Postmastectomy Radiation Therapy: An ASTRO-ASCO-SSO Clinical Practice Guideline

Rachel B. Jimenez, MD[1]; Yara Abdou, MD[2]; Penny Anderson, MD[3]; Parul Barry, MD[4]; Lisa Bradfield, BA[5]; Julie A. Bradley, MD[6]; Lourdes D. Heras, MPH[7]; Atif Khan, MD, MS[8]; Cindy Matsen, MD[9]; Rachel Rabinovitch, MD[10]; Chantal Reyna, MD, MHA[11]; Kilian E. Salerno, MD[12]; Sarah E. Schellhorn, MD[13]; Deborah Schofield, PhD[14]; Kekoa Taparra, MD, PhD, MPH[15]; Iman Washington, MD[16]; Jean L. Wright, MD[17]; Youssef H. Zeidan, MD, PhD[18]; Richard C. Zellars, MD[19]; and Kathleen C. Horst, MD[20]

DOI https://doi.org/10.1200/JCO-25-01747

ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases or stages of diseases. Guidance is based on review and analysis of relevant literature, and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete ASCO and ASTRO disclaimers in Appendix 1 (online only) for more.

PURPOSE This guideline provides recommendations on use of postmastectomy radiation therapy (PMRT) in breast cancer treatment. Updated recommendations detail indications for PMRT in the upfront surgical setting and after neoadjuvant systemic therapy, and provide guidance on appropriate target volumes, dosing, and treatment techniques.

METHODS A multidisciplinary American Society for Radiation Oncology–ASCO–Society of Surgical Oncology task force addressed four key radiation therapy (RT) questions in patients with breast cancer who undergo mastectomy: (1) indications for PMRT after upfront surgery, (2) indications for PMRT after neoadjuvant systemic therapy followed by surgery, (3) appropriate PMRT volumes and dose-fractionation regimens, and (4) treatment techniques. Recommendations were based on a systematic review and created using a predefined consensus-building methodology for quality of evidence grading and strength of recommendation.

RECOMMENDATIONS After upfront mastectomy, PMRT is indicated for most patients with node-positive breast cancer and select patients with node-negative disease. PMRT is also recommended after neoadjuvant systemic therapy for patients presenting with locally advanced disease and for those with residual nodal disease at the time of surgery. PMRT is conditionally recommended for patients with cT1-3N1 or cT3N0 breast cancer with pathologically negative nodes after neoadjuvant systemic therapy (ypN0). When PMRT is delivered, treatment to the ipsilateral chest wall or reconstructed breast and regional lymphatics is recommended, with moderate hypofractionation preferred, but with conventional fractionation approaches acceptable in rare cases. Computed tomography–based volumetric treatment planning with 3-dimensional conformal RT is recommended, with intensity-modulated RT advised when three-dimensional conformal RT is unable to achieve treatment goals. Deep inspiration breath-hold techniques are also recommended for normal tissue sparing. For patients with skin involvement, positive superficial margins, and/or lymphovascular invasion, use of a bolus is recommended, but routine use of tissue-equivalent bolus is not recommended.

Additional information is available at www.asco.org/breast-cancer-guidelines.

ACCOMPANYING CONTENT

Listen to the podcast by Brittany Harvey, Dr Kathleen Horst, Dr Rachel Jimenez, and Dr Yara Abdou at https://ascopubs.org/do/postmastectomy-radiation-therapy-astro-asco-sso-guideline

Appendix

Data Supplement

Accepted July 30, 2025
Published September 16, 2025

ASTRO Board of Directors approval: May 23, 2025
ASCO Evidence Based Medicine Committee approval: May 27, 2025
SSO Executive Committee approval: June 2, 2025

J Clin Oncol 43:3292-3311

View Online Article

TARGET POPULATION AND AUDIENCE

Target Population
Adults (age ≥18 years) who received a diagnosis of breast cancer and underwent mastectomy.

Target Audience
Radiation oncologists, surgical oncologists, medical oncologists, oncology nurses, patients, radiologists, and other relevant oncologic professionals.

INTRODUCTION

According to the WHO, in 2022, breast cancer was the second most common cancer and the fourth leading cause of cancer mortality worldwide.[1] Although some patients may undergo breast-conservation therapy, others undergo mastectomy either by medical necessity or by choice. For these patients, postmastectomy radiation therapy (PMRT), which delivers radiation therapy (RT) to the residual skin and soft tissue of the ipsilateral chest wall and regional draining lymphatics, can decrease the risk of a locoregional recurrence (LRR) and improve breast cancer mortality.[2] As the absolute benefit of PMRT can vary according to patient and tumor characteristics, it is important to individualize treatment decision making to balance considerations of LRR and breast cancer mortality with the side effects of treatment.

The American Society for Radiation Oncology (ASTRO), ASCO, and the Society of Surgical Oncology (SSO) sought to jointly develop a new guideline to clarify patient selection criteria and appropriate technical approaches for the delivery of PMRT. This evidence review was completed to replace the 2016 PMRT guideline[3] and to reflect the evolving understanding of the benefit of PMRT. With advancements in the management of breast cancer, including improved diagnostic imaging, trends in de-escalation of axillary surgery, newer and more tailored systemic therapy agents, and advances in RT techniques, there is a need to provide updated guidance regarding the appropriate indications for, and approaches to, PMRT in the modern era.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: (1) What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer? (2) What are the indications for PMRT in patients who receive neoadjuvant systemic therapy before mastectomy? (3) What are the appropriate treatment volumes (eg, chest wall or reconstructed breast, regional nodes, boost) and dose-fractionation regimens for patients who receive PMRT? (4) What are the appropriate techniques (eg, 3-dimensional conformal radiation therapy [3-D CRT], intensity-modulated radiation therapy [IMRT], protons, breath hold, bolus) for treating patients who receive PMRT?

METHODS

Guideline Development Process

This systematic review–based guideline product was developed by an ASTRO-ASCO-SSO joint task force that consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; a radiation oncology resident; a medical physicist; a patient representative, and an ASTRO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). This guideline was also developed in collaboration with the European Society for Radiotherapy and Oncology, which provided representatives and peer reviewers. This work was funded by ASTRO.

The joint task force used evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[4,5] The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Data Supplement 1 (online only) for a list of abbreviations used in the guideline.

Consensus Development

Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a five-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of 75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submitting for approval.

Scope of the Guideline

The scope of this guideline is to define the role of PMRT in the curative-intent management of invasive breast cancer, including the indications for PMRT after upfront surgery and following neoadjuvant systemic therapy, and to discuss the appropriate target volumes and technical specifications for PMRT. Given the rapid adoption of biologically tailored neoadjuvant systemic therapy and the de-escalation of axillary surgery with the use of sentinel lymph node biopsy or targeted axillary dissection, this guideline seeks to

TABLE 1. ASTRO Recommendation Grading Classification System

ASTRO's recommendations are based on evaluation of multiple factors including the qoe and panel consensus which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/Should"
Conditional	Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. Most informed people would choose the recommended course of action, but a substantial number would not. A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	Two or more well-conducted and highly generalizable RCTs or well-conducted meta-analyses of such randomized trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	One well-conducted and highly generalizable RCT or a meta-analysis including such a trial **OR** Two or more RCTs with some weaknesses of procedure or generalizability **OR** Two or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	One RCT with some weaknesses of procedure or generalizability **OR** One or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** Two or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert opinion[a]	Consensus of the panel based on clinical judgment and experience, due to the absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

NOTE. ASTRO's methodology allows for the use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. While each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

Abbreviations: ASTRO, American Society for Radiation Oncology; QoE, quality of evidence; RCTs, randomized controlled trials.

[a]A lower QoE, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there is still consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

address the indications and approaches for PMRT in the context of these advances in the multidisciplinary care of breast cancer. In this guideline, PMRT refers to treatment of the chest wall and ipsilateral regional nodes, including at-risk axillary, supraclavicular or infraclavicular, and internal mammary nodes (IMN). Specific situations where treatment volumes may be less comprehensive are noted in the text.

Evidence Review: KQs, Key Outcomes, and Inclusion and Exclusion Criteria

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs and then reviewed by the full task force. Using the PICOTS framework (Table 2), a systematic search of human participant studies retrieved from the Ovid MEDLINE and Embase databases was conducted for English-language publications between January 1, 2005, through October 2023, and then the search was updated through October 15, 2024.

The key outcomes of interest include LRR, disease-free survival (DFS), breast cancer mortality, distant metastasis-free survival, and overall survival (OS). Other key outcomes of interest include appropriate dose-fractionation regimens, nodal volumes considered for treatment, and optimal RT techniques to minimize toxicities. This guideline addresses only the subjects specified in the KQs (Table 2). There are several important questions in the management of patients with breast cancer that are outside the scope of this guideline, including inflammatory breast cancer, management of ductal carcinoma in situ after mastectomy, management of locally or regionally recurrent disease, and detailed discussions of chemotherapy regimens and surgical approaches, including axillary management. This guideline also does not encompass recommendations on reirradiation, RT in the setting of

TABLE 2. Key Questions in PICO Format

KQ	Population	Intervention	Comparator	Outcome
1. What are the indications for PMRT in patients who receive mastectomy as their initial treatment for breast cancer?				
	Adult patients with breast cancer	PMRT	No PMRT	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis-free survival Overall survival
2. What are the indications for PMRT in patients who receive neoadjuvant systemic therapy before mastectomy?				
	Same as KQ1	PMRT after neoadjuvant systemic therapy	No PMRT after neoadjuvant systemic therapy	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis-free survival Overall survival
3. What are the appropriate treatment volumes (eg, chest wall/reconstructed breast, regional nodes, boost) and dose-fractionation regimens for patients who receive PMRT?				
	Same as KQ1	Hypofractionation Chest wall/reconstructed breast without RNI RNI including IMNs Boost	Conventional fractionation Chest wall/reconstructed breast with RNI RNI without IMNs No boost	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis-free survival Toxicity and adverse effects
4. What are the appropriate techniques (eg, 3-D CRT, IMRT, protons, breath hold, bolus) for treating patients who receive PMRT?				
	Same as KQ1	IMRT (including VMAT) Electrons Protons Set-up verification, image guidance/surface guidance Respiratory management, gating, breath hold Bolus	3-D CRT PMRT with photons No bolus	Local recurrence Regional recurrence Locoregional recurrence Disease-free survival Breast cancer mortality Distant metastasis-free survival Toxicity and adverse effects

Abbreviations: 3-DCRT, 3-dimensional conformal radiation therapy; IMN, internal mammary nodes; IMRT, intensity-modulated radiation therapy; KQs, key questions; PICO, Population, Intervention, Comparator, Outcome; PMRT, postmastectomy radiation therapy; RNI, regional nodal irradiation; RT, radiation therapy; VMAT, volumetric modulated arc therapy.

oligometastatic or palliative disease, phyllodes tumors, or sarcomas of the breast.

Allowable publication types included prospective randomized controlled trials (RCTs), prospective nonrandomized studies, meta-analyses, and retrospective studies. The population of interest was adults (age ≥18 years) who received a diagnosis of breast cancer and underwent mastectomy. Trial size required for inclusion was ≥50 patients for RCTs and meta-analyses, and ≥100 patients for prospective nonrandomized and retrospective studies. KQ1 addresses indications for PMRT in patients who receive mastectomy as their initial treatment. Retrospective studies were excluded for KQ1 given the strength of the prospective data available for this question. Universal exclusion criteria included the following: preclinical and nonhuman studies; publication types such as abstract only, review articles, case reports, comments, or editorials; and study types such as dosimetric or contouring studies, health economics or cost analysis studies, or large registry database studies. For specific subquestions where limited data were available, expert opinion was relied on to support recommendations. Full-text articles were assessed by the task force to determine the final included study list resulting in 104 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[6,7] flow diagram showing the number of articles screened, excluded, and included in the evidence review, and Data Supplement 2 for the literature search strategy, which includes the evidence search parameters and inclusion and exclusion criteria).

Guideline Review and Approval

The guideline was reviewed by 17 official peer reviewers (Data Supplement 3) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from September to October 2024. The final guideline was approved by the ASTRO Board of Directors, the ASCO Evidence Based Medicine Committee, and SSO Executive Committee; and endorsed by the American Society of Breast Surgeons and the Royal Australian and New Zealand College of Radiologists.

Guideline Updating

Based on periodic formal review of the emerging literature, the respective organizations will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

The data used by the task force to formulate recommendations are summarized in evidence tables available in Data Supplement 4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

KQs AND RECOMMENDATIONS

KQ1: Indications for PMRT With Mastectomy as Initial Treatment (Table 3)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ1, and Figure 1.

What Are the Indications for PMRT in Patients Who Receive Mastectomy as Their Initial Treatment for Breast Cancer?

Over the last 4 decades, multiple RCTs and pooled analyses have shown a significant reduction in LRR and improved DFS and OS in women with pT3-4 and/or node-positive breast cancer who receive PMRT.[2,8-10,15-17] Support for the use of PMRT in patients with nodal involvement comes from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[2,11] This analysis included women who underwent mastectomy and axillary dissection, and were enrolled in trials evaluating PMRT to the chest wall and regional lymph nodes. PMRT significantly reduced breast cancer recurrence, breast cancer mortality, and all-cause mortality in patients with positive lymph nodes.[2,11] Among these patients, the risk of LRR and the benefit of PMRT increased with nodal burden, with the greatest absolute reduction of LRR and improvement in DFS and OS observed in patients with ≥4 positive nodes (pN2), but still with significant benefits for those with 1-3 positive nodes (pN1). Notably, there was no differentiation between patients with pN1 or pN1mic status after axillary dissection in these trials. However, among patients with pN1mic disease, the magnitude of benefit of PMRT is often considered to be lower than in those with higher nodal burden, and therefore, requires assessment of other clinicopathological features, as noted in the discussion of patients with node-negative disease to follow.

It should also be acknowledged that the EBCTCG meta-analysis was limited to trials initiated by 1995,[2,18] so while the majority of the included studies reflected the receipt of appropriate systemic therapies for the time period, most did not use current evidence-based systemic regimens (eg, immunotherapy, human epidermal growth factor receptor 2 [HER2]–directed therapy), which have been recognized to further confer a locoregional control and DFS benefit.[8,10,17] In this context, the benefit of PMRT for low-volume, node-positive disease (pN1) has been questioned. The Selective Use of Postoperative Radiotherapy after Mastectomy

TABLE 3. Indications for PMRT With Mastectomy as Initial Treatment

KQ1 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with node-positive (pN+) breast cancer, PMRT is recommended *Implementation remarks:* Omission of PMRT may be appropriate for select patients with pN1mic or low nodal burden pN1a disease following ALND who have favorable clinicopathologic features. Favorable clinicopathologic features include pT1-2 disease, low-to-intermediate grade HR-positive/HER2-negative subtype, postmenopausal status, absence of LVI, and a low 21-gene recurrence score.	Strong	High[2,8-12]
2. For patients with any pT4 breast cancer, PMRT is recommended even in the absence of any other risk factors.	Strong	High[2,8]
3. For patients with pT3N0 breast cancer, PMRT is conditionally recommended. *Implementation remark:* PMRT may be omitted or treatment volumes reduced (eg, chest wall alone) for patients with favorable clinicopathologic features including low-to-intermediate grade, HR-positive/HER2-negative subtype, postmenopausal status, absence of LVI, and a low 21-gene recurrence score.	Conditional	High[2,8,10]
4. For patients with pT1-2N0 breast cancer, PMRT is **not** recommended. *Implementation remark:* Select patients with pT1-2N0 breast cancer who have multiple unfavorable clinicopathologic features (eg, triple-negative, high histologic grade, LVI, young age, and/or central/medially located tumors) may benefit from PMRT.	Strong	Low[2,13,14]
5. For patients with positive surgical margins after mastectomy and no other indication for PMRT, RT to the chest wall/reconstructed breast alone is conditionally recommended.	Conditional	Expert opinion

Abbreviations: ALND, axillary lymph node dissection; HR/HER2, hormone receptor/human epidermal growth factor receptor 2; KQ, key question; LVI, lymphovascular invasion; PMRT, postmastectomy radiation therapy; RT, radiation therapy.

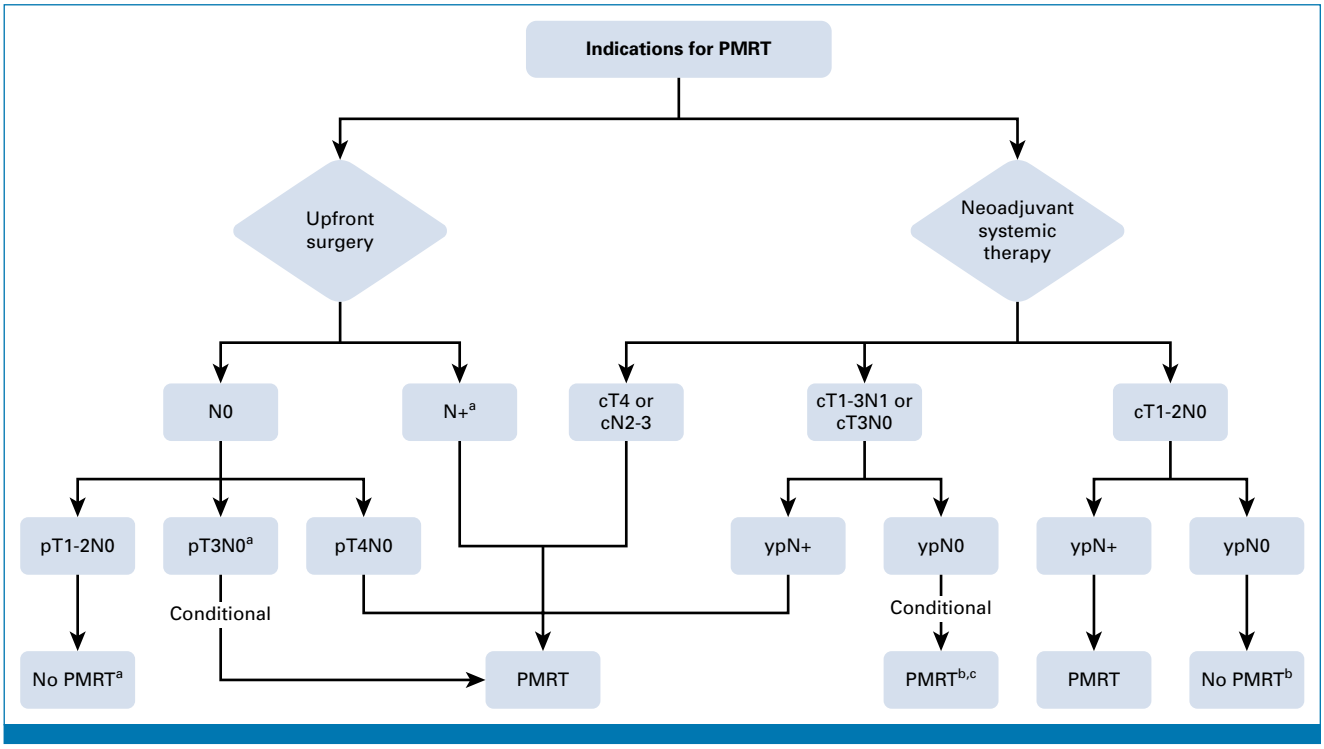


FIG 1. Indications for PMRT. [a]See implementation remarks in Table 3 for details. [b]See implementation remarks in Table 4 for details. [c]PMRT may be omitted in the setting of complete pathological response in the breast and lymph nodes (ypT0N0). PMRT, postmastectomy radiation therapy.

(SUPREMO; ClinicalTrials.gov identifier: NCT00966888) trial evaluated the impact of PMRT on OS for patients with limited nodal disease in the upfront surgical setting after axillary lymph node dissection with at least eight lymph nodes removed. Final results from this study will provide additional insights regarding the value of PMRT in this favorable-risk population.[19] Additionally, in an era where the biology of breast cancer guides systemic therapy, questions arise as to whether biology should also inform RT recommendations. Indeed, MA.39/TAILOR-RT (A Randomized Trial of Regional Radiotherapy in Biomarker Low-Risk Node-Positive Breast Cancer, ClinicalTrials.gov identifier: NCT03488693) randomizes patients with estrogen receptor (ER)–positive, HER2-negative pT1-2N1a disease and a non–high-risk recurrence score (recurrence score ≤25) to PMRT or no PMRT, with a primary end point of recurrence-free interval. The results from this trial will also inform recommendations for PMRT for patients receiving upfront surgery with limited axillary nodal disease including pN1mic and favorable ER-positive tumor biology. Notably, in this study, axillary lymph node dissection is not mandatory; however, there can be no more than two positive lymph nodes present if sentinel lymph node biopsy alone is performed.[20] While this study evaluates selective omission of PMRT in favorable-risk ER-positive, HER2-negative breast cancer, it should be noted that in historical studies evaluating the mortality benefit of PMRT, the magnitude of benefit was higher for patients with ER-positive biology, despite a comparatively lower local recurrence risk,[21] largely due to the competing risk for distant failure. Therefore, while LRR is an important end point, it need not be the sole consideration in recommendations for PMRT.

In the node-negative setting, data support the use of PMRT in patients with high-risk features. Larger tumor size (≥5 cm), younger age (<40 years), and hormone receptor–negative disease have all independently been associated with a greater benefit of PMRT in node-negative patients.[17,22,23] Although specific RCTs directly focusing on T4N0 breast cancer are limited, there are data supporting the benefits of PMRT in reducing LRR and improving survival outcomes in this patient population.[2,8–10,24,25] Invasion of the skin and pectoralis muscle has also been associated with higher rates of LRR,8 and were considered high-risk criteria for eligibility in both the Danish 82b/c trials.[24,25] For patients with pT3N0 breast cancer, who were included in these RCTs, there was a >50% reduction in LRR with PMRT.[24,25] However, this group comprised <10% of the study cohorts, modern systemic regimens known to reduce LRR were not used, and neither trial demonstrated a significant improvement in breast cancer–specific or OS in patients with pT3N0 breast cancer.[26] Multiple population data set analyses have demonstrated no breast cancer–specific survival benefit of PMRT across unselected patients with pT3N0 disease, even for patients

<50 years of age.[27-29] Patients with pT3N0 disease were included in the European Organisation for Research and Treatment of Cancer (EORTC) 22922 trial, which demonstrated a benefit of regional nodal irradiation (RNI) in terms of any breast cancer recurrence and breast cancer mortality, with no significant difference in OS. However, only 3.5% of the patients had pT3N0 disease. Given the demonstrated local regional control benefit and uncertain survival benefit of PMRT for patients with pT3N0 breast cancer, PMRT is conditionally recommended and when employed, smaller treatment volumes (eg, chest wall RT alone) may be used at the discretion of the provider.[2,8] PMRT may be omitted for patients with favorable clinicopathological features including low-to-intermediate grade, ER-positive, HER2-negative subtype, postmenopausal status, absence of lymphovascular invasion (LVI), and low 21-gene recurrence score. These patients are included in both the SUPREMO (ClinicalTrials.gov identifier: NCT00966888) and the TAILOR-RT (ClinicalTrials.gov identifier: NCT03488693) trials, and these results may better define the impact of PMRT in this patient population.

Few RCTs have evaluated PMRT in the pT1-2N0 setting.[13] A single study in patients with stage I or II triple-negative breast cancer demonstrated a relapse-free survival and OS benefit with PMRT following total mastectomy, partial axillary dissection, and adjuvant chemotherapy; however, the systemic therapy regimens used are no longer considered standard of care.[13] Additionally, 19% of patients had node-positive disease and no subset analysis was performed to determine if the benefit of PMRT was primarily in the node-positive subgroup.[13] EORTC 22922 also included patients with stage I and II breast cancer with lymph node-negative, central or medially located tumors, and identified a breast cancer recurrence and breast cancer mortality benefit with the addition of chest wall and RNI, although mastectomy patients comprised only approximately 25% of participants.[14] Overall, meta-analyses and retrospective studies of patients with pT1-2N0 breast cancer demonstrate excellent outcomes without PMRT for most patients, with reported 10-year LRR rates between 2.1% and 12.8%, and the majority reporting rates of 3% to 7%.[2,30] However, these data also suggest that LVI, young age, high histologic grade disease, and positive margins increase the risk of LRR such that PMRT may be beneficial, particularly for patients with multiple high-risk features.[30]

Finally, there are no RCTs evaluating the role of RT in patients with positive margins following mastectomy. Positive margins, however, are consistently associated with a greater risk of local recurrence.[31] Recognizing the consistent reduction in local recurrence of approximately 50% with the use of PMRT, PMRT is conditionally recommended in the setting of positive margins when re-excision is not feasible.[8] The extent and location of positive margins, tumor biology, consideration of other high-risk features (eg, LVI, young age, tumor grade), and plan for adjuvant therapies should be weighed together to determine the value of PMRT for an individual patient.

KQ2: Indications for PMRT With Neoadjuvant Systemic Therapy (Table 4)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ2 and Figure 1.

What Are the Indications for PMRT in Patients Who Receive Neoadjuvant Systemic Therapy Before Mastectomy?

Over the past decade, the use of neoadjuvant systemic therapy has increased for specific subsets of patients with

TABLE 4. Indications for PMRT With Neoadjuvant Systemic Therapy

KQ2 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with initial cT4 or cN2-3 breast cancer who receive neoadjuvant systemic therapy, PMRT is recommended regardless of pathologic response.	Strong	Moderate[32-36]
2. For patients with positive lymph nodes after neoadjuvant systemic therapy (ypN+), PMRT is recommended.	Strong	Moderate[37-41]
3. For patients with cT1-3N1 or cT3N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is conditionally recommended *Implementation remarks:* Patients with high-risk features (eg, young age, LVI, high residual cancer burden in the breast) may derive a greater benefit from PMRT. PMRT may be omitted in the setting of complete pathologic response in the breast and lymph nodes (ypT0N0).	Conditional	Moderate[37,38,40-50]
4. For patients with cT1-2N0 breast cancer with pathologic negative nodes after neoadjuvant systemic therapy (ypN0), PMRT is not recommended. *Implementation remark:* Patients with multiple high-risk features (eg, young age, LVI, high residual cancer burden in the breast) may benefit from PMRT.	Strong	Moderate[37,38,43-45,47-49]
5. For patients with positive surgical margins after neoadjuvant systemic therapy, PMRT is recommended	Strong	Expert opinion

Abbreviations: KQ, key question; LVI, lymphovascular invasion; PMRT, postmastectomy radiation therapy.

breast cancer, notably those with cT2 or greater or clinically node-positive disease to downstage the breast and axilla, and in those with HER2-positive or triple-negative biology.[42,51] Several studies have shown that patients with initial cT4 or cN2-3 (also defined by the American Joint Committee on Cancer 6th edition as stage III) breast cancer who receive neoadjuvant systemic therapy have improved LRR with PMRT regardless of their response to neoadjuvant therapy.[32-36] Some studies have also shown an improvement in OS, but these were small retrospective evaluations.[32,33] Based on the current evidence, PMRT is recommended for patients with initial presentation of cT4 or cN2-3 disease who receive neoadjuvant systemic therapy, regardless of pathological response.[32-36] In addition, several studies have demonstrated that residual nodal disease after neoadjuvant systemic therapy (ypN+) is associated with an increased risk of LRR.[37-39]

The extent of axillary nodal disease after neoadjuvant systemic therapy (ie, ypN1 *v* ypN2-3) is also an important risk factor.[37,40] This risk is further elevated in patients with cT3 tumors.[38] The addition of PMRT in patients with ypN+ improves locoregional control with incremental benefit noted in patients with increased axillary burden.[39,40] An OS benefit for PMRT has been reported for patients with ypN2-3 disease.[40] It is worth noting that the benefit of PMRT for residual nodal disease in these studies was evaluated in the setting of axillary nodal dissection. Results from the Alliance A011202 trial (ClinicalTrials.gov identifier: NCT01901094), evaluating whether RT to the undissected axilla and other regional lymph nodes after sentinel lymph node biopsy is noninferior to axillary lymph node dissection (with RT only to the undissected regional lymph nodes), will further clarify the value of extensive axillary surgery after neoadjuvant systemic therapy and provide guidance regarding the appropriate RT treatment volumes needed in this patient population.

In patients who begin treatment with clinically involved axillary lymph nodes (cN1) and convert to pathologically node-negative after neoadjuvant systemic therapy (ypN0), the full reporting of the NSABP B-51/Radiation Therapy Oncology Group 1304 trial (ClinicalTrials.gov identifier: NCT01872975), which randomly assigned these patients to PMRT or no RT, will help to resolve the clinical equipoise that exists on the use of PMRT in this setting. On this protocol, patients were eligible if they had clinical axillary nodal involvement (cN1) as assessed before neoadjuvant chemotherapy by palpation, ultrasound, computed tomography (CT) scan, magnetic resonance imaging, positron emission tomography (PET) scan, or PET/CT scan, and patients with N2-3 disease detected clinically or by imaging were ineligible.[52] Data from a 2022 prospective Dutch registry, in which patients with cT1-2N1 breast cancer (defined as 1-3 suspicious nodes on imaging before neoadjuvant chemotherapy), and had negative nodes at surgery (ypN0) and did not receive PMRT, demonstrated a low LRR rate of 2.1% at 5 years, supporting de-escalation of PMRT in patients with ypN0 disease after neoadjuvant systemic therapy.[53] Another pooled analysis showed a 5-year LRR rate of 3% after mastectomy without PMRT in patients with HER2-positive disease achieving ypN0.[39] Although several retrospective studies have shown similar LRR-free survival rates with and without PMRT after achieving ypN0,[43,44] a meta-analysis including 12 studies of over 17,000 patients who achieved a pathological complete response in the lymph nodes (ypN0) demonstrated a significant benefit with PMRT in all stages, with the greatest benefit in stage III disease.[35] For patients who achieve a pathological complete response in the nodes, certain features appear to increase the risk of LRR and may suggest a continued benefit with PMRT. For example, several reports have suggested that baseline clinicopathological factors including young age, cT3-4 disease, triple-negative subtype, and LVI may predict higher rates of LRR, so PMRT is conditionally recommended in patients with multiple high-risk factors.[33,37,38,43,45,46,54] Similarly, other pathological features after neoadjuvant systemic therapy are associated with demonstrably higher risks of LRR (eg, high-volume residual invasive disease in the breast, persistent LVI, residual HER2-positive and triple-negative disease, close margins) and may be indications for PMRT after neoadjuvant systemic therapy.[37,40,41,44,45,47,48,55,56]

The benefits of PMRT may be higher in younger women compared with older women.[32,43,57] In a retrospective study of young women (age <35 years) who received neoadjuvant anthracycline-based chemotherapy, the use of PMRT reduced LRR and improved OS.[32] This finding is consistent with a study from Korea that found age ≤40 years to be an independent predictor of LRR.[43] Treatment decision making regarding the role for PMRT should include a discussion of risks and benefits, particularly for young patients. For those who have residual invasive disease in the breast, the advances in adjuvant systemic therapy (eg, CDK 4/6 inhibitors, capecitabine, ado-trastuzumab emtansine-1, pembrolizumab) may further impact the risk-benefit ratio of PMRT.[58-60]

Although neoadjuvant systemic therapy is most often used for larger tumors and those with nodal involvement, there may be some patients with cT1-2N0 disease who receive neoadjuvant treatment, particularly those with HER2+ and triple-negative biological subtype. For these patients, PMRT is not recommended if the nodes are pathologically negative (ypN0) as the risk of an LRR after mastectomy alone is low.[38] However, the presence of multiple clinical and pathological risk factors (eg, young age, LVI, high residual cancer burden in the breast) increases the risk of an LRR such that PMRT may be an option.[37,38,43-45,47-49]

Finally, there are limited data to inform PMRT recommendations for patients with positive surgical margins after

neoadjuvant therapy. However, given that positive margins are a conditional indication for PMRT in the upfront surgery setting,[31] PMRT is recommended for positive margins after neoadjuvant systemic therapy when re-excision is not feasible based on expert opinion.

KQ3: PMRT Treatment Volumes and Dose-Fractionation Regimens (Table 5)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ3.

What Are the Appropriate Treatment Volumes (eg, chest wall or reconstructed breast, regional nodes, boost) and Dose-Fractionation Regimens for Patients Who Receive PMRT?

In the EBCTCG meta-analysis of 8,135 women pooled from trials comparing no PMRT with PMRT, inclusive of the chest wall and regional lymph nodes, PMRT significantly reduced both LRR, overall recurrence, and breast cancer mortality, with the chest wall being the most common site of LRR.[2] The meta-analysis also included eight trials that did not include the chest wall in the treatment fields (ie, only treated the regional lymph node basins) and found that RT in those studies did not have a significant impact on overall recurrence or breast cancer mortality. As 50%-80% of all local recurrences identified in RCTs were located in the chest wall,[9,17] inclusion of the chest wall as a PMRT target structure is recommended regardless of surgical margins, although direct comparisons of RT with versus without chest wall volumes are limited.

Several large RCTs have evaluated the value of RNI in patients with medially or centrally located tumors, positive lymph nodes, or in patients with high-risk node-negative breast cancer.[14,61,76] The EORTC 22922 trial randomly assigned patients who had centrally or medially located primary tumors, irrespective of axillary involvement, or laterally located tumors with axillary involvement, to either whole breast/chest wall irradiation and RNI (inclusive of IMNs) or whole breast, chest wall irradiation alone.[61] Approximately one quarter of these patients were treated with mastectomy. At 10 years, the addition of RNI resulted in a significantly improved breast cancer mortality rate, improved DFS, and a trend toward improved OS. The 15-year results continued to demonstrate a significant reduction in breast cancer mortality and any breast cancer recurrence with the addition of IMN or supraclavicular irradiation in patients with stage I to III breast cancer.[14] The Canadian Cancer Trials Group MA.20 trial also evaluated the addition of RT to the supraclavicular lymph nodes, axillary apical lymph nodes, and the IMNs for patients with node-positive disease or high-risk node-negative disease.[76] Although it did not include patients treated with mastectomy, it did demonstrate that the addition of RNI reduced the rate of any breast cancer recurrence, further supporting the use of RNI when defining target coverage for patients with node-positive or high-risk node-negative breast cancer. For those patients who have undergone an axillary

TABLE 5. PMRT Treatment Volumes and Dose-Fractionation Regimens

KQ3 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
1. For patients receiving PMRT, treatment to the ipsilateral chest wall/reconstructed breast and regional lymphatics (ie, at-risk axillary nodes, supra/infraclavicular nodes, and IMNs) is recommended. *Implementation remarks:* Treatment to the chest wall/reconstructed breast alone may be used in select patients (eg, pT3N0). Coverage of the IMNs may be individually determined based on tumor location (medial/central), tumor size, and extent of nodal involvement.	Strong	High[2,12,61-65]
2. For patients *without* breast reconstruction receiving PMRT, moderate hypofractionation is recommended. *Implementation remarks:* Moderate hypofractionation is preferred, given equivalent oncologic outcomes and reduced toxicity. Conventional fractionation may be an option in rare circumstances.	Strong	High[66-73]
3. For patients *with* breast reconstruction receiving PMRT, moderate hypofractionation (preferred) or conventional fractionation is recommended.	Strong	Moderate[65,74] (moderate hypofx) High[14,61,62,66,67,71-73,75] (conventional fx)
4. For patients with T4 breast cancer or close/positive margins receiving PMRT, a boost to the chest wall/scar is conditionally recommended.	Conditional	Low[66,67,74,76-80]
5. For patients with nodal disease not surgically addressed and at risk of harboring residual disease, a nodal boost is recommended.	Strong	Expert opinion

NOTE. Moderate hypofractionation is most frequently defined as 266 to 267 cGy per fraction for 15-16 fractions. Conventional fractionation is most frequently defined as 180 to 200 cGy per fraction for 25 to 28 fractions.[66-73]
Abbreviations: fx, fractionation; hypofx, hypofractionation; IMNs, internal mammary nodes; KQ, key question; PMRT, postmastectomy radiation therapy.

dissection and receive PMRT, data do not support a benefit to including the dissected stations of the axilla, typically axillary levels I and II; however, an increasing number of studies support the omission of axillary lymph node dissection after a positive sentinel lymph node biopsy and in these circumstances, coverage of all axillary nodal basins is advised.[2,10,81] Additionally, among patients who undergo an inadequate axillary dissection or whose pathological specimens demonstrate tumor deposits and/or emboli into the axillary fat, coverage of the dissected axilla is indicated. Although it is a departure from traditional PMRT to irradiate the chest wall without inclusion of the regional lymph node stations, this approach may be considered in select patients (eg, positive surgical chest wall margins as the only indication for PMRT or pT3N0 tumors in the absence of other high-risk factors), given the concern for local over regional recurrence risk.[2,17]

Although RNI in the EORTC 22922 and MA.20 trials included treatment of the IMNs, there is debate as to which patients might benefit most from IMN irradiation, particularly with the higher cardiopulmonary exposure associated with this approach and the potential for increased toxicity.[14,76] The benefit of IMN RT was specifically evaluated in studies from Denmark, France, and South Korea in which patients with breast cancer were treated with whole breast or chest wall RT, supraclavicular, and axillary apex irradiation with or without IMN RT.[62-64] The DBCG trial was a prospective, nonrandomized population-based cohort study that assigned IMN irradiation only to patients with right-sided disease to mitigate concerns for cardiac RT exposure among patients with left-sided cancer.[63,82] This study demonstrated a significant improvement in distant recurrence, death from breast cancer, and a 4.7% improvement in OS at 15 years among right-sided patients who received IMN RT. A French RCT enrolled patients with positive axillary lymph nodes or central, medial tumors with or without positive axillary lymph nodes and randomly assigned patients to receive RT to the chest wall and supraclavicular nodes with or without IMN RT.[64] This study did not demonstrate an OS benefit for IMN RT. In patients with positive axillary lymph nodes, a small but nonsignificant benefit was observed in favor of IMN RT. This study was underpowered and was performed in the 2-dimensional era of treatment planning, limiting its applicability.[64] Finally, the Korean Radiation Oncology Group 08-06 trial randomly assigned patients with pathologically confirmed, node-positive disease after mastectomy or breast-conservation surgery and axillary lymph node dissection to RNI with or without IMN RT.[62] The study demonstrated a nonstatistically significant 2.6% absolute decrease in distant metastases without a significant improvement in DFS. However, in an ad hoc subgroup analysis of patients with medial or centrally located tumors, both DFS and breast cancer-specific mortality at 7 years were significantly improved with the addition of IMN RT, suggesting that IMN RT in this subgroup of patients is beneficial.[62] Importantly, none of these trials, or the aforementioned RNI studies, demonstrated an increased risk of cardiac toxicity with treatment of the IMNs within the reported follow-up periods, lending support for the routine inclusion of IMN RT for patients with clinically or radiographically detected IMN nodes and those with central or medially located breast tumors, particularly when axillary lymph nodes are positive.[61-64,76]

Most of the studies evaluating PMRT have used conventional fractionation with doses approximating 5,000 cGy, EQD2.9 However, a number of retrospective analyses have suggested that moderately hypofractionated PMRT regimens result in reduced acute and late toxicity compared with conventional regimens, with comparable survival outcomes.[66,67,74,83-85] There is also precedent from RCTs to support the use of moderately hypofractionated regimens. In the landmark British Columbia study, 3,750 cGy in 16 fractions was used to deliver PMRT.[12] In the United Kingdom Standardization of Breast Radiotherapy A trial, enrolling 2,236 women with breast cancer, 15% underwent PMRT, and hypofractionated schedules resulted in similar locoregional failure rates, and lower adverse events, compared with conventional fractionation.[68] Additionally, the United Kingdom Standardization of Breast Radiotherapy B trial involved 2,215 women with breast cancer, with approximately 8% receiving PMRT.[69] At a median follow-up of 10 years, they found that 4,005 cGy in 15 daily fractions yielded comparable outcomes to 5,000 cGy in 25 daily fractions in terms of locoregional tumor control and lower late normal tissue effects, as assessed by both patient- and physician-reported photographs, and arm and shoulder symptoms.[69] In China, a noninferiority study randomly assigned 820 patients with at least four positive axillary nodes or T3-4 disease, excluding those with internal mammary or supraclavicular nodal involvement, to moderate hypofractionation (4,350 cGy in 15 fractions) or conventional fractionation (5,000 cGy in 25 fractions). At a median follow-up of 58.4 months, locoregional failure was deemed noninferior between arms (8.3% hypofractionation *v* 8.1% conventional fractionation), and there was a lower rate of grade 3 skin toxicity in the hypofractionation arm.[70] An additional RCT confirmed that there were no discernible differences in toxicities, LRR, distant failure rate, or DFS between PMRT regimens of 4,005 cGy in 15 fractions and 5,000 cGy in 25 fractions.[71] Given equivalent oncological outcomes and reduced toxicity, moderate hypofractionation is recommended for patients without breast reconstruction who are receiving PMRT, with careful consideration of dose selection for those with more advanced disease (eg, T4 and cN3 disease) or those with limited response to neoadjuvant systemic therapy.

None of these trials, however, were specifically designed to evaluate the impact of hypofractionation on cosmetic outcomes in the setting of breast reconstruction. As such, there has been hesitancy to transition to shorter treatment schedules for patients who opt for breast reconstruction, but there are increasing data to support its use.[74,83] The phase III Fractionation on Patient Outcomes After Breast

REConstruction trial randomly assigned 400 patients with stage 0-III breast cancer, excluding T4 disease, after mastectomy with implant-based reconstruction to hypofractionated RT (4,256 cGy in 16 fractions) or conventional RT (5,000 cGy in 25 fractions).[65] The primary end point was improvement in the Physical Well-Being domain of Functional Assessment of Cancer Therapy-Breast at 6 months. Results showed a significant reduction in patients requiring a treatment break with hypofractionation compared with conventional fractionation (2.7% *v* 7.7%). There was no difference in chest wall toxicity between the two groups at a median follow-up of 40.4 months.[65,86] Based on these data, the use of moderate hypofractionation is recommended as the preferred PMRT approach in the setting of implant-based reconstruction.[65]

Another completed RCT, Alliance A221505 (RT CHARM: Hypofractionated Post Mastectomy Radiation with Breast Reconstruction; ClinicalTrials.gov identifier: NCT03414970)[87] randomly assigned nearly 900 patients with T1-3N1-2 or T3N0 disease undergoing mastectomy with immediate or delayed reconstruction (implant-based or autologous) to hypofractionated PMRT (4,256 cGy in 16 fractions) or conventional PMRT (5,000 cGy in 25 fractions) with a primary end point of reconstruction complication rate. In this trial, patients with T4 and N3 disease, including IMN involvement, were excluded.[87] Final published results from this study will provide additional data on the clinical outcomes and toxicity of hypofractionated PMRT with reconstruction.[87] Until then, conventional fractionation is also recommended as an option.

It is important to note the variability in dose regimens and eligibility criteria used in each of the previously mentioned trials,[65,70,72,86,87] reflecting uncertainties regarding biologically effective dosing between conventional fractionation and moderate hypofractionation. Because of the evolving understanding of both the alpha/beta ratio of breast cancer and the effect of shorter treatment regimens on repopulation, care should be taken when selecting hypofractionated regimens, particularly for patients with high-risk features (eg, T4 or N3 disease), to ensure that definitive RT doses are used. In these scenarios, a separate boost to suspected residual disease, as could be employed in the conventional fractionation setting, may also be appropriate (see the subsequent discussion of a boost).

One limitation of these trials is the relatively small number of Black, Hispanic, or Asian patients enrolled, which limits the understanding of potential cosmetic differences in these populations. Prior studies have demonstrated Asian, Black, and Hispanic patients experience worse acute and long-term skin quality-of-life outcomes after breast RT than White patients.[88,89] Therefore, extra consideration in treatment planning and supportive care is advised in these patient populations, recognizing that their relative lack of representation on the available trials should not unduly limit their access to shorter, more convenient treatment schedules, particularly given recognized disparities in the receipt of PMRT among Black and Hispanic patients with stage III breast cancer.[90,91]

Finally, there is increasing interest in the use of ultrahypofractionated treatment regimens (ie, 2,600 cGy in five fractions) in breast cancer, although there are limited data in patients receiving PMRT. Early reports suggest comparable outcomes with ultrahypofractionation to the chest wall and nodal regions,[92] and additional trials are underway to further evaluate these abbreviated treatment regimens for patients requiring PMRT.[93,94]

Evidence supporting the administration of a chest wall scar boost to improve local control rates is limited and has never been established prospectively. Although the majority of LRRs after mastectomy occur on the chest wall,[9] only retrospective studies have examined the use of chest wall boosts for high-risk patients and have provided some support for doses up to 6,600 cGy using conventional fractionation.[95-98] Despite this, a survey among breast radiation oncologists demonstrated that 55% routinely use a chest wall boost following PMRT and an additional 18% prescribe a boost depending on margin status.[99] Pragmatically, the administration of a chest wall boost is conditionally recommended in cases of T4 disease and positive margins where concern for residual disease is enhanced. Of note, an evaluation of women who had undergone PMRT from the California Cancer Registry identified disparities in the receipt of a chest wall boost, with poor and Hispanic women more commonly receiving a chest wall boost than affluent and non-Hispanic women of similar cancer stage and biology.[100] This suggests that objective criteria for using a chest wall boost may not be uniformly applied and care should be taken, whenever possible, not only to follow consistent criteria, as detailed here, but to ensure representative enrollment of diverse patient populations in prospective studies evaluating treatment techniques.

Similarly, there are no randomized studies examining the use of a boost to gross disease in undissected nodal basins, such as the supraclavicular fossa or internal mammary chain, despite recognition that involvement of these nodes is a poor prognostic factor in breast cancer.[63,64] Institutional retrospective analyses suggested that an additional boost to involved supraclavicular and internal mammary chain nodes can be delivered safely and may improve local control rates, but these data are limited by small sample sizes.[101,102] However, if adding a boost to an undissected node, doses of 6,000 cGy EQD2 should be considered for microscopic disease and at least 6,600 cGy EQD2 for gross or residual disease.

KQ4: Appropriate PMRT Delivery Techniques (Table 6)

See evidence tables in Data Supplement 4 for the data supporting the recommendations for KQ4.

TABLE 6. Appropriate PMRT Delivery Techniques

KQ4 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
1. For patients receiving PMRT, CT-based volumetric treatment planning with 3-D CRT is recommended.	Strong	Moderate[14,62-64,82,103-105]
2. For patients receiving PMRT, IMRT (including VMAT) is recommended when 3-D CRT is unable to achieve treatment goals (ie, target coverage and normal tissue avoidance). *Implementation remark:* Use of IMRT (including VMAT) may increase OAR low-dose exposure compared with 3-D CRT.	Strong	Moderate[106-110]
3. For patients receiving PMRT, DIBH is recommended when lower doses to normal tissues, including the heart and lungs, can be achieved compared with free breathing. *Implementation remarks:* Other normal tissue sparing techniques may be used. For DIBH, use of a real-time monitoring device (eg, SGRT, spirometry-based systems, chest wall monitoring system) and image-guided verification are advised.	Strong	Moderate[109,111,112]
4. For patients receiving PMRT treated with IMRT (including VMAT), daily image guidance, in conjunction with regular 3-D assessments (eg, CBCT, SGRT), is recommended.	Strong	Low[113]
5. For patients with cT1-3 breast cancer receiving PMRT, the routine use of tissue-equivalent bolus is not recommended. *Implementation remark:* Bolus may be used in circumstances where improved dosimetric coverage of the skin is needed.	Strong	Moderate[114-119]
6. For patients with skin involvement, positive superficial margins, and those with dermal lymphatic involvement and/or extensive LVI, the use of tissue-equivalent bolus is recommended.	Strong	Expert opinion

Abbreviations: 3-D CRT, 3-dimensional conformal radiation therapy; CBCT, cone beam computed tomography; CT, computed tomography; DIBH, deep inspiration breath hold; IMRT, intensity-modulated radiation therapy; KQ, key question; LVI, lymphovascular invasion; OAR, organ at risk; PMRT, postmastectomy radiation therapy; SGRT, surface-guided radiation therapy; VMAT, volumetric modulated arc therapy.

What Are the Appropriate Techniques (eg, 3-D CRT, IMRT, protons, breath hold, bolus) for Treating Patients Who Receive PMRT?

High-quality evidence from RCTs directly evaluating various RT techniques for PMRT is limited, and most foundational studies used 2-dimensional or 3-D photon therapy, with or without an electron component.[8,12,14,62-64,82,103,120] Modern RT design is based on contouring of the target areas (chest wall and nodal basins as indicated) and the adjacent relevant organs at risk (OARs) as appropriate (ie, heart, left ventricle, left anterior descending [LAD] artery and/or right coronary artery, bilateral lungs, contralateral breast, spinal cord, thyroid, esophagus, humeral head, stomach, liver, and/or brachial plexus).[121,122] Use of contouring guidelines, such as those provided by the Radiation Therapy Oncology Group atlas, RADCOMP (Radiotherapy Comparative Effectiveness),[121] and European atlases,[122,123] may be used to assist with accurate target and OAR delineation. The goal of volumetric treatment planning is to use CT information to adequately cover the target volumes while minimizing dose to normal tissues, taking individual anatomic variation into account. While this approach has historically been underutilized in RT treatment planning for breast cancer compared with other disease sites, CT-based volumes should be used for individualized RT planning for breast cancer. The task force acknowledges that in many cases, more stringent planning parameters can be achieved than what is detailed in Table 7 and the concept of as low as reasonably achievable should prevail for all RT treatment plans. However, it is also recognized that the guidance provided may not be uniformly achievable for all patients' plans, given anatomic concerns. When intensity-modulated planning is employed, attention to low doses delivered to OARs that do not typically receive dose exposure with 3-D planning is advised (eg, spinal cord, stomach, liver).[14,62-64,82,103-105] Finally, given the current state of the data, specific dose constraints are not provided for all relevant vulnerable normal tissues (eg, LAD artery or right coronary artery); however, contouring of these structures is still advised to rationally constrain unnecessary exposure during treatment planning.

For PMRT field design, 3-D CRT treatment planning can use a variety of techniques, for example, partially wide tangent fields to include the IMN contour, a medial electron field matched to narrow photon tangents, or electrons to the chest wall alone with a match to a photon supraclavicular field with or without a posterior axillary field.[124] Advanced modulated planning techniques (eg, IMRT including volumetric modulated arc therapy [VMAT]) can be used to improve high-dose conformality and target coverage. Studies evaluating the treatment of patients with breast cancer using tomotherapy have also shown feasibility.[125,126] Studies comparing various techniques have shown low LRR rates regardless of technique.[66,103,105,106]

Treatment with inverse planned IMRT can decrease the high-dose exposure of OARs compared with 3-DCRT, and in some cases decrease the risk of toxicity.[66,107,108,127] A retrospective study of patients receiving PMRT comparing 3-D CRT with VMAT reported a reduction in RT pneumonitis in the cohort treated with VMAT.[66] Another study

TABLE 7. Guidance on Target Coverage

Structure	Goal	5,000-5,040 cGy in 25-28 fx	4,000-4,256 cGy in 15-16 fx
Ipsilateral chest wall[52,87]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc ≤110%	D0.1 cc ≤107%[b]
	Acceptable	D0.1 cc ≤115%Rx	D0.1 cc 115% Rx
Axilla[a,42,79]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc 110% Rx	D0.1 cc 107% Rx[b]
	Acceptable	D0.1 cc ≤115%Rx	D0.1 cc 115% Rx
Supraclavicular fossa[52,87]	Ideal	D95 ≥95% PTV	D95 ≥95% PTV
	Acceptable	D90 ≥90% PTV	D90 ≥90% PTV
	Ideal	D0.1 cc 115% Rx	D0.1 cc 112% Rx[b]
	Acceptable	D0.1 cc ≤120%Rx	D0.1 cc 115% Rx
Internal mammary nodes[52,87]	Ideal	D95 ≥90% PTV	D95 ≥90% PTV
	Acceptable	D90 ≥80% PTV	D90 ≥80% PTV

NOTE. This table is a combination of evidence-based constraints and expert opinion.
Abbreviations: PTV, planning target volume; Rx, prescription dose.
[a]If patient has undergone a completion axillary dissection, coverage goals apply only to the targeted axilla.
[b]Extrapolated from conventionally fractionated data.

demonstrated that adequate target coverage was achieved with both 3-D CRT and IMRT, with a decrease in moist desquamation in the cohort treated with IMRT (14.3% *v* 3.8%, respectively).[108] A third study described a decrease in moderate- and high-dose exposure to the shoulder in patients undergoing RNI with IMRT compared with 3-D CRT.[127] One tradeoff of reduced high-dose exposure to OARs with IMRT is an increase in low-dose OAR exposure. For example, one study described acute radiation-induced nausea associated with low-dose exposure of the upper abdominal structures,[128] side effects that are uncommon with 3-D CRT. Therefore, the use of IMRT (including VMAT) is recommended when 3-D CRT is unable to achieve treatment goals, with close attention to increased low-dose OAR exposure (see Table 8 for guidance on OARs).

Historically, a key cause of noncancer-related morbidity and mortality from PMRT came from undue cardiac exposure. Therefore, numerous studies comparing treatment planning techniques have been done with the goal of improving cardiac sparing.[134,135] Although a dose-dependent relationship between cardiac exposure to RT and heart disease has been demonstrated in several landmark studies,[136-140] no safe threshold has been established to prevent major cardiovascular events. Therefore, it is generally accepted that mean heart dose should be as low as reasonably achievable (Table 8). Special consideration should be given to minimizing RT exposure to the heart for patients with preexisting heart disease and certain risk factors (eg, diabetes, hypertension, and smoking), as these have been shown to be synergistic with cardiac RT exposure in increasing the risk of cardiac disease development.[141,142]

A deep inspiration breath hold (DIBH) technique is one strategy for reducing dose to normal tissues, including the heart and lungs. Suitability for DIBH should be evaluated based on a patient's ability to maintain the breath hold and individual cardiac anatomy.[111,112] Among patients for whom DIBH can be successfully implemented, cardiopulmonary dose can be reduced compared with a free-breathing 3-D CRT technique.[111,143] Notably, there is an understanding that dose exposure to cardiac substructures including the left ventricle and the LAD artery does not correlate with mean heart dose. Both have been implicated in RT-associated cardiac toxicity in patients receiving RT for breast cancer, so particular consideration should be given to these substructures.[139,144] An RCT comparing IMRT-DIBH with free-breathing 3-D CRT for patients with node-positive breast cancer showed lower mean doses for the ipsilateral lung, heart, and LAD artery, suggesting that patients receiving IMRT can also benefit from DIBH.[109] Although there was no difference in single-photon emission CT perfusion defects in the LAD territory or lung perfusion or function between groups, most patients in the IMRT-DIBH arm had stable or improved left ventricular ejection fraction at 1 year compared with a slightly declining left ventricular ejection fraction in the free-breathing cohort.[109] When DIBH is employed, use of a real-time monitoring device (eg, surface-guided radiation therapy [SGRT], spirometry-based or chest wall monitoring systems) and image-guided RT verification is advised to ensure the fidelity of respiratory displacement throughout treatment delivery.[109,111]

The use of proton therapy remains under investigation at the time of guideline development. Single-institution series,

TABLE 8. Guidance on Organs at Risk

Structure	Goal	5,000-5,040 cGy in 25-28 fx	4,000-4,256 cGy in 15-16 fx
Ipsilateral lung[52,87]		V5 Gy ≤75%	V4 Gy ≤65%[b]
	Ideal	V10 Gy ≤65%	V8 Gy ≤55%[b]
		V20 Gy ≤35%[a]	V17 Gy ≤25%[b]
	Acceptable	V20 Gy ≤40%	V17 Gy ≤35%
Contralateral lung[87]	Ideal	V5 Gy ≤10%	V4 Gy ≤10%[b]
	Acceptable	V5 Gy ≤15%	V4 Gy ≤15%[b]
Heart[c,87]	Ideal (left-sided)	Dmean ≤3 Gy	Dmean ≤2.4 Gy[b]
	Acceptable (left-sided)	Dmean ≤5 Gy	Dmean ≤4Gy[b]
	Ideal (right-sided)	Dmean <2 Gy	Dmean ≤1.6 Gy[b]
	Acceptable (right-sided)	Dmean ≤3 Gy	Dmean ≤2.4 Gy[b]
Contralateral breast/chest wall[52,87]	Ideal	V3 Gy ≤10%	V3 Gy ≤10%
	Acceptable	V5 Gy ≤10%	V5 Gy ≤10%
Additional considerations			
Brachial plexus[92]	Suggested	D0.1cc ≤105%Rx	D0.1 cc ≤105% Rx
Esophagus	Suggested	V10 Gy <30%/V20 Gy <15%[129]	V8 Gy <30%/V17 Gy <15%[b,130]
Left ventricle[131]	Suggested	V2 Gy <36%	V1.6 Gy <36%[b]
Spinal cord[a]	Suggested	D0.1 cc 45 Gy	D0.1 cc 38.54 Gy
Thyroid[132,133]	Suggested	Dmean <21 Gy	Dmean <21 Gy
Humeral head	Suggested	Dmean <20 Gy	Dmean <17 Gy
Stomach (left-sided)	Suggested	Dmean <3 Gy	Dmean <2.4 Gy
Liver (right-sided)	Suggested	Dmean <7 Gy	Dmean <5.6 Gy

NOTE. Where dose constraints differed by protocol, the more conservative guidelines were used. This table is a combination of evidence-based constraints and expert opinion and reflects guidance for routine treatments that do not employ a boost for gross or residual nodal disease.
Abbreviations: Dmean, mean dose received by an organ; HYPOG-1, Hypofractionated Radiotherapy for Breast Cancer Nodal Irradiation-1; Rx, prescription dose.
[a]Based on the HYPOG-1 trial protocol (ClinicalTrials.gov identifier: NCT03127995).
[b]Extrapolated from conventionally fractionated data.
[c]Cardiac dose should be constrained as low as reasonably achievable.

prospective registry reports, and retrospective studies have demonstrated improved dosimetric target coverage, alongside preservation of cardiac function, compared with 3-D CRT and IMRT, particularly in the setting of RNI, including IMN irradiation.[145-149] The RAD-COMP trial as well as the PARABLE and Danish Breast Proton trials are all evaluating major cardiac events between patients treated with proton versus photon RT and it is anticipated that these studies will provide more data on the appropriate role of proton PMRT in the future.[121,130]

There is currently a lack of evidence to support a single optimal strategy for image guidance in the PMRT setting. Minimally, daily planar imaging, in conjunction with regular 3-D assessments (eg, cone beam CT [CBCT], SGRT), is recommended for patient localization for complex planning and multifield techniques, such as IMRT (including VMAT).[150,151] Volumetric imaging (eg, CBCT) is valuable under these conditions to assess for evolving anatomic changes or setup variability that may adversely affect treatment accuracy. However, the planning target volume margins should account for setup variability and the type and frequency of image guidance used during treatment.[152]

Alternatively, SGRT using the patient's external surface and nonionizing radiation can assist in PMRT patient setup,[111,153] monitor intrafraction motion,[154,155] and verify breath hold position.[112,153] However, in addition to training and workflow issues,[155] significant tissue deformations and limitations in the technology to detect darker skin tones have been identified as potential drawbacks.[156] Currently, data are lacking to support the use of SGRT alone for daily PMRT treatment delivery. When SGRT is employed, it is advised to use it in conjunction with image-guided RT for setup verification. Guidance for the use of SGRT with image guidance, including common challenges and potential errors, has been published.[155]

Finally, tissue-equivalent bolus has historically been used in PMRT with the recognition that most chest wall recurrences occur superficially or just under the skin. The skin and most superficial layer of chest wall tissue are key components of the RT target, and depending on the RT technique and beam energy used, surface dose may only reach 70%– to 80% of the prescribed dose. Tissue-equivalent bolus can be used to bring the skin dose closer to prescription dose. However, the application of tissue-equivalent bolus over the chest wall in

PMRT can vary with respect to frequency and thickness, and several clinical trials have permitted bolus at the discretion of the treating physician,[52,86,157] thereby limiting the ability to formally evaluate the impact of bolus on clinical outcomes to help guide recommendations for the use of bolus with PMRT.

Multiple studies have identified a relationship between the use of bolus and increased skin toxicity.[114-118,158] At the same time, despite the historical assumption of benefit, the impact of bolus on local control has been questioned, including three small retrospective studies that did not identify a local control benefit with bolus.[116-118] One RCT of 59 patients, employing a risk-stratified bolus strategy with thicker and more frequent use of bolus in patients with frank skin involvement and no bolus versus 5-mm bolus on alternate days in standard-risk patients without skin involvement, found no decrement in chest wall local control within risk groups, although all patients in the high-risk group were treated with bolus.[114] Although these analyses are limited by patient and treatment heterogeneity, they suggest insufficient evidence for a local control benefit with the routine use of bolus for patients with cT1-3 disease without a high risk of skin involvement.[117,118] Understanding the value of bolus among patients with darker skin tones may be particularly critical, given the higher likelihood of skin toxicity and late skin effects from RT among non-White patients, although no studies to date have specifically evaluated the impact of bolus across different skin tones.[90,91] Therefore, the routine use of bolus is not advised for all patients, but may be used in circumstances where improved dosimetric coverage of the skin is needed. In addition, for those patients with an increased risk of skin recurrence, including patients who present with skin involvement, positive anterior surgical margins, dermal lymphatic invasion, or extensive LVI, the use of bolus is recommended based on expert opinion.[114]

CONCLUSIONS AND FUTURE DIRECTIONS

Multiple RCTs and the EBCTCG meta-analysis have confirmed that PMRT reduces the risk of LRR and improves breast cancer mortality. However, the absolute risk reduction varies across individuals. There are ongoing efforts to try to better characterize risk according to tumor biology, and in the era of tailored systemic therapy, to further personalize treatment recommendations. Unfortunately, there are few data from available clinical trials to guide tailored management recommendations for patients based on sociodemographic characteristics, including race and access to health care. It is critical that future trials of PMRT ensure diverse trial enrollment and participation.

In addition, there are several potentially practice-changing trials that remain in active accrual or have not yet been published at the time of this guideline including trials related to PMRT in favorable-risk disease (SUPREMO, MA.39/TAILOR-RT [ClinicalTrials.gov identifier: NCT03488693]), hypofractionation (RT CHARM [ClinicalTrials.gov identifier: NCT03414970],[87] HYPOG-01 [ClinicalTrials.gov identifier: NCT03127995], FAST FORWARD nodal substudy,[92] HYPORT-Adjuvant study[159]), PMRT after neoadjuvant chemotherapy (NSABP B-51 [ClinicalTrials.gov identifier: NCT01872975]),[52] particle therapy (RADCOMP [ClinicalTrials.gov identifier: NCT02603341], PARABLE (United Kingdom),[130] Danish Breast Proton Trial [ClinicalTrials.gov identifier: NCT04291378]),[160] and the role of axillary surgery (Alliance A011202 [ClinicalTrials.gov identifier: NCT01901094]) that will impact clinical decision making and future clinical practice.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

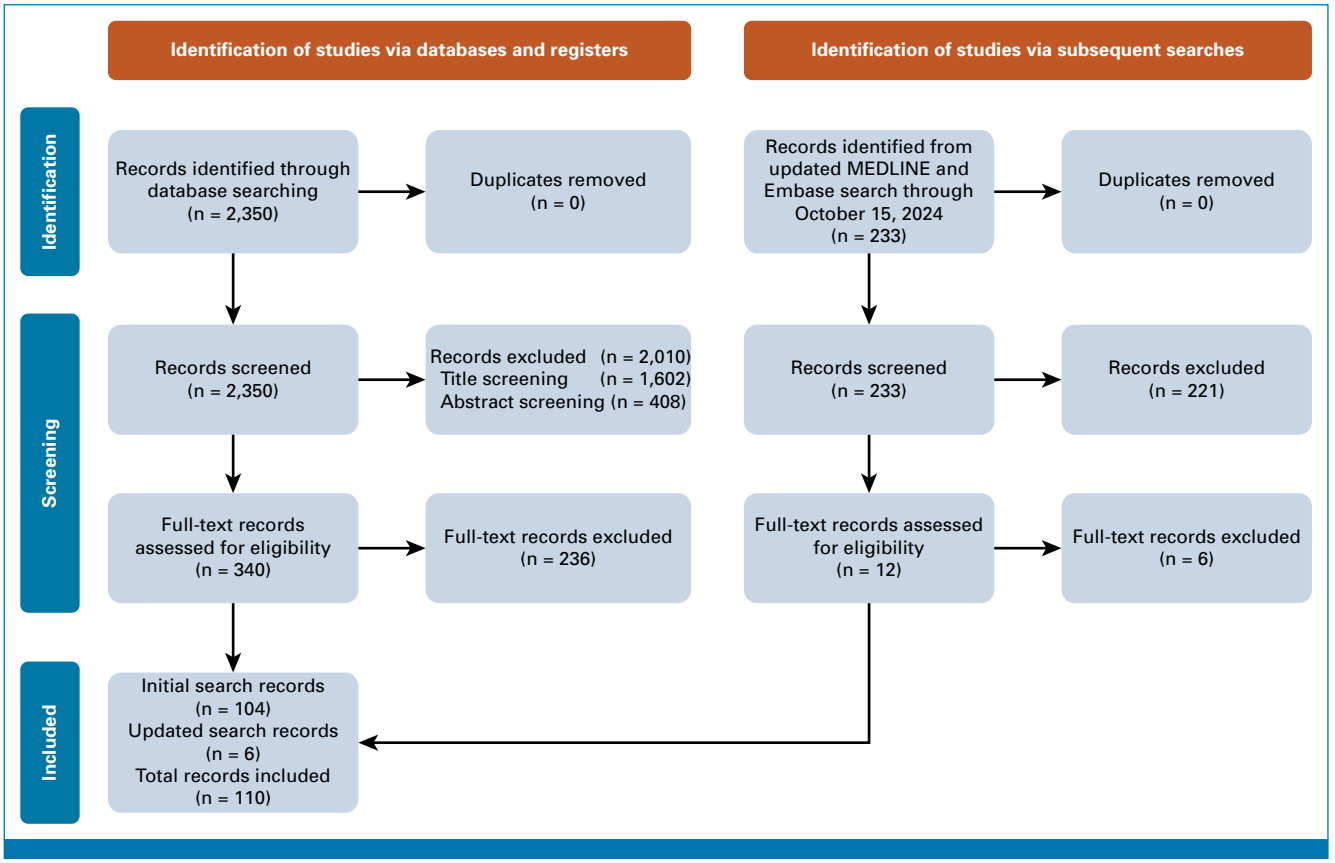
ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit www.asco.org/breast-cancer-guidelines. The Data Supplement for this guideline includes a list of abbreviations used in the guideline, the PICOTS and literature search strategies, a list of guideline peer reviewers, and data supporting the recommendations. Guideline recommendations are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

The task force welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of all patients. ASCO guidelines are intended to apply to, and be discussed clearly and compassionately with, all patients. For this reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.



PRISMA 2020 study selection diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

AFFILIATIONS

[1]Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA
[2]Department of Medical Oncology, University of North Carolina, Chapel Hill, NC
[3]Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA
[4]Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA
[5]American Society for Radiation Oncology, Arlington, VA
[6]Department of Radiation Oncology, University of Florida, Jacksonville, FL
[7]Patient Representative, Surviving Breast Cancer, Gilbert, AZ
[8]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[9]Department of Surgery, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT
[10]Department of Radiation Oncology, University of Colorado Denver, Aurora, CO
[11]Department of Surgery, Loyola University Medical Center, Chicago, IL
[12]Radiation Oncology Branch, National Cancer Institute, Bethesda, MD
[13]Department of Medicine, Yale School of Medicine, New Haven, CT
[14]Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, TX
[15]Department of Radiation Oncology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA
[16]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL
[17]Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC
[18]Department of Radiation Oncology, Florida International University and Lynn Cancer Institute, Boca Raton, FL
[19]Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN
[20]Department of Radiation Oncology, Stanford University, Stanford, CA

CORRESPONDING AUTHOR

American Society of Clinical Oncology; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/breast-cancer-guidelines. These evidence-based recommendations guide clinical practice on the use of PMRT in patients with breast cancer.

EQUAL CONTRIBUTION

R.B.J. and K.C.H. were Expert Panel vice chair and chair, respectively.

SUPPORT

Supported by the American Society for Radiation Oncology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-01747.

AUTHOR CONTRIBUTIONS

Conception and design: Rachel B. Jimenez, Yara Abdou, Penny Anderson, Parul Barry, Lisa Bradfield, Atif Khan, Chantal Reyna, Kilian E. Salerno, Youssef H. Zeidan, Richard C. Zellars, Kathleen C. Horst
Administrative support: Lisa Bradfield
Provision of study materials or patients: Youssef H. Zeidan
Collection and assembly of data: Rachel B. Jimenez, Yara Abdou, Penny Anderson, Parul Barry, Lisa Bradfield, Julie A. Bradley, Cindy Matsen, Kilian E. Salerno, Sarah E. Schellhorn, Kekoa Taparra, Youssef H. Zeidan, Richard C. Zellars, Kathleen C. Horst
Data analysis and interpretation: Rachel B. Jimenez, Yara Abdou, Penny Anderson, Parul Barry, Julie A. Bradley, Lourdes D. Heras, Atif Khan, Cindy Matsen, Rachel Rabinovitch, Chantal Reyna, Kilian E. Salerno, Sarah E. Schellhorn, Deborah Schofield, Kekoa Taparra, Iman Washington, Jean L. Wright, Youssef H. Zeidan, Richard C. Zellars, Kathleen C. Horst
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

ASCO wishes to thank Tiffinay Traina, MD, Rachel Yung, MD, and the Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline. The task force thanks the National Institutes of Health (NIH) Library biomedical librarians, Tracy C. Shields, MSIS, and Alicia A. Livinski, MPH, MA, for conducting the literature searches for this guideline; and Kekoa Taparra, MD, PhD, MPH (lead resident), Claire Baniel, MD, Katie Hwang, MD, Osagie Igiebor, MD, and Kaidi Wang, MD, for literature review assistance. The task force also thanks the peer reviewers for their comments and time spent reviewing the guideline. See Data Supplement for their names and disclosures. The authors also thank task force participant Angel Montero, MD, PhD, for serving as ESTRO's representative but who withdrew from authorship.

REFERENCES

1. Ferlay JEM, Lam F, Laversanne M, et al: Global Cancer Observatory: Cancer Today. Lyon, France, International Agency for Research on Cancer, 2024
2. EBCTCG Early Breast Cancer Trialists' Collaborative Group, McGale P, Taylor C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 383:2127-2135, 2014
3. Recht A, Comen EA, Fine RE, et al: Postmastectomy radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. Pract Radiat Oncol 6:e219-e234, 2016
4. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Graham RMM, Miller WD, Steinberg E (eds): Clinical Practice Guidelines We Can Trust. Washington, DC, National Academies Press, 2011
5. Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness, Eden JLL, Berg A, Morton S (eds): Finding What Works In Health Care: Standards for Systematic Reviews. Washington, DC, National Academies Press, 2011
6. Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Rev Esp Cardiol 74:790-799, 2021
7. Page MJ, Moher D, Bossuyt PM, et al: PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. BMJ 372:n160, 2021
8. Overgaard M, Nielsen HM, Tramm T, et al: Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish Breast Cancer Cooperative Group DBCG 82bc trial. Radiother Oncol 170:4-13, 2022
9. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, et al: Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: Long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 24:2268-2275, 2006
10. Nielsen HM, Overgaard M, Grau C, et al: Loco-regional recurrence after mastectomy in high-risk breast cancer–risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. Radiother Oncol 79:147-155, 2006
11. Early Breast Cancer Trialists' Collaborative Group EBCTCG: Radiotherapy to regional nodes in early breast cancer: An individual patient data meta-analysis of 14 324 women in 16 trials. Lancet 402:1991-2003, 2023
12. Ragaz J, Olivotto IA, Spinelli JJ, et al: Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97116-126, 2005
13. Wang J, Shi M, Ling R, et al: Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: A prospective randomized controlled multi-center trial. Radiother Oncol 100:200-204, 2011
14. Poortmans PM, Weltens C, Fortpied C, et al: Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol 21:1602-1610, 2020
15. Li Y, Moran MS, Huo Q, et al: Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: A meta-analysis. PLoS One 8:e81765, 2013
16. Sittenfeld SMC, Zabor EC, Hamilton SN, et al: A multi-institutional prediction model to estimate the risk of recurrence and mortality after mastectomy for T1-2N1 breast cancer. Cancer 128: 3057-3066, 2022
17. Karlsson P, Cole BF, Chua BH, et al: Patterns and risk factors for locoregional failures after mastectomy for breast cancer: An International Breast Cancer Study Group report. Ann Oncol 23: 2852-2858, 2012
18. Clarke M, Collins R, Darby S, et al: Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 366:2087-2106, 2005
19. Kunkler I: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10-year results of the BIG 2-04 MRC SUPREMO randomised trial. GS2-03; SESS-3537. Presented at the San Antonio Breast Cancer Symposium. San Antonio, TX, 2024
20. Lim SZ, Kusumawidjaja G, Mohd Ishak HM, et al: Outcomes of stage I and II breast cancer with nodal micrometastases treated with mastectomy without axillary therapy. Breast Cancer Res Treat 189:837-843, 2021
21. Kyndi M, Overgaard M, Nielsen HM, et al: High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82 b&c. Radiother Oncol 90:74-79, 2009
22. Rao X, Wang X, Jin K, et al: Outcomes with and without postmastectomy radiotherapy for pT3N0-1M0 breast cancer: An institutional experience. Cancer Med 13:e6927, 2024
23. Zhao R, He W, Guan X: Benefits of post-mastectomy radiation for T4N0M0 breast cancer patients: A SEER database study. Cancer Treat Res Commun 32:100586, 2022
24. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337:949-955, 1997
25. Overgaard M, Jensen MB, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353:1641-1648, 1999
26. Taghian AG, Jeong JH, Mamounas EP, et al: Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: Results from five national surgical adjuvant breast and bowel project randomized clinical trials. J Clin Oncol 24:3927-3932, 2006
27. McCammon R, Finlayson C, Schwer A, et al: Impact of postmastectomy radiotherapy in T3N0 invasive carcinoma of the breast: A Surveillance, Epidemiology, and End Results database analysis. Cancer 113:683-689, 2008
28. Yan W, Christos P, Nori D, et al: Is there a cause-specific survival benefit of postmastectomy radiation therapy in women younger than age 50 with T3N0 invasive breast cancer? A SEER database analysis: Outcomes by receptor status/race/age: Analysis using the NCI Surveillance, Epidemiology, and End Results (SEER) database. Am J Clin Oncol 36:552-557, 2013

29. Taghian A, Jeong JH, Mamounas E, et al: Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol 22:4247-4254, 2004
30. Peng G, Zhou Z, Jiang M, et al: Can a subgroup at high risk for LRR be identified from T1-2 breast cancer with negative lymph nodes after mastectomy? A meta-analysis. Biosci Rep 39: BSR20181853, 2019
31. Bundred J, Michael S, Bowers S, et al: Do surgical margins matter after mastectomy? A systematic review. Eur J Surg Oncol 46:P2185-P2194, 2020
32. Garg AK, Oh JL, Oswald MJ, et al: Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 69:1478-1483, 2007
33. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al: Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 68:1004-1009, 2007
34. Krug D, Lederer B, Seither F, et al: Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer: A pooled retrospective analysis of three prospective randomized trials. Ann Surg Oncol 26:3892-3901, 2019
35. Wang K, Jin X, Wang W, et al: The role of postmastectomy radiation in patients with ypN0 breast cancer after neoadjuvant chemotherapy: A meta-analysis. BMC Cancer 21:728, 2021
36. Murchison S, Nichol A, Speers C, et al: Locoregional recurrence and survival outcomes in breast cancer treated with modern neoadjuvant chemotherapy: A contemporary population-based analysis. Clin Breast Cancer 22:e773-e787, 2022
37. Arsenault D, Hurley J, Takita C, et al: Predictors of locoregional outcome in HER2-overexpressing breast cancer treated with neoadjuvant chemotherapy. Am J Clin Oncol 38:348-352, 2015
38. Mamounas EP, Anderson SJ, Dignam JJ, et al: Predictors of locoregional recurrence after neoadjuvant chemotherapy: Results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-27. J Clin Oncol 30:3960-3966, 2012
39. Saifi O, Bachir B, Panoff J, et al: Post-mastectomy radiation therapy in HER-2 positive breast cancer after primary systemic therapy: Pooled analysis of TRYPHAENA and NeoSphere trials. Radiother Oncol 184:109668, 2023
40. Huang Z, Zhu L, Huang XB, et al: Postmastectomy radiation therapy based on pathologic nodal status in clinical node-positive stage II to III breast cancer treated with neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 108:1030-1039, 2020
41. Haffty BG, McCall LM, Ballman KV, et al: Impact of radiation on locoregional control in women with node-positive breast cancer treated with neoadjuvant chemotherapy and axillary lymph node dissection: Results from ACOSOG Z1071 clinical trial. Int J Radiat Oncol Biol Phys 105:174-182, 2019
42. Schmid P, Cortes J, Pusztai L, et al: Pembrolizumab for early triple-negative breast cancer. N Engl J Med 382:810-821, 2020
43. Shim SJ, Park W, Huh SJ, et al: The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: A multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 88:65-72, 2014
44. Le Scodan R, Selz J, Stevens D, et al: Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 82:e1-e7, 2012
45. Kim D, Kim JH, Kim IA, et al: Impact of postmastectomy radiation therapy on breast cancer patients according to pathologic nodal status after modern neoadjuvant chemotherapy. Cancer Res Treat 55:592-602, 2023
46. Nagar H, Mittendorf EA, Strom EA, et al: Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer. Int J Radiat Oncol Biol Phys 81:782-787, 2011
47. Crown A, Gonen M, Le T, et al: Does failure to achieve pathologic complete response with neoadjuvant chemotherapy identify node-negative patients who would benefit from postmastectomy radiation or regional nodal irradiation? Ann Surg Oncol 28:1328-1335, 2021
48. Nagar H, Boothe D, Ginter PS, et al: Disease-free survival according to the use of postmastectomy radiation therapy after neoadjuvant chemotherapy. Clin Breast Cancer 15:128-134, 2015
49. Mailhot Vega RB, Wang S, Brooks ED, et al: Evaluating regional nodal irradiation allocation and association with oncologic outcomes in NSABP B-18, B-27, B-40, and B-41. Int J Radiat Oncol Biol Phys 113:542-551, 2022
50. Haffty BG, McCall LM, Ballman KV, et al: Patterns of local-regional management following neoadjuvant chemotherapy in breast cancer: Results from ACOSOG Z1071 (Alliance). Int J Radiat Oncol Biol Phys 94:493-502, 2016
51. Gianni L, Pienkowski T, Im YH, et al: Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncol 13:25-32, 2012
52. Mamounas E, Bandos H, White J, et al: Abstract GS02-07: Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: Primary outcomes of NRG oncology/NSABP B-51/RTOG 1304. Cancer Res 84:GS02-07, 2024 (suppl 9)
53. de Wild SR, de Munck L, Simons JM, et al: De-escalation of radiotherapy after primary chemotherapy in cT1-2N1 breast cancer (RAPCHEM; BOOG 2010-03): 5-year follow-up results of a Dutch, prospective, registry study. Lancet Oncol 23:1201-1210, 2022
54. Meattini I, Cecchini S, Di Cataldo V, et al: Postmastectomy radiotherapy for locally advanced breast cancer receiving neoadjuvant chemotherapy. Biomed Res Int 2014:719175, 2014
55. Gillon P, Touati N, Breton-Callu C, et al: Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: An analysis of the EORTC 10994/BIG 1-00 study. Eur J Cancer 79:226-234, 2017
56. Yang TJ, Morrow M, Modi S, et al: The effect of molecular subtype and residual disease on locoregional recurrence in breast cancer patients treated with neoadjuvant chemotherapy and postmastectomy radiation. Ann Surg Oncol 22:S495-S501, 2015 (suppl 3)
57. Werutsky G, Untch M, Hanusch C, et al: Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer 130: 92-101, 2020
58. Masuda N, Lee SJ, Ohtani S, et al: Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 376:2147-2159, 2017
59. von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
60. Schmid P, Cortes J, Dent R, et al: Overall survival with pembrolizumab in early-stage triple negative breast cancer. N Engl J Med 391:1981-1991, 2024
61. Poortmans PM, Collette S, Kirkove C, et al: Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 373:317-327, 2015
62. Kim YB, Byun HK, Kim DY, et al: Effect of elective internal mammary node irradiation on disease-free survival in women with node-positive breast cancer: A randomized phase 3 clinical trial. JAMA Oncol 8:96-105, 2022
63. Thorsen LB, Offersen BV, Danø H, et al: DBCG-IMN: A population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol 34: 314-320, 2016
64. Hennequin C, Bossard N, Servagi-Vernat S, et al: Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 86: 860-866, 2013
65. Wong JS, Uno H, Tramontano AC, et al: Hypofractionated vs conventionally fractionated postmastectomy radiation after implant-based reconstruction: A randomized clinical trial. JAMA Oncol 10:1370-1378, 2024
66. Kim N, Chang JS, Shah C, et al: Hypofractionated volumetric-modulated arc therapy for breast cancer: A propensity-score-weighted comparison of radiation-related toxicity. Int J Cancer 149: 149-157, 2021
67. Chitapanarux I, Klunklin P, Pinitpatcharalert A, et al: Conventional versus hypofractionated postmastectomy radiotherapy: A report on long-term outcomes and late toxicity. Radiat Oncol 14:175, 2019
68. START Trialists' Group, Bentzen SM, Agrawal RK, et al: The UK standardisation of breast radiotherapy (START) trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. Lancet Oncol 9:331-341, 2008
69. Haviland JS, Mannino M, Griffin C, et al: Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol 126:155-162, 2018
70. Wang SL, Fang H, Song YW, et al: Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: A randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 20:352-360, 2019
71. Maiti S, Meyur S, Mandal BC, et al: Comparison of conventional and hypofractionated radiation after mastectomy in locally advanced breast cancer: A prospective randomised study on dosimetric evaluation and treatment outcome. J Radiother Pract 20:30-38, 2021
72. Zhao XB, Ren GS: Analysis of radiotherapy optimization regimens after modified radical mastectomy. Eur Rev Med Pharmacol Sci 20:4705-4709, 2016
73. Zhang HJ, Qu BL, Meng LL, et al: Clinical observation of short-term efficacies of different hypofractionated radiation therapies after modified radical mastectomy for breast cancer. Eur J Gynaecol Oncol 39:524-532, 2018
74. Kim DY, Park E, Heo CY, et al: Influence of hypofractionated versus conventional fractionated postmastectomy radiation therapy in breast cancer patients with reconstruction. Int J Radiat Oncol Biol Phys 112:445-456, 2022

75. Matzinger O, Heimsoth I, Poortmans P, et al: Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). Acta Oncol 49:24-34, 2010
76. Whelan TJ, Olivotto IA, Parulekar WR, et al: Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373:307-316, 2015
77. Abdel-Rahman O: Impact of regional nodal irradiation on the outcomes of N1 breast cancer patients referred for adjuvant treatment: A patient-level pooled analysis of 2 clinical trials. Clin Breast Cancer 18:504-510, 2018
78. Panoff JE, Takita C, Hurley J, et al: Higher chest wall dose results in improved locoregional outcome in patients receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys 82:1192-1199, 2012
79. Marhin W, Wai E, Tyldesley S: Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. Int J Radiat Oncol Biol Phys 69:483-489, 2007
80. Albert A, Mangana S, Nittala MR, et al: The impact of a postmastectomy chest wall scar boost on local recurrence-free survival in high-risk patients. Clin Breast Cancer 19:363-369, 2019
81. Bartels SAL, Donker M, Poncet C, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-Year results of the randomized controlled EORTC 10981-22023 AMAROS trial. J Clin Oncol 41:2159-2165, 2023
82. Thorsen LBJ, Overgaard J, Matthiessen LW, et al: Internal mammary node irradiation in patients with node-positive early breast cancer: Fifteen-year results from the Danish breast cancer group internal mammary node study. J Clin Oncol 40:4198-4206, 2022
83. Chung SY, Chang JS, Shin KH, et al: Impact of radiation dose on complications among women with breast cancer who underwent breast reconstruction and post-mastectomy radiotherapy: A multi-institutional validation study. Breast 56:7-13, 2021
84. Tovanabutra C, Katanyoo K, Uber P, et al: Comparison of treatment outcome between hypofractionated radiotherapy and conventional radiotherapy in postmastectomy breast cancer. Asian Pac J Cancer Prev 21:119-125, 2020
85. Stokes EL, Tyldesley S, Woods R, et al: Effect of nodal irradiation and fraction size on cardiac and cerebrovascular mortality in women with breast cancer treated with local and locoregional radiotherapy. Int J Radiat Oncol Biol Phys 80:403-409, 2011
86. Wong JS, Uno H, Tramountano A, et al: Patient-reported and toxicity results from the FABREC study: A multicenter randomized trial of hypofractionated vs. conventionally-fractionated postmastectomy radiation therapy after implant-based reconstruction. IJROBP 117:e3-e4, 2023
87. Poppe MM, Le-Rademacher J, Haffty BG, et al: A randomized trial of hypofractionated post-mastectomy radiation therapy (PMRT) in women with breast reconstruction (RT CHARM, Alliance A221505). Int J Radiat Oncol Biol Phys 120:S11, 2024
88. Diao K, Lei X, He W, et al: Racial and ethnic differences in long-term adverse radiation therapy effects among breast cancer survivors. Int J Radiat Oncol Biol Phys 118:626-631, 2024
89. Wright JL, Takita C, Reis IM, et al: Racial variations in radiation-induced skin toxicity severity: Data from a prospective cohort receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys 90: 335-343, 2014
90. Fang P, He W, Gomez D, et al: Racial disparities in guideline-concordant cancer care and mortality in the United States. Adv Radiat Oncol 3:221-229, 2018
91. Ohri N, Moshier E, Ho A, et al: Postmastectomy radiation in breast cancer patients with pathologically positive lymph nodes after neoadjuvant chemotherapy: Usage rates and survival trends. Int J Radiat Oncol Biol Phys 99:549-559, 2017
92. Murray Brunt A, Haviland JS, Wheatley DA, et al: Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 395:1613-1626, 2020
93. Chakraborty S, Chatterjee S, Hyport Adjuvant Author Group: HYPORT adjuvant acute toxicity and patient dosimetry quality assurance results - Interim analysis. Radiother Oncol 174:59-68, 2022
94. ClinicalTrials.gov: Hypofractionated LocoRegional Radiotherapy in Breast Cancer (RHEAL). https://clinicaltrials.gov/study/NCT04228991
95. Liao Z, Strom EA, Buzdar AU, et al: Locoregional irradiation for inflammatory breast cancer: Effectiveness of dose escalation in decreasing recurrence. Int J Radiat Oncol Biol Phys 47:1191-1200, 2000
96. Bristol IJ, Woodward WA, Strom EA, et al: Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. Int J Radiat Oncol Biol Phys 72:474-484, 2008
97. Purswani JM, Oh C, Teruel JR, et al: Definitive radiation with nodal boost for patients with locally advanced breast cancer. Pract Radiat Oncol 13:e103-e114, 2023
98. Klusen ST, Peiler A, Schmidt GP, et al: Simultaneous integrated boost within the lymphatic drainage system in breast cancer: A single center study on toxicity and oncologic outcome. Front Oncol 13:989466, 2023
99. Mayadev J, Einck J, Elson S, et al: Practice patterns in the delivery of radiation therapy after mastectomy among the University of California Athena Breast Health Network. Clin Breast Cancer 15: 43-47, 2015
100. Hess C, Lee A, Fish K, et al: Socioeconomic and racial disparities in the selection of chest wall boost radiation therapy in Californian women after mastectomy. Clin Breast Cancer 15:212-218, 2015
101. Sachdev S, Goodman CR, Neuschler E, et al: Radiotherapy of MRI-detected involved internal mammary lymph nodes in breast cancer. Radiat Oncol 12:199, 2017
102. Diao K, Andring LM, Barcenas CH, et al: Contemporary outcomes after multimodality therapy in patients with breast cancer presenting with ipsilateral supraclavicular node involvement. Int J Radiat Oncol Biol Phys 112:66-74, 2022
103. Wang SL, Li YX, Song YW, et al: Postmastectomy chest wall radiotherapy with single low-energy electron beam: An assessment of outcome and prognostic factors. Pract Radiat Oncol 2:106-113, 2012
104. Osei E, Dang S, Darko J, et al: Dosimetric evaluation of 3 and/or 4 field radiation therapy of breast cancers: Clinical experience. J Radiother Pract 20:380-394, 2021
105. Grellier Adedjouma N, Chevrier M, Fourquet A, et al: Long-term results of a highly performing conformal electron therapy technique for chest wall irradiation after mastectomy. Int J Radiat Oncol Biol Phys 98:206-214, 2017
106. Van Parijs H, Miedema G, Vinh-Hung V, et al: Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. Radiat Oncol 7: 80, 2012
107. Rastogi K, Sharma S, Gupta S, et al: Dosimetric comparison of IMRT versus 3DCRT for post-mastectomy chest wall irradiation. Radiat Oncol J 36:71-78, 2018
108. Li W, Wang J, Cheng H, et al: IMRT versus 3D-CRT for post-mastectomy irradiation of chest wall and regional nodes: A population-based cmparison of normal lung dose and radiation pneumonitis. Int J Clin Exp Med 9:22331-22337, 2016
109. Jagsi R, Griffith KA, Moran JM, et al: A randomized comparison of radiation therapy techniques in the management of node-positive breast cancer: Primary outcomes analysis. Int J Radiat Oncol Biol Phys 101:1149-1158, 2018
110. Mehta A, Kumar P, Silambarasan NS, et al: Comparison of dosimetric parameters of three- dimensional conformal radiotherapy and intensity- modulated radiotherapy in breast cancer patients undergoing adjuvant radiotherapy after modified radical mastectomy. Asian J Oncol 08:1-7, 2022
111. Rice L, Goldsmith C, Green MML, et al: An effective deep-inspiration breath-hold radiotherapy technique for left-breast cancer: Impact of post-mastectomy treatment, nodal coverage, and dose schedule on organs at risk. Breast Cancer (Dove Med Press) 9:437-446, 2017
112. Gaál S, Kahán Z, Paczona V, et al: Deep-inspirational breath-hold (DIBH) technique in left-sided breast cancer: Various aspects of clinical utility. Radiat Oncol 16:89, 2021
113. Laaksomaa M, Aula A, Sarudis S, et al: Surface-guided radiotherapy systems in locoregional deep inspiration breath hold radiotherapy for breast cancer—A multicenter study on the setup accuracy. Rep Pract Oncol Radiother 29:176-186, 2024
114. Sapienza LG, Maia MAC, Gomes MJL, et al: Randomized clinical trial of tissue equivalent bolus prescription in postmastectomy radiotherapy stratified by skin involvement status. Clin Transl Radiat Oncol 39:100570, 2023
115. Pignol JP, Vu TT, Mitera G, et al: Prospective evaluation of severe skin toxicity and pain during postmastectomy radiation therapy. Int J Radiat Oncol Biol Phys 91:157-164, 2015
116. Yap ML, Tieu M, Sappiatzer J, et al: Outcomes in patients treated with post-mastectomy chest wall radiotherapy without the routine use of bolus. Clin Oncol (R Coll Radiol) 30:427-432, 2018
117. Tieu MT, Graham P, Browne L, et al: The effect of adjuvant postmastectomy radiotherapy bolus technique on local recurrence. Int J Radiat Oncol Biol Phys 81:e165-e171, 2011
118. Nichol A, Narinesingh D, Raman S, et al: The effect of bolus on local control for patients treated with mastectomy and radiation therapy. Int J Radiat Oncol Biol Phys 110:1360-1369, 2021
119. de Sousa CFPM, Neto ES, Chen MJ, et al: Postmastectomy radiation therapy bolus associated complications in patients who underwent 2-stage breast reconstruction. Adv Radiat Oncol 7: 101010, 2022
120. Thomsen MS, Berg M, Nielsen HM, et al: Post-mastectomy radiotherapy in Denmark: From 2D to 3D treatment planning guidelines of the Danish Breast Cancer Cooperative Group. Acta Oncol 47: 654-661, 2008
121. Bekelman JE, Lu H, Pugh S, et al: Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: The Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. BMJ Open 9:e025556, 2019
122. Nielsen MH, Berg M, Pedersen AN, et al: Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish breast cancer cooperative group. Acta Oncol 52:703-710, 2013
123. Kaidar-Person O, Vrou Offersen B, Hol S, et al: ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol 137:159-166, 2019
124. Kagkiouzis J, Platoni K, Kantzou I, et al: Review of the three-field techniques in breast cancer radiotherapy. J BUON 22:599-605, 2017

125. Pasquier D, Le Tinier F, Bennadji R, et al: Intensity-modulated radiation therapy with simultaneous integrated boost for locally advanced breast cancer: A prospective study on toxicity and quality of life. Sci Rep 9:2759, 2019
126. Bataille B, Raoudha B, Le Tinier F, et al: Prospective study of intensity-modulated radiation therapy for locally advanced breast cancer. Cancers 12:3852, 2020
127. Bazan JG, DiCostanzo D, Hock K, et al: Analysis of radiation dose to the shoulder by treatment technique and correlation with patient reported outcomes in patients receiving regional nodal irradiation. Front Oncol 11:617926, 2021
128. Lazzari G, Terlizzi A, Leo MG, et al: VMAT radiation-induced nausea and vomiting in adjuvant breast cancer radiotherapy: The incidental effect of low-dose bath exposure. Clin Translational Radiat Oncol 7:43-48, 2017
129. Yaney A, Ayan AS, Pan X, et al: Dosimetric parameters associated with radiation-induced esophagitis in breast cancer patients undergoing regional nodal irradiation. Radiother Oncol 155: 167-173, 2021
130. Kirby AM, Haviland JS, Mackenzie M, et al: Proton beam therapy in breast cancer patients: The UK PARABLE trial is recruiting. Clin Oncol (R Coll Radiol) 35:347-350, 2023
131. Honaryar MK, Locquet M, Allodji R, et al: Cancer therapy-related cardiac dysfunction after radiation therapy for breast cancer: Results from the BACCARAT cohort study. Cardiooncology 10:54, 2024
132. Kanyilmaz G, Aktan M, Koc M, et al: Radiation-induced hypothyroidism in patients with breast cancer: A retrospective analysis of 243 cases. Med Dosim 42:190-196, 2017
133. Zhao XR, Fang H, Jing H, et al: Radiation-induced hypothyroidism in patients with breast cancer after hypofractionated radiation therapy: A prospective cohort study. Int J Radiat Oncol Biol Phys 115:83-92, 2023
134. Cuzick J, Stewart H, Rutqvist L, et al: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 12:447-453, 1994
135. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. Early breast cancer Trialists' collaborative group. Lancet 355:1757-1770, 2000
136. Darby SC, Ewertz M, McGale P, et al: Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:987-998, 2013
137. Laugaard Lorenzen E, Christian Rehammar J, Jensen MB, et al: Radiation-induced risk of ischemic heart disease following breast cancer radiotherapy in Denmark, 1977-2005. Radiother Oncol 152:103-110, 2020
138. Carlson LE, Watt GP, Tonorezos ES, et al: Coronary artery disease in young women after radiation therapy for breast cancer: The WECARE study. JACC CardioOncol 3:381-392, 2021
139. van den Bogaard VA, Ta BD, van der Schaaf A, et al: Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. J Clin Oncol 35:1171-1178, 2017
140. Beaton L, Bergman A, Nichol A, et al: Cardiac death after breast radiotherapy and the QUANTEC cardiac guidelines. Clin Transl Radiat Oncol 19:39-45, 2019
141. Lee YC, Chuang JP, Hsieh PC, et al: A higher incidence rate of acute coronary syndrome following radiation therapy in patients with breast cancer and a history of coronary artery diseases. Breast Cancer Res Treat 152:429-435, 2015
142. Hooning MJ, Botma A, Aleman BM, et al: Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 99:365-375, 2007
143. Aznar MC, Carrasco de Fez P, Corradini S, et al: ESTRO-ACROP guideline: Recommendations on implementation of breath-hold techniques in radiotherapy. Radiother Oncol 185:109734, 2023
144. Jacob S, Camilleri J, Derreumaux S, et al: Is mean heart dose a relevant surrogate parameter of left ventricle and coronary arteries exposure during breast cancer radiotherapy: A dosimetric evaluation based on individually-determined radiation dose (BACCARAT study). Radiat Oncol 14:29, 2019
145. Mutter RW, Choi JI, Jimenez RB, et al: Proton therapy for breast cancer: A consensus statement from the particle therapy cooperative group breast cancer subcommittee. Int J Radiat Oncol Biol Phys 111:337-359, 2021
146. Holt F, Probert J, Darby SC, et al: Proton beam therapy for early breast cancer: A systematic review and meta-analysis of clinical outcomes. Int J Radiat Oncol Biol Phys 117:869-882, 2023
147. MacDonald SM, Patel SA, Hickey S, et al: Proton therapy for breast cancer after mastectomy: Early outcomes of a prospective clinical trial. Int J Radiat Oncol Biol Phys 86:484-490, 2013
148. Jimenez RB, Hickey S, DePauw N, et al: Phase II study of proton beam radiation therapy for patients with breast cancer requiring regional nodal irradiation. J Clin Oncol 37:2778-2785, 2019
149. Hassan MZO, Awadalla M, Tan TC, et al: Serial measurement of global longitudinal strain among women with breast cancer treated with proton radiation therapy: A prospective trial for 70 patients. Int J Radiat Oncol Biol Phys 115:398-406, 2023
150. Jaffray D, Kupelian P, Djemil T, et al: Review of image-guided radiation therapy. Expert Rev Anticancer Ther 7:89-103, 2007
151. Hartford AC, Palisca MG, Eichler TJ, et al: American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys 73:9-14, 2009
152. Jaffray DA, Langen KM, Mageras G, et al: Safety considerations for IGRT: Executive summary. Pract Radiat Oncol 3:167-170, 2013
153. Pazos M, Walter F, Reitz D, et al: Impact of surface-guided positioning on the use of portal imaging and initial set-up duration in breast cancer patients. Strahlenther Onkol 195:964-971, 2019
154. Reitz D, Carl G, Schönecker S, et al: Real-time intra-fraction motion management in breast cancer radiotherapy: Analysis of 2028 treatment sessions. Radiat Oncol 13:128, 2018
155. Freislederer P, Batista V, Öllers M, et al: ESTRO-ACROP guideline on surface guided radiation therapy. Radiother Oncol 173:188-196, 2022
156. Al-Hallaq HA, Cerviño L, Gutierrez AN, et al: AAPM task group report 302: Surface-guided radiotherapy. Med Phys 49:e82-e112, 2022
157. Blitzblau RC, Horton JK: Treatment planning technique in patients receiving postmastectomy radiation therapy. Pract Radiat Oncol 3:241-248, 2013
158. Dahn HM, Boersma LJ, de Ruysscher D, et al: The use of bolus in postmastectomy radiation therapy for breast cancer: A systematic review. Crit Rev Oncol Hematol 163:103391, 2021
159. Chatterjee S, Chakraborty S, HYPORT Adjuvant Author Group: Hypofractionated radiation therapy comparing a standard radiotherapy schedule (over 3 weeks) with a novel 1-week schedule in adjuvant breast cancer: An open-label randomized controlled study (HYPORT-Adjuvant)-study protocol for a multicentre, randomized phase III trial. Trials 21:819, 2020
160. Fuglsang Jensen M, Stick LB, Høyer M, et al: Proton therapy for early breast cancer patients in the DBCG proton trial: Planning, adaptation, and clinical experience from the first 43 patients. Acta Oncol 61:223-230, 2022

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Postmastectomy Radiation Therapy: An ASTRO-ASCO-SSO Clinical Practice Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Rachel B. Jimenez
Consulting or Advisory Role: Alexion Pharmaceuticals

Yara Abdou
Honoraria: WebMD/Medscape, MJH Associates, Clinical Care Options, Cancer Expert Now
Consulting or Advisory Role: AstraZeneca, Pfizer
Research Funding: Natera (Inst), Haystack Oncology (Inst)
Uncompensated Relationships: Exact Sciences

Parul Barry
Employment: UPMC Hillman Cancer Center/University of Pittsburgh School of Medicine
Honoraria: Osler Institute, OncLive/MJH Life Sciences, Varian Medical Systems
Consulting or Advisory Role: El-Sevier Pathways Consultant
Research Funding: Breast Cancer Research Foundation (Inst), ACRO New Practitioner Grant, NCTN (Inst), Beckwith Institute (Inst), Pittsburgh Foundation (Inst), Silverlon (Inst), Philanthropy (Inst)
Travel, Accommodations, Expenses: ACRO, American Society for Radiation Oncology
Other Relationship: ACRO Board Member, ARS Board, WIMS Scientific Program Chair, Rare Tumors—Senior Associate Editor, ASTRO HEDI Chair

Julie A. Bradley
Patents, Royalties, Other Intellectual Property: 2021: Provisional patent for Breast Tissue Expander ReDesign 2023: U.S. non-provisional application for Breast Tissue Expander ReDesign
Uncompensated Relationships: PTCOG-NA Vice President

Lourdes D. Heras
Employment: Gila River Health Care
Uncompensated Relationships: Surviving Breast Cancer.org

Atif Khan
Employment: Memorial Sloan-Kettering Cancer Center
Stock and Other Ownership Interests: Novavax, Xtrava Health, IgniteData
Consulting or Advisory Role: IgniteData
Research Funding: Clovis Oncology, Merck KGaA, Varian Medical Systems
Patents, Royalties, Other Intellectual Property: Use Patent for the Drug Riluzole Awarded to Rutgers University With Me as Inventor
Uncompensated Relationships: AI MindSystems Foundation

Rachel Rabinovitch
Stock and Other Ownership Interests: Bristol Myers Squibb, Intuitive Surgical

Sarah E. Schellhorn
Stock and Other Ownership Interests: Gilead Sciences, Coronado Biosciences, Roche
Honoraria: Cardinal Health
Consulting or Advisory Role: Eisai, Puma Biotechnology, Celgene, Cardinal Health
Research Funding: Genentech, Pfizer
Travel, Accommodations, Expenses: Cardinal Health
Open Payments Link: https://openpaymentsdata.cms.gov/physician/1076063

Deborah Schofield
Uncompensated Relationships: American College of Radiology, American Association of Physicists in Medicine

Kekoa Taparra
Employment: Stanford Health Care
Honoraria: MD Anderson Cancer Center, Stanford Health Care, American Association for Cancer Research, American Society of Hemotology, Genentech
Research Funding: Stanford Cancer Institute, Conquer Cancer Foundation
Travel, Accommodations, Expenses: ASTRO-Breast Cancer Research Foundation

Jean L. Wright
Employment: Johns Hopkins Hospital, University of North Carolina at Chapel Hill
Honoraria: American Society for Radiation Oncology, Physicians' Education Resource
Research Funding: Oncospace, Prostate Cancer Foundation-Pfizer Health Equity Challenge (Inst), Prostate Cancer Foundation-Pfizer Health Equity Challenge (Inst)
Patents, Royalties, Other Intellectual Property: Spouse receives royalties from Up To Date (I)
Expert Testimony: Wicker Smith
Travel, Accommodations, Expenses: Physicians' Education Resource
Uncompensated Relationships: American Society for Radiation Oncology, International Journal of Radiation Oncology Biology Physics

Richard C. Zellars
Employment: Veracyte
Stock and Other Ownership Interests: Lilly, Bristol Myers Squibb Co

No other potential conflicts of interest were reported.

APPENDIX 1

ASCO GUIDELINE DISCLAIMER

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist clinicians in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating clinician, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating clinician in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

ASCO GUIDELINE AND CONFLICTS OF INTEREST POLICY

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

ASTRO DISCLOSURE POLICY

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before the initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Data Supplement). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members

ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

TABLE A1. ASTRO-ASCO-SSO Joint PMRT Task Force Membership

Name	Affiliation	Role or Area of Expertise
Rachel B. Jimenez, MD (vice chair)	Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA	Radiation oncology
Kathleen C. Horst, MD (chair)	Department of Radiation Oncology, Stanford University, Stanford, CA	Radiation oncology
Yara Abdou, MD	Department of Medical Oncology, University of North Carolina, Chapel Hill, NC	Medical oncology (ASCO representative)
Penny Anderson, MD	Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA	Radiation oncology
Parul Barry, MD	Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA	Radiation oncology
Julie A. Bradley, MD	Department of Radiation Oncology, University of Florida, Jacksonville, FL	Radiation oncology
Lourdes D. Heras, MPH	Gilbert, AZ	Patient representative
Atif Khan, MD, MS	Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY	Radiation oncology
Cindy Matsen, MD	Department of Surgery, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT	Surgical oncology (SSO representative)
Rachel Rabinovitch, MD	Department of Radiation Oncology, University of Colorado Denver, Aurora, CO	Radiation oncology
Chantal Reyna, MD, MHA	Department of Surgery, Loyola University Medical Center, Chicago, IL	Surgical oncology (SSO representative)
Kilian E. Salerno, MD	Radiation Oncology Branch, National Cancer Institute, Bethesda, MD	Radiation oncology
Sarah E. Schellhorn, MD	Department of Medicine, Yale School of Medicine, New Haven, CT	Medical oncology (ASCO representative)
Deborah Schofield, PhD	Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, TX	Radiation oncology
Kekoa Taparra, MD, PhD, MPH	Department of Radiation Oncology, Stanford University, Stanford, CA	Radiation oncology
Iman Washington, MD	Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL	Radiation oncology
Jean L. Wright, MD	Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC	Radiation oncology
Youssef H. Zeidan, MD, PhD	Department of Radiation Oncology, Florida International University and Lynn Cancer Institute, Boca Raton, FL	Radiation oncology
Richard C. Zellars, MD	Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN	Radiation oncology
Lisa Bradfield, BA	American Society for Radiation Oncology, Arlington, VA	ASTRO Practice Guideline Staff

Abbreviations: ASTRO, American Society for Radiation Oncology; SSO, Society of Surgical Oncology.

Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012
doi:10.1093/annonc/mds232

Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1,2], N. Harbeck[3], L. Fallowfield[4], S. Kyriakides[5] & E. Senkus[6], on behalf of the ESMO Guidelines Working Group*

[1]European School of Oncology, Milan, Italy; [2]Breast Cancer Unit, Champalimaud Cancer Center, Lisbon, Portugal; [3]Breast Center, Department of Obstetrics and Gynaecology, and Comprehensive Cancer Center (CCC LMU), University of Munich, Germany; [4]Brighton and Sussex Medical School, University of Sussex, UK; [5]Europa Donna Cyprus, Cyprus; [6]Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

incidence and epidemiology

Breast cancer is the most common cancer in women in almost all countries, including developing countries. In 2008, 1 380 000 new cases and 458 000 breast cancer deaths were noted in the world and 332 000 new cases/89 000 deaths in the European Union. The age-standardized incidence in Europe was 62.8/100 000 and the mortality—16.7/100 000 women/year. Since 1990, the incidence rate has increased 1.5% annually. Owing to advances both in early detection and in adjuvant systemic therapy, mortality rates from breast cancer have been decreasing steadily in most Western countries since the early 1990s. However, it is still the leading cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed (189 000 deaths, 15.5% of total) regions. Approximately 5% to 10% of breast cancers are metastatic at diagnosis; of these, approximately one-fifth will survive 5 years. Depending on prognostic factors, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with this disease for several years; there is however, a major lack of accurate data on this prevalence in the great majority of countries since most cancer registries do not capture relapses. As there are significant variations in outcomes of early breast cancer among different regions, the burden of metastatic breast cancer (MBC) may differ from that of early disease.

diagnosis and pathology

Clinical suspicion must be confirmed by imaging. A minimal staging work-up should include a complete history and physical examination, hematology and biochemistry tests, imaging of chest, abdomen and bone; in certain situations, information may be provided by functional imaging such as PET–CT (positron emission tomography–computed tomography scan), DCE-MRI (dynamic contrast-enhanced magnetic resonance imaging) or MR-DWI (diffusion-weighted magnetic resonance) (in particular, in case of equivocal results of routine imaging or when these exams fail to detect the location of the relapse, or when pathology from suspicious lesion cannot be obtained).

Efforts should be made to obtain histopathological confirmation whenever technically feasible, particularly in the situation of an isolated metastatic lesion. Biological markers important for treatment decisions, such as steroid hormone receptors (ER, PR) and HER-2 status should be re-evaluated, at least once, in a metastatic lesion. Although there are no data to support the choice of therapy in case of discordance in HR/HER-2 status between primary and metastatic tumor, retrospective data suggest inferior outcome in 'discordant' patients (possibly due to inappropriate treatment, not adjusted for biomarker changes). It seems appropriate to recommend that, if at any given biopsy the receptors were positive, targeted therapy (endocrine and/or anti-HER-2 therapy) should be provided.

There is no proven value of routine 'screening' tests for metastatic disease in asymptomatic early breast cancer patients. However, the available data are from a time when neither biological therapy nor effective (in terms of local control) and less invasive (in terms of quality of life and side-effects) locoregional therapeutic techniques, such as radiosurgery for central nervous system (CNS) metastases or radiofrequency ablation for liver metastases, were available. In addition, new detection techniques are now available, such as MRI, PET-scan, PET–CT and others, that may allow the detection of very early metastatic disease. Therefore, new studies are needed to evaluate the role of early diagnosis of metastatic disease in the current context.

The occurrence of locoregional recurrence is often associated with distant spread and such patients should undergo full staging procedures before undergoing local treatments.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland; E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: August 2003, last update June 2012. This publication supersedes the previously published version—Ann Oncol 2011; 22 (Suppl 6): vi25–vi30.

Table 1. Staging and assessment of prognosis

Complete history, including
menopausal status
co-morbidities (e.g. cardiac diseases, diabetes mellitus, thromboembolic diseases, renal or liver disease)
detailed history of the primary tumor, its biology, management and status at the last follow-up
history of recurrent/metastatic disease, including duration, previous sites of involvement, previous treatments and their effect
current symptoms, performance status, socio-economic background and preferences (Table 2)
Detailed physical examination
Blood and other laboratory tests: complete blood count, liver and renal function tests, alkaline phosphatase, LDH, calcium and, if applicable, specific tests required for particular treatments such as urinary protein. The clinical value of tumor markers for diagnostic purposes has not been proven. However, they may assist in evaluating response to treatment (i.e. monitoring), particularly in patients with non-measurable disease
Assessment of visceral disease
Chest: preferably CT; chest X-ray has low sensitivity and should be replaced by chest CT whenever possible
Abdomen: ultrasound, CT (preferably) or MRI
Bone scan, with confirmation of lesions and further work-up (i.e. fracture risk, etc.) if needed by X-ray/CT/MRI
CT and/or MRI of the CNS should be symptom-driven; the value of 'screening' for asymptomatic brain metastases, even in breast cancer subtypes with higher risk of developing CNS involvement (HER-2-positive and triple-negative breast cancer), is not established and should not be carried out routinely
All imaging should be carried out in a way that will allow for future comparative assessment to evaluate the treatment effect
PET/PET–CT should not be used routinely as part of the initial work-up but can be useful for identifying the site of relapse when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify or confirm isolated locoregional relapse or isolated metastatic lesions, a situation where patients may benefit from a more aggressive multidisciplinary approach
Estrogen, progesterone and HER-2 receptors of the metastatic lesion should be obtained at least once in the evolution of the disease, if technically possible, and particularly if not available from the primary tumor
Cardiac assessments, in particular in HER-2-positive patients and those considered for anthracycline-based chemotherapy
Circulating tumor cells are still an experimental technique and should not be used outside a clinical trial
In case of lesions inaccessible for biopsy, functional imaging such as PET–CT, DCE-MRI or MR-DWI may be helpful to confirm their malignant character

The value of multigene assays used for recurrence risk assessment in early breast cancer has not been confirmed in advanced disease.

treatment: general statements

locoregional recurrence

Whenever possible, isolated locoregional recurrence should be treated with a curative intent (Figure 1). If feasible, complete excision of recurrent tumor is recommended. In patients previously treated by breast-conserving surgery, a mastectomy should be carried out [III, A]. In patients not previously irradiated, full-dose radiotherapy to chest wall and regional lymph node areas should be given [III, A]. In those previously irradiated, re-irradiation to limited areas of the chest wall may be applied, taking into consideration the duration of radiation-free period, intensity of existing late radiation effects and the risk of additional local–regional relapse [III, B]. Inoperable patients can, if feasible, undergo radical radiotherapy to chest wall and regional lymph node areas with boost to macroscopic disease sites. However, in these patients, primary systemic therapy to decrease the size of the tumor and render it operable is preferred [III, B].

Table 2. Factors to consider in risk assessment and treatment decision-making for MBC

Disease-related factors	Patient-related factors
Disease-free interval	Patient preferences
Previous therapies and response	Biological age
Biological factors (hormonal receptors, HER-2)	Menopausal status
Tumor burden (number and site of metastases)	Co-morbidities and performance status
Need for rapid disease/symptom control	Socio-economic and psychological factors
	Therapies available in the patient's country

The value of 'secondary' or 'pseudo-adjuvant' systemic treatment is not well proven. The role of chemotherapy in this setting is a subject of ongoing randomized studies [II, B]. Factors such as tumor biology and aggressiveness, prior adjuvant systemic therapy, patient co-morbidities and preferences should all be taken into account when deciding whether to propose 'pseudo-adjuvant' chemotherapy (expert opinion). Although not well proven, 'pseudo-adjuvant' endocrine therapy is a reasonable option in view of its expected benefit and low toxicity [II, B]. 'Pseudo-adjuvant' trastuzumab therapy is also acceptable, particularly in cases where adjuvant trastuzumab was not prescribed at the time of initial diagnosis (expert opinion).

In patients not suitable for local treatment with curative intent (e.g. inoperable, previously irradiated), systemic therapies remain the mainstay of treatment. Their choice depends on tumor biology, previous systemic treatments, duration of disease-free interval, patient co-morbidities and preferences.

metastatic disease

The management of MBC should involve all appropriate specialties in a multi/interdisciplinary team (medical, radiation, surgical and imaging oncologists, palliative care specialist, psychosocial support), and patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care.

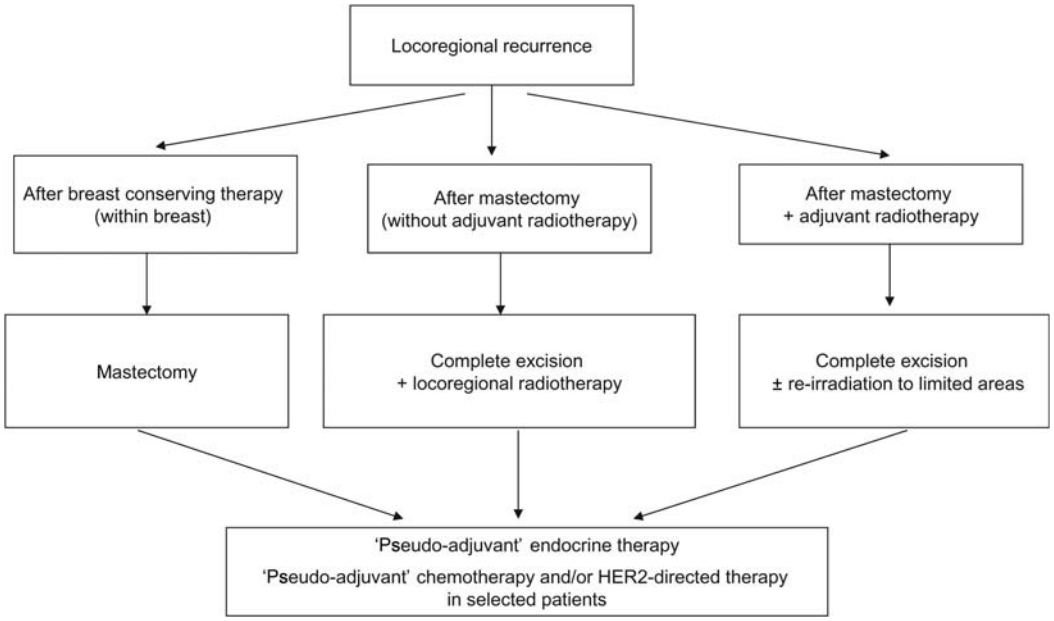


Figure 1 Management of locoregional recurrence.

Specialist breast nurses can provide crucial support, as well as coordination and continuity of care for patients with advanced breast cancer and should be available to all patients. Countries in which this nurse subspecialty does not yet exist, should make all efforts to establish it.

There are only a few proven standards of care in MBC management, therefore well-designed, independent, prospective randomized trials are a priority. Participation in such clinical trials should be offered to all eligible patients, whenever available.

The vast majority of MBC is incurable and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life and possibly prolonging survival.

The realistic treatment goals should be discussed with the patient and her/his caregivers from the beginning and the patient should be encouraged to actively participate in all decisions. Patient preferences should always be taken into account.

Systemic treatment options for MBC are endocrine therapy, chemotherapy, bone-directed agents (e.g. bisphosphonates, denosumab) and targeted biological agents such as trastuzumab and lapatinib [I, A].

The choice of therapy should be made after consideration of factors listed in Table 2.

For the majority of patients, overall survival outcomes from sequential use of single-cytotoxic drugs are equivalent to combination chemotherapy. The choice between these options should primarily take into account the need for a rapid and significant response, as well as quality of life. In patients without directly life-threatening or severely symptomatic disease, single-agent chemotherapy is the preferred option.

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

In HR-positive and HER-2-negative disease, endocrine therapy is the treatment of first choice independent of metastatic site, unless rapid response is needed. Limited visceral metastases are not a contraindication for endocrine therapy. Chemo and endocrine therapy should not be given concomitantly. Given its low toxicity, endocrine maintenance should be considered.

In patients with HER2, overexpressing/amplified early incorporation of targeted anti-HER-2 agents is highly recommended unless specific contra-indications exist.

The most common indications for palliative radiotherapy include:

Bone metastases which are painful or carry a risk of fracture and/or neurological complications (radiotherapy options include 'limited field' external beam irradiation, hemi-body irradiation and application of radioactive 'bone-seeking' isotopes);
Brain metastases—patients with extensive cerebral involvement usually require whole-brain radiotherapy (WBRT); in those with single or few metastatic foci, stereotactic radiosurgery can be used as an alternative to surgical resection, with improvement in local control and less side-effects than WBRT; addition of WBRT to surgery or stereotactic radiosurgery decreases the number of intracranial relapses but increases substantially side-effects, mainly cognitive, and should be discussed with the patient;
Painful or fungating soft-tissue masses.

For limited metastatic presentations, surgery or radical radiotherapy may be considered. Systemic tumor control should be the prerequisite for tumor-reduction local therapy in metastatic disease. Although no randomized data exist, a bulk of retrospective data suggest a significant survival benefit from the removal of the primary tumor (with clear margins) in patients

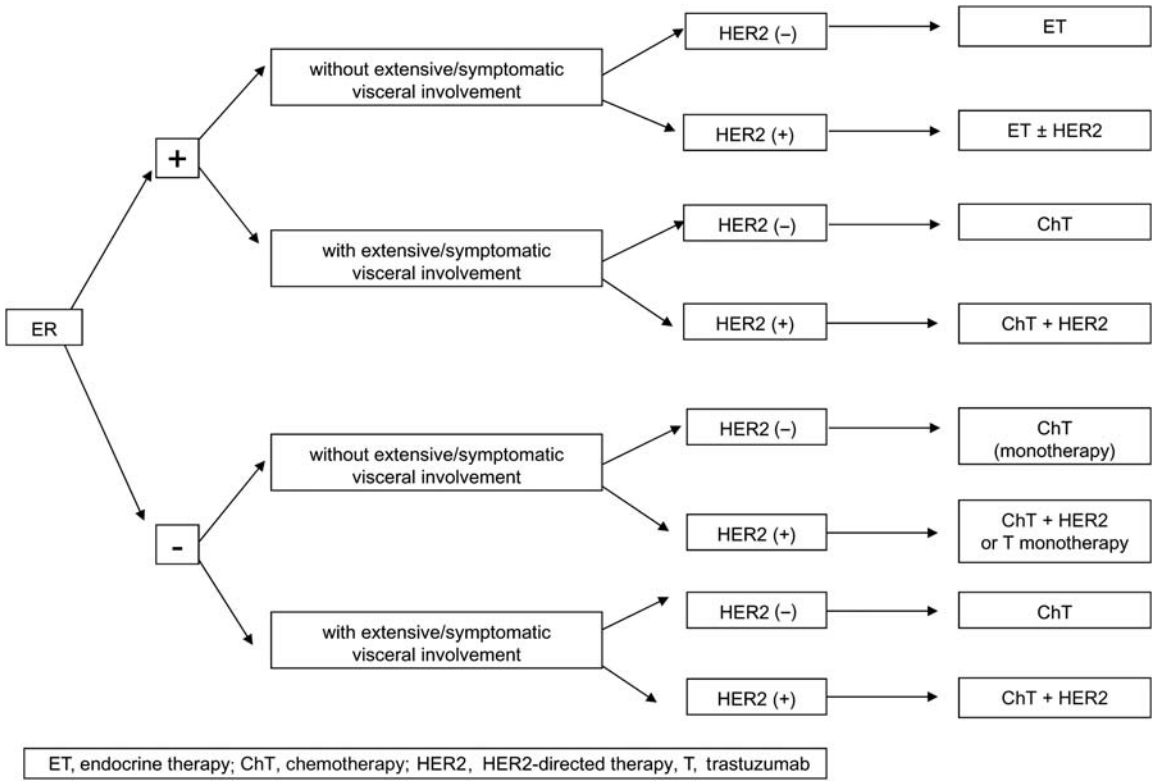


Figure 2 First-line systemic therapy for advanced breast cancer.

with primary metastatic disease. Prospective randomized trials addressing this question are currently ongoing.

Palliative surgery may be utilized to prevent or stabilize pathological fractures, remove fungating soft-tissue masses or relieve compression leading to neurological deficits.

Bisphosphonates or RANK-ligand antibody denosumab should be used for the treatment of clinically evident bone metastases (to palliate symptoms and decrease risk of bone events) [I, A]. Bone-directed therapy should be started following a diagnosis of bone metastases. Although the optimal duration of these treatments is unknown and the benefit of duration beyond 2 years has not been demonstrated in clinical trials, an ongoing risk of skeletal events persists, especially at times of disease progression and thus long-term treatment seems appropriate. The impact of bisphosphonate or denosumab-associated side-effects (including osteonecrosis of the jaw and nephrotoxicity) is minor, and for the vast majority of patients the benefit of treatment outweighs the risks. The choice between bisphosphonates and denosumab depends on drug availability, presence of possible contraindications (renal insufficiency) and patient preferences.

A multi-disciplinary discussion including pain control experts, radiation oncologists, medical oncologists, surgeons specialized in bone treatment and radiologists with expertise in vertebroplasty/kyphoplasty is crucial to determine the best therapeutic approach for the individual patient. A pathway for rapid (within 24 h) assessment of patients with spinal cord compression should be available with access to specialist spinal surgeons for decompression and stabilization of compressing or unstable spinal lesions when clinically appropriate.

Malignancy-related hypercalcemia should be treated with bisphosphonates and intravenous fluids.

The choice of drugs for MBC, their timing, optimal duration, methods of administration and side-effects should be considered individually, taking into account patient preferences, expected treatment acceptance and adherence. Availability and reimbursement issues must also be taken into account.

treatment-specific breast cancer subtypes

luminal breast cancer (hormone receptor-positive, irrespective of HER-2 status) (Figure 2)

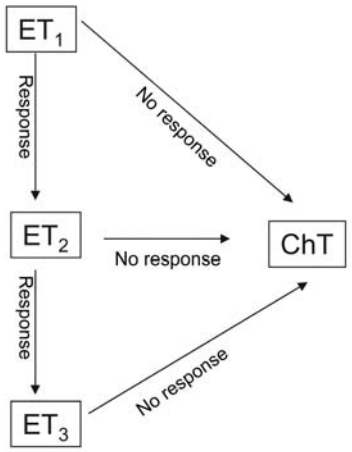
Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding endocrine responsiveness of the tumor. Available endocrine agents are listed in Table 3.

The choice of endocrine agent should be based on menopausal status, co-morbidities, agents received in the adjuvant setting and the drug safety profile.

Apart from combination of ovarian suppression with tamoxifen [or aromatase inhibitors (AIs)] in premenopausal patients, there is no rationale for the use of combination endocrine therapies.

Table 3. Available endocrine therapies for MBC

Class of agent	
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogues	Goserelin, leuprorelin, triptorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat
Estrogens	Estrogens



ET, endocrine therapy; ChT, chemotherapy

Figure 3 Management of endocrine-responsive advanced breast cancer.

The value of maintenance endocrine treatment after chemotherapy has not been confirmed by controlled clinical studies, but—given its low toxicity and potential benefits—is a reasonable approach (expert opinion).

Concomitant chemo-endocrine therapy should not be used outside clinical trials.

In case of ER-positive/HER-2-positive breast cancer with no indication for chemotherapy, endocrine therapies should be combined with anti-HER-2 therapies (trastuzumab, lapatinib) since they lead to a significant improvement in progression free survival (in this case equivalent to 'time without chemotherapy'), although no benefit in overall survival, compared with endocrine therapy alone.

premenopausal patients

If no prior adjuvant tamoxifen or if discontinued for >12 months, tamoxifen with ovarian ablation (luteinizing hormone-releasing hormone analogue, surgery or ovarian irradiation) is the preferred option [I, B]. Further treatment lines (in patients with ovarian ablation/suppression) do not differ from those used in postmenopausal population (as described below).

postmenopausal patients

If not used in the adjuvant setting or if discontinued for >12 months, AIs (anastrozole, letrozole, exemestane) are the preferred option since they have consistently shown superior results to tamoxifen as first-line therapy in terms of response rate, time to progression and, for letrozole, in 2-year overall survival [II, A]. Preferably, a nonsteroidal AI should be used after progression on a steroidal AI and vice versa. The risk of accelerated bone loss needs to be considered and calcium and vitamin D supplements are recommended.

Tamoxifen remains an acceptable first-line therapy. Although definitive data are still needed, it seems reasonable to advise patients under tamoxifen to avoid, whenever possible, the use of drugs modulating the activity of CYP2D6, such as some selective serotonin reuptake inhibitor antidepressants (e.g. paroxetine, fluoxetine). Fulvestrant at the dose of 500 mg every 4 weeks has demonstrated superiority compared with anastrozole in the first-line setting [II, A].

Second and further lines of endocrine therapy may include (if not previously used) tamoxifen, steroidal or nonsteroidal AIs, fulvestrant, progestins (e.g. megestrol acetate) and androgens. No definitive recommendation can be given for a specific endocrine treatment cascade, and particularly, the best option after progression on first-line AI therapy is currently unknown.

Recent evidence suggests that the addition of the m-TOR inhibitor everolimus to either a steroidal AI or tamoxifen may improve outcome, compared with endocrine therapy alone, in patients progressing on/after AI therapy but additional research is needed to clearly identify those patients who may benefit from this approach. Additionally, everolimus is not yet approved by the European Medicines Agency (EMA) or United States Food & Drug Administration (FDA) although it has been approved in some countries.

Patients with clear evidence of endocrine resistance should be offered chemotherapy. No overall recommendation can be made regarding the number of lines of endocrine therapy before switching to chemotherapy. Factors that need to be taken into account in this treatment decision include response to previous endocrine therapies and its duration, presence of symptoms and/or rapidly progressive or life-threatening disease, patient preference and performance status, as well as the estimated tolerability of chemotherapy (Figure 3).

'triple-negative' breast cancer (hormonereceptor-negative and HER-2-non-overexpressed/non-amplified)

Cytotoxic chemotherapy remains the mainstay of treatment in this group. Available agents/regimens are listed in Table 4.

The selection of the best agent/regimen should be individualized and should take into account the factors listed in Table 2. Taxane-based regimens are the only standard of care in first-line therapy in patients progressing after adjuvant anthracycline-based non-taxane-containing chemotherapy regimens [I, A].

Because of frequent visceral involvement, aggressive course and risk of rapid patient deterioration, combination

Table 4. Available chemotherapy agents/regimens for MBC

Anthracycline-containing
Doxorubicin or epirubicin monotherapy (weekly or tri-weekly)
Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide
Liposomal doxorubicin ± cyclophosphamide
Fluorouracil/doxorubicin/cyclophosphamide or fluorouracil/epirubicin/cyclophosphamide
Taxane-containing
Paclitaxel monotherapy weekly
Docetaxel monotherapy tri-weekly or weekly
Abraxane (nab-paclitaxel)
Anthracycline (doxorubicin or epirubicin)/taxane (paclitaxel or docetaxel)
Docetaxel/capecitabine
Paclitaxel/gemcitabine
Paclitaxel/vinorelbine
Paclitaxel/carboplatin
New cytotoxic agents
Eribulin
Ixabepilone (not approved by EMA)
Non-anthracycline-containing
Cyclophosphamide/methotrexate/fluorouracil (CMF)
Platinum-based combinations (e.g. cisplatinum + 5-fluorouracil; carboplatin + gemcitabine)
Capecitabine
Vinorelbine
Capecitabine + vinorelbine
Vinorelbine ± gemcitabine
Oral cyclophosphamide with or without methotrexate (metronomic chemotherapy)

chemotherapy is more often required. Triple-negative biology on its own, however, is not a sufficient reason to give combination chemotherapy. There is no standard approach for patients requiring second- or further-line chemotherapy treatment.

Duration of each regimen and number of regimens should be tailored to each individual patient. Continuing chemotherapy beyond third-line may be justified in patients with good performance status and response to previous chemotherapy.

High-dose chemotherapy with stem cell support should not be administered.

HER-2-positive (overexpressed/amplified) breast cancer

Anti-HER-2 therapy (i.e. trastuzumab, lapatinib) in combination with chemotherapy, endocrine therapy or alone should be offered early to all HER-2-positive MBC patients [I, A] who do not have contra-indications for these therapies.

Addition of pertuzumab to first-line chemotherapy–trastuzumab combination was associated with improved response rate, progression-free survival (PFS) and a trend toward improved overall survival in one randomized phase 3 trial. The patient population of this trial cannot, however, be considered representative of the majority of first-line ABC patients since patients had received little adjuvant therapies (90% did not receive adjuvant trastuzumab and ~50% did not receive adjuvant anthracycline/taxane-based chemotherapy). The added value of this approach, its cost-effectiveness and predictive biomarkers of response should be further evaluated. Pertuzumab has recently been approved by the FDA and a decision is awaited by the EMA.

Cytotoxic-antibody conjugate T-DM1 has demonstrated superior efficacy regarding PFS and a more favorable toxicity profile, when compared with the first-line docetaxel–trastuzumab combination. T-DM1 is not yet approved by the EMA or FDA.

Continuing trastuzumab, in combination with a different chemotherapy regimen, after the first disease progression is superior to chemotherapy alone [II, B]. The benefit of continuing anti-HER-2 therapy beyond first progression is based on less data but available evidence suggests to continue anti-HER-2 therapy for as long as possible.

Lapatinib in combination with capecitabine, compared with capecitabine alone, increases time to progression in patients progressing after/on trastuzumab, anthracyclines or taxanes. The question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open.

The combination of trastuzumab and lapatinib seems to be superior in terms of overall survival to lapatinib monotherapy in patients progressing after/on anthracyclines, taxanes or trastuzumab (not yet approved).

The addition of anti-HER-2 agents (trastuzumab or lapatinib) to endocrine therapy allows for prolongation of PFS and may be a viable option for some patients with ER/PR-positive and HER-2-positive tumors, in particular in those not considered for cytotoxic chemotherapy. In countries where anti-HER-2 treatment is reimbursed only with a single therapy treatment line, priority should be given to an anti-HER-2 + chemotherapy combination, as it may enable a more rapid and potentially more durable response (expert opinion).

other biological agents

- Bevacizumab, an anti-angiogenic agent, originally approved by the FDA and the EMA for first-line treatment of MBC, failed to consistently demonstrate clinically relevant improvement in PFS and has not improved overall survival. For this reason and because of an unfavorable efficacy–safety profile, the FDA revoked its conditional approval in 2011. In Europe, bevacizumab remains approved, only as first-line therapy in combination with paclitaxel or capecitabine. It may thus be considered in carefully selected patients with limited treatment options, requiring a well thought out balance between side-effects, benefits and costs.

response evaluation

Response evaluation is routinely recommended every 2 to 4 months of endocrine therapy and every two or four cycles of chemotherapy by clinical examination, evaluation of symptoms, blood tests (including tumor markers if initially elevated) and repeating the initially abnormal radiological examinations with comparative measurements. The main aim

of these assessments is to exclude progressive disease, in particular in patients for whom further treatment options exist or those who experience significant toxic effects from their treatment. The interval between assessments should be tailored to the clinical needs of the patient and to the aggressiveness of the disease and may be prolonged in case of indolent disease and long-lasting responses. In case of clinical suspicion of progressive disease, appropriate tests (imaging and laboratory) should be carried out irrespective of scheduled examinations, if necessary including areas not imaged in previous tests.

Bone scans should be used with caution and only if other imaging tests are unavailable to solely assess response in bone due to the risk of a flare response being confused with progression.

Serum tumor markers (such as CA 15-3 and/or CEA), if initially elevated, may be helpful in monitoring response, particularly in the case of non-measurable disease. However, a change in tumor markers alone should not be used as the only determinant for treatment decisions. Additionally, it is not uncommon for a phenomenon of flare of tumor markers to occur in the first 6 weeks of an efficacious therapy and this must be taken into account when interpreting serial values.

The role of PET/PET–CT in response assessment is still under investigation but it may be used to determine disease progression.

Maintenance of a good quality of life is paramount and can best be achieved with prompt amelioration of symptoms and side-effects of treatment. Psychometrically sound, well-validated questionnaires are available to measure patient reported outcomes. Efforts should be made to use them regularly to help assess the impact of treatment and to monitor symptoms that need prompt supportive intervention.

follow-up

Follow-up after curative treatment of local–regional recurrence should be carried out as for primary breast cancer.

Patients with MBC must be seen frequently enough to provide best possible palliation of symptoms and maintain quality of life, which generally means every 2–4 months if on endocrine therapy and every one or two cycles of chemotherapy (with toxic effects and blood counts checked before each chemotherapy cycle). If progression is suspected (due to aggravation or appearance of new signs/symptoms and/or significant increase in tumor marker levels), response evaluation should be done immediately.

There is no defined optimal visit schedule for MBC patients in disease remission with no active treatment; however, apart from scheduled visits, these patients should be instructed to contact their physician immediately in case of symptoms suggestive of progressive disease or treatment complications.

Patients need good quality information and a care plan outlining all aspects of treatment and care, clarification of the purpose of different treatments, their side-effects and potential impact on functional, emotional and social well-being.

Lifelong access to effective palliative care is mandatory.

Table 5. Summary of recommendations for management of metastatic breast cancer

The management of metastatic breast cancer should involve all appropriate specialties in a multi/interdisciplinary team
From the first diagnosis of metastatic breast cancer, patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care
Following thorough assessment and confirmation of metastatic breast cancer, the realistic treatment goals must be specified and discussed. Patients and caregivers (if patient agrees) should be invited to participate in decision making
An aggressive multidisciplinary approach including local therapy may be warranted in selected patients with limited metastatic disease
Minimal staging work-up for metastatic breast cancer includes a history and physical examination, complete hematology and biochemistry, imaging of chest, abdomen and bone. The clinical value of tumor markers is not well established for diagnosis or follow-up; however, their use for monitoring response to treatment, particularly in patients with non-measurable disease, is useful
Treatment choice should take into account tumor biology and disease burden, previous therapies and responses obtained, patient preferences, performance status and co-morbidities, socio-economic, psychological factors and therapies available in the patient's country
Endocrine therapy is the preferred option for hormone receptor-positive disease, unless rapid response is warranted or endocrine resistance is suspected
HER-2-directed therapy should be offered early to all HER-2-positive metastatic breast cancer patients, either as single agent, combined with chemo- or with endocrine therapy. Patients progressing on an anti-HER-2 therapy combined with a cytotoxic agent should be offered a second line of anti-HER-2 therapy
Sequential mono-chemotherapy is the preferred option in metastatic breast cancer in the absence of rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control
There are only a few proven standards of care in metastatic breast cancer management, and inclusion of patients in well-designed, independent, prospective randomized trials must be a priority
In view of rising costs of metastatic breast cancer treatment, balanced decisions should be made but patient well-being, length and quality of life must always be the main decision factors
Validated patient reported outcome measures provide useful information about symptom severity and the burden and the impact of these symptoms on overall quality of life, and should be collected and integrated with other clinical assessments, to form part of the treatment decision making

note

Table 5 summarizes the recommendations for the management of MBC. Levels of evidence [I–V] and grades of recommendation [A–E] as used by the European Society for Medical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

The authors have declared no potential conflicts of interest.

references

1. Al-Batran SE, Güntner M, Pauligk C et al. Anthracycline rechallenge using pegylated liposomal doxorubicin in patients with metastatic breast cancer: a pooled analysis using individual data from four prospective trials. Br J Cancer 2010; 103: 1518–1523.
2. Alba E, Ruiz-Borrego M, Margelí M et al. Maintenance treatment with pegylated liposomal doxorubicin versus observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study. Breast Cancer Res Treat 2010; 122: 169–176.
3. Albain KS, Nag SM, Calderillo-Ruiz G et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment: final results of a global phase III study. J Clin Oncol 2008; 26: 3950–3957.
4. Andersson M, Lidbrink E, Bjerre K et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol 2011; 29: 264–271.
5. Aoyama H, Shirato H, Tago M et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006; 295: 2483–2491.
6. Bachelot T, Bourgier C, Cropet C et al Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 2012; epub ahead of print May 7; PubMed PMID: 22565002.
7. Baselga J, Campone M, Piccart M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012; 366: 520–529.
8. Baselga J, Cortés J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366: 109–119.
9. Blackwell KL, Burstein HJ, Storniolo AM et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010; 28: 1124–1130.
10. Cardoso F, Bedard PL, Winer EP et al on behalf of the ESO-MBC Task Force. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 2009; 101: 1174–1181.
11. Cardoso F, Costa A, Norton L et al. First international consensus guidelines for advanced breast cancer (ABC 1). Breast 2012; 21(3): 242–252.
12. Chan S, Friedrichs K, Noel D et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999; 17: 2341–2354.
13. Colozza M, de Azambuja E, Personeni N et al. Achievements in systemic therapies in the pre-genomic era in metastatic breast cancer. Oncologist 2007; 12: 253–270.
14. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377: 914–923.
15. Costelloe CM, Rohren EM, Madewell JE et al. Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. Lancet Oncol 2009; 10: 606–614.
16. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–247.
17. ESO-MBC Task Force. Metastatic breast cancer. Recommendations proposal from the European School of Oncology (ESO)-MBC Task Force. Breast 2007; 16: 9–10.
18. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893–2917.
19. Gennari A, Amadori D, De Lena M et al. Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. J Clin Oncol 2006; 24: 3912–3918.
20. Gennari A, Stockler M, Puntoni M et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 2011; 29: 2144–2149.
21. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733–2743.
22. Ghersi D, Wilcken N, Simes J, Donoghue E. Taxane containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2005; (2). Art. No. CD003366. DOI: 10.1002/14651858.CD003366.pub2.
23. Gibson L, Lawrence D, Dawson C et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev 2009; (4). Art. No. CD003370. doi: 10.1002/14651858.CD003370.pub3.
24. Huober J, Fasching PA, Barsoum M et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. Breast 2012; 21: 27–33.
25. Johnston S, Pippen J, Jr, Pivot X et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. J Clin Oncol 2009; 27: 5538–5546.
26. Kaufman B, Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009; 27: 5529–5537.
27. Kiely BE, Soon YY, Tattersall MH et al. How long have I got? Estimating typical, best-case, and worst-case scenarios for patients starting first-line chemotherapy for metastatic breast cancer: a systematic review of recent randomized trials. J Clin Oncol 2011; 29: 456–463.
28. Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005; 23: 4265–4274.
29. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666–2676.
30. Mouridsen H, Gershanovich M, Sun Y et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 2003; 21: 2101–2109.
31. Network NCC. 2008. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 2, ASCO-Edition 2008.
32. O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002; 20: 2812–2823.
33. Pagani O, Senkus E, Wood W et al. International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst 2010; 102: 456–463.
34. Patchell RA, Tibbs PA, Regine WF et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998; 280: 1485–1489.
35. Robertson JF, Llombart-Cussac A, Rolski J et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol 2009; 27: 4530–4535.
36. Seidman AD, Brufsky A, Ansari RH et al. Phase III trial of gemcitabine plus docetaxel versus capecitabine plus docetaxel with planned crossover to the alternate single agent in metastatic breast cancer. Ann Oncol 2011; 22: 1094–1101.

37. Sideras K, Ingle JN, Ames MM et al. Coprescription of tamoxifen and medications that inhibit CYP2D6. J Clin Oncol 2010; 28: 2768–2776.
38. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783–792.
39. Stockler MR, Harvey VJ, Francis PA et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. J Clin Oncol 2011; 29: 4498–4504.
40. Stopeck AT, Lipton A, Body JJ et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010; 28: 5132–5139.
41. von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German breast group 26/breast international group 03-05 study. J Clin Oncol 2009; 27: 1999–2006.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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

F. Cardoso[1*], S. Paluch-Shimon[2], E. Senkus[3], G. Curigliano[4], M. S. Aapro[5], F. André[6], C. H. Barrios[7], J. Bergh[8], G. S. Bhattacharyya[9], L. Biganzoli[10], F. Boyle[11], M.-J. Cardoso[1,12], L. A. Carey[13], J. Cortés[14,15], N. S. El Saghir[16], M. Elzayat[17], A. Eniu[18], L. Fallowfield[19], P. A. Francis[20], K. Gelmon[21], J. Gligorov[22], R. Haidinger[23], N. Harbeck[24], X. Hu[25], B. Kaufman[26], R. Kaur[27], B. E. Kiely[28], S.-B. Kim[29], N. U. Lin[30], S. A. Mertz[31], S. Neciosup[32], B. V. Offersen[33], S. Ohno[34], O. Pagani[35], A. Prat[36,37,38], F. Penault-Llorca[39,40], H. S. Rugo[41], G. W. Sledge[42], C. Thomssen[43], D. A. Vorobiof[44], T. Wiseman[45], B. Xu[46], L. Norton[47], A. Costa[48,49] & E. P. Winer[30]

[1]Breast Unit, Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal; [2]Sharett Division of Oncology, Hadassah University Hospital, Jerusalem, Israel; [3]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; [4]Department of Oncology and Hemato-Oncology, European Institute of Oncology, IRCCS, Division of Early Drug Development, University of Milan, Milan, Italy; [5]Breast Center, Clinique de Genolier, Genolier, Switzerland; [6]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [7]Latin American Cooperative Oncology Group (LACOG), Grupo Oncoclínicas, Porto Alegre, Brazil; [8]Department of Oncology-Pathology, Karolinska Institute & University Hospital, Stockholm, Sweden; [9]Department of Medical Oncology, Salt Lake City Medical Centre, Kolkata, India; [10]Department of Medical Oncology, Nuovo Ospedale di Prato — Istituto Toscano Tumori, Prato, Italy; [11]The Pam McLean Centre, Royal North Shore Hospital, St Leonards, Australia; [12]Nova Medical School, Lisbon, Portugal; [13]Department of Hematology and Oncology, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, USA; [14]IOB Institute of Oncology, Quiron Group, Madrid & Barcelona; [15]Department of Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [16]Division of Hematology Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; [17]Europa Donna, The European Breast Cancer Coalition, Milan, Italy; [18]Interdisciplinary Oncology Service (SIC), Riviera-Chablais Hospital, Rennaz, Switzerland; [19]SHORE-C, Brighton & Sussex Medical School, University of Sussex, Brighton, UK; [20]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [21]Medical Oncology Department, BC Cancer Agency, Vancouver, Canada; [22]Breast Cancer Expert Center, University Cancer Institute APHP, Sorbonne University, Paris, France; [23]Brustkrebs Deutschland e.V., Munich, Germany; [24]Breast Centre, Department of Obstetrics and Gynaecology, University of Munich (LMU), Munich, Germany; [25]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [26]Department of Oncology, Sheba Medical Center, Ramat Gan, Israel; [27]Breast Cancer Welfare Association Malaysia, Petaling Jaya, Malaysia; [28]NHMRC Clinical Trials Centre, Sydney Medical School, Sydney, Australia; [29]Department of Oncology, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea; [30]Susan Smith Center for Women's Cancers — Breast Oncology Center, Dana-Farber Cancer Institute, Boston, USA; [31]Metastatic Breast Cancer Network, Inverness, USA; [32]Department of Medical Oncology, National Institute of Neoplastic Diseases, Lima, Peru; [33]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [34]Breast Oncology Centre, Cancer Institute Hospital, Tokyo, Japan; [35]Medical School, Geneva University Hospital, Geneva, Switzerland; [36]Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona; [37]Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona; [38]Department of Medicine, University of Barcelona, Barcelona, Spain; [39]Department of Biopathology, Centre Jean Perrin, Clermont-Ferrand; [40]University Clermont Auvergne/INSERM U1240, Clermont-Ferrand, France; [41]Breast Oncology Clinical Trials Education, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; [42]Division of Oncology, Stanford School of Medicine, Stanford, USA; [43]Department of Gynaecology, Martin Luther University Halle-Wittenburg, Halle, Germany; [44]Oncology Research Unit, Belong.Life, Tel Aviv, Israel; [45]Department of Applied Health Research in Cancer Care, The Royal Marsden Hospital NHS Foundation Trust, London, UK; [46]Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; [47]Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, USA; [48]European School of Oncology, Milan, Italy; [49]European School of Oncology, Bellinzona, Switzerland

Available online 23 September 2020

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

INTRODUCTION

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

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

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

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

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

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

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

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

METHODOLOGY

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

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

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

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

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

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

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

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

Section II. General guidelines		
Guideline statement	**LoE/GoR**	**Consensus**
The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation and surgical oncologists, imaging experts, pathologists, gynaecologists, psycho-oncologists, social workers, nurses and palliative care specialists) is crucial.	Expert opinion/A	100%
From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care and symptom-related interventions as a routine part of their care. The approach must be personalised to meet the needs of the individual patient.	Expert opinion/A	100%

Continued

Section II. Continued

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

Continued

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

In green, NEW/UPDATED ABC 5 statements.

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

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

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

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

Continued

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

In green, NEW/UPDATED ABC 5 statements.

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

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

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

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

Continued

Section IV. Continued

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

Continued

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

In green, NEW/UPDATED ABC 5 statements.

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

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

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

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

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

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

In green, NEW/UPDATED ABC 5 statements.

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

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

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

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

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

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

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

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

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

Section VI. Triple-negative ABC

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

In green, NEW ABC 5 statements.

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

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

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

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

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

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

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

Section VII. Hereditary ABC

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

In green, NEW ABC 5 statements.

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

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

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

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

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

Section VIII. Precision medicine

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

Continued

Section VIII. Continued

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

In green, NEW ABC 5 statements.

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

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

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

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

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

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

Section IX. Specific sites of metastases

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

Continued

Section IX. Continued		
Guideline statement	**LoE/GoR**	**Consensus**
this when discussing a potential local therapy technique. Local therapy should only be proposed in very selected cases of good PS, with limited liver involvement and no extrahepatic lesions, after adequate systemic therapy has demonstrated control of the disease. Currently, there are no data to select the best technique for the individual patient (surgery, stereotactic RT, intrahepatic ChT, etc.).		
Malignant pleural effusions		
Malignant pleural effusions require systemic treatment with/without local management.	III/A	86%
Thoracentesis for diagnosis should be performed if it is likely that this will change clinical management. False negative results are common.	III/B	
Drainage is recommended in patients with symptomatic, clinically significant pleural effusion.	III/A	
Use of an intrapleural catheter or intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) can be helpful.	III/B	
Clinical trials evaluating the best technique are needed.		
Chest wall and regional (nodal) recurrences		
Due to the high risk of concomitant distant metastases, patients with chest wall or regional (nodal) recurrence should undergo full restaging, including assessment of chest, abdomen and bone.	Expert opinion/A	100%
Chest wall and regional recurrences should be treated with surgical excision when feasible with limited risk of morbidity.	II/A	97%
Locoregional RT is indicated for patients not previously irradiated.	II/A	97%
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion/C	97%
In addition to local therapy (surgery and/or RT), in the absence of distant metastases, the use of systemic therapy (ChT, ET and/or anti-HER2 therapy) should be considered.	I/B	95%
ChT after first local or regional recurrence improves long-term outcomes in ER-negative disease and can be used.	I/B	95%
ET in this setting improves long-term outcomes for ER-positive disease and should be used.	I/B	95%
The choice of systemic treatment depends on tumour biology, previous treatments, length of DFI and patient-related factors (comorbidities, preferences, etc.).	Expert opinion/A	95%
In patients with disease not amenable to radical local treatment, the choice of palliative systemic therapy should be made according to principles previously defined for metastatic disease. These patients may still be considered for palliative local therapy.	Expert opinion/B	97%

In green, NEW ABC 5 statements.

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

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

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

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

Continued

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

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

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

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

Continued

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

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

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

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

Continued

Section XII. Continued

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

Continued

Section XII. Continued

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

Continued

Section XII. Continued

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

Continued

Section XII. Continued

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

In green, NEW ABC 5 statements.

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

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

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

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

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

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

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

Section XIII. Integrative medicine

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

Continued

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

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

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

CONCLUSIONS AND FUTURE DIRECTIONS

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

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

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

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Angela Corstorphine of Kstorfin Medical Communications Ltd; this support was funded by ESMO.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

MSA reports receipt of consultation fees from Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Novartis, Merck, Merck Serono, Mundipharma, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Tevam Vifor, G1 Therapeutics and Lilly; receipt of honoraria for symposia lectures from Amgen, Bayer, Schering, Cephalon, Chugai, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ Ortho Biotech, Kyowa Hakko Kirin, Merck, Merck Serono, Mundipharma, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Tevam Vifor, G1 Therapeutics and Lilly. CHB reports receipt of honoraria or consultation fees from Boehringer Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai, MSD, AstraZeneca and Bayer; receipt of grants/research support to the institution from AbbVie, Amgen, Astellas Pharma, AstraZeneca, BMS, Celgene, Covance, Lilly, Medivation, Merck Serono, MSD, Novartis, Pfizer, PharmaMar and Roche/Genentech. JB reports receipt of grants/research support grants to Karolinska Institute and University Hospital from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, Sanofi-Aventis; no personal payments; payment from UpToDate to Asklepios Medicine HB for a chapter on breast cancer prediction. LB reports receipt of grants/research support from Celgene, Genomic Health and Novartis; receipt of honoraria or consultation fees from AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Genomic Health, Ipsen, Lilly, Novartis, Pfizer, Pierre Fabre and Roche. FC reports receipt of honoraria or consultation fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, GSK, MacroGenics, Medscape, MSD, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics and Teva. JC reports acting as a consultant/advisor for Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, MSD, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim and Kyowa Kirin; received honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, MSD and Daiichi Sankyo; received research funding to the institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. Hoffmann-La Roche, Guardant Health, MSD, Pfizer, PIQUR Therapeutics, Puma C and Queen Mary University of London; holds stock, patents and intellectual property for MEDSIR; received travel, accommodation and expenses from Roche, Novartis, Eisai, Pfizer and Daiichi Sankyo. GC reports receipt of honoraria or consultation fees from Roche, Pfizer, Lilly, Novartis and SeaGen; participation in a sponsored speakers' bureau for SeaGen, Pfizer, Lilly and Novartis. NSES reports receipt of grants/research support to institution from Novartis; receipt of honoraria or consultation fees from Novartis, Roche, Pfizer, Lilly and AstraZeneca. ME reports acting in an advisory role for Novartis and Roche. AE reports receipt of grants/research support from AstraZeneca, Roche, Celltrion, Pfizer and Novartis. LF reports receipt of grants/research support from BMS, GSK, Myriad and Novartis; receipt of honoraria or consultation fees from BMS, AstraZeneca, Teva, Novartis, Eisai, Takeda, Pfizer, Lilly, Genomic Health and Myriad. PAF reports receipt of honoraria or consultation fees from AstraZeneca and Novartis; travel for lecture

for Pfizer and Ipsen. KG reports receipt of grants/research support from AstraZeneca, Pfizer and BMS; receipt of honoraria or consultation fees from Pfizer, AstraZeneca, Novartis, Nanostring, Merck, Mylan, Genomic Health, Roche and BMS. JG reports receipt of grants/research support from Amgen, Eisai, Genomic Health, Novartis, Pfizer and Roche/Genentech; receipt of honoraria or consultation fees from Daiichi, Eisai, Genomic Health, Ipsen, MacroGenics, MSD, Mylan, Novartis, Onxeo, Pfizer and Roche/Genentech; participation in a sponsored speakers' bureau for Eisai, Genomic Health, Ipsen, Novartis, Pfizer and Roche/Genentech. NH reports receipt of honoraria or consultation fees from Amgen, AstraZeneca, Celgene, Daiichi Sakyo, Lilly, MSD, Novartis, Odonate, Pfizer, Roche, Sandoz/Hexal and Seattle Genetics. RK reports receipt of grants/research support from Pfizer Malaysia. BEK reports receipt of grants/research support to institution from Roche; receipt of honoraria for advisory boards and educational presentations as well as travel and meeting expenses from Roche; receipt of honoraria for advisory boards and educational presentations from Novartis. SBK reports receipt of grants/research support to institution from Novartis, Sanofi-Aventis, Kyowa Kirin Inc. and DongKook Pharm Co.; receipt of consultancy fees from Novartis, AstraZeneca, Lilly, Enzychem, Daehwa Pharmaceutical Co. Ltd, ISU ABXIS and Daiichi Sankyo. NUL reports receipt of grants/research support from Genentech and Seattle Genetics; receipt of honoraria or consultation fees from Seattle Genetics, Daiichi Sankyo and Puma. SAM reports receipt of honoraria from Pfizer and Lilly; SN reports receipt of grants/research support from Roche, Pfizer, BMS and Novartis; participation in a sponsored speakers' bureau for Roche, Pfizer, BMS, Merck and Novartis. LN reports receipt of honoraria from Sermonix Oncology Ad Board, Prime Oncology, Sarah Lawrence Lecture, Context advisory board, Oncology Pioneers Science Lecture Series, BCRF programmatic review meeting and CSHL external advisory board meeting. SO reports receipt of grants/research support from Chugai, Eisai, Taiho, Daiichi Sankyo; participation in a sponsored speakers' bureau for Chugai, AstraZeneca, Eisai, Taiho, Pfizer and Lilly. OP reports participation in a sponsored speakers' bureau for Takeda, Roche, Pfizer, Novartis and Lilly. SPS has participated in a speakers' bureau and received honoraria from Roche, AstraZeneca, Novartis, Pfizer, Nanostring and Teva; reports consultancy for Roche, AstraZeneca, Novartis and Pfizer. FPL reports receipt of grants/research support from Roche; receipt of honoraria or consultation fees from Roche, Puma, Pierre Fabre and AstraZeneca. AP reports personal financial interests and lecture fees for Roche, Pfizer, Novartis, Amgen, BMS and Daiichi Sankyo; participation in an advisory role/consultancy for Roche, Pfizer, Novartis, Amgen, BMS, Puma and Oncolytics Biotech; institutional financial interests include contracted research for Novartis, Nanostring, Roche and Boehringer; lecture fees from Nanostring technologies; clinical trials for Novartis, Roche, Boehringer, Daiichi Sankyo, Pfizer, Lilly and Amgen. HSR reports receipt of grants/research support from Pfizer, Merck, Novartis, Lilly, Genentech, OBI, Odonate, Daiichi Sankyo, Eisai, Seattle Genetics, MacroGenics and Immunomedics. ES reports receipt of honoraria or consultation fees from Amgen, AstraZeneca, Clinigen, Egis, Eli Lilly, Genomic Health, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz and TLC Biopharmaceuticals; travel support from Amgen, AstraZeneca, Egis, Novartis, Pfizer and Roche; contracted research for Amgen, AstraZeneca, Boehringer, Eli Lilly, Merck, Novartis, Pfizer, Roche and Samsung; holds stock in Eli Lilly. EPW reports receipt of grants/research support from Merck and Genentech/Roche; receipt of honoraria or consultation fees from Carrick Therapeutics, Genentech/Roche, Genomic Health, GSK, Jounce, Leap, Lilly, Merck and Seattle Genetics; research fees to institute from Genentech/Roche and Merck; participation in a scientific advisory board for Leap. BX reports receipt of advisory fees from Novartis and Roche; fees for serving on a speakers' bureau from AstraZeneca, Pfizer, Roche and Eisai. FA, FB, BK, FEL, GWS, CT and TW have not reported any potential conflict of interest. GSB, MJC, LAC, AC, RH, XH, BVO and DAV have declared no significant conflict of interest.

REFERENCES

1. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast*. 2014;23(5):489-502.
2. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014;25(10):1871-1888.
3. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015). *Breast*. 2018;39:131-138.
4. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Based on November 2015 SEER Data Submission*. Bethesda, MD: SEER; 2016. Available at https://seer.cancer.gov/archive/csr/1975_2013/. Accessed July 10, 2020.
5. Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. *Breast*. 2017;31:46-50.
6. Kobayashi K, Ito Y, Matsuura M, et al. Impact of immunohistological subtypes on the long-term prognosis of patients with metastatic breast cancer. *Surg Today*. 2016;46(7):821-826.
7. Fietz T, Tesch H, Rauh J, et al. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer—results from the prospective German TMK cohort study. *Breast*. 2017;34:122-130.
8. Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur J Cancer*. 2018;96:17-24.
9. Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. *Eur J Cancer*. 2020;129:60-70.
10. Malmgren JA, Mayer M, Atwood MK, et al. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. *Breast Cancer Res Treat*. 2018;167(2):579-590.
11. Breast Cancer Foundation NZ. "I'm still here". Insights into living—and dying—with advanced breast cancer in New Zealand. Breast Cancer Foundation NZ. Available at https://www.breastcancerfoundation.org.nz/what-we-do/advocacy/abcinnz. Accessed July 10, 2020.
12. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
13. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
14. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin*

Infect Dis. 2001;33(2):139-144 (adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;1918:1421).
15. Mack JW, Weeks JC, Wright AA, et al. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol*. 2010;28(7):1203-1208.
16. Smith-Uffen MES, Johnson SB, Martin AJ, et al. Estimating survival in advanced cancer: a comparison of estimates made by oncologists and patients. *Support Care Cancer*. 2020;28(7):3399-3407.
17. Hagerty RG, Butow PN, Ellis PM, et al. Communicating prognosis in cancer care: a systematic review of the literature. *Ann Oncol*. 2005;16(7):1005-1053.
18. Fried TR, Bradley EH, O'Leary J. Prognosis communication in serious illness: perceptions of older patients, caregivers, and clinicians. *J Am Geriatr Soc*. 2003;51(10):1398-1403.
19. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *J Clin Oncol*. 2012;30(35):4387-4395.
20. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*. 2008;300(14):1665-1673.
21. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA*. 1998;279(21):1709-1714.
22. Pronzato P, Bertelli G, Losardo P, et al. What do advanced cancer patients know of their disease? A report from Italy. *Support Care Cancer*. 1994;2(4):242-244.
23. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. *Br J Cancer*. 2001;84(1):48-51.
24. Arraras JI, Greimel E, Chie WC, et al. Cross-cultural differences in information disclosure evaluated through the EORTC questionnaires. *Psychooncology*. 2013;22(2):268-275.
25. Fallowfield LJ, Jenkins VA, Beveridge HA. Truth may hurt but deceit hurts more: communication in palliative care. *Palliat Med*. 2002;16(4):297-303.
26. Barnett MM. Does it hurt to know the worst?—psychological morbidity, information preferences and understanding of prognosis in patients with advanced cancer. *Psychooncology*. 2006;15(1):44-55.
27. Enzinger AC, Zhang B, Schrag D, et al. Outcomes of prognostic disclosure: associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer. *J Clin Oncol*. 2015;33(32):3809-3816.
28. Gattellari M, Voigt KJ, Butow PN, et al. When the treatment goal is not cure: are cancer patients equipped to make informed decisions? *J Clin Oncol*. 2002;20(2):503-513.
29. Hagerty RG, Butow PN, Ellis PM, et al. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *J Clin Oncol*. 2005;23(6):1278-1288.
30. Smith TJ, Dow LA, Virago E, et al. Giving honest information to patients with advanced cancer maintains hope. *Oncology (Williston Park)*. 2010;24(6):521-525.
31. Kiely BE, McCaughan G, Christodoulou S, et al. Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience. *Support Care Cancer*. 2013;21(2):369-376.
32. Stockler MR, Tattersall MH, Boyer MJ, et al. Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer. *Br J Cancer*. 2006;94(2):208-212.
33. Kiely BE, Martin AJ, Tattersall MH, et al. The median informs the message: accuracy of individualized scenarios for survival time based on oncologists' estimates. *J Clin Oncol*. 2013;31(28):3565-3571.
34. Fallowfield LJ, Catt SL, May SF, et al. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits. *Support Care Cancer*. 2017;25(1):237-244.
35. Hey SP, Gyawali B, D'Andrea E, et al. A systematic review and meta-analysis of bevacizumab in first-line metastatic breast cancer: lessons for research and regulatory enterprises. *J Natl Cancer Inst*. 2020;112(4):335-342.
36. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381(4):307-316.
37. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514-524.
38. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36(24):2465-2472.
39. Sledge Jr GW, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, erbb2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2019;6(1):116-124.
40. Sledge Jr GW, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.
41. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19(7):904-915.
42. Tripathy D, Sohn J, Im S-A, et al. Abstract GS2-05: first-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial. *Cancer Res*. 2018;78(4 Supplement). GS2-05.
43. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936.
44. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375(18):1738-1748.
45. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat*. 2019;174(3):719-729.
46. di Leo A, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer. *Ann Oncol*. 2017;28(suppl 5):v605-v649.
47. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2−), advanced breast cancer (ABC). *J Clin Oncol*. 2017;35(15_suppl):1038.
48. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016;17(4):425-439.
49. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646.
50. Harbeck N, Iyer S, Bhattacharyya H, et al. Impact of disease progression status on time to deterioration of patient reported health related quality of life in first line ER+ HER2- advanced/metastatic breast cancer patients in the PALOMA-2 study. *Breast*. 2017;36:S43.
51. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*. 2019;5:5.
52. Rugo HS, Diéras V, Gelmon KA, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. *Ann Oncol*. 2018;29(4):888-894.

53. Verma S, O'Shaughnessy J, Burris HA, et al. Health-related quality of life (HRQoL) of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) treated with ribociclib + letrozole: results from MONALEESA-2. *J Clin Oncol*. 2017;35(15_suppl):1020.
54. Harbeck N, Iyer S, Turner N, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. *Ann Oncol*. 2016;27(6):1047-1054.
55. Kaufman PA, Toi M, Neven P, et al. Health-related quality of life in MONARCH 2: abemaciclib plus fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. *Oncologist*. 2020;25(2):e243-e251.
56. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
57. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). *Oncologist*. 2016;21(10):1165-1175.
58. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940.
59. Nunnery SE, Mayer IA. Management of toxicity to isoform α-specific PI3K inhibitors. *Ann Oncol*. 2019;30(suppl 10):x21-x26.
60. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with *PIK3CA*-mutated (mut) hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. *J Clin Oncol*. 2020;38(15_suppl):1006.
61. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for advanced breast cancer (ABC 4). *Ann Oncol*. 2018;29(8):1634-1657.
62. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609.
63. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619.
64. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
65. Rugo HS, Im S-A, Wright GLS, et al. SOPHIA primary analysis: a phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx). *J Clin Oncol*. 2019;37(15_suppl):1000.
66. Saura C, Oliveira M, Feng Y-H, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial. *J Clin Oncol*. 2019;37(15_suppl):1002.
67. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2015;33(14):1564-1573.
68. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121.
69. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(1):44-59.
70. Cortes J, Cescon DW, Rugo HS, et al. KEYNOTE-355: randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. *J Clin Oncol*. 2020;38(15_suppl):1000.
71. Cortés J, Lipatov O, Im S, et al. KEYNOTE-119: phase 3 study of pembrolizumab (pembro) versus single-agent chemotherapy (chemo) for metastatic triple-negative breast cancer (mTNBC). *Ann Oncol*. 2019;30(suppl 5):v851-v934.
72. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med*. 2019;380(8):741-751.
73. Paluch-Shimon S, Cardoso F, Sessa C, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol*. 2016;27(suppl 5):v103-v110.
74. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: a phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in DNA damage response (DDR) pathway genes (olaparib expanded). *J Clin Oncol*. 2020;38(15_suppl):1002.
75. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. 2019;30(4):558-566.
76. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533.
77. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379(8):753-763.
78. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib in germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from randomized phase 3 EMBRACA trial. AACR virtual annual meeting. 27-28 April 2020. Abstract CT071.
79. Dieras VC, Han HS, Kaufman B, et al. Phase 3 study of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic gBRCA-associated breast cancer. *Ann Oncol*. 2019;30(suppl 5):v851-v934.
80. Diaz Jr LA, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol*. 2014;32(6):579-586.
81. Alimirzaie S, Bagherzadeh M, Akbari MR. Liquid biopsy in breast cancer: a comprehensive review. *Clin Genet*. 2019;95(6):643-660.
82. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. *J Clin Oncol*. 2018;36(16):1631-1641.
83. Condorelli R, Mosele F, Verret B, et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2019;30(3):365-373.
84. Rugo HS, Mayer I, Conte P, et al. Abstract CT142: prevalence of *PIK3CA* mutations in patients with hormone receptor-positive, human epidermal growth factor-2-negative advanced breast cancer from the SOLAR-1 trial. *Cancer Res*. 2019;79(13 Supplement):CT142.
85. Juric D, Ciruelos E, Rubovszky G, et al. Abstract GS3-08: Alpelisib + fulvestrant for advanced breast cancer: subgroup analyses from the phase III SOLAR-1 trial. *Cancer Res*. 2019;79(4 Supplement). GS3-08.
86. Juric D, Andre F, Singer CF, et al. Abstract P4-10-04: clinical outcomes of alpelisib in hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer by next-generation sequencing-detected PIK3CA alteration status and phosphatase and tensin homolog loss: biomarker analysis from the SOLAR-1 study. *Cancer Res*. 2020;80(4 Supplement). P4-10-04.
87. Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer. *J Clin Oncol*. 2016;34(25):2961-2968.

88. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primers*. 2019;5(1):66.
89. Adam J, Le Stang N, Rouquette I, et al. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol*. 2018;29(4):953-958.
90. Rugo HS, Loi S, Adams S, et al. Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): post-hoc analysis of IMpassion130. *Ann Oncol*. 2019;30(suppl 5):v851-v934.
91. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122.
92. Gloyeske NC, Dabbs DJ, Bhargava R. Low ER+ breast cancer: is this a distinct group? *Am J Clin Pathol*. 2014;141(5):697-701.
93. Deyarmin B, Kane JL, Valente AL, et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. *Ann Surg Oncol*. 2013;20(1):87-93.
94. Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30(7):729-734.
95. Balduzzi A, Bagnardi V, Rotmensz N, et al. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. *Clin Breast Cancer*. 2014;14(4):258-264.
96. Yi M, Huo L, Koenig KB, et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. *Ann Oncol*. 2014;25(5):1004-1011.
97. Chen T, Zhang N, Moran MS, et al. Borderline ER-positive primary breast cancer gains no significant survival benefit from endocrine therapy: a systematic review and meta-analysis. *Clin Breast Cancer*. 2018;18(1):1-8.
98. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline update. *J Clin Oncol*. 2020;38(12):1346-1366.
99. Coleman R, Hadji P, Body J-J, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2020;31(12):1650-1663.
100. Franzoi MA, Hortobagyi GN. Leptomeningeal carcinomatosis in patients with breast cancer. *Crit Rev Oncol Hematol*. 2019;135:85-94.
101. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol*. 2017;28(suppl 4):iv84-iv99.
102. Le Rhun E, Preusser M, van den Bent M, et al. How we treat patients with leptomeningeal metastases. *ESMO Open*. 2019;4(suppl 2):e000507.
103. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133.
104. Cardoso F, Costa A, Norton L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). *Breast*. 2012;21(3):242-252.
105. Knaul FM, Farmer PE, Krakauer EL, et al. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the *Lancet* Commission report. *Lancet*. 2018;391(10128):1391-1454.
106. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;29(suppl 4):iv166-iv191.
107. Jones MR, Viswanath O, Peck J, et al. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther*. 2018;7(1):13-21.
108. Page R, Blanchard E. Opioids and cancer pain: patients' needs and access challenges. *J Oncol Pract*. 2019;15(5):229-231.
109. Cannabis and cannabinoids. *Med Lett Drugs Ther*. 2019;61(1585):179-182.
110. Alves P, Amaral C, Teixeira N, et al. Cannabis sativa: much more beyond Δ(9)-tetrahydrocannabinol. *Pharmacol Res*. 2020;157:104822.
111. Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst*. 2008;100(7):475-482.
112. Fahlén M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *Eur J Cancer*. 2013;49(1):52-59.
113. Duijts SF, van Beurden M, Oldenburg HS, et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol*. 2012;30(33):4124-4133.
114. Mann E, Smith MJ, Hellier J, et al. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. *Lancet Oncol*. 2012;13(3):309-318.
115. Stefanopoulou E, Grunfeld EA. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review. *J Psychosom Obstet Gynaecol*. 2017;38(3):210-225.
116. Lahart IM, Metsios GS, Nevill AM, et al. Physical activity for women with breast cancer after adjuvant therapy. *Cochrane Database Syst Rev*. 2018;1(1):Cd011292.
117. Hartman SJ, Nelson SH, Myers E, et al. Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: the memory & motion study. *Cancer*. 2018;124(1):192-202.
118. Ramaswami R, Villarreal MD, Pitta DM, et al. Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015;152(2):231-237.
119. Johns C, Seav SM, Dominick SA, et al. Informing hot flash treatment decisions for breast cancer survivors: a systematic review of randomized trials comparing active interventions. *Breast Cancer Res Treat*. 2016;156(3):415-426.
120. Shan D, Zou L, Liu X, et al. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020;222(6):564-579.e12.
121. Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr*. 2020;4(1):pkz088.
122. Chen WY, Giobbie-Hurder A, Gantman K, et al. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes. *Breast Cancer Res Treat*. 2014;145(2):381-388.
123. Innominato PF, Lim AS, Palesh O, et al. The effect of melatonin on sleep and quality of life in patients with advanced breast cancer. *Support Care Cancer*. 2016;24(3):1097-1105.
124. Mayer S, Iborra S, Grimm D, et al. Sexual activity and quality of life in patients after treatment for breast and ovarian cancer. *Arch Gynecol Obstet*. 2019;299(1):191-201.
125. Stute P. Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief? *Arch Gynecol Obstet*. 2013;288(6):1199-1201.
126. Serati M, Bogani G, Di Dedda MC, et al. A comparison between vaginal estrogen and vaginal hyaluronic for the treatment of dyspareunia in women using hormonal contraceptive. *Eur J Obstet Gynecol Reprod Biol*. 2015;191:48-50.
127. Origoni M, Cimmino C, Carminati G, et al. Postmenopausal vulvovaginal atrophy (VVA) is positively improved by topical hyaluronic acid application. A prospective, observational study. *Eur Rev Med Pharmacol Sci*. 2016;20(20):4190-4195.
128. Donders G, Bellen G, Neven P, et al. Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors. *Eur J Clin Microbiol Infect Dis*. 2015;34(10):2023-2028.
129. Buchholz S, Mögele M, Lintermans A, et al. Vaginal estriol-lactobacilli combination and quality of life in endocrine-treated breast cancer. *Climacteric*. 2015;18(2):252-259.

130. Mazzarello S, Hutton B, Ibrahim MFK, et al. Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. *Breast Cancer Res Treat*. 2015;152(1):1-8.
131. Caruso S, Cianci S, Amore FF, et al. Quality of life and sexual function of naturally postmenopausal women on an ultralow-concentration estriol vaginal gel. *Menopause*. 2016;23(1):47-54.
132. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R. ACOG Committee opinion no. 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. *Obstet Gynecol*. 2016;127(3):e93-e96.
133. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017;3(3):313-319.
134. Hersant B, SidAhmed-Mezi M, Belkacemi Y, et al. Efficacy of injecting platelet concentrate combined with hyaluronic acid for the treatment of vulvovaginal atrophy in postmenopausal women with history of breast cancer: a phase 2 pilot study. *Menopause*. 2018;25(10):1124-1130.
135. Romero-Otero J, Lauterbach R, Aversa A, et al. Laser-based devices for female genitourinary indications: position statements from the European Society for Sexual Medicine (ESSM). *J Sex Med*. 2020;17(5):841-848.
136. Bartula I, Sherman KA. The Female Sexual Functioning Index (FSFI): evaluation of acceptability, reliability, and validity in women with breast cancer. *Support Care Cancer*. 2015;23(9):2633-2641.
137. Mancha RG, Muñoz M, de la Cruz-Merino L, et al. Development and validation of a sexual relations satisfaction scale in patients with breast cancer - "SEXSAT-Q". *Health Qual Life Outcomes*. 2019;17(1):143.
138. Reese JB, Sorice KA, Zimmaro LA, et al. Communication about sexual health in breast cancer: what can we learn from patients' self-report and clinic dialogue? *Patient Educ Couns*. 2020;103(9):1821-1829.
139. Dai Y, Cook OY, Yeganeh L, et al. Patient-reported barriers and facilitators to seeking and accessing support in gynecologic and breast cancer survivors with sexual problems: a systematic review of qualitative and quantitative studies. *J Sex Med*. 2020;17(7):1326-1358.
140. Atkins L, Fallowfield LJ. Fallowfield's sexual activity questionnaire in women with without and at risk of cancer. *Menopause Int*. 2007;13(3):103-109.
141. Gompel A, Ramirez I, Bitzer J. Contraception in cancer survivors - an expert review Part I. Breast and gynaecological cancers. *Eur J Contracept Reprod Health Care*. 2019;24(3):167-174.
142. ABC Global Alliance. ABC Global Charter 2018. ABC Global Alliance. Available at https://www.abcglobalalliance.org/wp-content/uploads/2018/06/ABC-Global-Charter-Booklet-June-2018-Final.pdf. Accessed July 15, 2020.