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6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7)

Fatima Cardoso [a,*], Shani Paluch-Shimon [b], Eva Schumacher-Wulf [c], Leonor Matos [d], Karen Gelmon [e], Matti S. Aapro [f], Jyoti Bajpai [g], Carlos H. Barrios [h], Jonas Bergh [i], Elizabeth Bergsten-Nordström [j], Laura Biganzoli [k], Maria João Cardoso [l], Lisa A. Carey [m], Mariana Chavez Mac Gregor [n], Runcie Chidebe [o], Javier Cortés [p], Giuseppe Curigliano [q,r], Rebecca A. Dent [s], Nagi S. El Saghir [t], Alexandru Eniu [u], Lesley Fallowfield [v], Prudence A. Francis [w], Sandra X. Franco Millan [x], Jenny Gilchrist [y], Joseph Gligorov [z], William J. Gradishar [aa], Renate Haidinger [ab], Nadia Harbeck [ac], Xichun Hu [ad], Ranjit Kaur [ae], Belinda Kiely [af], Sung-Bae Kim [ag], Smruti Koppikar [ah], Marion J.J. Kuper-Hommel [ai], Frédéric E. Lecouvet [aj], Ginny Mason [ak], Shirley A. Mertz [al], Volkmar Mueller [am], Claire Myerson [an], Silvia Neciosup [ao], Birgitte V. Offersen [ap], Shinji Ohno [aq], Olivia Pagani [ar], Ann H. Partridge [as], Frédérique Penault-Llorca [at], Aleix Prat [au], Hope S. Rugo [av], Elzbieta Senkus [aw], George W. Sledge [ax], Sandra M. Swain [ay], Christoph Thomssen [az], Daniel A. Vorobiof [ba], Peter Vuylsteke [bb], Theresa Wiseman [bc], Binghe Xu [bd], Alberto Costa [be], Larry Norton [bf], Eric P. Winer [bg]

[a] *Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, and ABC Global Alliance, Lisbon, Portugal*
[b] *Hadassah University Hospital - Sharett Institute of Oncology, Jerusalem, Israel*
[c] *Mamma Mia, Kronberg, Germany*
[d] *Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal*
[e] *BC Cancer Agency, Department of Medical Oncology, Vancouver, Canada*
[f] *Cancer Center, Clinique de Genolier, Genolier, Switzerland*
[g] *Tata Memorial Centre, HBNI, Mumbai, India*
[h] *Latin American Cooperative Oncology Group (LACOG), Grupo Oncoclínicas, Porto Alegre, Brazil*
[i] *Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden*
[j] *Europa Donna - the European Breast Cancer Coalition, Norrkoping, Sweden*
[k] *Department of Oncology, Hospital of Prato - Azienda USL Toscana Centro Prato, Italy and European Society of Breast Cancer Specialists (EUSOMA), Italy*
[l] *Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation and Lisbon University, Faculty of Medicine, Lisbon, Portugal*
[m] *UNC Lineberger Comprehensive Cancer Center, Chapel Hill, USA*
[n] *Health Services Research, Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, USA and American Society of Clinical Oncology (ASCO), Houston, USA*
[o] *Project PINKBLUE, Abuja, Nigeria*
[p] *International Breast Cancer Center (IBCC), Madrid and Barcelona, Spain*
[q] *European Institute of Oncology, IRCCS, Milano, Italy*
[r] *Department of Oncology and Hemato-Oncology, University of Milano, Milano, Italy*
[s] *National Cancer Center Singapore, Singapore, Singapore*
[t] *NK Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon*
[u] *Hôpital Riviera-Chablais, Vaud-Valais Rennaz, Switzerland and European School of Oncology (ESO), United Kingdom*
[v] *Brighton & Sussex Medical School, University of Sussex, Brighton, United Kingdom*
[w] *Department of Medical Oncology, Peter MacCallum Cancer Centre, Sir Peter MacCallum Department of Oncology, University of Melbourne, Australia*
[x] *CTIC, Cancer Treatment and Research Center, Bogotá, Colombia*
[y] *Macquarie University, Sydney, Australia*
[z] *Department of Medical Oncology, Cancer Est APHP Tenon, University Paris VI, Nice/St Paul Guidelines, Paris, France*
[aa] *Northwestern Medicine, Illinois, USA and National Comprehensive Cancer Network (NCCN), USA*
[ab] *Brustkrebs Deutschland e.V., Munich, Germany*

* Corresponding author. Breast Unit, Champalimaud Clinical Center, Av. De Brasília s/n, 1400-038, Lisbon, Portugal.
E-mail address: fatimacardoso@fundacaochampalimaud.pt (F. Cardoso).

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[ac] Breast Centre, University of Munich, Munich and Arbeitsgemeinschaft Gynäkologische Onkologie, Kommission Mamma (AGO Guidelines), Germany
[ad] Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
[ae] Breast Cancer Welfare Association, Petaling Jaya, Malaysia
[af] NHMRC Clinical Trials Centre, Sydney Medical School, Sydney, Australia
[ag] Asan Medical Centre, Department of Oncology, Seoul, South Korea
[ah] Lilavati Hospital and Research Centre, Bombay Hospital Institute of Medical Sciences, Asian Cancer Institute, Mumbai, India
[ai] Te Whatu Ora Waikato, Midland Regional Cancer Centre, NZ ABC Guidelines, Hamilton, New Zealand
[aj] Department of Radiology, Institut Roi Albert II and Institut de Recherche Expérimentale et Clinique (IREC), Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium
[ak] Inflammatory Breast Cancer Research Foundation, West Lafayette, USA
[al] MBC US Alliance and Metastatic Breast Cancer Network US, Inverness, USA
[am] University Medical Center Hamburg-Eppendorf, Hamburg and Arbeitsgemeinschaft Gynäkologische Onkologie, Kommission Mamma (AGO Guidelines), Germany
[an] Breast Cancer Now, London, United Kingdom
[ao] Department of Medical Oncology, National Institute of Neoplastic Diseases, Lima, ABC Latin America Guidelines, Peru
[ap] Department of Oncology, Aarhus University Hospital, Aarhus, European Society for Radiotherapy and Oncology (ESTRO), Denmark
[aq] Breast Oncology Centre, Cancer Institute Hospital, Tokyo, Japan
[ar] Hôpital Riviera-Chablais, Vaud-Valais Rennaz, Switzerland
[as] Dana-Farber Cancer Institute, Department of Medical Oncology and Division of Breast Oncology, Boston, USA and American Society of Clinical Oncology (ASCO), USA
[at] Centre Jean Perrin, Université Clermont Auvergne, INSERM, U1240 Imagerie Moléculaire et Stratégies Théranostiques, F-63000, Clermont Ferrand, Nice/St Paul Guidelines, France
[au] Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain
[av] Breast Oncology and Clinical Trials Education, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA
[aw] Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland
[ax] Division of Oncology, Stanford School of Medicine, Stanford, USA
[ay] Georgetown University Lombardi Comprehensive Cancer Center and MedStar Health, Washington DC, USA
[az] Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle (Saale) and Arbeitsgemeinschaft Gynäkologische Onkologie, Kommission Mamma (AGO Guidelines), Germany
[ba] Belong.Life, New York, USA
[bb] University of Botswana, Gaborone, Botswana and CHU UCL Namur Hospital, UCLouvain, Belgium
[bc] The Royal Marsden NHS Foundation Trust, University of Southampton, United Kingdom and European Oncology Nursing Society (EONS), United Kingdom
[bd] Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[be] European School of Oncology, Milan, Italy and Bellinzona, Switzerland
[bf] Breast Cancer Programs, Memorial Sloan-Kettering Cancer Centre, New York, USA
[bg] Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA

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ABSTRACT

This manuscript describes the Advanced Breast Cancer (ABC) international consensus guidelines updated at the last two ABC international consensus conferences (ABC 6 in 2021, virtual, and ABC 7 in 2023, in Lisbon, Portugal), organized by the ABC Global Alliance. It provides the main recommendations on how to best manage patients with advanced breast cancer (inoperable locally advanced or metastatic), of all breast cancer subtypes, as well as palliative and supportive care. These guidelines are based on available evidence or on expert opinion when a higher level of evidence is lacking. Each guideline is accompanied by the level of evidence (LoE), grade of recommendation (GoR) and percentage of consensus reached at the consensus conferences. Updated diagnostic and treatment algorithms are also provided. The guidelines represent the best management options for patients living with ABC globally, assuming accessibility to all available therapies. Their adaptation (i.e. resource-stratified guidelines) is often needed in settings where access to care is limited.

1. Introduction

Since its first edition, in 2011, the Advanced Breast Cancer (ABC) International Consensus Conference has established itself as the major international conference for advanced breast cancer. It was created to address the fear and isolation of patients with ABC and the urgent need to change their outcomes. Unique characteristics of the ABC guidelines are the central role taken by patients with ABC and its truly global reach.

The conference's primary goal is the development of international consensus guidelines for the management of advanced breast cancer, known as the ABC Guidelines. These guidelines are based on the most up-to-date evidence and can be used to guide treatment decision making in many different health care settings globally, with the necessary adaptations due to differences in access to care. Throughout the years, these guidelines have been endorsed by several international and European organizations, and many organizations around the world have adapted these guidelines to their country specific environments, particularly in terms of accessibility of treatment modalities. The conference and guidelines started as a pioneering project from the European School of Oncology (ESO) [1] and from its 2nd to 5th edition [2–5], it was developed in collaboration with the European Society of Medical Oncology (ESMO). From 2021, both conference and guidelines started being organized by the ABC Global Alliance, an independent non-profit multi-stakeholder organization dedicated exclusively to improve and extend the lives of women and men living with ABC worldwide, that currently has more than 200 members in over 90 countries worldwide [6]. The ABC conference also aims to be a forum to analyze and discuss the latest scientific updates in the field, to identify research priorities based on the most important areas of unmet needs, as well as influence policy makers, regulatory and funding bodies, and ultimately improve standards of care, survival, and quality of life for all patients living with ABC worldwide. We strongly believe that health professionals working closely together with patients and advocates and with the strong support of the media can raise awareness and strongly lobby in favor of this often underserved and forgotten group of patients.

In the ABC guidelines, advanced breast cancer is defined as comprising both inoperable locally advanced breast cancer (LABC) and metastatic breast cancer (MBC), which includes both distant recurrent disease and stage IV at diagnosis or de novo MBC. Advanced/metastatic breast cancer remains a largely incurable disease, but important advances have occurred leading to an increase in the median overall survival (OS) from 2 to 3 years in the early 2000's to five or more years in

patients with Human Epidermal Growth Factor Receptor 2 (HER2) positive disease and those with estrogen positive/HER2 negative ABC [7,8]. This improvement in outcome is best achievable if a patient has access to high quality multidisciplinary care, innovative systemic therapies, high quality pathology and imaging, and radiotherapy, in a setting where there is attention to high-quality international guidelines. Unfortunately, inequalities in access to care are a major hurdle and lead to substantial differences in outcomes, not only between countries but also within each country.

Due to the COVID-19 pandemic, the 6th International Consensus Conference for Advanced Breast Cancer (ABC 6) was held virtually on 4th–6th November 2021 and brought together around 1.000 participants from 67 countries. The 7th International Consensus Conference for Advanced Breast Cancer (ABC 7) was held again in person, in Lisbon, Portugal, from 9th to November 11, 2023, and was attended by 1200 participants from 89 countries, including health professionals, patients, advocates, and journalists. The ABC 6 and 7 guidelines are endorsed by several international oncology organizations, such as Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO), European Cancer Organization (ECO), European Oncology Nursing Society (EONS), European School of Oncology (ESO), European Society for Radiotherapy and Oncology (ESTRO), European Society of Breast Cancer Specialists (EUSOMA), St. Paul Course and Senologic International Society (SIS)/International School of Senology (SIS) and have official representation from American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), Advanced Breast Cancer New Zealand (ABC NZ) and GECOPERU. The ABC 6 and 7 conferences were endorsed or run under the auspices from Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO), European Cancer Organization (ECO), (European Oncology Nursing Society (EONS), European School of Oncology (ESO), European Society for Surgical oncology (ESSO), European Society for Radiotherapy and Oncology (ESTRO), Global Breast Cancer Conference, the Organization of European Cancer Institutes (OECI), Senologic International Society (SIS)/International School of Senology (ISS) and Union for International Cancer Control (UICC), and held with the support from Breast Cancer Research Foundation (BCRF) and Susan G. Komen for the Cure.

This manuscript summarizes the guidelines developed at ABC 6 and 7. Each guideline statement is accompanied by the level of evidence (LoE), grade of recommendation (GoR), percentage of consensus reached at the conference, and supporting references. When available, the ESMO-MCBS (version 1.1) score is also added [9]. These guidelines are based on available evidence and on expert opinion when evidence is lacking. They represent the best management options for ABC patients globally, assuming access to all available therapies. Adaptation of these guidelines is often needed in settings where access to care is limited.

2. Methodology

As the ABC 6 conference was held virtually, the methodology followed in previous ABC consensus guidelines was adapted. Before the ABC 6 conference, initial guidelines statements on the management of ABC were prepared based on available published and presented data. These statements were circulated and intensively discussed among all 46 ABC 6 panel members by email. A final pre-conference set of guidelines was voted through an online confidential system. The guidelines were then presented and discussed during the live virtual consensus session of ABC 6. Required changes in the wording were made following the live discussion. Statements included under the supportive and palliative care section were not voted on but were discussed and unanimously agreed upon by email (100 % consensus agreement). For ABC 7, since it was held again face-to-face, the usual methodology was followed: before the conference, preliminary new recommendation statements on the management of ABC were prepared based on available published data. These recommendations were circulated to all 44 ABC 7 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 7. Additional changes in the wording of statements were made during the session. For both ABC 6 and ABC 7, all panel members were required to vote on all questions, but members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field), were instructed to vote ‘abstain’.

Two additional statements (on capivasertib and on datopotamab deruxtecan) were developed after the ABC 7 conference, due to presentation of important data and Food and Drug Administration (FDA) approval of capivasertib; these statements were circulated for revision and voted by all panel members by email. Statements related to the management of side effects and difficult symptoms, included under the supportive and palliative care section, were not voted on during the consensus sessions, but were discussed and unanimously agreed by email, and are therefore considered to have 100 % consensus agreement. As usual, guidelines statements from previous ABC consensus that did not require update or only minor changes were not re-voted but were reviewed and approved by all panel members by email.

The current manuscript presents all ABC guidelines recommendations currently approved, listed per subject. Only the new and updated recommendations voted during the ABC 6 and 7 consensus sessions are discussed in detail. We refer the reader to the previous ABC manuscripts for the detailed explanation of the other guidelines [1–5]. Supplementary table 1, describes the LoE and GoR system used [10]. The percentage of consensus was calculated as ratio of “yes” over total number of votes. Slides with all ABC guidelines statements are available online at http://www.abc-lisbon.org/ and at Supplementary material.

2.1. Section I: ABC definitions

Guideline statement	LoE/GoR	Consensus
Visceral crisis is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy. Examples: ***Liver visceral crisis***: rapidly increasing bilirubin >1.5x ULN in the absence of Gilbert's Syndrome or biliary tract obstruction. ***Lung visceral crisis***: rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion.	Expert opinion/NA	97%
Endocrine sensitivity/resistance **ET NAÏVE**: unknown if there is sensitivity or resistance to endocrine therapy (ET) since has never received ET. **PRIMARY ENDOCRINE RESISTANCE** is defined as: Relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET-based therapy for ABC (note: this definition is the same regardless of whether therapy included a CDK4/6i or not). **SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE** is defined as: All other clinical situations of endocrine-resistance. Examples include: 1) Relapse while receiving adjuvant ET but after at least 2 years; 2) PD after at least 6 months of 1st line ET-based therapy for ABC; 3) PD after any duration of 2nd+ line ET-based therapy for ABC; 4) Known *ESR1* mutation (note: definition unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs) **ENDOCRINE INSENSITIVITY** is defined as: PD within 2 months of later-line ET-based therapy for ABC and no additional ET-based approaches likely to result in clinically meaningful benefit.	Expert opinion/NA	95%
Patients with multiple chronic conditions are defined as patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease), which may decrease tolerance to treatment and impact outcomes and the incidence of toxicities. This limits the ability to extrapolate existing data and make evidence-based recommendations for care.	Expert opinion/NA	100%
Adequate OFS in the context of ABC: Adequate OFS for ABC premenopausal patients can be obtained through bilateral oophorectomy, continuous use of LHRH agonists or OFA through pelvic RT (the latter is the least preferred option). If an LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered. As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires a balance of the patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression and cost.	I/A II/B Expert opinion/B Expert opinion/NA	85% 85% 85% 85%
Maintenance therapy: in the context of ABC guidelines, maintenance therapy refers to the continuation of anti-HER2 therapy, immunotherapy and/or ET after discontinuation of ChT.	Expert opinion/NA	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/NA	100%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; AI: aromatase inhibitor; CDK4/6i: cyclin-dependent kinase 4 and 6 inhibitor; ChT: chemotherapy; ET: endocrine therapy; ESR1: Estrogen Receptor 1; GoR: grade of recommendation; HER2: human epidermal growth factor receptor 2; LHRH: luteinizing hormone-releasing hormone; LoE: level of evidence; mTOR: mammalian target of rapamycin; NA: not applicable; OFA: ovarian function ablation; OFS: ovarian function suppression; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD: disease progression; q4w: every 4 weeks; RT: radiotherapy; ULN: upper limit of normal.

2.2. New endocrine resistance definition

Clinical definitions of endocrine resistance are mostly important for clinical trials to promote comparisons between populations that are as similar as possible. They are less relevant for clinical practice and for treatment decisions, since sensitivity and resistance are a continuum and the exact level of resistance of a given tumor is difficult to ascertain with certainty.

Endocrine-naïve populations are defined as populations where it is not known if there is sensitivity or resistance to ET, since the patient has never previously received this treatment. In practical terms, these cases are considered ET-sensitive, until proven otherwise. Prior exposure to endocrine agents often leads to some degree of resistance. The updated definitions are broad and simplified but attempt to group tumors by response, as well as account for varying lengths of prior adjuvant therapy. **Primary endocrine resistance** is defined as relapse while on the first 2 years of adjuvant ET, or progressive disease within first 6 months of 1st line ET-based therapy for ABC, while on ET (regardless of CDK4/6 inhibitors use). **Secondary endocrine resistance** is defined as other clinical situations, including relapse while receiving, but after 2 years' adjuvant ET-based therapy, progressive disease after at least 6 months of 1st line ET-based therapy for ABC, progressive disease after any duration of 2nd or subsequent lines of ET-based therapy for ABC; and known ESR1 mutation (definition unaffected of receipt of CDK4/6 or mTOR/PI3K inhibitors, or other adjunctive drugs).

Resistance to adjunctive drugs does not equal to resistance to endocrine therapy. Resistance to adjunctive drugs can be de novo or acquired and its mechanisms are numerous. To the current knowledge, no such mechanism is known to affect ET decisions. It is therefore the opinion of the ABC consensus panel that the use of adjunctive drugs, such as CDK 4/6 or *PIK3CA* inhibitors, and the duration of such treatment does not contribute to or affect the definitions of endocrine sensitivity.

Endocrine insensitivity is defined as progression within 2 months of later-line ET-based therapy for ABC, and the absence of additional ET-based approaches likely to result in clinically meaningful benefit. Of all four situations described, this is the one with the biggest impact on clinical decision-making.

2.3. Section II: Oligometastatic disease

Guideline statement	LoE/GoR	Consensus
Oligometastatic disease is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status. Oligometastatic sites need to be solid; excludes pleural effusion, ascites, leptomeningeal disease. The definition of oligometastatic disease is highly dependent on the imaging method used. Trials are necessary to compare different imaging techniques specifically in breast cancer and to evaluate the exact benefit of local treatments.	Expert opinion/NA	87%
Oligometastatic disease in contralateral axilla: Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage IV metastatic breast cancer. However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach.	Expert opinion/NA	85%
Management of oligometastatic disease: A randomized phase 2 trial (NRG-BR002) in patients (n=125) with oligometastatic breast cancer (≤ 4 extra-cranial sites) evaluated the use of Stereotactic Body Radiation Therapy (SBRT) and/or Surgical Resection to all oligometastatic sites, in context of ≤ 12 months of first-line systemic therapy without progression. Most enrolled pts had oligometastatic recurrence (78%) and ER+/HER2-negative breast cancer (80%). The results showed no difference in median PFS and 3-yr OS, no difference in rate of metastases outside index area, and the trial did not proceed to phase 3. A small, randomized phase 2 trial (SABR-COMET) in patients with different types of advanced cancers including breast (18 patients only), evaluated the use of SBRT to all sites of oligometastatic disease, in the context of a controlled primary tumor, and showed a significant OS benefit. Based on available data, routine ablation of extra-cranial asymptomatic oligometastatic sites is not recommended, outside a clinical trial, until further data is available. It may however be discussed on an exceptional basis in a multidisciplinary tumor board and the patient should be informed about the uncertainty about impact on OS seen so far.	II/D	98%
Systemic therapy should be the 1st treatment initiated and decision about possible loco-regional treatments should be taken based on disease response. Results of additional ongoing trials are awaited. Further data specific to patients with *de novo* oligometastatic breast cancer is needed, as well as a better characterization of the subset of patients likely to benefit from a local-regional approach.	II/B	98%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; SBRT: Stereotactic Body Radiation Therapy; ER: Estrogen receptor; HER2: human epidermal growth factor receptor 2; PFS: Progression Free Survival; OS: Overall Survival; GoR: grade of recommendation; LoE: level of evidence; NA: not applicable.

Oligometastatic disease (OMD) is defined as low volume metastatic disease, with a limited number and size of metastatic lesions (usually up to 5 though not necessarily in the same organ) [11]. OMD sites need to be solid; pleural effusion, ascites and leptomeningeal disease are excluded due to their diffuse nature. OMD limited to 1–3 metastases is associated with a more favorable 10-year overall survival [12].

The definition of OMD is highly dependent on the imaging method used. Modern imaging modalities outperform standard imaging modalities such as bone scintigraphy and computed tomography (CT), which are still often the standard of care in many practices [13,14]. Currently, the most effective diagnostic techniques are 18F-fluorodeoxyglucose (18-FDG) positron emission tomography/computed tomography (PET/CT) and whole-body-magnetic resonance imaging (MRI) with diffusion-weighted sequences [15,16]. The optimal imaging work-up may be different according to the primary cancer histology and molecular subtype [17,18]. Metastases from invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) have different preferential tropisms and target organs in their metastatic spread, as well as different metabolic behaviors, resulting in dedicated imaging strategies [19,20]. It is crucial to confirm the presence of malignant disease through a biopsy.

Per definition, OMD is potentially amenable for local ablative treatment (also called metastasis directed treatment), aimed at achieving a complete remission status. The hypothesis behind this approach is that ablating the apparent disease could delay further seeding of other metastatic lesions. The most commonly technique used to treat bone or lung metastasis is stereotactic ablative body radiotherapy (SABR or SBRT). Surgical resection and radiofrequency ablation (RFA) have also been evaluated for liver lesions [21].

Currently, available data does not support the impact of local therapies on overall survival, therefore it cannot be recommended in routine clinical practice. It may be considered, in highly selected cases, after a careful multidisciplinary team discussion and shared decision with the patient, balancing potential gains and risks and explaining the lack of evidence regarding its impact on survival.

Observational data and phase 2 trials [22,23] raised the possibility of a benefit from metastasis directed treatment. The SABR-COMET randomized phase 2 trial, enrolled multiple tumor types including only 18 breast cancer patients, showed long term benefit in OS and PFS in patients with controlled primary tumors and up to five metastases [24], although at the cost of more toxicity [25]. More recently, the randomized NRG-BR002 phase 2 trial (n = 125) compared standard of care systemic therapy (SOC) with or without metastasis directed treatments (SBRT and/or surgical resection) for oligometastatic breast cancer with $\leq$4 extracranial lesions based on standard imaging, with controlled loco-regional disease and <12 months of initial systemic therapy. After 72 pre-specified events, the study did not show a benefit for the experimental arm, neither in the primary endpoint (PFS) nor in any of the secondary endpoints (OS, new metastases outside the index area or PFS by baseline circulating tumor cells). There were fewer new metastases inside the index area in the ablative arm at 7 % compared to 29 % for SOC [26]. This trial has some limitations: 79 % of cases were ER+/HER2 negative ABC, 78 % oligo-recurrent disease, baseline imaging had limited sensitivity and there was an imbalance in ET use (83 % SOC vs 68 % ablative arm).

The results of several other ongoing breast cancer specific phase 3 trials will provide further data on the impact of metastatic directed treatment on survival and determine if there are patients who may benefit from this approach [27]. At this time, standard of care first-line systemic therapies remain the recommended approach.

Of note, in patients with prior clinical benefit from CDK4/6 inhibitor plus aromatase inhibitors (AI), the possibility to delay a change in systemic therapy by use of SBRT, including the possibility of subsequent SBRT, for up to 5 sites of oligo-progressive disease was investigated in the AVATAR phase 2 trial (n = 32) with a median time until progression not amenable to further SBRT of 10.4 months [28]. The impact on survival was not reported. Although these results are interesting, more data are necessary before it can be recommended for routine clinical practice.

In situations of oligometastatic disease as well as initially inoperable locally advanced disease, it is very important to communicate with the patient regarding the decision taken at the multidisciplinary tumor board, regarding the duration of treatment proposed (continuous as in multi-metastatic disease or more limited in time, with duration of treatment more similar to the early setting).

2.4. *Section III: General guidelines (see Fig. 5)*

Guideline statement	LoE/GoR	Consensus
The management of ABC is complex and, therefore, involvement of all appropriate specialties in a **multidisciplinary team** (including but not restricted to medical, radiation and surgical oncologists, imaging experts, pathologists, gynecologists, 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 personalized to meet the needs of the individual patient.	Expert opinion/A	100%
Following a thorough assessment and confirmation of MBC, the **potential treatment goals of care should be discussed**. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances). This conversation should be conducted in the accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.	Expert opinion/A	97%
All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy-to-understand **information** about their disease and its management.	I/A	97%
Patients (and their families, caregivers or support network, if the patient agrees) should be **invited to participate in the decision-making process** at all times. When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network).	Expert opinion/A	100%
Every ABC patient must have access to **optimal cancer treatment and supportive care** according to the highest standards of patient-centered 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.	Expert opinion/A	100%

• Empowering patients to develop the capability of improving their own QoL within their cancer experience. • Always taking into account patient preferences, values and needs as essential to optimal cancer care. • Patients should have easy access to well-designed clinical studies since these are crucial for further improvement in the management of ABC.		
Every ABC patient should: • Have access to the most up-to-date treatments and innovative therapies at accessible breast units/centers. • Be treated in specialist breast units/centers/services (SBUs) by a specialized multidisciplinary team including specialized side effects management and a nurse experienced in the treatment of ABC. • Survivorship issues and palliative care should be addressed and offered at an early stage. • A quality assurance program covering the entire breast cancer pathway from screening and diagnosis to treatment, rehabilitation, follow-up and palliative care, including services and support for ABC patients and their caregivers, should be implemented by SBUs.	 Expert opinion/A I/A Expert opinion/A Expert opinion/B	 100% 100% 100% 100%
General statements: QoL		
PROs, e-PROs and Quality of Life Assessments Strong consideration, as part of routine clinical care, should be given to the integration of patients' reports of symptoms of disease and side effects of treatment. Several remote measurement systems exist but these must be evidence-based and shown to be simple enough for use in clinical practice, in particular employ user-friendly collection platforms e.g. tablets or smartphones appropriate for different patient groups. Such regular systematic monitoring may facilitate communication between patients and their treatment teams about the toxicities of anticancer therapies. Reporting does not have to be tied to regular follow-up visits so that it may permit earlier introduction of ameliorative interventions and supportive care services.	I/B	87%
Trials evaluating QoL in ABC should employ standardized PROMs and not focus exclusively on reporting CTCAE symptom grades. If generic measures are used, then appropriate symptom and treatment specific modules or subscales that exist within the EORTC and FACT systems should be incorporated.	Expert opinion/A	98%

Additionally, attention must 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 choosing between treatment options.		
General statements: clinical trials		
After appropriate informed consent, inclusion of patients in well-designed, prospective, independent trials must be a priority whenever such trials are available, and the patient is willing to participate.	Expert opinion/A	100%
The ABC community strongly calls for clinical trials addressing important unanswered clinical questions in this setting, and not just for regulatory purposes. Clinical trials should continue to be performed, even after approval of a new treatment, to provide real-world data on its performance, effectiveness and toxicity.	Expert opinion/A	100%
Maximum tolerated dose vs. minimal effective dose: In the treatment of human breast cancer, the biology of dose-response relationship curves for newer targeted medicines and even older chemotherapy drugs does not support the requirement that these agents always be employed at maximum tolerated dose, a concept that originated in the study of murine leukemia. This insight is amplified by considerations of feasibility, as well as quality of life and goals of care. From this perspective, finding and utilizing the optimal dose level and the best schedule should be an important part of the clinical development of any anticancer agent.	Expert opinion/NA	96%
General statements: affordability/cost effectiveness		
The ABC 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 prioritize 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 statements: survivorship		
As survival is improving in many patients with ABC, consideration of survivorship issues should be part of the routine care of these patients. Health professionals should therefore be ready to change and adapt treatment strategies to disease status, treatment of adverse effects and QoL, patients' priorities and life plans. Attention to chronic needs for home and family care, job and social requirements, should be incorporated in the treatment planning and periodically updated.	Expert opinion/A	95%
ABC patients who desire to **work** or need to work for financial reasons should have the opportunity to do so, with needed and reasonable flexibility in their working schedules to accommodate continuous treatment and hospital visits.	Expert opinion/A	100%
ABC patients with stable disease being treated as a 'chronic condition' should have the option to undergo **breast reconstruction**, if clinically appropriate.	Expert opinion/B	82%
In ABC patients with long-standing stable disease or complete remission, **breast imaging** is an option.	Expert opinion/C	83%
Breast imaging should also be performed when there is a suspicion of locoregional progression.	I/A	100%
General statements: other		
Relevant drug interactions: Special attention should be given to potential interactions between targeted agents and common medications for comorbidities, due to the risk of interference with efficacy and/or safety. Examples: • Tamoxifen and ribociclib – increased risk of QTc prolongation; • PPI and ribociclib/palbociclib/abemaciclib – likely decreased efficacy; • Corticosteroids and checkpoint inhibitors – possible decreased efficacy due to competing mechanisms of action (i.e. immunosuppression); • Antibiotics and checkpoint inhibitors – decreased efficacy due to possible interference with microbiota.	III/A	82%
Specialized oncology nurses (if possible specialized breast nurses) should be part of the multidisciplinary team managing ABC patients. In some countries, this role may be played by a physician assistant or another trained and specialized 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%
Support for caregivers: The wellbeing of all informal and formal caregivers of patients with ABC is frequently ignored and their pivotal role in supporting patients underestimated and undervalued. They too often need appropriate psychological and practical support. Working carers require protection from discrimination in the workplace (current and future). With the patient's agreement, culturally sensitive, up-to-date, and easy to understand information about their loved one's disease and its management throughout the whole trajectory from diagnosis to end-of-life should be provided by the healthcare team and needs to be congruent with that given to patients. Identification of formal and informal carers' needs and referral to appropriate resources should be available for all patients with ABC. For working carers, entitlement to continued employment and requests for reasonable adjustments, such as flexible working, to accommodate their caring responsibilities should be addressed. Country-specific political mediation may be required.	Expert opinion/NA	100%
Caring for patients with ABC during war and conflict: War and conflict can cause major disruption to delivery of care for patients with cancer. If access to medical care is disrupted or erratic, when possible, consider treatment with oral regimens and treatment regimens requiring minimal routine monitoring and blood work. Telemedicine should be utilized to ensure continuity of care and contact with patients. All efforts should be made to ensure access to pain medications and integrate in humanitarian packages. Providing online support for colleagues in regions of conflict, who may themselves be at risk but who are essential workers trying to ensure best delivery of oncology care under difficult circumstances, is meaningful and important.	Expert Opinion/B	100%
Caring for patients with ABC and pre-existing serious mental health illness: Individuals diagnosed with serious mental illness (SMI) (including but not limited to major depression, bipolar disorder, and schizophrenia) are more likely to be diagnosed with advanced stage cancer and to have poorer outcomes than individuals without SMI. Attention needs to be given to the special needs of patients with ABC and SMI and there should be no discrimination against them. The oncology team should endeavor to work together with the patient's psychiatrist and mental illness care team and endeavor to engage carers in order to ensure optimization, compliance and continuity of oncology care. Special attention needs to be given to drug-drug interactions between psychiatric medication and oncological therapies. Under certain circumstances steroid and medicinal cannabis use should be minimized to avoid triggering episodes of mania and psychosis.	IV/B	95%
Access of patients with ABC to Intensive Care Units (ICU): Patients with ABC should receive patient-centered communications regarding their prognosis and treatment options and have the right to forego treatment as well as to pursue treatments to the degree they desire, where available and appropriate for the disease setting. They should not be denied access to ICU based solely on their ABC diagnosis, in particular in cases of potentially reversible serious adverse events or complications or comorbidities other than ABC.	Expert Opinion/B	100%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; ASCO: American Society of Clinical Oncology; 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; ICU: Intensive Care Units; LoE: level of evidence; MBC: metastatic breast cancer; PPI: Proton pump inhibitors; PRO: patient-reported outcome; PROM: patient-reported outcome measure; QoL: quality of life; QTc: corrected QT interval; NA: not applicable.

2.5. Maximum tolerated dose vs minimum effective dose

A fundamental paradigm in medical oncology has long been that higher dose levels of cytotoxic drugs kill more cancer cells and that this results in benefit to the patient. This concept derived from the study of murine transplanted leukemia—the log-kill hypothesis [29]. One flaw in the extrapolation of these observations to human disease is that the experimental work used leukemia cell eradication as the desired result, rather than maximum time of disease control in settings in which cure was not possible. Another is that clinical solid tumors follow sigmoid growth kinetics rather than the exponential patterns seen in transplantable mouse leukemias [30]. Sigmoid growth might be the result of cancer self-seeding, stem cell kinetics, or a combination of factors [31]. But the net result is that dose-schedule relations favor frequent administration of moderate dose levels (increased density) over more widely spaced higher levels (dose level escalation) [32]. This has been proven in the post-operative breast cancer adjuvant setting by the results of prospective trials, which also challenged the paradigm of the general superiority of simultaneous, and hence more toxic, multi-agent combinations [33]. Furthermore, in preparation for the first of these trials—CALGB 9741—several studies demonstrated that higher dose levels do not convey advantages over more moderate levels in the treatment of advanced disease [34–36]. Subsequent trials extended these ideas into the design of less-toxic, at least equally efficacious schedules of paclitaxel and the oral cytotoxic drug capecitabine [37–40]. Optimal dose-scheduling of newer anti-cancer drugs, especially antibody-drug conjugates, might also favor less toxic, optimally timed, lower dose level approaches [41]. When duration of disease control, thereby maximizing clinical benefit, is the goal, the relevance of the maximum tolerated dose log-kill paradigm must be questioned. This concept has been further challenged with new agents and studies of new therapies should consider minimum effective dose to allow quality of life to be maintained, to provide less toxicity and to maintain efficacy of the treatments.

2.6. Attention to drug interactions

Several drug interactions have been recognized and in particular drugs that potentiate QTc prolongations or that may interfere with efficacy. Numerous drugs may prolong QTc if given with ribociclib including tamoxifen [42]. In most situations the panel suggested using alternative agents; in the example of ribociclib and tamoxifen, using an alternative endocrine therapy or CDK4/6 inhibitor. Clinicians are advised to order ECGs and to work with their pharmacists or online tools to ensure there are no drug interactions when prescribing. Proton-pump inhibitors (PPIs) may decrease the circulating levels of CDK4/6 inhibitors although the true impact on clinical benefit is still unknown [43,44]. Emerging data suggest a potential impact of antibiotics on the microbiome and consequent compromise of immune-checkpoint inhibitors efficacy [45]. The effect of steroid in the mechanism and activity of checkpoint inhibitors remains an area of debate and contradictory evidence [46].

2.7. Support for caregivers

The care of patients with ABC optimally involves caregivers, particularly as the disease progresses and their importance must be acknowledged, both in terms of providing emotional as well as physical and practical support. Health care providers need to recognize the roles as well as the needs of the caregivers and enable them to perform their work more effectively by providing easy access to information about both the disease as well as the goals and treatment of the individual patient. The wellbeing of all informal and formal caregivers of patients with ABC is frequently ignored but they also often need appropriate psychological and practical support [47,48]. Working carers require protection from discrimination in the workplace (current and future). Working as a team with the caregivers through the trajectory of the patient's journey with ABC is fundamental.

2.8. Caring for patients with ABC during war and conflict

During times of war and conflict, significant interruptions to health care delivery pose an immense challenge in cancer care delivery for patients with cancer, as well as care providers. Conflict and war may impact cancer care delivery for multiple reasons including (i) shortages in health care staff (ii) diversion of health care resources to the injured (iii) interruption in drug supplies (iv) challenges in accessing health care facilities for both patients and staff (v) exacerbation of mental health issues including anxiety, depression, loneliness and isolation (vi) displacement of individuals to other regions distancing them from their healthcare and possibly not having medical summaries of their medical history (vii) delays in diagnosis and interruption of screening (viii) interruption in food supply, possibly famine (ix) poverty because of interruption to employment and income (x) increase risk of infection and communicable diseases (xi) destruction of essential civilian infrastructure including roads and hospitals (xii) loss of family structure and carers [49–51]. Under these circumstances, preference should be given to oral therapies and therapies that require minimal blood work. Additionally, all efforts should be made to ensure a sustained supply in and access to essential medications including pain medication as an integral part of humanitarian aid. Telemedicine may be a preferred option for patient care when telecommunications have not been interrupted. Cross-border collaborations with neighboring countries not affected by the conflict and when circumstances permit, mobile clinics, may aid access to and provision of care [51]. In addition to the impact on oncology patients, the health care providers may also be impacted by the conflict and may themselves be in danger [51]. Providing online support for colleagues in regions of conflict, who may themselves be at risk but who are essential workers trying to ensure the best delivery of oncology care under difficult circumstances, is meaningful and important.

2.9. Caring for patients with ABC and pre-existing serious mental health illness

Serious mental illness (SMI) may include major depression, schizophrenia, bipolar disorder, and substance abuse disorders. It is well established that individuals with SMI have lower uptake of cancer screening [52,53], as well as significant risk factors for cancer incidence, including smoking and higher incidence of obesity. Individuals with SMI are more likely to be diagnosed with advanced disease from the outset and to have poorer outcomes. Research has shown that only 50 % of breast oncologists take into consideration and address the SMI when providing care for patients with breast cancer [54]. Notably, patients with SMI have been shown to be less-likely to receive guideline-based breast cancer care [55]. All efforts should be made to incorporate the psychiatric health care team and the patient's carers in order to optimize compliance and health care delivery. Particular attention needs to be given to drug-drug interactions between the psychiatric medications and oncology drugs, and any necessary changes in the psychiatric medication must be coordinated with the patient's psychiatrist. Under certain circumstances, steroids and medicinal cannabis use should be minimized to avoid triggering episodes of mania and psychosis and the treating psychiatrist should be consulted before use of these medications, particularly in individuals with bipolar disorder and schizophrenia.

2.10. Access of patients with ABC to intensive care units (ICU)

Efforts aimed at understanding and improving the quality of care for patients with ABC must consider that high quality care requires an understanding of and facilitation of individual patient preferences. While some patients might be interested in extending life as a primary goal,

others may prioritize specific domains of functioning or life goals, or general quality of life. Patient autonomy is a fundamental principle here, which should be considered in the context of the clinical situation and societal constraints. The COVID-19 pandemic served as a natural experiment as many life and death decisions had to be made, especially in the beginning of the pandemic when resources (such as ventilators) were scarce. In many countries, cancer patients in general and metastatic cancer patients in particular were often considered at the bottom of the priority list for access to ventilators and ICUs. Some types of advanced setting may be extremely indolent or well controlled for many years and others may have more deleterious trajectories such that the benefits of intensive treatment for a complication or unrelated comorbidity for a given patient must be considered in that context. For example, a patient with indolent metastatic breast cancer who gets an infectious disease should generally be treated similarly to a patient who doesn't have breast cancer given that the patient may have a several-year life expectancy otherwise. In contrast, heroic measures to treat a life-threatening comorbidity in a patient whose cancer has not been under control for some time or that is a complication of their cancer may be less worthwhile for that patient. While both governmental and non-governmental organizations have considered versions of cancer patients' bill of rights [56–59], limited attention to date has been paid to end of life care in this regard. Fortunately, a number of initiatives have focused on optimizing communication among patients with advanced cancer including breast cancer patients.

2.11. *Section IV: assessment and treatment general guidelines (see Fig. 1)*

Guideline statement	LoE/GoR	Consensus
Image and disease assessment guidelines		
Minimal staging work-up for ABC includes a history and physical examination, hematology and biochemistry tests and imaging of the chest, abdomen and bone.	II/A	67%
The clinical value of **tumor markers** is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. An increase in tumor 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 to 4 months for ET-based therapy or after 2 to 4 cycles for ChT, depending on the dynamics of the disease, the location and extent of metastatic involvement and type of treatment. Imaging of a target lesion may be sufficient in many patients. In certain patients, such as those with indolent disease, less frequent monitoring is acceptable. Additional testing should be performed in a timely manner, irrespective of the planned intervals, if PD is suspected or new symptoms appear. A thorough history and physical examination must always be performed.	Expert opinion/B	81%
Biopsy guidelines		
A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis, particularly when metastasis is diagnosed for the first time.	I/B	98%
Biological markers (especially **ER and HER2**) should be reassessed at least once in the metastatic setting, if clinically feasible.	I/A	98%
The value of **PgR** in the metastatic setting is limited and reserved only for confirmation of triple negative status. In the very rare cases of ER-/HER2-/PgR+ ABC, approved therapies for triple negative ABC can be used. Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist. The quality of IHC assessments is crucial to ensure adequate treatment decisions.	Expert Opinion/B	82%

If the results of ER and HER2 in the metastatic lesion differ from the primary tumor, 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 endocrine therapy or anti-HER2 therapy, respectively, when ER or HER2 are positive in at least one biopsy, regardless of timing.	Expert Opinion/B	71%
For tumors with **confirmed triple negative biology** in the primary tumor, if the results of any receptor status in the metastatic lesion differ, it is currently unknown which result should be used for treatment decision making. Since a clinical trial addressing this issue is difficult to undertake, the use of therapies specifically approved for triple negative, ER+/HER2 negative or HER2+ ABC should be discussed on a case-by-case basis.	Expert opinion/B	96%
Locoregional treatment general guidelines		
To date, the **removal of the primary tumor** in patients with ***de novo* stage IV breast cancer** has not been associated with prolongation of survival. However, it can be considered in selected patients, particularly to improve quality of life, always taking into account the patient's preferences, after a multidisciplinary discussion. Examples of situations where surgery of the primary may be considered include: • Symptomatic primary site (for control of symptoms); • Progression of the primary tumor when distant disease is controlled; • No evidence of disease except in the primary tumor; Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (i.e. complete removal of the disease) as in patients with early stage disease.	I/C II/B	98% 98%
Systemic treatment general guidelines		
Treatment choice should take at least these **factors** into account: ER and HER2 status, *BRCA* status in HER2 negative ABC, *PIK3CA* mutation status in ER-positive ABC and PD-L1 expression status in triple negative ABC, if targeted therapies are accessible. Previous therapies and their toxicities, DFI, tumor burden (defined as number and site of metastases), biological age, PS, comorbidities (including organ dysfunctions),	Expert opinion/A	95%

menopausal status (for ET), the need for rapid disease/symptom control, socio-economic and psychological factors, available therapies in the patient's country and patient's preference.		
The **age** of the patient should not be the sole reason to withhold effective therapy (in older patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment.	I/E	100%
Treatment holidays: Planned treatment holidays, with careful supervision, are an acceptable option in the case of long-term responders with controlled disease.	IV/B	98%
Stopping treatment in patients with **long-term complete remissions** has not been adequately studied but should be considered on a case-by-case basis, after extensive discussion with the patient. It is crucial that resuming the treatment if progression of disease occurs, is allowed in all countries.	Expert Opinion/B	98%
ChT general guidelines		
Both combination and sequential, single-agent ChT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for ABC. Combination ChT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control.	I/A	96%
In the absence of medical contraindications or patient concerns, anthracycline- or taxane-based regimens, preferably as single agents, would usually be considered as first-line ChT for **HER2-negative ABC** in those patients who have not received these regimens as (neo)adjuvant treatment and for whom ChT is appropriate. Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.	I/A	71%
In patients with taxane-naive and anthracycline-resistant ABC or with anthracycline maximum cumulative dose or toxicity (i.e. cardiac) who are being considered for further ChT, taxane-based therapy, preferably as single agent, would usually be considered as the treatment of 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, single-agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents,	I/A	77%

a different taxane and liposomal anthracyclines. The decision should be individualized 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 one year of DFI.	I/B	92%
If given in the adjuvant setting, provided that maximum cumulative dose has not been achieved and there are no cardiac contraindications, anthracyclines can be re-used in ABC, particularly if there has been at least one year of DFI.	I/B	93%
Metronomic ChT is a treatment option for patients not requiring rapid tumor response. Available regimens are CM (low-dose oral cyclophosphamide and methotrexate), capecitabine or oral vinorelbine-based regimens. Randomized trials are needed and underway to accurately compare metronomic ChT with standard dosing regimens.	I/B	98%
Duration of each regimen and the number of regimens should be tailored to each individual patient.	Expert opinion/A	96%
Usually, each regimen (except anthracyclines) should be given until PD or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.	I/B	72%
Other agents		
Bevacizumab combined with ChT as first-line therapy for ABC provides a moderate benefit in PFS and no benefit in OS. The absence of known predictive factors for bevacizumab efficacy renders recommendations on its use difficult. Bevacizumab can only therefore be considered as an option in selected cases and only in the first-line setting. **ESMO-MCBS v1.1 score: 2**	I/C	Yes – 42% No – 53%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; ChT: chemotherapy; *BRCA*: BReast CAncer gene; CM: cyclophosphamide/methotrexate; DFI: disease-free interval; ESMO-MCBS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ER: Estrogen receptor; ET: endocrine therapy; GoR: grade of recommendation; HER2: human epidermal growth factor 2; IHC: immunohistochemistry; LoE: available level of evidence; MBC: metastatic breast cancer; OS: overall survival; PD: Progressive Disease; PD-L1: programmed death-ligand 1; PFS: progression-free survival; *PIK3CA:* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PgR: Progesterone receptor; PS: performance status; QoL: quality of life; TNBC: triple-negative breast cancer.

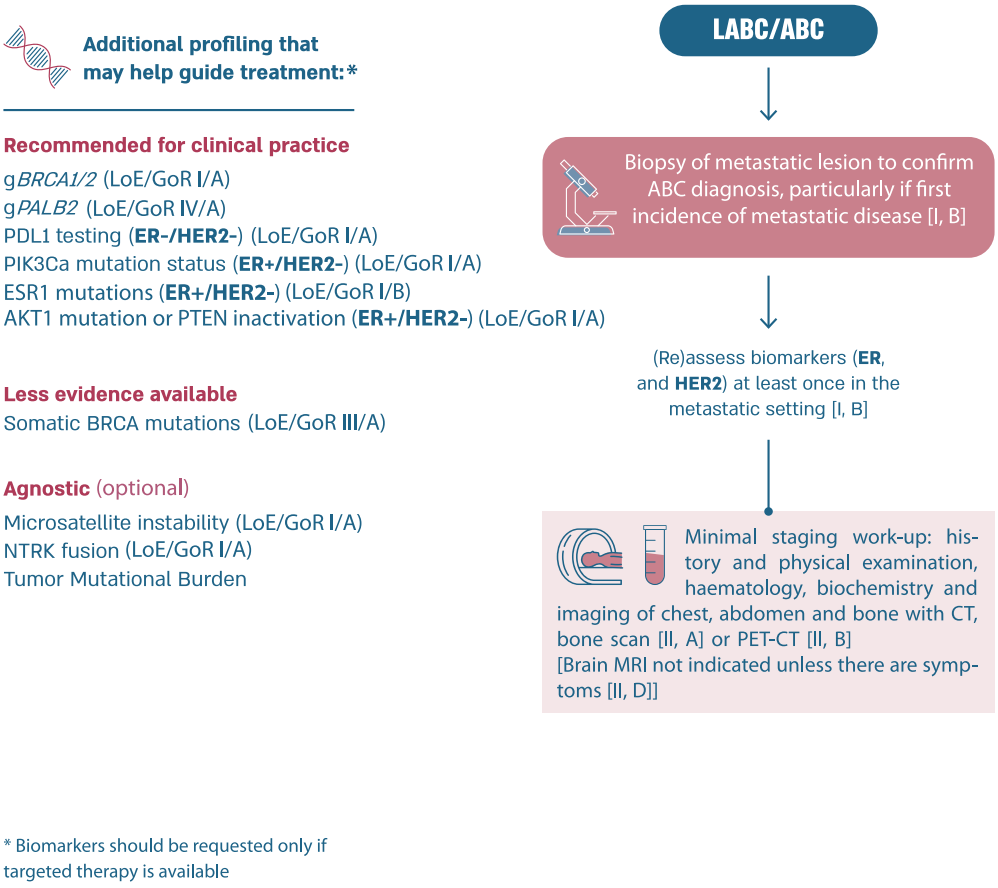

Fig. 1. ABC diagnostic work-up and staging.
Legend: ABC, advanced breast cancer; CT, computed tomography; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MRI, magnetic resonance imaging; PET, positron emission tomography.

2.12. Biopsy guidelines

All patients with newly diagnosed lesions should have a biopsy, if clinically feasible, to confirm the presence of breast cancer and to assess the subtype of the recurrence.

Biological markers (especially ER and HER2) should be reassessed at least once in the metastatic setting, even in case of a bone-only metastatic presentation. In this case, the oncologist must communicate with the interventional radiologist and the pathologist so that the decalcification of the bone biopsy is not carried out in an acidic solution but in EDTA which preserves the antigenic sites for immunohistochemistry and nucleic acids for in situ hybridization or molecular biology [60]. If a bone lesion is the biopsy site, it is preferable to biopsy a mixed lytic and sclerotic lesion rather than a pure sclerotic area to increase the chance of retrieving adequate high-quality cells to assess. In choosing the site it should be an active site on PET imaging or by history, safe to biopsy, and appropriate for testing (see liver biopsies and PD-L1 testing below). In cases where there is discordance in response between sites, more than one area should be biopsied and fully tested to obtain a clear picture of the biology of the disease and plan treatment accordingly.

In cases of discordance between the primary tumor and the metastatic site(s), the first step is to revise the full case, if possible with double-reading, and in some cases, consider re-biopsy.

The value of PR expression in the metastatic setting is limited and reserved only for confirmation of triple negative status. ER-/HER2-/PR + ABC is rare and data from early breast cancer show that they may not be responsive to endocrine treatment. As a clinical trial addressing this issue is difficult to undertake, we recommend considering therapies for triple negative ABC [61]. If an HER2 positive tumor becomes HER2-negative at re-biopsy, the result should be questioned. It is necessary to check by ISH, to re-check the HER2 status of the initial tumor for possible intratumoral heterogeneity, and finally not to hesitate to repeat HER2 testing in case of new progression [62,63].

PD-L1 expression should be tested in cases of first-line triple-negative ABC if treatment with immune checkpoint inhibitors is available, as a companion test for either the combination of pembrolizumab and chemotherapy, with a PD-L1 assay (with 22C3 antibody) and a combined score of 10 or more (CPS score) [65 and 66] or the combination of atezolizumab and nab-paclitaxel, with SP-142 antibody (Ventana) and a score of 1 % or more positive immune cells (IC score) [67]. If possible, consider avoiding PD-L1 determination in liver biopsy. Due to the general lack of immune cells in this organ, the PD-L1 status is consistently lower in liver biopsy as compared to other metastatic sites [68, 69].

2.13. "Treatment holidays"

The aim of any treatment for a patient with ABC must be not only to add quantity to life, but also quality, allowing the patient to continue to build and achieve life projects. With this goal in mind, and to be able to enjoy life to the full without the constraints or side-effects of the treatments, some patients ask for "treatment holidays". This notion should be understood as a period of surveillance without treatment. It is neither a definitive cessation of treatment, nor simply a lengthening of the interval between two courses of treatment. The response to this request must consider two parameters to adapt it to the risk of disease progression: the level of disease control at the time the decision is made and the biological ABC sub-type. The development of treatments has now

made it possible to achieve not only more responses, but also more complete responses, and for longer periods. This occurs more often at the start of treatment for metastatic disease [70]. It is particularly true for HER2-positive ABC with the addition of anti-HER2 agents, and for ER-positive ABC with the addition of CDK4/6 inhibitors [71]. HER2-positive ABC currently have the highest expected rate of complete and durable remissions, and one of the longest life expectancies in the metastatic setting [72]. There are some retrospective data analyzing "treatment holidays" in HER2-positive ABC. It seems that these are safer to consider in cases of complete and durable remission (>2 years) and perhaps in younger populations [73]. In ER+/HER2 negative ABC, early progression (<12 months) on a CDK4/6 inhibitor regimen is a strong clinical marker of a less favorable outcome [74]. If side-effects are not the main reason for "treatment holidays", some form of maintenance therapy could be the preferred option, to be discussed with the patient [75]. In the case of triple-negative ABC, even though certain targeted treatments can achieve significant benefits, only a very small proportion of patients experience long-term control of their disease (>12–18 months). Under these conditions, it is difficult to define criteria for "treatment holidays", and this decision must be made based on patient demand and clinical judgement, and should be limited in time.

2.14. Section V: ER-positive/HER2-negative (luminal-like) ABC (see Fig. 2)

Guideline statement	LoE/GoR	Consensus
ET-based therapy is the preferred option for ER-positive disease, even in the presence of visceral disease, unless there is visceral crisis.	I/A	93%
Many trials in ER-positive ABC have not included **premenopausal** women. Despite this, we recommend that young women with ER-positive ABC should have adequate OFS/OFA and then be treated in the same way as postmenopausal women, with endocrine agents with or without targeted therapies.	Expert opinion/A	95%
Future trials exploring new endocrine-based strategies should be designed to allow for enrolment of both pre- and postmenopausal women, and men.	Expert opinion/A	92%
For **premenopausal women**, for whom ET was decided, OFS/OFA combined with additional endocrine-based therapy is the preferred choice.	I/A	93%
OFA by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids the potential initial tumor flare seen with an LHRH agonist and may increase eligibility for clinical trials. Patients should be informed of the options for OFS/OFA and decisions should be made on a case-by-case basis.	Expert opinion/C	91%
Single-agent tamoxifen is the only available endocrine option for premenopausal women who decline OFS/OFA, but the panel believes it is a less effective option.	I/D	92%
The preferred first-line endocrine agent depends on the type and duration of adjuvant ET as well as the time elapsed from the end of adjuvant ET; it can be an AI, tamoxifen or fulvestrant for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	84%
A **CDK4/6 inhibitor** combined with ET is the standard of care for patients with ER-positive/HER2-negative ABC, since it achieves a substantial PFS benefit, significantly increases OS and either maintains or improves QoL. The CDK4/6 inhibitor can be combined with an AI or with fulvestrant (tamoxifen cannot be combined with ribociclib, but can be combined with abemaciclib or palbociclib), in *de novo* or recurrent ABC, in first or second-line and in cases of primary or secondary resistance (defined as per ABC guidelines).	I/A	97%

This recommendation applies to postmenopausal women, to premenopausal women in combination with an LHRH agonist and to men, preferably in combination with an LHRH agonist.		
The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with ET for ABC patients vary according to the setting and drug. They are the following, with the current available data and follow-up: • Ribociclib + ET 1st line Pre-menopausal; ESMO-MCBS: 5 • Ribociclib + AI 1st line Post-menopausal; ESMO-MCBS: 4 • Palbociclib + AI 1st line; ESMO-MCBS: 3 • Abemaciclib + AI 1st line; ESMO-MCBS: 3 • Palbociclib + Fulvestrant 2nd line; ESMO-MCBS: 4 • Ribociclib + Fulvestrant (1st, 2nd line); ESMO-MCBS: 4 • Abemaciclib + Fulvestrant 2nd line; ESMO-MCBS: 4 Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial.	I/A	89%
The SONIA trial attempted to answer the question whether a CDK4/6 inhibitor (90% palbociclib) combined with endocrine therapy should be given as 1st or 2nd line therapy for ER+/HER-2 neg ABC. No statistically significant differences were seen in PFS 2 (primary endpoint) nor OS nor QoL, at 37 months follow-up. It is currently unknown if these results would be the same with ribociclib or abemaciclib. In view of the totality of data (OS benefit and different 2nd line options), the panel still considers the use of a CDK4/6i + ET as the standard 1st line therapy for the majority of patients with ER+/HER-2 neg ABC. However, based on the SONIA trial results, it is an acceptable option to use ET alone as 1st line therapy for selected patients (e.g. low volume of disease, long DFI, patient preferences, accessibility constraints) with this ABC subtype.	I/A	93%
There are no data comparing a combination of CDK4/6 inhibitor and ET vs. ET alone as maintenance therapy after chemotherapy. Both options are acceptable.	Expert Opinion/B	75%

The use of a CDK4/6 inhibitor + ET after disease progression on a CDK4/6 inhibitor (i.e. **beyond progression**) has been evaluated in small phase 2 trials, with conflicting results and is not recommended for routine clinical practice, outside a clinical trial.	Expert Opinion/D	91%
Trials comparing the different combinations of endocrine + targeted agents with single agent ChT, in the 1st and later lines settings, are ongoing and some have been reported. In the PEARL trial, despite several trial limitations, ET + palbociclib and capecitabine yielded similar efficacy, while toxicity profiles were different. In Young-PEARL, for premenopausal women, ET + palbociclib was superior to capecitabine in terms of PFS. In view of the substantial survival benefit seen with ET + CDK4/6 inhibitors in 1st line, never seen before with chemotherapy, this combination should be considered the standard of care for 1st line therapy of ER+/HER2 negative ABC, for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	96%
In the RIGHT Choice trial, the combination of ribociclib + aromatase inhibitor (+ LHRH agonist in pre-menopausal women) was compared to combination chemotherapy (docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine) as 1st line therapy for pre/peri-menopausal women with ER+/HER2 neg ABC with **"clinically aggressive disease"**, defined as: symptomatic visceral metastases, rapid disease progression or impending visceral compromise, markedly symptomatic non-visceral disease, but with bilirubin <1.5xULN (therefore not in liver visceral crisis as defined by the ABC guidelines). The ET + CDK4/6i arm yielded a 12-month benefit in PFS, with similar ORR and similar time to onset of response in both arms, but substantially better toxicity profile. These results reinforce the place of ET + CDK4/6 inhibitors as standard of care for 1st line therapy for the majority of patients with ER+/HER2 negative ABC, including those with "clinically aggressive disease". Although the trial was performed only in pre/peri-menopausal women, the panel believes the results also apply to post-menopausal women and men with the same disease characteristics.	I/A Expert Opinion/B	95% 95%

The addition of **everolimus** to an AI is a valid option for some patients [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women] previously exposed to or naive of (in case CDK4/6 inhibitors are not available) ET, since it significantly prolongs PFS, albeit without evidence of an OS benefit. **ESMO-MCBS v1.1 score: 2**	I/B	88%
Tamoxifen or fulvestrant can also be combined with everolimus.	II/B	80%
Adequate prevention with steroid mouthwashes, close monitoring and proactive treatment of AEs is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the BOLERO-2 trial.	I/B	97%
Everolimus should not be used after disease progression on that agent (i.e. beyond progression), outside a clinical trial.	NA/E	74%
Alpelisib with fulvestrant is a treatment option for patients [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women] with *PIK3CA*-mutant tumors (in exons 9 or 20), previously exposed to an AI and with appropriate HbA1c levels, since it provided about 5 months benefit in median PFS, without statistically significant OS benefit. The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the SOLAR-1 study (i.e: pre-existing diabetes & baseline HbA1c), as well as the toxicity profile of alpelisib. **ESMO-MCBS v1.1 score: 2**	I/A	96%
Few patients previously treated with a CDK4/6i were included in the SOLAR-1. However, a non-randomized cohort study (ByLieve) seems to indicate that alpelisib retains its efficacy if used after a CDK4/6i. In view of the magnitude of OS benefit seen with ET + CDK4/6i, this approach is considered the standard of care for 1st line therapy and ET (fulvestrant or AI) + alpelisib should be reserved for the 2nd line setting, in cases of *PIK3CA*-mutant tumors.	I/B	93%
Patients receiving alpelisib in combination with ET for *PIK3CA*-mutated ABC should be instructed to take non-sedating antihistamines to prevent rash at the start of therapy. Antihistamines can be discontinued after 4 weeks as the risk for rash is primarily in the first 2 weeks of therapy.	I/B	93%
Elacestrant, an oral SERD, has been approved as 2nd/3rd line therapy for patients with ER+/HER2 negative ABC with an *ESR1* mutation, based on a randomized phase 3 trial demonstrating 1.9 months median PFS advantage (HR: 0.55). This	I/C	81%

. (*continued*).

advantage was most notable in patients who were previously treated with a CDK4/6 inhibitor for more than 6 months. Where available, single agent Elacestrant is an option for patients in 2nd/3rd line setting with an *ESR1* mutation**. ESMO-MCBS v1.1 score: 3**		
Capivasertib, an AKT inhibitor, combined with fulvestrant was compared to placebo plus fulvestrant, in patients [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women] with ER+/HER2 negative ABC, with 1 or 2 lines of previous ET and none or 1 line of chemotherapy for metastatic disease; recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC was required; about 70% of pts received prior CDK4/6i. The results showed a 3.6 months benefit in median PFS (HR: 0.60) in the overall population and a 4.2 months median PFS benefit (HR: 0.50) in the AKT pathway-altered population (i.e. *PIK3CA* and/or PTEN and /or AKT1 alteration). OS results are still immature. GI side effects, mainly diarrhea (72%), were seen. Based on these results, where approved, capivasertib added to fulvestrant may be used as a treatment option in endocrine resistant ER+/HER2 neg ABC with an AKT pathway-altered (i.e. *PIK3CA* and/or PTEN and /or AKT1 alteration). **ESMO-MCBS v1.1 score: 3.** It is unknown what is the efficacy of capivasertib after an ADC such as Trastuzumab deruxtecan or Sacituzumab govitecan or how it compares with everolimus or alpelisib.	I/B	95%
Sacituzumab govitecan was compared with chemotherapy of physician's choice, in patients with ER+/HER2 negative ABC, previously treated with at least 1 line of ET, taxane and CDK4/6 inhibitor in any setting and at least 2, but no more than 4, lines of ChT for metastatic disease (60% of pts have received 3 or more lines of ChT). Results showed a 1.5 months improvement in median PFS and 3.2 months in median OS, both in HER2 low and HER2 zero. No new safety signals were seen. Education, prophylaxis, and early management of side effects, in particular diarrhea and nausea/vomiting, remain important. The OS benefit seen in this heavily pretreated population makes sacituzumab govitecan a treatment option for this patient population. **ESMO-MCBS v1.1 score: 4**	I/B	95%

Datopotamab deruxtecan (Dato-DXd) was compared with chemotherapy of physician's choice (mostly eribulin), in patients with ER+/HER2 negative ABC, previously treated with 1–2 lines of chemotherapy in the inoperable or metastatic settings and experienced progression on ET and for whom ET was unsuitable, and led to a 2 months improvement in median PFS (HR: 0.63). Results from the dual primary endpoint OS are still awaited. Stomatitis, ocular events (mostly dry eye), nausea, vomiting and fatigue were the most common side effects. ILD/pneumonitis was uncommon. Education and preventive measures (i.e. mouthwashes, anti-emetics) are recommended. In view of the modest PFS difference, absence of OS data for the moment, side effect profile and availability of other treatment options, Dato-DXd cannot yet be recommended for routine clinical practice use.	I/D	66%
Trastuzumab deruxtecan (T-DXd) was compared to chemotherapy of physician's choice, in patients with **HER2 low ABC**, treated with 1-2 lines of chemotherapy in the metastatic setting and ER+ disease considered endocrine refractory, and yielded 6.1 months benefit in median OS and 4.6 months in median PFS (HR), making it a preferred treatment option in this setting. **ESMO-MCBS v1.1 score: 4** Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/A	100%
There are very few data regarding the best **sequence of administration of ADCs** for **ER+/HER2 low ABC**. In view of the populations treated and results of the trials of T-DXd and sacituzumab govitecan, the panel believes that T-DXd should be used earlier than sacituzumab.	Expert Opinion/B	95%
The **combination of a nonsteroidal AI and fulvestrant** as first-line therapy for postmenopausal patients resulted in significant improvement in both PFS and OS compared with AI alone in one phase 3 trial and no benefit in a second trial with a similar design. Notably, a suboptimal dose of fulvestrant was used in the study that demonstrated benefit. Subset analysis suggested that the benefit was limited to patients without prior exposure to adjuvant ET (tamoxifen). Based on these data, combination ET may be offered to some patients with ABC without prior exposure to adjuvant ET, in cases where a CDK4/6 inhibitor will not be given. **ESMO-MCBS v1.1 score: 2**	II/D	Yes: 38% No: 60% Abstain: 2%

Comparative data between this combination and a CDK4/6 inhibitor with ET are not available.		
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), duration of response to those agents, burden of the disease, patients' preference and availability.	I/A	100%
Options for treatment of ER-positive disease beyond second line include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megestrol acetate, low-dose estrogen). Single agent abemaciclib is also a potential option. Challenging a patient with an agent on which the disease previously progressed after an initial response is occasionally considered, but there are no robust data to support this approach. This applies to pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	II/B	98%
Concomitant ChT and ET has not shown a survival benefit and should not be performed outside a clinical trial.	II/D	100%
Endocrine treatment after ChT (**maintenance ET**) to maintain benefit is a reasonable option, though it has not been properly assessed in randomized trials.	III/B	88%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; ADC: Antibody-drug conjugate; AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ChT: chemotherapy; consensus, percentage of panel members in agreement with the statement; CT: Computed Tomography; DFI: Disease-free interval; ER, oestrogen receptor; ESMO-MBCS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET: endocrine therapy; *ESR1*: Estrogen Receptor 1; GoR, grade of recommendation; GI: Gastrointestinal; HR: Hazard ratio; HbA1c: glycated hemoglobin; HER2, human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinising hormone-releasing hormone; ILD: Interstitial Lung Disease; LoE: level of evidence; mTOR: mammalian target of rapamycin; n/a: not applicable; NSAI: non-steroidal aromatase inhibitor; OFS: ovarian function suppression; OFA: ovarian function ablation; ORR: Overall response rate; OS: overall survival; PD: progressive disease; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS: progression-free survival; PTEN: Phosphatase and tensin homolog; QoL: quality of life; SAI: steroidal aromatase inhibitor; SERD: selective estrogen receptor degrader; T-DXd: Trastuzumab-deruxtecan.

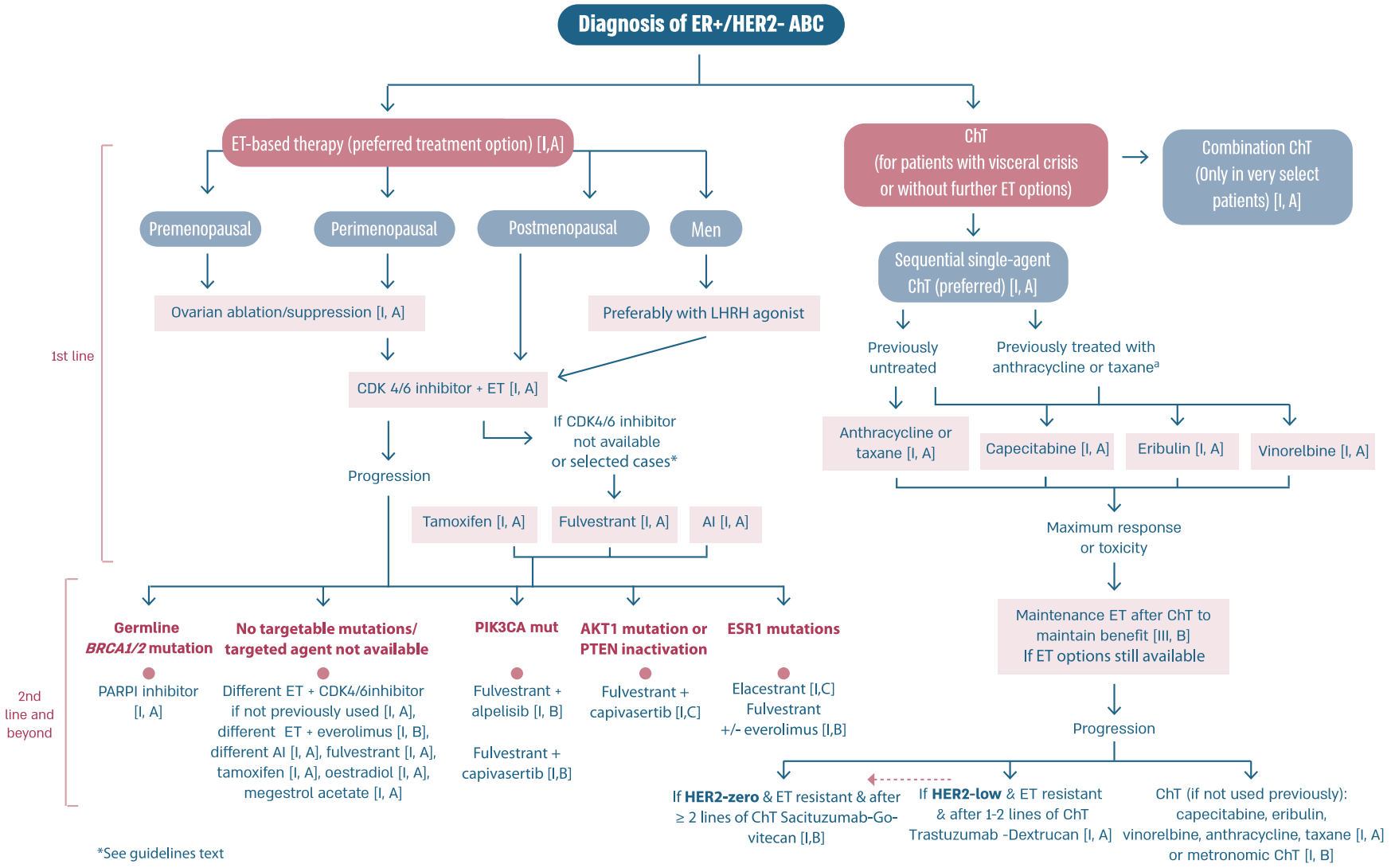

Fig. 2. Treatment of ER-positive/HER2-negative ABC
Legend: ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; DFI, disease-free interval; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PIK3CA, phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha. [a] Rechallenge with a taxane or anthracycline is possible if cumulative dose not reached and DFI ≥12 months.

The treatment of ER-positive/HER2 negative ABC has seen several advances in recent years [76–79]. Ribociclib combinations have shown statistically significant and clinically meaningful benefit in overall survival as well as progression free survival [80], both in pre and post-menopausal women and men. Other CDK4/6 inhibitors remain options, based on patient comorbidities, tolerance, availability. After ABC7, results of the final OS analysis from MONARCH 3 were presented, showing a numerical improvement of 13.1 months that did not reach statistical significance [81]. Studies comparing capecitabine to hormonal therapy and CDK4/6 inhibitors did not show a benefit for the early introduction of this chemotherapy [82,83]. Furthermore, the RIGHT Choice trial showed superiority in terms of PFS and tolerability for ribociclib plus ET, when compared with combination chemotherapy, in a patient population presenting with high disease burden [84]. The definition of visceral crisis in the RIGHT Choice trial was not according to the ABC 5 Guidelines since bilirubin could not be above 1.5 times the ULN, per inclusion criteria.

The role of continuing a CDK4/6 inhibitor beyond progression, either switching the endocrine backbone or switching to another CDK4/6 inhibitor, has been evaluated in three small phase 2 trials, with somewhat different outcomes: the MAINTAIN, PACE and PALMIRA trials [85–87]. In the MAINTAIN trial, both CDK4/6 inhibitor and ET were switched upon progression, leading to a small improvement in PFS [86]. In the PACE and PALMIRA trials, only ET was switched upon progression, failing to prove beneficial. In the PACE trial, a third arm was included with the addition of avelumab, a PD-L1 inhibitor, showing a PFS benefit, although not statistically significant [85]. Due to these conflicting results and weak evidence, continuing a CDK4/6 inhibitor upon progression is not recommended, outside a clinical trial. Results from phase 3 trials, such as the postMONARCH study, are still awaited [88].

While the optimal sequencing of treatments following progression on ET + CDK4/6 inhibitor remains to be defined, several options may be considered, favoring a sequential use of endocrine-based therapies, considering patient comorbidities, preferences, and emergence of potential targetable alterations. Alpelisib plus fulvestrant is an option for patients whose tumors harbor *PIK3CA* mutations, as 2nd line therapy, based on the results of the randomized SOLAR-1 study [89] and the non-randomized BYLieve study [90]. The latter provided relevant data on the benefit of alpelisib after prior exposure to CDK4/6 inhibitors, for pre-menopausal women and in combination with an AI. The ongoing phase 3 EPIK-B5 trial will better define the role of this combination upon progression to CDK4/6 inhibitors [91]. In the CAPItello-291 phase 3 trial, in particular in tumors exhibiting *PIK3CA*/AKT1/PTEN alterations, capivasertib with fulvestrant showed improved PFS and was approved following progression on at least one ET-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant ET [92].

The new generation of anti-estrogen therapies, the oral selective estrogen receptor degraders/downregulators (SERDs) were developed to try to overcome some of the mechanisms of endocrine resistance, especially acquired *ESR1* mutations, as well as to address limitations of current ET, such as intramuscular administration of fulvestrant and the agonist activity of tamoxifen. So far, only one of these agents, elascestrant, has been approved based on the results of the phase 3 EMERALD trial [93], which showed a small increase in PFS when compared to fulvestrant, after treatment with a CDK4/6 inhibitor. The magnitude of benefit was somewhat higher in tumors harboring an *ESR1* mutation.

A new treatment option for this ABC subtype are ADCs, namely trastuzumab-deruxtecan (T-DXd) and sacituzumab govitecan. For patients with ER-positive/HER2 low tumors (89 % of the trial population), the DESTINY-Breast04 trial established T-DXd as one of the preferred treatment options [94], as compared to mono-chemotherapy of physician's choice, in disease considered endocrine-refractory by the trial (not exactly according to the ABC definition), in view of the substantial benefit in OS (about 6 months) and PFS. These benefits need to be balanced against associated toxicity, with two adverse events of interest occurring more frequently with T-DXd: left ventricular dysfunction, largely asymptomatic, and interstitial lung disease, emphasizing the need for close monitoring and early interventions to prevent serious complications. For patients with ER-positive/HER2 negative tumors considered endocrine-resistant by the trial (not exactly according to the ABC definition), sacituzumab govitecan lead to improved PFS and OS (3, 3 months) in the phase 3 TROPiCS-02 trial [95,96], over mono-chemotherapy of physician's choice. So far, no head-to-head comparisons of T-DXd and sacituzumab govitecan were performed and no robust data exist regarding optimal sequencing of these agents. Given the magnitude of benefit of T-DXd in this ABC subtype, the panel recommends the use of this agent, when indicated, earlier than SG.

Datopotamab deruxtecan, a TROP2-directed ADC, showed modest improvement in PFS over standard ChT in the TROPION-Breast01 trial [97] (PFS 6.9 months vs 4.9 months) and OS data is not yet mature. These results and the fact that approval has not yet been granted, leads the panel to not recommend, at the present moment, this drug for use in routine clinical practice.

2.15. *Section VI: HER2-positive ABC (see Fig. 3)*

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 with disease progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway. The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered and the relapse-free interval. The optimal sequence of all available anti-HER2 therapies is currently unknown. The optimal duration of anti-HER2 therapy for MBC (i.e. when to stop these agents) is currently unknown.	I/A	91%
In patients whose tumors achieved 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%
For highly selected patients[a] with ER-positive/HER2-positive ABC, for whom ET + anti-HER2 therapy was chosen as first-line therapy, dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) can be used since it provides a benefit in PFS. This decision must be balanced against the higher side effects, higher costs and lack of OS benefit so far, as compared with ET + anti-HER2 monotherapy.	I/B	80%
For patients with ER-positive/HER2-positive ABC, for whom ChT + anti-HER2 therapy was chosen as first-line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy after stopping ChT, although this strategy has not been studied in randomized trials. Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request, and needs to be evaluated in clinical trials.	NA/B	80%

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.		
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. **ESMO-MCBS v1.1 score: 4**	I/A	86%
For patients previously treated [in the (neo)adjuvant setting] with anti-HER2 therapy, the combination of ChT + trastuzumab and pertuzumab is the preferred option for first-line therapy. **ESMO-MCBS v1.1 score: 4** Few (88) of these patients were treated in the CLEOPATRA trial and all with a trastuzumab-free interval >12 months.	I/A	76%
There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and ChT beyond progression and therefore dual blockade should not be given beyond progression outside clinical trials.	I/E	86%
In a HER2-positive ABC patient previously untreated with the combination of ChT + trastuzumab + pertuzumab, it is acceptable to use this treatment after first line.	II/B	76%
Trastuzumab deruxtecan (T-DXd) showed a 22-month benefit in median PFS and a 7.5% difference in 24-month survival when compared to T-DM1, in pretreated patients with HER2+ ABC. About 50% of patients received the treatment as 1st or 2nd line and the other 50% in later lines. **ESMO-MCBS v1.1 score: 4** Where approved, trastuzumab deruxtecan (T-DXd) is one of the preferred treatment options in the 2nd line setting, after exposure to trastuzumab and pertuzumab. Treatment with T-Dxd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I / A	89%

For patients without access to or with contra-indications for T-DXd, **T-DM1** remains the preferred 2nd line therapy, since it has proven superior efficacy (in terms of OS) relative to other HER2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice). **ESMO-MCBS v1.1 score: 4**	I/A	89%
If not used in the 2nd line setting, **trastuzumab deruxtecan** (T-DXd) is the preferred treatment option in later lines of therapy, including in heavily pretreated patients with HER2+ ABC, since it provided a 11 ms benefit in median PFS and a 12.7 ms benefit in median OS, when compared to capecitabine + trastuzumab or lapatinib**. ESMO-MCBS v1.1 score: 4** Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxicity and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/A	85%
Dual blockade with tucatinib + trastuzumab + capecitabine showed a benefit in median PFS (2.7 ms) and median OS (5.5 ms), over trastuzumab + capecitabine, in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with stable or active brain metastases. Where approved, it is a treatment option in this setting. Toxicity needs education and early intervention (i.e. diarrhea). **ESMO-MCBS v1.1 score: 4.**	I/A	91%
In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. **ESMO-MCBS v1.1 score: 4** There are, however, no data on the use of this combination after progression on pertuzumab, T-DM1, tucatinib or T-DXd.	I/B	84%
The combination of **neratinib + capecitabine** was compared with lapatinib + capecitabine as third line or beyond therapy for HER2-positive ABC, showing a marginal benefit in PFS, and with no significant difference in the co-primary end point of OS. There was no comparator arm with trastuzumab + capecitabine, which had previously been demonstrated to give superior OS to lapatinib + capecitabine. Therefore, the combination of neratinib + capecitabine is not recommended for routine clinical practice. **ESMO-MCBS v1.1 score: 1**	I/D	90%

Additional studies are needed to clearly establish the potential role of this combination in the treatment of brain metastases, as well as the role of neratinib for ABC.		
Margetuximab + ChT showed only a small PFS benefit (1 month) and no OS benefit when compared with trastuzumab + ChT for patients pretreated with pertuzumab and T-DM1, and cannot therefore be recommended for routine clinical practice. **ESMO-MCBS v1.1 score: 2** The role of *CD16A* genotype as a predictor of anti-HER2 antibody efficacy and selection of anti-HER2 agent should be further explored.	I/D	95%
Regarding the ChT component of HER2-positive ABC treatment: When pertuzumab is not given, first-line regimens for HER2-positive ABC can include trastuzumab combined with vinorelbine or a taxane. Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision. Other ChT agents can be administered with trastuzumab but are not as well studied and are not preferred.	I/A	88%
For later lines of therapy, trastuzumab can be administered with several ChT agents, including but not limited to, vinorelbine (if not given in first line), taxanes (if not given in first line), capecitabine, eribulin, liposomal anthracyclines, platinums, gemcitabine or metronomic CM. The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences and country availability.	II/A	91%
ChT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel [I/A] or paclitaxel [I/B]. Also possible are vinorelbine [II/A], nab-paclitaxel [II/B], capecitabine [I/A] and metronomic ChT for older patients [II/B].	See in statement	86%

In green, NEW/UPDATED ABC 6 & 7 statements.

ABC: advanced breast cancer; ChT: chemotherapy; CM: cyclophosphamide and methotrexate; consensus: percentage of panel members in agreement with the statement; DFI: disease-free interval; ESMO-MCBS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET: endocrine therapy; GoR: grade of recommendation; GI: Gastrointestinal; ILD: Interstitial lung disease; HER2: human epidermal growth factor receptor 2; LoE: level of evidence; MBC: metastatic breast cancer; n/a: not applicable; OS: overall survival; PFS: progression-free survival; T-DXd: Trastuzumab-deruxtecan; T-DM1: trastuzumab emtansine.[a] See definition in ABC 4 [97].

In the last few years, several new agents have demonstrated activity against advanced HER2-positive breast cancer and have been incorporated in the treatment algorithms [98,99]. T-DXd was evaluated in the large phase 2 study DESTINY-Breast01 study [100], for heavily pretreated patients (median 6 lines, range 2–27 lines including trastuzumab and T-DM1), yielding a response rate of 62.0 %, a median PFS of 19.4 months (95 % CI, 14.1–25.0) and a median OS of 29.1 months (95 % CI 24.6–36.1 months) [101]. T-DXd was associated with 15.8 % risk of interstitial lung disease (ILD)/pneumonitis, fatal in 2.7 % of cases, which needs appropriate and rapid diagnosis and treatment [101]. In the phase 3 study DESTINY-Breast02, T-DXd was compared to capecitabine combined with trastuzumab or lapatinib, in heavily pretreated patients with HER2 overexpressing ABC and showed 10.9 months benefit in PFS and 12.7 months benefit in OS. In this trial there were 4 toxic deaths, two of which due to ILD [102]. In the phase 3 trial DESTINY-Breast03, T-DXd was compared to T-DM1, the previous standard 2nd line therapy, in taxane- and trastuzumab-pretreated patients [64], and yielded a PFS improvement of 22 months, with median OS still not reached [104]. T-DXd was associated with 10.5 % of ILD events, but no grade 4 or grade 5 cases, showing that adequate monitoring and prompt management are crucial. For the safe utilization of this compound in current clinical practice, both active surveillance and education of patients and health care professionals are crucial to facilitate rapid diagnosis and management of ILD [103].

Tucatinib, a highly selective inhibitor of the HER2 tyrosine kinase, was tested in combination with capecitabine and trastuzumab in a population of patients with HER2-positive ABC pretreated with trastuzumab, pertuzumab and T-DM1 and reported an improvement in PFS (median 7.8 months vs 5.6 months) and OS (median 21.9 months and 17.4 months), compared to capecitabine-trastuzumab-placebo, in the HER2CLIMB-01 study [105,106]. Importantly, a similar benefit was observed in patients with brain metastases, including active brain metastases, a unique group of patients included in this trial. The experimental arm had increased toxicity, mostly diarrhea and elevated aminotransferase levels of grade 3 or higher, but this did not lead to treatment discontinuation nor significant impact on quality of life.

Two additional agents have not demonstrated clinically meaningful benefit in trials of pretreated HER2-positive ABC patients and are therefore not recommended for clinical practice by the ABC panel. Margetuximab was compared to trastuzumab (both combined with chemotherapy of physician's choice) and resulted in a 0.9 month PFS difference [107]. The potential role of CD16A genotype as a predictor of the type of anti-HER2 antibody efficacy was explored and deserves

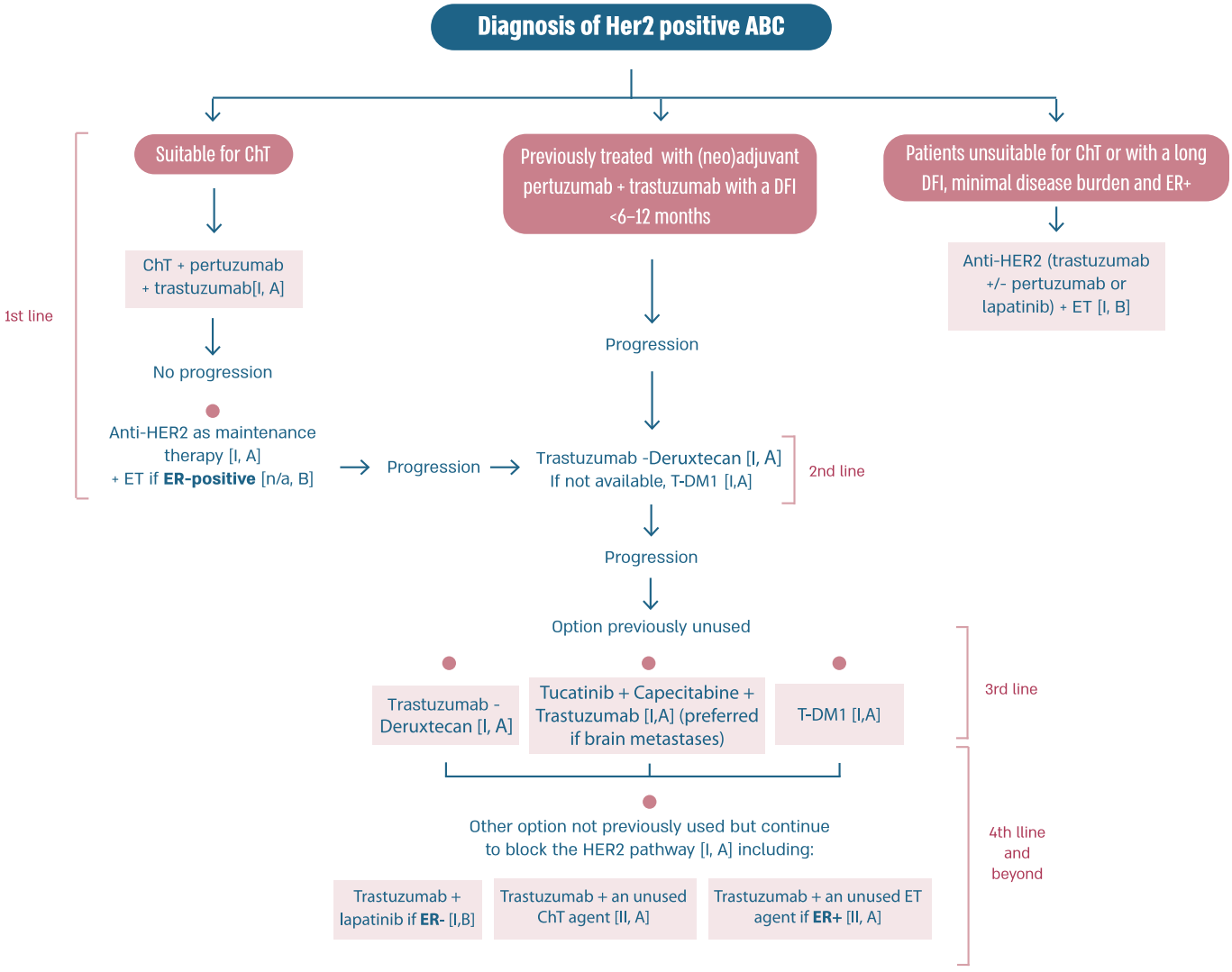

Fig. 3. Treatment of HER2-positive ABC
Legend: ABC, advanced breast cancer; ChT, chemotherapy; DFI, disease-free interval; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab-emtansine.

further evaluation. Neratinib was compared to lapatinib, both agents in combination with capecitabine, in the NALA trial, and provided a small reduction in the risk of disease progression of 24 %, a marginal difference in PFS and no impact on overall survival (co-primary endpoint) [108]. Furthermore, the NALA study has the important limitation of not having a comparator arm with trastuzumab + capecitabine, which was previously shown to provide superior OS to lapatinib + capecitabine [109].

In resource limited regions or countries, pyrotinib represents a treatment option that can be less expensive and, where regulatory approved, can be considered for treatment of patients with HER2-positive ABC [110,111].

2.16. Section VII: Triple negative ABC (see Fig. 4)

Guideline statement	LoE/GoR	Consensus
In patients with triple-negative ABC (regardless of *BRCA* status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, **carboplatin** demonstrated comparable efficacy and a more favorable toxicity profile compared to docetaxel and is, therefore, an important treatment option.	I/A	91%
For non-*BRCA*-associated triple-negative ABC, there are no data supporting different or specific ChT recommendations, besides platinum. Therefore, all ChT recommendations for HER2-negative disease also apply for triple-negative ABC.	I/A	98%
The androgen receptor (AR) is a potential target in triple-negative ABC. There are, however, no standardized 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 optimize and standardize the determination of AR.	II/D	85%
Checkpoint inhibitors + chemotherapy (pembrolizumab + taxane or carboplatin/gemcitabine) is the preferred treatment option for 1st line therapy for most patients with PD-L1+* triple negative ABC, either *de novo* or diagnosed at least 6 months from (neo)adjuvant chemotherapy. **ESMO-MCBS v1.1 score: 4**	I/A	91%
In countries where **atezolizumab** is available, its combination with nab-paclitaxel may be an option for 1st line therapy of patients with PD-L1+* triple negative ABC. **ESMO-MCBS v1.1 score: 3**	II/B	81%
Checkpoint inhibitor monotherapy in later lines for triple-negative ABC is not recommended due to low response rates.	I/E	89%
Several ongoing trials are evaluating the role of immunotherapy in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials.	NA/E	98%
Sacituzumab govitecan is the preferred treatment option for patients with triple negative ABC, treated with ≥ 2 lines (at least one of them in the metastatic setting), since it demonstrated 4.9 months benefit in OS and 3.1 months benefit in PFS. **ESMO-MCBS v1.1 score: 4**	I/A	96%
Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, are important.		
Trastuzumab deruxtecan (T-DXd) was compared to treatment of physician's choice, in 58 patients with **triple negative/HER2 low ABC**, treated with 1-2 lines of chemotherapy in the metastatic setting. In this small population the results in terms of PFS and OS were similar to the overall study population and T-DXd may therefore be considered a treatment option for patients with the same characteristics of those enrolled in the Destiny-Breast 04 trial. ILD/Pneumonitis can be fatal and requires active imaging surveillance with non-contrast CT scans, and proper management. Nausea and vomiting require adequate prophylaxis. **ESMO-MCBS v1.1 score: 4**	I/B	89%
There are very few data regarding the **best sequence of administration of ADCs** for **ER negative/HER2 low ABC**. In view of the results of the trials of T-DXd and sacituzumab govitecan in this patient population, the panel believes that sacituzumab govitecan should be used earlier than T-DXd.	II/A	90%

In green, NEW ABC 6 & 7 statements.

ABC: advanced breast cancer; ADC: Antibody-drug conjugate; AR: androgen receptor; *BRCA*: BReast CAncer gene; ChT: chemotherapy; consensus: percentage of panel members in agreement with the statement; ER: Estrogen receptor; ESMO-MCBS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; GoR: grade of recommendation; HER2: human epidermal growth factor receptor 2; ILD: Interstitial Lung Disease; LoE: level of evidence; n/a: not applicable; PD-L1: programmed death-ligand 1; T-DXd: Trastuzumab deruxtecan; T-DM1: Trastuzumab emtansine; TNBC: triple-negative breast cancer.

* For PD-L1 testing, see precision medicine statements.

After years of little progress in the treatment of triple negative (TN) ABC, new agents are showing promise. In the KEYNOTE -355 trial [65, 66] the addition of pembrolizumab to chemotherapy with paclitaxel, nab-paclitaxel or carboplatin/gemcitabine showed a significant benefit for patients with tumors that were Combined Positive Score (CPS) >=10 who were either de novo Stage IV or who had relapsed more than 6 months after adjuvant therapy with an OS of 23.0 months in the pembrolizumab–chemotherapy group and 16.1 months in the placebo–chemotherapy group [66]. The panel approved this regimen as the treatment of choice for first line TN ABC meeting eligibility criteria. There was discussion about the uncertainty for those with tumors that are CPS 1–10 and where more data are needed. It was recognized that in some countries atezolizumab is an option that can be considered in combination with nab-paclitaxel as there was benefit in PFS seen in the IMPASSION130 study [112], although OS results are controversial and the IMPASSION131 trial [113] with paclitaxel was negative. Sacituzumab govitecan has shown to offer a PFS and OS benefit for later lines of therapy following the results of the ASCENT study [114]. The benefit was independent of existence or not of low HER2 expression. With proper attention to toxicity, especially gastrointestinal, hematological and fatigue, this agent is relatively well tolerated. Results from the DESTINY-Breast04 trial have created a new therapeutic option for patients with ER-negative/HER2 low ABC, despite the fact that only 11 % of the trial population had this ABC subtype. The benefit of T-DXd, compared to standard chemotherapy options, was evaluated in an exploratory analysis in this sub-population and was similar to the whole trial population (median PFS 8.5 months vs 2.9 months, respectively) (71).

Similarly to what was discussed above for ER-positive/HER2-negative ABC, also for triple negative ABC no head-to-head comparisons of T-DXd and SG were performed and almost no data exist regarding optimal sequencing of these agents. Analyzing the totality of the data and in view of the higher level of evidence brought by the ASCENT trial, the panel recommends the use of SG earlier than T-DXd for triple negative ABC. It remains unclear if cross-resistance exists since both these ADCs include a topoisomerase I inhibitor.

2.17. Section VIII: Hereditary ABC

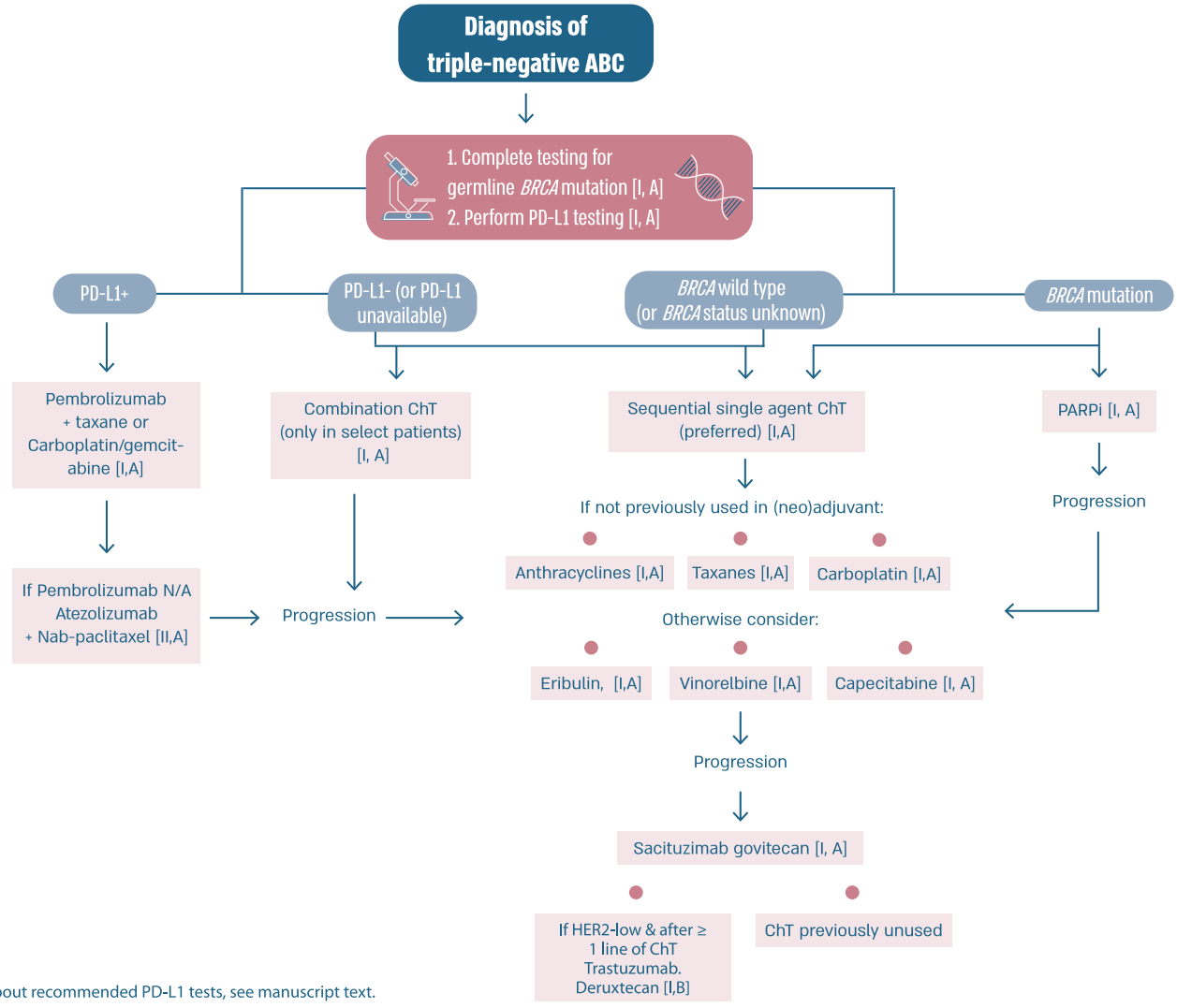

Fig. 4. Treatment of triple-negative ABC.
Legend: ABC, advanced breast cancer; ChT, chemotherapy; PARPI, poly-adenosine diphosphate ribose polymerase inhibitor; PD-L1, programmed death-ligand 1; N/A, not available.

Guideline statement	LoE/GoR	Consensus
Genetic testing		
For ABC patients, results from **germline genetic testing** have therapeutic implications and should therefore be performed as early as possible. Appropriate counselling should be provided to patients and their families if a pathogenic germline mutation is found.	I/A	88%
At present, only germline mutations in *BRCA* 1/2 have robust data for clinical utility and therapeutic impact.	I/A	93%
Testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, in particular because it may have implications for family members. However, it must be clarified to the patient that at present, a mutation in most other moderate-high penetrance genes has no direct clinical implications, for the patients themselves, in the setting of ABC, apart from germline PALB2 mutation for olaparib use.	Expert opinion/C	89%
***BRCA*-associated ABC**		
In patients with g*BRCA*-associated triple-negative ABC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a **platinum** regimen is the preferred ChT option, if not previously administered. All other ChT recommendations are similar to those for sporadic ABC.	I/A	100%
For patients with a g*BRCA* mutation, single agent PARP inhibitor (**olaparib or talazoparib**) is one of the preferred treatment options for those with triple negative or ER+/HER2 negative ABC, since they are associated with a PFS benefit, improvement in QoL and a favorable toxicity profile. **ESMO-MCBS v1.1 score: 4**	I/A	94%
Data from a small phase 2 trial demonstrated a benefit from **olaparib** for individuals with a **somatic *BRCA*1/2 mutation or a germline PALB2 mutation**. It is acceptable to offer this treatment to these patients, acknowledging the limitation of data, since it is unlikely that large trials will be run.	II/B	93%
It is unknown how single agent olaparib or talazoparib compare with platinum compounds in this setting, as well as to the optimal use with platinum (combined or sequential), and their efficacy in tumors progressing after platinum.	II/B	89%
In **ER+ g*BRCA*-associated ABC**, the **optimal sequence** between PARP inhibitor and ET+ CDK4/6i was not formally tested. However, given the OS benefit seen with CDK4/6i, the panel considers them the standard of care for 1st line therapy and recommends their use before a PARP inhibitor.	Expert opinion/A	94%
In **triple negative PD-L1+ and g*BRCA*-associated ABC**, the **optimal sequence** between PARP inhibitor and ChT + pembrolizumab was not formally tested. However, given the OS benefit seen with ChT + pembrolizumab, the panel considers it the preferred option for 1st line therapy, for the majority of the patients. More research is needed to answer questions related to treatment sequencing and other disease subtypes, i.e., HER2+ disease in the context of *BRCA*1/2 mutations.	Expert opinion/B	91%
BROCADE3 was the first phase 3 trial testing a PARP inhibitor (**veliparib**) in g*BRCA*-mutated MBC that included a platinum. Initial presentation of results showed a small benefit in PFS (1.9 months). However, durable PFS at 3 years was seen in a significant minority (one in four patients) during veliparib maintenance, which could provide patients lacking other maintenance treatment options with ChT-free time. Mature OS data are needed before this regimen can be recommended for routine clinical practice.	I/D	98%

In green, NEW ABC 6 & 7 statements.

ABC: advanced breast cancer; g*BRCA*: germline BReast CAncer gene; CDK: cyclin-dependent kinase; ChT: chemotherapy; consensus: percentage of panel members in agreement with the statement; ESMO-MCBS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET: endocrine therapy; GoR: grade of recommendation; HER2: human epidermal growth factor receptor 2; LoE: level of evidence; MBC: metastatic breast cancer; NA: not applicable; OS: overall survival; PFS: progression-free survival; QoL: quality of life.

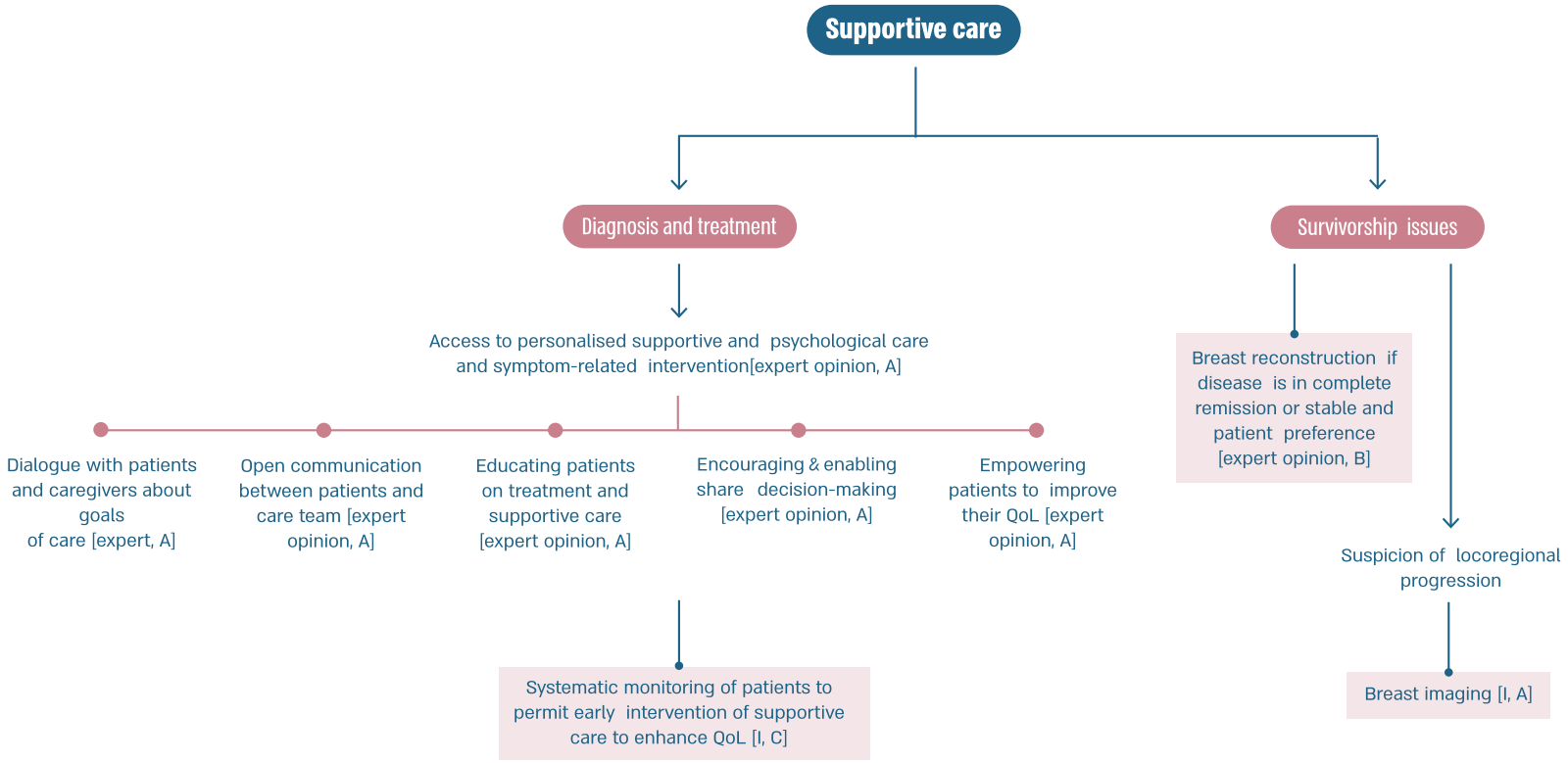

Fig. 5. ABC follow-up and supportive care.[a].
Legend: ABC, advanced breast cancer; QoL, quality of life. [a] Throughout the cancer pathway, adequate information should be provided to the patient.

Germline genetic testing for a pathogenic variant in *BRCA1/2* has therapeutic implications and should be performed as early as possible for any patient who would be eligible for a PARP inhibitor, all patients with triple-negative breast cancer, males with breast cancer and those meeting international/national guidelines for genetic testing for a hereditary cancer syndrome [115,116]. At present, pathogenic variants in other hereditary breast cancer associated syndromes do not impact choice of systemic therapy in ABC, outside of a clinical trial setting apart from a germline pathogenic variant in *PALB2*. Amongst women with a pathogenic variant in *BRCA1/2*, PARP inhibitors have consistently demonstrated superiority over standard single-agent chemotherapy (not including platinum agents) in both the OlympiaAD and EMBRACA studies that evaluated the efficacy of olaparib and talazoparib, respectively [117–122]. In both studies, patients receiving a PARP inhibitor had a significantly higher response rate, PFS and quality of life. The BROCADE study was the first phase 3 study in ABC comparing the addition of a PARP inhibitor to a platinum containing regimen, with a treatment protocol of paclitaxel and carboplatin with or without veliparib for g*BRCA* associated ABC. The study demonstrated a PFS benefit favoring the veliparib arm, with a median PFS of 14.5 compared to 12.6 months, with a suggestion of sustained response at two and three years favoring the veliparib arm that was receiving maintenance veliparib [123]. In light of the significant toxicity of combination chemotherapy (with or without veliparib), for the time being veliparib combined with chemotherapy is not recommended in the ABC setting.

There are no data assessing optimal treatment sequencing of PARP inhibitors with other subtype-specific therapies. Thus, for patients with a pathogenic variant in *BRCA1/2* and ER-positive/HER2 negative ABC the panel recommends commencing with first line ET + CDK4/6 inhibitor before the use of a PARP inhibitor, due to significant OS benefit seen with this combination. For patients with a pathogenic variant in *BRCA1/2* and PD-L1+ triple negative ABC, the panel recommends commencing with immunotherapy + ChT and using a PARP inhibitor as a subsequent line of therapy. In patients with PD-L1 negative triple negative ABC, a PARP inhibitor should be offered as an option for first line therapy.

A small phase 2 study demonstrated a benefit from olaparib in patients harboring a germline pathogenic variant in *PALB2* and in those with somatic mutations in *BRCA1/2* [124]. Although the study is small, it is unlikely that there will be further larger studies. Thus, based on this limited data, the panel supports offering olaparib in these cases.

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

2.18. *Section IX: precision medicine (see Fig. 1)*

Guideline statement	LoE/GoR	Consensus
Multigene panels, such as those obtained using NGS or other technology on tumor DNA have not yet proven beneficial in clinical trials for ABC; their impact on outcome remains undefined and should not be used in routine clinical practice. For patients who are suitable to participate in clinical trials of novel therapies and are readily able/motivated to attend a centre with relevant clinical trials, NGS testing may be used in the context of prospective molecular triage programmes to select patients for therapeutic trials. Specific tests (as distinguished from broad mutation profiles) are useful and discussed in separate statements; others may play a role in the future as the medicines they are linked with achieve regulatory approval.	I/D	83%
ctDNA assessment is not recommended for demonstration of disease progression.	I/D	97%
ctDNA assessment is an option for the detection of ***PIK3CA*** mutations for selection of patients eligible for *PIK3CA* inhibitors.	II/A	93%
At present, no validated predictive biomarkers other than hormone receptor status exist to identify patients who will/will not benefit from the addition of a CDK4/6 inhibitor or an mTOR inhibitor to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.	I/E	95%
Alpelisib should only be used in cases of ***PIK3CA***-mutated tumors.	I/A	95%
If treatment with the *PI3KCA* inhibitor, alpelisib, is available, patients should be tested for *PIK3CA* mutation (in exon 9 and 20) in a tissue (metastasis or primary) and/or in ctDNA testing in blood. Patients who do not have an available archival tissue sample and have an uninformative result using a liquid biopsy test could consider undergoing a tumor biopsy for *PIK3CA* mutation testing.	I/B	100%
Where ***ESR1*** mutation status is available, in the presence of an *ESR1* mutation, treatment with an aromatase inhibitor is not the optimal strategy. In case of disease progression under treatment with an AI +/- a targeted agent (i.e. CDK4/6 inhibitor), acquired *ESR1* mutations are common. In the next line of therapy, a non-AI-based option may therefore be a better option.	II/B	84%
Treatment should not be changed based on ***ESR1*** mutation status alone and confirmation of disease progression is mandatory. Availability of *ESR1* mutation status is not mandatory for the adequate management of ER+/HER2 negative ABC.	II/D	85%

PD-L1 status should be tested in cases of 1st line triple negative ABC, if treatment with immune checkpoint inhibitors is available, preferably in a metastatic tumor sample.	I/A	96%
PD-L1 status is the companion test for the use of the combination of pembrolizumab and ChT, as 1st line therapy for triple negative ABC, using PD-L1 IHC with a Combined Positive Score (CPS) ≥ 10 (CPS score: number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100).	I / A	89%
PD-L1 status is the companion test for the use of the combination of atezolizumab and nab-paclitaxel, as 1st line therapy for triple negative ABC, using IHC with the SP142 antibody (Ventana), and a cut-off of 1% of positive staining on immune cells (IC).	I/A	87%
Patients with **low (1%–10%) ER- (and PgR-) positive**, HER2-negative ABC should not be considered for ET exclusively. Patients with **low (1%–10%) ER- (and PgR-) positive**, HER2-negative ABC can be considered as patients with triple-negative ABC for clinical trials.	III/B	95%
To be eligible for treatment with trastuzumab-deruxtecan, the presence of **HER2-low** status on one sample is sufficient, regardless of the stage of the disease at which it was assessed (primary tumor or metastatic lesion). It is therefore advisable to systematically reassess HER2 status during the course of the disease if the initial HER2 status is zero.	I/A	95%
The pathology report must detail the HER2 score according to ASCO/CAP 2023 recommendations [0, 1+, 2+ (amplified or not amplified) or 3+]. It is desirable to report the percentage of labeled cells. It is recommended to detail in the conclusion: HER2 zero, HER2 low (1+ or 2+ non-amplified), HER2 positive (HER2 3+ or ISH amplified).	Expert opinion/A	98%
If a patient with ABC presents with a tumor with **MSI-H/MMR-D**, treatment with an anti-PD-1 agent is a possible consideration.	Expert opinion/C	Yes: 41% Abstain: 10% Insufficient data: 49%
If a patient with ABC presents with a tumor with an ***NTRK* fusion**, treatment with a TRKi is a possible consideration.	I/B	Yes: 29% Abstain: 24%
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.		Insufficient data: 47%

In green, NEW ABC 6 & 7 statements.

ABC: advanced breast cancer; consensus: percentage of panel members in agreement with the statement; ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; *BRCA*: BReast CAncer gene; CDK: cyclin-dependent kinase; ChT: chemotherapy; ctDNA: circulating tumor DNA; ER: estrogen receptor; *ESR1*: estrogen receptor 1; ET: endocrine therapy; GoR: grade of recommendation; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: *In situ* hybridization; LoE: level of evidence; MMR-D: mismatch repair deficiency; MSI-H: microsatellite instability-high; NGS: next-generation sequencing; NTRK: neurotrophic receptor tyrosine kinase; PD: progressive disease; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; PgR, progesterone receptor; PI3K: phosphoinositide 3-kinase; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TRKi: tropomyosin receptor kinase inhibitor.

Acquisition of *ESR1* mutations, frequent in patients with ABC previously treated with aromatase inhibitors (20%–40 %) is one of the mechanisms of resistance to endocrine therapies with some evidence that tumors with this mutation respond less well overall to endocrine treatments, not just to aromatase inhibitors [125,126]. There are encouraging but limited data in the PADA-1 trial [127], showing PFS benefit of a switch from letrozole to fulvestrant in combination with palbociclib, in case of a rising circulating *ESR1* mutation in ctDNA detected in sequential liquid biopsies, without tumor progression. The ABC panel considers that additional data are needed to change therapy based solely on *ESR1* mutation status, and that confirmation of disease progression is mandatory. Although knowledge of *ESR1* status is not mandatory for the management of a patient with ABC, if this technology is available and feasible, it may guide towards a non-aromatase inhibitor therapeutic strategy [128]. The ESCAT scale for *ESR1* mutations is Tier II-a [129]. The ongoing SERENA-6 trial, with a similar design, is using the next-generation oral SERD camizestrant (NCT04964934) [130].

Intrinsic subtyping by PAM50 has recently identified the presence of Luminal A, Luminal B, HER2-enriched and Basal-like tumors within HR+/HER2 negative ABC [131–133]. Of note, 15 % of HR+/HER2 negative ABC are HER2-enriched and 5 % Basal-like. Intrinsic subtype in HR+/HER2 negative ABC is a strong and consistent prognostic biomarker of PFS and OS following endocrine-based therapy, including endocrine therapy and CDK4/6 inhibitors [131,134,135]. From a predictive perspective, Basal-like disease is associated with a lack of benefit from endocrine therapy and CDK4/6i [131]. The predictive value of intrinsic subtype is currently being evaluated in the phase 3 HARMONIA clinical trial (NCT05207709).

Targeting low levels of HER2 expression has reshaped the treatment paradigm for approximately half of patients with ABC. Therefore, correctly stating low levels of HER2 expression in pathology reports, in the cases of tumors traditionally defined as “HER2-negative” (HER2 1+ or 2+ without amplification at in situ hybridization testing) is essential, since it provides the opportunity for treatment of ABC with potent, novel, HER2-directed agents [136–139]. Currently approved for the treatment of pretreated patients with HER2-low ABC is trastuzumab-deruxtecan, based on the results of the DESTINY-Breast04 phase 3 trial [94].

2.19. Section X: LABC[a] (inflammatory and non-inflammatory) and inflammatory ABC (IBC) (see Fig. 1)

Guideline statement	LoE/GoR	Consensus
IBC is a clinicopathological diagnosis that requires an interprofessional approach for diagnosis. IBC is designated as T4d or stage IV in case of metastatic disease at presentation. All of the following criteria must be met for a diagnosis of IBC: a) rapid onset of breast erythema, edema and/or *peau d'orange*, and/or warm breast, with or without an underlying palpable mass; b) duration of history no more than six months; c) erythema occupying at least one-third of the breast; d) pathologic confirmation of invasive carcinoma. A skin punch biopsy may help in the diagnosis, but it is not indispensable. Skin ulcerations are rare in IBC and more common in non-inflammatory LABC.	I/A	95%
BEFORE starting any therapy, at least one core biopsy providing histological type, grade and biomarker expression is indispensable to guide treatment decisions: Biomarkers include: a) For inoperable LABC and inoperable IBC : ER, PgR, HER2, Ki67; b) For metastatic IBC: ER, HER2, PD-L1 if TNBC and *PIK3CA* if ER+/HER2 negative ABC; For a) and b), patients should also have germline *BRCA*1, *BRCA*2 and *PALB2* testing, but this result is not necessary prior to starting treatment. If germline testing is negative, *BRCA*1/2 somatic testing can be done as it may impact treatment.	I/A	89%
Since patients with LABC and IBC have a substantial risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen and bone, before initiation of systemic therapy is highly recommended.	I/A	100%
For non-lobular invasive breast cancers PET-CT, if available, is preferred instead of and not in addition to CT-scans and bone scan. For most invasive lobular breast cancers CT-scans and bone scans or whole-body MRI are preferred.	II/A	95%
Systemic therapy (not surgery or RT) should be the initial treatment.	III/A	100%

If LABC remains inoperable after systemic therapy and eventual RT, 'palliative' mastectomy should not be done unless the surgery is likely to result in an overall improvement in QoL.	Expert opinion/D	100%
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and RT) is strongly indicated in the vast majority of cases.	I/A	100%
HR-positive LABC and IBC		
Options for **HR-positive inoperable LABC** include an anthracycline- and taxane-based primary chemotherapy regimen, or endocrine-based therapy (i.e. ET + CDK4/6 inhibitor).	I/A	96%
The choice of chemotherapy versus ET+CDK4/6 inhibitor, as initial treatment, depends on tumor characteristics (grade, biomarker expression, burden of disease,) and patient considerations (performance status, associated symptoms, comorbidities, preferences).	Expert opinion/A	89%
If chemotherapy is chosen, an anthracycline- and taxane-based primary chemotherapy regimen is recommended, followed by and endocrine-based therapy (ET + CDK4/6 inhibitor) post-operatively.	I/A	95%
Triple negative LABC and IBC		
Anthracycline- and taxane + platinum-based primary chemotherapy is recommended as initial treatment.	I/A	83%
Pembrolizumab should also be added, independently of PD-L1 status if non-metastatic disease and in PD-L1+ metastatic disease.	I/A	93%
HER2-positive LABC and IBC		
Concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR. The optimal anti-HER2 therapy is dual blockade with trastuzumab and pertuzumab.	I/A	96%
Anthracycline-based chemotherapy should be incorporated in the treatment regimen.	I/B	63%
When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.	I/A	87%
For patients with **HER-2+ LABC** (inflammatory or non-inflammatory), without distant metastases, who are in complete remission after appropriate pre-operative systemic therapy and appropriate loco-regional 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	91%

The optimal anti-HER2 therapy is double blockade with trastuzumab and pertuzumab.		
For patients with **HER-2+ LABC** (inflammatory or non-inflammatory), without distant metastases, who are not in complete remission after appropriate pre-operative systemic therapy and appropriate loco-regional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 14 courses of T-DM1 is recommended.	I/A	87%
g*BRCA*mut LABC		
Olaparib should be given for 1 year, after CTh and local treatments, for IBC or initially inoperable LABC in *gBRCAmut* as this is a potentially curable situation and fits with the results from the OLYMPIA study.	I/A	100%
It is currently unknown how to optimally integrate the use of olaparib with post-operative capecitabine or pembrolizumab, in *gBRCAmut* triple negative initially inoperable LABC or IBC, with residual disease after surgery. However, there are safety data allowing for the concomitant use of olaparib and pembrolizumab, and the panel prefers this option to the combination of capecitabine + pembrolizumab for these patients.	III/B	80%
It is also currently unknown how to optimally integrate the use of olaparib with post-operative abemaciclib, in *gBRCA mut* ER+/HER2 neg initially inoperable LABC or IBC. It is not possible to administer concomitantly olaparib and a CDK4/6 inhibitor (safety concerns); since there are data allowing for a later start of abemaciclib in the post-operative setting, it can be envisioned to administer olaparib first and then abemaciclib.	III/B	68%
LOCO-REGIONAL MANAGEMENT OF LABC NON-IBC		
Following effective preoperative systemic therapy with or without RT, surgery will be possible in many patients. This will consist of mastectomy with axillary dissection in the majority of cases, but in selected patients with a good response, BCS may be possible.	II/A	98%
In patients with axillary low burden of disease at presentation (previously cN0–cN1) with complete response after systemic treatment (ycN0), SLNB can be an option, provided all the recommendations for sentinel node after primary systemic treatment are followed (i.e. dual tracer, clipping/marking positive nodes, minimum of three sentinel nodes).	III/B	62%
LOCO-REGIONAL MANAGEMENT OF IBC		
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 IBC.	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 6 & 7 statements.

ABC: advanced breast cancer; BCS: breast-conserving surgery; *BRCA*: BReast CAncer gene; ChT: chemotherapy; consensus: percentage of panel members in agreement with the statement; CDK4/6: cyclin-dependent kinases 4/6; ChT: chemotherapy; CT: computed tomography; ER: oestrogen receptor; ET: endocrine therapy; GoR: grade of recommendation; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IBC: Inflammatory Breast Cancer; LABC: locally advanced breast cancer; LoE: level of evidence; pCR: pathological complete response; MRI: magnetic resonance imaging; PET: positron emission tomography; PgR: progesterone receptor; PS: performance status; ; PD-L1: programmed cell death ligand 1; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QoL: quality of life; RT: radiotherapy; SLNB: sentinel lymph node biopsy; TNBC: triple negative breast cancer.

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

Most patients who present with unresectable LABC, inflammatory or non-inflammatory, nonmetastatic disease should initiate treatment with primary systemic therapy. Upfront staging and biopsy are mandatory. 18-FDG PET-CT is the preferred imaging for the staging of all subtypes except invasive lobular cancers [140], as it is more sensitive and may up-stage inflammatory (IBC) and locally advanced (LABC) cancers in up to 52 % of cases, detecting 1/3 more metastases [141]. The choice of systemic treatment depends on the pathological features of the disease, therapeutic goals, comorbidities, and patient's choice, as biology predicts response to neo-adjuvant treatments [142]. For HER2-positive subtype, treatment should include dual blockade (pertuzumab and trastuzumab) as 40 % of patients included in the NeoSphere study had LABC or IBC [143]. For triple-negative subtype, treatment with pembrolizumab plus chemotherapy according to the KEYNOTE-522 regimen is the recommended treatment since approximately 25 % of included patients had LABC or IBC [144]. For ER+/HER2-negative subtype, the initial systemic treatment may be anthracycline- and taxane-based chemotherapy or ET + CDK4/6 inhibitor; the choice between these two options should be based on disease and patient characteristics.

If the disease is rendered resectable, systemic therapy should be followed by surgery, radiation therapy, and adjuvant treatment accordingly to residual disease, including T-DM1 for HER2 positive cancers [145] or olaparib for patients with germline *BRCA*1-or *BRCA*2-mutations [146]. The concomitant use of olaparib with immunotherapy in the post-operative setting for patients with TNBC and without pathologic complete response may be considered, based on existing safety data [147]. If the disease remains unresectable, consideration should be given to treating all sites of the original tumor extension with radiation, including a boost to the area of residual disease. In locally advanced non-inflammatory breast cancer, breast conservation, if possible after neoadjuvant systemic treatment, has loco-regional recurrence rates at 5–10 years similar to mastectomy. Breast reconstruction after mastectomy was not associated with higher rates of local recurrence nor worst OS, in large retrospective studies [148,149]. Sentinel node biopsy in N0 patients at presentation or targeted axillary dissection in N1 converted to N0 after treatment can be used, employing the same rules as used in early breast cancer. In patients with N2/N3 disease at presentation and in IBC there is no evidence to support any surgical procedure other than axillary lymph node dissection, even in cases of good response due to the high rate of false negatives. Clinical experience suggests that most durable remissions can be expected with an elective radiation 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 to all sites of macroscopic disease. In unresectable cases where radiation is the first local treatment, regular evaluations during the course of radiation are advised, to select patients that might become amenable for resection after 45–50 Gy. Interesting reports have been published on combined radiation and ChT such as cisplatin, 5-FU, docetaxel or vinorelbine. Further evaluation of the benefit of combining radiation with a PARP inhibitor is ongoing in a prospective trial in patients with LABC or metastatic TNBC and in non-responders to primary ChT [150–152].

2.20. Section XI: Specific populations

Guideline statement	LoE/GoR	Consensus
ABC IN MALE PATIENTS		
Male patients with ABC should be offered genetic counselling and testing.	II/A	100%
For ER+ Male ABC, which represents the majority of the cases, endocrine-based therapy is the preferred option, even in the presence of visceral disease, unless there is visceral crisis.	III/A	100%
For ER+ Male ABC, previously untreated or with a DFI longer than 12 months, 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 without LHRH agonist may also be considered, with close monitoring of response. Clinical trials are needed in this patient population.	IV/B	86%
Male patients with ER+ ABC should be treated with the same options as female patients, including access to targeted agents such as CDK4/6, mTOR and PI3KCA inhibitors.	II/A	96%
ABC IN A PREGNANT PATIENT (includes fertility issues)		
All persons of reproductive age with ABC should be counselled about use of non-hormonal contraception (independent of the tumor subtype) and the risks of conceiving while receiving treatment for ABC.	II/A	93%
Special attention should be given to persons of reproductive age with ABC being treated without OFS/OFA, since several therapies used for ABC have a low gonadotoxic effect and will not induce menopause.	II/A	100%
Management of a pregnant patient with ABC is a complex and delicate situation that requires multidisciplinary discussion and experienced care. Advice should be sought from experts in the field such as the International Advisory Board of CIP (Cancer In Pregnancy) (www.ab-cip.org). The preferences of the patient and of whomever the patient wishes to be involved must always be taken into account after appropriate and transparent sharing of information about all management options and their potential impact on the patient's survival, fetal health and the future of the child.	Expert opinion/A Expert opinion/A	98% 98%

The preferred imaging method to stage a pregnant patient with breast cancer is whole-body MRI including diffusion weighted imaging, where available.	Expert opinion/B	77%
Among all available systemic therapies, only chemotherapy can be safely administered during pregnancy and only in the 2nd and 3rd trimesters. The most complex situation relates to HER2+ disease diagnosed in the 1st and 2nd trimesters, because anti-HER2 therapy is critical for optimal disease control but cannot be administered during the entire pregnancy.	II/A Expert opinion/A	95% 95%
Termination of pregnancy is a major consideration in some circumstances and should be available for patients who decide in favor of it, within the first 12 weeks of pregnancy.	Expert opinion/A	95%
ABC IN A PATIENT WITH HIV		
Prevalence of HIV comorbidity in ABC patients depends on HIV endemicity (varies 6 - 26%). Patients living with HIV who develop breast cancer have consistently worse survival, both in early and metastatic settings. HIV+ breast cancer patients have worse toxicity, especially myelotoxicity and infections. Data on how to manage ABC in a patient living with HIV are scarce, especially concerning new anticancer agents. Breast cancer in patients living with HIV should be co-managed by an oncologist and HIV specialist working in a multidisciplinary way. HIV positivity, if under treatment and controlled (undetectable viral load), should no longer be an exclusion criterion in most clinical trials. People living with HIV have a higher incidence of other diseases such as tuberculosis and hepatitis. Before starting anticancer treatment, these diseases should be looked for and if diagnosed, treatment should be initiated.	Expert opinion/A Expert opinion/A Expert opinion/B	100% 100%
In general, the same ABC guidelines apply to HIV+ and HIV neg patients with ABC. However, careful consideration should be given to dose reductions and/or increased intervals (G-CSF recommended for myelotoxic ChT agents). Data suggest safety of immune-checkpoint inhibitors (IV/B) and there are no data regarding the use of CDK4/6 inhibitors (research needed)	Expert opinion/A Expert opinion/A Expert Opinion/NA	95% 95% 95%

Most cytotoxic agents can be safely initiated if viral load is undetectable and CD4+T-count is at least 200 under modern anti-retroviral therapy regimens.	Expert opinion/B	93%
HIV therapy should be initiated or continued during cancer therapy.	Expert opinion/A	93%
In anti-retroviral naïve patients, it is recommended to initiate anti-retroviral therapy and wait for about 2 weeks before starting anticancer therapies, if clinically possible.	Expert opinion/B	93%
Potential drug-drug interactions must always be checked. If interactions are a concern, it is recommended to check the viral load more often. For drugs that cause lymphopenia, CD4+ T-cell counts should be monitored more frequently.	Expert opinion/B	93%
ABC IN OLDER PATIENTS		
When no specific note is made, all ABC guidelines are to be implemented independently of the age of the patient.	Expert opinion/A	100%
Independent of age, all patients should be involved in the treatment decision making process if they wish to do so and their preferences should be taken into account.	Expert opinion/A	100%
Independent of age, all eligible patients should be informed about potential clinical trials and provided with the adequate information and informed consent to be able to decide if they wish to participate.	Expert opinion/A	100%
The age of the patient should not be the sole reason to withhold effective therapy (in older patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment.	I/E	100%
What determines the possibility to use a specific anticancer agent is not age by itself but the existence of co-morbidities with associated impact in adequate organ function such as liver, renal, cardiac and/or neurological functions, as well as bone marrow reserve.	I/A	95%
For treatment decision making, careful evaluation of co-morbidities, performance status and geriatric assessment are crucial and more relevant than chronological age. G8 assessment should be used initially, and a full geriatric assessment is needed if low G8 scores are found.	I/A	90%
Special attention should be given to potential drug interactions, in view of the common use of comedication/polypharmacy by older patients.	I/A	100%

The ABC Guidelines endorse the EUSOMA-SIOG guidelines for the management of older patients with breast cancer, namely the following statement: regarding systemic treatment for metastatic disease, different treatment schedules, dose reductions, or stepwise dose-escalation before reaching standard recommended dose might be required in older patients to reduce the risk of adverse outcomes.	Expert opinion/A	77%
In view of the substantial survival benefit seen with ET + CDK4/6 inhibitors, this combination is considered the standard of care for 1st line therapy for the majority of patients with ER+/HER2 negative ABC, independently of the patient's age. Real world-data suggest that ET+CDK4/6 inhibitors can be beneficial also in unfit older patients.	II/A III/B	93% 93%
In unfit patients, testing a reduced starting dose of the CDK4/6 inhibitor is a reasonable but not sufficiently studied strategy.	Expert opinion	91%
If no absolute cardiac contra-indications exist, older patients with HER2 positive ABC should have access to anti-HER2 agents. Certain anti-HER2 agents such as TKIs and ADCs, which are usually associated with more side effects, may need a lower starting dose, careful monitoring and dose adjustments according to toxicity in older frail patients.	I/A Expert opinion/A	100% 84%
Patient with ABC IN VISCERAL CRISIS		
Therapeutic options for patients with visceral crisis are limited and evidence is scarce since these patients are almost always excluded from clinical trials. In ER+/HER2 negative ABC with visceral crisis, ET + CDK4/6 inhibitor are not contraindicated and may be a better option than chemotherapy. In HER2+ ABC with visceral crisis, the use of anti-HER2 agents is crucial and feasible.	 II/B II/A	 95% 95%
In situations of liver visceral crisis, options are further limited by the severe liver function impairment. Weekly regimens and lower doses are recommended.	IV/B	93%
For bone marrow infiltration, weekly reduced dose paclitaxel or capecitabine or ET + CDK4/6 inhibitors (in case of ER+/HER2 neg disease) are among the best options.	IV/B	86%
In some situations, urgent surgery and/or radiation therapy and/or other interventional techniques (i.e. laser therapy for bronchial obstruction) may be needed. Admission to ICU should not be denied if there is a possibility of reversing the clinical situation, after careful discussion with the patient and family, and always respecting the patient's wishes.	IV/B Expert opinion/NA	98% 98%

In green, NEW ABC 6 & 7 statements.

ABC: advanced breast cancer; ADC: antibody-drug conjugate; AI: aromatase inhibitor; consensus: percentage of panel members in agreement with the statement; CDK4/6: cyclin-dependent kinases 4/6; ChT: Chemotherapy; DFI: Disease-free interval; EUSOMA-SIOG: European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG); ER: estrogen receptor; ET: endocrine therapy; GoR: grade of recommendation; G-CSF: Granulocyte-colony stimulating factors; HER2: human epidermal growth factor receptor-2; ICU: Intensive Care Unit; LHRH: luteinizing hormone-releasing hormone; LoE: level of evidence; MRI: magnetic resonance imaging; OFS/OFA: Ovarian function suppression/ovarian function ablation; TKI: tyrosine kinase inhibitors.

2.21. *ABC in a pregnant patient (includes fertility issues)*

Amongst young patients with ABC, issues of fertility and contraception are often overlooked. Additionally, pregnancy during ABC is a very complex issue. The desire for pregnancy amongst women with ABC can pose a challenge for health care providers both in terms of medical management and psychosocial management. Moreover, there are times when the medical team may not agree with the patient's choices. All patients with ABC need to be counseled about the need for effective non-hormonal contraception, irrespective of subtype, with a clear communication about the risks for the mother and the fetus of pregnancy while on treatment. Notably, it should be emphasized that for patients not receiving OFS, many therapies are not gonadotoxic and will not induce menopause [153,154]. In terms of fertility preservation, all women of reproductive age (irrespective of disease stage) should be counselled about the impact of cancer therapies on their fertility and the availability of fertility preservation techniques [153,154]. For the patient with ABC this discussion needs to be balanced and presented in the context of the diagnosis of an incurable disease and the need to constantly be on therapy with a clear explanation that interruption of therapy to conceive would likely endanger the mother by preventing much needed treatment for disease control and compromise prolongation of survival. The question of future pregnancy will be an increasing clinical challenge as women with ABC live longer in particular for those with prolonged clinical remissions. If ABC is suspected during pregnancy, the preferred imaging modality for staging is whole-body MRI including diffusion-weighted sequences, where available. If not available, then a combination of non-contrast MRI of the axial skeleton

(full-spine and pelvic bones), MRI of the liver including diffusion-weighted sequences, and low-dose chest computed tomography (with abdominal shielding) are suggested. Of note, the safety of the imaging methods depends on gestational age of pregnancy, with some methods being safe with shielding (e.g., chest X-ray or chest CT early in pregnancy). Ultrasound, namely breast or abdominal ultrasound, is safe anytime during pregnancy.

For patients diagnosed with ABC while pregnant, the treatment approach will depend on the trimester at diagnosis, disease subtype and patient preference. The preferences of the patient and of whomever the patient wishes to involve must always be considered after an appropriate and transparent sharing of information about all management options and their potential impact on the patient's survival, fetal health and the future of the child. Termination should be readily available to women who favor this approach and should be discussed in particular for women who are diagnosed in the first 12 weeks of pregnancy when no systemic therapy is considered safe. During the second and third trimester certain chemotherapy agents (anthracyclines, paclitaxel, cyclophosphamide) can be safely administered – the preferred regimens with the most robust safety data would be an anthracycline or paclitaxel [155,156]. Targeted therapies (including but not limited to anti-HER2 agents, ADCs, PARP inhibitors and CDK4/6 inhibitors), immunotherapy and endocrine therapy are contraindicated during pregnancy, because of established risk to the fetus or absence of safety data [155,156]. The greatest challenge is for patients with HER2+ ABC for whom anti-HER2 therapy would need to be delayed until after delivery, potentially compromising patient outcome – the extent of disease and week of pregnancy play a major factor in decision making about continuation or termination of pregnancy in this case. Noteworthy, prematurity is a significantly greater risk factor for impaired cognitive development in the exposed offspring than chemotherapy exposure [157]. Assuming the pregnancy is to be continued and there is no impending danger to the mother's life, the optimal timing for delivery is after week 37. The pregnant patient should be managed by a multi-disciplinary team, preferably in a tertiary, experienced center [153]. Advice should be sought from experts in the field such as the International Advisory Board of CIP (Cancer In Pregnancy) (www.ab-cip.org).

2.22. ABC in a patient with HIV

The incidence of breast cancer is similar for people living with HIV or without HIV, but people living with HIV are usually diagnosed at an earlier age and have a worse survival [158]. Cancer incidence is rising in HIV-endemic regions [159]: widespread use of antiretroviral therapy (ART) has turned HIV into a chronic condition, with latent immunosuppression leading to a higher incidence of non-AIDS defining cancers as breast cancer. HIV leads to a higher risk of chemotherapy-induced myelotoxicity and infections, leading to more dose reductions, lower relative dose intensities, and worse outcomes [160]. Even when equivalent relative dose intensities of ChT can be obtained with the use of granulocyte-colony stimulating factors (G-CSF), the pathological complete response rate is lower in people living with HIV on neoadjuvant ChT [161]. This may be due to exhaustion of the tumor infiltrating T cells [162]. More research is needed on breast cancer in people living with HIV, with inclusion in clinical trials, in particular if the viral load is low. In general, the same ABC guidelines apply to people living with HIV. ChT can be safely initiated if viral load is undetectable and $CD4^+$ T-count is above 200. As there is an increased risk of myelotoxicity under ChT, G-CSF should be recommended, especially to avoid dose reductions or delays. And given the higher incidence (or relapse) of tuberculosis and hepatitis B under ChT, these infections should be screened upfront, and treatment should be initiated when detected. Patient with ABC and HIV should be co-managed by an oncologist and HIV specialist, in a multidisciplinary way. If a patient is ART naïve, ART must be initiated as soon as possible as it will improve outcomes [163]. To manage the initial ART related side-effects, cancer treatment may be delayed by 1–2 weeks. If a patient is already under ART, it is important to continue ART and check for potential drug-drug interactions. Most 1st-line ART drugs do not interfere with most anticancer drugs. If interactions can lead to decreased activity of ART drugs, the evolution of the HIV viral load must be checked more often, and ART treatment adapted if viral load increases. And If CD-4 count goes down due to ChT whilst maintaining a stable viral load, opportunistic infections must be monitored. Some data suggest safety of immune-checkpoint inhibitors [164] but there are no data regarding CDK4/6 inhibitors' safety in these patients.

2.23. ABC in older patients

Age is a major risk factor of breast cancer and with life expectancy increasing, the incidence of breast cancer among older women is expected to increase. The underrepresentation of the older population in clinical trials and the heterogeneity of health status of these patients represent major challenges for an evidence-based management of older patients with ABC and may explain the poorer outcomes reported in this population [165]. It is now clearly apparent that chronological age by itself is neither a criterion to exclude older patients with ABC from active and innovative strategies, nor a reason to prevent their participating in clinical trials [166,167]. It is exceptional to see a solely age-dependent treatment effect in fit selected older patients included in clinical studies. Safety and treatment adherence might be an issue [168]. For this reason, a proper evaluation of the health status of older patients with ABC, starting with a frailty screen, or when it is possible, with a comprehensive geriatric assessment should be at the basis of treatment decision making [166,169]. Polypharmacy is common, especially in unfit patients, and therefore special attention should be given to potential interactions when prescribing anticancer agents [170,171]. Real-world data indicate that up to 70 % of older patients with ABC are at potential risk of frailty [172]. Consequently, the SIOG–EUSOMA recommendations on the management of older patients with breast cancer consider that different treatment schedules, dose reductions, or stepwise dose-escalation before reaching standard recommended dose might be required in to reduce the risk of adverse outcomes [173]. Testing a reduced starting dose in unfit patients, even if quite a common and reasonable procedure in clinical practice, is a strategy which needs adequate studies [166,174]. In patients with ER+/HER2 negative ABC, 1st line ET + CDK4/6 inhibitor is considered the standard, with evidence of benefit also in unfit older patients [166,172]. Access to anti-HER2 therapy should be provided, in the absence of cardiac contraindications, to older patients with HER2+ ABC [174]. The EUSOMA-SIOG recommendations about treatment "personalization" refer mainly to ChT but can be extrapolated to new treatments for which data on unfit patients are not yet available. As with patients of all ages, older patients with ABC should be involved in the decision-making process and their preferences taken into account [173].

2.24. Patient with ABC in visceral crisis

Visceral crisis is usually defined as severe organ dysfunction as assessed by signs, symptoms and laboratory studies, resulting from rapid progression of neoplastic disease and indicative of substantial visceral compromise that may serve as an indication for more aggressive therapeutic intervention [175]. The ABC guidelines further clarified visceral crisis as defined in liver as rapidly increasing bilirubin >1.5x ULN in the absence of an obstruction, and in lung as rapidly increasing dyspnea at rest in the absence of pleural effusion [176]. Visceral crisis is not only the presence of visceral metastases but is associated with life-threatening organ compromise requiring rapidly efficacious therapy – generally consisting of single agent or, in select cases, combination chemotherapy with or without targeted agents [177]. Visceral crisis at presentation of metastatic disease is thought to be rare, occurring in less

than about 15 % of patients, and more frequently in patients with de novo metastatic and highly proliferative breast cancer subtypes. The treatment of visceral crisis in later lines of therapy must be moderated by goals, toxicity and potential efficacy of available therapies. Treatment options vary by biologic subtype, site of disease, and line of therapy. For patients with ER+/HER2 negative ABC, endocrine maintenance therapy is recommended after disease response or stabilization with ChT [177]. For patients with modest visceral dysfunction, ET + CDK4/6 inhibitor appears to provide superior efficacy to combination ChT with less toxicity, as demonstrated in the RIGHT Choice Trial, although patients with true hepatic visceral crisis were not included [84]. For HER2 positive ABC, the combination of ChT and anti-HER2 monoclonal antibodies can rescue even severe organ dysfunction at initial presentation. Triple negative ABC presents the greatest challenge, with treatment dictated by immune markers. New antibody drug conjugates offer a potential highly effective alternative strategy that is currently under investigation. Treatment of patients with visceral crisis is complicated by lack of data regarding optimal dosing in situations of liver or renal dysfunction, and by the fact that patients with visceral disease are almost always excluded from clinical trials. Lower doses of weekly paclitaxel or nab-paclitaxel, platinum compounds, and other single agent ChT have been evaluated in patients with visceral crisis without a clearly most effective regimen, and significant variation in line of therapy and organ involvement [178]. The use of the correct definition of visceral crisis in clinical trials and in practice is critical. With new and highly effective therapies, the concept of impending visceral crisis needs to be re-visited, as evidenced by the data from the RIGHT Choice Trial, and will be addressed in a future update of the ABC guidelines.

2.25. *Section XII: Specific sites of metastases*

Guideline statement	LoE/GoR	Consensus
BONE METASTASES		
Radiological assessments are required in patients with persistent and localized pain due to bone metastases to determine whether there are impending or actual pathological fractures. If a fracture of a long bone or vertebrae is likely or has occurred, an orthopedic assessment is required as the treatment of choice may be surgical stabilization, which is generally followed by RT. In the absence of a clear fracture risk, RT is the treatment of choice.	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 orthopedic) may be required for surgical decompression. If no decompression/stabilization is feasible or indicated, emergency RT is the treatment of choice and vertebroplasty is also an option.	I/B	100%
Regarding the use of bone-targeted agents (bisphosphonate, denosumab), the ABC panel endorses the ESMO Guidelines [180] related to this subject.	Expert Opinion/A	100%
BRAIN METASTASES		
Brain imaging: Brain imaging should not be routinely performed in asymptomatic patients. This approach is applicable to all patients with ABC including those with HER-2+ and/or triple negative ABC.	II/D	85%
Patients with a single or a small number of potentially resectable brain metastases should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases.	I/B	92%
If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy, but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects.	I/C	72%
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 radiotherapy) 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**, for whom stereotactic radiotherapy is feasible and accessible, systemic therapy should not be changed.	I/D	89%
For patients with **HER2 positive ABC where brain metastases are the only site of recurrence** and for whom stereotactic radiotherapy is feasible and accessible, the addition of chemotherapy to local therapy is not known to alter the course of the disease and is not recommended. It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped. A possible alternative is the usage of tucatinib + Trastuzumab + Capecitabine, although this option may also be reserved for progression of the disease after local therapy.	I/D II/B I/A	83% 87% 91%
T-DM1 has also shown activity against active **HER2+** brain metastases in one prospective single arm study (KAMILLA) and is therefore a treatment option.	II/A	80%
For patients with **HER2 positive** ABC with **progressive brain metastases as the predominant site of disease burden** and no local therapy option available, treatment with tucatinib + Trastuzumab + Capecitabine is the best available option. If this treatment is not accessible and/or if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option.	I/A II/B	91% 93%
Trastuzumab deruxtecan (T-DXd) has shown activity against brain metastases from **HER2+ ABC**, previously treated or untreated with local therapy, and can be considered a treatment option.	II/B	98%
Radionecrosis after stereotactic radiotherapy 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 tumor progression is often difficult. Treatment of symptomatic patients with a course of high-dose steroids is the first treatment of choice. If no response, bevacizumab may be used, as an option to decrease the surrounding oedema, usually at a dose of 7.5 mg/kg every 2 weeks for a median of 4 cycles. Prospective randomized trials are needed to further validate this option.	III/B	61%
LEPTOMENINGEAL DISEASE (LMD)		

There is no accepted standard of care for breast cancer LMD. It is crucial that patients with LMD are included in clinical trials, namely in trials evaluating therapies for CNS disease. The choice of treatment (radiotherapy, intra-CSF therapy, systemic therapy, supportive care) should consider prognostic evaluation, multidisciplinary discussion and always an in-depth discussion with the patient and the caregivers. Staging of patients with LMD should include full spine imaging with MRI with gadolinium to assess the full extent of the disease.	Expert opinion/A Expert opinion/A Expert opinion/A	100% 100% 100%
Focal radiotherapy (brain or cranio-spinal) should be considered for circumscribed, particularly symptomatic lesions.	III/B	98%
WBRT can be considered for extensive nodular or symptomatic linear LMD.	III/B	98%
A ventriculoperitoneal shunt may be placed to palliate symptoms of increased intracranial pressure or symptomatic hydrocephalus.	Expert opinion/B	100%
Intra-CSF chemotherapy has not been proven to improve OS nor QoL but may palliate symptoms in some cases, although significant toxicity may also occur. It can be considered in selected cases, if systemic disease is stable. Intra-CSF trastuzumab has been evaluated in small studies and has shown some efficacy relative to historical control data. It may be used in some patients with HER2+ LMD.	III/C III/B	95% 95%
The choice of systemic therapy for LMD should take into account the breast cancer subtype and previous treatments. Albeit in very small case series, there are some efficacy data in LMD for capecitabine monotherapy, the combination capecitabine + trastuzumab + tucatinib and for T-DXd.	II/A V/B	100% 100%
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 randomized data supporting the effect of local therapy on survival, every patient must be informed of this when discussing a potential local therapy technique. Local therapy should only be proposed in very selected cases of good PS, with limited liver involvement and no extrahepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic RT, intrahepatic ChT, etc.).	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 performed 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%
Locoregional radiotherapy is indicated for patients not previously irradiated.	II/A	97%
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion/C	97%
In addition to local therapy (surgery and/or RT), in the absence of distant metastases, the use of systemic therapy (ChT, ET and/or anti-HER2 therapy) should be considered.	I/B	95%
ChT after first local or regional recurrence improves long-term outcomes in ER-negative disease and can be used.	I/B	95%
ET in this setting improves long-term outcomes for ER-positive disease and should be used.	I/B	95%
The choice of systemic treatment depends on tumor biology, previous treatments, length of DFI and patient-related factors (comorbidities, preferences, etc.).	Expert opinion/A	95%
In patients with disease not amenable to radical local treatment, the choice of palliative systemic therapy should be made according to principles previously defined for metastatic disease. These patients may still be considered for palliative local therapy.	Expert opinion/B	97%
PERITONEAL METASTASES AND ASCITES		
• Are more common in case of infiltrating lobular carcinoma. • Confer poor prognosis and have a negative impact on QoL, requiring early active palliative measures. • Early involvement of palliative care team is crucial. • Diagnosis is clinical, radiological and cytological (via paracentesis). Peritoneal carcinomatosis is often difficult to visualize radiologically and needs to be suspected clinically and actively sought for. • Symptoms include abdominal pain, nausea, anorexia, cachexia, distension, constipation, fatigue. • Attention must be given to cachexia and fatigue. The panel endorses the ESMO guidelines for management of these symptoms, emphasizing the importance of nutrition supplements.	I/A Expert Opinion/A	96%
Anti-emetics include metoclopramide, serotonin 5-HT3 receptor antagonists, neuroleptics; Octreotide (somatostatin analog) helps reduce nausea; steroids reduce nausea and alleviate obstructive symptoms.	I/A	89%
Treatment of underlying ABC disease with systemic therapy, according to the guidelines is recommended.	Expert Opinion/A	100%
More invasive interventions may include nasogastric tube for vomiting, surgery for GI obstructions and adhesions.	II/A	91%
Ascites management options include low sodium diet, diuretics, paracentesis, intraperitoneal catheters, intraperitoneal port, peritoneal-venous shunt.	I/A	96%

In green, NEW ABC 6 & 7 statements.

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

2.26. Brain metastases

Clinical trials for HER2+ or triple negative ABC generally require baseline brain imaging, however outside of the clinical trial setting, brain imaging is not recommended in asymptomatic patients. The role of brain imaging in routine management of asymptomatic patients is being evaluated in prospective clinical trials such as NCT04030507. Large randomized clinical trials evaluating local therapies in patients with brain metastases include patients with brain metastases from a variety of cancer types. The incidence of brain metastases in breast cancer patients is increasing mainly due to improved systemic therapies resulting in more durable control of extracranial metastatic disease and prolonged survival. The management of breast cancer brain metastases is challenging, even more so with the continued advancement of local and highly effective systemic therapies. Treatment of brain metastases should be based on multidisciplinary team discussions and a shared decision with the patient, considering the risks and benefits, aiming to prolong survival while maintaining quality of life. Strategies for graded prognostic assessment of brain metastasis from breast cancer have been proposed to help decision making [179]. For most patients, a metastases-directed initial ablative strategy including surgery and/or radiation therapy is preferred, especially when the metastatic burden is limited [180]. Surgical resection can be both diagnostic and informative in terms of providing histopathological confirmation of the tumor type and biomarkers, since changes might have occurred [181]. Surgical resection is often considered the preferred approach for lesions in the posterior fossa, where even minor volume changes (from e.g., edema) may result in a significant increase in symptoms. Stereotactic brain radiation therapy or stereotactic radiosurgery (SRS) should be the preferred local treatment option for most patients if they have a good performance status and metastatic disease without an indication for surgery. Although multiple lesions are often treated, the total volume and number must allow for effective and safe SRS [180]. Following SRS, if there are increased neurologic symptoms and/or increased local radiologic effects, it may be difficult to distinguish between local tumor progression versus radio-necrosis. Either may respond to steroids. In recent years, whole brain radiotherapy (WBRT) has fallen out of favor as the preferred strategy due to the concerns over cognitive impairment when anticipated survival is more than a few months, as well as the increasing availability of SRS. In the HER2Climb trial, patients with HER2+ ABC, who had received several lines of anti-HER2 therapies, were randomly assigned to tucatinib or placebo, combined with trastuzumab and capecitabine [106,182]. In the cohort of 291 patients (47.5 %) with brain metastases at baseline (including active brain metastases) the estimated 1-year PFS was 24.9 % (95 % CI, 16.5–34.3) in the tucatinib arm versus 0 % in the placebo arm, and the median PFS was 7.6 months versus 5.4 months. The adverse event profile was acceptable. In the subsequent OS analysis, in the baseline brain metastases cohort, the hazard ratio favored the tucatinib arm (HR 0.60; 95 % CI 0.444–0.81) [106]. Thus, a tucatinib-based regimen is a suitable therapy even in heavily pre-treated patients with HER2+ ABC. T-DM1 did not reduce the frequency of CNS recurrence in the post-neoadjuvant setting in the Katherine trial [183]. However, T-DM1 has been tested in patients with HER2+ ABC in a phase 3b single-arm study, where 398 patients had brain metastases at start of therapy [184]. All patients had received prior HER2-targeted systemic therapy, 6 % prior pertuzumab, and 56 % had also received prior brain radiation therapy. Results showed complete response and/or partial response in 21 % of the patients, and an additional 21 % had stable disease lasting minimum 6 months with a median PFS and OS of 5.5 and 18.9 months, respectively. T-DXd was compared to T-DM1 in the DESTINY-Breast03 Trial in previously treated HER2+ ABC [104]. T-DXd showed a significant improvement in PFS (HR 0.28; 95 % CI 0.22–0.37), with subgroup analysis supporting PFS benefit in those with baseline brain (n = 114) metastases (HR 0.38; 95 % CI 0.23–0.64). Encouraging data were also presented from the small subgroup with asymptomatic brain metastases (n = 24) treated with T-DXd in the DESTINY-Breast01 phase 2 trial, with a median PFS of 18.1 months (95 % CI, 6.7–18.1 months) [185]. A pooled analysis of patient with brain metastases (n = 148) treated with T-DXd in the DESTINY–Breast01, 02 and 03 trials, showed an intracranial response rate of 45 % and median CNS-PFS of 12.3 months in treated/stable BM and 18.5 months in untreated/active BM [186].

Leptomeningeal disease (LMD) is an aggressive complication of ABC with tumor cells infiltrating the leptomeninges, subarachnoid space, and CSF [187]. LMD is confirmed by positive CSF cytology or can be considered as probable (typical neurological signs and symptoms plus typical neuroimaging findings) or possible (atypical clinical and typical neuroimaging findings) [188,189]. LMD can be further classified into four subtypes based on MRI appearance: type A (typical linear MRI abnormalities), type B (nodular disease only), type C (both linear and nodular disease) and type D (no MRI abnormalities except possibly hydrocephalus). LMD occurs in the presence of CNS metastases in 43%–52 % of cases, and with extra-CNS metastases in 85%–88 % of cases [190,191]. The median time from the diagnosis of breast cancer to LMD is approximately 2.5–5.0 years [192,193]. Risk factors associated with the shortest LMD onset include TNBC subtype and lobular tumor histology [193–199]. LMD is usually associated with rapid neurological decline, reduction in QoL and limited life expectancy [188,194,200–203]. Therefore, treatment is aimed at improving or stabilizing neurological symptoms and QoL.

Treatment options for LMD include systemic and intrathecal pharmacotherapy as well as local radiotherapy. Given the limited data and usually poor prognosis, the choice of treatment (radiotherapy, intra-CSF therapy, systemic therapy, supportive care) should consider prognostic evaluation, multidisciplinary discussion and always an in-depth discussion with the patient and the caregivers. To evaluate treatment options, staging of patients with LMD should include both brain and full spine imaging with MRI with gadolinium to assess the full extent of the disease. Intra-CSF chemotherapy has not been proven to improve OS nor QoL but may palliate symptoms in some cases, although significant toxicity may also occur [204–208]. In an analysis from the real-world Epidemiological Strategy and Medical Economics (ESME) database, among 312 patients who received intra-CSF chemotherapy for LMD, median OS after LMD diagnosis was 5.1 months in HR+/HER2 negative, 5.6 months in HER2+ and 3.0 months in TN ABC disease [195]. Intra-CSF trastuzumab has been evaluated in small studies and has shown some efficacy relative to historical control data, with a favorable toxicity profile. It may be used in some patients with HER2+ LMD [202,209]. A ventriculoperitoneal shunt may be placed to palliate symptoms of increased intracranial pressure or symptomatic hydrocephalus. WBRT may be used in selected cases for symptomatic relief in patients with extensive nodular or symptomatic linear LMD or with coexisting CNS metastases, although it has not been proven to prolong survival [188,210]. Focal radiotherapy (brain or cranio-spinal) should be considered for circumscribed, particularly symptomatic lesions [211]. A recent randomized phase 2 study compared two techniques of radiotherapy, each targeting different volumes; the results suggested that proton craniospinal irradiation could improve survival without serious toxicity compared with local standard radiotherapy in patients with LMD. Therefore, this study may question the best radiotherapy method for patients with LMD [212]. As this technique is not available in most countries and given the limited data available, there was no voting on the topic. To date, there are a lack of high-quality clinical trial data supporting the use of specific systemic therapies in LMD despite some case series and retrospective cohort studies [213]. Patients, including those with a preserved general performance status at diagnosis of LMD, are often excluded from clinical trials in breast cancer; this is presumably due to the risk of rapidly progressing disease and short life expectancy [214,215]. Consequently, the results from clinical trials generally do not provide an accurate reflection of real-world clinical practice. It is

crucial that patients with LMD are included in clinical trials, namely in trials evaluating therapies for CNS disease. The choice of systemic therapy for LMD should consider the breast cancer subtype and previous treatments. Systemic regimens with reported benefit include capecitabine, platinum and platinum-based combinations, anthracyclines and endocrine-based therapy [213]. Albeit in very small case series, there are some efficacy data in LMD for capecitabine monotherapy, the combination capecitabine + trastuzumab + tucatinib [105,216] and for T-DXd [217].

Peritoneal carcinomatosis is more common in patients with invasive lobular carcinoma [218], usually represents advanced stages of disease, has a negative impact on quality of life, and confers a poor prognosis [219]. Patients may present with non-specific symptoms such as abdominal pain, decreased appetite, nausea, vomiting, weight loss, increased abdominal girth. Ascites is present in 50 % of patients. Imaging with ultrasound, CT scan or MRI scans may show peritoneal nodular deposits, thickening of peritoneal folds, diffuse thickening of peritoneum and layer between the bowels and abdominal wall, with or without variable amounts of ascites. Tumor markers and PET/CT scans may be helpful for following disease response. Sensitivity of paracentesis ranges between 40 and 70 % with a higher yield with multiple paracentesis. In some cases, laparoscopy and biopsy may be required for diagnosis [219]. Specific systemic management depends on the subtype of breast cancer. Attention to symptom management is important, namely cachexia (nutrition supplements), fatigue and nausea (anti-emetics such as metoclopramide, 5-HT3 receptor antagonists, neuroleptics, octreotide (somatostatin). Steroids may reduce nausea and alleviate obstructive symptoms. Invasive interventions may include nasogastric tube for vomiting, surgery for gastrointestinal obstructions and adhesions. Ascites management options include low sodium diet, diuretics, paracentesis, intraperitoneal catheters, intraperitoneal port and peritoneal-venous shunt. Palliative paracentesis is an ambulatory procedure usually done under ultrasound guidance and causes relief of symptoms in 90 % of patients. Active and early involvement of palliative care team is crucial [220–222].

2.27. Section XIII: Supportive and palliative care (see Fig. 6a, b, 6c and 6d)

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%
The ABC community is aware of the limitations that are being imposed worldwide, as a consequence of the opioid use disorders in certain areas of the world. The ABC community is united in insisting that cancer patients should not have restrictions placed that will limit their access to adequate pain control.	Expert opinion/N/A	100%
The panel encourages research on the potential role of cannabis to assist with pain and symptom control but strongly stresses that it cannot replace proven medicines such as morphine, for adequate pain control.	I/C	97%
Optimally, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. However, when active treatment no longer is able to control widespread and life-threatening disease, and the toxicities of remaining options outweigh the benefits, physicians and other members of the healthcare team should initiate discussions with the patient (and family members/friends, if the patient agrees) about end-of-life care.	Expert opinion/A	96%
Management of cancer-related FATIGUE		
Cancer-related fatigue is frequently experienced by patients with ABC, exerts a deleterious impact on QoL and limits physical, functional, psychological, and social well-being. The etiology of this fatigue is complex; therefore, effective management needs to be multidimensional. It is important to assess cancer-related fatigue using appropriate PROMs before implementing various non-pharmacological (such as exercise [I, A]), and, if needed, pharmacological interventions [II, B].	Expert Opinion/A	100%

Fatigue is particularly frequent and relevant in the **older population** and often underestimated. A close monitoring of fatigue, a very common adverse event induced by systemic therapies in older ABC patients is recommended due to its impact on function [I, A].		
Management of CDK4/6 INHIBITOR-INDUCED NEUTROPAENIA		
Neutropenia is the most common toxicity associated with CDK4/6 inhibition and is not generally associated with febrile neutropenia, although an increase in infections has been reported. Treatment should be delayed until neutrophils have recovered to at least 1000/µl; dose reduction can also be considered.	II/A	100%
Management of INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS DUE TO OTHER AGENTS THAN T-DXD		
ILD (also known as pneumonitis) is an uncommon complication of many cancer agents, including some chemotherapy agents, antibody drug conjugates, mTOR and Pi3KCA inhibitors, immunotherapy, radiation and rarely, CDK4/6 inhibitors. Differential diagnosis with carcinomatosis lymphangitis is sometimes difficult. Patient and provider education is critical to ensure early reporting and timely management. For symptomatic ILD grade 2 or higher, treatment interruption and systemic steroids are indicated, followed by a dose reduced rechallenge after resolution of symptoms. For ILD grade 3 or higher, treatment should be discontinued.	I/A	84%
Management of INTERSTITIAL LUNG DISEASE (ILD) / PNEUMONITIS DUE TO T-DXD		
For ILD/pneumonitis related to trastuzumab-deruxtecan, special precautions are necessary to prevent progression to life-threatening symptoms. For asymptomatic radiographic changes (ground glass opacities), T-DXd should be held, and systemic steroids (≥ 0.5 mg/kg prednisone or equivalent) should be considered. Treatment may be restarted at full dose if changes resolve within 28 days. For delayed recovery, T-DXd should be reduced by one dose level. For ILD grade 2 or higher, prompt steroid treatment is required (≥ 1 mg/kg prednisone or equivalent) and T-DXd should be permanently discontinued. It is also important to taper the steroids slowly for at least 4 weeks.	I/A	84%
Management of DYSPNOEA		

Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anemia or drug toxicity must be ruled out. Patient support is essential. Oxygen is of no use in non-hypoxic patients. Opioids are the drug of choice in the palliation of dyspnea. Benzodiazepines can be used in patients experiencing anxiety. Steroids can be effective in dyspnea 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).	 I/A I/A II/A Expert opinion/B	 100%
Management of NAUSEA AND VOMITING		
ESMO/MASCC guidelines [225] are available for the management of ChT-induced and morphine-induced nausea and vomiting, and these are endorsed by the ABC community. There is a need to study nausea and vomiting related to chronic use of anticancer drugs.	Expert opinion/A Expert opinion/A	100% 100%
Management of ENDOCRINE TOXICITIES from mTOR or *PIK3CA* inhibition		
Hyper glycaemia and hyperlipidemia are common, sub-acute complications of mTOR or *PIK3CA* inhibition. Evaluation of pre-existing diabetes or hyperglycemia at baseline is essential. Regular, careful monitoring of glycemia and lipid panel is needed to identify these toxicities. Management of grade 1 and 2 hyperglycemia includes treatment with oral antidiabetics and basal insulin, in accordance with international recommendations for diabetes mellitus treatment. Statins are indicated to treat grade 2 and 3 hypercholesterolemia, and fibrates should be introduced if the triglyceride level is >500 mg/dL (with attention to possible drug-drug interaction between everolimus and fibrates). Treatment interruption and dose reduction are generally effective for grade 2 and 3 toxicity. Treatment should be discontinued for grade 4 toxicity.	II/A	100%
Management of MUCOSITIS/STOMATITIS		
Steroid mouthwash should be used for the prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5 mg/5 ml dexamethasone, 10 ml to swish x 2 minutes, then spit out; q.i.d.). Early intervention is recommended.	I/B Expert opinion/A	100% 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)		
CIPN is frequent and potentially dose-limiting. Risk factors for neuropathy and pre-existing neuropathy need to be identified.	II/C	100%
No medical prevention can currently be recommended.	I/C	100%
Drug-related factors (dosing, timing, route) can lower the risk of CIPN.		
The use of tight gloves and socks during ChT may help reduce the incidence and severity of CIPN.	II/B	100%
There are limited evidence-based treatments for CIPN, with tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, duloxetine, pregabalin and gabapentin being most often used.		
High-quality studies are needed to evaluate strategies for the prevention and management of CIPN.		
Management of HAND AND FOOT SYNDROME (HFS)		
HFS is also described as palmar-plantar erythrodysesthaesia syndrome. Most frequent causes are capecitabine, pegylated liposomal doxorubicin and multikinase inhibitors.		
Patients should be instructed about early recognition of HFS.		
Drug-related factors (dosing, timing, route) can lower the risk of HFS.		
Treatment of hyperkeratosis/fungal infections, comfortable shoes and avoidance of friction and heat are recommended.	Expert opinion/A	100%
Intensive skin care of hands and feet (urea cream/ointment) is recommended.	II/A	100%
Limited data exists supporting use of acupuncture for risk reduction and alleviation of CIPN.		
High-quality studies are needed to evaluate strategies for the prevention and management of HFS.		
Management of POSTMENOPAUSAL SYMPTOMS		

Systemic hormone therapy is generally not recommended to treat postmenopausal symptoms in ABC patients, particularly not in ER-positive disease. The final decision belongs to the woman, after correct information, since in some cases these symptoms are highly impacting on QoL.	I/D	100%
Valid alternatives are:	I/B	100%
• For postmenopausal symptoms in general: Mind-body interventions, physical training and CBT are effective non-pharmacological treatment options.	I/B	100%
• For hot flushes: Venlafaxine, oxybutynin, gabapentin, clonidine and acupuncture are available options.	I/B	100%
• For sleep disturbances: Melatonin	II/C	100%
There is no convincing evidence that phytotherapeutic drugs improve postmenopausal symptoms. Possible drug interactions must be considered.	I/D	100%
SEXUAL HEALTH		
Sexuality is an experience on many levels and is not confined to the act of intercourse. Sexuality remains important for many patients with ABC. These patients frequently experience impaired sexual health and need specific attention. Openly addressing misconceptions and sexual challenges after treatment, as well as educating patients, have been shown to improve QoL. When life expectancy is limited, physical contact, affection, emotional communication and comfort are particularly important. Standardized instruments (questionnaires) may help to assess the grade of impairment.	Expert opinion/N/A	100%
DYSPAREUNIA		
Dyspareunia is often caused by vaginal dryness.		
The first choice for treating vaginal dryness and soreness are hormone-free lubricants and moisturizers (e.g. water-based gel, hyaluronic acid gel).	II/B	100%
If hormone-free measures are not effective, low-dose estrogen-containing vaginal medication may be used.	II/B	100%
The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.		
CANCER AND TREATMENT-RELATED COGNITIVE IMPAIRMENT (CRCI), aka "Onco-brain"		

Definition: • **Cognitive dysfunction associated with cancer diagnosis and treatment** has been increasingly reported by breast cancer patients, in the early and advanced settings, who did not have localized treatment to the brain nor other cognitive disorders. • Poor performance in neuropsychological tests and structural changes in brain imaging (e.g. volume reduction in grey matter, less connectivity and activation) are findings of this effect. However, self-reports of cognitive dysfunction are more prevalent than objective findings, probably due to the multidimensionality of this complaint. • Imaging studies should only be used to rule out CNS disease. The exact mechanisms of CRCI are not clear, probably multifactorial and is frequently associated with other cancer related symptoms such as fatigue, anxiety, depression, pain, distress, and sleep disorders.	III/NA	98%
Perform routine assessment of clinical symptoms of cognitive dysfunction and awareness/education.	II/A	91%
Routine physical activity is recommended (weekly: 150–300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity) in view of its association with neurogenesis in brain areas related to memory.	II/A	89%
Screening for potential reversible factors and corrective measures when possible. Such factors include medications and their side effects, emotional distress, depression/anxiety, symptom burden (specially pain, fatigue, and sleep disturbance), comorbidities, use of alcohol and other agents that may alter cognition, new-onset vitamin deficiencies and endocrinopathies (e.g. TSH, B12).	II/A	100%
If important impact on self-reported QoL, refer to neuropsychological assessment and cognitive rehabilitation.	III/A	96%

In green, NEW/UPDATED ABC 6 & 7 statements.

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

Interstitial lung disease (ILD), defined as inflammation that, untreated, results in eventual fibrosis of the lung interstitium, is an uncommon complication associated with hundreds of drugs and numerous drug classes as well as radiation or combinations of radiation and drugs [223]. In the treatment of breast cancer, ILD has been associated with antibody drug conjugates, mTOR inhibitors, HER-2/EGFR targeted oral tyrosine kinase inhibitors, PD-1 or PD-L1 inhibitors, radiation therapy and rarely, CDK4/6 inhibitors [224]. The key differential diagnosis is lymphangitic carcinomatosis, or an acute or subacute infection. Risk is increased in patients with a prior history of pneumonitis, and in those with Asian ethnicity. Additional risk factors are being evaluated [223]. Grading of ILD is provided by the NCITC [225]: grade 1 is defined as abnormalities on imaging, such as ground glass opacities (GGO) without symptoms; patients with grade 2 ILD have moderate symptoms with medical intervention indicated and limiting activities of daily living; grade 3 is associated with severe symptoms requiring oxygen; grade 4 ILD is life threatening with urgent intervention such as intubation and grade 5 is death. In general, grade 1 ILD requires close observation; for grade 2 ILD treatment should be withheld, and systemic steroids are indicated. Cautious retreatment when symptoms have resolved, usually with dose reduction, can be considered. However, with T-DXd, stricter criteria must be employed to avoid death from progressive ILD. Patients treated with T-DXd should have chest CT imaging no longer than at 12 weeks intervals during the first year of treatment. With asymptomatic GGO, drug should be held, and it is recommended that steroids at a dose of $\geq$0.5 mg/kg prednisone or equivalent be instituted. T-DXd can be restarted at full-dose if radiographic changes resolve within 28 days. If the GGO take longer than 28 days to resolve, T-DXd should be restarted with one dose reduction. Patients with symptomatic ILD, regardless of oxygenation should permanently discontinue treatment with T-DXd and steroids at a dose of $>$1 mg/kg prednisone or equivalent should be promptly instituted. Early diagnosis of ILD and close adherence to guidelines can prevent mortality from progressive respiratory dysfunction [103].

Cancer-relative cognitive impairment (CRCI), also called **onco-brain** describes the experience of cognitive complains associated with cancer treatments, such as impairments in short-term and working memory, attention, executive functions and/or processing speed, in patients with non-CNS cancers [227]. Objective findings include poor performance in neuropsychological tests and structural changes in brain imaging (i.e., volume reduction in grey matter, less connectivity and activation). Cognitive complaints are usually subtle or moderate, and most frequently related to ChT. However, other treatments, such as ET, targeted agents, and immunotherapy may also have an impact in cognitive function [228,229]. Most studies describing CRCI were conducted in the early breast cancer setting. CRCI is multifactorial and closely associated with cancer related symptoms such as fatigue, anxiety, depression, pain, and distress [227,229]. This calls for the need to assess the contributing factors in patients with ABC, and most importantly, to encourage studies on how to comprehensively assess all these factors (psychosocial, physical, treatment related) in this population. Such a tool would allow a more appropriate use of efficacious known interventions, as well to test new ones in this setting. Validated PROMs are available to assess subjective cognitive function. The EORTC

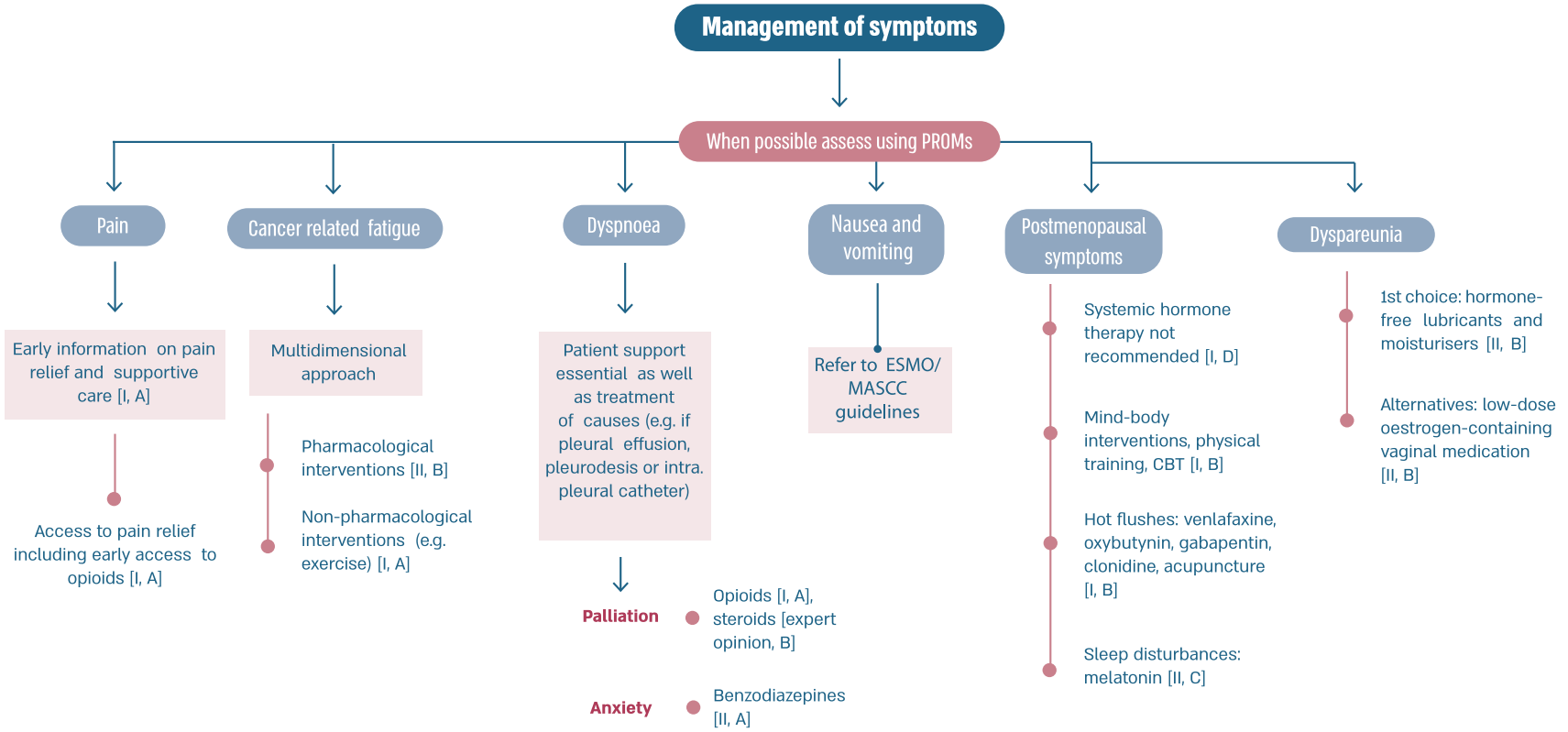

Fig. 6a. ABC Symptom control.
Legend: ABC, advanced breast cancer; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; PROM, patient-reported outcome measure; CBT, cognitive behavioural therapy. For ESMO/MASCC guideline please refer to [226].

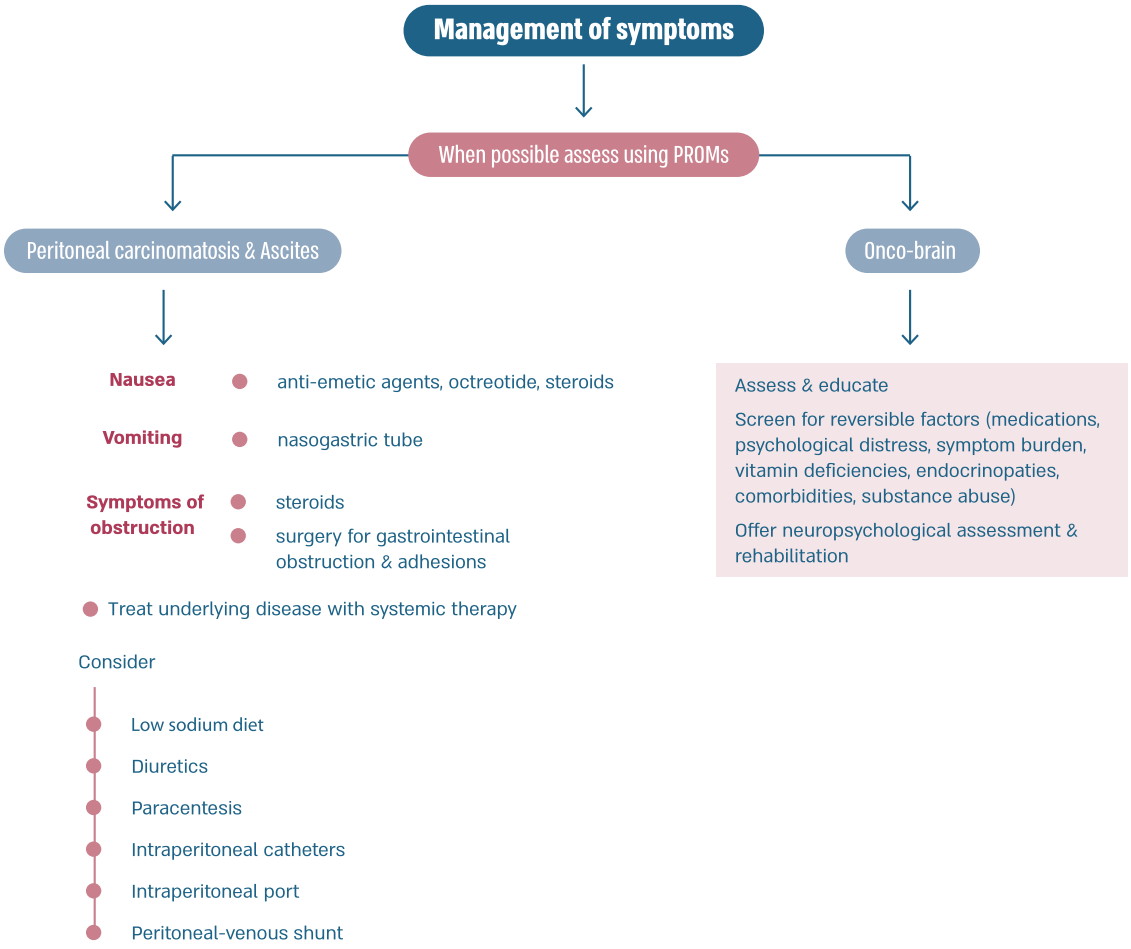

Fig. 6b. ABC Symptom control.

QLQ-C30 questionnaire that incorporates a cognitive function domain has been the most frequently used tool [230]. The Functional Assessment of Cancer Therapy-Cognitive Function questionnaire (FACT-Cog) is another available PRO tool that has been mainly used in the clinical research setting [231]. If symptoms of cognitive disfunction are present, contributing factors should be assessed, and corrected and/or optimized, including medications and their side effects, emotional distress, depression/anxiety, symptom burden (especially pain, fatigue and sleep disturbance), comorbidities, use of alcohol and other agents that may alter cognition, new-onset vitamin deficiencies and endocrinopathies (e.g., TSH, B12) [227,232]. If all the above have already been assessed and optimized, a referral for a neuropsychological specialist should be considered if cognitive dysfunction is creating an ongoing impact on QoL. The assessment should be directed to determining objective cognitive function and eligibility for cognitive rehabilitation programs [227,233]. Physical exercise is the most efficacious intervention tested, based on the biological rational of its association with neurogenesis in brain areas related to memory [234,235]. Current guidelines for cancer survivors recommend routine physical activity, more specifically, 150 min of moderate-intensity activity or 75 min of vigorous-intensity activity, weekly [232]. Small sample size studies are available in the advanced breast cancer setting concerning the benefits of physical activity [236,237]. Tailored exercise programs are urgently needed to find suitable exercise protocols and to determine the benefit of physical exercise on QoL in this setting.

2.28. *Section XIV: 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 centers/units/departments should be aware that the majority of their patients would like to be informed about CIM and that many of them are using it. Physicians should actively ask for information about its use in view of the potential deleterious interactions with specific anticancer therapies. If complementary therapies are not available at the center, certified contacts should be available to promote referral to practitioners qualified in the therapies people are interested in receiving.	Expert opinion/C	100 %
Some complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and therefore improve the QoL of patients with ABC.	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 PFS and OS.	I/B	100 %

(*continued on next page*)

(*continued*)

Guideline statement	LoE/GoR	Consensus
• MBSR programs, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side effects of anticancer therapies. • Acupuncture may help against ChT-induced nausea and vomiting, fatigue and hot flushes.		
Methods with no or unfavorable 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: o Antioxidant supplements; o Drugs outside the approved indication (e.g. methadone); o Herbs including Chinese herbal medicine; o Orthomolecular substances (selenium, zinc …); o Oxygen and ozone therapy; o Proteolytic enzymes, thymic peptides; o Phytoestrogens (soy food, isoflavones); o High-dose vitamins (vitamin C, D, E, carotenoids, etc.); o L-carnitine, laetrile.	II/E	100 %

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

3. Conclusions and future directions

The ABC consensus guidelines provide an invaluable guide to help healthcare providers and patients in treatment decision-making for advanced/metastatic breast cancer. They are also a powerful lobbying and advocacy tool to fight for the best available care for all patients living with this disease worldwide.

Clinical implementation of guidelines is often limited by inequalities in access to cancer care. In some regions of the world, adaptation of these guidelines is necessary and the ABC Global Alliance (https://www.abcglobalalliance.org) remains available to help with this complex endeavour. It is crucial to note that, even when access to the latest and

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 centers/units/departments should be aware that the majority of their patients would like to be informed about CIM and that many of them are using it. Physicians should actively ask for information about its use in view of the potential deleterious interactions with specific anticancer therapies. If complementary therapies are not available at the center, certified contacts should be available to promote referral to practitioners qualified in the therapies people are interested in receiving.	Expert opinion/C	100%
Some complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and therefore improve the QoL of patients with ABC.	Expert opinion/C	100%
Evidence suggests beneficial effects of the following methods, which can therefore be used: • Physical exercise/sport (equivalent to 3–5 hours of moderate walking per week) improves QoL, cardiorespiratory fitness, physical performance and fatigue, and it may also improve PFS and OS. • MBSR programs, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side effects of anticancer therapies. • Acupuncture may help against ChT-induced nausea and vomiting, fatigue and hot flushes.	I/B	100%
Methods with no or unfavorable 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);	II/E	100%
○ Herbs including Chinese herbal medicine; ○ Orthomolecular substances (selenium, zinc...); ○ Oxygen and ozone therapy; ○ Proteolytic enzymes, thymic peptides; ○ Phytoestrogens (soy food, isoflavones); ○ High-dose vitamins (vitamin C, D, E, carotenoids, etc.); ○ L-carnitine, laetrile.		

No new statements for this section were developed at ABC 6 & 7

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

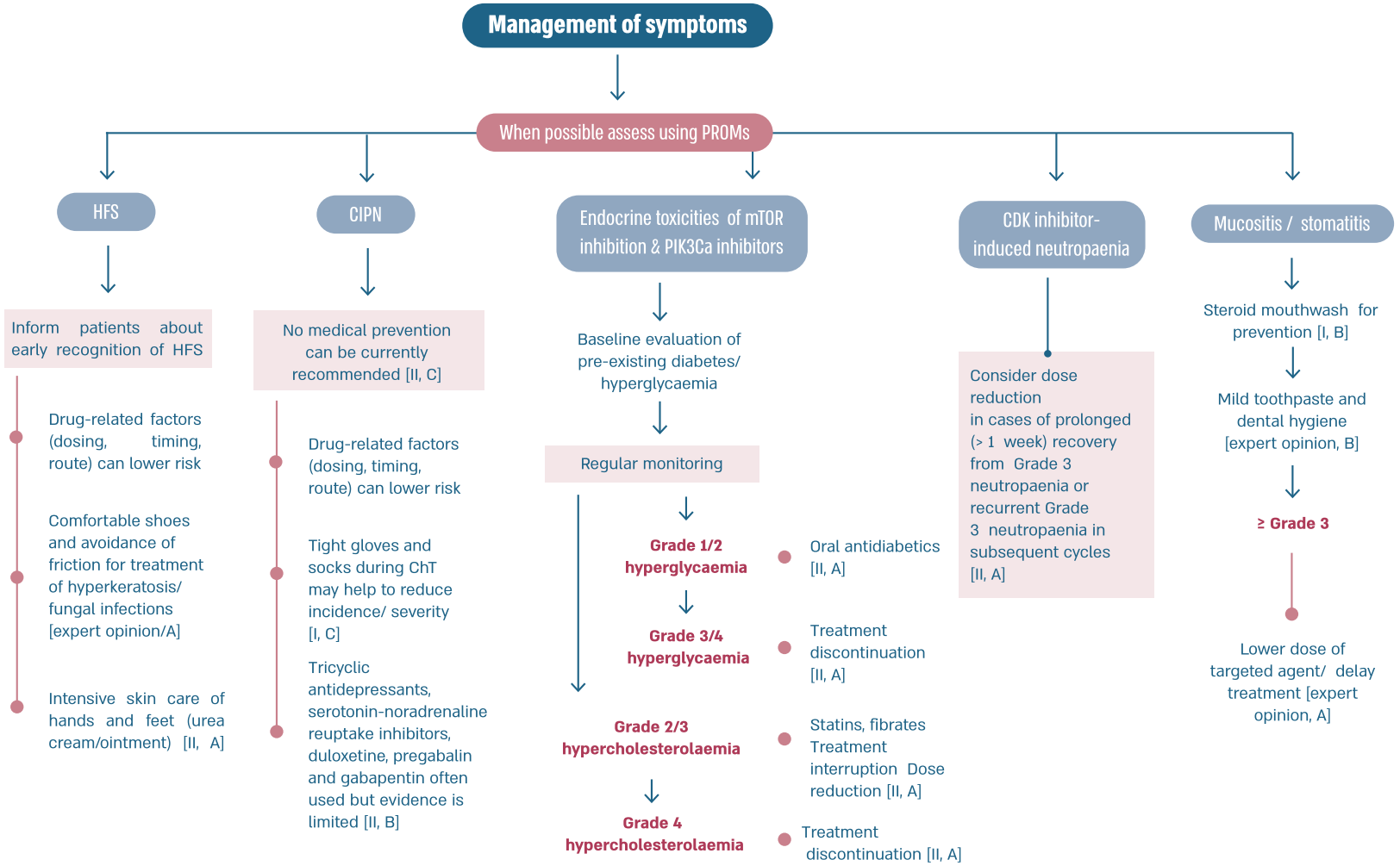

Fig. 6c. ABC Symptom control.
Legend: ABC, advanced breast cancer; CIPN, chemotherapy-induced peripheral neuropathy; HFS, hand and foot syndrome; mTOR, mammalian target of rapamycin; PROM, patient-reported outcome measure; CBT, cognitive behavioural therapy.

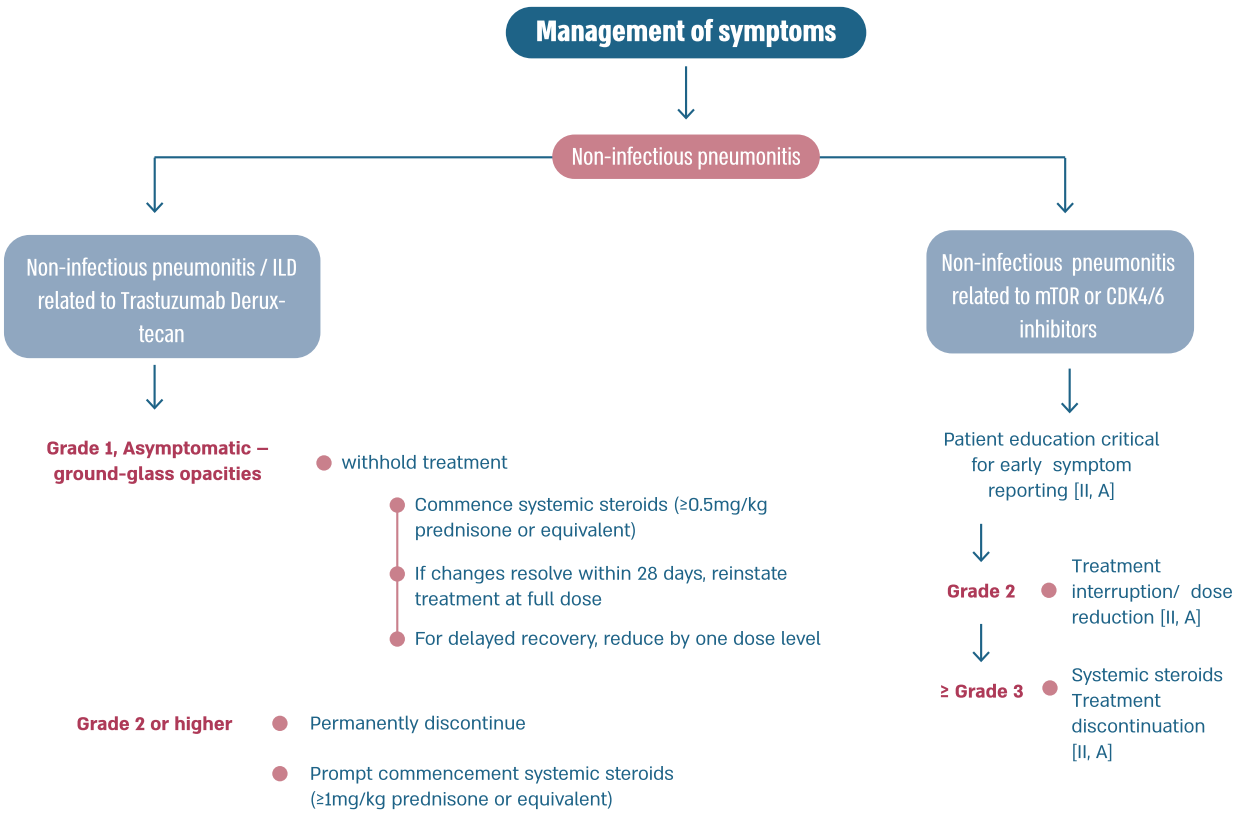

Fig. 6d. ABC Symptom control.
Legend: ABC, advanced breast cancer; ILD, interstitial lung disease; mTOR, mammalian target of rapamycin; CDK, cyclin-dependent kinase.

most expensive medicines is limited, a patient-centred approach, with careful balance between efficacy and toxicity, aiming at the longest survival with the best possible quality of life is not only achievable but also of paramount importance, and often cost-effective.

The level of evidence of each guideline is directly related to the quality of the research on the topic. Clinical trials in the field of advanced/metastatic breast cancer continue to exclude important subpopulations of patients, often the ones with the greatest unmet needs, and remain focused on endpoints that, albeit with some value, do not have the potential to dramatically change the outcomes of patients living with ABC. Only aiming higher, at improved survival and better quality of life, we will be able to transform this incurable disease into a chronic or even potentially curable one.

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