ASCO special articles

Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update

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abstract

PURPOSE This guideline updates recommendations of the ASCO guideline on chemotherapy and targeted therapy for patients with human epidermal growth factor receptor 2–negative metastatic breast cancer (MBC) that is either endocrine-pretreated or hormone receptor (HR)–negative.

METHODS An Expert Panel conducted a targeted systematic literature review guided by a signals approach to identify new, potentially practice-changing data that might translate into revised guideline recommendations.

RESULTS The Expert Panel reviewed abstracts from the literature review and retained 14 articles.

RECOMMENDATIONS Patients with triple-negative, programmed cell death ligand-1–positive MBC may be offered the addition of immune checkpoint inhibitor to chemotherapy as first-line therapy. Patients with triple-negative, programmed cell death ligand-1–negative MBC should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment, although combination regimens may be offered for life-threatening disease. Patients with triple-negative MBC who have received at least two prior therapies for MBC should be offered treatment with sacituzumab govitecan. Patients with triple-negative MBC with germline *BRCA* mutations previously treated with chemotherapy may be offered a poly (ADP-ribose) polymerase inhibitor rather than chemotherapy. Patients with HR-positive human epidermal growth factor receptor 2–negative MBC for whom chemotherapy is being considered should be offered single–agent chemotherapy rather than combination chemotherapy, although combination regimens may be offered for highly symptomatic or life-threatening disease. Patients with HR-positive MBC with disease progression on an endocrine agent may be offered treatment with either endocrine therapy with or without targeted therapy or single-agent chemotherapy. Patients with HR-positive MBC with germline *BRCA* mutations no longer benefiting from endocrine therapy may be offered a poly (ADP-ribose) polymerase inhibitor rather than chemotherapy. No recommendation regarding when a patient's care should be transitioned to hospice or best supportive care alone is possible.

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

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ASSOCIATED CONTENT

See accompanying Oncology Grand Rounds on page 3890

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Breast cancer remains an important area for research, and there is always a need for the most up-to-date guidance. In 2021, in the United States, an estimated 284,200 new cases of breast cancer will be diagnosed in both sexes combined (281,550 women and 2,650 men).[1] Of all patients with breast cancer, the expected 2021 mortality is 44,130 (43,600 women and 530 men).[1] Despite advances in detection and treatment, breast cancer is the most commonly diagnosed cancer in women (representing 30% of all new cancers) and the second-leading cause of cancer death (representing 15% of all cancer mortality in women).[1]

The purpose of this guideline update is to gather and examine the evidence published since the 2014 guideline by Partridge et al[2] and offer a series of updated recommendations for advanced human epidermal growth factor receptor 2 (HER2)–negative breast cancer, if warranted. That 2014 guideline examined evidence published between 2009 and May 2013 and addressed the following four research questions: (1) What are the indications for chemotherapy

THE BOTTOM LINE

Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update

Guideline Question

What is the optimal chemotherapy and/or targeted therapy for patients with HER2-negative metastatic breast cancer?

Target Population

Women or men with HER2-negative MBC that is HR-positive but endocrine-pretreated or triple negative.

Target Audience

This guideline is targeted to both health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team) and patients.

Methods

An Expert Panel was reconvened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature (Appendix Table A1, online only).

Recommendations

Recommendation 1.1. Patients with metastatic triple-negative breast cancer with expression of programmed cell death ligand-1 (PD-L1–positive) and no existing contraindications may be offered the addition of immune checkpoint inhibitor to chemotherapy (atezolizumab plus nab-paclitaxel or pembrolizumab plus chemotherapy) as first-line therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong; Appendix Table A2, online only).

Recommendation 1.2. Patients with metastatic triple-negative breast cancer without expression of programmed cell death ligand-1 (PD-L1–negative) should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Patients may be offered either platinum-based or nonplatinum-based regimens on the basis of individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 1.3. Patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease should be offered treatment with sacituzumab govitecan (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.4. Patients with metastatic triple-negative breast cancer with germline *BRCA1* or *2* mutations who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting may be offered an oral poly (ADP-ribose) polymerase (PARP) inhibitor (olaparib or talazoparib) rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Recommendation 2.1. Patients with metastatic HR-positive breast cancer with disease progression on a prior endocrine agent with or without targeted therapy may be offered treatment with either ET with or without targeted therapy (refer to the companion ASCO guideline on Endocrine Therapy and Targeted Therapy for Hormone Receptor–Positive Metastatic Breast Cancer[13] for details) or single-agent chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Treatment choice should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 3.1. Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1 or 2* mutations who are no longer benefiting from ET may be offered an oral PARP inhibitor in the first-through to third-line setting rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Recommendation 3.2. Patients with HR-positive HER2-negative MBC no longer benefiting from ET should be offered single-agent chemotherapy rather than combination therapy, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Choice of chemotherapy agent should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 4.1. No recommendation regarding at which point a patient's care should be transitioned to hospice or best supportive care only is possible at this time (Type: consensus; benefits/harms ratio unknown; Evidence quality: N/A; Strength of recommendation: strong).

Practical information. Given the heterogeneity of breast cancer and the treatment goals of patients with breast cancer, it is not possible to identify a universal optimal time to transition to hospice or best supportive care. When to transition is a decision that should be shared between the patient and clinician in the context of an ongoing conversation regarding goals of care. The conversation about integration of supportive care and eventual consideration of hospice care should start early in the management of MBC.

See the clinical algorithm (Figs 1 and 2) for a graphical representation of the recommendations.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. 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.net.

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.

versus endocrine therapy in ER-positive first relapse metastatic breast cancer? (2) Is there an optimal first-line chemotherapy and/or targeted therapy regimen for patients with HER2-negative advanced breast cancer? (3) Is there an optimal second- or greater-line chemotherapy and/or targeted therapy regimen? and (4) At what point should anticancer therapy be discontinued? Accompanying subquestions were also included for questions for (2), (3), and (4). Because of advances in treatment since 2014, the research questions were re-examined and revised by the reconvened panel.

The present update was prompted largely by the recent publication of multiple clinical trials relevant to patients with metastatic breast cancer (MBC). For patients with metastatic hormone receptor (HR)–positive disease that has progressed on a nonsteroidal aromatase inhibitor (AI), these include the BOLERO-6[3] and PEARL[4] trials. For patients with metastatic triple-negative breast cancer (both HR-negative and HER2-negative), these include the ASCENT trial,[5] the TNT trial,[6] CALGB 40502/NCCTG N063H,[7] and the EMBRACE trial.[8] For patients with metastatic triple-negative breast cancer with expression of programmed cell death ligand-1 (PD-L1–positive tumors), these include the IMpassion130[9] and KEYNOTE-355[10] trials. For patients with MBC with germline *BRCA1 or 2* mutations, these include the OlympiAD[11] and EMBRACA[12] trials.

Note that although this guideline provides recommendations for chemotherapy and targeted therapy for patients with HER2-negative MBC that is either endocrine-pretreated or HR-negative, a companion guideline provides endocrine therapy (ET) and targeted therapy recommendations, including cyclin-dependent kinase (CDK) 4/6 and PI3 kinase inhibition, for HR-positive MBC patients.[13]

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: (1) Is there an optimal sequence of chemotherapy and/or targeted therapy (first-line, second-line, or greater) for patients with triple-negative metastatic breast cancer (with or without *BRCA1* or *BRCA2* germline mutations)? (2) What are the indications for chemotherapy versus endocrine therapy in endocrine-pretreated ER-positive metastatic breast cancer? (3) Is there an optimal sequence of nonendocrine agents for patients with hormone receptor–positive but HER2-negative metastatic breast cancer who are no longer benefiting from endocrine therapy (with or without *BRCA1* or *BRCA2* germline

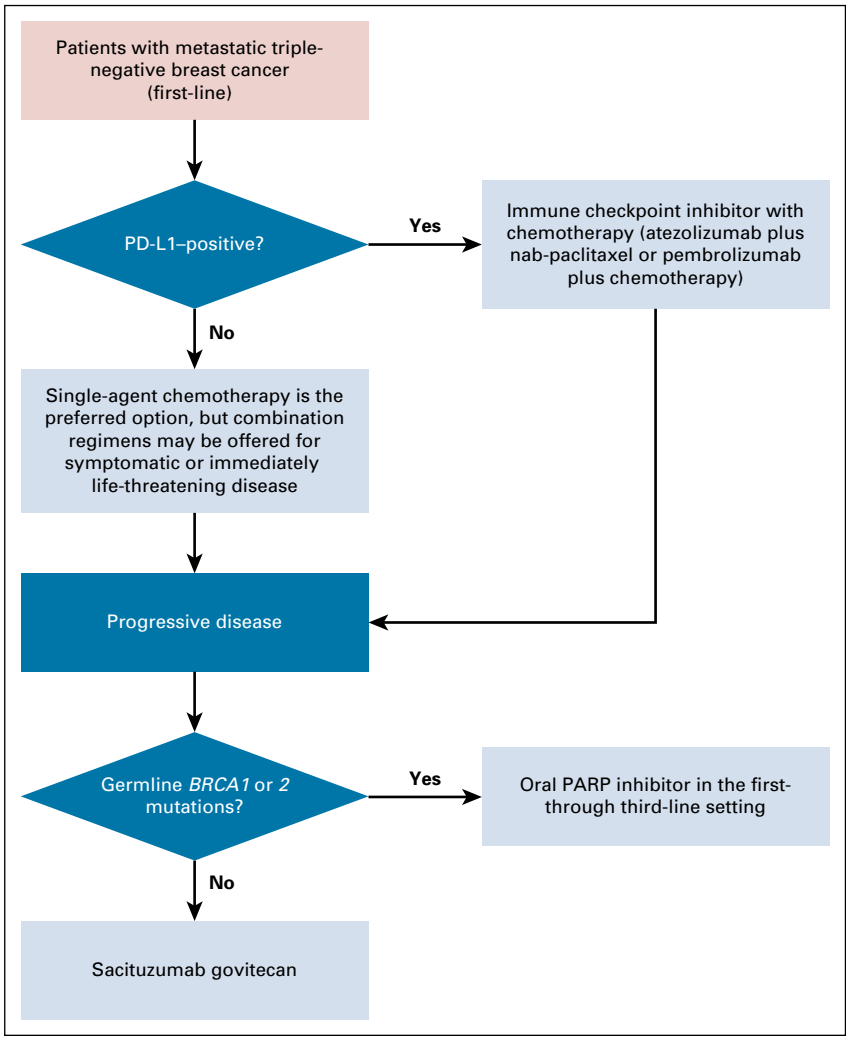

FIG 1. Treatment algorithm for first-line treatment for patients with metastatic triple-negative breast cancer. PARP, poly (ADP-ribose) polymerase.

mutations)? (4) At what point should a patient be transitioned to hospice or best supportive care only?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included patient representatives and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via teleconference or webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of PubMed (January 1, 2014-February 29, 2020; updated with a targeted search in April 2021), with or without meta-analysis, phase II or III randomized clinical trials (RCTs), and clinical experience. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Population: Women or men with HER2-negative MBC that is HR-positive but endocrine-pretreated or triple-negative

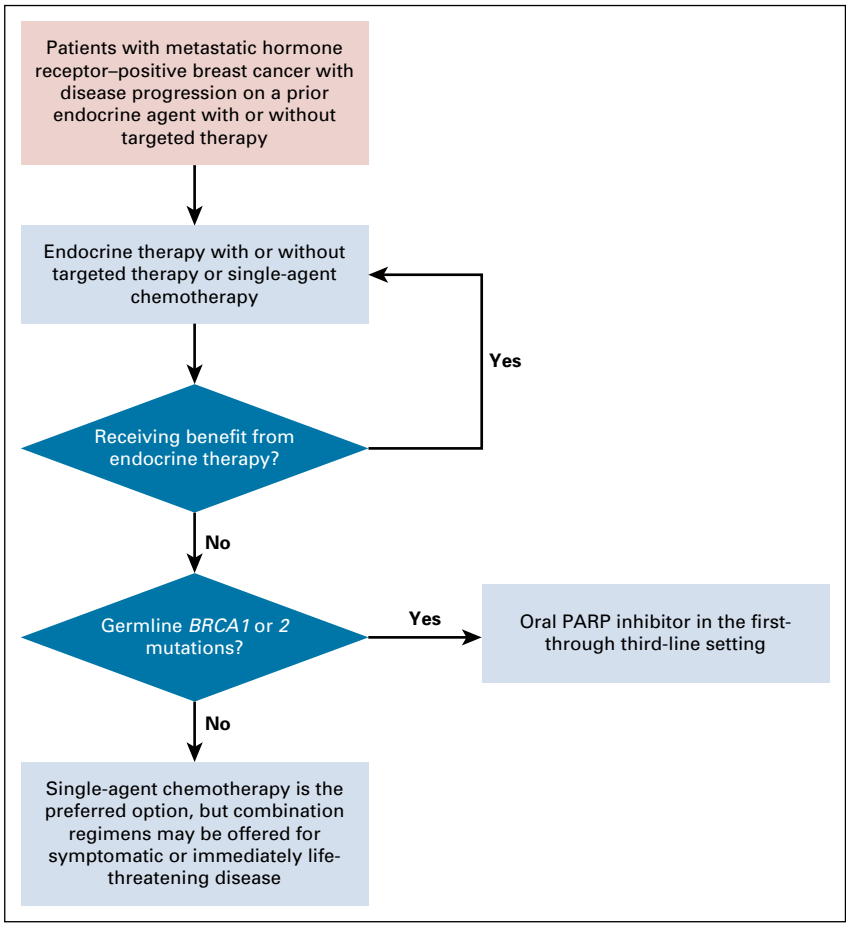

FIG 2. Treatment algorithm for chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death ligand-1.

- Fully published English-language reports of phase II or III RCTs or systematic reviews, with or without meta-analysis.

Articles were excluded from the systematic review if they were (1) meeting abstracts; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[14] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. Any updated searches would be restricted to articles published in English and to phase III RCTs or systematic reviews, with or without meta-analysis. 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.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). 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.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 14 papers published from 2015 to 2021 were obtained for this guideline update, comprising two systematic reviews,[15,16] one clinical practice guideline,[17] three trials that compared chemotherapy against endocrine-based treatment,[3,4,18] four that compared chemotherapy against chemotherapy,[5-8] two that compared chemotherapy and immunotherapy against chemotherapy,[9,10] and two that compared PARP inhibitors against chemotherapy.[11,12] The primary outcome for most of these trials was progression-free survival (PFS), although many also reported on overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR), quality of life (QoL), and severe adverse effects. See Table 1 for the results of the systematic reviews and clinical practice guidelines and Table 2 for the results of the randomized trials.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Manual for more information and definitions of ratings for overall potential risk of bias. For systematic reviews, quality was assessed using the A MeaSurement Tool to Assess systematic Reviews[20] (AMSTAR-2), tool and for clinical practice guidelines, the Appraisal of Guidelines, Research and Evaluation[21] (AGREE 2) tool was used. Grading of Recommendations, Assessment, Development and Evaluations[22] (GRADE) was used to assess the risk of bias for all the included randomized trials.

For the two systematic reviews, the review by Wilson et al[16] scored 9.5 of 15 on AGREE-2 because of several missing items on the checklist, including no a priori protocol described, data extraction was not performed in duplicate, no list of excluded studies provided, funding sources for included studies were not reported, individual studies of risk of bias were not explicitly considered when interpreting the results of the review. The review by Egger et al[15] scored 15 of 15 with no deficits in reporting or process. For the single clinical practice guideline obtained, reported by Giordano et al,[17] AGREE-2 scores were low because of deficits in reporting.

As seen in Table 2, the certainty level of the evidence was formally assessed using GRADE for the 11 RCTs identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as risk of bias, inconsistency, indirectness, and publication bias generally indicating a moderate to high certainty level of the evidence for the identified evidence, with a moderate rating associated with open-label trials. Refer to Methodology Manual for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

Clinical Question 1

Is there an optimal sequence of chemotherapy and/or targeted therapy (first-line, second-line, or greater) for patients with triple-negative MBC (with or without *BRCA1* or *BRCA2* germline mutations)?

Recommendation 1.1. Patients with metastatic triple-negative breast cancer with expression of programmed

TABLE 1. Main Findings From Systematic Reviews and/or Meta-Analyses

Study	Publication Type	Evidence-Base	Main Findings	Quality Assessment Score
Wilson et al[16]	Systematic review with network meta-analysis	57 RCTs that examined PFS results for AI plus palbociclib *v* chemotherapy agents	First-line therapy: 22 studies including a total of 8,152 patients detected a PFS benefit for palbociclib plus letrozole compared with capecitabine (intermittent) or mitoxantrone (fixed effects model and same analysis performed using the random-effects model were nonsignificant) Second-line therapy: 44 studies including 14,708 patients detected a PFS benefit for palbociclib plus letrozole compared with capecitabine (both intermittent and continuous), mitoxantrone, and pegylated liposomal doxorubicin	AMSTAR-2 score: 9.5 of 15 (qualitative summary question #15 N/A). Missed items were the following: No a priori protocol was described Data extraction was not performed in duplicate No list of excluded studies was provided Funding sources for the included studies were not reported Individual studies' RoB was not explicitly considered when interpreting the results of the review
Egger et al[15]	Systematic review (Cochrane)	10 studies including 1,349 women examining platinum-containing regimens *v* nonplatinum regimens in TNBC	Analysis suggests that platinum-containing regimens might have demonstrated small survival benefits to patients with mTNBC (hazard ratio, 0.85; 95% CI, 0.73 to 1.00; 958 women; moderate-quality evidence) with no evidence of heterogeneity ($P = .41$; $I^2 = 1\%$). Platinum regimens may improve PFS/TTP (hazard ratio, 0.77; 95% CI, 0.68 to 0.88; 1,077 women; very low-quality evidence); however, there was marked evidence of heterogeneity in that analysis ($P < .0001$; $I^2 = 80\%$). There was low-quality evidence of better tumor response for platinum recipients (RR, 1.40; 95% CI, 1.22 to 1.59; 1,205 women) with evidence of heterogeneity ($P = .01$; $I^2 = 58\%$). The observed heterogeneity for the PFS/TTP and OTRR outcomes may reflect between-study differences and general difficulties in assessing tumor response, as well as the varying potencies of the comparators Compared with women receiving nonplatinum regimens: rates of grade 3 and 4 nausea or vomiting were higher for platinum recipients (RR, 4.77; 95% CI, 1.93 to 11.81; 655 women; low-quality evidence) and rates of grade 3 and 4 anemia were higher for platinum recipients (RR, 3.80; 95% CI, 2.25 to 6.42; 843 women; low-quality evidence). In general, however, relatively few intervention comparisons could be included in meta-analyses for adverse events	AMSTAR-2 score: 15 of 15 (qualitative summary question #15 N/A)
Giordano et al[17]	Guidelines	NCCN Guidelines Update Sequence of chemotherapy and/or targeted therapy (first-line, second-line, or greater) in patients with triple-negative metastatic breast cancer (with or without *BRCA1* or *BRCA2* germline mutations)	If not previously used in the neoadjuvant or adjuvant setting, first-line chemotherapy should be a taxane (paclitaxel is the preferred agent) or anthracycline Sequential single agents are the preferred approach Combination therapy has demonstrated higher response rates but are not associated with improved overall survival and are an option in response to visceral crisis Although eribulin and capecitabine and platins are possibly superior to gemcitabine and vinorelbine, line of therapy *v* agents used may be more predictive of response Resistance to chemotherapy can develop quickly, and lines of treatment past the second have demonstrated diminished returns	AGREE-2 score: Domain 1: scope and purpose: 33% Domain 2: stakeholder involvement: 11% Domain 3: rigor of development: 23% Domain 4: clarity of presentation: 17% Domain 5: applicability: 0 Domain 6: editorial independence: 8% Overall guideline assessment: Overall quality: 6 Recommended: Yes

Abbreviations: AI, aromatase inhibitor; mTNBC, metastatic triple negative breast cancer; N/A, not applicable; NCCN, National Comprehensive Cancer Network; OTRR, objective tumor response rate; PFS, progression-free survival; RCT, randomized clinical trial; RoB, risk of bias; RR, relative risk; TNBC, triple-negative breast cancer; TTP, time to progression.

cell death ligand-1 (PD-L1–positive) and no existing contraindications may be offered the addition of immune checkpoint inhibitor to chemotherapy (atezolizumab plus nab-paclitaxel or pembrolizumab plus chemotherapy) as first-line therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Literature update and analysis. Patients with metastatic PD-L1–positive triple-negative breast cancer.

The systematic review identified two studies that support the use of checkpoint inhibitors for patients with metastatic PD-L1–positive triple-negative breast cancer. The IMpassion130[9] trial analyzed the safety and efficacy of the checkpoint inhibitor atezolizumab with nab-paclitaxel in patients with metastatic triple-negative breast cancer who had not received treatment in the metastatic setting. IMpassion130 randomly assigned 902 patients to receive nab-paclitaxel with atezolizumab or placebo. Analyses revealed that the addition of atezolizumab modestly improved PFS in the entire study population. However, in a prospectively planned subset analysis, the addition of atezolizumab improved both PFS and OS in the PD-L1–positive subset of patients. The PFS was 7.5 versus 5 months, hazard ratio = 0.62, 95% CI, 0.49 to 0.78, and the OS was 25 versus 15.5 months, hazard ratio = 0.62, 95% CI, 0.45 to 0.86. Final OS analysis at a 20-month follow-up demonstrated continuous improved survival in the PD-L1–positive subset with the addition of atezolizumab to nab-paclitaxel when compared with placebo (25 *v* 18 months). Adverse events were similar in both treatment arms with 23% of patients receiving atezolizumab experiencing thyroid disease and approximately 10% with other immune-related adverse events. There were three treatment-related deaths among the 451 patients who received atezolizumab (0.7%). Adverse events led to treatment discontinuation in 16% in the atezolizumab arm versus 8% in the control arm. In the IMpassion130 study, PD-L1 positivity was defined as tumor-infiltrating immune cells of any intensity staining ≥ 1% of the tumor area using the SP142 antibody.

The KEYNOTE-355[10] trial analyzed the safety and efficacy of chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) with the checkpoint inhibitor pembrolizumab or placebo in 847 patients with previously untreated metastatic triple-negative breast cancer. Overall, the addition of pembrolizumab resulted in a modest improvement in median PFS (7.5 *v* 5.6 months; hazard ratio, 0.82; 95% CI, 0.69 to 0.97). The results were stratified according to combined positive score (CPS), ie, the percentage of total cells (tumor cells, lymphocytes, and macrophages) that stain for PD-L1 using the 22C3 antibody. The results suggested that benefit was limited to patients with CPS ≥ 10, for whom the addition of pembrolizumab to chemotherapy improved median PFS by approximately 2 months (9.7 *v* 5.6 months; hazard ratio, 0.65; 95% CI, 0.49 to 0.86). Severe adverse events were comparable between the two groups (grade 3 and 4 events were approximately 70%), although one patient in the pembrolizumab arm died from treatment-related toxicity. OS data have not yet been reported.

Clinical interpretation. The risks of adding checkpoint inhibitor–mediated immune therapy to a patient's chemotherapy should be considered on an individual basis, particularly for patients with a history of autoimmune disease. Although IMpassion130 did demonstrate a survival benefit, crossover to atezolizumab in the placebo arm was not permitted on study.

Of importance, the results of IMpassion131 have been reported in an abstract.[23] This phase III randomized study showed that the addition of atezolizumab to paclitaxel did not improve median PFS in the PD-L1–positive subgroup of patients (6.0 *v* 5.7 months; hazard ratio, 0.82; $P = .20$). Therefore, atezolizumab for metastatic PD-L1–positive triple-negative breast cancer (TNBC) should be paired with nab-paclitaxel, not paclitaxel.

Of note, there were some differences in the inclusion criteria between the IMpassion130 and KEYNOTE-355 clinical trials. For example, patients must have completed operable therapy at least 12 months before enrollment in IMpassion 130 compared with at least 6 months in KEYNOTE-355. Furthermore, both trials had different definitions of PD-L1 positivity. In KEYNOTE-355, a CPS of ≥1 with the (US) Food and Drug Administration (FDA)–approved 22C3 PD-L1 IHC assay was required, whereas in IMpassion130, an immune cell score of ≥1% with the Ventana SP142 antibody was required.

Recommendation 1.2. Patients with metastatic triple-negative breast cancer without expression of programmed cell death ligand-1 (PD-L1–negative) should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Patients may be offered either platinum-based or nonplatinum-based regimens on the basis of individualized patient and provider assessment of preferences, risks, and benefits.

Literature update and analysis. Patients with metastatic PD-L1–negative triple-negative breast cancer.

A meta-analysis[15] of 10 randomized trials comparing platinum-containing versus nonplatinum-containing regimens in 958 women with metastatic TNBC revealed that the death rate at 1 year in the platinum group was 46% versus 51% in the nonplatinum group (hazard ratio, 0.85; 95% CI, 0.73 to 1.00). However, grade 3 and 4 toxicities were higher

TABLE 2. Trial Outcomes

Source	Intervention or Comparisons	Primary End Points	No. of Patients Randomly Assigned (evaluated)	Survival		Overall Response Rate, %	CBR, %	QoL	Grade 3-5 Adverse Events, %	GRADE Certainty Level Score
				OS	PFS					
Chemotherapy *v* endocrine therapy										
Martin et al[4] PEARL NCT02028507	Cohort 1: palbociclib plus exemestane *v*	PFS	Cohort 1, ESR1 wild-type patients: 104		8.0 months	27.8	NR	NR	4.0	Moderate
	Capecitabine		89		10.6 months adjusted hazard ratio, 1.11; 95% CI, 0.87 to 1.41; $P = .404$	36.9	NR	NR	10.4	
	Cohort 2: palbociclib plus fulvestrant *v*		Cohort 2, ESR1 wild-type patients: 102		7.5 months	26.7	NR	NR	3.4	
	Capecitabine		98		10.0 months adjusted hazard ratio, 1.13; 95% CI, 0.85 to 1.50; $P = .398$	33.3	NR	NR	10.4	
Park et al[18] NCT02592746	Palbociclib plus endocrine	PFS	92	NR, median survival not reached at a 17-month follow-up	20.1 months	37	80	NR	2	Moderate
	Capecitabine		86		14.4 months hazard ratio, 0.659; 95% CI, 0.437 to 0.994; $P = ·02$	34	67	NR	17	
Jerusalem et al[3] BOLERO-6 NCT01783444	Everolimus plus exemestane	PFS	104	23.1 months	8.4 months	20 (90% CI, 13.9 to 27.8)	57 (90% CI, 48.2 to 65.0)	NR	36	Moderate
	Everolimus		103	29.3 months Everolimus plus exemestane *v* everolimus: hazard ratio, 1.27; 90% CI, 0.95 to 1.70; $P =$ NS, NR	6.8 months Everolimus plus exemestane *v* everolimus: hazard ratio, 0.74; 90% CI, 0.57 to 0.97; $P < .05$, NR	12 (90% CI, 6.9 to 18.2)	42 (90% CI, 33.5 to 50.3)	NR	29	
	Capecitabine		102	25.6 months Everolimus plus exemestane *v* capecitabine: hazard ratio, 1.33; 90% CI, 0.99 to 1.79; $P =$ NS, NR	9.6 months Everolimus plus exemestane *v* capecitabine: hazard ratio, 1.26; 90% CI, 0.96 to 1.66; $P =$ NS, NR	23 (90% CI, 15.9 to 30.4)	52 (90% CI, 43.4 to 60.5)	NR	29	
Chemotherapy *v* chemotherapy										
Bardia et al[5] ASCENT	Sacituzumab govitecan	PFS	235 without brain metastases	12.1 months	5.6 months	35	45	NR	15	High
	One of either eribulin, vinorelbine, capecitabine, or gemcitabine		233 without brain metastases	6.7 months Hazard ratio, 0.48; 95% CI, 0.38 to 0.59; $P < .001$	1.7 months Hazard ratio, 0.41; 95% CI, 0.32 to 0.52; $P < .001$	5	9	NR	8	

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TABLE 2. Trial Outcomes (continued)

Source	Intervention or Comparisons	Primary End Points	No. of Patients Randomly Assigned (evaluated)	Survival		Overall Response Rate, %	CBR, %	QoL	Grade 3-5 Adverse Events, %	GRADE Certainty Level Score
				OS	PFS					
Tutt et al[6] TNT	Carboplatin	ORR	All patients: 188 *BRCA 1/2*: 25	All patients: 12.8 months *BRCA 1/2*: NR, NS	All patients: 3.1 months *BRCA 1/2*: 6.8 months	All patients: 31 *BRCA 1/2*: 68	NR	NR	NR	Moderate
	Docetaxel		All patients: 188 *BRCA 1/2*: 18	All patients: 12 months 95% CI: 10.2 to 13.0; $P = .96$ *BRCA 1/2*: NR, NS	All patients: 4.4 months 95% CI, 2.4 to 4.2; $P = .4$ *BRCA 1/2*: 4.4 months $P = .002$	All patients: 34 absolute difference: 2.6%; 95% CI, −12.1 to 6.9; $P = .66$ *BRCA 1/2*: 33.3 $P = .03$	NR	NR	NR	
Rugo et al[7] CALGB 40502/ NCCTG N063H NCT00785291	Paclitaxel	PFS	283 (275)	27.4 months	11 months	38	NR	NR	22	High
	Nab-paclitaxel		271 (267)	26.5 months *v* paclitaxel: hazard ratio, 1.17; 95% CI, 0.92 to 1.47; $P = .20$	9.3 months *v* paclitaxel: hazard ratio, 1.20; 95% CI, 1.00 to 1.45; $P = .054$	34 *v* paclitaxel: OR = 0.84; $P = .33$	NR	NR	55	
	Ixabepilone		245 (241)	23.6 months *v* paclitaxel: hazard ratio, 1.31; 95% CI, 1.03 to 1.66; $P = .027$	7.4 months *v* paclitaxel: hazard ratio, 1.59; 95% CI, 1.31 to 1.93; $P < .001$	27% *v* paclitaxel: OR = 0.57; $P = .0038$	NR	NR	12	
Kaufman et al[8] EMBRACE NCT00337103	Eribulin	OS and PFS	554 previously treated with an anthracycline and a taxane	15.9 months	4.1 months	11	26.2	NR	17.5	Moderate
	Capecitabine		548 previously treated with an anthracycline and a taxane	14.5 months Hazard ratio, 0.88; 95% CI, 0.77 to 1.00; $P = .056$	4.2 months Hazard ratio, 1.08; 95% CI, 0.93 to 1.25; $P = .30$	11.5	26.8 $P = .84$	NR $P = .958$	21.1	
Immunotherapy *v* chemotherapy										
Cortes et al[10] KEYNOTE-355 NCT02819518	Pembrolizumab plus chemotherapy	PFS and OS	566	NR	For patients with CPS ≥ 10: 9.7 months For patients with CPS ≥ 1: 7.6 months	NR	NR	NR	68	High
	Placebo plus chemotherapy		281	NR	For patients with CPS ≥ 10: 5.6 months Hazard ratio for progression or death, 0.65; 95% CI, 0.49 to 0.86; one-sided $P = \cdot.012$ For patients with CPD ≥ 1: 5.6 months Hazard ratio, 0.74; 95% CI, 0.61 to 0.90; one-sided $P = \cdot.014$	NR	NR	NR	67	

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TABLE 2. Trial Outcomes (continued)

Source	Intervention or Comparisons	Primary End Points	No. of Patients Randomly Assigned (evaluated)	Survival		Overall Response Rate, %	CBR, %	QoL	Grade 3-5 Adverse Events, %	GRADE Certainty Level Score
				OS	PFS					
Schmid et al[9] IMpassion130 NCT02425891	Atezolizumab plus nab-paclitaxel	PFS	451	All patients: 21.3 months Patients with PD-L1–positive tumors: 25.0 months	All patients: 7.2 months Patients with PD-L1–positive tumors: 7.5 months	All patients: 56 months Patients with PD-L1–positive tumors: 58.9 months	NR	NR	All patients: 48.7	High
	Placebo plus nab-paclitaxel		451	All patients: 17.6 months Hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; $P = .08$ Patients with PD-L1–positive tumors: 15.5 months Hazard ratio, 0.62; 95% CI, 0.45 to 0.86; $P < .05$	All patients: 5.5 months Hazard ratio for progression or death, 0.80; 95% CI, 0.69 to 0.92; $P = .002$ Patients with PD-L1–positive tumors: 5.0 months Hazard ratio, 0.62; 95% CI, 0.49 to 0.78; $P < .001$	All patients: 45.9 Patients with PD-L1–positive tumors: 42.6	NR	NR	All patients: 42.2	
PARP inhibitors *v* chemotherapy, TN patients										
Litton et al[12] EMBRACA NCT01945775	Talazoparib	PFS	130 TN patients of 287 total patients with *BRCA 1/2* mutations	All patients: 22.3 months		All patients: 62.6	All patients: 68.6 at 24 weeks	NR	All patients: 55	Moderate
	Standard therapy (capecitabine, eribulin, gemcitabine, or vinorelbine)		60 TN patients of 144 total patients with *BRCA 1/2* mutation	All patients: 19.5 months Hazard ratio, 0.76; 95% CI, 0.55 to 1.06; $P = .11$	Hazard ratio for progression or death, 0.60; 95% CI, 0.41 to 0.87; $P < .05$, NR (N = NR, favors talazoparib)	All patients: 27.2	All patients: 36.1 at 24 weeks	NR	All patients: 38	

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TABLE 2. Trial Outcomes (continued)

Source	Intervention or Comparisons	Primary End Points	No. of Patients Randomly Assigned (evaluated)	Survival		Overall Response Rate, %	CBR, %	QoL	Grade 3-5 Adverse Events, %	GRADE Certainty Level Score
				OS	PFS					
Robson et al[11] QoL[19] OlympiAD NCT02000622	Olaparib	PFS	102 TN patients of 205 total with *BRCA 1/2* mutation	All patients: 54.1%	Progression events: 79.4%	NR	NR	All patients reporting improvements according to QLQ-C30 Fatigue: 32.7% Pain: 34.6% Nausea or vomiting: 16.6% Dyspnea: 18% Insomnia: 23.9% Appetite loss: 19.5% Constipation: 16.6% Diarrhea: 11.2%	All patients: 36.6	Moderate
	Standard therapy (capecitabine, eribulin, or vinorelbine)		48 TN patients of 97 total with *BRCA 1/2* mutation	All patients: 52.6% P = NS, NR	Progression events: 83.3% Hazard ratio, 0.43; 95% CI, 0.29, 0.63; $P < .05$, NR	NR	NR	All patients reporting improvements according to QLQ-C30 Fatigue: 18.6% Pain: 16.5% Nausea or vomiting: 13.4% Dyspnea: 7.2% Insomnia: 12.4% Appetite loss: 8.2% Constipation: 5.2% Diarrhea: 7.2%	All patients: 50.5	
PARP inhibitors *v* chemotherapy, hazard ratio+ patients										
Litton et al[12] EMBRACA NCT01945775	Talazoparib	PFS	157 hazard ratio+ patients of 287 total patients with *BRCA 1/2* mutations	All patients: 22.3 months		All patients: 62.6%	All patients: 68.6% at 24 weeks	NR	All patients: 55	Moderate
	Standard therapy (capecitabine, eribulin, gemcitabine, or vinorelbine)		84 hazard ratio+ patients of 144 total patients with *BRCA 1/2* mutations	All patients: 19.5 months Hazard ratio, 0.76; 95% CI, 0.55 to 1.06; P = .11	Hazard ratio for progression or death, 0.47; 95% CI, 0.32 to 0.71; $P < .05$, NR (N = NR, favors talazoparib)	All patients: 27.2	All patients: 36.1 at 24 weeks	NR	All patients: 38	

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TABLE 2. Trial Outcomes (continued)

Source	Intervention or Comparisons	Primary End Points	No. of Patients Randomly Assigned (evaluated)	Survival		Overall Response Rate, %	CBR, %	QoL	Grade 3-5 Adverse Events, %	GRADE Certainty Level Score
				OS	PFS					
Robson et al[11] QoL[19] OlympiAD NCT02000622	Olaparib	PFS	103 hazard ratio+ of 205 total patients with *BRCA 1/2* mutation	All patients: 54.1%	Progression events: 79.6%	NR	NR	All patients reporting improvements according to QLQ-C30 Fatigue: 32.7% Pain: 34.6% Nausea or vomiting: 16.6% Dyspnea: 18% Insomnia: 23.9% Appetite loss: 19.5% Constipation: 16.6% Diarrhea: 11.2%	All patients: 36.6	Moderate
	Standard therapy (capecitabine, eribulin, or vinorelbine)		49 hazard ratio+ of 97 total patients with *BRCA 1/2* mutation	All patients: 52.6% *P* = NS, NR	Progression events: 63.3% Hazard ratio, 0.82; 95% CI, 0.55 to 1.26; *P* = NS, NR	NR	NR	All patients reporting improvements according to QLQ-C30 Fatigue: 18.6% Pain: 16.5% Nausea or vomiting: 13.4% Dyspnea: 7.2% Insomnia: 12.4% Appetite loss: 8.2% Constipation: 5.2% Diarrhea: 7.2%	All patients: 50.5	

Abbreviations: CBR, clinical benefit rate; CPS, combined positive score; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ITT, intent to treat; NR, not reported; NS, not significant; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; QoL, quality of life; TN, triple-negative.

among platinum recipients, including nausea or vomiting (relative risk, 4.8) and anemia (relative risk, 3.8).

Although not restricted to triple-negative breast cancer, the phase III CALGB 40502/NCCTG N063H[7] trial evaluated optimal first-line chemotherapy for patients with MBC. This trial randomly assigned 799 patients to receive paclitaxel versus nab-paclitaxel versus ixabepilone, all given with bevacizumab. The ixabepilone arm was closed at the first interim analysis for futility. The median PFS for paclitaxel was 11 months, ixabepilone was inferior to paclitaxel (PFS, 7.4 months; hazard ratio, 1.59; 95% CI, 1.31 to 1.93; $P <$ .001), and nab-paclitaxel was not superior to paclitaxel (PFS, 9.3 months; hazard ratio, 1.20; 95% CI, 1.00 to 1.45; $P = .054$). Although included in the trial according to treatment convention at the time, there is no biologically plausible rationale for an interaction of bevacizumab effect with the cytotoxic drugs studied in the trial.

The TNT[6] trial randomly assigned 376 patients with metastatic triple-negative breast cancer in the first-line treatment setting to treatment with carboplatin versus docetaxel. Overall response rates were similar between carboplatin and docetaxel (ORR, 31.4% *v* 34.0%, respectively; $P = .66$). The trial had a crossover design, and no statistically significant OS difference was seen by arm and type of initial treatment. Febrile neutropenia, diarrhea, alopecia, arthralgias, and peripheral neuropathy were more commonly seen in the docetaxel-treated group.

In 2018, NCCN issued a guideline[17] update that recommends first-line chemotherapy with a taxane (paclitaxel is the preferred agent) or an anthracycline, if not previously used in the neoadjuvant or adjuvant setting. It endorses sequential single-agent chemotherapy as the preferred approach.

Clinical interpretation. There is no single optimal first-line chemotherapy. Either platinum-based or nonplatinum-based regimens are appropriate, with a choice driven by individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 1.3. Patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease should be offered treatment with sacituzumab govitecan (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature update and analysis. Patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease.

The systematic review identified two studies of metastatic triple-negative breast cancer in third- or greater-line chemotherapy. The ASCENT[5] trial supports the use of sacituzumab govitecan for patients with metastatic triple-negative breast cancer who have received at least two prior therapies in the metastatic setting. Sacituzumab govitecan is an antibody drug conjugate that targets trophoblast cell-surface antigen 2 (Trop-2) with a humanized monoclonal antibody connected to SN-38, an active metabolite of the topoisomerase II inhibitor irinotecan.

The ASCENT[5] trial allocated 529 patients with metastatic TNBC who had received at least two prior lines of therapy to sacituzumab or single-agent chemotherapy of physician's choice (eribulin, capecitabine, gemcitabine, or vinorelbine). Among the 468 without brain metastases (the primary end point), sacituzumab govitecan improved PFS compared with standard therapy (median PFS 5.6 months *v* 1.7 months; hazard ratio, 0.41; $P <$ .0001). Sacituzumab govitecan also improved OS compared with standard therapy (median OS 12.1 months *v* 6.7 months; hazard ratio, 0.48; $P <$ .0001). The most common severe toxicities were neutropenia (51% *v* 33%), diarrhea (10% *v* < 1%), leukopenia (10% *v* 5%), anemia (8% *v* 5%), and febrile neutropenia (6% *v* 2%). Treatment discontinuation rate because of adverse events on sacituzumab govitecan was low (5%). On the basis of the results of this trial, the FDA approved the use of sacituzumab govitecan for treatment of metastatic TNBC who received two or more previous systemic therapies, with at least one therapy in the metastatic setting.

Although not restricted to triple-negative breast cancer, the phase III EMBRACE trial randomly assigned 1,102 patients with MBC who had received prior anthracycline and taxane to receive eribulin versus capecitabine. Approximately one quarter had triple-negative disease. The median OS for eribulin and capecitabine was 15.9 and 14.5 months, respectively (hazard ratio, 0.88; 95% CI, 0.77 to 1.00; $P = .056$). Median PFS times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (hazard ratio, 1.08; 95% CI, 0.93 to 1.25; $P = .30$). In the triple-negative subset, a prespecified secondary analysis suggested greater efficacy of eribulin (OS 14.4 *v* 9.4 months, hazard ratio = 0.70, 95% CI, 0.54 to 0.91; PFS 2.9 *v* 2.3 months, hazard ratio = 0.80, 95% CI, 0.61 to 1.05).[24] Global health status and overall quality-of-life scores over time were similar in the treatment arms.

Clinical interpretation. The PFS and OS advantage in heavily pretreated patients with reasonable toxicity profile makes the use of sacituzumab govitecan appropriate in the third- or later-line setting. The choice among other chemotherapy options in later-line settings should be driven by individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 1.4. Patients with metastatic triple-negative breast cancer with germline *BRCA1 or 2* mutations who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting may be offered an oral PARP inhibitor (olaparib or talazoparib) rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Literature update and analysis. Patients with metastatic triple-negative breast cancer with *BRCA* germline mutation.

The systematic review identified two studies that support the use of oral PARP inhibitors for patients with metastatic triple-negative breast cancer with *BRCA1 or 2* germline mutation and one study that analyzed the optimal chemotherapy choice for patients with metastatic triple-negative breast cancer with *BRCA1 or 2* germline mutation.

The OlympiAD[11] trial randomly assigned, in a 2:1 ratio, 302 patients with metastatic HR+ or triple-negative breast cancer to receive olaparib versus standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine). Among the 302 total patients, 102 patients had metastatic triple-negative disease. In the overall study population, median PFS was significantly longer in the olaparib group than in the standard therapy group (7.0 months vs 4.2 months; hazard ratio, 0.58; 95% CI, 0.43 to 0.80; $P < .001$). The rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard therapy group, and the rate of treatment discontinuation because of toxic effects was 4.9% and 7.7%, respectively. The PFS benefit of olaparib compared with standard therapy was more pronounced in the subset of 102 *BRCA* mutation carriers with metastatic triple-negative disease (PFS hazard ratio, 0.39; 95% CI, 0.2 to 0.57).

Similarly, the EMBRACA[12] trial randomly assigned, in a 2:1 ratio, 431 patients with metastatic HR+ or triple-negative breast cancer to receive talazoparib versus standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine). In the overall study population, median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months *v* 5.6 months; hazard ratio, 0.54; 95% CI, 0.41 to 0.71; $P < .001$). Hematologic grade 3-4 adverse events (primarily anemia) occurred in 55% of the patients who received talazoparib and in 38% of the patients who received standard therapy. Patient-reported outcomes favored talazoparib. In the 190 patients with triple-negative disease in the EMBRACA trial, talazoparib improved PFS relative to standard therapy (hazard ratio, 0.60; 95% CI, 0.41 to 0.87).

As described previously, the TNT[6] trial randomly assigned 376 patients with metastatic triple-negative breast cancer in the first-line treatment setting to treatment with carboplatin versus docetaxel. Overall response rates were similar between carboplatin and docetaxel (ORR, 31.4% *v* 34.0%, respectively; $P = .66$). However, among the 43 women with a known germline *BRCA1 or 2* mutation, carboplatin resulted in a higher response rate (68% *v* 33%; 95% CI, 6.3 to 63.1) and PFS (6.8 *v* 4.4 months; absolute difference 2.6 months, 95% CI, 0.11 to 5.12). However, the trial had a crossover design and no statistically significant OS difference was seen.

Clinical interpretation. It should be noted that both the OlympiAD and EMBRACA clinical trials randomly assigned patients to receive PARP inhibitor versus standard chemotherapy of physician's choice. However, standard chemotherapy did not include anthracyclines, taxanes, or platinums in these studies and generally represented drugs used in second- or later-line. Therefore, it is not known whether PARP inhibitors are superior to platinum, anthracycline, or taxane chemotherapy in the metastatic setting. Since PARP inhibitors and platinums have overlapping mechanisms of action and resistance mechanisms, the results of these trials should be interpreted in the context of ongoing and previous trials, especially of platinum therapy, in MBC patients with *BRCA1* or *2* germline mutations.

Clinical Question 2

What are the indications for chemotherapy versus endocrine therapy in endocrine-pretreated ER-positive metastatic breast cancer?

Recommendation 2.1. Patients with metastatic HR-positive breast cancer with disease progression on a prior endocrine agent with or without targeted therapy may be offered treatment with either ET with or without targeted therapy (refer to the companion ASCO guideline on Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer[13] for details) or single-agent chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Treatment choice should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Literature update and analysis. The systematic review identified three clinical trials and a meta-analysis addressing optimal therapy for women with metastatic HR-positive breast cancer with progressive disease on a nonsteroidal AI.

The phase II BOLERO-6[3] trial randomly assigned 309 patients whose disease had progressed on nonsteroidal AIs to three treatment regimens: everolimus plus exemestane versus everolimus alone versus capecitabine alone. The primary objective of the study was PFS for everolimus plus exemestane versus everolimus alone. Everolimus plus exemestane improved PFS compared with everolimus alone with hazard ratio of 0.74 (90% CI, 0.57 to 0.97). Everolimus plus exemestane had similar PFS compared

with capecitabine with hazard ratio of 1.26 (90% CI, 0.96 to 1.66). The investigators noted potential informative censoring between treatment arms and therefore performed a stratified multivariate Cox regression model to account for imbalances in baseline characteristics. This demonstrated a consistent hazard ratio for everolimus plus exemestane versus everolimus (hazard ratio, 0.73; 90% CI, 0.56 to 0.97), but the hazard ratio approached one for everolimus plus exemestane versus capecitabine (hazard ratio, 1.15; 90% CI, 0.86 to 1.52). Grade 3 to 4 adverse events were more frequent with capecitabine (74%; n = 75) versus everolimus plus exemestane (70%; n = 73) or everolimus alone (59%; n = 61). Serious adverse events were more frequent with everolimus plus exemestane (36%; n = 37) versus everolimus alone (29%; n = 30) or capecitabine (29%; n = 30).

The phase III randomized PEARL[4] trial for patients with metastatic HR-positive breast cancer resistant to AIs enrolled two cohorts. In cohort 1, 296 patients were allocated to palbociclib plus exemestane versus capecitabine. Because of concern regarding acquired ESR1 mutations and resistance to AIs, the protocol was amended and a second cohort of 305 patients were allocated to palbociclib plus fulvestrant versus capecitabine. The trial failed to meet either primary superiority end point, finding that palbociclib plus fulvestrant was not superior to capecitabine (median PFS: 7.5 *v* 10.0 months; adjusted hazard ratio, 1.13; 95% CI, 0.85 to 1.50), nor was palbociclib plus ET superior to capecitabine in wild-type *ESR1* patients (median PFS: 8.0 *v* 10.6 months; adjusted hazard ratio, 1.11; 95% CI: 0.87 to 1.41). The most frequent grade 3-4 toxicities with palbociclib plus exemestane, palbociclib plus fulvestrant, and capecitabine were neutropenia (57.4%, 55.7% and 5.5%), hand-foot syndrome (0%, 0%, and 23.5%), and diarrhea (1.3%, 1.3%, and 7.6%), respectively. Palbociclib plus ET demonstrated better QoL compared with capecitabine (adjusted hazard ratio for time to deterioration of global health status = 0.67; 95% CI, 0.53 to 0.85).

The randomized phase II KCSG-BR15-10[18] trial compared safety and efficacy of palbociclib plus ET versus capecitabine in premenopausal women with HR-positive breast cancer who had progressed on tamoxifen. This study randomly assigned 184 premenopausal women to receive either aromatase inhibitor-ovarian function suppression (AI-OFS) (exemestane plus leuprolide) plus palbociclib versus capecitabine. Treatment with AI-OFS plus palbociclib demonstrated improved PFS compared with capecitabine (20 *v* 14 months; hazard ratio, 0.66; 95% CI, 0.44 to 0.99). Nonhematologic toxicities were less common with AI-OFS plus palbociclib compared with capecitabine (grade 1-4: diarrhea, 13% *v* 39%; hand-foot syndrome, 1% *v* 100%, respectively), but hematologic toxicity was more common (grade ≥ 3 neutropenia, 64% *v* 16%, respectively).

A systematic review[16] compared ET plus palbociclib versus chemotherapy in metastatic HR-positive disease. In this review, a meta-analysis of 60 randomized controlled trials published from January 2000 to January 2016 demonstrated in the first line, palbociclib plus letrozole showed statistically significant improvements in PFS/TTP versus capecitabine (intermittent: hazard ratio, 0.28; 95% CI, 0.11 to 0.72) and mitoxantrone (hazard ratio, 0.28; 95% CI, 0.13 to 0.61) and trended toward improvements versus paclitaxel (hazard ratio, 0.59; 95% CI, 0.19 to 1.96), docetaxel (hazard ratio, 0.51; 95% CI, 0.14 to 2.03), and other monotherapy or combination agents (hazard ratios ranging from 0.24 to 0.99). In the second line, palbociclib plus fulvestrant showed statistically significant improvements in PFS/TTP versus capecitabine (intermittent: hazard ratio, 0.28; 95% CI, 0.13 to 0.65), mitoxantrone (hazard ratio, 0.26; 95% CI, 0.12 to 0.53), and pegylated liposomal doxorubicin (hazard ratio, 0.19; 95% CI, 0.07 to 0.50) and trended toward improvements versus paclitaxel (hazard ratio, 0.48; 95% CI, 0.16 to 1.44), docetaxel (hazard ratio, 0.71; 95% CI, 0.24 to 2.13), and other monotherapy or combination agents (hazard ratios ranging from 0.23 to 0.89).

Clinical interpretation. The treatment choice between ET with targeted agents such as CDK 4/6 inhibitors, everolimus, and alpelesib and single-agent chemotherapy should be based on individualized assessments of risks and benefits, prior treatment response, tumor burden, pace of disease, and patient preferences. Individual considerations should include the robustness of the patient's prior response to ET, QoL, side effects, comorbid conditions, and out-of-pocket treatment costs. Notably, the results of the systematic review should be interpreted with caution since there were significant limitations, including stage migration and unmeasured variables that might have led to patients enrolling in a chemotherapy rather than an ET clinical trial.

Clinical Question 3

Is there an optimal sequence of nonendocrine agents for patients with HR-positive but HER2-negative MBC that are no longer benefiting from ET (with or without *BRCA1* or *BRCA2* germline mutations)?

Recommendation 3.1. Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1 or 2* mutations who are no longer benefiting from ET may be offered an oral PARP inhibitor in the first-through to third-line setting rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Literature update and analysis. As described previously in Recommendation 2.4, the OlympiAD trial[11] randomly assigned, in a 2:1 ratio, 302 patients with metastatic HR-positive or triple-negative breast cancer to receive olaparib

versus standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine). Among the 302 total patients, 100 patients had metastatic HR-positive disease. In the overall study population, median PFS was significantly longer in the olaparib group than in the standard therapy group (7.0 months *v* 4.2 months; hazard ratio, 0.58; 95% CI, 0.43 to 0.80; $P < .001$). However, in the metastatic HR-positive subset of 100 *BRCA* mutation carriers, olaparib did not improve PFS compared with chemotherapy (hazard ratio for progression or death 0.91; 95% CI, 0.60 to 1.41).

Similarly, the EMBRACA[12] trial randomly assigned, in a 2:1 ratio, 431 patients with metastatic HR-positive or triple-negative breast cancer to receive talazoparib versus standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine). In the overall study population, median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months *v* 5.6 months; hazard ratio, 0.54; 95% CI, 0.41 to 0.71; $P < .001$). In the 241 *BRCA* mutation carriers with HR-positive disease in the EMBRACA trial, talazoparib improved PFS relative to standard therapy (hazard ratio, 0.47; 95% CI, 0.32 to 0.71).

Clinical interpretation. Given the lower toxicity of PARP inhibitors compared with chemotherapy, after 1-2 prior lines of ET, PARP inhibition is preferable to chemotherapy, although it should be noted that neither of these trials involved comparisons with taxanes or with platinums. Therefore, it is not known whether PARP inhibitors are superior to platinum or taxane chemotherapy in the metastatic setting.

Recommendation 3.2. Patients with HR-positive HER2-negative MBC no longer benefiting from ET should be offered single-agent chemotherapy rather than combination therapy, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Choice of chemotherapy agent should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Literature update and analysis. As described previously in Recommendation 2.2, the phase III CALGB 40502/NCCTG N063H[7] trial evaluated optimal first-line chemotherapy for patients with MBC. This trial randomly assigned 799 patients to receive paclitaxel versus nab-paclitaxel versus ixabepilone. All patients also received bevacizumab as part of the treatment protocol. The ixabepilone arm was closed at the first interim analysis for futility. The median PFS for paclitaxel was 11 months, and at 7.4 months, ixabepilone was inferior to paclitaxel (hazard ratio, 1.59; 95% CI, 1.31 to 1.93; $P < .001$). Nab-paclitaxel was also not superior to paclitaxel (PFS, 9.3 months; hazard ratio, 1.20; 95% CI, 1.00 to 1.45; $P = .054$).

Also, as described previously in Recommendation 2.2, NCCN[17] issued a guideline update that recommends first-line chemotherapy with a taxane (paclitaxel is the preferred agent) or an anthracycline, if not previously used in the neoadjuvant or adjuvant setting. It endorses sequential single-agent chemotherapy as the preferred approach.

Clinical Question 4

At what point should a patient be transitioned to hospice or best supportive care only?

Recommendation 4.1. No recommendation regarding at which point a patient's care should be transitioned to hospice or best supportive care only is possible at this time (Type: consensus; benefits/harms ratio unknown; Evidence quality: N/A; Strength of recommendation: strong).

Practical information. Given the heterogeneity of breast cancer and the treatment goals of patients with breast cancer, it is not possible to identify a universal optimal time to transition to hospice or best supportive care. When to transition is a decision that should be shared between the patient and clinician in the context of an ongoing conversation regarding goals of care.[25] The conversation about integration of supportive care and eventual consideration of hospice care should start early in the management of MBC.[26]

Literature update and analysis. The systematic review did not reveal any studies that provided evidence to guide a recommendation for this important question.

Clinical interpretation. Although direct evidence is lacking to inform the oncology community as to when the care of a patient be transitioned to hospice or best supportive care only, the consensus of the panel is that this is an individualized decision between the patient and clinician that involves complex factors. Ongoing and candid discussions about individual patient's treatment goals and preferences at the end of life are necessary. Balancing the risks and benefits of additional anticancer therapy with careful assessment of a patient's overall clinical status also helps to inform the optimal time for this transition. Related ASCO guidelines serve as additional resources.[13,25,26]

PATIENT AND CLINICIAN COMMUNICATION

All the following items were identified by the two patient representatives on the panel as key factors that both patients and clinicians should be aware of throughout the treatment continuum:

- These recommendations are independent of age, recognizing that treatment choices involve many more important considerations such as existing comorbidities, receptor status, patient preferences, and treatment outcome goals.
- Clarity in communications with patients is critical to frame appropriate expectations and informed decisions and to offer patients the chance to ask important

questions on the basis of individual QoL perspective and treatment goals.
- Highest-quality communications also include links or resources, staff such as nurse educators and social workers, to better understand guidelines and recommendations, opportunities for clinical trials, and second opinions.

Best care also involves access to support systems, including medical, nursing, education, psych, family, counseling, pharmacy/meds/side effects, social work, financial counseling, and similar resources.

There is a wide spectrum of patient perspectives so an open, honest, and ongoing dialogue between the patient, the physician, and the health care team is key to optimized outcomes.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[25]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[26] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[27-30] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[31]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population. Because many patients for whom guideline recommendations apply present with MCCs, any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs, highlighting the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

For female patients with breast cancer who are age under 65 years, the 10 most common comorbid conditions are hypertension, hyperlipidemia, depression, arthritis, anemia, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, and heart failure. For female patients with breast cancer who are over age 65 years, the 10 most common comorbid conditions are hypertension, hyperlipidemia, arthritis, anemia, ischemic heart disease, diabetes, cataracts, heart failure, depression, and chronic kidney disease. Refer to the table in the Data Supplement (online only) for details on the number of patients affected by these comorbid conditions and other supplementary information.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[32,33] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[34,35]

Discussion of cost can be an important part of shared decision making.[36] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[36]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which might have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[36]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data, agents that are not currently available in either the United States or Canada, and/or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from April 12, 2021, to April 26, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with the number of written comments received. As of April 19, 2021, 13 respondents had completed the open comment. A total of 93% of the 13 respondents either agreed or agreed with slight modifications to the recommendations and 7% of the respondents disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. The one recommendation that a respondent did not agree with was revised, as this was also noted in the external peer review. All changes were incorporated before Clinical Practice Guidelines Committee (CPGC) review and approval.

The draft was also submitted to three external reviewers (Dr Tiffany Traina, Dr Giuseppe Curigliano, and Dr Kevin Kalinsky) with content expertise. It was rated as high quality, and it was agreed that it would be useful in practice. Received comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the CPGC. Specifically, to better support Recommendation 1.1, some of the differences in inclusion criteria between the Impassion130 and KEYNOTE-355 trials with respect to prior therapy and differences in the definitions for PD-L1 positivity were elaborated on. Additionally, we noted that as a result of the ASCENT trial, the FDA approved the use of sacituzumab govitecan for treatment of metastatic TNBC for patients who received 2 or more prior systemic therapies, with at least one therapy in the metastatic setting, and this was added to the literature update and analysis section for Recommendation 1.3. This final revision also addressed the same item raised during the open comment.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative in the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation that a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. Other items raised during the PGIN review were the following:

- A practice may require access to a genetic counselor to offer germline mutation testing to all patients with MBC.
- Clinicians like pharmacists may not understand germline *BRCA1* and *2* versus somatic.
- The use of PARP inhibitors will require access to genetic testing and to a specialty pharmacy. Practices will need resources to assist patients with Foundation support, drug vouchers, copay assistance, etc.

The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the Journal of Clinical Oncology. See the Data Supplement for full results of the PGIN survey, which was completed by two clinician PGIN representatives on the expert panel.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

Next-generation sequencing (NGS) is an evolving technology in the management of advanced malignancies. The timing, application, and method (tissue *v* liquid biopsy) of NGS in HER2-negative, HR-positive, and negative breast tumors remain controversial (outside of PIC3KA testing as discussed in a 2015 ASCO guideline[37]). Improved understanding and management of heterogeneity within a metastatic site, between metastatic sites, and over time with the influence of time and selective drug pressures may improve the clinical utility of NGS.[38] The Expert Panel awaits the important clinical trial data from NCI-MATCH (EAY131; NCT02465060), ASCO TAPUR (NCT02693535), and other trials to provide informed guidance on the use of NGS in breast cancer. Likewise, therapies targeting germline mutations other than *BRCA1/2* (such as *PALB2*) illustrate promise for patients.[1]

Clinical trials remain the most important mechanism to improve the survival and QoL of patients with MBC and are crucial for optimizing current and future therapies.

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

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Endocrine Therapy and Targeted Therapy for Hormone Receptor–Positive, HER2-negative Metastatic Breast Cancer[13] (http://doi.org/10.1200/JCO.21.01392)
- Integration of Palliative Care into Standard Oncology Practice[26] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[25] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology (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, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update

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Research Funding: Syndax, Immunomedics, Novartis, NanoString Technologies, AbbVie, Seattle Genetics, Veracyte
Patents, Royalties, Other Intellectual Property: Royalty-sharing agreement, investorship interest in licensed IP to startup company, Falcon Therapeutics, that is designing neural stem-cell–based therapy for glioblastoma multiforme
Uncompensated Relationships: Sanofi, Novartis, G1 Therapeutics, Genentech/Roche, GlaxoSmithKline, AstraZeneca/Daiichi Sankyo, Aptitude Health, Exact Sciences, Eisai
Open Payments Link: https://openpaymentsdata.cms.gov/physician/179671

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update Expert Panel

Name	Affiliation or Institution	Role or Area of Expertise
Beverly Moy, MD, MPH, cochair	Massachusetts General Hospital, Boston, MA	Medical oncology
Lisa A. Carey, MD, ScM, cochair	UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC	Medical oncology
Avan Armaghani, MD	Moffitt Cancer Center, Tampa, FL	Medical oncology
Mariana Chavez-MacGregor, MD, MSc	MD Anderson Cancer Center, Houston, TX	Medical oncology
Steven E. Come, MD	Beth Israel Deaconess Medical Center, Boston, MA	Medical oncology
Michael A. Danso, MD	Virginia Oncology Associates, Norfolk, VA	Practice guidelines implementation network representative
Nancy E. Davidson, MD	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Medical oncology
Angelo Di Leo, MD, PhD[†]	Hospital of Prato, Istituto Toscano Tumori, Prato, Italy	Medical oncology
Natalie Dickson, MD, MMHC	Tennessee Oncology, Nashville, TN	Practice guidelines implementation network representative
Julie R. Gralow, MD	University of Washington, Seattle, WA	Medical oncology
Gabriel N. Hortobagyi, MD	MD Anderson Cancer Center, Houston, TX	Medical oncology
William J. Irvin Jr, MD	Bon Secours St Francis, Midlothian, VA	Medical oncology
Heather L. McArthur, MD, MPH	Cedars-Sinai, Los Angeles, CA	Medical oncology
Rita Nanda, MD	University of Chicago, Chicago, IL	Medical oncology
Cheryl L. Perkins, MD	Dallas, TX	Patient representative
Katherine E. Reeder-Hayes, MD, MBA, MS	UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC	Medical oncology
Kathryn J. Ruddy, MD	Mayo Clinic, Rochester, MN	Medical oncology
Ian E. Smith, MD	Royal Marsden Hospital, London, UK	Medical oncology
Laura Spring, MD	Massachusetts General Hospital, Boston, MA	Medical oncology
Sophie S. Turner, MD	New York, NY	Patient representative
Paul S. Unger, MD	University of Vermont Health Network, Burlington, VT	Medical oncology
Shaveta Vinayak, MD	Seattle Cancer Care Alliance and University of Washington, Seattle, WA	Medical oncology
Douglas Yee, MD	University of Minnesota, Minneapolis and Saint Paul, MN	Medical oncology
R. Bryan Rumble, MSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

NOTE. [†]Deceased.

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not