ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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SPECIAL ARTICLE

4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†

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†These guidelines were developed by the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO).

Key words: breast cancer, metastatic, advanced, guidelines, ABC, ESO-ESMO

Advanced Breast Cancer (ABC) comprises both locally advanced breast cancer (LABC) and metastatic breast cancer (MBC) [1]. Although treatable, MBC remains virtually an incurable disease with a median overall survival (OS) of ~3 years and a 5-year survival of only ~25% [2, 3]. The MBC Decade Report [2] shows that progress has been slow in terms of improved outcomes, quality of life (QoL), awareness and information regarding ABC. More recently, some studies seem to indicate an improvement in OS, mostly due to advances in human epidermal growth factor receptor 2 (HER2)-positive ABC [4–6]. The better survival is seen in an environment with access to the best available care and particularly in *de novo* ABC, while recurrent ABC seems to become harder to manage [7, 8].

The last decade has seen an improvement in the levels of evidence (LoEs) used for many of the ABC recommendations, however, still far from the LoEs existing for the majority of early

breast cancer guidelines. More and better, more innovatively designed trials are urgently needed, in particular to address clinically important questions, not necessarily related to a specific therapeutic agent. The use of real world evidence and the application of big data analysis to oncology may soon become important additional pathways to acquire the necessary LoEs.

At the research level, efforts continue to better understand the biology and heterogeneity of ABC, as well as mechanisms of tumour resistance and biomarkers predictive of response to the different therapeutic options. However, the majority of the recent research highlights are not yet ready for routine clinical practice implementation.

The 4th International Consensus Conference for ABC (ABC 4) took place in Lisbon, Portugal on 2–4 November 2017, bringing together 1300 participants from 88 countries, including health professionals, patient advocates and journalists. Its primary aim is the development of international consensus guidelines for the management of ABC patients. These guidelines are based on the most up-to-date evidence and can be used to guide treatment decision making in many different healthcare settings globally, with the necessary adaptations due to different access to care.

The ABC guidelines are developed as a joint effort from ESO and ESMO and are endorsed by EUSOMA (European Society of Breast Cancer Specialists), ESTRO (European Society of Radiation Oncology), UICC (Union for International Cancer Control), SIS (Senologic International Society) and Flam (FederatiónLatinoAmericana de Mastologia). There was also official representation of ASCO (American Society of Clinical Oncology) in the consensus panel. The ABC 4 Conference was also organised under the auspices of OECI (Organization of European Cancer Institutes) and with the support of the BCRF (Breast Cancer Research Foundation) and the Susan G Komen for the Cure.

The present manuscript summarises the guidelines developed at ABC 4 and is supported with the LoEs, grades of recommendation (GoRs), percentages of consensus reached at the Conference and supporting references. In addition, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) was applied to new European Medicines Agency (EMA)-approved drugs [9], and ESMO-MCBS scores for new therapies/indications are included. ESMO-MCBS version 1.1 (v1.1) [9] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016.

Methodology

Before the ABC 4 Conference, a set of preliminary recommendation statements on the management of ABC were prepared, based on available published data and following the ESMO guidelines methodology. These recommendations were circulated to all 42 panel members by email for comments and corrections on content and wording. A final set of recommendations was presented, discussed and voted upon during the consensus session of ABC 4. All panel members were instructed to vote on all questions, with members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field) instructed to vote 'abstain'. A new possible answer was included in the Precision Medicine statements: 'Insufficient data', which should be selected if the panel member believes the existent data were not enough to vote 'yes' or 'no', highlighting an area where research is needed. Additional changes in the wording of statements were made during the session.

The statements related to management of side effects and difficult symptoms, included under the Supportive and Palliative Care section, were not voted on during the consensus session, but discussed and unanimously agreed by email, and are considered to have 100% agreement. Previous ABC recommendations that did not require update or only minor changes were not re-voted but were reviewed by all panel members by email and remain valid. To provide a full overview of all ABC guidelines currently approved, the authors have listed all recommendations per subject, highlighting those that were discussed, voted and approved in ABC 4.

Supplementary Table S1, available at *Annals of Oncology* online, describes the new grading system used, as per ESMO guidelines methodology, adapted from [10]; see http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology.

Supplementary Table S2, available at *Annals of Oncology* online, lists all members of the ABC 4 consensus panel and their disclosures of any relationships with the pharmaceutical industry that could be perceived as a potential conflict of interest.

Supplementary Figures, available at *Annals of Oncology* online, features updated ABC diagnostic and treatment algorithms.

Slides with all ABC guidelines statements are available online at http://www.abc-lisbon.org/ and http://oncologypro.esmo.org/Guidelines/ESMO-Consensus-Conferences/Breast-Cancer.

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 visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.	Expert opinion/ n/a	95%
Primary endocrine resistance is defined as relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of first-line ET for ABC, while on ET.	Expert opinion/ n/a	67%
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 $\geq$ 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 5 and not necessarily in	Expert opinion/ n/a	78%

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Guideline statement	LoE/GoR	Consensus
the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.		
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 pre-menopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or OFA through pelvic RT (this latter is not always effective and therefore is the least preferred option).	I/A	85%
If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to guarantee optimal OFS.	II/B	85%
Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum oestradiol, even in the presence of amenorrhoea, especially if an AI is administered.	Expert opinion/ B	85%
As all endocrine interventions for pre-menopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time and cost.	Expert opinion/ B	85%
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 ABC 4 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 2; LHRH, luteinising hormone-releasing hormone; LoE, available level of evidence; OFA, ovarian function ablation; OFS, ovarian function suppression; PD, disease progression; q4w, every 4 weeks; RT, radiotherapy.

Following the effort to standardise definitions and homogenise the use of certain medical terms, ABC 4 provides three additional definitions.

Adequate ovarian function suppression (OFS) or ablation (OFA) is a somewhat controversial but crucial issue in the treatment of pre-menopausal patients with oestrogen receptor (ER)-positive ABC. As already extensively discussed in previous editions, the main recommendation for these patients is the induction of OFS/OFA, to which an additional endocrine agent should be added [1, 11]. The method for inducing OFS or OFA may vary due to patient's preferences, logistical and financial issues. Bilateral salpingo-oophorectomy by a minimal invasive approach is a reasonable option and should be discussed with patients. The confirmation that ovarian function is adequately suppressed when chemically induced [i.e. luteinising hormone-releasing hormone (LHRH) agonist] is not always straightforward but it is indispensable if an aromatase inhibitor (AI) is given concomitantly, in view of the oestrogen-inducing effect of these agents in the absence of OFS. The best way to obtain this confirmation [i.e. testing oestradiol levels with or without levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH)] and the timing and frequency of confirmation tests are not well established and there was substantial discussion among panel members. It was decided, as a compromise, to recommend serial measures of serum oestradiol during the initial months of treatment with an AI + LHRH agonist. When a LHRH agonist is used, the majority of the panel recommends the use of the q4w (every 4 weeks) regimen. There are, however, some recent data regarding the use of the 3-monthly regimen with concurrent tamoxifen that yielded similar results in terms of pharmacodynamic and safety profiles [12, 13] in two randomised trials of 222 and 170 patients, respectively, and may, therefore, be considered a valid option when combined with tamoxifen for selected patients.

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, 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%

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Guideline statement	LoE/GoR	Consensus
Following a thorough assessment and confirmation of ABC, the potential treatment goals of care should be discussed. Patients should be told that ABC is incurable but treatable, and that some patients can live with ABC for extended periods of time (many years in some circumstances).	Expert opinion/ A	97%
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.	Expert opinion/ A	100%
Every ABC patient should:		
• Have access to the most up-to-date treatments and to innovative therapies at accessible Breast Units/Centres.	Expert opinion/ A	100%
• 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.	I/A	
• Survivorship issues and palliative care should be addressed and offered at an early stage.	Expert opinion/ A	
• 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/ B	
General: 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 specific 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: clinical trials		
There are few proven standards of care in ABC management. After appropriate informed consent, inclusion of patients in well-designed, prospective, independent trials must be a priority whenever such trials are available, and the patient is willing to participate.	Expert opinion/ A	100%
The ABC community strongly calls for clinical trials addressing important unanswered clinical questions in this	Expert opinion/ A	100%

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Guideline statement	LoE/GoR	Consensus
setting, and not just for regulatory purposes. Clinical trials should continue to be carried out, even after approval of a new treatment, providing real world data on its performance, efficacy and toxicity.		
General: 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 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.	I/A	90%
General: 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 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, screening breast imaging should be an option.	Expert opinion/ C	Yes: 53% No: 47%
Breast imaging should also be carried out 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: 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 ABC 4 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, available level of evidence; PRO, patient-reported outcome; PROM, patient-reported outcome measure; QoL, quality of life.

The majority of general recommendations from previous ABC conferences still stand as all available new data reinforces the guidelines and, in some cases, increases the LoE and/or GoR.

Access to the best available therapies as well as treatment by a specialised and multidisciplinary team are crucial to achieve the best outcomes. However, access to treatments is very

heterogeneous between different countries and within each country, depending largely on financial, reimbursement and coverage issues. All guidelines that are related to a certain treatment depend, obviously, on the availability of that treatment. In all ABC guidelines, when 'preferred option' or 'standard of care' terms are used, they assume availability of the agent(s) discussed. Currently, some efforts are being made to adapt the ABC Guidelines to different environments, such as Africa, South America and Asia, but these are separate projects, outside the scope of the main guidelines and this manuscript.

One possible way to minimise the issue of cost is the use of biosimilars. In line with the ESMO position [14], the ABC community strongly supports the use of biosimilars both for treatment of breast cancer (i.e. trastuzumab) and for supportive care (i.e. growth factors). Importantly, only those biosimilars that pass the stringent development and validation processes required by the EMA or the Food and Drug Administration (FDA) or other similarly strict authority should be used. Additionally, in order to lead to a significant economic impact and making treatment available to more patients with breast cancer, the price of biosimilars should be substantially lower than the original compounds.

Accessibility to multidisciplinary care is also very uneven throughout the world, for all cancer patients but particularly for advanced cancer patients, who usually continue to be managed by a single isolated physician. In Europe, the fight for the establishment of Specialised Breast Units/Centres/Services (SBUs) has been long and slow, with scattered implementation despite recommendations from the European Parliament for the last decade [15].

Fortunately, some ABC patients can now live several years, especially those who achieve long-lasting complete remissions. This is more frequent in situations of oligometastatic disease or with HER2-positive disease. Survivorship issues have therefore started to be discussed also for ABC patients. A highly sensitive issue is fertility preservation and motherhood in ABC patients. Every patient has the right to be informed about the potential negative impact on fertility of anticancer therapies. This is particularly complex for luminal ABC where induction of OFS or OFA is the mainstay of therapy. If a desire for pregnancy exists or if pregnancy inadvertently occurs, a delicate and thorough discussion should occur with the patient and partner regarding the long-term prognosis of the disease and the potential consequences of stopping any ongoing therapy. However, after full information, the final decision lays with the patient and should be respected [16–19].

Discussions about the risk/benefits of different further active anticancer treatments in ABC can be challenging, especially if the drugs offered might not reduce symptom burden or prolong survival but do have significant toxicities. Patients need good information, collected systematically with reliable tools, about likely harms and benefits to enable balanced decision making. Although more trials of novel therapies do now build in health-related QoL (HRQoL) assessment, many publications still give precedence to physician recorded side effects grades using Common Terminology Criteria for Adverse Events (CTCAE) criteria rather than patient-reported outcomes (PROs). Studies show that for many common toxicities, there is poor concordance between physician reported and patient-reported side effects in terms of both frequency and severity. Even when trials do employ standardised PROs, they are often inappropriate measures, more suitable for use in early-stage disease. Both the European Organisation for Research and Treatment of Cancer (EORTC) and Functional Assessment of Cancer Therapy (FACT) systems have site and treatment specific modules or subscales that should be incorporated with more generic HRQoL measures. 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. In addition, specific tools developed for HRQoL assessment in ABC patients are needed and are the goal of an ongoing collaborative project between the EORTC Quality of Life and Breast Cancer Groups.

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 chest, abdomen and bone.	II/A	67%
Brain imaging should not be routinely carried out in asymptomatic patients. This approach is applicable to all patients with ABC including those with HER2-positive and/or metastatic TNBC.	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. A change 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 two to four cycles for ChT, depending on the dynamics of the disease, the location and extent of metastatic involvement and type of treatment. Imaging of target lesions may be sufficient in many patients. In certain patients, such as those with indolent disease, less frequent monitoring is acceptable. Additional testing should be carried out in a timely manner, irrespective of the planned intervals, if PD is suspected or new symptoms appear. Thorough history and physical examination must always be carried out.	Expert opinion/ B	81%

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Guideline statement	LoE/GoR	Consensus
Biopsy guidelines		
A biopsy (preferably providing histology) of a metastatic lesion should be carried out, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.	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, 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 carried out 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%

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Guideline statement	LoE/GoR	Consensus
Systemic treatment general guidelines		
Treatment choice should take into account at least these factors: HR and HER2 status, 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), need for a rapid disease/symptom control, socio-economic and psychological factors, available therapies in the patient's country and patient's preferences.	Expert opinion/ A	100%
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 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 treatment of choice. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.	I/A	59%
In patients pre-treated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, and who do not need combination ChT, single-agent	I/A	77%

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Guideline statement	LoE/GoR	Consensus
capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes and liposomal anthracyclines. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability.		
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 DFS.	I/B	92%
If given in the adjuvant setting, provided that maximum cumulative dose has not been achieved and that there are no cardiac contraindications, anthracyclines can be re-used in ABC, particularly if there has been at least 1 year of DFS.	I/B	93%
Metronomic ChT is a reasonable treatment option for patients not requiring rapid tumour response. The better studied regimen is CM (low-dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine). Randomised trials are needed to accurately compare metronomic ChT with standard dosing regimens.	I/B	88%
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- or second-line therapy for ABC provides only a moderate benefit in PFS and no benefit in OS. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases in these settings and is not recommended after first/second line.	I/C	74%

No new statements for this section were developed at ABC 4.

ABC, advanced breast cancer; ChT, chemotherapy; Consensus, percentage of panel members in agreement with the statement; ET, endocrine therapy; DFI, disease-free interval; DFS, disease-free survival; GoR, grade of recommendation; HER2, human epidermal growth factor 2; HR, hormone receptor; LoE, available level of evidence; OS, overall survival; PD, disease progression; PFS, progression-free survival; PS, performance status; QoL, quality of life; TNBC, triple-negative breast cancer.

Section IV: ER-positive/HER2-negative (luminal) 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 or concern/proof of endocrine resistance.	I/A	93%
Many trials in ER-positive ABC have not included **PRE-MENOPAUSAL** 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 post-menopausal women, with endocrine agents and 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 post-menopausal women, and men.	Expert opinion/ A	92%
For pre-menopausal women, for whom ET was decided, OFS/OFA combined with additional ET is the preferred choice.	I/A	93%
OFA by laparoscopic bilateral oophorectomy ensures definitive oestrogen suppression and contraception, avoids potential initial tumour flare with LHRH agonist and may increase eligibility for clinical trials. Patients should be informed on the options of 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 pre-menopausal women who decline OFS/OFA, but the panel believes it is a less effective option.	I/D	92%
The preferred first-line ET 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 peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women.	I/A	84%
The addition of a CDK 4/6 inhibitor to an AI, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is, therefore, one of the preferred treatment options for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women. Patients relapsing <12 months from the end of adjuvant AI	I/A	90%

Continued

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Guideline statement	LoE/GoR	Consensus
were not included in the published studies and may not be suitable for this combination. OS results are still awaited. QoL was comparable to that with ET alone.		
ESMO-MCBS v1.1 score: 3		
The addition of a CDK 4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6–7 months) as well as improvement in QoL, and is one of the preferred treatment options, if a CDK 4/6 inhibitor was not previously used, for pre- and peri-menopausal women with OFS/OFA and post-menopausal women and men. OS results are awaited.	I/A	90%
ESMO-MCBS v1.1 score: 4		
The addition of everolimus to an AI is a valid option for some patients [for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women] previously exposed to ET, since it significantly prolongs PFS, albeit without evidence of OS benefit. The decision to treat must take into account the toxicities associated with this combination, lack of statistical significant OS benefit, cost and availability.	I/B	88%
ESMO-MCBS v1.1 score: 2		
Tamoxifen or fulvestrant can also be combined with everolimus.	II/B	80%
Adequate prevention, close monitoring and proactive treatment of adverse events 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%
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used [in the (neo)adjuvant or advanced settings], the burden of the disease, patients' preference, costs and availability. Available options [for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women] include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK 4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and oestradiol, as well as repetition of previously used agents, may be used.	I/A	95%

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Guideline statement	LoE/GoR	Consensus
It is currently unknown how the different combinations of endocrine + targeted agents compare with each other, and with single-agent ChT. Trials are ongoing.		
Everolimus and CDK 4/6 inhibitors should not be used after PD on that specific agent (i.e. beyond progression).	n/a/E	74%
At present, no validated predictive biomarkers other than HR status exist to identify patients who will/will not benefit from the addition of a targeted agent (i.e. CDK 4/6 inhibitor, mTOR inhibitor) to ET and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.	I/E	95%
The combination of a non-steroidal AI and fulvestrant as first-line therapy for post-menopausal 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. 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.	II/C	Yes: 33% No: 53% Abstain: 14%
Concomitant ChT and ET has not shown a survival benefit and should not be carried out 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 assessed in randomised trials.	III/B	88%

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; Consensus, percentage of panel members in agreement with the statement; ER, oestrogen 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 2; HR, hormone receptor; LHRH, luteinising hormone-releasing hormone; LoE, available level of evidence; mTOR, mechanistic target of rapamycin; OFA, ovarian function ablation; OFS, ovarian function suppression; OS, overall survival; PD, disease progression; PFS, progression-free survival; QoL, quality of life.

Most of the revised guidelines at ABC 4 relate to ER-positive/HER2-negative or luminal ABC, in which most of the recent advances in the field occurred. As in previous ABC guidelines and in accordance with all national guidelines, the preferred treatment for luminal ABC is endocrine therapy (ET) in the majority of cases, excluding only those with visceral crisis or concern or

proof for endocrine resistance (both defined in Section I). Unfortunately, this recommendation continues to be very often ignored in current clinical practice, mainly due to financial reasons and reimbursement rules that are not patient-focused, that pressure for the use of i.v. therapies (discussed in [20]).

Two conceptual changes were introduced at ABC 4 regarding pre-menopausal patients and lines of therapy. As previously discussed, the optimal management of pre-menopausal patients with luminal ABC consists of the induction of OFS or OFA, in combination with another endocrine agent [21]. Since the first step is to render the patient post-menopausal, we believe that all other recommendations should be common to both post-menopausal and initially pre- or peri-menopausal patients. Furthermore, resources should not be wasted running duplicate and separate trials for pre- and post-menopausal patients, but rather pre-menopausal patients should be eligible for trials if OFS or OFA is carried out. The definition of optimal OFS/OFA in the context of ABC is described in Section I. Furthermore, the ABC panel strongly advocates against unrealistic, unnecessary and sometimes expensive clinical trial requirements on contraception, with clear negative impact on QoL, for pre-menopausal women who do not undergo OFS/OFA, such as multiple contraceptive methods [e.g. intrauterine device (IUD) plus condoms plus spermicide] or complete abstinence, which are sometimes required to be continued for 6 months after the completion of study drug.

The choice among different available agents as well as their sequence depends largely on which agents were previously administered and the response obtained, due to the link with endocrine resistance. For this reason, previous exposure, and not only line of treatment, should guide the recommendations.

With the publication of the Falcon study [22], available options for initial single-agent ET include an AI, fulvestrant and tamoxifen. The choice will be largely determined by previous exposure in the adjuvant setting.

The last 2 years saw the approval of three cyclin-dependent kinase (CDK) inhibitors—palbociclib, ribociclib and abemaciclib—by the FDA and the first two by the EMA (it is foreseen that abemaciclib will soon be approved by EMA as well). Currently, several open questions remain regarding the optimal integration of these agents in clinical practice, such as: (i) accurate identification, if possible by biomarkers, of the patients who need the combination of ET and a CDK inhibitor, those who need to be treated with chemotherapy (ChT) and those who can be adequately treated with endocrine agents alone; (ii) optimal sequence for the individual patient and (iii) optimal treatment after progression on CDK inhibitors.

When applying the ESMO-MCBS version 1.1 [9] to each drug in each setting, both efficacy and toxicity/QoL must be taken into account. Unfortunately, and as discussed above, some trials do not assess HRQoL and others do not use the most adequate tools to assess it. The use of CDK inhibitors in the first-line setting has been associated with a substantial (about 10 months) benefit in PFS [23–29], while OS results are still awaited. They have a favourable safety profile, with neutropaenia not associated with infections being the most common side effect. However, in this setting their use has not been associated with an improvement in HRQoL [30, 31], except perhaps in MONALEESA-7 [27]. A more recent evaluation in PALOMA-2 indicates that disease progression (PD) is associated with degradation of HRQoL, both in the palbociclib arm and the placebo arm [32]. For the reasons described, the use of a CDK inhibitor in the first-line setting reaches an ESMO-MCBS score of 3. In the second-line setting, their use has been associated with a 6–7 months progression-free survival (PFS) benefit [33, 34] and an HRQoL improvement [35, 36], and hence their ESMO-MCBS score is 4. There are some differences in the safety profile among the three CDK inhibitors, with less neutropaenia and more diarrhoea associated with abemaciclib, less hepatotoxicity with palbociclib and potential for QT interval prolongation with ribociclib. Abemaciclib has shown important single-agent activity [37, 38] as well as potential for crossing the blood-brain barrier [39].

Combination of an endocrine agent (AI, tamoxifen or fulvestrant) with everolimus has shown a PFS benefit, albeit without a statistically significant OS benefit [40, 41] in the second-line setting and, more recently, also in the first-line setting [42], and is an available option for patients previously exposed to ET. Its use is associated with substantial toxicity, which downgrades its ESMO-MCBS score to 2. However, as more experience is gained regarding the use of everolimus and the management of its toxicities, its clinical use becomes easier, in particular regarding management of mucositis, as described in Section XII. Adequate prevention, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the BOLERO-2 trial [43].

Areas where research efforts must continue are predictive biomarkers, optimal sequence and best management for patients who progressed during or less than 1 year after adjuvant AIs, since these patients have been consistently and unfortunately excluded from most first-line therapy trials.

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	I/A	91%

Continued

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Guideline statement	LoE/GoR	Consensus
sequence of all available anti-HER2 therapies is currently unknown. The optimal duration of anti-HER2 therapy for ABC (i.e. when to stop these agents) is currently unknown.		
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 the 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, when 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%
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.	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 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 this three-drug regimen should not be given beyond progression outside clinical trials.	Expert opinion/ 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. However, there are no data on the use of T-DM1 after dual blockade with trastuzumab + pertuzumab.	I/A	88%
In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. There are however, no data on the use of this combination after progression on pertuzumab or T-DM1.	I/B	84%
Regarding the ChT component of HER2 positive ABC treatment: When pertuzumab is not given, first-line regimens for HER2 ABC can include trastuzumab combined with vinorelbine or a taxane. Differences in toxicity between these regimens should be considered	I/A	88%

Continued

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Guideline statement	LoE/GoR	Consensus
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.		
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, platinum, 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] and capecitabine [II/A].	See in statement	86%

[a]See definition in text.

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; ChT, chemotherapy; CM, low-dose oral cyclophosphamide and methotrexate; Consensus, percentage of panel members in agreement with the statement; DFI, disease-free interval; ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor 2; LoE, available level of evidence; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

In ABC 3, almost all guidelines for the management of HER2-positive ABC were reviewed, and few new data were presented/published in the last 2 years. The exception is related to the subgroup of ER-positive/HER2-positive disease for which the ALTERNATIVE trial results were presented at ASCO 2017 [44]. This trial evaluated the role of ET + anti-HER2 therapy (trastuzumab alone, lapatinib alone or dual blockade with trastuzumab + lapatinib) in 355 patients with ABC progressing during or following prior trastuzumab + ChT in the neo(adjuvant) and/or first-line metastatic setting. Initially, the study was designed to evaluate the OS benefit of ET + trastuzumab + lapatinib, and it had been a request from the regulatory agencies for the development of lapatinib. With the publication of the CLEOPATRA trial [45] results showing a substantial OS benefit, a non-data-driven protocol amendment was made to change the primary endpoint to PFS, in agreement with the regulatory authorities. For the primary comparison, ALTERNATIVE has shown a PFS benefit of 5.3 months for ET + dual blockade versus ET + trastuzumab [11.0 versus 5.7 months; hazard ratio (HR): 0.62 (0.45, 0.88), $P = 0.0064$]. As a secondary endpoint, PFS was compared between the three arms showing a PFS of 8.1 months for ET + lapatinib. OS was not statistically significantly different in the three arms: 46 versus 40 versus 45 months for the dual blockade, trastuzumab and lapatinib arms, respectively.

After considering all available data on both ET and ChT combinations with anti-HER2 agents, a small update was made to the guideline but retaining its main message, i.e. in the absence of valuable biomarkers, the approach of ET + anti-HER2 agents should be reserved for highly selected patients, including those with contraindications to ChT, patients with a strong preference against ChT or those with a long disease-free interval (DFI), minimal disease burden (in particular in terms of visceral involvement) and/or strong ER/progesterone receptor (PgR) expression [11]. Trials directly comparing ChT plus anti-HER2 therapy versus ET plus anti-HER2 therapy or assessing ET + anti-HER2 therapy as maintenance are currently ongoing [Detect V/CHEVENDO (NCT02344472), SYSUCC-002 (NCT01950182) and PERNETTA trials], and their results will allow for better recommendations.

Furthermore, in several countries, anti-HER2 therapy, namely trastuzumab, can only be used once in the metastatic setting since its use beyond progression is either not approved or not reimbursed; in those cases, preference should be given to a combination of ChT plus anti-HER2 therapy in view of the OS benefit observed.

The use of a combination of ET plus anti-HER2 therapy as maintenance therapy for ER-positive/HER2-positive ABC, after initial cycles of ChT plus anti-HER2 therapy, is a reasonable option, most probably delaying PD and the consequent need for a change in therapy. Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request and needs to be evaluated in clinical trials since no randomised trials exist. Of note, in the CLEOPATRA trial, maintenance therapy was carried out with anti-HER2 agents alone, which is also an option.

Guideline statement	LoE/GoR	Consensus
For non-*BRCA*-associated advanced TNBC, there are no data supporting different or specific ChT recommendations.	I/A	98%

Continued

Continued

Guideline statement	LoE/GoR	Consensus
Therefore, all ChT recommendations for HER2-negative disease also apply for advanced TNBC.		
In advanced TNBC 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%
The AR is a potential target in advanced TNBC. 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%

In green, NEW ABC 4 statements.

AR, androgen receptor; ChT, chemotherapy; Consensus, percentage of panel members in agreement with the statement; GoR, grade of recommendation; HER2, human epidermal growth factor 2; LoE, available level of evidence; TNBC, triple-negative breast cancer.

Section VI: Advanced TNBC

Few advances have also been made in these last 2 years in the management of advanced triple-negative breast cancer (TNBC). ChT remains the only available non-investigational systemic treatment option for non-*BRCA*-mutated advanced TNBC, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds.

The ongoing characterisation of different subgroups within this breast cancer subtype, may lead to the development of specific therapies for each of the subgroups. One of these subgroups is defined by an important expression of androgen receptor (AR; luminal AR subtype). The fact that bicalutamide, an anti-androgen approved for the treatment of prostate cancer, is available, has led to some off-label use in advanced TNBC. However, the panel believes that this type of agent should not be used in routine clinical practice, in view of the very limited data that exist [46–48] and until the determination of the AR is optimised and standardised. Unfortunately, the development of enzalutamide, another anti-androgen, in breast cancer has been put on hold.

Section VII: Hereditary ABC

Guideline statement	LoE/GoR	Consensus
Genetic testing		
In the ABC setting, results from genetic testing may have therapeutic implications and should therefore be considered as early as possible.	Expert opinion/ B	100%
Genes to be tested for depend on personal and family history; however, at present, only germline mutations in *BRCA*1/2 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. However, it must be clarified to the patient that at present, a mutation in another moderate- to 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 *BRCA*1/2 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 *BRCA*-associated advanced TNBC 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 option, if not previously administered and no suitable clinical trial is available. All other treatment recommendations are similar to sporadic ABC.	II/A	86%
A **PARPi (olaparib or talazaparib)** is a reasonable treatment option for patients with *BRCA*-associated advanced TNBC or luminal (after progression on ET) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favourable toxicity profile. OS results are awaited. It is unknown how PARPis compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumours.	I/B	80%

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; Consensus, percentage of panel members in agreement with the statement; ET, endocrine therapy; GoR, grade of recommendation; LoE, available level of evidence; OS, overall survival; PARPi, poly adenosine diphosphate ribose polymerase inhibitor; PFS, progression-free survival; QoL, quality of life; TNBC, triple-negative breast cancer.

With the approval of olaparib, results from genetic testing in the setting of ABC may have immediate therapeutic implications and should therefore be carried out as early as possible. Genetic testing should be guided by international/national guidelines [49] and may also be considered for all patients with triple-negative disease. Genes to be tested for depend on personal and family history, however at present only germline mutations in *BRCA*1/2 have any clinical utility and therapeutic impact.

Although *BRCA*1/2 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; however, it must be clarified to the patient that at present a mutation in another moderate- to high-penetrance gene has no direct clinical implications in the setting of ABC.

When a hereditary cancer syndrome is suspected in ABC and a mutation in *BRCA*1/2 has not been identified, and the patient still seeks information, multi-gene panel testing may be considered. Practice should be guided by high-quality international/national guidelines. As commercially available multi-gene panels include different genes, the choices of the specific panel and quality-controlled laboratory are crucial. Development of quality-controlled genetic counselling services is strongly encouraged [50, 51].

The OlympiAD trial [52] evaluated the role of the poly adenosine diphosphate ribose polymerase (PARP) inhibitor olaparib monotherapy in 302 patients with germline *BRCA* mutation and advanced ER-positive/HER2-negative or TNBC, who had received no more than two previous ChT regimens for metastatic disease. If prior platinum was used, no evidence of progression during treatment in the advanced setting or $\geq$12 months since (neo)adjuvant platinum treatment was required. The comparator was standard monoChT per physician's choice (capecitabine, eribulin or vinorelbine). Median PFS was longer in the olaparib group [7.0 versus 4.2 months; HR: 0.58; 95% confidence interval (CI): 0.43–0.80; $P < 0.001$]. At this follow-up time, there were no differences in OS. Toxicity and rate of treatment discontinuation due to side effects were higher in the ChT arm, while QoL was significantly better in the olaparib arm.

In the San Antonio Breast Cancer Symposium 2017, the first results of the EMBRACA trial were presented [53]. With a similar design to OlympiAD, this trial evaluated the role of talazaparib in 431 ABC patients with a *BRCA* mutation, when compared with monoChT per physician's choice (capecitabine, eribulin, vinorelbine or gemcitabine). Most patients had not received prior platinum-based therapy. At a median follow-up time of 11.2 months, PFS was longer in the talazaparib arm (8.6 versus 5.6 months; HR: 0.54; 95% CI: 0.41–0.71; $P < 0.0001$); no difference was seen, at this time, in OS and QoL was significantly better in the talazaparib arm.

While these trials are positive and met their primary endpoint, the benefit seen was less than anticipated. Nevertheless, the tolerability of these agents when given as monotherapy, the ChT-free approach with improved QoL makes it an attractive option for *BRCA*-related ABC. Further studies are needed to clarify the value of PARP inhibitors in platinum-resistant disease, as well as their value when 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) may play a role in the future as the medicines they are linked with achieve regulatory approval.	I/D	83%
ctDNA assessment is not ready for routine clinical practice use and is not recommended, either for demonstration of PD or selection of targeted therapies.	I/D	74%
In case an ABC patient was tested in the context of a clinical trial and the information is available:	Expert opinion/ C	Yes: 41% Abstain: 10% Insufficient data: 49%
• If an ABC patient presents with a tumour with **MSI-H/MMR deficiency**, treatment with an anti-PD-1 agent is a possible consideration. • 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.	Expert opinion/ C	Yes: 29% Abstain: 24% Insufficient data: 47%

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Continued

Guideline statement	LoE/GoR	Consensus
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 4 statements.

ABC, advanced breast cancer; Consensus, percentage of panel members in agreement with the statement; ctDNA, circulating tumour DNA; GoR, grade of recommendation; LoE, available level of evidence; MMR, mismatch repair; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NTRK, neurotrophic receptor tyrosine kinase; PD, disease progression; PD-1, programmed death 1; TRKi, tropomyosin receptor kinase inhibitor.

Next-generation sequencing (NGS) assesses mutations and copy number changes in many genes in the same assay. Multigene sequencing is now available widely by companies and in many institutions.

Multigene sequencing assesses four different sets of alterations. First, it can detect level I/II alterations, i.e. a few alterations for which targeted therapies provide clinical benefit (level I) or objective responses (level II). In breast cancer, there are five somatic genomic alterations that have been associated with objective response in phase I/II trials. These are *PIK3CA*, *AKT1*, *ERBB2*, *ESR1* mutations and *NTRK* fusions. There is not yet evidence from prospective randomised trials that targeting these alterations improves survival. Second, multigene panels can detect genomic alterations associated with drug sensitivity in pre-clinical models, but for which clinical evidence of actionability is lacking (level III). In breast cancers there are 15–20 level III genomic alterations, including genomic alterations on *TP53*, *MAP2K4*, *PIK3R1*, *SF3B1*, *ATM*, *ATR*, *NOTCH* etc. alterations. Third, multigene panels can detect genomic alterations located on other cancer-related genes (several hundreds), for which pre-clinical and clinical studies are lacking (level IV). There is no evidence that matching a therapy to these level IV alterations improves outcome. Multigene panels can also detect mutational load, mutational processes and genomic score, including mismatch repair (MMR) deficiency and microsatellite instability (MSI). There is evidence that MSI can be used to match patients to immune checkpoint inhibitors. There is currently no evidence from prospective clinical trials (e.g. SAFIR and SHIVA trials) that using a multigene panel improves outcome of patients [54, 55]. The current potential value of using multigene panels is only to steer patients to clinical trials exploring the efficacy of *PI3K*, *AKT*, *HER2*, *NTRK* inhibitors or selective oestrogen receptor degraders (SERDs). Moreover, it is important to recognise that the wide use of multigene panels outside of a research programme could generate an increase in the use of drugs off-label despite the lack of evidence that patients truly benefit from this practice. However, multigene panels could be used to detect MMR/MSI if the assay includes the relevant markers, and direct patients toward the use of pembrolizumab in the USA.

It is important to note that almost half of the panel considered that there is insufficient data to issue guidelines regarding what to do in the presence of an MSI-high (MSI)/MMR deficiency or *NTRK* fusion. In conclusion, multigene assays should not be used in routine clinical practice for breast cancer patients (with possible exception of MMR/MSI in the USA only). These assays should be used in context of molecular triage programmes where patients are potential candidates for appropriately targeted clinical trials.

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 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, emergency RT is the treatment of choice and vertebroplasty is also an option.	I/B	100%
A **bone-modifying agent** (bisphosphonate, denosumab) should be routinely used in combination with other systemic therapy in patients with ABC and bone metastases.	I/A	95%
Three-monthly zoledronic acid seems to be not inferior to standard monthly schedule.	I/B	95%
Supplementation of calcium and vitamin D3 is mandatory, unless contraindications exist.	I/A	95%

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Guideline statement	LoE/GoR	Consensus
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 carried out, 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 cause 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 four cycles. Prospective randomised trials are needed to validate further this option.	III/B	61%
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 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, 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.).	Expert opinion/ C	83%
Malignant pleural effusions		
Malignant pleural effusions require systemic treatment with/without local management.	III/A	86%
Thoracentesis for diagnosis should be carried out if it is likely that this will change clinical management. False negative results are common.	III/B	86%
Drainage is recommended in patients with symptomatic, clinically significant pleural effusion.	III/A	86%
Use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful.	III/B	86%
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%

Continued

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Guideline statement	LoE/GoR	Consensus
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 primarily 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 ABC. These patients may still be considered for palliative local therapy.	Expert opinion/ B	97%

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; ChT, chemotherapy; Consensus, percentage of panel members in agreement with the statement; DFI, disease-free interval; ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor 2; LoE, available level of evidence; MRI, magnetic resonance imaging; PS, performance status; RCT, randomised controlled trial; RT, radiotherapy; WBRT, whole brain radiotherapy.

With the development of several efficacious anti-HER2 therapies, the survival of HER2-positive ABC patients has increased, even after the appearance and treatment of brain metastases. For these reasons, radionecrosis, a rare but possible medium-term complication of stereotactic radiotherapy (RT) for brain metastases may occur. In the absence of a biopsy or surgical excision, differential diagnosis with tumour progression is often difficult. When symptomatic, treatment with a course of high-dose steroids is the first treatment of choice. Bevacizumab has been evaluated in some studies [56–61] with limited number of patients, as an option to decrease the surrounding oedema, if no response is obtained with steroids. Different doses and durations have been evaluated, usually a dose of 7.5 mg/kg every 2 weeks, for a median of four cycles. More prospective randomised trials are needed to validate further this option.

Section X: Specific populations

Guideline statement	LoE/GoR	Consensus
Advanced male breast cancer		
For ER-positive male ABC, which represents the majority of the cases, ET is the preferred option, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response.	III/A	100%
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 4.

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

Section XI: LABC

Guideline statement	LoE/GoR	Consensus
Before starting any therapy, a core biopsy providing histology and biomarker (ER, PgR, HER2, proliferation/grade) expression 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 chest and abdomen (preferably with 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 bone scan).	II/B	100%
Systemic therapy (not surgery or RT) should be the initial treatment.	III/A	100%

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Guideline statement	LoE/GoR	Consensus
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	100%
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and RT) is strongly indicated in the 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%
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 in 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 neoadjuvant 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 neoadjuvant 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), sentinel lymph node biopsy 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 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%

In green, NEW ABC 4 statements.

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

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

The majority of patients who present with unresectable non-metastatic disease should first be treated with primary systemic therapy. If rendered resectable, this should be followed by surgery and RT. If the disease remains unresectable, RT should be considered to treat all sites of the original tumour extension, with a boost to residual disease. Most durable remissions can be expected with an elective dose up to an equivalent of 50 Gy to regions with a high likelihood of bearing subclinical disease and a boost up to 60–76 Gy (depending on the dose to the organs at risk) to all sites of macroscopic disease. Regular evaluation during the course of RT is advised, to select patients that might become amenable for resection after 45–50 Gy. Interesting reports are published on combined RT and ChT like 5-FU, docetaxel or vinorelbine [62]. Further evaluation of the influence of combining RT with systemic treatment using a PARP inhibitor is ongoing in a prospective trial in patients with LABC or metastatic TNBC cancer and in non-responders to primary ChT [63].

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 inexpensive) is necessary for all patients in need of pain relief.	I/A	100%
Optimally, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. However, when active treatment no longer is able to control widespread and life-threatening disease, and the toxicities of remaining options outweigh benefits, physicians and other members of the healthcare team should initiate discussions with the patient (and family members/friends, if the patient agrees) about end-of-life care.	Expert opinion/ 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 approaches, such as exercise [I, A], and, if needed, pharmacological interventions [II, B].	See in statement	100%
Management of CDK inhibitor-induced neutropaenia		
Neutropaenia is the most common toxicity associated with CDK 4/6 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%

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Guideline statement	LoE/GoR	Consensus
Management of non-infectious pneumonitis		
NIP is an uncommon complication of mTOR inhibition. Patient education is critical to ensure early reporting of respiratory symptoms. Treatment interruption and dose reduction are generally effective for grade 2 symptomatic NIP with use of systemic steroids and treatment discontinuation for grade 3 or greater toxicity.	II/A	100%
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	100%
Benzodiazepines can be used in patients experiencing anxiety.	II/A	100%
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	100%
Management of nausea and vomiting		
ESMO/MASCC guidelines [64] are available for management of ChT-induced and morphine-induced nausea and vomiting, and these are endorsed by the ABC community.	n/a	100%
There is a need to study nausea and vomiting related to chronic use of anticancer drugs.	Expert opinion/ A	100%
Management of endocrine toxicities of mTOR inhibition		
Hyperglycaemia and hyperlipidaemia are common sub-acute complications of mTOR 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. Management of grade 1 and 2 hyperglycaemia includes treatment with oral antidiabetics and basal insulin, in accordance with international	II/A	100%

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Guideline statement	LoE/GoR	Consensus
recommendation for diabetes mellitus treatment. Statins are indicated to treat grade 2 and 3 hypercholesterolaemia, and fibrates should be introduced if triglyceride level >500 mg/dL (with attention to possible drug–drug interaction between everolimus and fibrates). Treatment interruption and dose reduction are generally effective for grade 2 and 3 toxicity. Treatment should be discontinued for grade 4 toxicity.		
Management of mucositis/stomatitis		
Steroid mouthwash should be used for prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5 mg/5 mL dexamethasone, 10 mL to swish×2 min, then spit out; qid).	I/B	100%
Early intervention is recommended.	Expert opinion/ A	100%
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	100%
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	100%
Management of chemotherapy-induced peripheral neuropathy		
CIPN is frequent and potentially dose-limiting. Risk factors for neuropathy and pre-existing neuropathy need to be identified.	–	100%
No medical prevention can currently be recommended.	II/C	100%
Drug-related factors (dosing, timing, route) can lower the risk of CIPN.	–	100%
The use of tight gloves and socks during ChT may help reduce the incidence and severity of CIPN.	Expert opinion/ C	100%
There are limited evidence-based treatments for CIPN, with tricyclic antidepressants, serotonin-noradrenaline re-uptake inhibitors, pregabalin and gabapentin being most often used.	II/B	100%
High-quality studies are needed to evaluate strategies for prevention and management of CIPN.	–	100%
Management of hand and foot syndrome		
HFS is also described as palmar–plantar erythrodysesthaesia syndrome. Most frequent causes are capecitabine; pegylated liposomal doxorubicin; multikinase inhibitors.	–	100%
Patients should be instructed about early recognition of HFS.	–	100%
Drug-related factors (dosing, timing, route) can lower the risk of HFS.	–	100%
Treatment of hyperkeratosis/fungal infections, comfortable shoes, avoidance of friction and heat are recommended.	Expert opinion/ A	100%
Intensive skin care of hands and feet (urea cream/ointment) is recommended.	II/A	100%
High-quality studies are needed to evaluate strategies for prevention and management of HFS.	–	100%

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; Consensus, percentage of panel members in agreement with the statement; ESMO, European Society for Medical Oncology; GoR, grade of recommendation; HFS, hand and foot syndrome; LoE, available level of evidence; MASCC, Multinational Association of Supportive Care in Cancer; mTOR, mechanistic target of rapamycin; NIP, non-infectious pneumonitis; PROM, patient-reported outcome measure; qid, four times a day; QoL, quality of life; RT, radiotherapy.

As in previous editions, the ABC panel issued several recommendations concerning the management of disease and treatment-related symptoms, a problem faced daily by patients and practicing oncologists, that can significantly affect a patient's QoL. At ABC 4, the recommendations for management of mucositis/stomatitis have been slightly updated [reflecting the FDA approval of steroid mouthwash for stomatitis induced by mechanistic target of rapamycin (mTOR) inhibitors] [65, 66], and new recommendations have been made for management of hand and foot syndrome (HFS) and ChT-induced peripheral neuropathy (CIPN) [67–69].

When adverse events are addressed systematically and at an early stage, they often become simple and inexpensive to treat, allowing for a higher probability of continuation of the planned therapy. When they get to a late stage, the adverse events become more severe, and, as a result, management becomes more complex, expensive, time-consuming and potentially less effective. As a result, treatment modifications need to be carried out. Prophylactic measures, early detection, diagnosis and early intervention are critical. The primary objectives of adverse event management strategies are to avoid disrupting the patient's activities of daily living, maintain or restore patient comfort and QoL, and

maintain therapy for as long as needed. In order to monitor and recognise adverse events adequately, some key points should be addressed: (i) educate the patient before treatment about the adverse events which may appear and about prophylactic measures; (ii) communication with the patient and their support system is essential to avoid dose modifications and maintain QoL; tell patients why, who, when and how they can contact their healthcare professionals; (iii) monitor the patient more frequently for the first 12 weeks on every new treatment; from week 13 on, actively monitor every one or two cycles, depending on the treatment schedule and the adverse events that may have developed; (iv) grade adverse events accurately with an appropriate tool; (v) treat symptoms early as this may prevent them from getting worse; (vi) adjust management strategies based on the opinion of the patient regarding tolerability; (vii) consider dose modifications (reductions, delays); and (viii) continue systemic treatment whenever possible.

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 complementary and integrative medicine and that many of them are using it.	Expert opinion/ C	100%
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.		
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 h 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 flashes.	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) • high-dose vitamins (vitamin C, D, E, carotenoids etc.) • L-carnitine, laetrile.	II/E	100%

In green, NEW ABC 4 statements.

ABC, advanced breast cancer; ChT, chemotherapy; Consensus, percentage of panel members in agreement with the statement; DFS, disease-free survival; GoR, grade of recommendation; LoE, available level of evidence; MBSR, mindfulness-based stress reduction; OS, overall survival; QoL, quality of life.

Complementary and integrative medicine (CIM) represents the use of complementary treatments side by side with conventional approaches in a proper therapeutic environment [70]. Alternative therapies (i.e. therapies used instead of scientifically based medicines) are not recommended in any phase or stage of cancer treatment. For that reason, the acronym CAM—complementary and alternative medicine—has been replaced by CIM excluding the alternative word from current use [70]. The term 'integrative oncology' represents the application of CIM to cancer patients. However, even in settings in which the term integrative oncology has been used to refer to the combination of complementary medicine therapies with conventional cancer treatments the term has been defined in many different ways. Because of this lack of consensus, it has been difficult to communicate what is meant by integrative oncology to oncologists and other health professionals, as well as to key stakeholders such as patients. The current definition of the term integrative oncology is a patient-centred, evidence-informed field of cancer care that utilises mind and body practices, natural products, and/or

lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimise health, QoL and clinical outcomes across the cancer care continuum, to empower people to prevent cancer and to become active participants before, during and beyond cancer treatment [71].

Some complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and, therefore, improve the QoL of breast cancer patients. The research and evidence of the effects of complementary treatments specifically for ABC patients is very limited and applications are usually extrapolated from indications in early breast cancer patients.

Evidence suggests beneficial effects of the following methods, which can, therefore, be used: (i) physical exercise/sport (equivalent to 3–5 hours of moderate walking per week) improves cardiorespiratory fitness, physical performance and fatigue, and it may also improve DFS and OS in breast cancer patients; additionally, a supervised and individualised exercise results in an improvement in functional ability and QoL functions in women with ABC [72] [IV/B]; (ii) mindfulness-based stress reduction (MBSR) programmes, hypnosis and yoga may improve QoL and fatigue, improve sleep and help reduce anxiety, distress and some side effects of anticancer therapies; and (iii) acupuncture may help against ChT-induced nausea and vomiting, fatigue and hot flashes [70, 73].

Evidence suggests that the following complementary therapies should not be recommended in ABC patients since available evidence shows no effect at best, or even association with worse outcome: (i) antioxidant supplements; (ii) drugs outside the approved indication (e.g. methadone); (iii) herbs including Chinese herbal medicine; (iv) orthomolecular substances (selenium, zinc etc.); (v) oxygen and ozone therapy; (vi) proteolytic enzymes, thymic peptides; phytoestrogens (soy food, isoflavones); (vii) high-dose vitamins (vitamin C, D, E, carotenoids, L-carnitine, laetrile etc.) [70, 73].

Discussion

Conclusions and future directions

To facilitate the use of these guidelines in clinical practice, all statements have been organised by subject, highlighting those who were recently developed at ABC 4. A new, ESMO-adapted LoE/GoR system was introduced and, when indicated, the ESMO-MCBS was applied and v1.1 scores were added. Should another agent be approved by EMA before the next ABC Consensus Conference, ESMO will apply the ESMO-MCBS and the result will be made available as an eUpdate to the present guidelines.

To address some of the needs highlighted by the ABC guidelines, two projects are ongoing: the development of HRQoL tools specific for ABC patients (a collaboration between the EORTC Quality of Life and Breast Cancer Groups), and the development of quality indicators for ABC, which will in the future be included in the certification process of breast units/centres/services. The latter project is a collaboration between EUSOMA and ESO, under the umbrella of the ABC Global Alliance (https://www.abcglobalalliance.org).

Efforts must continue not only in research dedicated to ABC, but also ensuring that ABC patients worldwide have access to the best available therapies, including multidisciplinary care as well as early and adequate access to supportive and palliative care. Reimbursement rules in all countries should be patient-centred and be an incentive, not work against, the clinical implementation of high-quality international guidelines. Only united and with common projects and goals, the ABC community will be able to achieve success. This was the main objective of the creation of the ABC Global Alliance, which is a multi-stakeholder platform for all those (advocacy groups, pharma, cooperative groups, societies, individuals) interested in collaborating in common projects relating to ABC around the world and is a continuation of the work developed through the ABC International Consensus Conference and Guidelines. Its mission and vision are to improve and extend the lives of women and men living with ABC in all countries worldwide, to fight for a cure for ABC, to raise awareness of ABC and to lobby worldwide for improvement in the lives of ABC patients. As a first step, the Global Alliance has developed an ABC Global Charter, defining 10 achievable and measurable goals for a period of 10 years (till 2025) [74]. These goals include doubling the median survival of patients by 2025, improving QoL in clinical practice, increasing availability and access to multidisciplinary care, offering communication skills training, improving availability of robust epidemiology and outcomes data, improving access to non-clinical supportive services, protecting workforce rights for ABC patients and increasing public understanding about ABC to fight the still existent stigma.

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Disclosure

The authors' conflicts of interest are detailed in Supplementary Table S2, available at *Annals of Oncology* online.

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