The Breast 90 (2026) 104921

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)

Fatima Cardoso [a,b,*], Joana Mourato Ribeiro [c], Eva Schumacher-Wulf [d], Sandra M. Swain [e], Shani Paluch-Shimon [f], Frederique Penault-Llorca [g], Nancy U. Lin [h], Prudence A. Francis [i], Marion Kuper-Hommel [j], Anne May [k], Florentine Hilbers [l], Angel Guerrero [m,n], Matti S. Aapro [o], Rania Azmi [p], Jyoti Bajpai [q], Carlos Barrios [r], Laura Biganzoli [s], Fran Boyle [t], Valeria Caceres [u], Lisa A. Carey [v], Mariana Chavez-MacGregor [w], Javier Cortés [x], Rebecca Dent [y], Amanda Drury [z], Nagi S. El Saghir [aa], Hesham Elghazaly [ab], Alexandru Eniu [ac], Lesley Fallowfield [ad], Sandra Ximena Franco Millan [ae], Karen Gelmon [af], Jenny Gilchrist [ag], Joseph Gligorov [ah], William J. Gradishar [ai], Nadia Harbeck [aj], Xichun Hu [ak], Orit Kaidar-Person [al], Ranjit Kaur [am], Belinda Kiely [an], Sung-Bae Kim [ao], Sarah Kutika Nyagabona [ap], Maryam Lustberg [aq], Volkmar Mueller [ar], Miriam Mutebi [as], Silvia Neciosup [at], Shinji Ohno [au], Barbara Pistilli [c], Hope S. Rugo [av], Tanja Spanic [aw], Janice Tsang [ax], Peter Vuylsteke [ay], Binghe Xu [az], Larry Norton [ba], Eric P. Winer [bb]

[a] ABC Global Alliance, Lisbon, Portugal
[b] Centre Antoine Lacassagne, Nice, France
[c] Gustave Roussy, Villejuif, France
[d] Mamma Mia, Kronberg, Germany
[e] Georgetown University Lombardi Comprehensive Cancer Center and MedStar Health, Washington, USA
[f] Hadassah University Hospital - Sharett Institute of Oncology and Faculty of Medicine, Hebrew University, Jerusalem, Israel
[g] Centre Jean Perrin, Université Clermont Auvergne, INSERM, U1240 Imagerie Moléculaire et Stratégies Théranostiques, Clermont Ferrand, France
[h] Dana-Farber Cancer Institute, Boston, USA
[i] Peter MacCallum Cancer Centre Melbourne, Australia
[j] Te Whatu Ora-Health New Zealand, Te Manawa Taki, Waikato District, Hamilton, New Zealand
[k] University Medical Center Utrecht, Netherlands
[l] Netherlands Cancer Institute, The Netherlands and AURORA Steering Committee, Amsterdam, Netherlands
[m] Instituto Valenciano de Oncologia, Valencia, Spain
[n] AURORA Steering Committee, Valencia, Spain
[o] IMO Clinique de Genolier, Institut Multidisciplinare d'Oncologie, Genolier, Switzerland
[p] Fadia Survive & Thrive, Salmiya, Kuwait
[q] Tata Memorial Hospital, Mumbai, India
[r] Centro de Pesquisa em Oncologia, Hospital São Lucas, PUCRS and Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil
[s] Department of Oncology, Hospital of Prato, Azienda USL Toscana Centro, Prato, Italy
[t] The Pam McLean Centre, Royal North Shore Hospital, St. Leonards, Australia
[u] Instituto de Oncología "Ángel H. Roffo", Buenos Aires, Argentina
[v] UNC Lineberger Comprehensive Cancer Center, Chapel Hill, USA
[w] The University of Texas MD Anderson Cancer Center, Houston, USA
[x] International Breast Cancer Center (IBCC), Madrid and Barcelona, Spain
[y] National Cancer Center Singapore, Singapore
[z] Trinity Centre for Healthcare Practice and Innovation, School of Nursing and Midwifery, Trinity College Dublin, Ireland
[aa] NK Basile Cancer Institute American University of Beirut Medical Center, Beirut, Lebanon
[ab] Breast and Gynaecological International Cancer Society, Cairo, Egypt
[ac] Breast Center, Genolier Cancer Center, Genolier, Switzerland
[ad] Sussex Health Outcomes Research & Education in Cancer, Brighton & Sussex Medical School, University of Sussex, Brighton, UK
[ae] CTIC Cancer Treatment and Research Center, Bogotá, Colombia

* Corresponding author. Advanced Breast Cancer (ABC), Global Alliance and Centre Antoine Lacassagne, 33 Avenue de Valombrose., Cedex 2, 06189, Nice, France.
E-mail address: fcardoso@abcglobalalliance.org (F. Cardoso).

https://doi.org/10.1016/j.breast.2026.104921
Received 8 September 2026; Accepted 10 September 2026
Available online 17 September 2026
0960-9776/© 2026 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[af] British Columbia Cancer Agency, Vancouver, Canada
[ag] Macquarie University, Sydney, Australia
[ah] Cancer Est APHP Tenon, University Paris VI, Paris, France
[ai] Robert H. Lurie Comprehensive Cancer Center and Northwestern University Feinberg School of Medicine, Chicago, USA
[aj] Breast Centre, University of Munich, Munich, Germany
[ak] Fudan University Shanghai Cancer Center, Shanghai, China
[al] Sheba Medical Center, Ramat Gan and Gray Faculty of Medical & Health Sciences, Tel Aviv University, Israel
[am] National Cancer Society Malaysia (NCSM), Kuala Lumpur, Malaysia
[an] NHMRC Clinical Trials Centre, Sydney Medical School, Sydney, Australia
[ao] Asan Medical Centre, University of Ulsan College of Medicine, Seoul, Republic of Korea
[ap] Muhimbili National Hospital, Dar es Salaam, Tanzania
[aq] Yale Cancer Center, New Haven, USA
[ar] University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[as] Aga Khan University, Department of Surgery, Nairobi, Kenya
[at] National Institute of Neoplastic Diseases, Lima, Peru
[au] Sagara Hospital, Kagoshima, Japan
[av] City of Hope Comprehensive Cancer Center, San Francisco, USA
[aw] Europa Donna Slovenia, Ljubljana, Slovenia
[ax] The University of Hong Kong, Hong Kong Special Administrative Region of China
[ay] CHU Brugmann Hospital, Brussels, Belgium
[az] National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China
[ba] Memorial Sloan-Kettering Cancer Centre, New York, USA
[bb] Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA

ARTICLE INFO

Keywords:
ABC
MBC
Advanced
Metastatic
Breast cancer
Guidelines
Consensus

ABSTRACT

The Advanced Breast Cancer (ABC) 8th international consensus conference took place on 6-8 November 2025, in Lisbon, and updated the previous ABC international consensus guidelines that are described in this manuscript. These guidelines reflect the work of a large and global consensus panel, comprising healthcare professionals and patients, and provide recommendations on how to best manage patients with advanced breast cancer (inoperable locally advanced or metastatic), of all breast cancer subtypes. The guidelines are based on the best available evidence or on expert opinion when a higher level of evidence is lacking and aim to cover the needs of the person living with ABC, including but also beyond the main therapeutic recommendations. Each guideline is accompanied by the level of evidence (LoE), the grade of recommendation (GoR), and the percentage of consensus reached at the consensus session. Updated diagnostic and treatment algorithms are also provided. These guidelines are endorsed by several international oncology organizations (AGO, AORTIC, ECO, EONS, ESO, ESTRO, EUSOMA, GECO Perú, SUMA, MASCC, French Breast Cancer Guidelines and AMAAC) and have official representation from ASCO, NCCN and ABC-NZ.

Inequalities in access to high-quality care have increased in the last decade, both between and within countries, and are a major concern. The ABC guidelines provide guidance on the best available management options for patients living with ABC globally, assuming availability of the recommended therapies. Their adaptation is often needed in resource-constrained settings, and the grading of each recommendation may help in prioritizing access to available options.

1. Introduction

The Advanced Breast Cancer (ABC) International Consensus Conference is the major international conference for advanced breast cancer and was created, in 2011, to address the unmet needs of patients living with ABC and to contribute to improving their outcomes. The main objective of the conference is the development of the international consensus guidelines for the management of advanced breast cancer, known as the ABC Guidelines. These unique guidelines are co-developed by breast cancer experts and patients living with ABC, originating from the main regions of the world, including high-, middle- and low-income countries. They are based on the most recent scientific evidence and aim to guide management decision-making for patients living with ABC globally. In view of the growing problem of inequities in access to high-quality cancer care [1], in resource-constrained settings, adaptations of the guidelines are often needed. The classification of each recommendation with the level of evidence (LoE), the grade of recommendation (GoR) and the percentage of consensus reached at the consensus session may serve as a tool to help prioritize access to the therapies providing the biggest clinical benefit for most patients.

The conference and guidelines started as a pioneering project from the European School of Oncology (ESO) [2] and from its 2nd to 5th edition [3–6], it was developed in collaboration with the European Society of Medical Oncology (ESMO). From 2021, both conference and guidelines are 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 310 members in over 120 countries worldwide [7].

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 (*de novo)* MBC. Advanced/metastatic breast cancer is still an incurable disease for the vast majority of patients. However, important advances took place in the last decade, as described in detail in the ABC Global Decade Report 2015-2025 [8,9], which highlights the substantial improvement in median overall survival (OS) for two of the three ABC subtypes (HER-2+ ABC and estrogen receptor positive/HER2 negative ABC), only if access to the best available therapies (systemic and loco-regional) as well as high quality diagnostics, multidisciplinary care and treatment according to guidelines exists.

The 8th International Consensus Conference for Advanced Breast Cancer (ABC8) was held in a hybrid format in Lisbon, on 6-8 November 2025, drawing 1200 participants from 84 countries. The ABC8 guidelines are endorsed by several international oncology organizations, such as Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO), African Organization for Research and Training in Cancer (AORTIC), 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), Grupo de Estudios Clínicos Oncológicos del Perú (GECO Perú), Grupo Cooperativo Argentino para el Estudio y la Investigación del Cáncer de Mama (SUMA), Multinational Association of Supportive Care in Cancer (MASCC), Cours St. Paul (French Breast Cancer Guidelines) and Arab Medical Association Against Cancer (AMAAC), and have additional official representation from the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and Advanced Breast Cancer New Zealand Guidelines (ABC-NZ). The ABC8 conference was endorsed by or run under the auspices of AGO, AORTIC, ECO, EONS, ESO, European Society for Surgical Oncology (ESSO), ESTRO, EUSOMA, MASCC, Organisation of European Cancer Institutes (OECI), Cours St Paul, SUMA, and Union for International Cancer Control (UICC), and was held with support from the Breast Cancer Research Foundation (BCRF).

This manuscript describes the guidelines developed at ABC8. Each guideline statement is accompanied by the LoE, GoR, percentage of consensus reached at the conference, and supporting references. Updated diagnostic and treatment algorithms are also provided, as well as slides with all available recommendations for educational and training purposes.

2. Methodology

The ABC8 conference was held face-to-face, and the methodology used in previous ABC consensus guidelines was followed. Before the conference, preliminary new recommendation statements on the management of ABC were prepared based on available published and presented data. These recommendations were circulated by email to the 49 ABC8 panel members, for comments and revisions on content and wording. A final set of recommendations was presented, discussed, and voted upon during the live consensus session at ABC8, with wording revised as needed before voting.. Additional changes in the wording of statements were made during the session. Following the presentation of new important data at the San Antonio Breast Cancer Symposium (SABCS) 2025, additional changes were made to some of the recommendation statements and new recommendations were developed based on data from ASCENT-07, EPIK-B5, HER2CLIMB-05 and DESTINY-Breast11 trials. These new statements and the revised ones were circulated among panelists for comments and for voting.

All the 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'.

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 ABC8 live consensus session are discussed in detail. We refer the reader to the previous ABC manuscripts for the detailed explanation of the other guidelines [2–6,10]. Supplementary Table 1, describes the LoE and GoR system used [11]. The percentage of consensus was calculated as ratio of "yes" over total number of votes (abstentions were not excluded). In resource-limited settings, where prioritization is usually necessary, GoR generally takes precedence over consensus percentage, while percentage of consensus is particularly useful when LoE is low.

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 **PREMISES** • **Endocrine resistance is a continuum and is a very complex, not yet fully understood biological phenomenon.** • **These definitions may be helpful for clinical trials but not necessarily for clinical practice; they are general guidelines and are not truly distinct categories. Pragmatically, they can be associated with the likelihood of ET-clinical benefit spectrum.** • **This classification assumes compliance to prescribed ET-based therapies.** • **This classification of levels of endocrine resistance has mostly prognostic value. Some biomarkers that predict resistance have both prognostic and predictive value (e.g. *ESR1*, *PIK3CA*).** • **A given mechanism of resistance can occur in any of the types of endocrine resistance.** • **In general, when resistance occurs, a change in the mechanism of action of the endocrine +/- targeted treatment is recommended; a possible exception is when relapse occurs 12 months or more after completion of adjuvant ET, when the same ET or the same targeted agent can be reused.** **PRIMARY ENDOCRINE RESISTANCE is defined as:**	III/B	95%
1) Relapse while on the first 2 years of adjuvant ET; or **2) PD within the first 6 months of 1st line ET-based therapy for ABC.** **This definition is the same regardless of whether therapy included a CDK4/6i or not. It is associated with a lower likelihood of ET-based therapy clinical benefit.** **SECONDARY or ACQUIRED ENDOCRINE RESISTANCE is defined as:** **1) All other clinical situations of endocrine-resistance.** **This definition is unaffected by therapy with CDK4/6i, mTOR/PI3Ki, or other adjunctive drugs.** **EARLY ACQUIRED: 1) Relapse while receiving adjuvant ET but after at least 2 years; or 2) PD after at least 6 months but less than 12 months of 1st line ET-based therapy for ABC. It is associated with an intermediate likelihood of ET-based therapy clinical benefit.** **LATE ACQUIRED: 1) Relapse after 12 months of completing adjuvant ET; or 2) PD after at least 12 months of 1st line ET-based therapy for ABC. It is associated with a higher likelihood of ET-based therapy clinical benefit.** **ET NAÏVE: unknown if there is sensitivity or resistance to endocrine therapy (ET) since has never received ET (for example, de novo tumors). The likelihood of ET-based clinical benefit is unknown.** **ENDOCRINE INSENSITIVITY is defined as:** **PD within ≤ 3 months of any line of ET-based therapy for ABC.** **In this case, the next line of therapy probably should not be ET-based, unless a targetable alteration is identified that would support combining a targeted agent, not previously used, with further ET.** **The decision regarding use of ET-based vs a cytotoxic agent should take into consideration multiple factors, namely symptoms, burden of disease and patient's preferences.** **In later lines ET-based therapy can be used again.** **It is associated with a very low likelihood of ET-based clinical benefit.**	Expert Opinion/NA	93%

Patients with multiple chronic conditions are defined as patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease, poorly controlled metabolic diseases), 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).	I/A	85%
If an LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS.	II/B	85%
It is recommended to initially confirm the efficacy of OFS analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered.	Expert opinion/B	85%
As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires a balance of the patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression and cost.		
Maintenance therapy: in the context of ABC guidelines, maintenance therapy refers to the continuation of anti-HER2 therapy, immunotherapy and/or ET-based 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 8 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 [71].

2.1.1. *New endocrine resistance definition*

The endocrine resistance definition was again revisited and, this time, in collaboration with the AURORA Molecular Screening Initiative, based on new data.

Endocrine resistance is a continuum and a complex biological phenomenon that is not yet fully understood. The definitions presented in this guideline are primarily intended to support the design of clinical trials by facilitating the inclusion of patients with comparable prognoses. They are less helpful for routine clinical decision-making, as they are general guidelines that do not represent truly distinct categories. Pragmatically, they can be linked with the anticipated spectrum of clinical benefit from endocrine therapy. It is important to retain that endocrine sensitivity/resistance is a continuum.

Although some biomarkers, such as mutations in *ESR1* or *PIK3CA*, may hold both prognostic and predictive value, the classification of endocrine resistance presented here should be regarded as mostly prognostic. A given mechanism of resistance can occur in any of the endocrine resistance categories.

In general, when resistance emerges, switching the mechanism of action of endocrine therapy, with or without adding targeted treatment, is recommended. A possible exception is relapse occurring twelve months or more after completion of adjuvant endocrine therapy, in which case the same endocrine therapy or targeted agent may be reused.

The definition of **endocrine therapy naïve** includes patients who have not previously received endocrine therapy, such as those presenting with *de novo* metastatic breast cancer. In these patients it is unknown whether the disease is sensitive or resistant to endocrine therapy, and thus the likelihood of clinical benefit for an individual patient cannot be predicted. As a group, however, endocrine therapy naïve patients have a relatively high likelihood of deriving clinical benefit from endocrine therapy-based treatment [12].

In patients with prior exposure to endocrine therapy, some degree of endocrine resistance is frequently present. Since the last ABC guideline update, additional data have improved our understanding of how specific patterns of endocrine therapy exposure influence prognosis and response to subsequent endocrine therapy-based treatment. This emerging evidence has guided the refinement of the endocrine resistance definitions outlined below. This classification assumes compliance with prescribed endocrine therapy-based therapies and is unaffected by adjunctive treatment with other drugs, such as CDK4/6, mTOR or PI3K inhibitors.

Primary endocrine resistance is defined as relapse while on the first two years of adjuvant endocrine therapy for early breast cancer, or progressive disease within the first six months of first line endocrine therapy-based treatment for advanced breast cancer. It is associated with a lower likelihood of clinical benefit from subsequent endocrine therapy-based treatment [12–14].

Secondary or acquired endocrine resistance encompasses all remaining clinical situations of endocrine resistance. Data from observational and exploratory studies support the definition of two subgroups with different outcomes on subsequent endocrine therapy lines.

The first subgroup, **early acquired endocrine resistance**, includes relapse while receiving endocrine therapy but after the first two years, relapse within one year of completing adjuvant endocrine therapy, or progressive disease occurring after at least six months, but less than twelve months, of first line endocrine therapy-based treatment for advanced breast cancer. This subgroup is associated with an intermediate likelihood of clinical benefit from further endocrine therapy-based treatment [12–15].

The second subgroup, **late acquired endocrine resistance**, is defined as relapse more than twelve months after completing adjuvant endocrine therapy, or progressive disease after at least twelve months of first line endocrine therapy-based treatment for advanced breast cancer. This subgroup is associated with a higher likelihood of clinical benefit from subsequent endocrine therapy-based treatment [12,14,15].

Endocrine insensitivity is a more clinically oriented definition,

defined as progressive disease within three months of any line of endocrine therapy-based treatment for advanced breast cancer. It is associated with a very low likelihood of clinical benefit from further endocrine therapy-based approaches. Therefore, the next line of treatment should generally not rely on endocrine therapy, unless a targetable alteration is identified that would justify the use of a previously unused targeted agent in combination with endocrine therapy.

When choosing between endocrine therapy-based treatment and cytotoxic agents, multiple factors, such as symptoms, disease burden and patient's preference, should be taken into account.

Even if a choice is made to initiate cytotoxic therapy (traditional chemotherapy or antibody-drug conjugates), it is possible, and often advisable, to reconsider endocrine therapy-based therapies in later treatment lines..

2.2. *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%

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.

2.3. Section III: General guidelines (see Fig. 1)

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, palliative care specialists, pharmacologists/pharmacists) 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 almost always 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%
The ABC consensus panel endorses the ABC Global Charter for 2025-2035: Goal1: Further improve SURVIVAL in people with ABC by doubling median overall survival. Goal 2: Optimize care and outcomes for people with ABC by collecting HIGH-QUALITY DATA. Goal 3: Improve the QUALITY OF LIFE of people with ABC. Goal 4: Ensure that every person with ABC is treated and cared for by a specialized MULTI-DISCIPLINARY team according to high-quality GUIDELINES. Goal 5: Improve COMMUNICATION between healthcare professionals and people with ABC and their caregivers. Goal 6: Meet the INFORMATIONAL needs of patients with ABC. Goal 7: Ensure all people with ABC have access to comprehensive, person-centered SUPPORT SERVICES. Goal 8: Reduce MISCONCEPTIONS, STIGMA, and ISOLATION by improving understanding of ABC. Goal 9: Improve ACCESS to comprehensive CARE for people with ABC, regardless of their ability to pay. Goal 10: Improve the LEGAL RIGHTS of people with ABC, including the right to continue or return to WORK.	Expert opinion/A	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	100%
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. 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.	Expert opinion/A	98%
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	Expert opinion/NA	96%
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.		
The panel expressed that particular attention needs to be given to clinical trial designs in order to optimize progress in the management of ABC. The panel wished to emphasize the following issues: • Concern about the growing number of clinical trials with inappropriate and inadequate control arms • Concern that inequitable availability of subsequent standard-of-care therapies is skewing outcomes, making the generalizability of results for all geographical regions questionable • The importance and unwavering support for use of cross-over options in clinical trials • The necessity of using appropriate measures of HRQoL and PROMs that provide data that are meaningful for patients • The need to collect post-progression data, to understand the efficacy of an agent after another • The need to collect post-progression data in adjuvant trials, to understand if an agent used in the (neo)adjuvant setting retains its efficacy in the metastatic setting.	Expert opinion/A	98%
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 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, denosumab) 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%
Clinical studies support the benefit of ***structured exercise*** *as a safe, beneficial, and evidence-based component of advanced breast cancer management. Regular, supervised physical activity improves physical function, reduces treatment-related fatigue, enhances quality of life, and positively affects symptoms such as pain and dyspnea. Additionally, exercise has been shown to help maintain muscle mass, improve cardiovascular health and sexual function, and may positively influence treatment tolerance and overall outcomes.* Structured and tailored exercise should be incorporated into comprehensive ABC care. Ideally, the exercise program should be supervised, when the necessary resources are available. Exercise programs need to be tailored for the patients' disease burden, site of metastases and physical limitations. Patients with skeletal metastases should have stable bone disease and no known impending fractures when engaging in an exercise program.	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; • Some SSRIs and CDK4/6i – increased risk of arrhythmia; • 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	Expert Opinion/B	100%

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.		
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 of comorbidities other than ABC.	Expert Opinion/B	100%
Artificial Intelligence is not synonymous with evidence-based medicine and therefore cannot replace rigorous evidence-based medicine. Artificial intelligence systems should only be integrated into the clinical setting if they are evidence-based, quality controlled, validated and approved. Artificial Intelligence may support, not replace, shared decision making by oncologists and patients with ABC. Artificial intelligence can be an information enabler however, must be used with caution.	Expert opinion/A	98%

In green, NEW/UPDATED ABC 8 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.

2.3.1. The ABC Global Charter for 2025-2035

The ABC Global Alliance was created in 2016, building upon the work of the ABC International Consensus Conferences and Guidelines. A multistakeholder organization, with more than 310 member organizations in over 120 countries, has the mission and vision of improving and extending the lives of women and men living with advanced/metastatic breast cancer worldwide and to fight for a cure. In 2025, the Global Status of ABC/MBC Decade Report 2005–2015 was published [9], highlighting critical gaps in patient care, scientific research and overall support for patients living with this disease. It also raised major issues related to inequalities in diagnosis and treatment, inadequate data collection and stigma and isolation faced by these patients. The findings of this report formed the basis for the development of the first ABC Global Charter for the decade 2015-2025, which defined ten objective and measurable goals aimed at transforming ABC care and substantially improving the outcomes of these patients [9]. This charter, developed by a range of different stakeholders including patients living with ABC and advocates, has guided much of the work developed in this field in the last decade. As the decade reached its end, a new **Global Decade Report 2015-2025** was produced and published, summarizing the key advances and remaining gaps for each of the ten goals. While important progress has been made, including the doubling of the median overall survival for two of the three ABC subtypes, the disease remains incurable for the vast majority of patients and inequities in access to the best diagnostic and therapeutic options and to high quality, multidisciplinary, evidence-based care have increased in the last decade. The divide (gap, inequalities) has increased not only between high-income countries and low- and middle-income countries but also within each country, with underserved populations increasing in virtually all high-income countries. Based on the findings of this 2nd global report, a new ABC Global Charter for the next decade was developed [9]. The ABC8 consensus panel endorses the **ABC Global Charter 2025-2035** and emphasizes its role as a key awareness, advocacy and lobbying tool to fight for the rights and unmet needs of all patients living with ABC worldwide.

2.3.2. Special considerations for clinical trials

With a growing body of therapies under development and an abundance of clinical trial data being generated, extra vigilance is required by the discerning clinician when interpreting new study results and as a research community we need to continue to align expectations between academia, pharmaceutical companies and regulatory bodies about planning, execution and presentation of trials and trial results.

We strongly encourage investigators to support crossover trial designs for the ultimate outcome evaluation, even though this may make interpretation of study survival outcomes more complex. When comparing studies evaluating similar agents, we must be prudent that we take these factors into consideration when deeming whether or not a drug does or does not provide OS benefit. We need to ensure that the

comparator arms include a true standard of care arm as is current at the time of study initiation. Failure to do so renders study interpretation hypothesis generating at best, and at worst uninterpretable.

As a community we should not accept outcome results that have deviated from preplanned statistical design to be presented in important forums in leading scientific symposiums. By doing so we mislead the audience and infer that statistical design is disposable if an impressive enough ad-hoc analysis is generated. Importantly, while unplanned findings may be hypothesis generating, they also have a higher risk of being chance findings.

The generalizability of clinical trial findings must be considered in the context of the populations enrolled. Trial participants are often highly selected with respect to performance status, comorbidities and disease characteristics, and may not reflect the broader population encountered in routine clinical practice. Greater inclusion of patients with adverse prognostic features, including active brain metastases, leptomeningeal disease, ECOG performance status 2-3, older age, and rapidly progressive or early relapsing disease, should be encouraged. Where such populations are under-represented or excluded, the applicability of trial findings to these patients should be interpreted with appropriate caution.

The interpretation of an OS benefit should also take into account the geographic context of the study and the availability of effective post-progression therapies across participating regions. Differences in access to subsequent standard-of-care treatments may influence survival outcomes and potentially affect the magnitude of the observed treatment effect. Assessment of OS should therefore consider whether benefit was consistent across geographic subgroups or disproportionately influenced by regions in which access to established post-progression therapies was limited.

Assessment of treatment-related toxicity should extend beyond the frequency and severity of clinician-reported adverse events. Rates of treatment discontinuation due to toxicity should be considered alongside patient-reported outcomes (PROs) and validated measures of health-related quality of life, including the specific domains assessed and the completeness of their reporting. The availability of evidence to guide the recognition, prevention and management of novel toxicities is also important, particularly following the introduction of new therapeutic agents, when clinical experience with less familiar adverse effects may initially be limited.

Post-progression treatment data provide essential context for the interpretation of trial outcomes within an increasingly complex and rapidly evolving therapeutic landscape. This is particularly relevant in studies that do not permit crossover, where subsequent therapies may influence OS results. We therefore advocate for the systematic collection and reporting of post-progression treatment data, including the number, type and, where possible, sequence of subsequent therapies received.

We recommend caution regarding the use of PFS2 as an endpoint, unless clearly defined in the protocol as a prospectively ascertained endpoint.

Collectively, these factors, including trial population representativeness, access to post-progression therapies, toxicity, quality of life and subsequent treatment patterns, should be considered when determining the ESMO? Magnitude of Clinical Benefit Scale (ESMO-MCBS) score. Incorporating these considerations may reduce the risk of either overestimating or underestimating the clinical value of a therapy within a particular treatment setting.

2.3.3. Structured exercise in advanced breast cancer management

Clinical evidence supports structured exercise as a safe and beneficial component of ABC management. The multinational PREFERABLE-EFFECT randomized controlled trial demonstrated that individualized, supervised exercise in patients with MBC significantly reduced physical fatigue and improved HRQoL, with additional gains in physical and social functioning and reductions in pain and dyspnea scores at six months [16,17]. Beyond symptom management, systematic reviews confirm that exercise improves physical function, preserves muscle mass and strength, and enhances cardiovascular health - including improvements in VO2 peak and blood pressure - outcomes of particular importance given the cardiotoxic burden of many ABC treatments [18,19]. Exercise has also been shown to help counteract sarcopenia, which affects up to 32.5% of breast cancer patients and negatively impacts treatment tolerance [20,21]. As confirmed in the PREFERABLE-EFFECT study, regular physical activity positively influences sexual function and intimacy - domains frequently compromised by endocrine hormonal therapies and systemic treatment in this population [22]. In addition, the incorporation of exercise into cancer care reduced healthcare utilization and costs and showed a high probability of being cost-effective [23]. It resulted in fewer hospitalizations, reduced treatment-related complications, and lower expenditure related to managing fatigue and functional decline [24]. Given this broad extent of evidence, structured and tailored exercise should be recommended and incorporated into comprehensive ABC care, ideally under the supervision of qualified exercise professionals when resources permit. For patients with skeletal metastases, the International Bone Metastases Exercise Working Group recommends that exercise prescription account for lesion location and presentation, with participation limited to those with stable (i.e. not at risk for fracture) bone disease and no impending fractures — a framework supported by safety data from the PREFERABLE-EFFECT trial, in which no exercise-related skeletal complications occurred [25].

2.3.4. Artificial intelligence

The ABC8 panel recognizes the growing impact of artificial intelligence in oncology but considers that its current role should be to support, rather than replace, clinical decision-making. Artificial intelligence should serve as an information enabler, assisting clinicians in synthesizing increasingly complex clinical information and facilitating treatment discussions. Final therapeutic decisions should always remain the responsibility of the multidisciplinary team and be made in partnership with informed patients, considering individual clinical circumstances, patient preferences, values and goals of care.

Future artificial intelligence systems should be prospectively validated in diverse patient populations and evaluated for predictive accuracy and for their impact on clinical outcomes, health equity, patient trust, and healthcare resource utilization.

2.4. Section IV: Assessment and treatment general guidelines (see Fig. 2)

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.	I/C	Yes – 42% No – 53%

ABC: advanced breast cancer; ChT: chemotherapy; *BRCA*: BReast CAncer gene; CM: cyclophosphamide/methotrexate; DFI: disease-free interval; 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.

2.5. *Section V: ER-positive/HER2-negative (luminal-like) ABC (see Figs. 3a, 3b, and 3c)*

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%
We recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA), throughout the entire course of metastatic disease, and then be treated in the same way as post-menopausal 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 pre-menopausal women who decline ovarian suppression or ablation (OFS/OFA) but is a less effective option.	I/C	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 aromatase inhibitor, 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 endocrine therapy is the standard of care for patients with ER+/HER-2 neg ABC, since it very substantially increases OS, as well as PFS and either maintains or improves QoL. The CDK4/6 inhibitor can be combined with an AI or with fulvestrant (tamoxifen can not be combined with ribociclib but can be combined with abemaciclib or palbociclib), in de novo or recurrent ABC, in 1st or 2nd line, and in cases of primary or secondary resistance (as defined per ABC guidelines).	I/A	97%
This recommendation applies to post-menopausal women, to premenopausal women in combination with an LHRH agonist, and to men preferably in combination with an LHRH agonist.		
The SONIA trial explored 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 significant differences were seen in PFS 2 (primary endpoint) nor OS nor QoL, although for some comparisons statistical significance cannot be claimed. In a post-hoc subgroup analysis, premenopausal patients seem to derive bigger benefit from the use of CDK4/6i in 1st line. 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 post-menopausal patients (e.g. low volume of disease, long DFI, patient preferences, accessibility constraints, very frail patients) with this ABC subtype.	I/A	96%
For patients **who received a CDK4/6i in the adjuvant setting**, although there are no data from randomized clinical trials, the 1st line treatment options include the re-use of a CDK4/6i + ET, if the relapse occurred 12 months or more after the completion of the adjuvant CDK4/6i, provided the tumor remains ER+ at relapse and in the absence of visceral crisis.	Expert Opinion/B	96%
For patients, whose relapse occurs within the first 12 months of completion of adjuvant CDK4/6i or during this treatment, re-use of a CDK4/6i is not a preferred approach. Another ET-based strategy, based upon the biomarker status of the tumor (e.g. *ESR1mut, PIK3CA mut, AKT/PTEN* alterations) and/or BRCA status is recommended, unless there is a visceral crisis, where a cytotoxic agent may be the best option.	Expert Opinion/B	72%
There are no data comparing a combination of CDK4/6 inhibitor and ET vs. ET alone as maintenance therapy after chemotherapy, for ER+/HER-2 negative ABC. 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 in one relatively small phase 3 trial (postMONARCH), that has shown a difference of 0.7 months in median PFS (6.0 vs 5.3 months) and a HR of 0.73, in favor of abemaciclib + fulvestrant vs fulvestrant alone.	II/C	92%

In view of the limitations of the control arm (ET alone, instead of ET + a different targeted agent) and the availability of other treatment options, the use of a CDK4/6i after progression on a CDK4/6i is a less preferred option, unless there are no other targeted agents available to combine with ET and the prior treatment duration on CDK4/6i was longer than 12 months. In case it is used, it is advisable to change both the CDK4/6i and the endocrine agent.		
Several trials (including PEARL, Young-PEARL, PADMA, RIGHT-CHOICE, AMBRE) comparing different combinations of endocrine + CDK4/6i with ChT, in the 1st and later lines settings. In view of the substantial benefit seen with ET + CDK4/6 inhibitors in 1st line, not seen with chemotherapy, this combination is considered the standard of care for 1st line therapy of ER+/HER2 negative ABC, for the vast majority of patients.	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%
***Inavolisib** combined with palbociclib and fulvestrant was compared to palbociclib and fulvestrant, as 1st line treatment of **ER+/HER-2 neg/PIK3CAmut ABC [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women]**, progressing during or within 12 months of adjuvant ET completion (INAVO 120 trial) and showed a benefit of 9.9 months in median PFS (17.2 vs 7.3 months) and a HR: 0.42, as well as a benefit of 7 months in median OS (34 vs 27 months) with a HR: 0.67. Of note, no patients had received adjuvant CDK4/6i.* These results make this triple combination one of the preferred options for patients meeting the criteria of the INAVO 120 study, including the criteria for glycemic control. As with all *PIK3CA* inhibitors, careful monitoring and pro-active management of side effects (namely, hyperglycemia, rash, diarrhea, stomatitis) is warranted.	I/A	85%
*The strategy of switching AI to **camizestrant**, an oral SERD and complete ER antagonist, with continuation of CDK4/6i, guided by the emergence of ESR1 mutations during 1st line therapy ahead of disease progression by imaging was evaluated in the randomized phase 3 trial SERENA-6, in patients who received at least 6 months of AI+CDK4/6i [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women]. The switch to camizestrant led to an improvement of 6.2 months in median PFS (HR: 0.44). OS data is still pending. Toxicity profile was favorable, with neutropenia being the most frequent side effect, and there was an improvement in the time to deterioration of QoL.* In view of the lack of crossover to camizestrant in the control arm at the time of imaging progression, the clinical utility of serial ctDNA testing as a strategy for treatment modification without clinical progression is not yet determined and more information on long-term outcomes is needed before adoption. If approved, camizestrant may be used similarly to other approved oral SERDs.	 I/D I/C	 90% 100%
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 (Bolero-2 trial). Tamoxifen or fulvestrant can also be combined with everolimus.	I/B II/B	88% 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. **Everolimus** should not be used after disease progression on that agent (i.e. beyond progression), outside a clinical trial.	I/B NA/E	97% 74%
Alpelisib with fulvestrant is a treatment option for patients 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 (SOLAR-1 trial) [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women]. 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. In countries where less toxic *PIK3CA* targeting agents are available, alpelisib is a less preferred option. The value of a subsequent regimen targeting the *PI3K/AKT/PTEN* pathway either directly or some time after receiving a prior targeted drug against the same pathway requires investigation.	I/B	96%
Few patients previously treated with a CDK4/6 inhibitor were included in the Solar-1 trial. However, a non- randomized cohort study (ByLieve) seems to indicate that ***alpelisib*** *retains its efficacy if used after a CDK4/6 inhibitor.* 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.	I/B	93%
Alpelisib *with fulvestrant was evaluated as a treatment option for patients with ER+/HER-2 neg/ PIK3CA-mutant ABC, previously treated with ET + CDK4/6i and with ≤ 1 line of ChT in the metastatic setting, in the EPIK-B5 phase 3 trial* [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women]. *It provided 4.6 months benefit in median PFS (HR: 0.52); OS data is still immature (there was 40% of crossover) but the study is not powered to claim an OS benefit. These data confirm that alpelisib + ET retains its efficacy when given after a CDK4/6i + ET. The toxicity profile was similar to the one in the Solar-1 trial, with high rates of dose reductions, delays and discontinuations.*	I/B	96%
Alpelisib + fulvestrant is a treatment option for 2nd line, after CDK4/6i + ET. The decision to give alpelisib should take into consideration a careful balance between efficacy, toxicity and pre-existing conditions (i.e. diabetes & baseline HbA1c). Prophylactic measures and active management of side effects are crucial. In countries where less toxic *PIK3CA* targeting agents are available, alpelisib is a less preferred option.		
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%
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 (CAPItello-291 trial). 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). 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%
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; median PFS: 3.8 months) (EMERALD Trial). All patients were pretreated with CDK4/6 inhibitor and 22% received one of previous chemotherapy. [Data only available in post-menopausal women and men, but pre-menopausal women with*	I/C	94%

OFS/OFA should have access]. This 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. Elacestrant may also be combined with abemaciclib (median PFS: 14.2 months as ≥ 2nd line in the small phase 2 Elevate trial) or with everolimus (median PFS: 8.3 months as ≥ 2nd line in a small phase 2 Elevate trial).		
***Imlunestrant**, an oral SERD, as monotherapy (vs. endocrine SOC fulvestrant or exemestane) or combined with abemaciclib (vs. Imlunestrant) was evaluated in a randomized phase 3 trial, as 1st (if recurrence on or within 12 months of completion of AI ± CDK4/6i) or 2nd line (if progression on 1st line AI ± CDK4/6i) endocrine therapy for patients with ER+/HER2 negative ABC (EMBER-3 trial) [pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women]. About 60% of patients had previously received a CDK4/6i, about 40% ESR1mut and about 40% Pi3KCAmut. Imlunestrant monotherapy provided a 1,7 month difference in median PFS (HR: 0.62) over ET SOC, in ESR1mut tumors (primary endpoint) and no benefit in unselected patients. It also provided a 11,4 months benefit in OS (HR: 0.60) in ESR1mut tumors). Imlunestrant + Abemaciclib, compared to Imlunestrant monotherapy provided a 5.4 months difference in median PFS (HR: 0.59) in unselected patients (primary endpoint), and a 5.6 months difference in median PFS (HR: 0.49) in ESR1mut tumors. Imlunestrant was well tolerated, with fatigue and GI side effects being the most frequent. A limitation of this trial was the lack of comparison with ET SOC + abemaciclib. While imlunestrant monotherapy has received regulatory approval, the combination of imlunestrant and abemaciclib has not been approved.* Imlunestrant monotherapy is an option for patients with ER+/HER-2 neg *ESR1mut* ABC, in 1st (if recurrence on or within 12 months of completion of adjuvant AI ± CDK4/6i) or 2nd (if progression on 1st line AI ± CDK4/6i) line settings.	I/B	98%
***Vepdegestrant,** a PROTAC ER degrader, was compared, in a randomized phase 3 trial, to fulvestrant, as 2nd or 3rd line endocrine therapy for patients with ER+/HER2 negative ABC with an ESR1 mutation, all previously treated with a CDK4/6i and no prior ChT (VERITAC-2 trial). Vepdegestrant provided a 2.9 months median PFS advantage (HR: 0.57), with a very favorable toxicity profile. OS data is still immature.*	I/C	81%
If and where approved, vepdegestrant is an option for patients with ER+/HER-2 neg ESR1mut ABC, in the 2nd/3rd line setting.		
***Giredestrant**, an oral SERD, combined with everolimus was compared, in a randomized phase 3 trial, to SOC ET with everolimus, as 2nd or 3rd line endocrine therapy for patients with ER+/HER2 negative ABC, all previously treated with a CDK4/6i and no prior ChT (evERA trial). Giredestrant + everolimus provided a 4.5 months improvement in median PFS (HR: 0.38) in the ESR1mut population, and a 3,3 months difference in median PFS (HR: 0.56) in all patients. OS data is still immature. The combination of giredestrant + everolimus was associated with 47% stomatitis, without mandatory steroid-based mouthwash, which should be used. Bradycardia was seen in 3.8% of patients, all grade 1-2.* If and where approved, giredestrant + everolimus is an option for patients with ER+/HER-2 neg *ESR1mut* ABC, in the 2nd/3rd line setting.	I/B	87%
***Gedatolisib**, a multitarget PIK3CA/AKT/mTOR inhibitor, combined with fulvestrant with or without palbociclib, was compared, in a randomized phase 3 trial, to fulvestrant, as 2nd/3rd line endocrine therapy for patients with ER+/HER2 negative/PIK3CA wild-type ABC, progressing on or after ET + CDK4/6i and without ChT for ABC, with optional crossover in the control arm (VIKTORIA-1 trial). The triplet yielded a 7.3 months improvement in median PFS (HR: 0.24) and the doublet a 5.4 months improvement in median PFS (HR: 0.33) vs. fulvestrant alone. OS data is still immature. Stomatitis was seen in 69% and 56% of patients with the triplet and doublet, respectively. Other GI and hematological side effects were seen, while rates of hyperglycemia were low. Both gedatolisib regimens delayed time to definitive deterioration of well-being (EQ-5D-5L) vs fulvestrant.* Based on these results, gedatolisib + fulvestrant ± palbociclib is a treatment option, as 2nd /3rd line therapy for ER+/HER2 negative/*PIK3CA* wild-type ABC, if and where approved. Education, prophylaxis and active management of side effects is crucial. Of note, this protocol involves three modalities of administration (IV + IM + PO) possibly making it less appealing for some patients.	I/B	94%
There are no data on the use of a *PIK3CA/AKT/PTEN* inhibitor after progression on another *PIK3CA/AKT/PTEN* inhibitor and, therefore, this strategy is not recommended, outside clinical trials.	NA/D	96%

There are no data on the use of an oral SERD after progression on another oral SERD and, therefore, this strategy is not recommended, outside clinical trials.	NA/D	100%
There are little data on the best sequence of between *PIK3CA/AKT/PTEN* inhibitors and oral SERDs. In the cases where **a *PIK3CA/AKT/PTEN*-alteration and an *ESR1mut* co-exist**, any sequence of targeted-treatments is reasonable, balancing disease burden, toxicity and patient preferences	Expert Opinion/C	83%
Trastuzumab Deruxtecan (T-DXd) was compared to chemotherapy of physician's choice (60% capecitabine), in patients with HER-2 low ABC, treated with a median of 2 lines of ET-based therapy (90% prior CDK4/6i) and no chemotherapy in the metastatic setting (DESTINY-Breast 06 trial), and yielded a 5.1 months benefit in median PFS (HR: 0.62), in the phase 3 Destiny-Breast 06 trial. OS data is not yet mature. Only 17% of patients (76 in each arm) enrolled had HER-2 ultra-low ABC; in prespecified exploratory analyses, T-DXd led to a non-statistically significant improvement of median PFS. T-DXd is an option for patients with HER-2 low ABC, as 1st line cytotoxic therapy. Choice between T-DXd and other ChT options must balance efficacy, toxicity, burden of disease and patients' preferences. For patients with HER-2 ultra-low ABC more data is necessary before T-DXd can be recommended. 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 CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	 I/A I/C	 91% 53%
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 (Destiny-Breast 04 trial), 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. 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 CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/A	100%
Sacituzumab govitecan *was compared with mono-chemotherapy of physician's choice, as 1st line cytotoxic therapy, in patients with ER+/HER2 negative ABC, previously treated with ≥ 2 lines of ET ± targeted therapy in the metastatic setting or with disease progression < 6 months of starting 1L ET ± CDK4/6i or having recurrence <24 months of starting adjuvant ET + CDK4/6i and no longer a candidate for additional ET for ABC (ASCENT-07). Median PFS by BICR was 8.3 months in both arms (HR: 0.85, not statistically significant). The safety profile was similar to previous trials with sacituzumab govitecan.* Sacituzumab govitecan is not recommended as 1st line cytotoxic therapy for ER+/HER2 negative ABC.	I/E	96%
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 CT for metastatic disease (60% of pts have received 3 or more lines of CT) (TROPiCS-02 study). Results showed a 1.5 months improvement in median PFS and 3.2 months median OS, both in HER2 low and HER2 zero.* The OS benefit seen in this heavily pretreated population makes sacituzumab govitecan a treatment option for this patient population. Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, are crucial since fatal side effects were observed due to infections.	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 setting, who experienced progression on ET and for whom further ET was unsuitable (TROPION-Breast01 trial), and led to a 2 months improvement in median PFS (HR: 0.63) without improvement in OS. Stomatitis, ocular events (mostly dry eye), nausea, vomiting and fatigue were the most common side effects. ILD/pneumonitis was uncommon.* In view of the modest PFS difference, absence of OS data, side effect profile and availability of other treatment options, Dato-DXd in this setting is not a preferred option. Education and preventive measures (i.e. mouthwashes, anti-emetics) are recommended.	I/C	83%
There are very few data regarding the best ***sequence of administration of ADCs*** *for* ***ER+/HER2 low ABC****.*		

In view of the negative results of Ascent-07 trial and the totality of the available data, T-DXd is the preferred ADC to be used in this subtype of ABC, when the decision to give an ADC is taken. Given the absence of validated predictive biomarkers and the limited efficacy observed in real-world, unselected populations, routine sequencing of ADCs cannot currently be recommended. Prospective clinical trial data are needed to better define optimal sequencing strategies.	I/A Expert Opinion/C	98% 98%
*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. Comparative data between this combination and a CDK4/6 inhibitor with ET are not available.	II/D	Yes: 38% No: 60% Abstain: 2%
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, availability and, where accessible, *ESR1mutation* and *PIK3CA mutation* status. This applies to pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	100%
Options for treatment of ER positive disease in later lines include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megesterol acetate, low dose estrogen). 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 CT + ET has not shown a survival benefit and should not be performed outside a clinical trial, with the exception of LHRH agonist in pre-menopausal women to maintain OFS.	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 8 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.

The treatment landscape of ER-positive/HER2-negative ABC has continued to evolve since ABC7, with new phase 3 data informing the optimal sequencing of CDK4/6 inhibitor-based therapy, the role of novel endocrine and targeted agents, and the positioning of antibody-drug conjugates (ADCs).

Regarding the optimal timing of CDK4/6 inhibitor use, the randomized phase 3 SONIA trial — in which palbociclib represented 90% of CDK4/6 inhibitor use — found no statistically significant differences in PFS2 (primary endpoint), OS, or QoL when CDK4/6i-based therapy was administered in the first-versus second-line setting [26], although a post hoc subgroup analysis suggested a greater OS benefit from first-line CDK4/6i use in premenopausal patients, but not in postmenopausal patients. In view of the totality of evidence, including robust OS data from prior trials, the panel maintains CDK4/6i combined with ET as the standard first-line approach for the majority of patients, while acknowledging ET alone as an acceptable alternative for carefully selected patients (e.g., low disease burden, prolonged disease-free interval, significant comorbidities, patient preference, or access constraints).

With the increasing use of CDK4/6 inhibitors in the adjuvant setting (monarchE [27], NATALEE [28]), the management of patients relapsing after adjuvant CDK4/6i has become a clinically relevant challenge. In the absence of randomized data specifically addressing this setting, the panel recommends that patients relapsing 12 or more months after completion of adjuvant CDK4/6i may receive a CDK4/6i + ET as first-line therapy for ER-positive disease, in the absence of visceral crisis ; for those relapsing within 12 months or during adjuvant CDK4/6i, re-use of this drug class is not preferred, and an ET-based strategy guided by the tumor biomarker profile (*ESR1, PIK3CA, AKT/PTEN* alterations, *BRCA* status) is recommended, unless visceral crisis mandates cytotoxic chemotherapy.

The question of CDK4/6 inhibition beyond progression was previously addressed by three small phase 2 trials with conflicting results [29–31]. The first phase 3 data are now available from the post-MONARCH study [32], in which abemaciclib + fulvestrant demonstrated a statistically significant but modest PFS improvement over fulvestrant alone (HR 0.73) in patients with disease progression on a CDK4/6i + aromatase inhibitor, with OS remaining immature [32]. In view of the modest absolute benefit, the suboptimal control arm, and the availability of multiple biomarker-driven options in the post-CDK4/6i setting, the panel considers continued CDK4/6i beyond progression a less preferred strategy, reserving it for patients without access to other targeted therapies and in whom prior CDK4/6i benefit exceeded 12 months; when used, both the CDK4/6i and the endocrine agent should be changed.

Since the approval of elacestrant based on the EMERALD trial [33], the class of oral SERDs has expanded with new agents now supported by phase 3 evidence. Across this body of evidence, a consistent pattern emerges of modest absolute clinical benefit in *ESR1-mutated* tumors, with hazard ratios generally in the 0.55–0.62 range. In the EMBER-3 trial Imlunestrant demonstrated a clinically meaningful numerical improvement in OS in patients with *ESR1-mutant* tumors although the prespecified threshold for statistical significance was not met [34]. Camizestrant showed encouraging results in the SERENA-6 trial using a ctDNA-guided switch strategy upon emergence of *ESR1 mutations*, though the clinical utility of treatment modification without radiological progression remains to be established [35]. The oral route of administration and generally favorable tolerability of these agents represent meaningful advantages for patients, particularly compared to intramuscular fulvestrant. Rechallenge with one oral SERD after progression on another is not recommended outside clinical trials.

The *PI3K/AKT/mTOR* pathway inhibitor class has also been enriched with new data. The EPIK-B5 trial confirmed that alpelisib + fulvestrant retains meaningful activity after CDK4/6i-based therapy in *PIK3CA-mutated* disease (median PFS improvement of 4.6 months; HR: 0.52), consolidating this combination as a valid option in the absence of contraindications [36]. Inavolisib, a selective *PI3Kα inhibitor* and degrader, combined with palbociclib and fulvestrant, demonstrated remarkable efficacy in INAVO120 (9.9-month improvement in median PFS (HR: 0.42) and a 7-month OS benefit) [37,38], making this triple combination one of the preferred options for patients with *PIK3CA-mutated* disease recurring on or within 12 months of adjuvant ET (without prior adjuvant CDK4/6i). Gedatolisib, a multitarget *PI3K/AKT/mTOR* inhibitor, showed encouraging PFS results in the VIKTORIA-1 trial, but with a demanding administration schedule and significant stomatitis burden requiring careful management [39]. The use of a *PI3K/AKT/mTOR* inhibitor after progression on another agent of the same class is not recommended outside clinical trials.

As multiple targeted agents are now available following progression on a CDK4/6i, the optimal sequence remains undefined; until prospective comparative data are available, the eligibility criteria of individual trials and the tumor biomarker profile should guide treatment selection.

In the ADC landscape, DESTINY-Breast06 showed that T-DXd can be an option for patients with HER2-low disease when the decision to initiate cytotoxic therapy is made, now earlier in the treatment sequence, as first-line cytotoxic therapy after progression on endocrine therapy and for whom further endocrine therapy was considered unsuitable, based on a 5.1-month improvement in median PFS over physician's choice chemotherapy (HR: 0.62), OS showed no statistically significant improvement [40]. For patients with HER2 ultra-low disease, the available data remain limited and further evidence is required before a recommendation can be made. Datopotamab deruxtecan (Dato-DXd) showed a modest 2-month PFS benefit (HR:0.63) in the TROPION-Breast01 trial without demonstrated OS benefit in patients with ER+/HER2-negative ABC previously treated with 1–2 lines of chemotherapy [41]. The main side effects include stomatitis, ocular events (predominantly dry eye), nausea, vomiting, and fatigue; ILD/pneumonitis was uncommon. In view of the modest PFS improvement, the absence of mature OS data, the side effect profile, and the availability of other treatment options, Dato-DXd in this setting is not a preferred option at present. Ophthalmologic surveillance is important if this agent is considered. Sacituzumab govitecan has moved to a less favored position in this subtype following the negative results of ASCENT-07, which failed to demonstrate superiority over single-agent chemotherapy as first-line cytotoxic therapy in ER+/HER2-negative ABC (median PFS by BICR: 8.3 months in both arms; HR: 0.85) [42].

As the number of available ADCs increases, the question of optimal sequencing and the potential for cross-resistance — particularly relevant given the shared topoisomerase I inhibitor payload between T-DXd and Dato-DXd — remains unanswered. In the absence of validated predictive biomarkers and robust evidence from prospective clinical trials, routine sequencing of ADCs in this setting cannot currently be recommended. The choice between T-DXd and Dato-DXd, when both are considered, will likely be guided by individual patient toxicity profiles, comorbidities, drug availability, and cost considerations.

2.6. Section VI: HER2-positive ABC (see Figs. 4a and 4b)

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 re-challenge is available in case of progression. Using clearance of ctDNA as a decision-making aid in these settings is under investigation in clinical trials and is not yet an established clinical tool to help decide whether to stop therapy.	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%
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%
One of the standards **1st line therapies** for patients previously untreated with anti-HER2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population (CLEOPATRA trial).	I/A	86%
For patients previously treated [in the (neo)adjuvant setting] with anti-HER2 therapy, the combination of ChT + trastuzumab and pertuzumab is one of the preferred options for first-line therapy. Few (88, approximately 11% of the total 808-patient population) of these patients were treated in the CLEOPATRA trial and all with a trastuzumab-free interval >12 months.	I/A	76%
*The randomized phase 3 PATINA trial evaluated the combination **palbociclib + anti-HER-2 therapy + ET** vs anti-HER-2 therapy + ET as maintenance after induction treatment for ER+/HER-2+ ABC (6-8 cycles of trastuzumab ± pertuzumab and taxane/vinorelbine), for all patients without progressive disease. At median FU of 52.6 months, the triple combination led an improvement of 15.2 months in median PFS (HR: 0.74). OS results are still immature. No unexpected side effects were seen.* Based on these results, maintenance therapy with palbociclib + anti-HER-2 therapy + ET is the preferred option for ER+/HER-2+ ABC, after induction treatment.	I/A	94%
In settings where palbociclib is not available for this indication, maintenance therapy after stopping ChT can be done with ET + anti-HER2 therapy. Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request.	Expert Opinion/B	80%
*The randomized phase 3 HER2CLIMB-05 trial evaluated the combination **dual anti-HER-2 blockade +/- ET + tucatinib** vs dual anti-HER-2 blockade +/- ET as maintenance after induction treatment for HER-2+ ABC (about 51% were ER+ and of these only 44% received ET) with 4-8 cycles of taxane + trastuzumab + pertuzumab), for all patients without progressive disease. At median FU of 23 months, the addition of tucatinib led an improvement of 9.6 months in median PFS (HR: 0.64); the PFS benefit was 12.3 months for ER neg and 6.9 months for ER+ subgroup. OS results are still immature. No unexpected side effects were seen.*	I/A	98%

Based on these results, maintenance therapy with tucatinib + dual anti-HER-2 blockade is the preferred option for ER neg/HER-2+ ABC and maintenance therapy with tucatinib + dual anti-HER-2 blockade + ET is one option for ER+/HER-2+ ABC, after induction treatment.		
T-DXd + pertuzumab *was compared, in a randomized phase 3 trial, to taxane + trastuzumab + pertuzumab, as 1st line therapy for patients with HER-2+ ABC, with DFI >6 months since last ChT or anti-HER-2 therapy in the (neo)adjuvant setting (DESTINY-Breast 09 trial). 52% had de novo ABC; only 29% received anti-HER-2 therapy in the (neo)adjuvant setting. Only 10% of patients in the control arm received T-DXd at any line after progression. Furthermore, T-DXd was given until PD or unacceptable toxicity, while taxane was given for 6 cycles. T-DXd + pertuzumab yielded a 13.8 months benefit in median PFS (HR: 0.56), at median FU of 29 months. OS data is still immature and the T-DXd monotherapy arm has not yet been reported. There were 13 treatment related deaths (3,4%), of which two due to pneumonitis, in the T-DXd + pertuzumab arm. Overall treatment tolerability was similar, albeit numerically better for THP arm.* Based on these results, T-DXd + pertuzumab is an option for 1st line therapy of HER-2+ ABC, where approved. The decision should balance the PFS difference with the lack of OS so far, the higher toxicity, the longer duration of cytotoxic therapy and the significant efficacy of T-DXd in 2nd and later lines of therapy. T-DXd can lead to ILD/Pneumonitis that can be fatal and requires active imaging surveillance with CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/A	98%
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 (Destiny-Breast 03 trial).*	I / A	89%
Trastuzumab deruxtecan (T-DXd) is one of the preferred treatment options in the 2nd line setting, after exposure to trastuzumab and pertuzumab, if not used previously. 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 CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.		
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, EMILIA trial) and beyond (vs. treatment of physician's choice, TH3RESA trial).	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 months benefit in median PFS and a 12.7 months benefit in median OS, when compared to capecitabine + trastuzumab or lapatinib (Destiny-Breast 02 trial).* Treatment with T-DXd was associated with ILD/pneumonitis (including toxic deaths), increased GI toxici ty and fatigue. ILD/Pneumonitis can be fatal and requires active imaging surveillance with 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 months) and median OS (5.5 months), over trastuzumab + capecitabine, in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with stable or active brain metastases (HER2CLIMB trial). Based on these results, the triplet combination is a treatment option in this setting. Toxicity needs education and early intervention (i.e. diarrhea).	I/A	91%
In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. There are, however, no randomized 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 (NALA trial). 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. Additional studies are needed to clearly establish the potential role of this combination in the treatment of brain metastases, as well as the role of neratinib for ABC.	I/D	90%
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 (SOPHIA trial) and cannot therefore be recommended for routine clinical practice. 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, platinum, 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] or Eribulin (LoE/GoR: I/A). Also possible are vinorelbine [II/A], nab-paclitaxel [II/B], capecitabine [I/A].	See in statement	86%

In green, NEW/UPDATED ABC 8 statements.
ABC: advanced breast cancer; BICR: Blinded Independent Central Review; ChT: chemotherapy; CM: cyclophosphamide and methotrexate; consensus: percentage of panel members in agreement with the statement; DFI: disease-free interval; 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 [5].

The combination of docetaxel, pertuzumab, and trastuzumab from the landmark CLEOPATRA trial established the standard of care for first line advanced breast cancer in 2012 [43] with a significant OS benefit at 8 years of 37% [44]. Most patients stopped the taxane after 6-8 cycles and continued maintenance therapy with dual blockade. No endocrine therapy was given in the maintenance setting but it has become an accepted standard to add ET to anti-HER-2 therapy as maintenance after induction ChT + anti-HER-2.

Trastuzumab deruxtecan (T-DXd) has shown high efficacy in the 2nd line ABC setting in the DESTINY Breast03 trial compared to the current 2nd line therapy TDM-1 [45,46]. DESTINY Breast09, a randomized phase III trial, was a direct comparison in the 1st line setting, in patients with ABC HER2+ with DFI > 6 months since last chemotherapy or anti-HER-2 therapy in the (neo)adjuvant setting, of T-DXd + pertuzumab (T-DXd-P) vs taxane + trastuzumab + pertuzumab (THP) [47]. Only 29% of patients had received previous HER2 targeted therapy, 52% had *de novo* metastatic disease, and only 10% of patients in the control arm received T-DXd after progression. T-DXd was given until PD or unacceptable toxicity (median time of T-DXd administration 21 months), while taxane was given for 6 cycles followed by maintenance HP. Endocrine therapy was permitted in both arms after completion of taxane in the control arm (38.3% received ET in this manner) or 6 cycles T-DXd (13.5% received ET) in the investigational arms. The results reported a median PFS of 40.7 months for continuous T-DXd-P vs 26.9 months for induction THP (HR 0.56 CI 0.44-0.71.) The objective response rate with T-DXd P was 85.1%, with 15% of complete responses vs ORR of 78.6% and 8.5% complete responses for the THP arm. The arm of T-DXd monotherapy has not yet been reported and OS for the whole trial is immature. ILD occurred in 12.1% of T-DXd-P treated patients, with 2 fatal cases, and in THP 1.0%, all grade 1 and 2. Left ventricular dysfunction occurred in 11% with T-DXd-P vs 7.1% with THP. All grade nausea was 71.1% for T-DXd-P vs 28.8% for THP. Treatment related deaths occurred in 13 (3.4%) with T-DXd-P vs 3 (0.8%) with THP.

The PFS difference without reported OS data, higher toxicity (ILD and nausea), long duration of cytotoxic therapy, and significant efficacy of T-DXd in 2nd line and later lines of therapy should be considered in the decision making to give T-DXd-P instead of THP as 1st line therapy. It is also crucial to consider that the THP regimen is now commonly used followed by a maintenance regimen as discussed below, leading to longer PFS and good tolerability. Treatment with T-DXd requires active imaging surveillance with CT scans for ILD and adequate nausea and vomiting prophylaxis.

The randomized phase 3 PATINA trial in ER+/HER2+ ABC evaluated the combination of palbociclib + anti-HER-2 therapy + ET vs anti-HER-2 therapy + ET as maintenance, after 1st line induction treatment of 6-8 cycles of THP (taxane or vinorelbine) and no progression during induction. The maintenance regimen was given until progression or unacceptable toxicity [48]. At a median FU of 52.6 months, PFS for the palbociclib combination was 44.3 months vs 29.1 months for control arm (HR: 0.75 CI 0.59-0.96). OS results are still immature. No unexpected side effects were seen. In settings where palbociclib is not available for this indication, it is recommended to add endocrine therapy to anti-HER-2 therapy in the maintenance phase.

The randomized phase 3 HER2CLIMB-05 trial evaluated the combination dual anti-HER-2 blockade+/-ET + tucatinib vs dual anti-HER-2 blockade+/-ET as maintenance, for HER-2+ ABC, after 1st line induction treatment with 4-8 cycles of taxane + trastuzumab + pertuzumab and no progression during induction [49]. About 51% of cases were ER+ and of these 44% received additional ET. At median FU of 23 months, median PFS for the tucatinib arm was 24.9 months vs 16.3 months for THP with HR: 0.64 (CI:0.514-0.799). PFS benefit was 12.3 months in the ER neg and 6.9 months in the ER + subgroup [50]. OS results are still immature. No unexpected side effects were seen.

The results of these 2 trials have led to their clinical implementation, with a preference for the PATINA regimen for HER-2+/ER + ABC and for the HER2CLIMB-05 regimen for HER-2+/ER neg ABC.

2.7. *Section VII: Triple negative ABC (see Figs. 5a and 5b)*

Guideline statement	LoE/GoR	Consensus
Pembrolizumab + chemotherapy (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 (Keynote 355 trial).	I/A	91%
Pembrolizumab + sacituzumab-govitecan *was compared to pembrolizumab + SOC ChT (paclitaxel or nab-paclitaxel or gemcitabine + carboplatin) in a randomized phase 3 trial, as 1st line therapy for triple negative/**PD-L1+*** *ABC, ≥ 6 months since treatment in curative setting. Only 4% of patients in each arm received prior anti-PD-[L]1 in the (neo)adjuvant setting (ASCENT-04/KEYNOTE-D19 trial). The study allowed for cross-over and 81% of patients who received any subsequent treatment after discontinuation of pembrolizumab + SOC ChT received SG. Pembrolizumab + sacituzumab-govitecan showed a 3.4 months difference in median PFS (HR: 0.65). OS data is still immature.* Pembrolizumab + sacituzumab-govitecan may be an option for 1st line therapy for triple negative/PD-L1+ ABC, where available. Education, prophylaxis and early management of side effects, in particular diarrhea, nausea and vomiting, are crucial. Fatal side effects were observed due to infections thus, special attention is needed in the management of neutropenia and G-CSF should be incorporated as clinically indicated.	I/A	92%
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.	II/B	81%
Checkpoint inhibitor monotherapy in later lines for triple-negative ABC is not recommended due to low response rates.	I/E	89%
Sacituzumab govitecan *was compared, in a randomized phase 3 trial, to SOC ChT (either a taxane or carboplatin + gemcitabine), as 1st line therapy for patients for whom **immunotherapy was not an option** (either because the tumors are PD-L1-negative, or PD-L1-positive but with a recurrence after receipt of an ICI in the (neo)adjuvant setting or medical contra-indication) (ASCENT-03 trial). Notably it included patients with rapid disease recurrence, however with a minimal DFI of 6 months from completion of (neo)adjuvant therapy. Crossover was included by protocol and of patients who initiated subsequent treatment 82% received sacituzumab govitecan. At a medium FU of 13,2 months, sacituzumab govitecan showed a 2.8 months improvement in median PFS (HR: 0.62). OS data is still immature. Physical functioning scores were maintained in the sacituzumab govitecan group, while a gradual worsening was observed in the ChT group over time; nausea/vomiting and diarrhea were worse with SG, dyspnea was worse with ChT and fatigue was similar.* Based on these results, sacituzumab govitecan is an option as 1st line therapy of patients with triple negative ABC who are not candidates for immunotherapy. Education, prophylaxis and early management of side effects, in particular neutropenia, diarrhea, nausea and vomiting, are crucial. Fatal side effects were observed due to infections thus, special attention is needed in the management of neutropenia and G-CSF should be incorporated as clinically indicated.	I/A	98%
Datopotamab-deruxtecan (Dato-DXd) *was compared, in a randomized phase 3 trial, to SOC ChT (mostly taxanes or eribulin), as 1st line therapy for patients for whom **immunotherapy was not an option** (either because the tumors are PD-L1-negative, or PD-L1-positive but with a recurrence after receipt of an ICI in the (neo)adjuvant setting or medical contra-indication) (TROPION-Breast02 trial). The trial included patients with rapid disease recurrence (15% experienced recurrence within 6 months of completion of adjuvant therapy). However, there was no crossover. At a medium FU of 27.5 months, Dato-DXd showed a 5.2 months benefit in median PFS (HR: 0.57) and a 5.0 months benefit in OS (HR: 0.79). Side effects included stomatitis, nausea and dry eyes.* Based on these results, datopotamab-deruxtecan is an option for 1st line therapy of patients with triple negative ABC who are not candidates for immunotherapy (situations described above*). For patients who experience very early relapse (within 6 months of completion of adjuvant therapy), Dato-DXd is the preferred 1st line option. Side effects included stomatitis, nausea and dry eyes should be addressed pro-actively with anti-emetics, steroid mouth washes and eye drops.	I/A	94%
If not used earlier, **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 a 4.9 months benefit in OS and a 3.1 months benefit in PFS (ASCENT trial). Education, prophylaxis and early management of side effects, in particular neutropenia, diarrhea, nausea and vomiting, are crucial. Fatal side effects were observed due to infections	I/A	96%

thus, special attention is needed in the management of neutropenia and G-CSF should be incorporated as clinically indicated.		
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 (Destiny-Breast 04 trial). 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 CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/B	89%
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%

In green, NEW ABC 8 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; 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.

The treatment landscape for 1st line triple negative ABC has undergone significant evolution with recent data from pivotal trials examining ADCs across different PD-L1 populations. For the approximately 30% of patients with PD-L1-positive disease (combined positive score [CPS] ≥10), the ASCENT-04/KEYNOTE-D19 trial demonstrated that the combination of sacituzumab govitecan + pembrolizumab significantly improved PFS compared to standard chemotherapy + pembrolizumab, with a median PFS of 11.2 months versus 7.8 months (HR 0.65; 95% CI 0.51-0.84; $p < 0.001$), representing a 35% reduction in the risk of disease progression or death [51]. The median duration of response was notably prolonged at 16.5 months with the ADC combination vs 9.2 months with standard chemotherapy + pembrolizumab. OS data remains immature. Importantly, the study allowed for crossover and 81% of patients who received any subsequent treatment after discontinuation of pembrolizumab + standard chemotherapy received sacituzumab govitecan [51]. Only 4% of patients in each arm received prior anti-PD-[L]1 in the (neo)adjuvant setting, which renders the trial not informative for this subgroup of patients. In the absence of a mature OS data, standard chemotherapy + pembrolizumab [52] will remain an important option for this group of patients, since the design of the ASCENT-04/KEYNOTE-D19 (with crossover) allows a comparison between the combination versus sequential use of pembrolizumab and sacituzumab govitecan strategies.

For the substantial majority of patients (60 to 70%) who are not candidates for immunotherapy - either due to PD-L1 negativity (CPS <10) or medical contraindications to checkpoint inhibition, or prior exposure to an immune checkpoint inhibitor in the (neo)adjuvant setting - two landmark phase 3 trials reported at ESMO 2025 have provided practice-changing evidence [53,54]. The ASCENT-03 trial demonstrated that sacituzumab govitecan improved median PFS to 9.7 months compared with 6.9 months for conventional chemotherapy (HR 0.62; 95% CI 0.50-0.77; $p < 0.001$), with a median duration of response of 12.2 months versus 7.2 months [53]. Notably, the trial design allowed crossover from chemotherapy to sacituzumab govitecan upon progression, with 82% of patients with PD in the chemotherapy arm subsequently receiving the ADC. OS data is still immature. The TROPION-Breast02 trial evaluating datopotamab deruxtecan demonstrated superior PFS (median 10.8 months vs 5.6 months; HR 0.57; 95% CI 0.47-0.69; $p < 0.0001$) and a statistically significant OS benefit at a median follow-up of 27.5 months (median OS 23.7 months vs 18.7 months; HR 0.79; 95% CI 0.64-0.98; $p = 0.0291$) [54]. This represents the first phase 3 trial to demonstrate an OS benefit in the 1st line setting, for this patient population. The objective response rate was also higher with datopotamab deruxtecan (62.5% vs 29.3%). However, and critically, TROPION-Breast02 did not allow crossover to ADC therapy after progression, which may have contributed to the observed survival benefit.

Direct cross-trial comparisons must be interpreted cautiously given key differences in study design and patient populations. Notably, TROPION-Breast02 enrolled a borader population that included patients with poor prognostic features, including patients with disease recurrence less than 6 months from completion of curative-intent therapy and a higher proportion with brain metastases, potentially reflecting a more aggressive disease biology [54]. The chemotherapy backbones also differed between trials. Furthermore, the crossover designs—permitted in ASCENT-03 but not in TROPION-Breast02—limit the interpretation of long-term outcomes and benefits on overall survival. The toxicity profiles of these TROP2-directed ADCs also diverge: sacituzumab govitecan carries higher rates of hematologic toxicity and gastrointestinal adverse events (particularly diarrhea), whereas datopotamab deruxtecan demonstrates lower rates of these toxicities but increased incidence of stomatitis and ocular adverse events [53,54]. The administration schedule differs - sacituzumab govitecan is administered day 1, 8 on a 21-day schedule and datopotamab deruxtecan is administered day 1 of a 21-day schedule and requires regular ophthalmologic evaluations. This may be a consideration for patients living in geographically remote areas or those wishing to spend less time in the hospital day care. These multiple factors underscore the importance of shared decision making in the management of first-line mTNBC.

Given the absence of definitive comparative data and the differing trial designs, the optimal first-line TROP2-directed ADC for PD-L1-negative or immunotherapy-ineligible patients remains uncertain. However, specific clinical scenarios may guide treatement selection. For patients with early disease recurrence (disease-free interval <6 months following completion of curative -intent therapy), datopotamab deruxtecan represents the only ADC with positive phase 3 data specifically including this high-risk population, where as ASCENT-03 uniquely permitted enrollment of patients with a disease-free interval of ≥6 months [53,54]. This is particularly relevant given that this subset has historically derived less benefit from standard chemotherapy-based regimens. Additional considerations for ADC selection may include toxicity profile considerations for individual patients, and regional drug availability. It is important to note that both ASCENT-03 and TROPION-Breast02 included only a small proportion of patients previously treated with pembrolizumab in the early setting, thus these results may not be entirely applicable to a more contemporary population.

As discussed for ER+/HER-2 low ABC, the question of optimal sequencing and the potential for cross-resistance between them remains unanswered. In the absence of validated predictive biomarkers and robust evidence from prospective clinical trials, routine sequencing of ADCs for triple negative ABC cannot currently be recommended. A potential strategy, although not supported by prospective evidence, could be the use of standard chemotherapy following an ADC and before considering a different ADC.

For germline *BRCA*-mutated triple negative ABC, PARP inhibitors (olaparib, talazoparib) are treatment options as discussed in detail in previous ABC guidelines [55,56]. The optimal sequence between PARP inhibitors and pembrolizumab-based therapy has not been prospectively evaluated. However, in patients with PD-L1-positive disease (CPS ≥10) eligible for pembrolizumab, given the OS benefit demonstrated with pembrolizumab, the panel considers this the preferred first line option for most patients, reserving a PARP inhibitor for 2nd or later lines of therapy, the efficacy of PARP inhibitor rechallenge after prior adjuvant olaparib is unknown.

2.8. Section VIII: Hereditary ABC

Guideline statement	LoE/GoR	Consensus
Genetic testing		
For ABC patients, results from **germline genetic testing** have therapeutic implications and should therefore be performed as early as possible. 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 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.	I/A	94%
*Data from a small phase 2 trial demonstrated a benefit from **olaparib** for individuals with a **somatic BRCA1/2 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+ gBRCA-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, until the results of ongoing trials are available.	Expert opinion/A	94%
*In **triple negative PD-L1+ and gBRCA-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 gBRCA ABC 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.* This regimen is not approved or recommended for routine clinical practice.	I/D	98%

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; 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.

2.9. *Section IX: Precision medicine (see Fig. 2)*

Guideline statement	LoE/GoR	Consensus
Multigene panels, such as those obtained using next generation sequencing (NGS) or other technology on ctDNA can be utilized in ABC both to triage eligible patients into clinical trials and to assess the potential role of treatments targeting individual breast tumor biology such as *ESR1mut* and alterations in the *PIK3CA/AKT/PTEN* pathway. The timing of testing depends on the alteration. Plasma and tissue may provide complementary information. Use of plasma is preferred to detect *ESR1mut*. These tests should not routinely be performed unless relevant treatment options that may be identified will be accessible and clinically suitable for the patient.	I/B	98%
ctDNA assessment is not yet recommended for demonstration of disease progression.	I/D	100%
ctDNA assessment is an option for the detection of mutations such as in the *PIK3CA/AKT/PTEN* pathway and *ESR1* mutations, for selection of patients eligible for targeted agents against these alterations.	II/A	100%
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%
If treatment with a *PIK3CA/AKT/PTEN* inhibitor, is available, patients should be tested for ***PIK3CA* mutation** (in exon 7, 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%
In patients with HR+/HER2- ABC, ***ESR1* mutation** should be tested in ctDNA testing in blood at the time of disease progression, if targeted therapies are available. In the absence of detectable *ESR1 mutations* in ctDNA, a concomitant tissue biopsy can be tested. Under continued ET-based therapy, testing may be repeated if it will impact treatment choices.	I/B	89%
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. If this sample is negative, the primary tumor should be tested as the presence of a positive PD-L1 status on one sample is sufficient, regardless of the stage of the disease at which it was assessed (primary tumor or metastatic lesion) for treatment eligibility in the metastatic setting.	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.	I/A	87%
Patients with **low (1%–10%) ER- (and PR-) positive**, HER2-negative ABC should not be considered for ET exclusively. Patients with **low (1%–10%) ER- (and PR-) 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 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%

For patients with ER+/HER-2 negative ABC, the HER-2 zero category may be split into HER2-null (HER-2 zero without membrane staining) and **HER-2 ultra-low** (HER-2 zero with membrane staining e.g. ≤ 10% of tumor cells with incomplete faint membrane staining).	Expert opinion/A	81%
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. Patients must be informed about the amount of data available for ABC specifically. Research on the best companion diagnosis tools and techniques is needed. Prospective registries should be created to collect data from all patients treated with these innovative approaches, after proper consent.	I/B	Yes: 29% Abstain: 24% Insufficient data: 47%
HER2-mutations *are present in about 8% of HR+/HER2-neg ductal ABC and in about 15% of lobular ABC. The phase 2 SUMMIT basket study, evaluating therapy in patients with solid tumors harboring HER2 mutations, included 57 ABC patients. The combination trastuzumab + neratinib + fulvestrant showed an ORR of 39%, both in ductal (ORR 39%) and lobular (ORR 41%) ABC, and a median PFS of 8.3 months, as 2nd line or later. Notably in the triplet therapy arm 53% experienced G3 diarrhea. The study also included a small HR- cohort (n=11) treated with monotherapy neratinib who experienced an ORR of 36.4%. The phase 2 SGNTUC-019 basket study, evaluating tucatinib + trastuzumab +/- fulvestrant in patients with HER2-altered solid tumors, included 31 ABC patients. The combination showed an ORR of 41.9% and a median PFS of 9.5 months, in later lines.* Based on these results, for patients with HER2-mutant ABC the combinations trastuzumab + tucatinib + *fulvestrant* or trastuzumab + neratinib + fulvestrant are treatment options after at least one line of therapy in the advanced setting. Education and pro-active management of diarrhea is crucial.	II/B	90%

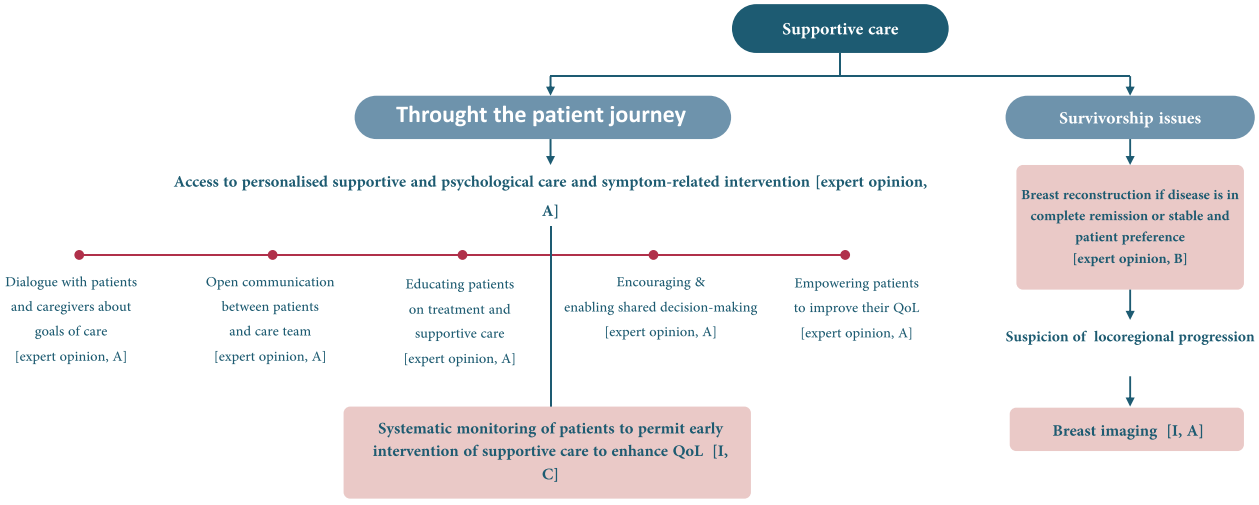
In green, NEW ABC 8 statements.
ABC: advanced breast cancer; consensus: percentage of panel members in agreement with the statement; ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; *BRCA*: BReast CAncer gene; CDK: cyclin-dependent kinase; ChT: chemotherapy; ctDNA: circulating 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; PR, progesterone receptor; PI3K: phosphoinositide 3-kinase; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TRKi: tropomyosin receptor kinase inhibitor.

The most important evolution in the precision medicine section is the broadening of the recommendation for multigene panels in ABC (LoE/GoR: I/B), now explicitly supporting the use of multigene assays performed on plasma ctDNA and/or tissue, not only to facilitate enrollment into clinical trials but also to identify clinically actionable alterations, particularly *ESR1* mutations and alterations in the *PIK3CA/AKT/PTEN* pathway. The statement also clarifies two practical points with direct clinical implications: the timing of testing depends on the alteration being sought, and plasma and tissue should be considered complementary rather than competing sources of genomic information; in particular, plasma is preferred for *ESR1* testing. Finally, we appropriately restrict routine testing to situations in which the result is expected to open a realistic therapeutic option for the patient. This modification reflects the maturation of the field from exploratory molecular profiling toward treatment-linked precision oncology, driven by the availability of approved therapies targeting *ESR1* and *PI3K/AKT/PTEN* pathway alterations [57–59].

The updated ctDNA statement draws a clear boundary between validated clinical use and premature overinterpretation. We do not recommend ctDNA assessment for the demonstration of disease progression, while recognizing that ctDNA is an appropriate option to detect actionable genomic alterations for treatment selection. This position remains justified because ctDNA has not been validated as a replacement for standard clinic-radiologic criteria for progression assessment in routine ABC care, and current expert recommendations continue to support ctDNA primarily as a genotyping tool rather than a universal progression-monitoring assay [60,61]. The clinical utility of treatment modification without radiological progression evaluated in the SERENA 6 trial [35] remains to be proven, since the design of this trial does not allow confirmation of the clinical utility of this strategy (camizestrant not provided at radiological progression in the control arm). If future trials provide different insights, the statement may be revisited.

The new ABC8 statement on *ESR1* mutation testing reflects one of the clearest examples of a biomarker becoming immediately practice-changing in ER-positive/HER2-negative ABC. The recommendation to test blood ctDNA at disease progression, provided that a targeted treatment is available, is consistent with the biology of *ESR1* mutations as acquired mechanisms of endocrine resistance, their enrichment after aromatase inhibitor exposure, and the fact that plasma may better capture their polyclonal emergence than a single tissue biopsy. The recommendation to consider tissue testing when plasma is negative, and to repeat testing under continued endocrine-based therapy if the result would influence treatment choice, is clinically sound and consistent with both regulatory developments and real-world clinic-genomic data [59,60].

The modified statement on HER2-ultralow disease acknowledges the therapeutic relevance of further refining the historical "HER2-zero" category, by distinguishing HER2-null tumors from HER2-ultralow tumors with faint incomplete membrane staining. However, this



ABC, advanced breast cancer; QoL, quality of life.
a Throughout the cancer pathway, adequate information should be provided to the patient.

Fig. 1. ABC follow-up and supportive care.[a].

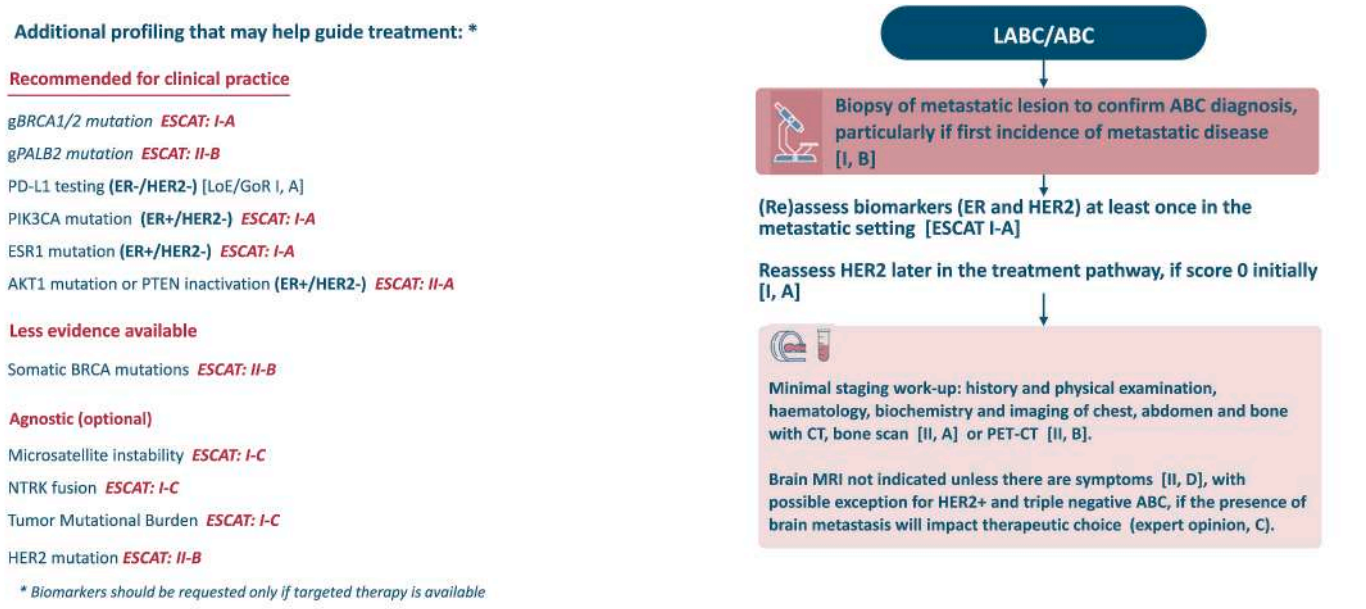


Fig. 2. ABC diagnostic work-up and staging.

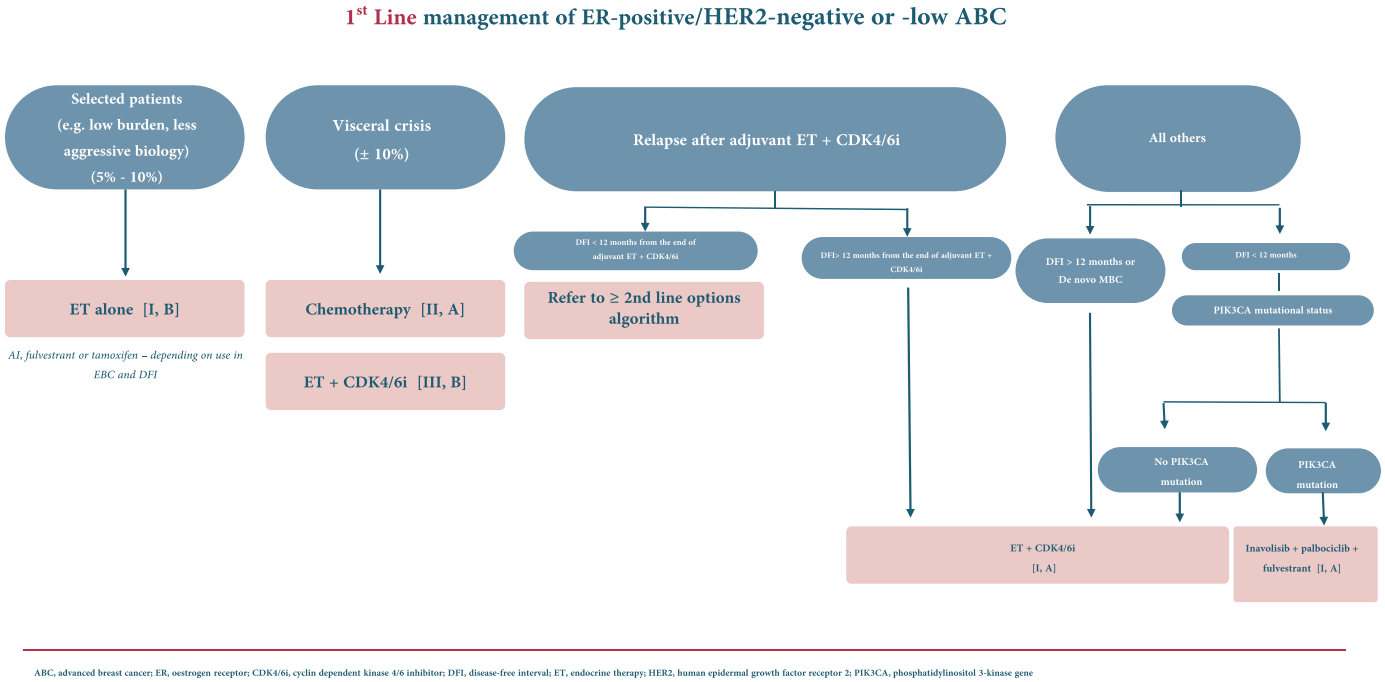
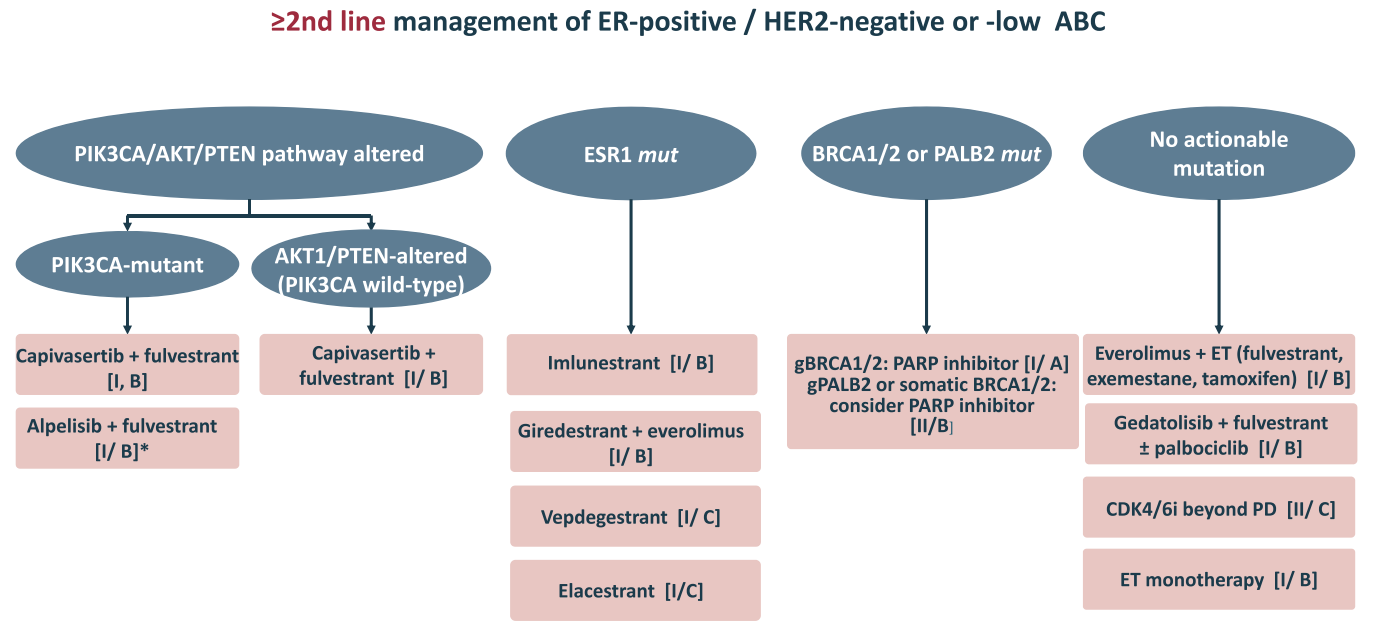


Fig. 3a. Treatment of ER-positive/HER2-negative or -low ABC – first line options.

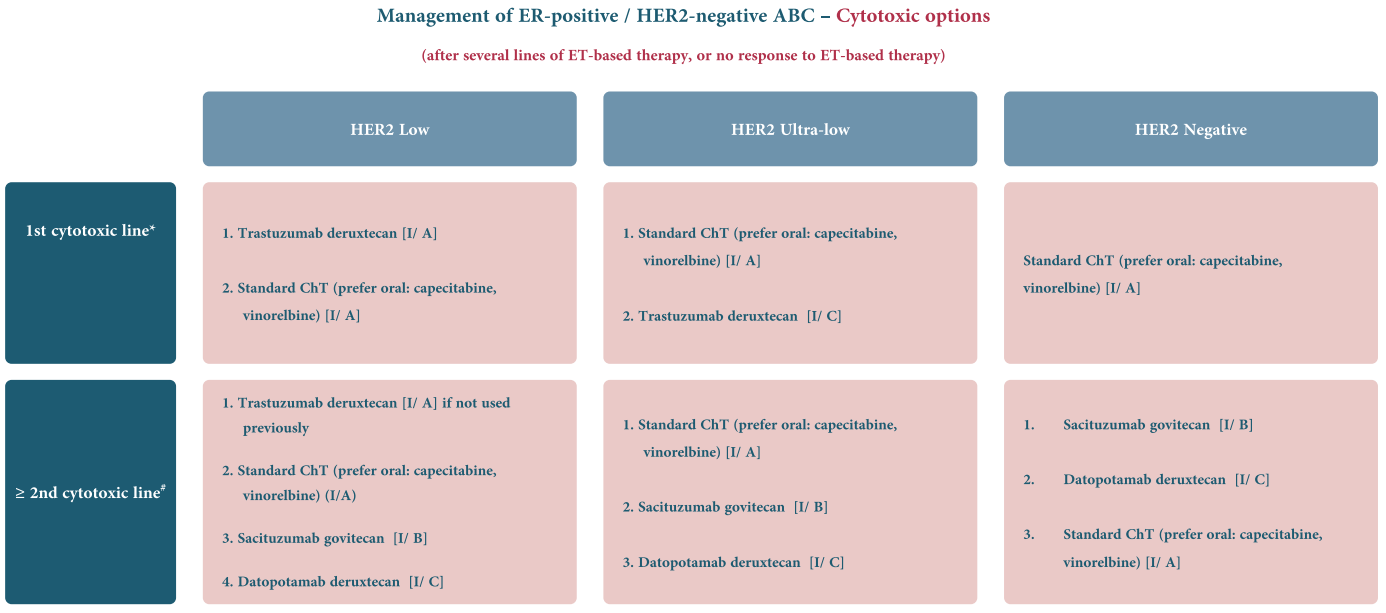
recommendation only has an expert-opinion level of evidence because this new biologic and therapeutic category raise substantial diagnostic challenges, especially regarding pre-analytical variables, assay standardization, and interobserver reproducibility at the lower end of HER-2 expression [62–64].

Finally, the new ABC8 recommendation on HER2-mutant ABC is a strong signal that genomic alterations in *ERBB2/HER-2* should now be considered actionable beyond *HER-2* amplification or overexpression. This is particularly relevant in a subgroup of cases (approximately 8% of ER+/HER2-negative ductal ABC and in up to 15% of lobular ABC) for which conventional HER-2 IHC/ISH testing would classify tumors as HER2-negative, underscoring the value of broader genomic profiling in selected patients. The consensus is supported by two phase II basket studies: the SUMMIT trial demonstrated that the triplet trastuzumab + neratinib + fulvestrant yielded an ORR of 39% (ductal: 39%; lobular: 41%) and a median PFS of 8.3 months in 57 patients with ABC, treated in the 2nd line or beyond, albeit at the cost of grade 3 diarrhea in 53% of patients, mandating aggressive loperamide prophylaxis and proactive



ABC, advanced breast cancer; AKT, AK strain transforming; BRCA, breast cancer gene; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, oestrogen receptor; ESR1, oestrogen receptor 1 mutation; ET, endocrine therapy; gBRCA, germline breast cancer gene; HER2, human epidermal growth factor receptor 2; PALB2, partner and localizer of BRCA2; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PIK3CA, phosphatidylinositol 3-kinase gene; PTEN, phosphatase and tensin homolog

Fig. 3b. Treatment of ER-positive/HER2-negative or -low ABC - ≥ 2nd line options.



* *Options are listed by preferred order.*

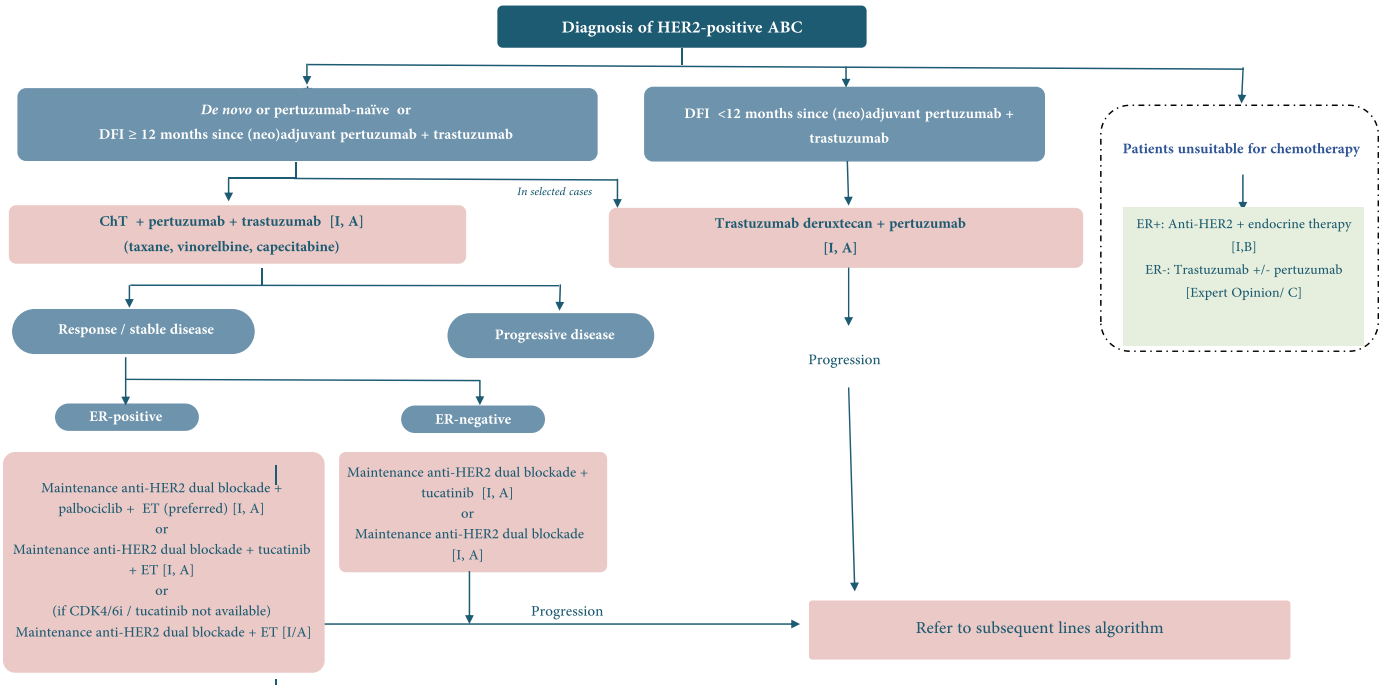
For subsequent lines of cytotoxic therapy, use therapeutic options not yet used. Routine sequencing of ADCs is not recommended (see text).

ABC, advanced breast cancer; ADCs, antibody drug conjugates; ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2

Fig. 3c. Treatment of ER-positive/HER2-negative or -low ABC – Cytotoxic options.

management [65]. A small HR-negative cohort treated with neratinib monotherapy achieved an ORR of 36.4% (n = 11). The SGNTUC-019 trial evaluated tucatinib + trastuzumab in 31 patients with *HER2*-mutant ABC, demonstrating an ORR of 41.9% and a median PFS of 9.5 months in later lines [66]. Based on these results and acknowledging that both trials are phase 2 basket studies with limited ABC-specific sample sizes, trastuzumab + tucatinib or trastuzumab + neratinib + fulvestrant represent options for later lines of therapy for patients with *HER2*-mutant ABC. The choice between these two regimens should consider the histological subtype, hormone receptor status, concomitant medications, and individual toxicity risk, with diarrhea education and proactive management being essential for both combinations.

Taken together, these statements illustrate a coherent transition from "precision medicine as testing" to precision medicine as a "treatment-oriented biomarker strategy". The strongest conceptual advance is the multigene-panel recommendation, because it integrates several previously separate biomarker decisions into a more pragmatic framework: use the right assay, at the right time, in the right sample, and only when the result can realistically alter management.



ABC, advanced breast cancer; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ChT, chemotherapy; DFI, disease-free interval; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2

Fig. 4a. Treatment of HER2-positive ABC – initial options.

2.10. *Section X: LABC[a] (inflammatory and non-inflammatory) and inflammatory ABC (IBC)*

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, PR, HER2, Ki67; b) For metastatic IBC: ER, HER2, PD-L1 if TNBC and *PIK3CA/AKT/PTEN* 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 an 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		
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%
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%
Based on the results of the Destiny-Breast 09 phase 3 trial, T-DXd + pertuzumab is an option for 1st line therapy of **HER-2+ locally advanced inoperable, inflammatory or non-inflammatory**, where approved. T-DXd can lead to	I/A	79%

ILD/Pneumonitis that can be fatal and requires active imaging surveillance with CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.		
*For **HER-2+ inoperable LABC without distant metastases (Inflammatory or non-inflammatory)** meeting the inclusion criteria of the DESTINY-Breast 11 trial (70% HR+, 90% node +), and being treated with a potential curative intent, 4 cycles of T-DXd followed by 4 cycles taxane + dual anti-HER-2 blockade (THP) was compared to 4 cycles of 4 AC/EC followed by 4 cycles of THP and 8 cycles of T-DXd monotherapy and showed an improvement of 11.2% in pCR rate (9.1% for HR+ and 16.1% for HR neg). EFS is still immature. The T-DXd monotherapy arm was closed early by IDMC recommendation and has not yet been reported.* Based on these results, 4 cycles of T-DXd + 4 cycles of THP may be an option for 1st line therapy of HER-2+ locally advanced inoperable, inflammatory or non-inflammatory, where approved, in patients being treated with a curative intent. T-DXd can lead to ILD/Pneumonitis that can be fatal and requires active imaging surveillance with CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	II/B	98%
For patients with **HER-2+ LABC** (inflammatory or non-inflammatory), without distant metastases, who are in pathological 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. The optimal anti-HER2 therapy is double blockade with trastuzumab and pertuzumab.	I/A	91%
*14 cycles of T-DXd was compared to 14 cycles of T-DM1 in patients with **HER-2+ inoperable LABC without distant metastases (Inflammatory or non-inflammatory)**, who had residual disease after appropriate preoperative systemic therapy (not including T-DXd) and appropriate loco-regional therapy (DESTINY-Breast05 trial), and being treated with a potential curative intent, and showed an improvement of 8.7% in IDFS (HR: 0.47). OS data is still immature.* If and where approved, T-DXd is the preferred option for patients meeting the inclusion criteria of the Destiny-Breast 05 trial (including not having previously received T-DXd). T-DXd can lead to ILD/Pneumonitis that can be fatal and requires active imaging surveillance with CT scans, and proper management. Nausea and vomiting require adequate prophylaxis.	I/B	100%
In patients with **HER-2+ inoperable LABC without distant metastases (Inflammatory or non-inflammatory)**, who had residual disease after appropriate preoperative systemic therapy and appropriate loco-regional therapy, being treated with a potential curative intent, and for whom T-DXd is not available or indicated, 14 courses of T-DM1 is the recommended treatment (KATHERINE trial).	I/A	100%
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 8 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; PR: 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.

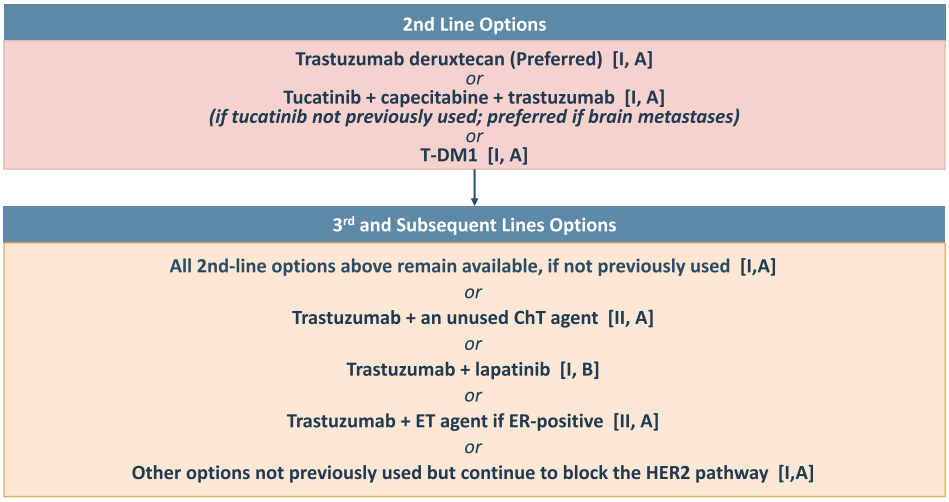
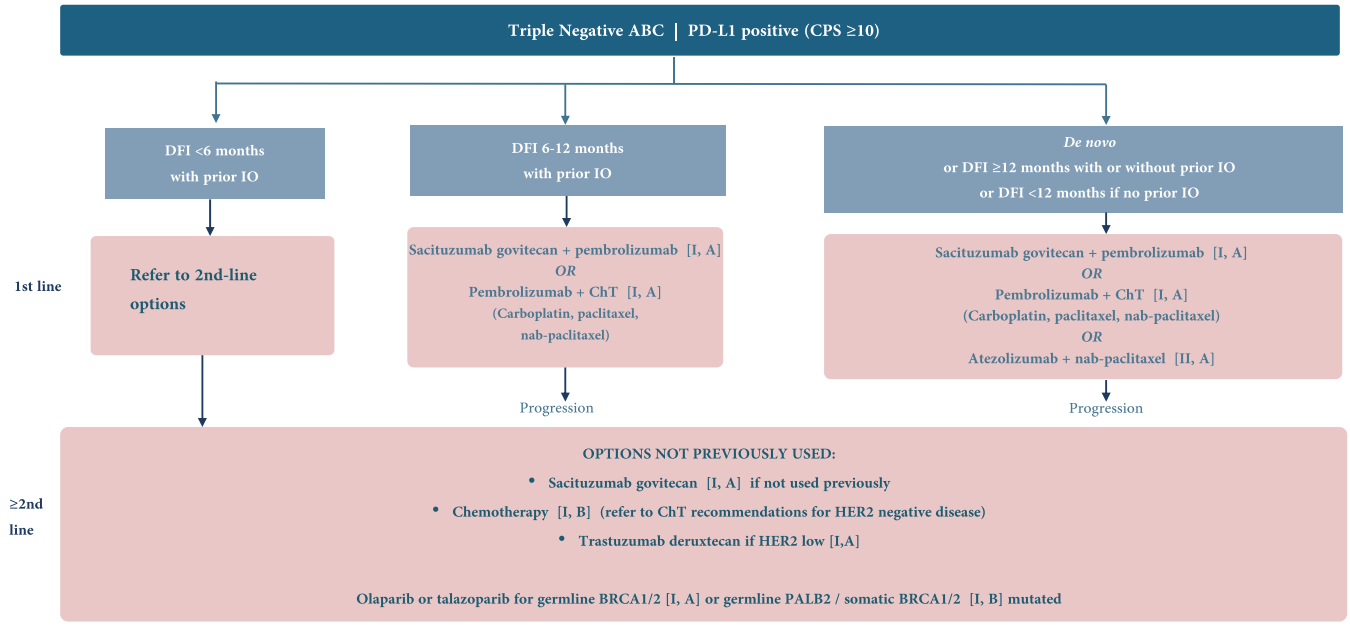


Fig. 4b. Treatment of HER2-positive ABC –subsequent lines.

For HER-2+ inoperable LABC without distant metastases (inflammatory or non-inflammatory) meeting the inclusion criteria of the DESTINY-Breast 11 trial (70% HR+, 90% node positive), and being treated with a potential curative intent, 4 cycles of T-DXd followed by 4 cycles taxane + dual anti-HER-2 blockade (T-DXd-THP) was compared to 4 cycles of AC/EC followed by 4 cycles of THP (ddAC-THP) and 8 cycles of T-DXd monotherapy [67]. The pathological complete response (pCR) rates were: 43.0% (T-DXd), 67.3% (T-DXd-THP) and 56.3% (ddAC-THP). Between T-DXd-THP and ddAC-THP the absolute pCR rate difference was 11.2% [95% CI 4.0% to 18.3] with a benefit in HR+/HER-2+ disease of 9.1% (61.4% vs 52.3%) and in HR-/HER-2+ disease of 16.1% (83.1% vs 67.1%). EFS is still immature. The T-DXd monotherapy arm was closed early by IDMC recommendation and has not yet been reported. All-grade adjudicated drug-related interstitial lung disease/pneumonitis rates were low and similar across arms (T-DXd, 4.9%; T-DXd-THP, 4.4%; ddAC-THP, 5.1%). Three treatment-related deaths occurred with 1 on T-DXd-THP and 2 on ddAC-THP. Based on these results, and considering the poor prognosis of inoperable LABC, especially if inflammatory, 4 cycles of T-DXd followed by 4 cycles of THP may be an option for 1st line therapy of HER-2+ locally advanced inoperable, inflammatory or non-inflammatory, where approved, in patients being treated with a curative intent. It remains to be defined the best treatment option for patients with residual disease after receiving neoadjuvant treatments based on DESTINY-Breast 11.

The DESTINY-Breast 05 trial [68] compared 14 cycles of T-DXd to 14 cycles of T-DM1 in patients with HER-2+ disease that was inoperable at presentation (inflammatory or non-inflammatory) with residual disease after adequate neoadjuvant therapy (not including T-DXd) or with operable disease at presentation but found to have axillary lymph node positive disease at the time of surgery, after appropriate loco-regional therapy and treated with a potentially curative intent. Invasive-disease events or deaths were reported in 6.2% in the T-DXd group and 12.5% in the T-DM1 group (HR 0.47; 95% CI: 0.34 to 0.66), with 3-year invasive disease–free survival of 92.4% and 83.7%, respectively. OS data are still immature. The incidence of adjudicated drug-related interstitial lung disease was higher with T-DXd than with T-DM1

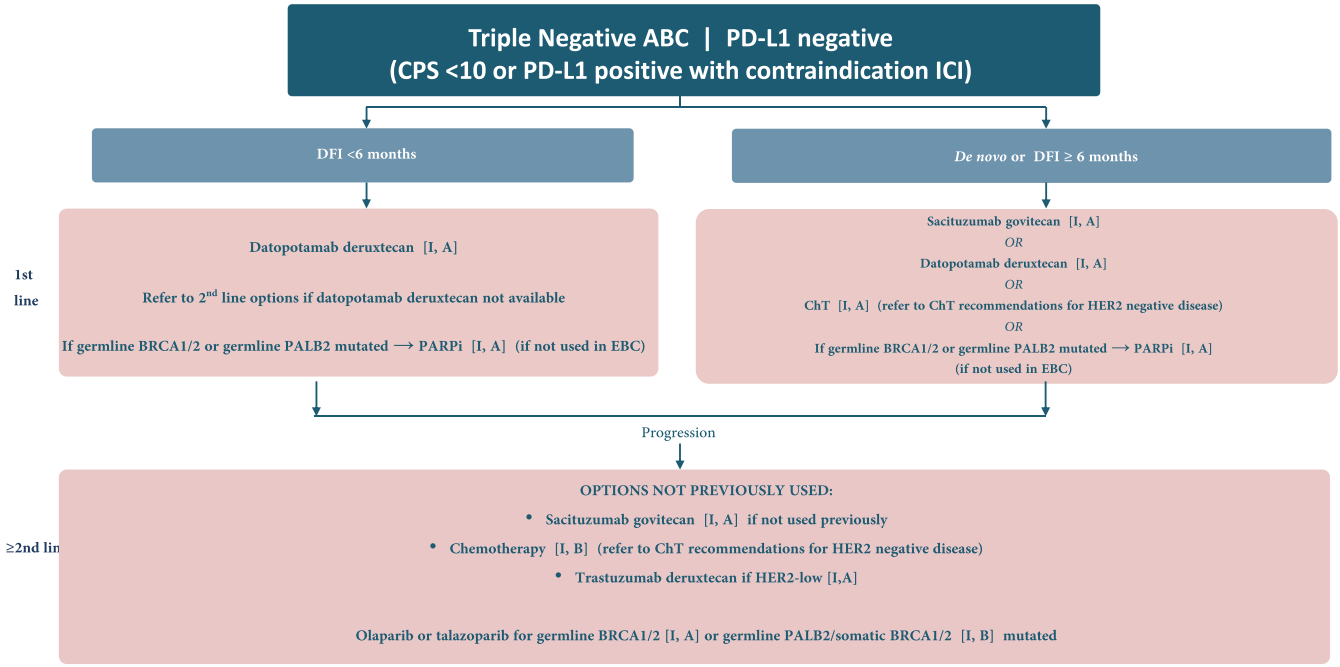


Options are listed by preferred order.

For subsequent lines of cytotoxic therapy, use therapeutic options not yet used. Regarding sequencing of ADCs, please refer to the text and respective guideline recommendation.

ABC, advanced breast cancer; ADCs, antibody drug conjugates; BRCA, breast cancer gene; ChT, chemotherapy; DFI, disease-free interval; HER2, human epidermal growth factor receptor 2; IO, immunotherapy; PALB2, partner and localizer of BRCA2; PD-L1, programmed death-ligand 1

Fig. 5a. Treatment of Triple Negative ABC –PD-L1 positive.

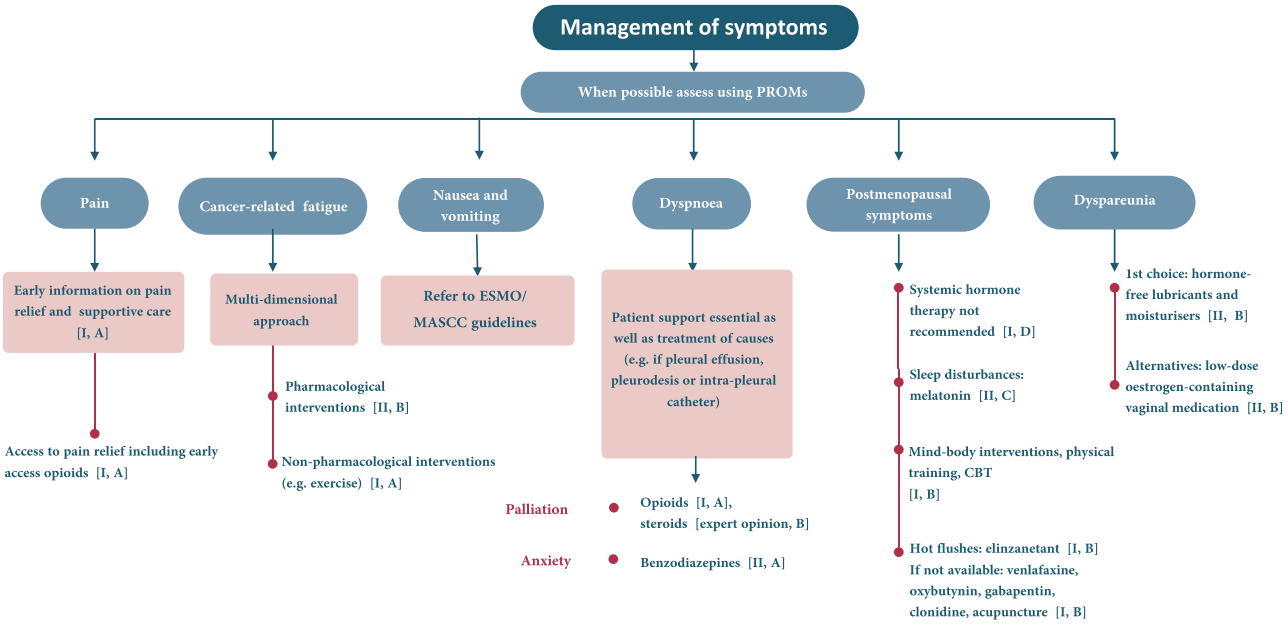


Options are listed by preferred order.

For subsequent lines of cytotoxic therapy, use therapeutic options not yet used. Regarding sequencing of ADCs, please refer to the text and respective guideline recommendation.

ABC, advanced breast cancer; ADCs, antibody drug conjugates; BRCA, breast cancer gene; ChT, chemotherapy; CPS, combined positive score; DFI, disease-free interval; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; ICI; immune checkpoint inhibitor; PALB2, partner and localizer of BRCA2; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-L1, programmed death-ligand 1

Fig. 5b. Treatment of Triple Negative ABC – PD-L1 negative.

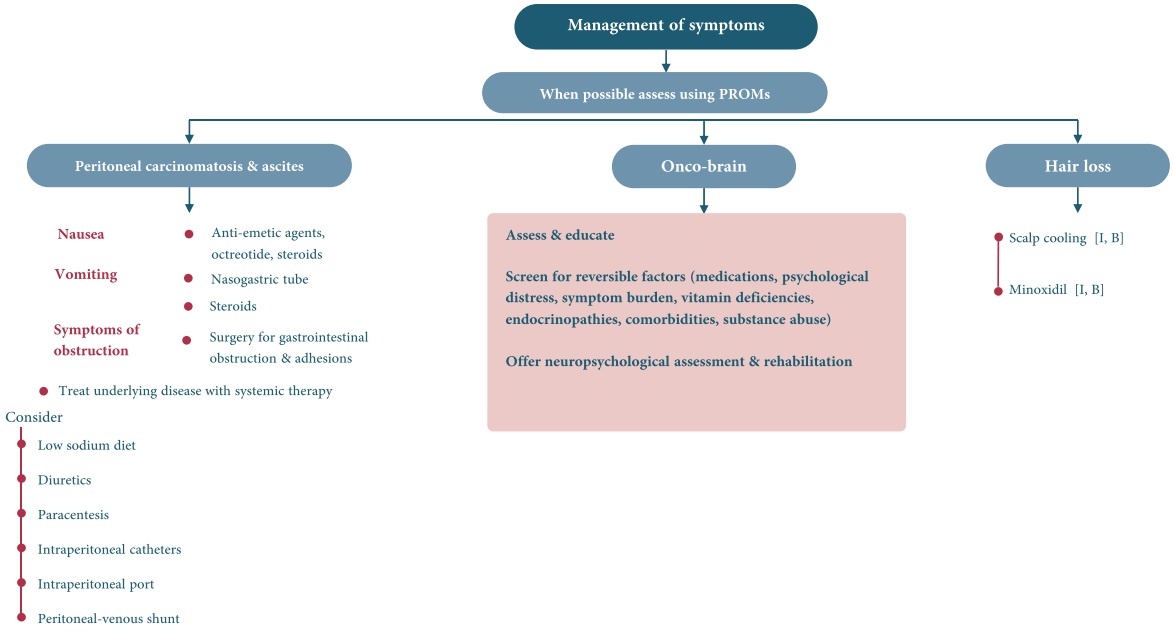


ABC, advanced breast cancer; CBT, cognitive behavioural therapy; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; PROM, patient-reported outcome measure

Fig. 6a. ABC symptom control.

(9.6% vs. 1.6%). Two patients with interstitial lung disease in the T-DXd group died. Based on these results, if and where approved, T-DXd is the preferred option for patients meeting the inclusion criteria of the Destiny-Breast 05 trial (including not having previously received T-DXd).

In patients with HER-2+ inoperable LABC without distant metastases (Inflammatory or non-inflammatory), who had residual disease after appropriate preoperative systemic therapy and appropriate loco-regional therapy, being treated with a potential curative intent and for whom T-DXd is not available or indicated, 14 courses of T-DM1 is the recommended treatment based on the results of the KATHERINE trial [69,70].



ABC, advanced breast cancer; PROM, patient-reported outcome measure

Fig. 6b. ABC symptom control.

2.11. *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 one of the preferred ET agent. It can safely be combined with abemaciclib and palbociclib.	IV/B	83%
For male patients with ABC who need to receive an AI, a concomitant LHRH agonist or orchiectomy is the preferred option. Aromatase inhibitor 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 inhibitors, mTOR inhibitors, Pi3KCA/AKT/PTEN inhibitors, ADCs and others.	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).	Expert opinion/A Expert opinion/A	98% 98%
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.		
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% 100%
In general, the same ABC guidelines apply to HIV+ and HIV neg patients with ABC.	Expert opinion/A Expert opinion/A	95% 95%

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/NA	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. HIV therapy should be initiated or continued during cancer therapy. 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. 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 Expert opinion/A Expert opinion/B Expert opinion/B	93% 93% 93% 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. 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 Expert opinion/A Expert opinion/A	100% 100% 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. 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/E I/A	100% 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%

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.

2.12. *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 [71] related to this subject.	Expert Opinion/A	100%
BRAIN METASTASES		
While data are limited, in subsets of asymptomatic patients with HER2+ and/or TNBC ABC, **brain imaging** may be considered if the presence of CNS metastases will impact the choice of systemic therapy or when there is a high burden of metastatic disease that increases the chance of CNS metastases. In cases where asymptomatic CNS metastases are detected, decisions on their management must be made in a multi-disciplinary tumor board, with cautious consideration of the benefits of treatment vs the harms of overtreatment when deciding on treatment modalities.	Expert Opinion/C	98%
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, and available techniques (such as hippocampal sparing and the use of neuroprotective agents such as memantine) should be used to minimize neurotoxicity.	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 one of the best available options. 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 is also a treatment option.	II/B	98%

Radionecrosis after stereotactic radiotherapy for brain metastases is a possible 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.	Expert opinion/A	100%
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.	Expert opinion/A	100%
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	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.	III/C	95%
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/B	95%
The choice of systemic therapy for LMD should take into account the breast cancer subtype and previous treatments.	II/A	100%
Albeit limited, there are some efficacy data in LMD for capecitabine monotherapy, the combination capecitabine + trastuzumab + tucatinib, and for T-DXd.	III/B	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 8 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.

2.12.1. *Central nervous system (CNS) metastases*

Brain metastases occur frequently in patients with ABC, particularly those with HER2+ or triple-negative subtypes [72,73]. Older retrospective studies have reported mixed results on the impact of screening asymptomatic patients with ABC for intracranial disease, with many reporting no OS impact [74,75]. Furthermore, there has historically been a dearth of data quantifying the impact of screening on other important outcomes. At the same time, a large international survey of physicians and patients found that 79% of physicians would order CNS screening if it changed treatment strategy, and 85% of patients expressed a desire to undergo CNS screening, even in the absence of definite evidence for benefit [76]. Data from a non-randomized, prospective screening study in patients with ABC reveal that approximately one-quarter of patients across all subtypes (HR+/HER2-negative, TNBC, and HER2+) who undergo a baseline and 6-month screening MRI will be diagnosed with brain metastases [77]. Data from a second prospective screening study in newly diagnosed patients with ABC, with a brain MRI done at diagnosis of metastatic disease and at time of switch to 2nd and 3rd line systemic therapy, reported that 24% of those with TNBC and 17% with HER2+ ABC were found to have asymptomatic brain metastases [78]. Observational, real-world evidence comparing screened versus non-screened patients show consistent patterns of fewer and smaller brain metastases, fewer neurologic symptoms, fewer seizures, and less use of whole brain radiotherapy (WBRT) in screened populations [79,80]. As the use of stereotactic radiosurgery (SRS) or fractionated stereotactic radiation (FSRT) increases [81,82], due to the improved neuro-cognitive, functional and QoL outcomes compared to WBRT, even in those with multiple lesions, the benefit of identifying brain metastases at a smaller size also proportionally increases, given that the efficacy of SRS decreases and toxicity of SRS (including risk of radionecrosis) increases with increasing lesion size [83]. Finally, knowledge of the presence or absence of brain metastases may now influence systemic therapy choices in a way that was not the case in the past. For example, both the HER2CLIMB regimen (tucatinib + trastuzumab + capecitabine) and T-DXd have substantial CNS activity, in contrast to regimens such as taxane + trastuzumab + pertuzumab [84,85]. Multiple additional prospective trials of CNS screening in patients with ABC are expected to be reported in the next 1-2 years. As we await these data, the existing evidence base, though limited, provides rationale to consider screening in patients at high risk of developing brain metastases and in situations where the knowledge of brain metastases status would impact the choice of systemic therapy.

Crucially, in cases where asymptomatic CNS metastases are detected, decisions on their management must be made in a multi-disciplinary tumor board and with shared decision with the patient, with cautious consideration of the benefits of treatment versus the harms of overtreatment when deciding on treatment modalities.

2.13. ***Section XIII: Supportive and palliative care (see Figs. 6a, 6b, 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. Some supportive care interventions have shown to have a positive impact on survival.	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/A	100%
The panel acknowledges that there is a 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% 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].		100%
Management of CDK4/6 INHIBITOR-INDUCED NEUTROPENIA		
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.	I/A	100%
Patient support is essential. Oxygen is of no use in non-hypoxic patients.	I/A	100%
Opioids are the drug of choice in the palliation of dyspnea.	I/A	100%
Benzodiazepines can be used in patients experiencing anxiety.	II/A	100%
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).	Expert opinion/B	100%
Management of NAUSEA AND VOMITING		
ESMO/MASCC guidelines [86] are available for the management of ChT-induced and morphine-induced nausea and vomiting, and these are endorsed by the ABC community.	Expert opinion/A	100%
There is a need to study nausea and vomiting related to chronic use of anticancer drugs.	Expert opinion/A	100%
Management of ENDOCRINE TOXICITIES 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.).	I/B	100%
Early intervention is recommended.	Expert opinion/A	100%
For grade >2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended.	Expert opinion/A	100%
Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis.	Expert opinion/B	100%
Consider adding steroid dental paste to treat developing ulcerations.	Expert opinion/B	100%
Management of CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)		
CIPN is frequent and potentially dose-limiting. Risk factors for neuropathy and pre-existing neuropathy need to be identified.		100%
No medical prevention can currently be recommended.	II/C	100%
Drug-related factors (dosing, timing, route) can lower the risk of CIPN.	I/A	100%
Cooling and compression (cold and/or tight gloves and socks) are effective and recommended to reduce the incidence and severity of CIPN.	I/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.	II/B	100%
Limited data exists supporting use of acupuncture for risk reduction and alleviation of CIPN.	II/C	100%
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.	I/A	100%
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/topical diclofenac gel) is recommended. 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.	II/A II/C	100% 100%
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. Valid alternatives are: • For postmenopausal symptoms in general: Mind-body interventions, physical training and CBT are effective non-pharmacological treatment options. • For hot flushes: Venlafaxine, oxybutynin, gabapentin, clonidine and acupuncture are available options. • For sleep disturbances: Melatonin There is no convincing evidence that phytotherapeutic drugs improve postmenopausal symptoms. Possible drug interactions must be considered.	I/D I/B I/B II/C I/D	100% 100% 100% 100% 100%
Elinzanetant, *a dual NK1 and NK3 antagonist, was highly effective and well tolerated in a randomized, placebo-controlled phase 3 trial (OASIS-4), for women with early breast cancer taking ET and experiencing >35 high/moderate hot flushes per week.* *Fezolinetant, a NK3 antagonist, is also available for the management of hot flushes, but has not been evaluated in breast cancer patients and has potential liver toxicity.* Where approved, Elinzanetant is an option for patients with ABC as well, if no drug interactions exist with ongoing anticancer therapies.	I/A	94%
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/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). If hormone-free measures are not effective, low-dose estrogen-containing vaginal medication may be used. The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear.	II/B II/B	100% 100%
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.*		
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%
HAIR LOSS		
Chemotherapy induced alopecia is a common and distressing side effect contributing to poor self-image and loss of identity. The incidence and degree of hair loss depend on the drug dose, route and schedule. Scalp cooling is a safe method of minimizing chemotherapy-induced alopecia and has been shown to effectively reduce the incidence of hair loss in certain circumstances.	I/B	100%
Endocrine therapy can cause poor hair regrowth and hair loss similar to male pattern or androgenetic alopecia. The incidence of alopecia from treatment with CDK4/6 inhibitors and endocrine therapy is more than double that of endocrine therapy alone and often more severe, with presentation resembling both androgenetic alopecia and diffuse alopecia. Daily application of topical minoxidil 5% solution or low dose oral minoxidil (1.25mg daily) can be effective in increasing hair shaft and follicle density, with benefit seen after 3 to 6 months. Patients using oral minoxidil should be warned of the possibility of unwanted hair growth on the face.	I/B	96%

In green, NEW/UPDATED ABC 8 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 [86].

3. Management of postmenopausal symptoms

Vasomotor symptoms (VMS; also known as hot flashes) are common side effects of endocrine therapy, in particular in young women receiving LHRH analogs. VMS associated with endocrine therapy or with bilateral oophorectomy are usually more severe than the ones occurring in natural menopause. VMS are often accompanied by sleep disturbances, and both negatively affect quality of life and are associated with treatment non-compliance mainly in the early breast cancer setting.

Elinzanetant 120 mg/day is a non-hormonal, selective dual NK1 and NK3 receptor antagonist approved for the treatment of moderate-to-severe VMS associated with endocrine therapy for breast cancer, based on the OASIS-4 randomized, placebo-controlled phase 3 trial [87] It is well tolerated, with mild somnolence and fatigue being the most common side effects (in about 10% of patients) and no liver toxicity was reported.

Fezolinetant, a NK3 antagonist, is also available for the management of hot flushes, but has not been evaluated in breast cancer patients and has potential liver toxicity [88].

Although the OASIS-4 trial did not include patients with metastatic breast cancer patient, the panel believes that elinzanetant is an option for patients with ABC as well, if no drug interactions exist with ongoing anticancer therapies. Elinzanetant is a weak inhibitor and sensitive substrate of CYP3A4 and based on drug-drug interactions studies, does not need dose adjustments when co-administered with the following medicines: palbociclib, abemaciclib, everolimus, capivasertib, talazoparib, niraparib, olaparib, fulvestrant, imlunestrant, elacestrant, neratinib, capecitabine. Co-administration with ribociclib 400 mg requires elinzanetant dose reduction to 60 mg/day and should be avoided with ribociclib 600 mg (ribociclib at 400 mg is a moderate and at 600 mg is a strong CYP3A4 inhibitor). Co-administration with alpelisib and inavolisib calls for caution and possible elinzanetant dose reduction based on in vitro data. Coadministration with tucatinib, a strong CYP3A4 inhibitor, should be avoided [89].

3.1. Management of hair loss

Alopecia is a common distressing treatment toxicity that negatively impacts body image, quality of life and psycho-social functioning. It is most frequent and severe with cytotoxic agents (particularly anthracyclines or taxanes) and whole brain radiation. However, hair loss may occur with ADCs, CDK4/6 inhibitors and endocrine therapy (male-pattern androgenetic alopecia). Some patients decline cytotoxic options that cause alopecia. Options for alopecia include prevention and treatment. Prevention is applicable to intravenous cytotoxics for which scalp cooling ("cold capping") provides a safe method to reduce temporary chemotherapy-induced alopecia [90,91], although it is variably effective in preserving sufficient hair, with type of chemotherapy regimen being a relevant factor [92]. There is a risk of persistent chemotherapy-induced alopecia affecting the scalp and eyebrows, particularly after higher cumulative doses of docetaxel, and scalp cooling also appears to mitigate against this risk for the scalp [93]. Scalp cooling requires longer time on each treatment day and patients may not persist due to cold intolerance. With longer-term alopecia, improvement over months may be seen from treatment with daily topical minoxidil 5% solution [93] and/or low dose 1.25 mg oral minoxidil daily [94], with the latter potentially associated with unwanted facial hair growth [95]. Topical bimatoprost has shown promise in treating chemotherapy-induced eyelash loss (milphosis) [96] and may also be helpful for eyebrows [97].

3.2. *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 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: 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%

No new statements for this section were developed at ABC 8.
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.

4. Conclusions and future directions

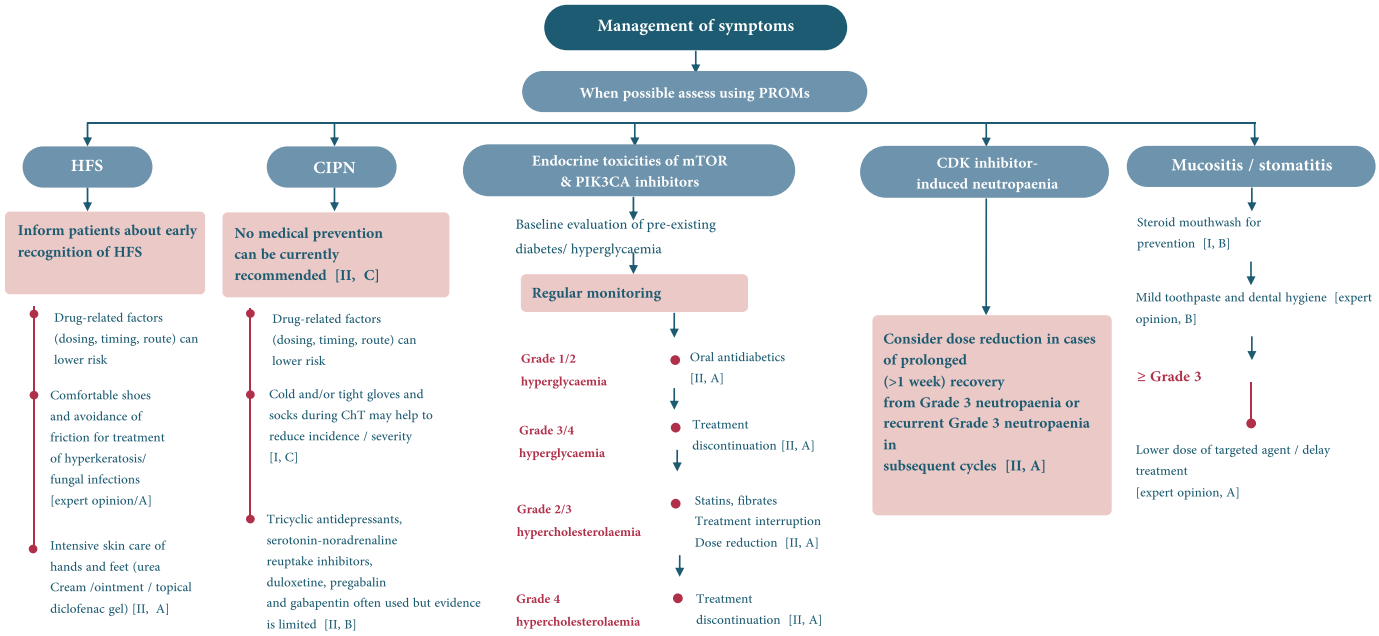
The last 10 years have seen important advances in the management of ABC, which is now much more complex with several new agents and corresponding biomarkers. Since ABC7, advances have occurred in all three main ABC subtypes, and we now have treatment options that significantly impact overall survival and quality of life in all subtypes. Unfortunately, availability in clinical practice of all these new options is very unequal throughout the world, even among high-income countries and within each country, according to individual health coverage.

The ABC consensus guidelines remain one of the most relevant tools for both healthcare providers and patients in treatment decision-making for advanced/metastatic breast cancer. Each guideline has its level of evidence, grade of recommendation and percentage of consensus. Among the more than 300 current recommendations, only in 2 consensus was not reached. Their clinical implementation is often limited by availability, and national or regional adaptations may be needed. The ABC Global Alliance remains available to help with this complex endeavour.

Adequate information and communication are crucial to achieve true shared decision making and patient-centered care, with an individualized balance between efficacy and toxicity of each available option, respecting individual preferences for quality and length of life.

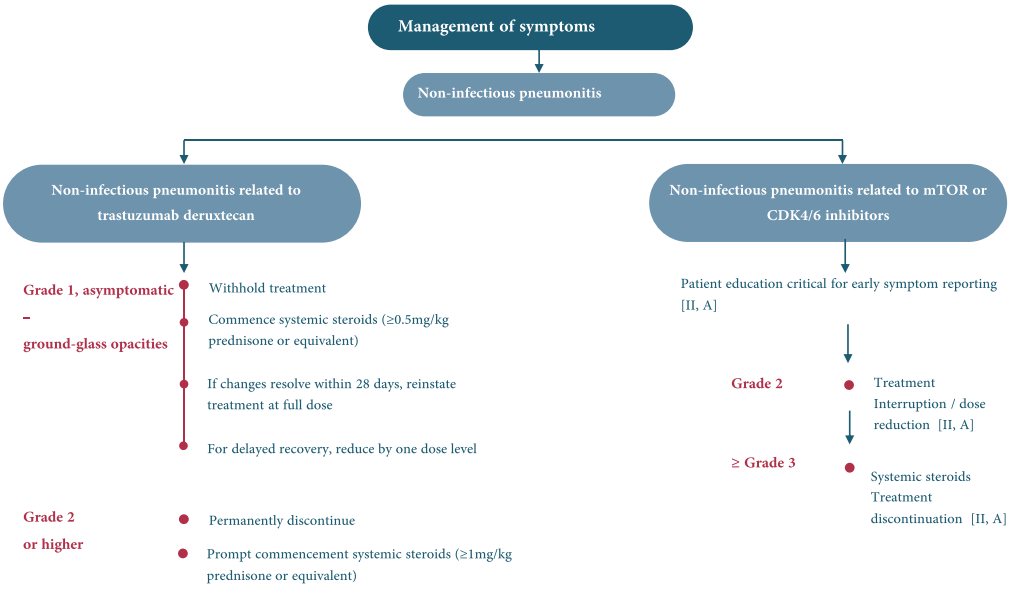
Continuous research, addressing clinically relevant questions, such as optimal treatment sequencing, is fundamental and funding of academic research is crucial. Despite all the advances, advanced/metastatic breast cancer remains an incurable disease for the vast majority of patients.

These guidelines and the updated ABC Global Charter are also powerful tools to advocate for the best available options for the management of people living with ABC, independently of their availability to pay.



ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; HFS, hand and foot syndrome; mTOR, mammalian target of rapamycin; PIK3CA, phosphatidylinositol 3-kinase gene; PROM, patient-reported outcome measure

Fig. 6c. ABC symptom control.



ABC, advanced breast cancer; CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin

Fig. 6d. ABC symptom control.

CRediT authorship contribution statement

Fatima Cardoso: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Joana Mourato Ribeiro:** Writing – original draft, Writing – review & editing. **Eva Schumacher-Wulf:** Writing – review & editing. **Sandra M. Swain:** Writing – original draft, Writing – review & editing. **Shani Paluch-Shimon:** Writing – original draft, Writing – review & editing. **Frederique Penault-Llorca:** Writing – original draft, Writing – review & editing. **Nancy U. Lin:** Writing – original draft, Writing – review & editing. **Prudence A. Francis:** Writing – original draft, Writing – review & editing. **Marion Kuper-Hommel:** Writing – review & editing, Writing – original draft. **Anne May:** Writing – original draft, Writing – review & editing. **Florentine Hilbers:** Writing – original draft, Writing – review & editing. **Angel Guerrero:** Writing – original draft, Writing – review & editing. **Matti S. Aapro:** Writing –

review & editing. **Rania Azmi:** Writing – review & editing. **Jyoti Bajpai:** Writing – review & editing. **Carlos Barrios:** Writing – review & editing. **Laura Biganzoli:** Writing – review & editing. **Fran Boyle:** Writing – review & editing. **Valeria Caceres:** Writing – review & editing. **Lisa A. Carey:** Writing – review & editing. **Mariana Chavez-MacGregor:** Writing – review & editing. **Javier Cortés:** Writing – review & editing. **Rebecca Dent:** Writing – review & editing. **Amanda Drury:** Writing – review & editing. **Nagi S. El Saghir:** Writing – review & editing. **Hesham Elghazaly:** Writing – review & editing. **Alexandru Eniu:** Writing – review & editing. **Lesley Fallowfield:** Writing – review & editing. **Sandra Ximena Franco Millan:** Writing – review & editing. **Karen Gelmon:** Writing – review & editing. **Jenny Gilchrist:** Writing – review & editing. **Joseph Gligorov:** Writing – review & editing. **William J. Gradishar:** Writing – review & editing. **Nadia Harbeck:** Writing – review & editing. **Xichun Hu:** Writing – review & editing. **Orit Kaidar-Person:** Writing – review & editing. **Ranjit Kaur:** Writing – review & editing. **Belinda Kiely:** Writing – review & editing. **Sung-Bae Kim:** Writing – review & editing. **Sarah Kutika Nyagabona:** Writing – review & editing. **Maryam Lustberg:** Writing – review & editing. **Volkmar Mueller:** Writing – review & editing. **Miriam Mutebi:** Writing – review & editing. **Silvia Neciosup:** Writing – review & editing. **Shinji Ohno:** Writing – review & editing. **Barbara Pistilli:** Writing – review & editing. **Hope S. Rugo:** Writing – review & editing. **Tanja Spanic:** Writing – review & editing. **Janice Tsang:** Writing – review & editing. **Peter Vuylsteke:** Writing – review & editing. **Binghe Xu:** Writing – review & editing. **Larry Norton:** Writing – review & editing. **Eric P. Winer:** Writing – review & editing.

Disclosures

Fatima Cardoso: Receipt of honoraria or consultation fees: Amgen, Astellas/Medivation, AstraZeneca, Bayer, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, Touchim. **Joana Ribeiro:** Receipt of honoraria or consultation fees, either personal or institutional: AstraZeneca, Daiichi-Sankyo, Gilead, MSD, Novartis, Roche/Genentech. **Sandra M. Swain:** Receipt of honoraria or consultation fees: AstraZeneca, Chugai, Merck. Stock shareholder: Immunome BOD, stock options only. Other support (please specify): Travel in kind: Genentech/Roche, Chugai, Immunome. Consulting TerSera. Napo Pharmaceuticals scientific advisory board. Roche steering committee SaFina and INAVO 122. **Shani Paluch-Shimon:** Receipt of grants/research supports: BCRF, Pfizer, SPCC. Receipt of honoraria or consultation fees: Roche, AstraZeneca, Novartis, Lily, Pfizer, MSD, Exact Sciences, Gilead, Stemline, Summit therapeutics. Participation in a sponsored speakers' bureau: Roche, AstraZeneca, Novartis, Lily, Pfizer, MSD, Exact Sciences, Gilead, Stemline. **Frédérique Penault-Llorca**: Receipt of honoraria or consultation fees: AbbVie, Amgen, Astellas, AstraZeneca, Beigene, BMS, Core2ed, EISAI, Exact Sciences, Gilead, GSK, Illumina, Invitae, Lilly, Menarini/Stemline, MSD, Myriad, Nanostring, Novartis, Pierre-Fabre, Pfizer, Roche. Institutional grants and research supports: AbbVie, Astellas, AstraZeneca, Bayer, BMS, Genomic Health, Illumina, Lilly, Medscape, MSD, Myriad, Nanostring, Novartis, Pfizer, Pierre-Fabre, Roche. Travel grants: AbbVie, AstraZeneca, BMS, Gilead, Lilly, MSD, Novartis, Pfizer, Pierre-Fabre, Roche. **Nancy U. Lin:** Institutional Research Support: Genentech, Pfizer, Merck, Seattle Genetics, Zion Pharmaceuticals, Olema Pharmaceuticals, AstraZeneca. Consulting Honoraria: Seattle Genetics, Daichii-Sankyo, AstraZeneca, Olema Pharmaceuticals, Janssen, Blueprint Medicines, Stemline/Menarini, Artera Inc., Eisai, Shorla Oncology. Royalties – Up to date (book). Travel: Olema, AstraZeneca. **Prudence A. Francis:** Receipt of honoraria or consultation fees: Eli Lilly. **Marion Kuper-Hommel:** Receipt of honoraria or consultation fees: AstraZeneca, Novartis. **Anne May:** Receipt of honoraria or consultation fees: Fee paid to institution for developing an e-learning on exercise and cancer (Eli Lilly). **Angel Guerrero**: Advisory/Consultancy: AstraZeneca, Novartis, MSD, Pierre-Fabre, Exact Sciences. Speaker Bureau/Expert testimony: Roche, AstraZeneca, Novartis, MSD, Pfizer, Lilly, Pierre-Fabre. Research grant/Funding (institution): Pfizer, Lilly. Travel/Accommodation/Expenses: Roche, Novartis, Pfizer, Gilead. **Matti S. Aapro:** Receipt of grants/research supports: Amgen, Helsinn, Novartis, Pfizer, Sandoz, Vifor. Receipt of honoraria or consultation fees: Amgen, Astellas, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo, Genomic Health (Exact Sciences), GSK, Helsinn Healthcare SA, Knight Therapeutics Inc., Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, and Vifor Pharma. **Jyoti Bajpai:** Receipt of grants/research supports: Institutional support from AstraZeneca, MSD Pharmaceuticals, Eli Lilly (within 2 years in either current or prior institution). Receipt of honoraria or consultation fees: Merck Specialities Private Limited, Eisai Phamaceuticals India Private Limited, Novartis Healthcare, Private Limited, Astella Pharma India Private Limited, GlaxoSmithKline Phamaceuticals Limited, AstraZeneca, Lupin Limited, Bristol Myers Squibb, MSD Pharmaceuticals, Pfizer, FoundationOne, Intas Pharmaceuticals Limited, Emcure, DRL, Alkem Laboratories Ltd, Advance Medilink Private Limited, Mankind Oncology, Zydus, Samarth Lifescience, MSN Labs, Onecell Diagnostics. **Carlos Barrios**: Grants/research support to the institution: Amgen, Astra Zeneca, Aveo Oncology, Beigene, Bicycle, BioNTech, Boehringer Ingelheim, BMS, Celcuity, CELLTRION, Daiichi Sankyo, Dizal Pharma, Fortrea, Genmab, Gilead Sciences, GSK, ICON, IQVIA, Intrials, Janssen, Jazz Pharmaceuticals, Labcorp, Lilly, Abxience Research, Medpace, MEDSIR, Merus, Mirati Therapeutics, MSD, Novartis, Novocure, Nuvisan, OBI Pharma, Parexel, Pfizer, PharmaMar, PPD, Regeneron, Roche/Genentech, Samsung, Sandoz, Seagen, Servier, Shanghai Henlius, Stemline Therapeutics, Syneos Health, Taiho, Tolmar, TRIO, Worldwide. Ownership or Stocks: Tummi, MEDSir, CPO. Advisory Boards, Consulting, Travel, Presentation Honoraria: Adium, Novartis, Pfizer, Roche/Genentech, MSD, Astra Zeneca, Lilly, Daiichi, Gilead. **Laura Biganzoli:** Receipt of grants/research supports: Celgene, Genomic Health, Novartis. Receipt of honoraria or consultation fees: Amgen, AstraZeneca, Boehringer-Ingelheim, Daiichi-Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Menarini, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, SeaGen. Other support (please specify): Travel support: AstraZeneca, Daiichi-Sankyo, Pfizer, Roche. **Frances Boyle:** Receipt of honoraria or consultation fees: Pfizer, Novartis, Roche, Gilead, Lilly, Menarini, AZ. Other support (please specify): MBC Action Australia receives AZ support. **Valeria Caceres:** Receipt of grants/research supports: Gilead, AZ, Roche, MSD. Participation in a sponsored speakers' bureau: Gilead, AZ, Roche, MSD, ABBVIE. **Mariana Chavez-MacGregor:** Receipt of grants/research supports: Lilly. Receipt of honoraria or consultation fees: Gilead, Exact Sciences, Pfizer, Novartis, AZ, Genentech. **Javier Cortés:** Receipt of grants/research supports: Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F.Hoffman-La Roche, Guardant health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Iqvia, Queen Mary University of London. Receipt of honoraria or consultation fees: Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp&Dohme, Daiichi Sankyo, AstraZeneca, Gilead, Steamline Therapeutics. Stock shareholder: MAJ3 Capital, Leuko (relative). Other support (please specify): Consulting/Advisor: Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, BridgeBio, Biontech, Biocon, Circle Pharma, Delcath Systems. Travel, accommodation, expenses: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead, Merck Sharp&Dhome, Stemline Therapeutics. Patents: Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés.US 2019/0338368 A1. LICENSED.

Rebecca Dent: Receipt of grants/research supports: AstraZeneca & Roche. Receipt of honoraria or consultation fees: AstraZeneca, MSD, Pfizer, Eisai, Novartis, Daiichi Sankyo, Roche, Eli Lilly & Company (DKSH), Genentech, Gilead, BioNtech. Other support (please specify): Travel & Advisory Board: AstraZeneca, MSD, Pfizer, Eisai, Novartis, Daiichi Sankyo, Roche, Eli Lilly & Company (DKSH), Genentech, Gilead, BioNtech. **Amanda Drury:** Receipt of grants/research supports: Sharing Progress in Cancer Care/Pfizer – Grant to develop, implement and evaluate an eLearning programme in advanced breast cancer for nurses (ABC4Nurses). Receipt of honoraria or consultation fees: Sharing Progress in Cancer Care – Honoraria – Reviewer for the RFP Project in Early Breast Cancer; European Commission – Consultancy – Horizon Europe Cancer Mission Board. **Nagi S. El Saghir**: Honoraria for lectures from AstraZeneca, Novartis and Roche. **Alexandru Eniu:** Receipt of grants/research supports: AstraZeneca, Roche, Pfizer, Novartis. Receipt of honoraria or consultation fees: Gilead, Sanofi, Novartis, Janssen, Daiichi- Sankyo, AstraZeneca, Eli Lilly. **Lesley Fallowfield:** Receipt of grants/research supports: Exact Sciences, Veracyte, A2, Lilly. Receipt of honoraria or consultation fees: A2, Novartis, Pfizer, Lilly, Beigene. **Sandra Ximena Franco Millan**: Receipt of grants/research supports: Only to my institution MSD/ROCHE. Receipt of honoraria or consultation fees: AstraZeneca, Gilead, Novartis, Lilly, Pfizer, MSD. Participation in a sponsored speakers' bureau: AstraZeneca, Gilead, Novartis, Lilly, Pfizer, MSD, Roche. **Karen Gelmon:** Receipt of grants/research supports: BMS. Receipt of honoraria or consultation fees: AstraZeneca, Novartis, Pfizer, Gilead, Eli Lilly, Celcuity, City of Hope, Merck. Participation in a sponsored speakers' bureau: Novartis, AstraZeneca. **Jenny Gilchrist:** Receipt of honoraria or consultation fees: AstraZeneca, Lilly, Novartis, Gilead. Participation in a sponsored speakers' bureau: AstraZeneca, Lilly, Novartis, Gilead. **William J. Gradishar**: DMC/advisory boards: Gilead, AZ, Pfizer, Carrick, Caris, Genentech, Lilly. **Ranjit Kaur:** Receipt of honoraria or consultation fees: Pfizer, Roche. **Belinda Kiely:** Receipt of honoraria or consultation fees: Novartis, Gilead Sciences. Participation in a sponsored speakers' bureau: Gilead, AstraZeneca, Esai, MSD, Eli Lilly. Other support (please specify): conference fees: Novartis, MSD, Pfizer, Eli Lilly. **Sung-Bae Kim:** Receipt of grants/research supports: Sanofi-Genzyme. Receipt of honoraria or consultation fees: AstraZeneca, Beigene, BNT, DaeHwa Pharma Daiichi-Sankyo, Lilly, OBI Pharma. Stock shareholder: Genopeaks. Other support (please specify): Lilly (medical travel). **Sarah Kutika Nyagabona:** Receipt of grants/research supports: Pfizer Inc. (through MNH Quality Improvement support for Patient Navigation). **Maryam Lustberg:** Receipt of honoraria or consultation fees: Lilly, AZ, Daiichi, Bayer, Menarini, Novartis, Sandoz. Participation in a sponsored speakers' bureau: Lilly. **Volkmar Mueller:** Receipt of grants/research supports: Institutional research support: Novartis, Roche, Seagen, Genentech, AstraZeneca. Receipt of honoraria or consultation fees: Roche, Pierre Fabre, PINK, ClinSol, Novartis, MSD, Daiichi-Sankyo, Eisai, Lilly, Seagen, Gilead, Stemline. Participation in a sponsored speakers' bureau: AstraZeneca, arsTempi, Daiichi-Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Lilly, Medscape, Gilead, Pierre Fabre, iMED Institut. Other support (please specify): Travel grants: AstraZeneca, Roche, Pfizer, Daiichi Sankyo, Gilead. **Silvia Neciosup**, Receipt of grants/research supports: Roche, AstraZeneca. Receipt of honoraria or consultation fees: Roche, Novartis. Participation in a sponsored speakers' bureau: Roche, Novartis, AstraZeneca. **Shinji Ohno**: Participation in a sponsored speakers' bureau: Eisai, Kyowa Kirin, Lilly, Nippon Kayaku. **Barbara Pistilli:** Receipt of grants/research supports: Astra Zeneca, Daiichi-Sankyo, Gilead, Seagen, MSD. Receipt of honoraria or consultation fees: AstraZeneca (institutional), Seagen (institutional), Gilead (institutional), Novartis (institutional), Lilly (institutional), MSD (institutional), Pierre Fabre (personal), Daiichi-Sankyo (institutional/personal). Other support (please specify): Travel support: AstraZeneca; Pierre Fabre; MSD; Daiichi-Sankyo; Pfizer, Accord and Roche. **Hope S. Rugo:** Receipt of grants/research supports: Novartis, Stemline, Merck, Lilly, Gilead Sciences, AstraZeneca, Genentech, Daiichi Sankyo, Pfizer, Ambryx. Receipt of honoraria or consultation fees: Napo, Bristol Myers Squibb, Helsinn. **Janice Tsang:** Receipt of honoraria or consultation fees: AstraZeneca, Daiichi Sankyo. Participation in a sponsored speakers' bureau: AstraZeneca, Daiichi Sankyo, Lilly, Lucence, Novartis. **Peter Vuylsteke:** Receipt of honoraria or consultation fees: Roche, Novartis, MSD. Participation in a sponsored speakers' bureau: MSD. Other support (please specify): Travel grant: MSD.

Eva Schumacher-Wulf, Rania Azmi, Lisa Carey, Xichun Hu, Orit Kaidar-Person, Julia Maues, Miriam Mutebi, Lesley Stephen and Florentine Hilbers reported no significant relationships.

Hesham Elghazaly, Joseph Gligorov, Larry Norton, Tanja Spanic, and Eric P. Winer have not submitted a **declaration** of competing interest form.

Editorial note

Given their role as editorial board member, Fatima Cardoo, Karen Gelmon, Volkmar Mueller and Hope Rugo had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Funding

No funding has been received for the preparation of these guidelines.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Given their role as editorial board member, Fatima Cardoso, Karen Gelmon, Volkmar Mueller and Hope Rugo had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2026.104921.

References

[1] Eniu A, Chidebe RCW, Vuylsteke P, Chavez-MacGregor M, Penault-Llorca F, Lopes G, et al. Improving equitable access to comprehensive care for people with advanced breast cancer: a global expert review and call-to-action for 2025–2035 (Goal 9). Breast 2025;84:104612. https://doi.org/10.1016/j.breast.2025.104612.
[2] Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 2012;21:242–52. https://doi.org/10.1016/j.breast.2012.03.003.
[3] Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014;25:1871–88. https://doi.org/10.1093/annonc/mdu385.
[4] Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, et al. 3rd ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 2017;28:16–33. https://doi.org/10.1093/annonc/mdw544.
[5] Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4). Ann Oncol 2018;29:1634–57. https://doi.org/10.1093/annonc/mdy192.
[6] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623–49. https://doi.org/10.1016/j.annonc.2020.09.010.
[7] https://www.abcglobalalliance.org/n.d.
[8] Cardoso F, Ventura R, Attfield G, Lewis A, Gelmon K. Knowledge in motion: a decade reviewed, a future defined – the ABC global alliance 2015–2025 decade report and 2025–2035 global charter. Breast 2025;84:104601. https://doi.org/10.1016/j.breast.2025.104601.
[9] ABC Global Alliance. ABC global charter report (2015–2025). ABC Global Alliance; 2025. https://www.abcglobalalliance.org/abc-global-charter-report#2015-2025. [Accessed 28 April 2026].

[10] Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, Matos L, Gelmon K, Aapro MS, et al. 6th and 7th international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). Breast 2024;76:103756. https://doi.org/10.1016/j.breast.2024.103756.
[11] Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001;33:139–44. https://doi.org/10.1086/321805.
[12] Agostinetto E, Sotiriou C, Ignatiadis M, Antoniolli Crestani T, Venet D, Tyekucheva S, et al. Clinico-molecular characteristics associated with outcomes in breast cancer patients treated with CDK4/6 inhibitors: results from the AURORA molecular screening initiative. J Clin Oncol 2023;41. https://doi.org/10.1200/JCO.2023.41.16_suppl.1019. 1019–1019.
[13] Lambertini M, Blondeaux E, Bisagni G, Mura S, De Placido S, De Laurentiis M, et al. Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies. EClinicalMedicine 2023;59:101931. https://doi.org/10.1016/j.eclinm.2023.101931.
[14] Guerrero A, Alvarez I, Antolín Novoa S, Cruz Jurado J, Rodriguez Sanchez CA, Martinez P, et al. Comprehensive clinical characteristics and ctDNA mutational profile analysis of endocrine resistance/sensitivity to adjuvant ET therapy in luminal breast cancer from the GEICAM/2014-03_RegistEM registry. J Clin Oncol 2024;42. https://doi.org/10.1200/JCO.2024.42.16_suppl.1011. 1011–1011.
[15] Llombart-Cussac A, Pérez-García JM, Bellet M, Dalenc F, Gil-Gil M, Ruiz-Borrego M, et al. Extended follow-up of palbociclib with fulvestrant or letrozole for endocrine-sensitive, hormone receptor-positive/HER2-negative advanced breast cancer in the PARSIFAL trial. ESMO Open 2025;10:105309. https://doi.org/10.1016/j.esmoop.2025.105309.
[16] Hiensch AE, Depenbusch J, Schmidt ME, Monninkhof EM, Pelaez M, Clauss D, et al. Supervised, structured and individualized exercise in metastatic breast cancer: a randomized controlled trial. Nat Med 2024;30:2957–66. https://doi.org/10.1038/s41591-024-03143-y.
[17] Schmidt ME, Hiensch AE, Depenbusch J, Monninkhof EM, Belloso J, Clauss D, et al. Impact of exercise on sexual health, body image, and therapy-related symptoms in women with metastatic breast cancer: the randomized controlled <scp>PREFERABLE</scp> - <scp>EFFECT</scp> trial. Int J Cancer 2025;157:490–503. https://doi.org/10.1002/ijc.35429.
[18] Wang S, Yang T, Qiang W, Shen A, Zhao Z, Chen X, et al. Effectiveness of physical exercise on the cardiovascular system in breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Compl Ther Clin Pract 2021;44:101426. https://doi.org/10.1016/j.ctcp.2021.101426.
[19] Yamani N, Ahmed A, Khan M, Wilson Z, Shakoor M, Qadri SF, et al. Effectiveness of exercise modalities on breast cancer patient outcomes: a systematic review and meta-analysis. Cardio-Oncology 2024;10:38. https://doi.org/10.1186/s40959-024-00235-z.
[20] Jang MK, Park S, Raszewski R, Park CG, Doorenbos AZ, Kim S. Prevalence and clinical implications of sarcopenia in breast cancer: a systematic review and meta-analysis. Support Care Cancer 2024;32:328. https://doi.org/10.1007/s00520-024-08532-0.
[21] Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Breast Cancer Res Treat 2016;158:497–507. https://doi.org/10.1007/s10549-016-3900-2.
[22] Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc 2019;51:2375–90. https://doi.org/10.1249/MSS.0000000000002116.
[23] Schouten AEM, Hiensch AE, Frederix GWJ, Monninkhof EM, Schmidt ME, Clauss D, et al. Supervised exercise for patients with metastatic breast cancer: a cost-utility analysis alongside the PREFERABLE-EFFECT randomized controlled trial. J Clin Oncol 2025;43:1325–36. https://doi.org/10.1200/JCO-24-01441.
[24] Gubler-Gut BE, Pöhlmann J, Flatz A, Schwenkglenks M, Rohrmann S. Cost-effectiveness of physical activity interventions in cancer survivors of developed countries: a systematic review. J Cancer Surviv 2021;15:961–75. https://doi.org/10.1007/s11764-021-01002-0.
[25] Campbell KL, Cormie P, Weller S, Alibhai SMH, Bolam KA, Campbell A, et al. Exercise recommendation for people with bone metastases: expert consensus for health care providers and exercise professionals. JCO Oncol Pract 2022;18:e697–709. https://doi.org/10.1200/OP.21.00454.
[26] Sonke GS, van Ommen-Nijhof A, Wortelboer N, van der Noort V, Swinkels ACP, Blommestein HM, et al. Early versus deferred use of CDK4/6 inhibitors in advanced breast cancer. Nature 2024;636:474–80. https://doi.org/10.1038/s41586-024-08035-2.
[27] Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38:3987–98. https://doi.org/10.1200/JCO.20.02514.
[28] Slamon D, Lipatov O, Nowecki Z, McAndrew N, Kukielka-Budny B, Stroyakovskiy D, et al. Ribociclib plus endocrine therapy in early breast cancer. N Engl J Med 2024;390:1080–91. https://doi.org/10.1056/NEJMoa2305488.
[29] Mayer EL, Ren Y, Wagle N, Mahtani R, Ma C, DeMichele A, et al. PACE: a randomized phase II study of fulvestrant, palbociclib, and avelumab after progression on cyclin-dependent kinase 4/6 inhibitor and aromatase inhibitor for hormone receptor–positive/human epidermal growth factor receptor–negative metastatic breast cancer. J Clin Oncol 2024;42:2050–60. https://doi.org/10.1200/JCO.23.01940.
[30] Kalinsky K, Accordino MK, Chiuzan C, Mundi PS, Sakach E, Sathe C, et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor–positive, human epidermal growth factor receptor 2–Negative metastatic breast cancer: MAINTAIN trial. J Clin Oncol 2023;41:4004–13. https://doi.org/10.1200/JCO.22.02392.
[31] Llombart-Cussac A, Harper-Wynne C, Perelló A, Hennequin A, Fernández-Ortega A, Colleoni M, et al. Second-line endocrine therapy with or without palbociclib rechallenge in patients with hormone receptor–positive/human epidermal growth factor receptor 2–Negative advanced breast cancer: PALMIRA trial. J Clin Oncol 2025;43:2084–93. https://doi.org/10.1200/JCO-24-01865.
[32] Kalinsky K, Bianchini G, Hamilton E, Graff SL, Park KH, Jeselsohn R, et al. Abemaciclib plus fulvestrant in advanced breast cancer after progression on CDK4/6 inhibition: results from the phase III postMONARCH trial. J Clin Oncol 2025;43:1101–12. https://doi.org/10.1200/JCO-24-02086.
[33] Bidard F-C, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–Negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol 2022;40:3246–56. https://doi.org/10.1200/JCO.22.00338.
[34] Jhaveri KL, Neven P, Casalnuovo ML, Kim S-B, Tokunaga E, Aftimos P, et al. Imlunestrant with or without Abemaciclib in advanced breast cancer. N Engl J Med 2025;392:1189–202. https://doi.org/10.1056/NEJMoa2410858.
[35] Bidard F-C, Mayer EL, Park YH, Janni W, Ma C, Cristofanilli M, et al. First-line camizestrant for emerging *ESR1* -Mutated advanced breast cancer. N Engl J Med 2025;393:569–80. https://doi.org/10.1056/NEJMoa2502929.
[36] De Laurentiis M, Ferreira AM, Gligorov J, Dobi E, Costa L, Vidal M, et al. Abstract RF7-02: alpelisib plus fulvestrant for PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer after a CDK4/6 inhibitor (EPIK-B5): phase III, randomized, double-blind, placebo-controlled, multicenter study. Clin Cancer Res 2026;32. https://doi.org/10.1158/1557-3265.SABCS25-RF7-02. RF7-02-RF7-02.
[37] Turner NC, Im S-A, Saura C, Juric D, Loibl S, Kalinsky K, et al. Inavolisib-based therapy in *PIK3CA* -Mutated advanced breast cancer. N Engl J Med 2024;391:1584–96. https://doi.org/10.1056/NEJMoa2404625.
[38] Jhaveri KL, Im S-A, Saura C, Loibl S, Kalinsky K, Schmid P, et al. Overall survival with Inavolisib in *PIK3CA* -Mutated advanced breast cancer. N Engl J Med 2025;393:151–61. https://doi.org/10.1056/NEJMoa2501796.
[39] Hurvitz SA, Layman RM, Curigliano G, André F, Cristofanilli M, Kim S-B, et al. VIKTORIA-1 trial of gedatolisib plus fulvestrant with or without palbociclib in hormone Receptor–Positive/HER2−/PIK3CA wild-type advanced breast cancer. J Clin Oncol 2026;44:1108–19. https://doi.org/10.1200/JCO-25-02643.
[40] Bardia A, Hu X, Dent R, Yonemori K, Barrios CH, O'Shaughnessy JA, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. N Engl J Med 2024;391:2110–22. https://doi.org/10.1056/NEJMoa2407086.
[41] Bardia A, Jhaveri K, Im S-A, Pernas Simon S, De Laurentiis M, Wang S, et al. LBA11 Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer (BC): primary results from the randomised phase III TROPION-Breast01 trial. Ann Oncol 2023;34:S1264–5. https://doi.org/10.1016/j.annonc.2023.10.015.
[42] Jhaveri KL, Park Y, Barrios C, Curigliano G, Iwata H, Cortés J, et al. Abstract GS1-09: sacituzumab govitecan vs chemotherapy as first therapy after endocrine therapy in HR+/HER2− (IHC 0, 1+, 2+/ISH−) metastatic breast cancer: primary results from ASCENT-07. Clin Cancer Res 2026;32. https://doi.org/10.1158/1557-3265.SABCS25-GS1-09. GS1-09-GS1-09.
[43] Baselga J, Cortés J, Kim S-B, Im S-A, Hegg R, Im Y-H, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–19. https://doi.org/10.1056/NEJMoa1113216.
[44] Swain SM, Miles D, Kim S-B, Im Y-H, Im S-A, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:519–30. https://doi.org/10.1016/S1470-2045(19)30863-0.
[45] Cortés J, Kim S-B, Chung W-P, Im S-A, Park YH, Hegg R, et al. Trastuzumab deruxtecan versus Trastuzumab emtansine for breast cancer. N Engl J Med 2022;386:1143–54. https://doi.org/10.1056/NEJMoa2115022.
[46] Cortés J, Hurvitz SA, Im S-A, Iwata H, Curigliano G, Kim S-B, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. Nat Med 2024;30:2208–15. https://doi.org/10.1038/s41591-024-03021-7.
[47] Tolaney SM, Jiang Z, Zhang Q, Barroso-Sousa R, Park YH, Rimawi MF, et al. Trastuzumab Deruxtecan plus pertuzumab for HER2-Positive metastatic breast cancer. N Engl J Med 2026;394:551–62. https://doi.org/10.1056/NEJMoa2508668.
[48] Metzger O, Mandrekar S, Goel S, Gligorov J, Lim E, Ciruelos E, et al. Palbociclib for Hormone-Receptor–Positive, HER2-Positive advanced breast cancer. N Engl J Med 2026;394:451–62. https://doi.org/10.1056/NEJMoa2511218.
[49] Dieras V, Curigliano G, Martin M, Lerebours F, Tsurutani J, Savard M-F, et al. HER2CLIMB-05: a phase III study of tucatinib versus placebo in combination with trastuzumab and pertuzumab as first-line maintenance therapy for HER2+ metastatic breast cancer. J Clin Oncol 2026;44:1597–607. https://doi.org/10.1200/JCO-25-02600.

[50] Hamilton E, Curigliano G, Martin M, Lerebours F, Tsurutani J, Savard M, et al. Abstract GS1-01: Her2climb-05: a randomized, double-blind, phase 3 study of tucatinib versus placebo in combination with trastuzumab and pertuzumab as maintenance therapy for her2+ metastatic breast cancer. Clin Cancer Res 2026;32. https://doi.org/10.1158/1557-3265.SABCS25-GS1-01. GS1-01-GS1-01.
[51] Tolaney SM, de Azambuja E, Kalinsky K, Loi S, Kim S-B, Yam C, et al. Sacituzumab Govitecan plus pembrolizumab for advanced triple-negative breast cancer. N Engl J Med 2026;394:354–66. https://doi.org/10.1056/NEJMoa2508959.
[52] Cortes J, Rugo HS, Cescon DW, Im S-A, Yusof MM, Gallardo C, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med 2022;387:217–26. https://doi.org/10.1056/NEJMoa2202809.
[53] Cortés J, Punie K, Barrios C, Hurvitz SA, Schneeweiss A, Sohn J, et al. Sacituzumab Govitecan in untreated, advanced triple-negative breast cancer. N Engl J Med 2025;393:1912–25. https://doi.org/10.1056/NEJMoa2511734.
[54] Dent R, Shao Z, Schmid P, Cortes J, Cescon DW, Saji S, et al. Datopotamab deruxtecan in patients with untreated, advanced triple-negative breast cancer (TROPION-Breast02): a randomised, open-label, international, phase III trial. Ann Oncol 2026;37:1066–80. https://doi.org/10.1016/j.annonc.2026.03.008.
[55] Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. N Engl J Med 2017;377:523–33. https://doi.org/10.1056/NEJMoa1706450.
[56] Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018;379:753–63. https://doi.org/10.1056/NEJMoa1802905.
[57] Mosele MF, Westphalen CB, Stenzinger A, Barlesi F, Bayle A, Bièche I, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO precision medicine working group. Ann Oncol 2024;35:588–606. https://doi.org/10.1016/j.annonc.2024.04.005.
[58] Burstein HJ, DeMichele A, Fallowfield L, Somerfield MR, Henry NL, Henry NL, et al. Endocrine and targeted therapy for hormone receptor–positive, human epidermal growth factor receptor 2–Negative metastatic breast Cancer—Capivasertib-Fulvestrant: ASCO rapid recommendation update. J Clin Oncol 2024;42:1450–3. https://doi.org/10.1200/JCO.24.00248.
[59] Bhave MA, Quintanilha JCF, Tukachinsky H, Li G, Scott T, Ross JS, et al. Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+) HER2(−) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. Breast Cancer Res Treat 2024;207:599–609. https://doi.org/10.1007/s10549-024-07376-w.
[60] Pascual J, Attard G, Bidard F-C, Curigliano G, De Mattos-Arruda L, Diehn M, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO precision medicine working group. Ann Oncol 2022;33:750–68. https://doi.org/10.1016/j.annonc.2022.05.520.
[61] Burstein HJ, DeMichele A, Somerfield MR, Henry NL. Testing for *ESR1* mutations to guide therapy for hormone receptor–positive, human epidermal growth factor receptor 2–Negative metastatic breast cancer: ASCO guideline rapid recommendation update. J Clin Oncol 2023;41:3423–5. https://doi.org/10.1200/JCO.23.00638.
[62] Rakha EA, Tan PH, Van Bockstal MR, Allison KH, Brogi E, Callagy G, et al. International expert consensus recommendations for HER2 reporting in breast cancer: focus on HER2-Low and ultralow categories. Mod Pathol 2026;39:100925. https://doi.org/10.1016/j.modpat.2025.100925.
[63] Solarewicz J, Allison KH. Hormone receptor and HER2 testing in breast cancer. Surg Pathol Clin 2025;18:735–50. https://doi.org/10.1016/j.path.2025.07.004.
[64] Dong Y, Xu Y, Jiang X, Xu L, Yu R-J, Wang R, et al. HER2-low and ultralow expression of invasive breast carcinoma: clinicopathological features and immunohistochemical consistency analysis. NPJ Breast Cancer 2025;12:9. https://doi.org/10.1038/s41523-025-00872-2.
[65] Jhaveri K, Eli LD, Wildiers H, Hurvitz SA, Guerrero-Zotano A, Unni N, et al. Neratinib + fulvestrant + trastuzumab for HR-positive, HER2-negative, HER2-mutant metastatic breast cancer: outcomes and biomarker analysis from the SUMMIT trial. Ann Oncol 2023;34:885–98. https://doi.org/10.1016/j.annonc.2023.08.003.
[66] Okines AFC, Curigliano G, Mizuno N, Oh D-Y, Rorive A, Soliman H, et al. Tucatinib and trastuzumab in HER2-mutated metastatic breast cancer: a phase 2 basket trial. Nat Med 2025;31:909–16. https://doi.org/10.1038/s41591-024-03462-0.
[67] Harbeck N, Modi S, Pusztai L, Ohno S, Wu J, Kim S-B, et al. Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11): a randomised, open-label, multicentre, phase III trial. Ann Oncol 2026;37:166–79. https://doi.org/10.1016/j.annonc.2025.10.019.
[68] Loibl S, Park YH, Shao Z, Huang C-S, Barrios C, Abraham J, et al. Trastuzumab deruxtecan in residual HER2-Positive early breast cancer. N Engl J Med 2026;394:845–57. https://doi.org/10.1056/NEJMoa2514661.
[69] von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-Positive breast cancer. N Engl J Med 2019;380:617–28. https://doi.org/10.1056/NEJMoa1814017.
[70] Geyer CE, Untch M, Huang C-S, Mano MS, Mamounas EP, Wolmark N, et al. Survival with trastuzumab emtansine in residual HER2-Positive breast cancer. N Engl J Med 2025;392:249–57. https://doi.org/10.1056/NEJMoa2406070.
[71] Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO clinical practice guidelines. Ann Oncol 2020;31:1650–63. https://doi.org/10.1016/j.annonc.2020.07.019.
[72] Kuksis M, Gao Y, Tran W, Hoey C, Kiss A, Komorowski AS, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. Neuro Oncol 2021;23:894–904. https://doi.org/10.1093/neuonc/noaa285.
[73] Sammons SL, Sanglier T, Leone JP, Erick TK, Lambert P, Montemurro F, et al. Prevalence by therapy line and incidence of breast cancer brain metastases in 18 075 patients. J Natl Cancer Inst: J Natl Cancer Inst 2025;117:1565–72. https://doi.org/10.1093/jnci/djaf048.
[74] Miller KD, Weathers T, Haney LG, Timmerman R, Dickler M, Shen J, et al. Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. Ann Oncol 2003;14:1072–7. https://doi.org/10.1093/annonc/mdg300.
[75] Niwińska A, Tacikowska M, Murawska M. The effect of early detection of occult brain metastases in HER2-Positive breast cancer patients on survival and cause of death. Int J Radiat Oncol Biol Phys 2010;77:1134–9. https://doi.org/10.1016/j.ijrobp.2009.06.030.
[76] Matos L, van Ramshorst M, Müller V, Agostinetto E, Linn S, Lambertini M, et al. Brain imaging screening in metastatic breast cancer: patients' and physicians' perspectives. Breast 2025;84:104558. https://doi.org/10.1016/j.breast.2025.104558.
[77] Ahmed KA, Kim Y, Armaghani AJ, Arrington JA, Costa RL, Czerniecki BJ, et al. Phase II trial of brain MRI surveillance in stage IV breast cancer. Neuro Oncol 2025;27:1550–8. https://doi.org/10.1093/neuonc/noaf018.
[78] Kim GM, Sohn JH, Kim MH, Kim S-G, Park HS, Jang JH, et al. Abstract PO2-27-09: clinical impact of routine MRI screening for brain metastases in patients with HER2 positive or triple negative metastatic breast cancer. Cancer Res 2024;84. https://doi.org/10.1158/1538-7445.SABCS23-PO2-27-09. PO2-27-09-PO2-27–09.
[79] Griguolo G, Bottosso M, Landa G, Bonomi G, Miglietta F, Guarascio MC, et al. Proactive brain screening using contrast-enhanced brain CT scans in HER2+ metastatic breast cancer. Clin Cancer Res 2026;32:1790–8. https://doi.org/10.1158/1078-0432.CCR-25-3557.
[80] Cagney DN, Martin AM, Catalano PJ, Brown PD, Alexander BM, Lin NU, et al. Implications of screening for brain metastases in patients with breast cancer and non–small cell lung cancer. JAMA Oncol 2018;4:1001. https://doi.org/10.1001/jamaoncol.2018.0813.
[81] Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Cicone F, et al. Single-fraction versus multifraction (3 × 9 gy) stereotactic radiosurgery for large (>2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis. Int J Radiat Oncol Biol Phys 2016;95:1142–8. https://doi.org/10.1016/j.ijrobp.2016.03.013.
[82] Aizer A, Tanguturi SK, Benham G, Brown PD, Cagney D, Catalano PJ, et al. Stereotactic radiation versus hippocampal avoidance whole brain radiation in patients with 5-20 brain metastases: a multicenter, phase 3 randomized trial. J Clin Oncol 2025;43. https://doi.org/10.1200/JCO.2025.43.16_suppl.2011. 2011–2011.
[83] Aizer AA, Shin K-Y, Catalano PJ, Ricca I, Johnson M, Benham G, et al. Treatment for brain metastases with stereotactic radiation vs hippocampal-avoidance whole brain radiation: a randomized clinical trial. JAMA 2026;335:1127–36. https://doi.org/10.1001/jama.2026.0076.
[84] Lin NU, Murthy RK, Abramson V, Anders C, Bachelot T, Bedard PL, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases. JAMA Oncol 2023;9:197. https://doi.org/10.1001/jamaoncol.2022.5610.
[85] Harbeck N, Ciruelos E, Jerusalem G, Müller V, Niikura N, Viale G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med 2024;30:3717–27. https://doi.org/10.1038/s41591-024-03261-7.
[86] Herrstedt J, Clark-Snow R, Ruhlmann CH, Molassiotis A, Olver I, Rapoport BL, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open 2024;9:102195. https://doi.org/10.1016/j.esmoop.2023.102195.
[87] Cardoso F, Parke S, Brennan DJ, Briggs P, Donders G, Panay N, et al. Elinzanetant for vasomotor symptoms from endocrine therapy for breast cancer. N Engl J Med 2025;393:753–63. https://doi.org/10.1056/NEJMoa2415566.
[88] Nappi RE, Johnson KA, Stute P, Blogg M, English M, Morga A, et al. Treating moderate-to-severe menopausal vasomotor symptoms with fezolinetant: analysis of responders using pooled data from two phase 3 studies (SKYLIGHT 1 and 2). Menopause 2024;31:512–21. https://doi.org/10.1097/GME.0000000000002354.
[89] Brennan DJ, Dolezal M, Rottman A, Schultze-Mosgau M-H, Wahyudi LA, Cardoso F. 234P Elinzanetant in breast cancer care: potential drug–drug interaction profile with targeted systemic therapies. ESMO Open 2026;11:107188. https://doi.org/10.1016/j.esmoop.2026.107188.
[90] Nangia J, Wang T, Osborne C, Niravath P, Otte K, Papish S, et al. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer. JAMA 2017;317:596. https://doi.org/10.1001/jama.2016.20939.
[91] Rugo HS, Klein P, Melin SA, Hurvitz SA, Melisko ME, Moore A, et al. Association between use of a scalp cooling device and alopecia after chemotherapy for breast cancer. JAMA 2017;317:606. https://doi.org/10.1001/jama.2016.21038.
[92] Brook TS, Seetsen T, Dercksen MW, van Riel A, Derleyn VA, van den Bosch J, et al. Results of the Dutch scalp cooling registry in 7424 patients: analysis of determinants for scalp cooling efficacy. Oncologist 2024;29:e1386–95. https://doi.org/10.1093/oncolo/oyae116.
[93] Martín M, de la Torre-Montero JC, López-Tarruella S, Pinilla K, Casado A, Fernandez S, et al. Persistent major alopecia following adjuvant docetaxel for breast cancer: incidence, characteristics, and prevention with scalp cooling. Breast Cancer Res Treat 2018;171:627–34. https://doi.org/10.1007/s10549-018-4855-2.

[94] Kang J, Lee JW, Kwon O. Efficacy of low-dose oral minoxidil in the management of anticancer therapy-induced alopecia in patients with breast cancer: a retrospective cohort study. J Am Acad Dermatol 2023;88:1170–3. https://doi.org/10.1016/j.jaad.2022.12.005.

[95] Zaminski D, Sikora M, Nohria A, Desai D, Buontempo M, Caplan AS, et al. Tolerability and effectiveness of low-dose oral minoxidil for alopecia in patients with breast cancer: a retrospective cohort study. J Am Acad Dermatol 2025;92:906–9. https://doi.org/10.1016/j.jaad.2024.11.048.

[96] Gaumond SI, Warp PV, Abdin R, Jimenez JJ. Efficacy of bimatoprost in treating chemotherapy-induced milphosis: a comprehensive review of randomized controlled trials. JAAD Rev 2025;4:167–74. https://doi.org/10.1016/j.jdrv.2025.03.015.

[97] Carruthers J, Beer K, Carruthers A, Coleman WP, Draelos ZD, Jones D, et al. Bimatoprost 0.03% for the treatment of eyebrow hypotrichosis. Dermatol Surg 2016;42:608–17. https://doi.org/10.1097/DSS.0000000000000755.