special article

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

F. Cardoso1*, A. Costa2,3, L. Norton4, E. Senkus5, M. Aapro6, F. André7, C. H. Barrios8, J. Bergh9, L. Biganzoli10, K. L. Blackwell11, M. J. Cardoso12, T. Cufer13, N. El Saghir14, L. Fallowfield15, D. Fenech16, P. Francis17, K. Gelmon18, S. H. Giordano19, J. Gligorov20, A. Goldhirsch21, N. Harbeck22, N. Houssami23, C. Hudis24, B. Kaufman25, I. Krop26, S. Kyriakides27, U. N. Lin28, M. Mayer28, S. D. Merajver29, E. B. Nordström30, O. Pagani31, A. Partridge32, F. Penault-Llorca33, M. J. Piccart24, H. Rugo35, G. Sledge36, C. Thomssen37, L. van’t Veer38, D. Vorobiof39, C. Vrieling40, N. West41, B. Xu42 & E. Winer26

1European School of Oncology & Breast Unit, Champalimaud Cancer Center, Lisbon, Portugal; 2European School of Oncology, Milan, Italy; 3European School of Oncology, Bellinzona, Switzerland; 4Breast Cancer Program, Memorial Sloan-Kettering Cancer Centre, New York, USA; 5Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; 6Division of Oncology, Institut Multidisciplinaire d’Oncologie, Genolier, Switzerland; 7Department of Medical Oncology, Gustave-Roussy Institute, Villejuif, France; 8Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; 9Department of Oncology/Radiation Oncology, Karolinska Institutet & Cancer Center Karolinska and Karolinska University Hospital, Stockholm, Sweden; 10Department of Medical Oncology, Sandro Pitigliani Oncology Centre, Prato, Italy; 11Breast Cancer Clinical Program, Duke Cancer Institute, Durham, USA; 12Breast Unit, Champalimaud Cancer Center, Lisbon, Portugal; 13University Clinic Golk, Medical Faculty Ljubljana, Ljubljana, Slovenia; 14NK Basile Cancer Institute Breast Center of Excellence, American University of Beirut Medical Center, Beirut, Lebanon; 15Brighton & Sussex Medical School, University of Sussex, Falmer, UK; 16Breast Care Support Group, Europa Donna Malta, Mtarfa, Malta; 17Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia; 18BC Cancer Agency, Vancouver, Canada; 19Departments of Health Services Research and Breast Medical Oncology, UT MD Anderson Cancer Center, Houston, USA; 20APHP Tenon, IUC-UPMC, Francillean Breast Intergroup, AROME, Paris, France; 21Program of Breast Health, European Institute of Oncology, Milan, Italy; 22Brustzentrum der Universität München, Munich, Denmark; 23Screening and Test Evaluation Program, School of Public Health, Sydney Medical School, University of Sydney, Sydney, Australia; 24Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, USA; 25Sheba Medical Center, Tel Hashomer, Israel; 26Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; 27Europa Donna Cyprus, Nicosia, Cyprus; 28AdvancedBC.org, New York; 29University of Michigan Medical School and School of Public Health, Ann Arbor, USA; 30Europa Donna Sweden & Bröstcancerförbundets Riksorganisation, BKO, Sundbyberg, Sweden; 31Oncology Institute of Southern Switzerland and Breast Unit of Southern Switzerland, Bellinzona, Switzerland; 32Department of Medical Oncology, Division of Women’s Cancers, Dana-Farber Cancer Institute, Boston, USA; 33Jean Perrin Centre, Comprehensive Cancer Centre, Clermont Ferrand, France; 34Department of Medicine, Institut Jules Bordet, Brussels, Belgium; 35Department of Medicine, Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; 36Indiana University Medical CTR, Indianapolis, USA; 37Department of Gynaecology, Martin-Luther University Halle-Wittenberg, Halle an der Saale, Germany; 38Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; 39Sandton Oncology Centre, Johannesburg, South Africa; 40Department of Radiotherapy, Clinique des Grangettes, Geneva, Switzerland; 41Nursing Division, Health Board, Cardiff and Vale University, Cardiff, UK; 42Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Received 5 August 2014; accepted 11 August 2014

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 in 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 in
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 Mastología), and organized under the auspices of UICC (Union Internationale Contre Le Cancer), OECl (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.

| Grade of recommendation | Methodological quality of supporting evidence | Implications |
|-------------------------|---------------------------------------------|--------------|
| 1A (strong recommendation, high-quality evidence) | Strong recommendation, can apply to most patients in most circumstances without reservation | Strong recommendation, but may change when higher quality evidence becomes available |
| 1B (strong recommendation, moderate-quality evidence) | Strong recommendation, can apply to most patients in most circumstances without reservation | Weak recommendation, best action may differ depending on circumstances of patients or societal values |
| 2A (weak recommendation, high-quality evidence) | Weak recommendation, best action may differ depending on circumstances of patients or societal values | Very weak recommendation, other alternatives may be equally reasonable |
| 2B (weak recommendation, moderate-quality evidence) | Weak recommendation, best action may differ depending on circumstances of patients or societal values | Very weak recommendation, other alternatives may be equally reasonable |

Table 1. Level of evidence grading system [15].
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. 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. 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. | IC | 89.4% (34) yes 5.2% (2) abstain (38 voters) |
| Expert opinion | 92.1% (35) yes 7.8% (3) abstain (37 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 (CTCAE) 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-C30 (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].
‘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. | 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. | Expert opinion | 66.6% (22) Yes 21.2% (7) abstain (33 voters) |
| **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 | 100% (37) Yes 0% (0) abstain (37 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.
**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: 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.**

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.
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. 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. |
| IC                                                                                 | 82.5% (33) yes 12.5% (5) abstain (40 voters) |

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...
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 extrahepatic 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, intrahepatic CT, or other). | Expert opinion | 83.3% (25) yes 16.6% (5) |

### Malignant Pleural Effusions

Malignant pleural effusions require systemic treatment with/without local management. Thoracentesis for diagnosis should be performed if it is likely that this will change clinical management. False negative results are common. Drainage is recommended in patients with symptomatic, clinically significant pleural effusion. 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.

### 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.

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...
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; 95% CI 0.36–0.95; P = 0.011). 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...
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, pneumonia, 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 (39 voters) |
| IA | 10.2% (4) abstain |
| IA | 89.7% (35) yes (39 voters) |
| 10.2% (4) abstain |
| 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. | IB | 87.5% (35) yes (40 voters) |
| IA | 12.5% (5) abstain |
| In a HER-2 + MBC patient previously untreated with pertuzumab, it is acceptable to use pertuzumab beyond the first line. | IIC | 87.5% (35) yes (37 voters) |
| IA | 12.5% (5) abstain |
| 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. 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. 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 (37 voters) |
| IC | 10.8% (4) abstain |
| 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. |
Table 2. Advanced breast cancer (ABC)1 statements [10] with minor update or with no update

| General recommendations | LoE | Consensus |
|-------------------------|-----|-----------|
| 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 | LoE | Consensus |
|-----------------------|-----|-----------|
| 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% (0) abstain (30 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. 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. | Expert opinion | 81% (25) yes 10% (3) abstain (31 voters) |
| | 1C* | 96% (27) yes 0% (0) abstain (28 voters) |
Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible.

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.

**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.

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.

**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.

For premenopausal women, ovarian suppression/ablation combined with additional ET is the first choice.

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.

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.

Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, although this approach has not been assessed in randomized trials.

Concomitant CT + ET has not shown a survival benefit and should not be administered outside of a clinical trial.

**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.

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.

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.
Table 2. Continued

| Patients who have received any type of (neo)adjuvant anti-HER-2 therapy should not be excluded from clinical trials for HER-2+ MBC. | LoE | Consensus |
| --- | --- | --- |
| 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 capectabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

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 capectabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

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.

Duration of each regimen and the number of regimens should be tailored to each individual patient.

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.

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.

**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.

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.

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.

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.

---

**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 capectabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

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 capectabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

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.

Duration of each regimen and the number of regimens should be tailored to each individual patient.

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.

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.

**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.

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.

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.

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.
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.

| Supportive and palliative care |
|--------------------------------|
| Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan. |

**Early** introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.

| Access to effective pain treatment (including morphine, which is inexpensive) is necessary for all patients in need of pain relief. |
|------------------------------------------------------------------------------------------------------------------|
| 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. |

**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.

For ER+ male MBC, tamoxifen is the preferred option.

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

Continued

### 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 breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that | IIB | 100% (29) yes |

Continued
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 newly high-quality 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 indispensable 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.

**references**

1. Cardoso F. Metastatic breast cancer patients: the forgotten heroes! The Breast 2009; 18: 271–272.
2. Largiller R, Ferrero J-M, Doyen J et al. Prognostic factors in 1038 women with metastatic breast cancer. Ann Oncol 2008; 19: 2012–2019.
3. Andre F, Slimane K, Bachet J et al. Breast cancer with synchronous metastases: trends in survival during a 14-year period. J Clin Oncol 2004; 22: 3302–3308.
4. Sundquist M, Eriksson Z, Teijer G et al. Trends in survival in metastatic breast cancer. Eur J Cancer 2010; 8(3): 191 (abstract 453).
5. Foukas T, Formander T, Lekberg T et al. Age-specific trends of survival in metastatic breast cancer: 26 years longitudinal data from a population-based cancer registry in Stockholm, Sweden. Breast Cancer Res Treat 2011; 130(2): 553–560.
6. Fotini F, Villanueva C, Bazan F et al. Long-term follow-up of patients with metastatic breast cancer treated by trastuzumab: impact of institutions. The Breast 2014; 23: 165–169.
7. Hébert-Croteau N, Brisson J, Latreille J et al. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol 2004; 22(18): 3685–3693.
8. Griggs JJ, Culakova E, Sorbero ME et al. Social and racial differences in selection of breast cancer adjuvant chemotherapy regimens. J Clin Oncol 2007; 25(18): 2522–2527.
9. Hassett MJ, Hughes ME, Niland JC et al. Selecting high-priority quality measures for breast cancer quality improvement. Med Care 2008; 46(8): 762–770.
10. Cardoso F, Costa A, Norton L et al. 1st International consensus guidelines for advanced breast cancer (ABC1). The Breast 2012; 21(3): 242–252.

11. Metastatic breast cancer. Recommendations proposal from the European School of Oncology (ESO)-MBC Task Force. The Breast 2007; 16: 9–10.

12. Cardoso F, Bedard PL, Winer EP et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 2009; 101: 1174–1181.

13. Pagani O, Senkus-Konefka E, Wood W et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: can metastatic breast cancer be cured? J Natl Cancer Inst 2010; 102: 1–8.

14. Lin NU, Thomssen C, Cardoso F et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, Staging, and Evaluation of Patients with Early-Stage and Metastatic Breast Cancer. The Breast 2013; 22(3): 203–210.

15. Guyatt G, Gutterman D, Baumann MH et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. Chest 2006; 129(1): 174–181.

16. Freeman HP. Patient navigation: a community centered approach to reducing cancer mortality. J Cancer Educ 2006; 21(1 suppl): S11–S14.

17. Freund KM, Battaglia TA, Calhoun E et al. National Cancer Institute Patient Navigation Research Program: methods, protocol, and measures. Cancer 2008; 113: 3391–3399.

18. Hopkins J, Numbere MD. Patient navigation through the cancer care continuum: an overview. J Oncol Pract 2009; 5(4): 150–152.

19. Robinson-White S, Conroy B, Slavish KH, Rosenzweig M. Patient navigation: evidence for improved access and effective use of health-care resources for breast cancer survivors. Cancer Nurs 2010; 33(2): 127–140.

20. Ko NY, Darnell JS, Calhoun E et al. Can patient navigation improve receipt of recommended breast cancer care? Evidence from the national patient navigation research program. J Clin Oncol 2014 July 28 [Epub ahead of print].

21. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med 2010; 362: 865–869.

22. Biganzoli L, Wildiers H, O’Mallem C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SOG) and European Society of Breast Specialists (EUSOMA). Lancet Oncol 2012; 13: e148–e160.

23. Cardoso F, Lobli S, Pagani O et al. The EUSOMA recommendations for the management of young women with breast cancer. Eur J Cancer 2012; 48(18): 3355–3377.

24. Partridge AH, Pagani O, Abukhair O et al. First international consensus guidelines for breast cancer in young women (BCY1). The Breast 2014; 23(3):209–220.

25. Zimmermann C, Swani N, Krzyzanowska M et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 2014; 383(9930): 1721–1730.

26. Ganz PA, Yip CH, Gralow JR et al. Supportive care after curative treatment for breast cancer: resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. The Breast 2013; 22(5): 606–615.

27. Cardoso F, Bese N, Distelhorst SR et al. Supportive care during treatment for breast cancer: resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. The Breast 2013; 22(5): 593–605.

28. Silverman R, Smith L, Sundar S. ‘Is it my last christmas dinner?’ Survival of cancer patients having palliative chemotherapy during christmas period. BMJ Support Palliat Care 2014; 4(Suppl 1): A56.

29. El Saghir NS, Adebamowo CA, Anderson BO et al. Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. The Breast 2011; 20(Suppl 2): S3–11.

30. Macdonald SM, Harris EE, Arthur DW et al. ACR appropriateness criteria(R) locally advanced breast cancer. Breast J 2011; 17: 579–585.

31. Chia S, Swain SM, Byrd DR, Manielli DA. Locally advanced and inflammatory breast cancer. J Clin Oncol 2008; 26: 786–790.

32. Giordano SH. Update on locally advanced breast cancer. Oncologist 2003; 8: 521–530.

33. Yamauchi H, Woodward WA, Valero V et al. Inflammatory breast cancer: what we know and what we need to learn. Oncologist 2012; 17: 891–899.

34. Brennan ME, Houssami N. Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. The Breast 2012; 21: 112–123.

35. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344(11): 783–792.

36. Buzdar AU, Suman V, Bernstam F. ACOGOS Z1041 (Alliance): definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P + T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P + T – FEC + T) in HER2+ operable breast cancer. Lancet Oncol 2013; 14(13): 1317.

37. Ellis MJ, Suman VJ, Hoog J et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen-receptor-positive stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype—ACOGOS Z1031. J Clin Oncol 2011; 29: 2342–2349.

38. Cataliotti L, Buzdar AU, Noguchi S et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the PRe-Operative ‘Arimidex’ Compared to Tamoxifen (PROACT) trial. Cancer 2006; 106: 2095–2103.

39. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res Treat 2007; 105(Suppl 1): S33–S39.

40. Smith IE, Dowsett M, Ebbs SR et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23: 5108–5116.

41. Lobli S, Blohmer JU, Fasching PA et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular carcinoma of the breast. Abstr. 9th European Breast Cancer Conference, Glasgow, Scotland, 2014, abstr. 398.

42. Masuda N, Sagara Y, Kinoshita T et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol 2012; 13: 345–352.

43. Srinacci M, Badzio A, Welinka-Jaskiewicz M et al. Pattern of care in locally advanced breast cancer: focus on local therapy. Breast 2011; 20: 145–150.

44. Dawood S, Menayer SD, Viens P et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22: 515–523.

45. Cox C, Hollaway CM, Shaheta A et al. What is the burden of axillary disease after neoadjuvant therapy in women with locally advanced breast cancer? Curr Oncol 2013; 20: 111–117.

46. Byrski T, Gronwald J, Huzarski T et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 2010; 28: 375–379.

47. Gronwald J, Byrski T, Huzarski T et al. Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2009; 115: 359–363.

48. Byrski T, Foszczyńska-Kloda M, Huzarski T et al. Cisplatin chemotherapy in the treatment of BRCA1-positive metastatic breast cancer (MBC). Breast Cancer Res 2012; 14: R110.

49. Sliek WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC on pathologic complete response in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance). Abstr. 2013 San Antonio Breast Cancer Symposium, San Antonio, USA, S5–01.

50. von Minckwitz G, Schneweiss A, Salita C et al. A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2 positive early breast cancer (GeparSoto). J Clin Oncol 2014; 15(7): 747–756.

51. Petrelli F, Cioni A, Borgonovo K et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014; 144(2): 223–232.
93. Gelmon KA, Boyle F, Kaufman B et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2-metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK ERF 108919. J Clin Oncol 2012; 30 (Suppl: LB4A1). 94. Pivt K, Semiglazov V, Zuzaraski V et al. CEREBEL (EGF11438): an open label randomized phase III study comparing the incidence of CNS metastases in patients with HER2-metastatic breast cancer, treated with lapatinib plus capecitabine versus trastuzumab plus capecitabine. Ann Oncol 2012; 23(Suppl 9): (abstr L–1030). 95. Piccart-Gebhart M, Holmes AP, Basset J et al. First results from the phase III ALTO trial (BIG 02-06: NCT006330) comparing one year of anti-HER2 therapy with lapatinib alone (T), trastuzumab alone (T), their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). J Clin Oncol 2014; 32 (Suppl 5c; abstr LB4A). 96. Basset J, Cortes J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366: 109–119. 97. Swain SM et al. Confirmatory overall survival (OS) analysis of CLEOPATRA: a randomized, double-blind, placebo controlled Phase III study with pertuzumab (P), trastuzumab (T) and docetaxel (D) in patients (pts) with HER2-positive first-line (1L) metastatic breast cancer (MBC). Lancet Oncol 2013; 14(6): 461–471. 98. Cortés J, Fumoleau P, Bianchi GV et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012; 30(14): 1954–1960. 99. Blackwell KL, Miles D, Gianni L et al. Primary results from EML1, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (C) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. J Clin Oncol 2012; 30: 5s (suppl 15; abstr LB14). 100. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367: 1783–1791. 101. Wilhers H, Kim SB, Gonzalez-Martin A et al. T-DM1 for HER2-positive metastatic breast cancer (MBC): primary results from THRESA, a phase 3 study of T-DM1 as treatment of physician’s choice. Presented at the European Cancer Congress, Amsterdam, The Netherlands, September 27–October 1, 2013 (abstr LB15). 102. Dear RF, McGeechan K, Jenkins MC et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2013; (12): 008792. 103. Piccart-Gebhart MJ, Buzyczewski T, Buyse M et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008; 26(12): 1980–1986. 104. Stackler MR, Harvey VJ, Francis PA et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. J Clin Oncol 2011; 29(4): 4498–4504. 105. Blum JL, Barrios CH, Feldman N et al. Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer. Breast Cancer Res Treat 2012; 136: 777–788. 106. Robert NJ, Dieras V, Glaspy J et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase II trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011; 29: 1252–1260. 107. O’Shaughnessy JA, Blum J, Mosienyko V et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001; 12: 1247–1254. 108. Brufsky AM, Hunvitz S, Perez E et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2011; 29: 4286–4293. 109. Talbot DC, Mosienyko V, Van Belle S et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. Br J Cancer 2002; 86: 1367–1372.