platinum compound [49–51]. However, which patients definitely benefit is not yet clear since there is also one negative GEICAM study adding carboplatin to epidoxorubicin–cyclophosphamide-docetaxel in basal-like breast cancer [52]. Fewer data exist for inclusion of platinum in the treatment of metastatic disease, although the benefit in the TNBC population seems to be larger than in other breast cancer patients [53].

Taking available evidence into account, most of the ABC2 panel supported the inclusion of platinum-containing regimens in the treatment of BRCA1/2 mutant patients pre-treated with anthracyclines and taxanes and demonstrated to be endocrine-resistant.

ABC1-issued several recommendations for the treatment of male patients with ABC [10] that still remain valid for ABC2 (Table 2). One additional recommendation is added at this point, related to the use of aromatase inhibitors in this patient population.

There are concerns about the efficacy of these agents when used in monotherapy in male patients, due to the hypothalamic–pituitary negative feedback.

Important differences exist in the physiology of estrogen production between men and women. In men, 80% of circulating estrogens result from the peripheral aromatization of androgens, whereas 20% are directly secreted in the testicles [54–56]. Adrenals secrete <1% of circulating sex steroids, but precursors can undergo peripheral aromatization. So, peripheral conversion results in <5% of all testosterone, 80% of all dihydrotestosterone and estradiol, and nearly all of estrone (98%) [56, 57]. Additionally, estradiol levels are 3–4 times higher in older males than in postmenopausal females.

For these reasons, and despite the lack of prospective and randomized data, the majority of panel members recommend that

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when an aromatase inhibitor needs to be used in male ABC patients, a concomitant luteinizing-hormone–releasing hormone agonist or orchiectomy should be added to further down-regulate testicular function.

VI. specific sites of metastases

Guideline statements	LoE	Consensus
Prospective randomized clinical trials of local therapy for breast cancer ***liver metastases*** are urgently needed, since available evidence comes only from series in highly selected patients. Since there are no randomized data supporting the effect of local therapy on survival, every patient must be informed of this when discussing a potential local therapy technique. Local therapy should only be proposed in very selected cases of good performance status, with limited liver involvement, no extra-hepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic RT, intra-hepatic CT, or other).	Expert opinion	83.3% (25) yes 16.6% (5) (30 voters)
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. The 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.	IIB	86.4% (32) yes 10.8% (4) abstain (37 voters)
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% (38) yes 0% (0) abstain (38 voters)
Chest wall and regional recurrences should be treated with surgical excision when feasible with a limited risk of morbidity.	IB	97.3% (37) yes 2.6% (1) abstain (38 voters)
Locoregional radiotherapy is indicated for patients not previously irradiated.	IB	97.3% (37) Yes 2.6% (1) abstain (38 voters)
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion	97.3% (37) yes 2.6% (1) abstain (38 voters)
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. 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. The choice of systemic treatment depends on tumour biology, previous treatments, length of disease-free interval, and patient-related factors (co-morbidities, preferences, etc.).	IB	94.8% (37) yes 5.1% (2) abstain (39 voters)
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. These patients may still be considered for palliative local therapy.	Expert opinion	97.3% (37) yes 2.6% (1) abstain (38 voters)

MBC: metastatic breast cancer; LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; CT: chemotherapy; RT: radiotherapy; ET: endocrine therapy.

Due to the lack of prospective randomized data for the management of liver metastases from breast cancer, and the existence of several locoregional techniques, local therapy of liver metastases should only be considered in highly selected patients. Each case should be discussed with a multidisciplinary tumour board, before a decision is made. Inclusion in a clinical trial, when available, is considered the best option.

When breast cancer recurs only on the chest wall after mastectomy, the use of intensive local–regional therapy should be

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considered. Therapy can include surgical excision alone, surgical excision followed by radiation therapy, radiation therapy alone (when surgical excision is not feasible), or concurrent chemotherapy and radiation. Complete surgical resection reduces the total required dose of radiation therapy and also maximizes the likelihood of long-term disease control. Complete excision alone can lead to a 5-year disease-free survival rate of 35% [58]. Complete resection followed by locoregional radiotherapy results in a 5-year local–regional control ranging from 60% to 77% [59, 60]. Long-term predictors of disease-free survival after a local–regional recurrence include a disease-free interval of >24 months and a complete excision [59].

With modern radiotherapy techniques, it is often possible to re-irradiate with full dose without too many side-effects [61]. The first results of retreatment with stereotactic body radiotherapy techniques have been published recently, describing promising local control rates [62].

Concurrent chemoradiation has both preclinical rationale and clinical efficacy in many solid tumour types. Potential mechanisms of chemotherapy and radiotherapy interactions include increasing radiation damage, inhibition of DNA repair processes, enhanced activity against hypoxic and radioresistant cells, and prevention of regrowth of tumour after radiation [63]. In patients who have received prior radiation, chemoradiation can be considered, as the residual tumour should be considered radioresistant unless combined with a potentiating agent, provided that the patient is judged a candidate and can tolerate additional radiation therapy. Agents having shown potential synergy with radiation include platinum analogues [64], antimetabolites, [65–67], and taxanes [68]. Several novel therapeutics are also being studied in the trial setting in combination with radiation, including EGFR inhibitors [69], HER-2 inhibitors [70], and poly (ADP-ribose) polymerase inhibitors [71]. Patients who have residual isolated local–regional recurrence after attempted resection, or minimal systemic disease, might derive benefit from consideration of this multimodality approach.

Hyperthermia has a proven benefit for the treatment of superficial malignancies, acting as a radiosensitizer. Trials evaluating the role of hyperthermia in combination with radiotherapy in patients with chest wall recurrences have shown a significant improvement in complete response rates with the addition of hyperthermia, especially in previously irradiated patients (e.g. complete response: 24%–31% in the no-hyperthermia arm versus 57%–68% in the hyperthermia arm) [72, 73]. However, there was no difference in survival between the two treatment arms. Recent studies have analysed the combination of radiotherapy, hyperthermia, and concurrent chemotherapy in this patient population [74].

Finally, systemic therapy (both endocrine and chemotherapy) has been shown to benefit patients after complete resection of a first locoregional isolated recurrence [75, 76]. The CALOR study [76], a randomized phase 3 study, allocated to 162 patients to either physician's choice chemotherapy or no chemotherapy. The use of chemotherapy after surgery resulted in a significant reduction in systemic recurrence (hazard ratio, HR 0.59; $P = 0.046$). In the subgroup of patients with ER-negative tumours, there was also a significant improvement in survival. This study provides important data in support of use of systemic chemotherapy after surgical resection of isolated locoregional recurrence of ER-negative breast cancer.

VII. update on ER-positive/ HER-2-negative ABC

Guideline statements	LoE	Consensus
The preferred first-line ET for postmenopausal patients is an aromatase inhibitor or tamoxifen, depending on the type and duration of adjuvant ET.	IA	83.3% (30) yes 16.6% (6) abstain (36 voters)
Fulvestrant HD is also an option.	IB	83.3% (30) yes 16.6% (6) abstain (36 voters)
The addition of everolimus to an aromatase inhibitor is a valid option for some postmenopausal patients with disease progression after a non-steroidal aromatase inhibitor, since it significantly prolongs PFS by a median interval of 5 months. There is a survival prolongation of similar magnitude (4.4 months), although this difference is not statistically significant. The decision to treat must take into account the relevant toxicities associated with this combination and should be made on a case-by-case basis. At present, no predictive biomarker exists to identify those patients who will benefit from this approach.	IB	100% yes (30 voters)

LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; ET: endocrine therapy; PFS: progression-free survival.

ABC2 reinforces the ABC1 recommendations for ER-positive/HER-2-negative ABC regarding the preferential use of endocrine therapy, even in the presence of visceral metastases. Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine resistance. Most ABC1 recommendations remain unchanged (see Table 2). The two changes refer to the preferred first-line endocrine therapy for postmenopausal women and the use of everolimus.

The preferred first-line endocrine therapy for postmenopausal women depends on the type and duration of adjuvant endocrine therapy. Available data support the use of an aromatase inhibitor, tamoxifen, or fulvestrant HD (i.e. 500 mg, every 4 weeks) [77–88]. Fulvestrant HD is well tolerated and numerically associated with a 4.1-month difference in median OS compared with fulvestrant 250 mg [80]. Only the lower, less-efficacious dose was compared to aromatase inhibitors and found to have similar efficacy; so far, no data directly comparing fulvestrant HD with an aromatase inhibitor exist.

Endocrine resistance is a common and important clinical problem. It may be primary or secondary (see above ABC definitions). The main identified mechanisms of endocrine resistance are related to ESR alterations (mutations, amplifications, or

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translocations), and upregulation of alternative pathways, such as the HER growth factor pathways and the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway.

The mTOR inhibitor everolimus when added to exemestane, in patients progressing on non-steroidal aromatase inhibitor, provided a significant PFS prolongation of about 5 months [89, 90]. The overall survival data, presented after ABC2, demonstrated a non-significant 4-month increase in median survival (HR 0.89) [91]. Overall survival prolongation was also observed, in an exploratory analysis of the randomized phase II TAMRAD study comparing the combination of tamoxifen and everolimus to tamoxifen alone in aromatase inhibitor (AI)-resistant patients [92]. These benefits must be weighed against relevant toxicities associated with this compound, particularly stomatitis, pneumonitis, and hyperglycaemia. Decisions on everolimus use must thus be made on a case-by-case basis, after discussion with a well-informed patient, and administered by physicians experienced in managing adverse effects of this compound.

VIII. update on HER-2-positive ABC

Guideline statements	LoE	Consensus
In the first-line setting, for HER-2 + MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS.	IA	84.6% (33) yes 10.2% (4) abstain (39 voters)
In first-line therapy, the combination of CT + trastuzumab and pertuzumab is superior to CT + trastuzumab, primarily for previously untreated HER-2 + MBC, making it the preferred treatment option since it is associated with an OS benefit. It is currently unknown how this treatment compares with other anti-HER-2 options such as T-DM1.	IA	89.7% (35) yes 10.2% (4) abstain (39 voters)
There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab associated with CT beyond the first line, after treatment with trastuzumab + pertuzumab + CT in the first line (i.e. continuing dual blockade beyond progression) and, therefore, this three drug regimen should not be given beyond the first line outside clinical trials.		85.0% (34) yes 12.5% (5) abstain (40 voters)
In a HER-2 + MBC patient previously untreated with pertuzumab, it is acceptable to use pertuzumab beyond the first line.	IIC	43.7% (14) yes 21.8% (7) abstain (32 voters)
After first-line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the second line (versus lapatinib + capecitabine) and beyond (versus treatment of physician's choice). T-DM1 should be preferred in patients who have progressed through at least one line of trastuzumab-based therapy, since it provides an OS benefit.	IA	89.7% (35) yes 10.2% (4) abstain (39 voters)
All patients with HER-2 + MBC who relapse after adjuvant 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.	IB	87.5% (35) yes 12.5% (5) abstain (40 voters)
Because patients with HER-2-positive 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).	IC	89.1% (33) yes 10.8% (4) abstain (37 voters)

MBC: metastatic breast cancer; LoE: available level of evidence; consensus: percentage of panel members in agreement with the statement; CT: chemotherapy, RT: radiotherapy; T-DM1: trastuzumab emtansine.

In the last 2 years, several trials in HER-2-positive ABC have been reported, which led to an update on several ABC1 recommendations regarding this specific subtype.

Evidence from three trials, two in advanced and one in early breast cancer, supports the recommendation that combinations of chemotherapy with trastuzumab are superior to chemotherapy and lapatinib.

The MA.31 trial [93] randomly compared taxanes plus trastuzumab (weekly paclitaxel or three weekly docetaxel) or the same taxane plus lapatinib, as the first-line treatment of 636 HER-2-positive MBC patients, a substantial percentage of whom had *de novo* MBC. With a median follow-up of 13.6 months, the taxane–lapatinib arm had inferior PFS compared with the taxane–trastuzumab (8.8 versus 11.4 months). There was no difference in OS and toxicity was significantly higher in the lapatinib arm.

The CEREBEL trial [94] compared lapatinib plus capecitabine with trastuzumab plus capecitabine, as first-line therapy for HER-2-positive MBC with no evidence of central nervous system (CNS) disease. The primary end point was incidence of CNS metastases as a first site of relapse. With a planned population of 475 patients, the study was terminated at the time of the interim analysis due to a low number of CNS events (3% and

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Table 2. Advanced breast cancer (ABC)1 statements [10] with minor update or with no update

	LoE	Consensus
General recommendations		
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% (29) yes 0% (0) abstain (29 voters)
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% (30) yes 0% (0) abstain (30 voters)
Following a thorough assessment and confirmation of metastatic breast cancer (MBC), the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances). This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.	Expert opinion	97% (29) yes 3% (1) abstain (30 voters)
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, and support network).	Expert opinion	100% (30) yes 0% (0) abstain (30 voters)
There are few proven standards of care in ABC management. After appropriate informed consent, inclusion of patients in well-designed, prospective, randomized independent trials must be a priority whenever such trials are available and the patient is willing to participate.	Expert opinion	100% (30) yes 0% (0) abstain (30 voters)
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% (32) yes 0% (0) abstain (32 voters)
Assessment guidelines		
Minimal staging workup for MBC includes a history and physical examination, haematology and biochemistry tests, and imaging of chest, abdomen, and bone.	2C	67% (20) yes 3% (1) abstain (30 voters)
Brain imaging should not be routinely carried out in asymptomatic patients. This approach is applicable to all patients with MBC including those patients with HER-2+ and/or triple-negative breast cancer MBC.	Expert opinion	94% (30) yes 0% abstain (32 voters)
The clinical value of tumour 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 tumour markers *alone* should not be used to initiate a change in treatment.	2C	89% (24) yes 4% (1) abstain (27 voters)
Evaluation of response to therapy should generally occur every 2–4 months for endocrine therapy (ET) or after two to four cycles for chemotherapy (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 carried out in a timely manner, irrespective of the planned intervals, if progressive disease is suspected or new symptoms appear. Thorough history and physical examination must always be performed.	Expert opinion	81% (25) yes 10% (3) abstain (31 voters)
A biopsy (preferably providing histology) of a metastatic lesion should be carried out, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.	1C[a]	96% (27) yes 0% (0) abstain (28 voters)

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Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible.	2C	90% (26) yes 7% (2) abstain (29 voters)
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)
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 the 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, socioeconomic and psychological factors, available therapies in the patient's country and patient preference.	Expert opinion	100% (30) yes 0% (0) abstain (30 voters)
A small but very important subset of patients with MBC, for example those with oligometastatic 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 0% abstain (26 voters)
ER+/HER-2-negative ABC		
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.	IA	100% (29) yes 0% (0) abstain (29 voters)
For premenopausal women, ovarian suppression/ablation combined with additional ET is the first choice.	IA	97% (29) yes 0% (0) abstain (30 voters)
The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proved. An aromatase inhibitor is also a viable option, but absolutely mandates the use of ovarian suppression/ablation. Fulvestrant has not been adequately studied in premenopausal women.	IB	97% (29) yes 0% (0) abstain (30 voters)
Optimal post-aromatase inhibitor treatment is uncertain. Available options include, but are not limited to, tamoxifen, another aromatase inhibitor (with a different mechanism of action), fulvestrant HD, megestrol acetate, and everolimus + aromatase inhibitor.	IA	97% (30) yes 3% (1) abstain (31 voters)
Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, although this approach has not been assessed in randomized trials.	IC	88% (28) yes 9% (3) abstain (32 voters)
Concomitant CT + ET has not shown a survival benefit and should not be administered outside of a clinical trial.	IB	100% (30) yes 0% (0) abstain (30 voters)
HER-2-positive ABC		
Anti-HER-2 therapy should be offered *early* to all patients with HER-2+ MBC, except in the presence of contraindications to the use of such therapy.	IA	91% (30) yes 3% (1) abstain (33 voters)
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 ET (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 progression-free survival (PFS) benefit (i.e. 'time without CT') compared with ET alone. The addition of anti-HER-2 therapy in this setting has not led to a survival benefit.	IA	90% (27) yes 10% (3) abstain (30 voters)
Patients whose tumours progress 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.	IB	97% (29) yes 0% (0) abstain (30 voters)

Continued

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Table 2. *Continued*

	LoE	Consensus
Patients who have received any type of (neo)adjuvant anti-HER-2 therapy should not be excluded from clinical trials for HER-2+ MBC.	IB	100% (23) yes 0% (0) abstain (27 voters)
In the case of progression on trastuzumab, the combination of trastuzumab + lapatinib is also a reasonable treatment option in the course of the disease.	IB	83% (24) yes 10% (3) abstain (29 voters)
Chemotherapy and biological therapy		
In the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as a single agent, 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.	IA	71% (17) yes 4% (1) abstain (24 voters)
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 a single agent, would usually be considered as the 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.	IA	59% (14) yes 8% (2) abstain (24 voters)
If given in the adjuvant setting, a taxane can be re-used in the metastatic setting, particularly if there has been at least 1 year of disease-free survival.	IA	92% (22) yes 8% (2) abstain (24 voters)
Duration of each regimen and the number of regimens should be tailored to each individual patient.	Expert opinion	96% (26) yes 0% (0) abstain (27 voters)
Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.	IB	72% (21) yes 7% (2) abstain (29 voters)
Bevacizumab combined with chemotherapy as first- or second-line therapy for MBC provides only a moderate benefit in PFS and no benefit in overall survival. 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 a first/second line.	IA	74% (17) yes 17% (4) abstain (23 voters)
Specific sites of metastases: bone and brain		
A bone modifying agent (bisphosphonate or denosumab) should be routinely used in combination with other systemic therapy in patients with MBC and bone metastases.	IA	96% (26) yes 4% (1) abstain (27 voters)
Radiological assessments are required in patients with persistent and localized pain due to bone metastases to determine whether there are impending or actual pathological fractures. If a fracture of a long bone is likely or has occurred, an orthopaedic assessment is required as the treatment of choice may be surgical stabilization, which is generally followed by radiotherapy (RT). In the absence of a clear fracture risk, RT is the treatment of choice.	IA	96% (23) yes 4% (1) abstain (24 voters)
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.	I B	100% (24) yes 0% (0) abstain (24 voters)
Patients with a single or small number of potentially resectable brain metastases should be treated with surgery or radiosurgery. Radiosurgery is an option for some unresectable brain metastases.	IB	92% (22) yes 4% (1) abstain (24 voters)

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If surgery/radiosurgery is carried out 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 against the risk of neurocognitive effects.	IB	72% (18) yes 16% (4) abstain (25 voters)
Supportive and palliative care		
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.	IA	100% (26) yes 0% (0) abstain (26 voters)
Early introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.	IA	100% (26) yes 0% (0) abstain (26 voters)
Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief.	IA	100% (27) yes 0% (0) abstain (27 voters)
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 health-care 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 0% (0) abstain (26 voters)
Metastatic male breast cancer		
For ER+ male MBC, which represents the majority of 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% (25) yes 0% (0) abstain (25 voters)
For ER+ male MBC, tamoxifen is the preferred option.	Expert opinion	83% (15) yes 6% (1) abstain (18 voters)

[a]LoE changed since ABC1 from 2C to 1C based on new published data [128–130].

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5%, respectively). PFS, a secondary end point, was lower in the lapatinib arm (6.6 versus 8.0 months).

Additional evidence comes from the adjuvant ALTTO trial, where the lapatinib-alone arm was closed early, due to futility in a non-inferiority comparison to trastuzumab, and patients offered cross-over to receive trastuzumab [95].

The CLEOPATRA trial [96, 97] showed superior results, in terms of PFS (18.5 versus 12.4 months) and 1-year survival (23.6% versus 17.2%), of the triplet trastuzumab + pertuzumab + docetaxel compared with trastuzumab + docetaxel as first-line therapy. Importantly, the majority (≈90%) of the patients were trastuzumab-naive; if previously treated with trastuzumab, a 12-month disease-free interval was required. Therefore, this trial did not address, and therefore cannot support, the use of this combination in patients with truly trastuzumab-resistant tumours. There are also no data supporting the use of the dual blockade with trastuzumab + pertuzumab with CT beyond first line, after treatment with trastuzumab + pertuzumab + CT in the first line (i.e. continuing a dual blockade beyond progression) and, therefore, this regimen should not be given beyond first line outside clinical trials.

The panel could not reach a consensus regarding the possible use of pertuzumab beyond first line in patients previously untreated with this drug (14 votes 'yes', 11 'no', and 7 'abstain'). The only available data regarding this issue come from a phase II single arm study [98]. This phase II also showed that pertuzumab does not work by itself, but needs to be combined with trastuzumab.

T-DM1 (trastuzumab emtansine) has shown consistent and substantial benefits in terms of PFS and OS, both in the second line (versus lapatinib + capecitabine, in the EMILIA trial) [99, 100] and beyond (versus treatment of physician's choice, in the TH3RESA trial) [101]. These results make T-DM1 the preferred choice for patients with disease progression after treatment with at least one line of trastuzumab-based therapy.

There are almost no data regarding the treatment of patients with HER-2-positive ABC who relapse on or shortly after adjuvant trastuzumab and urgent trials are needed for this poor prognosis population. In the EMILIA trial, the overall survival advantage (HR) for T-DM1 versus lapatinib plus capecitabine in the subset of 118 patients who were randomized in the first-line setting, having relapsed on or within 6 months of adjuvant trastuzumab, appeared similar to the effect seen in the overall trial [100].

Several ABC1 recommendations for HER-2-positive ABC remain unchanged and are listed in Table 2.

IX. update on HER-2-negative ABC

Guideline statements	LoE	Consensus
Sequential monotherapy is 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.	IA	96% (25) yes 4% (1) abstain (26 voters)
Continued		
In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination chemotherapy, 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.	IB	77.1% (27) yes 20.0% (7) abstain (35 voters)

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

Regarding the use of chemotherapy, the main recommendation remains unchanged and relates to the sequential use of single agents, with combination chemotherapy reserved for situations of visceral crisis, rapidly progressive or highly symptomatic disease. Available literature has been previously reviewed [12] and a recent Cochrane meta-analysis [102] confirms and provides level 1 evidence for this recommendation.

Although taxanes can be used as first-line therapy, they have not shown superior benefit to anthracyclines in a meta-analysis carried out in a mostly taxane-naive, anthracycline-pre-treated patient population [103]. Considerations regarding toxicity and patient preferences (namely wish to avoid alopecia) should be taken into consideration in the choice of cytotoxic agent.

Capecitabine has shown consistent results as first- and second-line therapy [104–112].

Vinorelbine yielded equal or superior results to both paclitaxel and docetaxel, when combined with trastuzumab in the HER-2-positive ABC in the HERNATA [113] and TRAVIOTA trials [114].

Eribulin has provided an OS benefit in heavily pre-treated patients (up to five lines of treatment) [115] and similar PFS and OS results to capecitabine after prior treatment with an anthracycline and taxane [116].

X. update on surgery of the primary tumour in stage IV at diagnosis

Guideline statements	LoE	Consensus
The true value of the removal of the primary tumour in patients with *de novo* stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that	IIB	100% (29) yes 0% (0) abstain (29 voters)
Continued		

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Continued

Guideline statements	LoE	Consensus
surgery is only valuable if carried out with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease.		

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

Available data regarding the value of removal of the primary tumour in patients with stage IV at diagnosis were extensively reviewed and published in one of the ESO-ABC Task Force manuscripts [13]. All but one study published after this 2010 paper support the surgical removal of the primary tumour in patients with stage IV disease, reinforcing the importance of the ongoing prospective trials evaluating this approach since existing data come almost exclusively from retrospective studies [117–121]. In the beginning of 2012, the British Columbia large retrospective series reinforced the importance of treating the primary with the most favourable survival rates observed in subsets of patients with young age, good performance status, ER-positive disease, distant disease limited to one site, bone-only involvement, or fewer than five metastatic lesions [122]. A meta-analysis of 15 publications also published in 2012 reinforced the idea that surgery of the primary tumour appeared to be an independent factor for improved survival in the multivariate analyses from the individual studies, with an HR of 0.69 ($P < 0.00001$) [123].

Since 2011 several randomized trials have started accrual comparing locoregional treatment of primary versus no treatment in stage IV patients at presentation [124, 125].

In 2013, very early data from two prospectively randomized trials presented at San Antonio Breast Cancer Symposium could not confirm the previous conclusions. In these two studies, only a limited subgroup of patients with solitary bone metastases seemed to profit from surgery, while patients with multiple visceral metastases showed a worse prognosis with initial surgery. However, these trials were small, had short follow-up time, and included all-comers [126, 127].

More studies and better patient selection are necessary to resolve this question, and several other prospective randomized trials are ongoing. Until these results are available, ABC2 retains the ABC1 recommendation, which considers that surgery of the primary should not be offered as a routine practice but can be discussed on a case-by-case basis and offered to selected patients.

conclusions

Advances in survival outcomes for ABC, particularly for MBC, have been frustratingly slow. MBC remains a virtually incurable disease and LABC patients generally have a poor prognosis with a high risk of distant recurrence.

In the last few years, a deeper focus on this historically neglected patient population has occurred, with new and better designed clinical trials, a dedicated conference and the development of international consensus guidelines. Patient surveys have shown a slight improvement in patient satisfaction about the several steps of their care, but emphasize that much remains to be done. Implementation of guidelines is very heterogeneous between countries but also within countries, according to the environment where the patient is treated and cost of treatment.

The complexity of this disease, the multiple factors that must be taken into account, the lack of high-level evidence for several clinical situations, and new highly specialized techniques available for local management of specific sites of metastases, all constitute strong reasons for the treatment of these patients by a specialized multidisciplinary team, rather than management by an isolated oncologist regardless of his/her skills or experience.

Our plea for a strong commitment of all involved parties (academia, pharmaceutical industry, independent funding sources, and advocacy groups) to develop well-designed, high-quality multidisciplinary (involving other issues than drug-development) trials for ABC remains of critical importance. Many questions are still unanswered, related to management strategies, optimal drug use, and individualized treatment (based on predictive markers and eventually new technologies aiming at better characterization of the individual tumour).

Research and education are the two pillars for advances in oncology today. Research is indispensible for improving the management and outcome of patients with cancer, now and in the future. Education, including implementation of carefully developed high-quality guidelines such as the current ABC International Consensus Guidelines, allows the appropriate application of current knowledge to patient care, which will substantially improve the long-term outcomes of current ABC patients worldwide.

disclosure

All conflict of interest details were included in the supplementary material section.

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