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SPECIAL ARTICLE

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)☆

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INTRODUCTION

For the purpose of advanced breast cancer (ABC) guidelines, ABC comprises both inoperable locally advanced breast cancer (LABC) and metastatic breast cancer (MBC).[1,2] Advanced/metastatic breast cancer remains a virtually incurable disease, with a median overall survival (OS) of about 3 years and a 5-year survival rate of around 25%,[3,4] even in countries without major accessibility problems. Survival is strongly related to breast cancer subtype, with the major advances seen in human epidermal growth factor receptor 2 (HER2)-positive ABC.[5-9] ABC is a treatable disease with several available therapies and many others in development. However, their impact on survival and quality of life (QoL) of ABC patients has been slow[3] and different for *de novo* versus recurrent ABC, with the latter becoming much harder to treat in recent years.[10] Outcomes are also strongly related to access to the best available care, which includes not only the most efficacious medicines, but also multidisciplinary, specialised care, implementation of

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guidelines, high-quality pathology, imaging and radiotherapy (RT). Lack of any of these crucial pillars of modern oncological care inevitably results in substantially worse outcomes, as exemplified in the New Zealand report "I am still here".[11] While mortality rates have decreased in the majority of developed countries, most deaths are currently seen in less developed societies, and access issues explain the majority of these inequalities.[12]

The application of the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)[13] to the field of ABC (P Shimon, personal communication) shows that the quality of clinical research has improved over the last decade and that better therapies have been developed, providing hope that a substantial improvement in the median OS of ABC patients might soon be seen. However, some clinically relevant questions are still unanswered and may be difficult to address through traditional clinical trials, such as the best sequence of therapies for each individual patient. The application of computer analytics to big data and real-world data is one of the potential ways forward. In-depth discussion must take place regarding the impact of this 'new' level of evidence (LoE) in current treatment guidelines and their integration with clinical trial data.

The 5th International Consensus Conference for Advanced Breast Cancer (ABC 5) took place in Lisbon, Portugal, on 14th-16th November 2019, bringing together 1500 participants from 94 countries worldwide, including health professionals, patient advocates and journalists. Since its first edition in 2011, the main goal of the ABC conference has been the development of high-quality international consensus guidelines for the management of ABC. These guidelines are based on available evidence and on expert opinion when evidence is lacking. They represent the best management options for ABC patients globally, assuming accessibility to all available therapies. Adaptation of these guidelines is often needed in settings where access to care is suboptimal.

The ABC 5 guidelines are jointly developed by ESO and ESMO, and have been endorsed by several international oncology organisations, such as the European Society of Breast Cancer Specialists (EUSOMA), European Society for Radiotherapy and Oncology (ESTRO), European Society of Gynaecological Oncology (ESGO), Union for International Cancer Control (UICC), Senologic International Society (SIS)/ International School of Senology (ISS), Federación Latino-Americana de Mastologia (FLAM), European Oncology Nursing Society (EONS), European Society of Surgical Oncology (ESSO), Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) and the International Society of Geriatric Oncology (SIOG), and have official representation from the American Society of Clinical Oncology (ASCO). The ABC 5 conference was also organised under the auspices of the Organisation of European Cancer Institutes (OECI) and with the support of the Breast Cancer Research Foundation (BCRF), Susan G. Komen and the ABC Global Alliance.

This manuscript summarises the guidelines developed at ABC 5, each of which are accompanied by the LoE, grade of recommendation (GoR), percentage of consensus reached at the conference and supporting references. In addition, the ESMO-MCBS version 1.1[13] (v1.1) was used to calculate scores for new therapies/indications approved by the European Medicines Agency (EMA) since the last ABC guidelines, as well as a few new therapies that have been scored but are still under EMA evaluation (https://www.esmo.org/Guidelines/ESMO-MCBS). A table with these scores is included (see supplementary Table S1, available at https://doi/org/10.1016/j.annonc.2020.09.010).

METHODOLOGY

Before the ABC 5 conference, preliminary recommendation statements on the management of ABC were prepared based on available published data and following the ESMO guidelines methodology (see http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). These recommendations were circulated to all 44 panel members by e-mail for comments and corrections on content and wording. A final set of recommendations was presented, discussed and voted upon during the consensus session of ABC 5. All panel members were instructed to vote on all questions, and any members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field) were instructed to vote 'abstain'. Additional changes in the wording of statements were made during the session. As some important studies were presented a few weeks later at the 2019 San Antonio Breast Cancer Symposium, particularly for new anti-HER2 therapies, three additional statements were developed after the ABC 5 conference, circulated for revision and voted by all panel members. Statements related to the management of side-effects and difficult symptoms, included under the supportive and palliative care section, were not voted on during the consensus session, but were discussed and unanimously agreed by e-mail, and are therefore considered to have 100% consensus agreement. Previous ABC recommendations that did not require update or only minor changes were not re-voted but were reviewed by all panel members by e-mail and remain valid. To provide a full overview of all ABC guidelines currently approved, this manuscript includes a list of all recommendations per subject, highlighting those that were discussed, voted and approved in ABC 5. However, this manuscript only describes the evidence for newly developed or updated guidelines. We refer the reader to the manuscripts of previous ABC guidelines for the detailed explanation of guidelines not updated/added during ABC 5.

Supplementary Table S2, available https://doi/org/10.1016/j.annonc.2020.09.010, describes the LoE and GoR system used,[14] as per ESMO guidelines methodology.

Supplementary Figures, available at https://doi/org/10.1016/j.annonc.2020.09.010, feature updated ABC diagnostic and treatment algorithms.

Slides with all ABC guideline statements are available online at http://www.abc-lisbon.org/ and https://www.esmo.org/guidelines/breast-cancer/consensus-recommendations-advanced-breast-cancer-abc-5.

Section I. ABC definitions		
Guideline statement	**LoE/GoR**	**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 organ compromise leading to a clinical indication for the most rapidly efficacious therapy. Examples: ***Liver visceral crisis***: rapidly increasing bilirubin >1.5× ULN in the absence of Gilbert's syndrome or biliary tract obstruction. ***Lung visceral crisis***: rapidly increasing dyspnoea at rest, not alleviated by drainage of pleural effusion.	Expert opinion/n/a	97%
Primary endocrine resistance is defined as relapse while on the first 2 years of adjuvant ET, or PD within the first 6 months of first-line ET for ABC, while on ET. **Secondary endocrine resistance** is defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥6 months after initiating ET for ABC, while on ET.	Expert opinion/n/a	67%
Oligometastatic disease is defined as low-volume metastatic disease with limited number and size of metastatic lesions (up to five and not necessarily in the same organ), potentially amenable for local treatment aimed at achieving a complete remission status.	Expert opinion/n/a	78%
Patients with multiple chronic conditions are defined as patients with additional comorbidities (e.g. cardiovascular, impaired renal or liver function, autoimmune disease) making it difficult to account for all of the possible extrapolations to develop specific recommendations for care.	Expert opinion/n/a	100%
Adequate OFS in the context of ABC		
Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or OFA through pelvic RT (the latter is not always effective and therefore is the least preferred option).	I/A	85%
If an LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimise OFS.	II/B	85%
Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhoea, especially if an AI is administered.	Expert opinion/B	85%
As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires a balance of the patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression and cost.		
Maintenance therapy: in the context of ABC guidelines, maintenance therapy refers to the continuation of anti-HER2 therapy and/or ET after discontinuation of ChT.	Expert opinion/n/a	100%
Integrative medicine: complementary and integrative medicine (CIM) represents the use of complementary treatments side by side with conventional approaches in a proper therapeutic environment.	Expert opinion/n/a	100%

In green, NEW/UPDATED ABC 5 statements.
ABC, advanced breast cancer; AI, aromatase inhibitor; consensus, percentage of panel members in agreement with the statement; ChT, chemotherapy; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence; n/a, not applicable; OFA, ovarian function ablation; OFS, ovarian function suppression; PD, disease progression; q4w, every 4 weeks; RT, radiotherapy; ULN, upper limit of normal.

Given the aim of standardising definitions and homogenising the use of certain medical terms, ABC has provided several definitions throughout the years. At ABC 5, the definition of visceral crisis was revisited, with some examples added (i.e. liver and lung visceral crisis) to better clarify the definition and avoid any misunderstanding between the mere existence of visceral metastases and the presence of visceral crisis. This situation is estimated to occur in only around 10%-15% of first-line ABC cases and requires the use of the most rapidly efficacious therapy, which is not necessarily chemotherapy (ChT) in all situations.

A more subjective and difficult to define situation is 'impending visceral crisis', where the criteria for visceral crisis are not yet met but, without rapidly efficacious measures, it is foreseen to happen. An example is a situation where more than 70% of the liver is occupied by metastases, the liver enzymes are substantially altered but bilirubin is still normal. In this type of situation, we also recommend the use of the most rapidly efficacious therapy.

Section II. General guidelines		
Guideline statement	**LoE/GoR**	**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 and surgical oncologists, imaging experts, pathologists, gynaecologists, psycho-oncologists, social workers, nurses and palliative care specialists) is crucial.	Expert opinion/A	100%
From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care and symptom-related interventions as a routine part of their care. The approach must be personalised to meet the needs of the individual patient.	Expert opinion/A	100%

Continued

Section II. Continued

Guideline statement	LoE/GoR	Consensus
Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances). This conversation should be conducted in the accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.	Expert opinion/A	97%
All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy-to-understand information about their disease and its management.	I/A	97%
Patients (and their families, caregivers or support network, if the patient agrees) should be invited to participate in the decision-making process at all times. When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network).	Expert opinion/A	100%
Every ABC patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient-centred care, as defined by: • Open communication between patients and their cancer care teams as a primary goal. • Educating patients about treatment options and supportive care, through development and dissemination of evidence-based information in a clear, culturally appropriate form. • Encouraging patients to be proactive in their care and to share decision making with their healthcare providers. • Empowering patients to develop the capability of improving their own QoL within their cancer experience. • Always taking into account patient preferences, values and needs as essential to optimal cancer care. • Patients should have easy access to well-designed clinical studies since these are crucial for further improvement in the management of ABC.	Expert opinion/A	100%
Every ABC patient should: • Have access to the most up-to-date treatments and innovative therapies at accessible breast units/centres. • Be treated in specialist breast units/centres/services (SBUs) by a specialised multidisciplinary team including specialised side-effects management and a nurse experienced in the treatment of ABC. • Survivorship issues and palliative care should be addressed and offered at an early stage. • A quality assurance programme covering the entire breast cancer pathway from screening and diagnosis to treatment, rehabilitation, follow-up and palliative care, including services and support for ABC patients and their caregivers, should be implemented by SBUs.	Expert opinion/A I/A Expert opinion/A Expert opinion/B	100%
General statements: QoL		
Strong consideration should be given to the use of validated PROMs for patients to record the symptoms of disease and side-effects of treatment experienced as a regular part of clinical care. These PROMs should be simple and user-friendly to facilitate their use in clinical practice and thought needs to be given to the easiest collection platform e.g. tablets or smartphones. Systematic monitoring would facilitate communication between patients and their treatment teams by better characterising the toxicities of all anticancer therapies. This would permit early intervention of supportive care services enhancing QoL.	I/C	87%
Specific tools for evaluation of QoL in ABC patients should be developed.	Expert opinion/A	100%
Until then, trials evaluating QoL in this setting should use standardised PROs (instead of focusing exclusively on CTCAEs) and incorporate site- and treatment-specific modules or subscales that exist both in the EORTC and FACT systems.	Expert opinion/A	100%
Additionally, attention needs to be paid to collection methods, timing of assessments and handling of missing data. More sophisticated statistics should also be employed to ensure that clinicians have better, reliable data to help patients when choosing between treatment options.	Expert opinion/A	100%
General statements: clinical trials		
After appropriate informed consent, inclusion of patients in well-designed, prospective, independent trials must be a priority whenever such trials are available and the patient is willing to participate.	Expert opinion/A	100%
The ABC community strongly calls for clinical trials addressing important unanswered clinical questions in this setting, and not just for regulatory purposes. Clinical trials should continue to be performed, even after approval of a new treatment, to provide real-world data on its performance, efficacy and toxicity.	Expert opinion/A	100%
General statements: affordability/cost effectiveness		
The medical community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients' well-being, length of life and preferences should always guide decisions.	Expert opinion/A	100%
We strongly recommend the use of objective scales, such as the **ESMO-MCBS** or the **ASCO Value Framework**, to evaluate the real magnitude of benefit provided by a new treatment and help prioritise funding, particularly in countries with limited resources.	Expert opinion/A	88%
The ABC community strongly supports the use of **biosimilars** both for treatment of breast cancer (i.e. trastuzumab) and for	I/A	90%

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Section II. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
supportive care (i.e. growth factors). To be used, the biosimilar must be approved after passing the stringent development and validation processes required by the EMA or the FDA or other similarly strict authority.		
General statements: survivorship		
As survival is improving in many patients with ABC, consideration of survivorship issues should be part of the routine care of these patients. Health professionals should therefore be ready to change and adapt treatment strategies to disease status, treatment of adverse effects and QoL, patients' priorities and life plans. Attention to chronic needs for home and family care, job and social requirements, should be incorporated in the treatment planning and periodically updated.	Expert opinion/A	95%
ABC patients who desire to work or need to work for financial reasons should have the opportunity to do so, with needed and reasonable flexibility in their working schedules to accommodate continuous treatment and hospital visits.	Expert opinion/A	100%
ABC patients with stable disease being treated as a 'chronic condition' should have the option to undergo breast reconstruction if clinically appropriate.	Expert opinion/B	82%
In ABC patients with long-standing stable disease or complete remission, breast imaging is an option.	Expert opinion/C	83%
Breast imaging should also be performed when there is a suspicion of locoregional progression.	I/A	100%
Fertility preservation: the impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age, and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).	Expert opinion/B	100%
General statements: other		
Specialised oncology nurses (if possible specialised breast nurses) should be part of the multidisciplinary team managing ABC patients. In some countries, this role may be played by a physician assistant or another trained and specialised healthcare practitioner.	Expert opinion/A	92%
The use of **telemedicine** in oncology to help management of patients with ABC living in remote places is an important option to consider when geographic distances are a problem and provided that issues of connectivity are solved.	Expert opinion/B	93%

In green, NEW/UPDATED ABC 5 statements.

ABC, advanced breast cancer; ASCO, American Society of Clinical Oncology; consensus, percentage of panel members in agreement with the statement; CTCAE, Common Terminology Criteria for Adverse Events; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FACT, Functional Assessment of Cancer Therapy; FDA, Food and Drug Administration; GoR, grade of recommendation; LoE, level of evidence; MBC, metastatic breast cancer; PRO, patient-reported outcome; PROM, patient-reported outcome measure; QoL, quality of life.

Fortunately, these last few years have seen the development and approval of several new therapies for ABC, some with an impact on OS. Consequently, some ABC patients can live many years with their disease under control or in complete remission. Since the usual methods for systemic imaging of metastatic disease do not provide good imaging of the breast, the panel believes that breast imaging is an option to consider in the surveillance follow-up of these patients. Additionally, and importantly, if at any time locoregional relapse or progression is suspected, breast imaging must be carried out.

At ABC 5, several discussions took place regarding how best to provide information regarding prognosis and length of life to ABC patients. Conversations about prognosis, priorities and end-of-life care are vitally important for those affected by advanced cancer and should be part of routine care.[15] Information about prognosis and likely survival time with and without different anticancer treatments is important to enable fully informed and educated decision making by patients. It also helps patients to plan for the future, arrange finances and work, maximise time with loved ones, plan special events and prepare for death. Misunderstandings about prognosis are common[16-18] and are associated with increased exposure to futile treatments.[19-22] Most patients want considerably more information than many healthcare professionals expect, but the type and amount of information sought should be clarified.[23] There are some significant cultural variations, in particular the involvement of the family in filtering information, which can make disclosure about prognosis and survival especially challenging.[24] Although some physicians may avoid discussing prognosis for fear of upsetting the patient or destroying hope, there is no evidence that increased information about prognosis with sensitive communication is harmful to patients, or that it increases anxiety or distress.[25-30] For patients wanting quantitative information on life expectancy, providing ranges for worst-case, typical and best-case scenarios is more helpful and conveys more hope than providing a single point estimate of median survival.[31] Ranges for survival scenarios are also more accurate than a single point estimate of expected survival.[16,32,33] Oncologists should offer prognostic information to all patients with ABC, allowing patients to determine the type and extent of information required. The patient's needs for prognostic information are likely to fluctuate over time, and as their disease progresses, so it is important for oncologists to repeatedly determine the information required throughout the illness from diagnosis to death. Oncologists also need guidance and communication skills training on how to handle these difficult discussions, as there is evidence that some oncologists are overly optimistic about survival benefits from anticancer treatments while others are unduly nihilistic about the benefits of good quality supportive care.[34]

Section III. Assessment and treatment general guidelines		
Guideline statement	**LoE/GoR**	**Consensus**
Image and disease assessment guidelines		
Minimal staging work-up for ABC includes a history and physical examination, haematology and biochemistry tests and imaging of the chest, abdomen and bones.	II/A	67%
Brain imaging should not be routinely performed in asymptomatic patients. This approach is applicable to all patients with ABC, including those with HER2-positive and/or triple-negative ABC.	II/D	94%
The clinical value of tumour markers is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. An increase in tumour markers alone should not be used to initiate a change in treatment.	II/C	89%
Evaluation of response to therapy should generally occur every 2-4 months for ET or after 2-4 cycles for ChT, depending on the dynamics of the disease, the location and extent of metastatic involvement and type of treatment. Imaging of a target lesion may be sufficient in many patients. In certain patients, such as those with indolent disease, less frequent monitoring is acceptable. Additional testing should be performed in a timely manner, irrespective of the planned intervals, if PD is suspected or new symptoms appear. A thorough history and physical examination must always be performed.	Expert opinion/B	81%
Biopsy guidelines		
A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis, particularly when metastasis is diagnosed for the first time.	I/B	98%
Biological markers (especially HR and HER2) should be reassessed at least once in the metastatic setting, if clinically feasible. Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.	I/B	98%
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-HER2 therapy) when receptors are positive in at least one biopsy, regardless of timing.	Expert opinion/B	87%
Locoregional treatment general guidelines		
To date, the **removal of the primary tumour** in patients with ***de novo*** **stage IV breast cancer** has not been associated with prolongation of survival, with the possible exception of the subset of patients with bone-only disease. However, it can be considered in selected patients with controlled systemic disease, particularly to improve QoL, always taking into account the patient's preferences.	I/C	70%
Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. complete removal of the disease) as in patients with early-stage disease. Additional prospective clinical trials evaluating the value of this approach, the best candidates and best timing are currently ongoing.	II/B	70%
A small but very important subset of patients with ABC, for example those with **oligometastatic disease or low-volume metastatic disease** that is highly sensitive to systemic therapy, can achieve complete remission and a long survival. A multimodal approach, including locoregional treatments with curative intent, should be considered for these selected patients. A prospective clinical trial addressing this specific situation is needed.	Expert opinion/B	91%
Systemic treatment general guidelines		
Treatment choice should take at least these factors into account: HR and HER2 status and germline *BRCA* status, *PIK3CA* in HR-positive and PD-L1 in TNBC, if targeted therapies are accessible. Previous therapies and their toxicities, DFI, tumour burden (defined as number and site of metastases), biological age, PS, comorbidities (including organ dysfunctions), menopausal status (for ET), the need for rapid disease/symptom control, socio-economic and psychological factors, available therapies in the patient's country and patient's preference.	Expert opinion/A	95%
The age of the patient should not be the sole reason to withhold effective therapy (in elderly patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment.	I/E	100%
ChT general guidelines		
Both combination and sequential, single-agent ChT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for ABC. Combination ChT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control.	I/A	96%
In the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as single agents, would usually be considered as first-line ChT for HER2-negative ABC in those patients who have not received these regimens as (neo)adjuvant treatment and for whom ChT is appropriate. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.	I/A	71%
In patients with taxane-naive and anthracycline-resistant ABC or with anthracycline maximum cumulative dose or toxicity (i.e. cardiac) who are being considered for further ChT, taxane-based therapy, preferably as single agent, would usually be considered as the treatment of	I/A	59%

Continued

Section III. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
choice. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.		
In patients pretreated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, single-agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, a different taxane and liposomal anthracyclines. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability.	I/A	77%
If given in the adjuvant setting, a taxane can be re-used as first-line therapy, particularly if there has been at least 1 year of DFI.	I/B	92%
If given in the adjuvant setting, provided that maximum cumulative dose has not been achieved and there are no cardiac contraindications, anthracyclines can be re-used in ABC, particularly if there has been at least 1 year of DFI.	I/B	93%
Metronomic ChT is a treatment option for patients not requiring rapid tumour response. Available regimens are CM (low-dose oral cyclophosphamide and methotrexate), capecitabine or oral vinorelbine-based regimens. Randomised trials are needed and underway to accurately compare metronomic ChT with standard dosing regimens.	I/B	98%
Duration of each regimen and the number of regimens should be tailored to each individual patient.	Expert opinion/A	96%
Usually, each regimen (except anthracyclines) should be given until PD or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.	I/B	72%
Other agents		
Bevacizumab combined with ChT as first-line therapy for ABC provides a moderate benefit in PFS and no benefit in OS. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases and only in the first-line setting. **ESMO-MCBS v1.1 score: 2**	I/C	Yes: 42% No: 53%

In green, NEW/UPDATED ABC 5 statements.

ABC, advanced breast cancer; ChT, chemotherapy; CM, cyclophosphamide/methotrexate; consensus, percentage of panel members in agreement with the statement; DFI, disease-free interval; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor 2; HR, hormone receptor; LoE, level of evidence; MBC, metastatic breast cancer; OS, overall survival; PD, disease progression; PD-L1, programmed death-ligand 1; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PS, performance status; QoL, quality of life; TNBC, triple-negative breast cancer.

Germline *BRCA* status, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) for estrogen receptor (ER)-positive ABC and programmed death-ligand 1 (PD-L1) for triple-negative ABC were included as important factors to take into consideration when making treatment decisions. Details about how to evaluate these factors and their clinical implications are discussed in the respective sections of the guidelines.

The statement about the use of bevacizumab was rewritten but consensus was still not achieved. In the discussion, it became clear that the main reasons for this lack of consensus were the withdrawal of approval by the Food and Drug Administration (FDA), rendering it an unavailable option in the United States, and the fact that for many panellists, bevacizumab should not be considered a treatment option. The available data show that bevacizumab combined with ChT as first-line therapy for ABC provides a moderate benefit in progression-free survival (PFS) and no benefit in OS. The ESMO-MCBS v1.1 score for bevacizumab is two.[35] Some experts believe it can be a good option for situations of extensive cutaneous inflammatory disease due to its potential antiangiogenic effect.

Section IV. ER-positive/HER2-negative (luminal-like) ABC		
Guideline statement	**LoE/GoR**	**Consensus**
ET is the preferred option for HR-positive disease, even in the presence of visceral disease, unless there is visceral crisis, for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	93%
Many trials in ER-positive ABC have not included **premenopausal** women. Despite this, we recommend that young women with ER-positive ABC should have adequate OFS/OFA and then be treated in the same way as postmenopausal women, with endocrine agents with or without targeted therapies.	Expert opinion/A	95%
Future trials exploring new endocrine-based strategies should be designed to allow for enrolment of both pre- and postmenopausal women, and men.	Expert opinion/A	92%
For premenopausal women, for whom ET was decided, OFS/OFA combined with additional endocrine-based therapy is the preferred choice.	I/A	93%
OFA by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids the potential initial tumour flare seen with an LHRH agonist and may increase eligibility for clinical trials. Patients should be informed of the options for OFS/OFA and decisions should be made on a case-by-case basis.	Expert opinion/C	91%
Single-agent tamoxifen is the only available endocrine option for premenopausal women who decline OFS/OFA, but the panel believes it is a less effective option.	I/D	92%
The preferred first-line agent depends on the type and duration of adjuvant ET as well as the time elapsed from the end of adjuvant ET; it can be an AI, tamoxifen or fulvestrant for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	84%

Continued

Section IV. Continued

Guideline statement	LoE/GoR	Consensus
A CDK4/6 inhibitor combined with ET is the standard of care for patients with ER-positive/HER2-negative ABC, since it achieves a substantial PFS benefit, significantly increases OS and either maintains or improves QoL.	I/A	97%
The CDK4/6 inhibitor can be combined with an AI or with fulvestrant, in *de novo* or recurrent ABC, in first or second line and in cases of primary or secondary resistance (defined as per ABC guidelines).		
This recommendation applies to postmenopausal women, to premenopausal women in combination with an LHRH agonist and to men preferably in combination with an LHRH agonist.		
The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with ET for ABC patients vary according to the setting and drug. They are the following, with the current available data and follow-up: • Palbociclib + AI first line: efficacy score: 3 (PFS); no improved QoL; **ESMO-MCBS v1.1 score: 3** • Abemaciclib + AI first line: efficacy score: 3 (PFS); no QoL reported; **ESMO-MCBS v1.1 score: 3** • Ribociclib + AI first line postmenopausal: efficacy score: 3 (PFS); no improved QoL; **ESMO-MCBS v1.1 score: 3** • Ribociclib + ET first line premenopausal: efficacy score: 4 (PFS & OS); QoL improved; **ESMO-MCBS v1.1 score: 5** • Palbociclib + fulvestrant second line: efficacy score: 3 (PFS & OS); improved QoL; **ESMO-MCBS v1.1 score: 4** • Ribociclib + fulvestrant first, second line: efficacy score: 4 (PFS & OS); no improvement in QoL; **ESMO-MCBS v1.1 score: 4** • Abemaciclib + fulvestrant second line: efficacy score: 4 (PFS & OS); no QoL benefit; **ESMO-MCBS v1.1 score: 4**	I/A	100%
Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial.		
It remains unclear if CDK4/6 inhibitors should be preferably administered in the first- or second-line setting. However, the majority of panellists preferred giving a CDK4/6 inhibitor in the first-line setting for the majority of their patients.	Expert opinion/n/a	100%
There are no data supporting the use of a combination of CDK4/6 inhibitor and ET as maintenance therapy after ChT.	n/a/D	66%
Maintenance therapy, in this situation, should be carried out with ET alone.		
The addition of everolimus to an AI is a valid option for some patients [for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women] previously exposed to or naive of (in case CDK4/6 inhibitors are not available) ET, since it significantly prolongs PFS, albeit without evidence of an OS benefit. **ESMO-MCBS v1.1 score: 2**	I/B	88%
The decision to treat must take into account the toxicities associated with this combination, the lack of a statistically significant OS benefit, cost and availability.		
Tamoxifen or fulvestrant can also be combined with everolimus.	II/B	80%
Adequate prevention, close monitoring and proactive treatment of AEs is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the BOLERO-2 trial.	I/B	97%
Everolimus and CDK4/6 inhibitors should not be used after PD on that specific agent (i.e. beyond progression), outside a clinical trial.	n/a/E	74%
Alpelisib with fulvestrant is a treatment option for patients with *PIK3CA*-mutated tumours (in exons 9 or 20), previously exposed to an AI and with appropriate HbA1c levels, since it provided about 5 months of benefit in median PFS.	I/B	88%
The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the SOLAR-1 study (i.e. pre-existing diabetes and baseline HbA1c), as well as the toxicity profile of alpelisib.		
Its efficacy after exposure to CDK4/6 inhibitors is unknown, since only 6% of patients in the SOLAR-1 trial had been previously treated with those agents. **ESMO-MCBS v1.1 score: 3**		
Patients receiving alpelisib in combination with ET for *PIK3CA*-mutated ABC should be instructed to take non-sedating antihistamines to prevent rash at the start of therapy. Antihistamines can be discontinued after 4 weeks as the risk for rash is primarily in the first 2 weeks of therapy.	I/B	93%
At present, no validated predictive biomarkers other than hormone receptor status exist to identify patients who will/will not benefit from the addition of a CDK4/6 inhibitor or an mTOR inhibitor to ET and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.	I/E	95%
Alpelisib should only be used in cases of *PIK3CA*-mutated tumours.	II/A	95%
The combination of a non-steroidal AI and fulvestrant as first-line therapy for postmenopausal patients resulted in significant improvement in both PFS and OS compared with AI alone in one phase III trial and no benefit in a second trial with a similar design. Notably, a suboptimal dose of fulvestrant was used in the study that demonstrated benefit.	II/D	Yes: 38% No: 60% Abstain: 2%
Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen). Based on these data, combination ET may be offered to some patients with ABC without prior exposure to adjuvant ET in cases where a CDK4/6 inhibitor will not be given. **ESMO-MCBS v1.1 score: 2**		
Comparative data between this combination and a CDK4/6 inhibitor with ET are not available.		
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used [in the (neo) adjuvant or advanced settings], duration of response to those agents, burden of the	I/A	100%

Continued

Section IV. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
disease, patients' preference and availability. Available options for first and second line include AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus, fulvestrant + alpelisib (for *PIK3CA*-mutated tumours), AI, tamoxifen, fulvestrant. This applies to pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.		
Options for treatment of ER-positive disease beyond second line include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megestrol acetate, low-dose estrogen). Single-agent abemaciclib is also a potential option.	II/B	98%
Challenging a patient with an agent on which the disease previously progressed after an initial response is occasionally considered, but there are no robust data to support this approach. This applies to pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	Expert opinion/B	98%
Trials comparing the different combinations of endocrine + targeted agents with single-agent ChT are ongoing. Initial results from phase II and III randomised trials comparing combinations of endocrine + targeted agents to single-agent ChT do not show significant differences in terms of efficacy, and the former compares favourably in terms of safety.	II/B	Not voted
Concomitant ChT and ET has not shown a survival benefit and should not be performed outside a clinical trial.	II/D	100%
Endocrine treatment after ChT (maintenance ET) to maintain benefit is a reasonable option, though it has not been properly assessed in randomised trials.	III/B	88%

In green, NEW/UPDATED ABC 5 statements.

ABC, advanced breast cancer; AE, adverse event; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ESMO-MBCS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence; mTOR, mammalian target of rapamycin; n/a, not applicable; NSAI, non-steroidal aromatase inhibitor; OFS, ovarian function suppression; OFA, ovarian function ablation; OS, overall survival; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; QoL, quality of life; SAI, steroidal aromatase inhibitor.

The last 2 years have seen the establishment of cyclin-dependent kinase (CDK)4/6 inhibitors combined with endocrine therapy (ET) as the standard of care for ER-positive/HER2-negative ABC in view of the OS benefit seen in several trials,[36-42] both in the first- and second-line settings, substantial PFS benefit and good toxicity profile.[36-57] These agents can be combined with an aromatase inhibitor (AI) or fulvestrant, and are effective in *de novo* or recurrent ABC, in first or second line, in cases of primary or secondary resistance, in postmenopausal and premenopausal women (the latter with ovarian function suppression/ablation), and in men (preferably with a luteinising hormone-releasing hormone agonist). Of note, the combination of tamoxifen and ribociclib led to increased cardiotoxicity (arrhythmia) and should be avoided.[36] Notwithstanding these results, the panel acknowledges that there is a small group of patients who can be treated with ET alone; although clear identification of these patients is not possible at this time, factors such as limited burden of metastatic disease and features of less aggressive biology [i.e. very long disease-free interval (DFI)] can help with this identification. There are currently no biomarkers to enable accurate identification of these patients. The ESMO-MCBS scores provided are based on available data at the time of publication of this manuscript. These scores may change in the future, with new data being published, and updates will be provided on the ESMO website.

The SOLAR-1 phase III, randomised, placebo-controlled trial evaluated the role of alpelisib, an oral inhibitor of the phosphoinositide 3-kinase alpha (PI3Kα) isoform, in combination with fulvestrant, for postmenopausal women and men who had previously been treated with an AI.[58] In the *PIK3CA*-mutated cohort, alpelisib provided a PFS benefit of 11.0 months versus 5.7 months [hazard ratio (HR) for progression or death: 0.65; 95% confidence interval (CI) 0.50-0.85, $P < 0.001$]. OS data are not yet available. Toxicity was substantially increased in the alpelisib arm, especially hyperglycaemia, rash, gastrointestinal (GI) complaints (nausea, vomiting, loss of appetite, mucositis, diarrhoea) and fatigue, which lead to dose reductions/interruptions in around 70% of patients and discontinuations in 25%. Alpelisib, in combination with fulvestrant, was EMA-approved for use in this setting in July 2020. The ESMO-MCBS for alpelisib in combination with fulvestrant was established at three because this scoring system does not consider the percentages of dose alterations and/or discontinuations as a marker of important toxicity, which in the opinion of the ABC panel, is a shortcoming of the v1.1 of the scale (scheduled to be changed in the upcoming version 1.2 of the ESMO-MCBS). In view of the balance between efficacy and toxicity, it is crucial to carefully select patients who may be candidates for this treatment, considering the inclusion/exclusion criteria in SOLAR-1 and comorbidities, especially pre-existing diabetes and baseline HbA1c levels. It is also recommended that patients take non-sedating antihistamines to prevent rash at the start of therapy[59,60]; these can be discontinued after 4 weeks as the risk of rash is primarily in the first 2 weeks of therapy. The ABC panel considers alpelisib a treatment option for patients with ER-positive/HER2-negative *PIK3CA*-mutated ABC, but in view of the higher benefit provided by CDK4/6 inhibitors, alpelisib plus ET should be used after CDK4/6 plus ET. Only 20 patients (6%) in SOLAR-1 had been previously exposed to a CDK4/6 inhibitor. However, this is a common issue in oncology, where standards of care might change during the course of a trial. Furthermore, the large phase II BYLieve trial has shown efficacy of alpelisib after CDK4/6 inhibitor use.[60] Based on all of the available data, the ABC panel acknowledges that no data exist to determine the best sequence of therapies for this ABC subtype but believes that the most adequate sequence, in settings where availability of all drugs exist, is the use of a CDK4/6 inhibitor plus ET as first line, followed by alpelisib plus ET in patients with *PIK3CA*-mutated tumours or everolimus plus ET in patients with *PIK3CA*-wild type or unknown tumours.

Section V. HER2-positive ABC		
Guideline statement	**LoE/GoR**	**Consensus**
Anti-HER2 therapy should be offered early (as first line) to all patients with HER2-positive ABC, except in the presence of contraindications to the use of such therapy.	I/A	98%
Patients progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway. The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered and the relapse-free interval. The optimal sequence of all available anti-HER2 therapies is currently unknown. The optimal duration of anti-HER2 therapy for MBC (i.e. when to stop these agents) is currently unknown.	I/A	91%
In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost. Stopping anti-HER2 therapy after several years of sustained complete remission may be considered in some patients, particularly if treatment rechallenge is available in case of progression.	Expert opinion/C	93%
Patients who have received any type of (neo) adjuvant anti-HER2 therapy should not be excluded from clinical trials for HER2-positive ABC. These patients remain candidates for anti-HER2 therapies.	I/B	100%
For highly selected patients[a] with ER-positive/HER2-positive ABC, for whom ET + anti-HER2 therapy was chosen as first-line therapy, dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) can be used since it provides a benefit in PFS. This decision must be balanced against the higher side-effects, higher costs and lack of OS benefit so far, as compared with ET + anti-HER2 monotherapy.	I/B	80%
For patients with ER-positive/HER2-positive ABC, for whom ChT + anti-HER2 therapy was chosen as first-line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy after stopping ChT, although this strategy has not been studied in randomised trials. Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request, and needs to be evaluated in clinical trials. There are no data to decide between single-agent anti-HER2 or dual blockade to combine with maintenance ET after stopping ChT in ER-positive/HER2-positive ABC.	n/a/B	80%
In the first-line setting, for HER2-positive ABC previously treated (in the adjuvant setting with DFI >12 months) or untreated with trastuzumab, combinations of ChT + trastuzumab are superior to combinations of ChT + lapatinib in terms of PFS and OS.	I/A	95%
		Continued

Section V. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
The standard first-line therapy for patients previously untreated with anti-HER2 therapy is the combination of ChT + trastuzumab and pertuzumab because it has proven to be superior to ChT + trastuzumab in terms of OS in this population. **ESMO-MCBS v1.1 score: 4**	I/A	86%
For patients previously treated [in the (neo) adjuvant setting] with anti-HER2 therapy, the combination of ChT + trastuzumab and pertuzumab is an important option for first-line therapy. Few (88) of these patients were treated in the CLEOPATRA trial and all with a trastuzumab-free interval >12 months.	I/A	76%
There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and ChT beyond progression (i.e. continuing dual blockade beyond progression) and therefore dual blockade should not be given beyond progression outside clinical trials.	I/E	86%
In a HER2-positive ABC patient previously untreated with the combination of ChT + trastuzumab + pertuzumab, it is acceptable to use this treatment after first line.	II/B	76%
After first-line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER2-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, because it provides an OS benefit. **ESMO-MCBS v1.1 score: 4**	I/A	88%
In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. **ESMO-MCBS v1.1 score: 4** There are, however, no data on the use of this combination after progression on pertuzumab or T-DM1.	I/B	84%
The combination of neratinib + capecitabine was compared with lapatinib + capecitabine as third line or beyond therapy for HER2-positive ABC, showing a marginal benefit in PFS, and with no significant difference in the co-primary end point of OS. There was no comparator arm with trastuzumab + capecitabine, which had previously been demonstrated to give superior OS to lapatinib + capecitabine. Therefore, the combination of neratinib + capecitabine is not recommended for routine clinical practice. **ESMO-MCBS: No manuscript publication; precludes scoring.**	I/D	90%
Additional studies are needed to clearly establish the potential role of this combination in the treatment of brain metastases, as well as the role of neratinib for ABC.	I/D	90%
Trastuzumab deruxtecan (DS-8201) showed important activity in a phase II study in	II/B	98%
		Continued

Section V. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
heavily pretreated patients with HER2-positive ABC (median lines of therapy: 6), and is a treatment option in this setting, where approved. Pulmonary toxicity (interstitial lung disease/pneumonitis) can be fatal and requires active surveillance and proper management. **ESMO-MCBS v1.1 score: 2.**		
Dual blockade with tucatinib + trastuzumab + capecitabine showed a small benefit in median PFS (2 months) and median OS (4 months) over trastuzumab + capecitabine in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with brain metastases, at the expense of higher toxicity (i.e. diarrhoea). If approved, it can be considered a treatment option in this setting. **ESMO-MCBS v1.1 score: 3.**	II/B	98%
Margetuximab + ChT showed only a small PFS benefit (1 month) when compared with trastuzumab + ChT for patients pretreated with pertuzumab and T-DM1, and cannot therefore be recommended for routine clinical practice. **ESMO-MCBS: No manuscript publication; precludes scoring.**	I/D	95%
The role of *CD16A* genotype as a predictor of anti-HER2 antibody efficacy and selection of anti-HER2 agent should be further explored.		
Regarding the ChT component of HER2-positive ABC treatment: When pertuzumab is not given, first-line regimens for HER2-positive ABC can include trastuzumab combined with vinorelbine or a taxane. Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision. Other ChT agents can be administered with trastuzumab but are not as well studied and are not preferred.	I/A	88%
For later lines of therapy, trastuzumab can be administered with several ChT agents, including but not limited to, vinorelbine (if not given in first line), taxanes (if not given in first line), capecitabine, eribulin, liposomal anthracyclines, platinums, gemcitabine or metronomic CM. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability.	II/A	91%
ChT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel [I/A] or paclitaxel [I/B]. Also possible are vinorelbine [II/A], nab-paclitaxel [II/B], capecitabine [I/A] and metronomic ChT for older patients [II/B].	See in statement	86%

In green, NEW/UPDATED ABC 5 statements.

ABC, advanced breast cancer; ChT, chemotherapy; CM, cyclophosphamide and methotrexate; consensus, percentage of panel members in agreement with the statement; DFI, disease-free interval; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC, metastatic breast cancer; n/a, not applicable; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

[a] See definition in ABC 4.[61]

After years of relatively limited progress in the management of advanced HER2-positive breast cancer, the last year has enriched our armamentarium of drugs effective in this ABC subtype. A number of new representatives of the most relevant classes of drugs—monoclonal antibodies, antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs)—have demonstrated activity superior to previously-available options in patients pretreated with standard first- and second-line treatments.

Tucatinib, a highly selective inhibitor of the HER2 tyrosine kinase, used in combination with capecitabine and trastuzumab in a population of ABC patients pretreated with trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1), demonstrated improvement of PFS (median 7.8 months versus 5.6 months, HR 0.54; 95% CI 0.42-0.71, $P < 0.001$) and OS (median 21.9 months versus 17.4 months, HR 0.66; 95% CI 0.50-0.88; $P = 0.005$) compared with patients treated with capecitabine/trastuzumab/placebo.[62] This was achieved at the expense of increased toxicity, mostly diarrhoea and elevated aminotransferase levels of grade $\geq$3, but did not lead to frequent treatment discontinuation. Importantly, a reduction in the risk of CNS progression or death by 69% was observed in patients with stable brain metastases, while a confirmed objective response rate of 47% and a reduced risk of death by 51% were observed in patients with active brain metastases.[63]

Trastuzumab deruxtecan (DS-8201), an ADC composed of trastuzumab, a cleavable tetrapeptide-based linker and a cytotoxic topoisomerase I inhibitor, demonstrated a response rate of 60.6% (95% CI 53.4-68.0) and an unprecedented median PFS of 16.4 months (95% CI 12.7—not reached) in a phase II study of heavily pretreated patients (median six lines, range 2-27 lines, including trastuzumab and T-DM1).[64] Trastuzumab deruxtecan was associated with a 13.6% risk of interstitial lung disease (ILD)/pneumonitis, fatal in 2.2% of cases, which needed appropriate and rapid diagnosis and treatment. For the safe utilisation of this compound in clinical practice (i.e. outside clinical trials), active surveillance and education regarding the signs and symptoms, for both patients and healthcare professionals, are crucial to enable rapid diagnosis and management. Confirmatory results from phase III studies are eagerly awaited and needed to accurately determine the role of this very promising drug in the HER2-positive ABC setting.

Both tucatinib and trastuzumab deruxtecan are FDA-approved and await evaluation by the EMA.

Another two agents which demonstrated formally positive (although clinically of questionable value) trial results in pretreated HER2-positive ABC patients are margetuximab (a monoclonal antibody) and neratinib. Margetuximab resulted in only a 0.9-month PFS prolongation (HR 0.76; 95% CI 0.59-0.98, $P = 0.033$) compared with trastuzumab (both combined with ChT of physician's choice), no OS benefit and a good toxicity profile.[65] The potential role of *CD16A* genotype as a predictor of anti-HER2 antibody efficacy was explored and initial results were encouraging and deserve further evaluation. Margetuximab is currently under evaluation by the FDA and EMA and is not yet approved for use in ABC.

Neratinib provided a small reduction in the risk of disease progression of 24% (95% CI 0.63-0.93; $P = 0.006$, medians not provided), a marginal difference in PFS and no impact on OS (co-primary end point) compared with lapatinib (both in combination with capecitabine), at the cost of increased toxicity.[66] Furthermore, the NALA study has a severe limitation of not having a comparator arm with trastuzumab plus capecitabine, which was previously shown to provide superior OS to lapatinib plus capecitabine in the first- and second-line settings.[67] As of October 2020, neratinib in combination with capecitabine is FDA-approved for pretreated metastatic HER2-positive breast cancer, but is still under evaluation by the EMA in this setting.

It is especially important to emphasise that there are no comparative data between these four new anti-HER2 agents and that the question regarding the optimal sequence of treatments after trastuzumab, pertuzumab and T-DM1 is currently unknown.

Section VI. Triple-negative ABC

Guideline statement	LoE/GoR	Consensus
In triple-negative ABC patients (regardless of *BRCA* status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile compared with docetaxel and is, therefore, an important treatment option.	I/A	91%
For non-*BRCA*-associated triple-negative ABC, there are no data supporting different or specific ChT recommendations, besides platinum. Therefore, all ChT recommendations for HER2-negative disease also apply for triple-negative ABC.	I/A	98%
The AR is a potential target in triple-negative ABC. There are, however, no standardised methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice. More definitive trials are needed, and research efforts must continue to optimise and standardise the determination of AR.	II/D	85%
Atezolizumab + nab-paclitaxel is an option for first-line therapy for PD-L1-positive[a] triple-negative ABC, either *de novo* or at least 12 months since (neo)adjuvant ChT. **ESMO-MCBS v1.1 score: 3**	I/B	95%
Checkpoint inhibitor monotherapy in later lines for triple-negative ABC is not recommended due to low response rates.	I/E	89%
Several ongoing trials are evaluating the role of immunotherapy in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials.	n/a/E	98%
Immunotherapy, with a checkpoint inhibitor, for any biological subtype of ABC should not be used in routine clinical practice outside clinical trials. Several ongoing trials are evaluating the role of this type of treatment in all ABC subtypes.	III/D	85%

In green, NEW ABC 5 statements.

ABC, advanced breast cancer; AR, androgen receptor; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; n/a, not applicable; PD-L1, programmed death-ligand 1; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer.

[a] For PD-L1 testing, see precision medicine statements.

Recent years have brought about the beginning of a significant change in the approach to triple-negative ABC with the recognition that both clinically and molecularly this is not one but many diseases. For most patients, ChT remains the only available non-investigational systemic treatment option for non-*BRCA*-mutated triple-negative ABC, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds for patients with *BRCA*-mutated triple-negative ABC. However, immunotherapy has emerged as an option in the first-line setting for those with PD-L1 $\geq$1% in immune cells. IMpassion-130 is a phase III randomised, placebo-controlled trial that compared atezolizumab and nab-paclitaxel with nab-paclitaxel alone.[68] The study had co-primary end points of PFS and OS in the intention-to-treat (ITT) population and had a hierarchal design that allowed for evaluation of OS in the PD-L1-positive population if the OS in the ITT population was significantly improved from the addition of atezolizumab. In the ITT population, atezolizumab provided a benefit in PFS of 7.2 versus 5.5 months with a HR of 0.8 (95% CI 0.69-0.92, $P = 0.002$). In the PD-L1 positive group, atezolizumab provided a PFS benefit of 7.5 versus 5 months with a HR of 0.62 (95% CI 0.49-0.78, $P < 0.001$). In the ITT population, there was no significant benefit in OS with the addition of atezolizumab; median OS was 21.3 months versus 17.6 months (HR 0.84; 95% CI 0.69-1.02, $P = 0.08$). However, despite the hierarchal statistical design that precluded an OS analysis in the PD-L1-positive population if the OS in the ITT population was not significant, an analysis was conducted and presented, and showed an OS of 25 months versus 15.1 months favouring the atezolizumab arm. Based on these data, atezolizumab in combination with nab-paclitaxel was approved and may be considered an option in the first-line setting for *de novo* advanced/metastatic disease or disease that has developed at least 12 months after completion of (neo)adjuvant ChT in tumours that have PD-L1 expression $\geq$1% based on staining of the immune cells using the companion test of SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems).[68] Recently,

these data were updated showing a PFS difference of 2.5 months and an OS difference of 7 months in the PD-L1-positive population.[69] More recently, at ASCO 2020 virtual meeting, data from the KEYNOTE-355 trial was presented. KEYNOTE-355 was a randomised double-blind, phase III trial evaluating the role of pembrolizumab plus ChT for previously untreated triple-negative ABC, which showed an improvement in PFS with the addition of pembrolizumab (9.7 versus 5.6 months; HR 0.65; CI 0.49-0.86, $P = 0.0012$) for PD-L1-positive (combined positive score $\geq$10), triple-negative ABC.[70]

Checkpoint inhibitor monotherapy in later lines for triple-negative ABC is not recommended due to low response rates, as seen in the KEYNOTE-199 trial.[71] In patients with triple-negative ABC and a germline *BRCA* mutation, a poly-adenosine diphosphate ribose polymerase (PARP) inhibitor is a preferred treatment option (please refer to section on hereditary ABC). In the small proportion of patients with both PD-L1-positive disease and *BRCA1/2* mutations, the selection of immunotherapy or a PARP inhibitor for first-line treatment remains an area of debate.

No further data to support antiandrogen therapy for triple-negative ABC with expression of the androgen receptor has been published since ABC 4 and therefore it cannot be recommended for routine clinical use outside a clinical trial.

Sacituzumab govitecan-hziy has demonstrated promising activity in advanced lines for triple-negative ABC in a phase I/II study of 108 patients who had received a range of 2-10 prior treatments for metastatic disease.[72] The overall response rate was 33.3% (95% CI 24.6-43.1), with a median duration of response of 7.7 months (95% CI 4.9-10.8). Of the patients with a response to sacituzumab govitecan-hziy, 55.6% maintained their response for $\geq$6 months and 16.7% maintained their response for $\geq$12 months. Based on these preliminary results, the FDA has granted accelerated approval. However, phase III results are needed to confirm efficacy and establish the role of this agent in the management of triple-negative ABC.

Section VII. Hereditary ABC

Guideline statement	LoE/GoR	Consensus
Genetic testing		
For ABC patients, results from germline genetic testing have therapeutic implications and should therefore be performed as early as possible.	I/A	88%
Appropriate counselling should be provided to patients and their families if a pathogenic germline mutation is found.		
At present, only germline mutations in *BRCA1/2* have proven clinical utility and therapeutic impact.	I/A	100%
Testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, in particular because they may have implications for family members. However, it must be clarified to the patient that at present, a mutation in another moderate-/high-penetrance gene has no direct clinical implications for the patients themselves in the setting of ABC.	Expert opinion/C	100%
The therapeutic implications of somatic *BRCA1/2* mutations in breast tumours need to be further explored within a research setting and should not be used for decision making in routine clinical practice.	n/a/E	83%
***BRCA*-associated ABC**		
In patients with g*BRCA*-associated triple-negative ABC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred ChT option, if not previously administered.	I/A	86%
All other ChT recommendations are similar to those for sporadic ABC.		
For patients with a g*BRCA* mutation, single-agent PARPi (olaparib or talazoparib) is a preferred treatment option for those with triple-negative ABC.	I/A	78%
In ER-positive g*BRCA*-associated ABC, the optimal sequence between a PARPi and ET with or without a CDK4/6 inhibitor is unknown. Given the OS benefit seen with CDK4/6 inhibitors, the panel recommends their use before a PARPi.	Expert opinion/B	78%
Single-agent PARPis (olaparib or talazoparib) are associated with a PFS benefit, improvement in QoL and a favourable toxicity profile. Results suggest that any benefit in OS may be limited to the first-line setting. **ESMO-MCBS v1.1 score: 4**	Expert opinion/B	78%
It is unknown how PARPis (olaparib or talazoparib) compare with platinum compounds in this setting, the optimal use with platinum (combined or sequential) and their efficacy in tumours progressing after platinum.	Expert opinion/n/a	90%
More research is needed to answer questions related to treatment sequencing.		
BROCADE3 was the first phase III trial testing a PARPi (veliparib) in g*BRCA*-mutated MBC that included a platinum. Initial presentation of results showed a small benefit in PFS (1.9 months). However, durable PFS at 3 years was seen in a significant minority (one in four patients) during veliparib maintenance, which could provide patients lacking other maintenance treatment options with ChT-free time. Mature OS data are needed before this regimen can be recommended for routine clinical practice.	I/D	98%
ESMO-MCBS: No manuscript publication; precludes scoring.		

In green, NEW ABC 5 statements.

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC, metastatic breast cancer; n/a, not applicable; OS, overall survival; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; PFS, progression-free survival; QoL, quality of life.

For ABC patients, results from germline genetic testing for a mutation in *BRCA1/2* have therapeutic implications and should therefore be discussed with the patient and carried out as early as possible. Genetic testing should be guided by national/international guidelines,[73] should be proposed to all male breast cancer patients and may also be considered for all patients with triple-negative disease. Genes to be tested depend on personal and family history. However, at present, only germline mutations in *BRCA1/2* have any clinical utility and therapeutic impact. Although *BRCA1/2* are the most frequently mutated genes, testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, but it must be clarified to the patient that, at present, a mutation in another moderate- to high-penetrance gene has limited clinical implications in the setting of ABC—this is an area of research with several ongoing clinical trials and emerging phase II data suggesting a benefit of PARP inhibitors (PARPis) in patients with germline *PALB2* mutations.[74]

Since ABC 4, further data from the OlympiAD study suggested an OS benefit for olaparib when given in the first-line setting, with a median OS of 22.6 versus 14.7 months (HR 0.51; 95% CI 0.29-0.90, $P = 0.02$) in a subgroup analysis of predefined stratification subgroups,[75] lending further support to existing data for a PFS benefit with olaparib in the ITT population of the study.[76]

The EMBRACA study[77] had a similar design to the OlympiAD study, comparing talazoparib with ChT monotherapy per physician's choice (capecitabine, eribulin, vinorelbine or gemcitabine). Most patients had not received prior platinum-based therapy. At a median follow-up of 11.2 months, PFS was longer in the talazoparib arm (8.6 versus 5.6 months, HR 0.54; 95% CI 0.41-0.71, $P < 0.0001$). Recently, at the American Association for Cancer Research (AACR) 2020 virtual meeting, an update was presented and no benefit was demonstrated in OS.[78] However, it is worth noting that nearly 60% of patients in the control arm went on to receive a PARP inhibitor or platinum agent. At the ESMO 2019 annual meeting, data was presented from the BROCADE3 study—the first phase III study in ABC comparing the addition of a PARPi (veliparib) to a platinum-containing regimen (paclitaxel and carboplatin) for germline *BRCA*-mutated ABC.[79] The study demonstrated a PFS benefit favouring the veliparib arm, with a median PFS of 14.5 versus 12.6 months (HR 0.71; 95% CI 0.57-0.88, $P = 0.002$) and a suggestion of sustained response at 2 and 3 years favouring the arm that was receiving maintenance veliparib but at the expense of significant toxicity. Peer-reviewed publication of the data is awaited, and further data are needed before this combination can be recommended for germline *BRCA*-mutated ABC.

Further studies are also needed to clarify the value of PARPis in platinum-resistant disease, as well as their value compared with platinum compounds.

Section VIII. Precision medicine

Guideline statement	LoE/GoR	Consensus
Multigene panels, such as those obtained using NGS or other technology on tumour DNA, have not yet proven beneficial in clinical trials for ABC; their impact on outcome remains undefined and should not be used in routine clinical practice. For patients who are suitable to participate in clinical trials of novel therapies and are readily able/motivated to attend a centre with relevant clinical trials, NGS testing may be used in the context of prospective molecular triage programmes to select patients for therapeutic trials. Specific tests (as distinguished from broad mutation profiles) are useful and discussed in separate statements; others may play a role in the future as the medicines they are linked with achieve regulatory approval.	I/D	83%
ctDNA assessment is not recommended for demonstration of disease progression.	I/D	97%
ctDNA assessment is an option for the detection of *PIK3CA* mutations for a selection of patients eligible for alpelisib.	II/A	93%
If treatment with the PI3K inhibitor, alpelisib, is available, patients should be tested for *PIK3CA* mutation (in exon 9 and 20) in a tissue (metastasis or primary) and/or by ctDNA testing in blood. Patients who do not have an available archival tissue sample and have an uninformative result using a liquid biopsy test could consider undergoing a tumour biopsy for *PIK3CA* mutation testing.	I/B	100%
ESR1 mutation status assessment is not ready for routine clinical practice use and is not recommended, either for demonstration of disease progression or selection of ET (such as a switch from AI to fulvestrant).	I/D	90%
PD-L1 status should be tested in cases of first-line triple-negative ABC if treatment with immune checkpoint inhibitors is available.	I/A	97%
PD-L1 status is the companion test for the use of the combination of atezolizumab and taxane as first-line therapy for triple-negative ABC, using IHC with the SP142 antibody (Ventana) and a cut-off of 1% of positive staining on immune cells.	I/A	97%

Continued

Section VIII. Continued

Guideline statement	LoE/GoR	Consensus
Patients with low (1%-10%) ER-positive (and PgR-positive), HER2-negative ABC should not be considered for ET exclusively. Patients with low (1%-10%) ER-positive (and PgR-positive), HER2-negative ABC can be considered as patients with triple-negative ABC for clinical trials.	III/B	95%
If an ABC patient presents with a tumour with **MSI-H/MMR-D**, treatment with an anti-PD-1 agent is a possible consideration.	Expert opinion/C	Yes: 41% Abstain: 10% Insufficient data: 49%
If an ABC patient presents with a tumour with an ***NTRK* fusion**, treatment with a TRKi is a possible consideration. Patients must be informed about the amount of data available for ABC specifically. Research on the best companion diagnosis tools and techniques is needed. Prospective registries should be created to collect data from all patients treated with these innovative approaches after proper consent.	I/B	Yes: 29% Abstain: 24% Insufficient data: 47%

In green, NEW ABC 5 statements.

ABC, advanced breast cancer; consensus, percentage of panel members in agreement with the statement; ctDNA, circulating tumour DNA; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LoE, level of evidence; MMR-D, mismatch repair deficiency; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NTRK, neurotrophic receptor tyrosine kinase; PD, disease progression; PD-1, programmed cell death protein 1; PgR, progesterone receptor; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TRKi, tropomyosin receptor kinase inhibitor.

Circulating DNA assays assess cell-free tumour DNA qualitatively and quantitatively for molecular alterations in a non-invasive fashion from a simple blood sample. Different technologies are available from single-gene assay by quantitative polymerase chain reaction (qPCR) to whole genome sequencing by next-generation sequencing (NGS).[80,81] Standardisation is a critical point, especially for NGS-based analysis. There is insufficient evidence of clinical validity and utility for the majority of circulating tumour DNA (ctDNA) assays in advanced cancer.[82] Thus, ctDNA assessment is not recommended for demonstration of disease progression in ABC. However, for single biomarkers using targeted assays, ctDNA assessment is an option for the detection of *PIK3CA* mutations for selection of patients eligible for alpelisib.

The progress of precision medicine has helped to describe around 40 recurrent driver alterations in breast cancer. ESMO has recently developed a scale for clinical actionability of molecular targets (ESCAT) to interpret the targetability of genomic alterations in the context of clinical practice.[83] The aim is to help clinicians to prioritise treatment after NGS results. The tool ranks genomic alterations in tiers, based on the strength of their clinical validation (from I to V and X). *ERBB2* amplification, germline deleterious *BRCA 1* and *2* mutations and *PIK3CA* mutations are all classified as tier IA. The majority of *PIK3CA* mutations affect hot spots i.e. the three most frequent in exons 9 and 20 (exon 9: E542K, E545K, helicase domain; exon 20: H1047R, kinase domain). They are present in up to 40% of metastatic luminal breast cancer. The mutations activate the alpha isoform of PI3K and drive oncogenicity. There were three sub-analyses of the SOLAR-1 trial[58] which showed that the benefit seen with alpelisib was independent of the type of *PIK3CA* test, i.e. tissue biopsy from the primary or the metastasis, liquid or tissue biopsy, NGS or targeted PCR test.[84-86] If treatment with the PI3K inhibitor, alpelisib, is available, patients should be tested for *PIK3CA* mutation (in exons 9 and 20) in tissue (metastasis or primary) and/or by ctDNA testing in blood. Patients who do not have an available archival tissue sample and have an uninformative result using the liquid biopsy test could consider undergoing a new biopsy for *PIK3CA* mutation testing.

Acquisition of *ESR1* mutations, frequent in ABC patients previously treated by AIs (20%-40%), is one of the mechanisms of resistance to hormonal therapies. The consequence is a ligand-independent, constitutive activity of ER. To assess the impact of the presence of *ESR1* mutations in plasma samples of ABC patients, the *post hoc* prospective-retrospective analysis of the SOFEA trial failed to demonstrate a statistically significant impact of *ESR1* mutations on response to AI versus fulvestrant (interaction test between the two regimens $P = 0.07$). The analysis of the PALOMA-3 trial showed that the presence of plasma *ESR1* mutations had no impact on response to palbociclib (interaction test between the two regimens $P = 0.74$).[87] Despite promising preclinical data and statistical trends, the ESCAT scale for *ESR1* mutations is tier II.[83] Therefore, *ESR1* mutation status assessment is not ready for routine clinical use and is not recommended, either for demonstration of disease progression or selection of hormonal treatment (such as a switch from AI to fulvestrant).

Increased counts of tumour-infiltrating lymphocytes (TILs) are prognostic for survival in triple-negative breast cancer (TNBC), making this disease a potential target for immunotherapy.[88] Based on the results of the IMpassion-130 trial,[68] atezolizumab was approved with the Ventana PD-L1 (SP142) assay as a companion diagnostic immunohistochemistry (IHC) assay. Therefore, PD-L1 status should be tested in cases of first-line triple-negative ABC if treatment with immune checkpoint inhibitors is available. Several IHC assays are available to assess PD-L1 status.[89] SP263 (Ventana) and 22-C3 (Dako), both of which are widely used in pathology laboratories for other tumour types, have been evaluated for their clinical validity in the context of the IMpassion-130 trial but failed to reproduce SP142 clinical validity.[90] Thus, PD-L1 status by SP142 is the companion test for the use of atezolizumab in combination with a taxane for first-line therapy in triple-negative ABC, with a cut-off of 1% positive staining on immune cells. It is critical for medical oncologists and pathologists to know the available assays and their relevance to the therapeutic options in order to develop a workflow for IHC testing.

Tumours with staining of ER <1% and progesterone receptor (PgR) <1% and with HER2-negative results by IHC and/or *in situ* hybridisation are defined as TNBC.[91] Patients with a low (1%-10%) expression of hormone receptors and HER2-negative account for 2%-3% of breast cancers. They may share morphological (high grade, poor differentiation)[92] and biological features[93,94] with TNBC and experience a similarly poor survival.[95,96] A meta-analysis assessing the survival benefit of ET for ER-low (<10%) primary breast cancer showed lower endocrine responsiveness compared with ER-positive tumours [odds ratio (OR) 0.52, $P = 0.034$].[97] Recently, the ASCO-College of American Pathologists (CAP) guidelines acknowledged that patients with tumours between 1% and 10% of ER staining represent a new reporting category, stipulating the lack of data concerning benefit from ET and the proximity to ER-negative breast cancer of this patient group.[98] We recommend that this strategy is also adopted for ABC patients with a low ER-positive status.

Section IX. Specific sites of metastases

Guideline statement	LoE/GoR	Consensus
Bone metastases		
Radiological assessments are required in patients with persistent and localised pain due to bone metastases to determine whether there are impending or actual pathological fractures. If a fracture of a long bone or vertebrae is likely or has occurred, an orthopaedic assessment is required as the treatment of choice may be surgical stabilisation, which is generally followed by RT. In the absence of a clear fracture risk, RT is the treatment of choice.	I/A	96%
Neurological symptoms and signs which suggest the possibility of spinal cord compression must be investigated as a matter of urgency. This requires a full radiological assessment of the 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/stabilisation is feasible or indicated, emergency RT is the treatment of choice and vertebroplasty is also an option.	I/B	100%
Regarding the use of bone-targeted agents (bisphosphonate, denosumab), the ABC panel endorses the ESMO CPG[99] related to this subject.	n/a	100%
Brain metastases		
Patients with a single or a small number of potentially resectable brain metastases should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases.	I/B	92%
If surgery/radiosurgery is performed it may be followed by WBRT, but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects.	I/C	72%
HER2-positive ABC and brain metastases		
Because patients with HER2-positive ABC and brain metastases can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to WBRT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).	I/A	89%
In patients with HER2-positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.	I/D	95%
For patients with HER2-positive ABC where brain metastases are the only site of recurrence, the addition of ChT to local therapy is not known to alter the course of the disease and is not recommended.	I/D	83%
It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.	I/B	83%
For patients with HER2-positive ABC with progressive brain metastases as the predominant site of disease burden, if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option, preferably in clinical trials.	III/A	85%
Radionecrosis after stereotactic RT for brain metastases is an uncommon complication that may occur, especially with longer survival and follow-up, and in particular in cases of re-irradiation. Differential diagnosis with tumour progression is often difficult. Treatment of symptomatic patients with a course of high-dose steroids is the first treatment of choice. If no response, bevacizumab may be used, as an option to decrease the surrounding oedema, usually at a dose of 7.5 mg/kg every 2 weeks for a median of 4 cycles. Prospective randomised trials are needed to further validate this option.	III/B	61%
LMD		
There is no accepted standard of care for breast cancer LMD. The choice of treatment (RT, intra-CSF therapy, systemic therapy, supportive care) should consider prognostic evaluation and multidisciplinary discussion.	Expert opinion	95%
Focal RT should be considered for circumscribed, notably symptomatic lesions.	Expert opinion	95%
WBRT can be considered for extensive nodular or symptomatic linear LMD.	Expert opinion	95%
Addition of intrathecal to systemic therapy has no OS or QoL advantage and no clinically meaningful effect on CSF progression.	II/D	95%
Intrathecal therapy can be considered if systemic disease is stable and there is normal CSF flow, when there is evidence of malignant cells in the CSF (type I LMD). Significant toxicity may occur.	Expert opinion	95%
Liver metastases		
Prospective RCTs 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 randomised data supporting the effect of local therapy on survival, every patient must be informed of	Expert opinion/C	83%

Continued

Section IX. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
this when discussing a potential local therapy technique. Local therapy should only be proposed in very selected cases of good PS, with limited liver involvement and 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 ChT, etc.).		
Malignant pleural effusions		
Malignant pleural effusions require systemic treatment with/without local management.	III/A	86%
Thoracentesis for diagnosis should be performed if it is likely that this will change clinical management. False negative results are common.	III/B	
Drainage is recommended in patients with symptomatic, clinically significant pleural effusion.	III/A	
Use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful.	III/B	
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.	Expert opinion/A	100%
Chest wall and regional recurrences should be treated with surgical excision when feasible with limited risk of morbidity.	II/A	97%
Locoregional RT is indicated for patients not previously irradiated.	II/A	97%
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion/C	97%
In addition to local therapy (surgery and/or RT), in the absence of distant metastases, the use of systemic therapy (ChT, ET and/or anti-HER2 therapy) should be considered.	I/B	95%
ChT after first local or regional recurrence improves long-term outcomes in ER-negative disease and can be used.	I/B	95%
ET in this setting improves long-term outcomes for ER-positive disease and should be used.	I/B	95%
The choice of systemic treatment depends on tumour biology, previous treatments, length of DFI and patient-related factors (comorbidities, preferences, etc.).	Expert opinion/A	95%
In patients with disease not amenable to radical local treatment, the choice of palliative systemic therapy should be made according to principles previously defined for metastatic disease. These patients may still be considered for palliative local therapy.	Expert opinion/B	97%

In green, NEW ABC 5 statements.

ABC, advanced breast cancer; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; CPG, Clinical Practice Guideline; CSF, cerebrospinal fluid; DFI, disease-free interval; ER, estrogen receptor; ESMO, European Society for Medical Oncology; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LMD, leptomeningeal disease; LoE, level of evidence; MRI, magnetic resonance imaging; OS, overall survival; PS, performance status; QoL, quality of life; RCT, randomised controlled trial; RT, radiotherapy; WBRT, whole-brain radiotherapy.

The ABC panel decided to endorse the ESMO Clinical Practice Guideline (CPG) related to the use of bone-targeted agents (bisphosphonate, denosumab), which replace all previous statements regarding this subject.[99]

Leptomeningeal disease (LMD) is a rare complication of breast cancer with a 5% incidence rate. LMD carries a poor prognosis, with a median OS of approximately 4 weeks which can be prolonged to a few months in some patients with aggressive multimodal treatment.[100] Its diagnosis is based on clinical evaluation, cerebrospinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis. The European Association of Neuro-Oncology (EANO) and ESMO have proposed classifying LMD using two major criteria: presence (type I) or not (type II) of positive CSF and neuroimaging findings.[101] The same authors have proposed defining the therapeutic plan based on the presentation of the disease [nodular (A) or linear (B) or mixed (C) meningeal involvement, positive CSF cytology, presence or not of extracerebral disease, etc.] and taking into account the patient's life expectancy.[102] Available active treatment options are RT, intra-CSF therapy and systemic therapy. The choice of treatment should always involve multidisciplinary discussion. Currently, there is no accepted standard of care for breast cancer LMD and recommendations are essentially expert opinion-based. The EANO-ESMO CPG recommends considering focal RT for circumscribed, notably symptomatic lesions, and whole-brain RT (WBRT) for extensive nodular or symptomatic linear LMD.[101] The use of intrathecal therapy is controversial. It is recommended in cases where tumour cells are present in the CSF; it is optional in cases of linear metastatic meningeal disease.[100-102] This strategy is not recommended in patients with obstructive hydrocephalus (RT can be used to restore CSF flow and successful restoration should be checked before the use of any intrathecal treatment) or in patients with nodular meningeal metastases only. Three agents are commonly used for intrathecal treatment of LMD: methotrexate, cytarabine (including liposomal cytarabine) or thioTEPA.[100-102] Their use can cause a spectrum of toxicities ranging from myelosuppression to neurotoxicity. Methotrexate is the most commonly used agent. Neurotoxicity is increased with the use of methotrexate and RT and this combination is not recommended. Other agents, such as trastuzumab for HER2-positive disease, are under evaluation. Intrathecal therapy can be considered in cases where systemic disease is stable. However, two prospective trials have shown that the addition of intrathecal to systemic therapy has no OS or QoL advantage.[102] Retrospective data suggest some activity of different agents used systemically.[100-102] Since its onset,

Section X. Specific populations		
Guideline statement	**LoE/GoR**	**Consensus**
Advanced male breast cancer		
For ER-positive male ABC, which represents the majority of cases, ET is the preferred option unless there is visceral crisis or rapidly progressive disease needing a fast response.	III/A	100%

Continued

Section X. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
For ER-positive male ABC, tamoxifen is the preferred option.	IV/B	83%
For male patients with ABC who need to receive an AI, a concomitant LHRH agonist or orchidectomy is the preferred option. AI monotherapy may also be considered with close monitoring of response.	IV/B	86%
Clinical trials are needed in this patient population.		

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; AI, aromatase inhibitor; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence.

Section XI. LABC[a]		
Guideline statement	**LoE/GoR**	**Consensus**
Before starting any therapy, a core biopsy providing histology and biomarker expression (ER, PgR, HER2, proliferation/grade) is indispensable to guide treatment decisions.	I/A	97%
Since LABC patients have a significant risk of metastatic disease, a full staging work-up, including a complete history, physical examination, laboratory tests and imaging of the chest and abdomen (preferably with a CT scan) and bone before initiation of systemic therapy is highly recommended.	I/A	100%
PET-CT, if available, may be used (instead of and not in addition to CT scans and a bone scan).	II/B	100%
Systemic therapy (not surgery or RT) should be the initial treatment.	III/A	100%
If LABC remains inoperable after systemic therapy and eventual RT, 'palliative' mastectomy should not be done unless the surgery is likely to result in an overall improvement in QoL.	Expert opinion/D	
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and RT) is strongly indicated in the vast majority of cases.	I/A	100%
Options for **HR-positive LABC** include an anthracycline- and taxane-based ChT regimen, or ET.	I/A	85%
The choice of ChT versus ET as initial treatment will depend on tumour (grade, biomarker expression) and patient (menopausal status, PS, comorbidities, preference) considerations.	Expert opinion/A	85%
For **triple-negative LABC**, anthracycline- and taxane-based ChT is recommended as initial treatment.	I/A	85%
A platinum can be combined with the taxane.		
For **HER2-positive LABC**, concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR.	I/A	92%
For **HER2-positive LABC**, anthracycline-based ChT should be incorporated into the treatment regimen.	I/A	72%
When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.	I/A	87%
For patients with **HER2-positive LABC** (inflammatory or non-inflammatory), without distant metastases, who are in complete remission after appropriate preoperative systemic therapy and appropriate locoregional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 1 year of anti-HER2 therapy should be used.	I/A	85%
Following effective preoperative systemic therapy with or without RT, surgery will be possible in many patients. This will consist of mastectomy with axillary dissection in the majority of cases, but in selected patients with a good response, BCS may be possible.	II/A	98%
In patients with axillary low burden of disease at presentation (previously cN0-cN1) with complete response after systemic treatment (ycN0), SLNB can be an option, provided all the recommendations for sentinel node after primary systemic treatment are followed (i.e. dual tracer, clipping/marking positive nodes, minimum of three sentinel nodes).	III/B	62%
Inflammatory LABC		
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment.	I/A	93%
Mastectomy with axillary dissection is recommended in almost all cases, even when there is a good response to primary systemic therapy.	I/A	95%
Immediate reconstruction is generally not recommended in patients with inflammatory LABC.	IV/E	95%
Locoregional RT (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy.	I/A	98%

Continued

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; BCS, breast-conserving surgery; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ChT, chemotherapy; CT, computed tomography; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LABC, locally advanced breast cancer; LoE, level of evidence; pCR, pathological complete response; PET, positron emission tomography; PgR, progesterone receptor; PS, performance status; QoL, quality of life; RT, radiotherapy; SLNB, sentinel lymph node biopsy.

[a] For the purpose of these recommendations, LABC means inoperable, non-metastatic locally advanced breast cancer.

Section XII. Supportive and palliative care		
Guideline statement	**LoE/GoR**	**Consensus**
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.	I/A	100%
Early introduction of expert palliative care, including effective control of pain and other symptoms, should be a priority.	I/A	100%
Access to effective pain treatment (including morphine, which is	I/A	100%

Continued

Section XII. Continued

Guideline statement	LoE/GoR	Consensus
inexpensive) is necessary for all patients in need of pain relief.		
The ABC community is aware of the limitations that are being imposed worldwide, as a consequence of the opioid use disorders in certain areas of the world. The ABC community is united in insisting that cancer patients should not have restrictions placed that will limit their access to adequate pain control.	Expert opinion/n/a	100%
The panel encourages research on the potential role of cannabis to assist with pain and symptom control but strongly stresses that it cannot replace proven medicines such as morphine for adequate pain control.	I/C	97%
Optimally, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. However, when active treatment is no longer able to control widespread and life-threatening disease, and the toxicities of remaining options outweigh the benefits, physicians and other members of the healthcare team should initiate discussions with the patient (and family members/friends, if the patient agrees) about end-of-life care.	Expert opinion/A	96%
Management of cancer-related fatigue		
Cancer-related fatigue is frequently experienced by patients with ABC, exerts a deleterious impact on QoL and limits physical, functional, psychological and social well-being. The aetiology of this fatigue is complex; therefore, effective management needs to be multidimensional.		100%
It is important to assess cancer-related fatigue using appropriate PROMs before implementing various non-pharmacological (such as exercise [I, A]), and, if needed, pharmacological interventions [II, B].	I/A II/B	
Management of CDK inhibitor-induced neutropaenia		
Neutropaenia is the most common toxicity associated with CDK4/6 inhibition and is not generally associated with febrile neutropaenia, although an increase in infections has been reported. Treatment should be delayed until neutrophils have recovered to at least 1000/μl; dose reduction can also be considered.	II/A	100%
Management of NIP		
NIP is an uncommon complication of mTOR inhibition or CDK4/6 inhibition. Patient education is critical to ensure early reporting of respiratory symptoms. Treatment interruption and dose reduction are generally effective for grade 2 symptomatic NIP with the use of systemic steroids and treatment discontinuation for grade 3 or greater toxicity.	II/A	100%

Continued

Section XII. Continued

Guideline statement	LoE/GoR	Consensus
Management of dyspnoea		
Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anaemia or drug toxicity must be ruled out. Patient support is essential. Oxygen is of no use in non-hypoxic patients.		100%
Opioids are the drugs of choice in the palliation of dyspnoea.	I/A	
Benzodiazepines can be used in patients experiencing anxiety.	II/A	
Steroids can be effective in dyspnoea caused by lymphangitis carcinomatosis, RT or drug-induced pneumonitis, superior vena cava syndrome, an inflammatory component or in (cancer-induced) obstruction of the airways (in which case laser/stent is to be considered).	Expert opinion/B	
Management of nausea and vomiting		
ESMO/MASCC guidelines[103] are available for the management of ChT-induced and morphine-induced nausea and vomiting, and these are endorsed by the ABC community.		100%
There is a need to study nausea and vomiting related to chronic use of anticancer drugs.	Expert opinion/A	
Management of endocrine toxicities from mTOR or *PIK3CA* inhibition		
Hyperglycaemia and hyperlipidaemia are common, sub-acute complications of mTOR or *PIK3CA* inhibition. Evaluation of pre-existing diabetes or hyperglycaemia at baseline is essential. Regular, careful monitoring of glycaemia and lipid panel is needed to identify these toxicities.	II/A	100%
Management of grade 1 and 2 hyperglycaemia includes treatment with oral antidiabetics and basal insulin, in accordance with international recommendations for diabetes mellitus treatment. Statins are indicated to treat grade 2 and 3 hypercholesterolaemia, and fibrates should be introduced if the triglyceride level is >500 mg/dl (with attention to possible drug—drug interaction between everolimus and fibrates). Treatment interruption and dose reduction are generally effective for grade 2 and 3 toxicity. Treatment should be discontinued for grade 4 toxicity.		
Management of mucositis/stomatitis		
Steroid mouthwash should be used for the prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5 mg/5 ml dexamethasone, 10 ml to swish × 2 min, then spit out; q.i.d.).	I/B	100%
Early intervention is recommended.	Expert opinion/A	
For grade >2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended.	Expert opinion/A	

Continued

Section XII. Continued

Guideline statement	LoE/GoR	Consensus
Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis.	Expert opinion/B	100%
Consider adding steroid dental paste to treat developing ulcerations.	Expert opinion/B	
Management of CIPN		
CIPN is frequent and potentially dose-limiting. Risk factors for neuropathy and pre-existing neuropathy need to be identified.		
No medical prevention can currently be recommended.	II/C	
Drug-related factors (dosing, timing, route) can lower the risk of CIPN.		
The use of tight gloves and socks during ChT may help reduce the incidence and severity of CIPN.	I/C	
There are limited evidence-based treatments for CIPN, with tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, duloxetine, pregabalin and gabapentin being most often used.	II/B	
High-quality studies are needed to evaluate strategies for the prevention and management of CIPN.		
Management of HFS		
HFS is also described as palmar-plantar erythrodysesthaesia syndrome. Most frequent causes are capecitabine, pegylated liposomal doxorubicin and multikinase inhibitors.		100%
Patients should be instructed about early recognition of HFS.		
Drug-related factors (dosing, timing, route) can lower the risk of HFS.		
Treatment of hyperkeratosis/fungal infections, comfortable shoes and avoidance of friction and heat are recommended.	Expert opinion/A	
Intensive skin care of hands and feet (urea cream/ointment) is recommended.	II/A	
High-quality studies are needed to evaluate strategies for the prevention and management of HFS.		
Management of postmenopausal symptoms		
Systemic hormone therapy is generally not recommended to treat postmenopausal symptoms in ABC patients, particularly not in ER-positive disease.	I/D	100%
Valid alternatives are:		
• For postmenopausal symptoms in general: mind-body interventions, physical training and CBT are effective non-pharmacological treatment options.	I/B	
• For hot flushes: venlafaxine, oxybutynin, gabapentin, clonidine and acupuncture are available options.	I/B	
• For sleep disturbances: melatonin.	II/C	
There is no convincing evidence that phytotherapeutic drugs improve postmenopausal symptoms. Possible drug interactions must be considered.	I/D	

Continued

Section XII. Continued

Guideline statement	LoE/GoR	Consensus
Sexual health		
Sexuality is an experience on many levels and is not confined to the act of intercourse. Sexuality remains important for many ABC patients. ABC patients frequently experience impaired sexual health and need specific attention. Openly addressing misconceptions and sexual challenges after treatment, as well as educating patients, have been shown to improve QoL. When life expectancy is limited, physical contact, affection, emotional communication and comfort are particularly important. Standardised instruments (questionnaires) may help to assess the grade of impairment.	Expert opinion/n/a	100%
Dyspareunia		
Dyspareunia is often caused by vaginal dryness.		
The first choice for treating vaginal dryness and soreness are hormone-free lubricants and moisturisers (e.g. water-based gel, hyaluronic acid gel).	II/B	100%
If hormone-free measures are not effective, low-dose estrogen-containing vaginal medication may be used.	II/B	100%
The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.		

In green, NEW ABC 5 statements.

ABC, advanced breast cancer; CBT, cognitive behavioural therapy; CDK, cyclin-dependent kinase; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ESMO, European Society for Medical Oncology; GoR, grade of recommendation; HFS, hand and foot syndrome; LoE, level of evidence; MASCC, Multinational Association of Supportive Care in Cancer; mTOR, mammalian target of rapamycin; n/a, not applicable; NIP, non-infectious pneumonitis; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROM, patient-reported outcome measure; q.i.d., four times a day; QoL, quality of life; RT, radiotherapy.

ABC meetings and guidelines have highlighted and fought for early and equal access to effective pain treatment (including morphine, which is inexpensive) for all patients in need of pain relief.[104] Yet, in Europe and all over the world, there is inadequate and very unequal access to pain control,[105] and the recent ESMO guidelines[106] are difficult to follow in those countries where the majority of patients experiencing cancer pain live. Recent years have seen a drawback in adequate cancer pain management, even in wealthy countries, due to what is known as the opioid epidemic, which has a myriad of causes and will not be solved by any simple solution.[107] Consequent to a staggering increase in opioid-related deaths in the United States, various governmental inputs and stakeholder strategies have been proposed and implemented with varying success. Recent trends in opioid-related data demonstrate an almost fourfold increase in overdose deaths from 1999 to 2008. Stricter prescribing practices and prescription monitoring programmes have been instituted but unfortunately these have raised obstacles for cancer patients. Several organisations, such as ASCO,[108] have been calling for measures to

ensure adequate protection of cancer patients. The ABC panel strongly supports this position and states that no restrictions should be in place that limit cancer patients' access to adequate pain control.

Recent data on cannabidiol for medical use has not yet substantiated claims indicating that it is effective in cancer pain management to the same level as morphine[109] and more research is needed.[110]

Many therapies for ABC are associated with estrogen deprivation and patients often suffer from menopausal symptoms such as hot flushes, night sweats, sleep disturbances, fatigue, arthralgia, cognitive impairment, depression and vaginal dryness, as well as impaired sexual functioning (e.g. loss of sexual desire, dyspareunia). Hormone replacement therapy is contraindicated due to the endocrine character of the disease and should not be used to treat complaints. Nevertheless, the final decision belongs to the patient, after adequate information, since in some cases these symptoms are impacting significantly on QoL.[111,112] For menopausal symptoms in general, mind-body interventions, physical training and cognitive behavioural therapy should be recommended as effective non-pharmacological treatment options.[113-117] To control hot flushes, valid alternatives are venlafaxine, oxybutynin, gabapentin and clonidine.[118-121] Sleep disturbances may be treated with melatonin.[122,123] There is no convincing evidence that phytotherapeutic drugs may improve menopausal symptoms. Possible drug interactions must be considered.

Sexuality is an experience on many levels and is not confined to the act of intercourse. ABC patients frequently experience impaired sexual health and need specific attention. A recent retrospective study showed that breast cancer patients are more affected than patients with ovarian cancer or healthy controls: decreased or no interest in sexual activity was frequently reported with a significant association to less satisfaction and more discomfort (dyspareunia); however, the lack of desire was not associated with global health status, QoL or the ability to experience orgasms; estrogen deprivation (gonadotropin-releasing hormone agonists, AIs) seemed to have more impact than tamoxifen.[124]

Dyspareunia is often caused by vaginal dryness. The first choice for treating vaginal dryness and soreness are hormone-free lubricants (e.g. water-based gel, hyaluronic acid gel).[125-127] If hormone-free measures are not effective, low-dose estriol-containing vaginal medication may be used.[128-132] The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.[133-135] In summary, gynaecological and sexual symptoms are important challenges for most ABC patients. In particular, even in an anonymous setting, patients are often too shy to report their problems regarding impaired sexual life. Therefore, active verbalisation of gynaecological and sexual symptoms in an adequate and trustful atmosphere is a mandatory part of follow-up visits. Openly addressing misconceptions and sexual challenges after treatment, as well as educating patients, have been shown to improve QoL. When life expectancy is limited, physical contact, affection, emotional communication and comfort are particularly important. Standardised instruments (questionnaires) may help to assess the grade of impairment.[136-140] At first recurrence, one out of four patients is younger than 50 years old and premenopausal. Therefore, issues of fertility and contraception must be discussed, and for the latter, only hormone-free contraceptives can be recommended.[141]

Section XIII. Integrative medicine

Guideline statement	LoE/GoR	Consensus
Alternative therapies (i.e. therapies used instead of scientifically-based medicines) are not recommended in any phase or stage of cancer treatment.	n/a/E	100%
Breast cancer centres/units/departments should be aware that the majority of their patients would like to be informed about CIM and that many of them are using it. Physicians should actively ask for information about its use in view of the potential deleterious interactions with specific anticancer therapies. If complementary therapies are not available at the centre, certified contacts should be available to promote referral to practitioners qualified in the therapies people are interested in receiving.	Expert opinion/C	100%
Some complementary therapies have the potential to reduce disease symptom burden and/or side-effects of anticancer therapies, and therefore improve the QoL of ABC patients.	Expert opinion/C	100%
Evidence suggests beneficial effects of the following methods, which can therefore be used: • Physical exercise/sport (equivalent to 3-5 hours of moderate walking per week) improves QoL, cardiorespiratory fitness, physical performance and fatigue, and it may also improve DFS and OS. • MBSR programmes, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side-effects of anticancer therapies. • Acupuncture may help against ChT-induced nausea and vomiting, fatigue and hot flushes.	I/B	100%
Methods with no or unfavourable effects The following methods of alternative medicine are not recommended in ABC since available evidence shows no effect at best, or even association with worse outcome: • Antioxidant supplements • Drugs outside the approved indication (e.g. methadone) • Herbs including Chinese herbal medicine • Orthomolecular substances (selenium, zinc, etc.) • Oxygen and ozone therapy • Proteolytic enzymes, thymic peptides • Phytoestrogens (soy food, isoflavones)	II/E	100%

Continued

Section XIII. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
• High-dose vitamins (vitamin C, D, E, carotenoids, etc.) • L-carnitine, laetrile		

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; ChT, chemotherapy; CIM, complementary and integrative medicine; consensus, percentage of panel members in agreement with the statement; DFS, disease-free survival; GoR, grade of recommendation; LoE, level of evidence; MBSR, mindfulness-based stress reduction; n/a, not applicable; OS, overall survival; QoL, quality of life.

CONCLUSIONS AND FUTURE DIRECTIONS

ABC guidelines provide a useful tool for the management of ABC in clinical practice. Each guideline has an associated LoE, GoR and percentage of consensus. Additionally, v1.1 of the ESMO-MCBS[13] was applied to drugs approved by the EMA after 2016. As usual, if additional new agents are approved by the EMA before the next ABC Consensus Conference, the ESMO-MCBS will be applied and the result will be made available as an e-update to the present guidelines.

We acknowledge that in many areas of the world, some of these guidelines may not be implemented due to the existence of disparities in access. It is the mission of the ABC Global Alliance[142] to fight for better outcomes for all ABC patients around the world. For this goal to be achieved, efforts must continue not only in research but also in public policy to ensure equal access to multidisciplinary, specialised care, including anticancer, palliative and end-of-life care, and full implementation of these guidelines. We emphasise again that reimbursement rules in all countries should be patient-centred and be an incentive to, not work against, the clinical implementation of high-quality international guidelines. Clinical trials and consequent approval and reimbursement must not continue to exclude certain groups of patients, such as premenopausal women and men, which keep seeing their treatment options reduced in many countries.

At a time when the world is facing the COVID-19 pandemic, the ABC community must unite to maintain or increase the resources needed to face the ever-rising cancer 'epidemic', which is responsible for 18.1 million new cases and 9.6 million deaths annually worldwide, with half a million deaths annually due to ABC.[12]

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