ASCO special articles

Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

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abstract

PURPOSE To update the ASCO Biomarkers to Guide Systemic Therapy for Metastatic Breast Cancer (MBC) guideline.

METHODS An Expert Panel conducted a systematic review to identify randomized clinical trials and prospective-retrospective studies from January 2015 to January 2022.

RESULTS The search identified 19 studies informing the evidence base.

RECOMMENDATIONS Candidates for a regimen with a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for *PIK3CA* mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine eligibility for alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used. Patients who are candidates for poly (ADP-ribose) polymerase (PARP) inhibitor therapy should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations to determine eligibility for a PARP inhibitor. There is insufficient evidence for or against testing for a germline *PALB2* pathogenic variant to determine eligibility for PARP inhibitor therapy in the metastatic setting. Candidates for immune checkpoint inhibitor therapy should undergo testing for expression of programmed cell death ligand-1 in the tumor and immune cells to determine eligibility for treatment with pembrolizumab plus chemotherapy. Candidates for an immune checkpoint inhibitor should also undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab, as well as testing for tumor mutational burden. Clinicians may test for *NTRK* fusions to determine eligibility for TRK inhibitors. There are insufficient data to recommend routine testing of tumors for *ESR1* mutations, for homologous recombination deficiency, or for TROP2 expression to guide MBC therapy selection. There are insufficient data to recommend routine use of ctDNA or circulating tumor cells to monitor response to therapy among patients with MBC.

Additional information can be found at www.asco.org/breast-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

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

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INTRODUCTION

ASCO published a guideline in 2015 on the use of biomarkers to guide decisions on systemic therapy for patients with metastatic breast cancer (MBC).[1] ASCO updates its guidelines at intervals determined by the Expert Panel leadership, on the basis of targeted literature searching and the expertise of ASCO guideline panel members to identify signals in the literature.[2] Signals are new, potentially practice-changing data that may translate into major revisions to current practice recommendations.

The Update Panel revisited recommendations from the 2015 guideline and expanded the scope of the guideline to address topics that have emerged since the publication of the 2015 guideline: testing for *PIK3CA* and *ESR1* somatic variants and germline *BRCA1*, *BRCA2*, and *PALB2* pathogenic variants (mutations) to guide therapy; testing tumors for homologous recombination deficiency (HRD), expression of programmed cell death ligand-1 (PD-L1), deficient mismatch repair/microsatellite instability (dMMR/MSI), tumor mutational burden (TMB), neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions, and trophoblast cell-surface antigen 2 (TROP2) expression to determine eligibility for selected treatments; and the use of cell-free, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) for monitoring treatment

THE BOTTOM LINE

Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

Guideline Question

For patients with metastatic breast cancer (MBC), which biomarkers should be used to guide decisions on systemic therapy?

Target Population

Patients with MBC being considered for systemic therapy or for changes in the drug or regimen they are receiving.

Target Audience

Oncology specialists, other health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), caregivers, and patients.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations

A quick summary of the 2022 recommendations is presented in Table 1. Refer to Appendix Table A3 for a list of all recommendations including the 2015 guidelines recommendations that did not require an update.

Recommendation 1.1. Patients with locally recurrent unresectable or metastatic hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)–negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and a hormonal therapy should undergo testing for *PIK3CA* mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.1. There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for hormone receptor–positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with *ESR1* mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 3.1. Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. There is insufficient evidence to support a recommendation either for or against testing for a germline *PALB2* pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statements. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* pathogenic variants and somatic *BRCA1/2* 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.[3,4]

Recommendation 4.1. There are insufficient data at present to recommend routine testing of tumors for homologous recombination deficiency to guide therapy for MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.1. Patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an immune checkpoint inhibitor (ICI) should

(continued on following page)

THE BOTTOM LINE (CONTINUED)

undergo testing for expression of programmed cell death ligand-1 in the tumor and immune cells with a US Food and Drug Administration–approved test to determine eligibility for treatment with the ICI pembrolizumab plus chemotherapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.1. Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 7.1. Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for tumor mutational burden to determine eligibility for pembrolizumab monotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 8.1. Clinicians may test for *NTRK* fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 9.1. There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor–negative, HER2-negative MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 10.1. There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 11.1. There are insufficient data to recommend routine use of circulating tumor cells to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). 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.

response. The complete list of recommendations can be found in Appendix Table A3 (online only).

The recommendations of the Update Panel are specifically focused upon biomarkers that aid clinicians in making therapeutic decisions. As such, these recommendations are informed by the US Food and Drug Administration (FDA) approval of medications that are approved with companion biomarker tests. In cases where such companion biomarkers tests exist, the Panel has noted the specific test(s) approved by the FDA for each indication. In some cases, there is controversy regarding the most accurate or appropriate test for a biomarker. Additional controversy surrounds biomarkers that accompany tumor-agnostic drug approvals. These approvals may have been based upon studies that did not include patients with breast cancer, or for biomarkers that are extremely rare in breast cancer, such as *NTRK* fusions. The Panel noted that, although there may be insufficient data to support testing all patients with MBC for such alterations, clinicians should be aware of these should they be incidentally detected, or for the patient who has exhausted all other treatment options. These controversies are discussed in the Clinical Interpretation section of each question. The clinician must weigh these issues, along with requirements to obtain therapy when making testing decisions for an individual patient.

FOCUSED GUIDELINE QUESTIONS

- Clinical question 1: What is the role of *PIK3CA* mutation testing to guide the decision to use alpelisib in patients with hormone receptor–positive MBC?
- Clinical question 2: What is the role of testing for *ESR1* mutations to guide therapy for hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative MBC?

- Clinical question 3: What is the role of testing for germline *BRCA 1/2* and *PALB2* pathogenic mutations to guide the decision to use an oral poly (ADP-ribose) polymerase (PARP) inhibitor in patients with hormone receptor–positive or hormone receptor–negative, HER2-negative MBC?
- Clinical question 4: What is the role of testing tumors for HRD in treatment selection for patients with MBC?
- Clinical question 5: What is the role of testing for expression of PD-L1 in the tumor and immune cells in patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an immune checkpoint inhibitor (ICI)?
- Clinical question 6: What is the role of testing for dMMR/microsatellite instability-high (MSI-H) in treatment selection for patients with MBC to identify candidates for ICI monotherapy?
- Clinical question 7: What is the role of testing for TMB for patients with MBC to identify candidates for ICI monotherapy?
- Clinical question 8: What is the role of testing for *NTRK* fusions in treatment selection for patients with MBC to identify candidates for treatment with tyrosine kinase inhibitors (larotrectinib or entrectinib)?
- Clinical question 9: What is the role of testing tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor–negative, HER2-negative MBC?
- Clinical question 10: What is the role of using ctDNA for monitoring response to treatment?
- Clinical question 11: What is the role of using CTCs for monitoring response to treatment?

METHODS

Guideline Update Process

ASCO uses a signals approach to facilitate guideline updating. This approach identifies new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted literature searching and the expertise of ASCO guideline panel members to identify signals.

This systematic review-based guideline product was developed by an ASCO multidisciplinary Expert Panel, which included a patient representative and an ASCO staff member with health research methodology expertise. The Expert Panel searched the PubMed database to identify any additional randomized clinical trials (RCTs) that addressed the update's main clinical questions. The electronic searches were supplemented by articles identified by Expert Panel members and by reviews of the bibliographies of relevant articles. The Methodology Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach. Additional information about the results of the updated literature search and search strategy strings is reported in the Data Supplement (online only).

The Expert Panel met one time by teleconference to consider the evidence for each of the 2022 recommendations. The guideline was circulated in draft form to the Expert Panel. The entire Expert Panel (Appendix Table A1, online only) contributed to the development of the guideline, provided critical review, and finalized the guideline recommendations. The ASCO Evidence Based Medicine Committee reviews and approves all ASCO guidelines before publication. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers 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 provider, 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 provider 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.

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 https://www.asco.org/guideline-methodology). All members of the Expert Panel completed

TABLE 1. At-a-Glance Guide to ASCO Biomarker Testing in Metastatic Breast Cancer Recommendations

Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker tests recommended by the ASCO expert panel			
PIK3CA	Evidence-based	High	Strong
Germline *BRCA1* and *BRCA2*	Evidence-based	High	Strong
PD-L1	Evidence-based	Intermediate	Strong
dMMR/MSI-H	Informal consensus-based	Low	Moderate
TMB	Informal consensus-based	Low	Moderate
NTRK fusions	Informal consensus-based	Low	Moderate
Biomarker tests not recommended by the ASCO expert panel			
ESR1	Evidence-based	Insufficient	Moderate
PALB2	Evidence-based	Low	Moderate
HRD	Informal consensus-based	Low	Moderate
TROP2 expression	Informal consensus-based	Low	Moderate
ctDNA	Informal consensus-based	Low	Moderate
CTCs	Informal consensus-based	Low	Moderate

Abbreviations: CTC, circulating tumor cell; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; PD-L1, programmed cell death ligand-1; TMB, tumor mutational burden.

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

Targeted PubMed literature searches (from January 1, 2015, to January 1, 2022) were conducted to identify articles on the biomarkers covered by the focused research questions (see the Data Supplement for the corresponding literature search strings). No signals for updating the 2015 guideline recommendations,[1] which address estrogen receptor/progesterone receptor testing, HER2 testing, and carcinoembryonic antigen testing, were identified by the Panel co-chairs via the formal update assessment they completed. Thus, no updated electronic searches were conducted on those topics. After review of the identified abstracts, 19 full-text articles met selection criteria and were included in the systematic review. With some notable exceptions, biomarker test articles were limited to studies that provided evidence for the clinical utility of the biomarker in question.[1,5] Articles selected for inclusion in the systematic review of the evidence were thus generally phase III RCTs or retrospective analyses of biologic samples from patients enrolled onto already completed prospective RCTs (prospective-retrospective studies). However, recommendations for use of dMMR/MSI, TMB, and *NTRK* gene fusions are based on Panel informal consensus in the absence of studies designed to evaluate the clinical utility of the markers specifically for treatment of MBC. These recommendations are informed by articles identified by the Expert Panel, including two articles that reported the results of analyses of the phase II KEYNOTE-158 study of pembrolizumab in patients with advanced solid tumors,[6,7] one article that reported results from the Targeted Agent and Profiling Utilization Registry (TAPUR) phase II basket trial analysis of single-agent pembrolizumab in patients with MBC,[8] and four articles that reported results of analyses related to *NTRK* gene fusions.[9-12] The Panel offers these recommendations, despite the paucity of data on the efficacy of either ICI monotherapy or NTRK inhibitor therapy in patients with MBC, in light of the FDA approvals of ICIs for the treatment of unresectable or metastatic dMMR/MSI-H or TMB-high solid tumors, and FDA approvals of tropomyosin receptor kinase (TRK) inhibitors for the treatment of tumors with *NTRK* gene fusions. The evidence supporting unchanged recommendations is reviewed in prior guideline publications.[1]

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; or (3) published in a non-English language. The results of articles included in the systematic review are summarized in the Data Supplement. Study quality was formally assessed (Data Supplement). Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally

indicating a low-to-intermediate potential risk of bias for most of the identified evidence. Refer to the Methodology Manual for definitions of ratings for overall potential risk of bias. QUOROM diagrams of the updated searches and the clinical questions are provided in the Data Supplement.

FOCUSED UPDATE RECOMMENDATIONS

Clinical Question 1

What is the role of *PIK3CA* mutation testing to guide the decision to use alpelisib in patients with hormone receptor–positive MBC?

Recommendation 1.1 (adapted from the ASCO endocrine treatment and targeted therapy for hormone receptor–positive, HER2-negative MBC guideline[4]). Patients with locally recurrent unresectable or metastatic hormone receptor–positive and HER2-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase (PI3K) inhibitor and a hormonal therapy should undergo testing for *PIK3CA* mutations using next-generation sequencing (NGS) of tumor tissue or ctDNA in plasma to determine their eligibility for treatment with the PI3K inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong; see the Burstein et al[4] guideline for the corresponding recommendation concerning the use of alpelisib in patients with PIK3CA-mutated, advanced breast cancer or MBC.

Literature review and analysis. Evidence from the SOLAR-1 trial[13-15] provides support for the clinical utility of biomarker testing to detect *PIK3CA* mutations in patients with hormone receptor–positive, HER2-negative MBC. Andre et al[13,14] evaluated the efficacy and safety of alpelisib-fulvestrant in two cohorts of patients, one cohort with PIK3CA-mutated cancer and one proof-of-concept cohort without *PIK3CA*-mutated cancer. Patients in both cohorts were randomly assigned to receive either alpelisib-fulvestrant or placebo-fulvestrant. The prolongation of progression-free survival (PFS) observed with alpelisib-fulvestrant in the cohort of patients with *PIK3CA*-mutated cancer was not observed in the cohort of patients without *PIK3CA*-mutated cancer, demonstrating clinical utility as evidenced by improved patient outcomes from the use of a tumor biomarker test result to select treatment strategy.[1,16]

In the final overall survival (OS) results from the SOLAR-1 trial, the authors reported that no statistically significant differences in OS were detected between treatment groups.[14] There was an improvement of 7.9 months in OS in the *PIK3CA*-mutated breast cancer cohort who received alpelisib-fulvestrant (39.3 months; 95% CI, 34.1 to 44.9) compared with patients who received placebo-fulvestrant (31.4 months; 95% CI, 26.8 to 41.3). However, the OS results did not cross the prespecified efficacy boundary. No new safety signals were seen in this follow-up analysis.

Analyses of specimens from patients enrolled in SOLAR-1 found low agreement between plasma ctDNA and tumor tissue identification of *PIK3CA* mutations, albeit with a non–error-corrected polymerase chain reaction (PCR)–based assay. Just 177 of 317 (56%) patients with *PIK3CA* mutations that were confirmed in tumor tissue were found to have *PIK3CA* mutations identified in the plasma specimen.[17] Given the risk of false-negative results and the low agreement between tumor tissue and ctDNA, the FDA-approved labeling recommends a reflex approach in which plasma testing is followed by tissue testing if no *PIK3CA* mutation is detected in a plasma specimen.[17] Although *PIK3CA* mutations can be found throughout all stages of breast cancer, mutations can be acquired during treatment in the metastatic setting. Therefore, every attempt should be made to test the most recent tumor tissue sample, and if no sample is available, in some cases, plasma testing may be a preferred first step.

Clinical interpretation. *PIK3CA* mutations are common in hormone receptor–positive, HER2-negative MBC. On the basis of data from the SOLAR-1 randomized phase III trial,[13] patients whose tumors harbored at least one of 11 specific *PIK3CA* mutations had prolonged PFS when treated with fulvestrant in combination with the PI3K inhibitor alpelisib compared with placebo, although no OS benefit has been demonstrated.[14] Therefore, testing of hormone receptor–positive, HER2-negative breast tumors for *PIK3CA* mutations in plasma and/or tumor specimens is indicated. As noted previously, it may be appropriate to perform noninvasive ctDNA testing of a plasma specimen initially, to have a recent sample from which to determine *PIK3CA* mutation status. However, a negative result from a plasma sample could represent a false-negative finding. Therefore, if the result is negative, testing of a tumor specimen with NGS should be performed when possible to minimize the risk of failing to identify a potential treatment option for a patient. A tumor specimen from a metastatic site should be tested when possible, since a *PIK3CA* mutation could have arisen since the original primary breast tumor was resected. Finally, it is important to note that eligibility for the SOLAR-1 *PIK3CA*-mutated cancer cohort required identification of at least one of 11 prespecified *PIK3CA* mutations in exons 7, 9, and 20. Therefore, caution is needed when NGS is performed to confirm that the identified *PIK3CA* mutation is one that was tested in the SOLAR-1 trial, since it is unknown whether other mutations are associated with response to PI3K inhibitor therapy.

Clinical Question 2

What is the role of testing for *ESR1* mutations to guide therapy for hormone receptor–positive, HER2-negative MBC?

Recommendation 2.1 (adapted from the ASCO endocrine treatment and targeted therapy for hormone receptor–positive, HER2-negative MBC guideline[4]). There are insufficient data at present to recommend routine testing for

ESR1 mutations to guide therapy for hormone receptor–positive, HER2-negative MBC. Existing data suggest reduced efficacy of AIs compared with the selective estrogen receptor degrader (SERD) fulvestrant in patients who have tumor or ctDNA with *ESR1* mutations (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review and analysis. The Expert Panel reviewed the available data on *ESR1* to guide therapy for hormone receptor–positive, HER2-negative MBC and concluded that there is no evidence for the clinical utility of testing for *ESR1* mutations.

Clinical interpretation. Although *ESR1* mutations are uncommon in primary breast cancer, data have demonstrated that they are more commonly detected in tumor biopsies from patients with MBC who have had at least one line of endocrine therapy in the metastatic setting. Retrospective analysis of two phase III trials[18] demonstrated that, for patients with *ESR1* mutations detected in baseline ctDNA analysis, fulvestrant improved PFS compared with exemestane in patients who had previously progressed on a nonsteroidal AI. To date, however, data are insufficient to support the clinical utility of *ESR1* mutation status for guiding treatment recommendations. There are ongoing clinical trials addressing this issue, including the PADA-1 trial, which is evaluating the effect of the switch to fulvestrant from AI therapy versus remaining on AI therapy when *ESR1* mutations are detected in the blood. However, although preliminary findings are suggestive of a possible PFS benefit from switching therapy, data have not yet been published.[19]

Clinical Question 3

What is the role of testing for germline *BRCA 1/2* and *PALB2* pathogenic mutations to guide the decision to use an oral PARP inhibitor in patients with hormone receptor–positive or hormone receptor-negative, HER2-negative MBC?

Recommendation 3.1. Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a PARP inhibitor should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong; see the Burstein et al[4] guideline for the corresponding recommendation concerning the use of the use of PARP inhibitors in the treatment of patients with HER2-negative MBC.

Literature review and analysis (adapted from the ASCO endocrine treatment and targeted therapy for hormone receptor–positive, HER2-negative metastatic breast cancer guideline[4]). The systematic literature review identified two RCTs that bear on the question of the role of *BRCA1/2* testing to guide the use of PARP inhibitors in the treatment of patients with HER2-negative MBC.[20-24] In an open-label, phase III RCT (OlympiAD), Robson et al[20] compared the efficacy and safety of the PARP inhibitor, olaparib (n = 205), with the efficacy and safety of standard therapy with single-agent chemotherapy (capecitabine, eribulin mesylate, or vinorelbine; n = 91) in women with HER2-negative MBC and a germline *BRCA* mutation. The primary end point was PFS. Median PFS was significantly longer in the group that received olaparib monotherapy than in the group that received standard chemotherapy (7.0 months *v* 4.2 months; hazard ratio [HR] for disease progression or death, 0.58; 95% CI, 0.43 to 0.80). The risk of disease progression or death in the olaparib group was 42% lower than in the standard therapy group, and the response rate was almost two times the response rate in the standard therapy group (59.9% *v* 28.8%). The rate of grade 3 or higher adverse events (AEs) in patients who received olaparib was 36.6%; it was 50.5% in the group that received standard chemotherapy. Health-related quality of life (QoL) measures were also superior with olaparib than with chemotherapy: treatment with olaparib led to improvements in the functioning, symptoms, and health-related QoL. One exception was the nausea and vomiting symptom score, which was worse among patients who received olaparib.[21]

In 2019, Robson et al[22] reported the results of the prespecified final analysis of OS in the OlympiAD study (at 64% data maturity) and on the long-term tolerability of olaparib. Analyses showed that, compared with chemotherapy treatment of physician's choice (TPC), there was no statistically significant improvement in OS with olaparib: median OS was 19.3 months with olaparib compared with 17.1 months with TPC (HR, 0.90; 95% CI, 0.66 to 1.23; $P = .513$). The safety profile in the OS analysis was comparable with that seen in the primary analysis and there was no evidence of cumulative toxicity with extended olaparib exposure.

Litton et al[24] reported the results of an open-label, phase III randomized controlled trial (EMBRACA) that compared the efficacy and safety of the PARP inhibitor, talazoparib (n = 287), with standard single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine; n = 144) for the treatment of advanced breast cancer in women with a germline *BRCA1/2* mutation. Median PFS in the talazoparib group was significantly longer than that in the standard chemotherapy group (8.6 months *v* 5.6 months; HR for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; $P < .001$). Benefits were seen in patients with either triple-negative or estrogen receptor–positive breast cancer. There were also differences in the patient-reported outcomes of global health status (GHS), QoL, and breast symptoms. Compared with standard chemotherapy, talazoparib treatment resulted in a significant delay in the onset of clinically meaningful deterioration; in significant improvement in GHS/QoL; and in improvement in breast symptom scale score from baseline.

In a final analysis of OS, Litton et al[23] found that talazoparib did not significantly improve OS over standard, physician's choice of single-agent chemotherapy (HR, 0.848; 95% CI, 0.670 to 1.073; $P = .17$). Median OS was 19.3 months with talazoparib (95% CI, 16.6 to 22.5) compared with 19.5 months (95% CI, 17.4 to 22.4) with chemotherapy, although these results were confounded by significant crossover following progression from placebo to PARP inhibitor. Consistent with the primary analysis, the incidence of grade 3-4 AEs was 69.6% among patients who received talazoparib and 64.3% among patients who received chemotherapy. Analyses of patient-reported outcomes[25] demonstrated a positive risk-benefit profile of talazoparib. These analyses revealed overall improvement in global health status (GHS)/QoL from baseline for talazoparib compared with statistically significant deterioration for physician's choice chemotherapy (3.0 [95% CI, 1.2 to 4.8] *v* –5.4 [95% CI, –8.8 to –2.0]; between arms, $P < .0001$). There was also a statistically significant greater delay in time to deterioration in GHS/QoL in favor of talazoparib (HR, 0.38; 95% CI, 0.26 to 0.55).

Clinical interpretation. For patients with germline *BRCA1/2* mutations and HER2-negative advanced breast cancer, treatment with a PARP inhibitor has been shown to improve PFS compared with a selection of physician's choice chemotherapy with favorable effects on QoL, although there was no demonstrated OS benefit (a secondary end point). Given this positive benefit-risk profile, it is important to consider germline genetic testing for patients with HER2-negative MBC to identify patients who may be candidates for this therapy. In addition, although there is evidence of the efficacy of taxane, anthracycline, and platinum chemotherapy for treatment of MBC, it remains unknown whether PARP inhibitor therapy would yield superior PFS and QoL compared with these classes of chemotherapy agents.

Recommendation 3.2. There is insufficient evidence to support a recommendation either for or against testing for a germline *PALB2* pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statements. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* pathogenic variants and somatic *BRCA1/2* 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.[3,4]

Literature review and analysis. The systematic review did not identify any studies, either RCTs or prospective-retrospective studies, that investigated the use of biomarker results to inform the recommendation for use of PARP inhibitors in patients with *PALB2* germline mutations and hormone receptor–positive, HER2-negative MBC. Evaluating PARP inhibitors in patients with germline mutations resulting in defective DNA repair other than *BRCA1/2* is extremely challenging because of the low prevalence of these mutations; randomized trials are not feasible. The data from Tung et al,[26] albeit from a single-arm, phase II trial, are quite striking in patients with germline *PALB2* mutations, with 10 of 11 patients having at least some tumor shrinkage and one patient with no change in tumor size. In addition, other case reports support the efficacy of PARP inhibition in patients with germline *PALB2* mutations. However, the view of the Panel was that this was an insufficient number of patients to make a formal recommendation. The original trial has been expanded to include an additional 30 patients with germline *PALB2* mutations and 30 patients with somatic *BRCA* mutations, in whom encouraging responses were also seen.[26]

Clinical interpretation. It is recognized that most patients who undergo germline genetic testing are tested for a panel of pathogenic mutations as opposed to variants in single genes. Therefore, although there is a paucity of data examining the effects of PARP inhibitors in patients with germline mutations in other DNA repair genes or whose cancers have somatic mutations in *BRCA1/2*, it is likely that patients will be identified through routine testing who harbor mutations in these genes. Additional data are awaited to clarify the benefit of PARP inhibitor therapy in these settings.

Clinical Question 4

What is the role of testing tumors for HRD in treatment selection for patients with MBC?

Recommendation 4.1. There are insufficient data at present to recommend routine testing of tumors for HRD to guide therapy for MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The Expert Panel reviewed the available data on HRD testing to guide therapy for MBC and concluded that there is no evidence for the clinical utility of testing for HRD.

Clinical Interpretation. Although there are emerging data from other solid tumors to support the use of HRD testing to guide therapy, current data do not support the assessment of HRD in the management of breast cancer. Available data from a subset analysis of the TNT trial of carboplatin versus docetaxel in metastatic triple-negative breast cancer[27] suggested no increase in efficacy of carboplatin in cancers with HRD.

Clinical Question 5

What is the role of testing for expression of PD-L1 in the tumor and immune cells in patients with locally recurrent unresectable or metastatic hormone receptor–negative and

HER2-negative breast cancer who are candidates for a treatment regimen that includes an ICI?

Recommendation 5.1. Patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for expression of PD-L1 in the tumor and immune cells with an FDA-approved test to determine eligibility for treatment with the ICI pembrolizumab plus chemotherapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. The systematic literature review identified two RCTs that addressed the question of the role of testing for expression of PD-L1 in patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an ICI. The placebo-controlled, double-blind, randomized, phase III KEYNOTE-355 trial[28] compared the efficacy and safety of the anti–programmed cell death protein monoclonal antibody, pembrolizumab (200 mg, once every 3 weeks), plus standard chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin; n = 566) versus placebo plus standard chemotherapy (n = 281) in patients with untreated metastatic triple-negative breast cancer (TNBC). The two primary efficacy end points were PFS and OS. At the second interim analysis reported by Cortes et al[28] (median follow-up of 25.9 months and 26.3 months in the pembrolizumab-chemotherapy and placebo-chemotherapy groups, respectively), pembrolizumab-chemotherapy significantly improved PFS compared with placebo-chemotherapy among patients with a PD-L1 combined positive score (CPS) of ≥ 10; the median PFS was 9.7 months with pembrolizumab-chemotherapy and 5.6 months with placebo-chemotherapy (HR for progression or death, 0.65; 95% CI, 0.49 to 0.86; one-sided $P = .0012$). Among patients with CPS of ≥ 1, the median PFS in the pembrolizumab-chemotherapy group was 7.6 months versus 5.6 months in the placebo-chemotherapy group (HR 0.74; 95% CI, 0.61 to 0.90; one-sided $P = .0014$). However, given the prespecified statistical criterion of $\alpha = .00111$, the between-treatment group PFS difference was not statistically significant for this PD-L1 subgroup. The incidence of grade 3 or higher treatment-related AEs was 68% among patients in the pembrolizumab-chemotherapy group and 67% among patients in the placebo-chemotherapy group. The most common grade 3 or higher AEs were anemia (16% *v* 15%), neutropenia (30% *v* 30%), and nausea (2% *v* 1%). In the pembrolizumab-chemotherapy group, any-grade immune-mediated AEs occurred in 26% of patients; any-grade immune-related AEs occurred in 6% of patients in the placebo-chemotherapy group. Grade 3 or higher immune-related AEs occurred in 5% of pembrolizumab-chemotherapy group patients and in 0% of placebo-chemotherapy group patients.

In the randomized, open-label, phase III KEYNOTE-119 trial, Winer et al[29] compared pembrolizumab monotherapy (200 mg, once every 3 weeks; n = 312) with investigator-choice, single-drug chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine; n = 310) as second-line or third-line treatment of patients with metastatic TNBC. The primary end point of the trial was OS. At the final analysis (median follow-up of 31.4 months and 31.5 months in the pembrolizumab and chemotherapy groups, respectively), there was no significant improvement in OS observed for pembrolizumab monotherapy compared with chemotherapy, either for the overall study population (HR 0.97; 95% CI, 0.82 to 1.15) or for patient subgroups defined by PD-L1 tumor status (HR 0.78; 95% CI, 0.57 to 1.06; log-rank $P = .057$ in patients with a PD-L1 CPS ≥ 10 or more; HR 0.86; 95% CI, 0.69 to 1.06; log-rank $P = .073$ in patients with a CPS ≥ 1). In analyses of secondary end points, pembrolizumab monotherapy did not improve PFS, objective response rate (ORR), or disease control (DC) rate versus chemotherapy in all participants. However, in a post hoc, exploratory, hypothesis-generating analysis of the pembrolizumab treatment effect in study participants with PD-L1 CPS of ≥ 20—about 18% of the overall study population—median OS was 14.9 months for the pembrolizumab group and 12.5 months for the chemotherapy group (HR 0.58; 95% CI, 0.38 to 0.88). The incidence of grade 3 or higher treatment-related AEs was 14% (43 of 309) among patients in the pembrolizumab monotherapy group and 36% (105 of 292) among patients in the chemotherapy group. The most common grade 3 or higher AEs were anemia (1% *v* 3%), decreased white blood cells (< 1% *v* 5%), decreased neutrophil count (< 1% *v* 10%), and neutropenia (0% *v* 13%). In the pembrolizumab group, 20% of patients had a serious AE; 20% of patients in the chemotherapy group had a serious AE. Immune-mediated AEs occurred in 15% of patients in the pembrolizumab monotherapy group and 3% of patients in the chemotherapy group. Grade 1-2 hypothyroidism was the most common immune-mediated AE.

Clinical interpretation. PD-L1 testing is very complex, as different assays can yield different results. This variability stems in part from the use of different antibodies, as well as from testing different cell types (tumor cells, lymphocytes, macrophages) in the tumor and/or stroma. The FDA approved pembrolizumab in combination with chemotherapy for treatment of triple-negative breast cancer that has tested positive for PD-L1 using the specific 22C3 companion assay. The 22C3 assay evaluates PD-L1 staining the tumor and surrounding stroma to calculate a CPS, which is the number of PD-L1 staining tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells, multiplied by 100. Tumors should therefore be tested using this assay to determine suitability for treatment with pembrolizumab plus chemotherapy, with positive defined as a CPS of at least 10. Trials of other ICIs, such as those

investigating atezolizumab,[30,31] have used other assays for PD-L1 detection. When selecting an ICI for potential therapy, the specific assay used in the trial supporting the use of that agent should be obtained.

Clinical Question 6

What is the role of testing for dMMR/MSI-H in treatment selection for patients with MBC to identify candidates for ICI monotherapy?

Recommendation 6.1 Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for dMMR/MSI-H to determine eligibility for dostarlimab-gxly or pembrolizumab (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The systematic review did not identify any studies, either RCTs or prospective-retrospective studies, that investigated the use of biomarker results to inform the recommendation for use of an ICI in patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer and dMMR/MSI-H. This recommendation is based on the results of analysis of the phase II KEYNOTE-158 study of pembrolizumab in patients with advanced solid tumors[6]; and on Expert Panel informal consensus in the absence of studies designed to test for clinical utility specifically for treatment of MBC that demonstrated a favorable balance of benefits and harms to patients.

Marabelle et al[6] reported the results from an analysis of data from the nonrandomized, phase II KEYNOTE-158 trial that evaluated the safety and antitumor activity of pembrolizumab (200 mg once every 3 weeks for 2 years) in patients with previously treated, advanced MSI-H/dMMR noncolorectal cancer. The primary end point of the KEYNOTE-158 was ORR, or the proportion of patients with confirmed complete response (CR) or partial response (PR); secondary end points included PFS, OS, duration of response, safety, and tolerability. Among the 233 patients enrolled in the trial, 27 tumor types were represented; the most common tumor types were endometrial cancer (21.0%), gastric cancer (10.3%), cholangiocarcinoma (9.4%), pancreatic cancer (9.4%), cancer of the small intestine (8.2%), and ovarian cancer (6.4%). With a median follow-up duration of 13.4 months, the ORR was 34.3% (95% CI, 28.3 to 40.8). Twenty-three (9.9%) patients had a confirmed CR and 57 (24.5%) had a confirmed PR. The median PFS was 4.1 months (95% CI, 2.4 to 4.9); median OS was 23.5 months (95% CI, 13.5 to not reached). Response durations of $\geq$ 12 months were observed in an estimated 86.9% of patients, and response durations of $\geq$ 24 months were observed in an estimated 77.6% of patients. Treatment-related AEs occurred in 64.8% (151 of 233); 34 patients (14.6%) had grade 3-5 treatment-related AEs. Fatigue, pruritus, diarrhea, and asthenia were the most common treatment-related AEs of any grade.

Clinical interpretation. MSI-H reflects defective mismatch repair genes, such as is found in Lynch syndrome, and is typically identified by examining alterations in repeated nucleotide sequences in microsatellites. By contrast, diagnosis of dMMR uses immunohistochemistry to identify loss of expression of key proteins including MLH1, MSH2, MSH6, or PMS2. Although the original studies assessed dMMR and MSI-H using immunohistochemistry and PCR, respectively, the FDA subsequently approved an NGS platform for use in selecting candidates for ICI therapy.

Clinical Question 7

What is the role of testing for TMB for patients with MBC to identify candidates for ICI monotherapy?

Recommendation 7.1. Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for TMB to determine eligibility for pembrolizumab monotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The systematic review did not identify any studies, either RCTs or prospective-retrospective studies, that investigated the use of biomarker results to inform the recommendation for use of an ICI in patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer and TMB. These recommendations are based on the results of an analysis of the phase II KEYNOTE-158 study of pembrolizumab in patients with advanced solid tumors[7]; on the results of an analysis of data from the nonrandomized, phase II TAPUR study of single-agent pembrolizumab in patients with MBC[8]; and on Expert Panel informal consensus in the absence of studies designed to test for clinical utility specifically for treatment of MBC that demonstrated a favorable balance of benefits and harms to patients.

In a prospective, exploratory analysis of data from KEYNOTE-158 study, Marabelle et al[7] evaluated the association between TMB and antitumor activity among patients with advanced solid tumors who were treated with pembrolizumab monotherapy (200 mg once every 3 weeks). The proportion of patients with an objective response (OR) was the primary end point. This analysis of KEYNOTE-158 data included 790 patients who had one of 10 tumor types and had evaluable tissue TMB (tTMB) scores. tTMB-high status was defined as at least 10 mutations per megabase. Of the 790 patients included in the efficacy analysis, 102 had tTMB-high status and 688 had non-tTMB-high status. In the tTMB-high group, 30 (29%; 95% CI, 21 to 39) of 102 patients had an OR; in the non-tTMB-high group, 43 (6%; 5 to 8) had an OR. This predictive value of tTMB was observed independent of MSI-H status and tumor PD-L1 expression. In the safety population (n = 105 patients who had received at least one dose of pembrolizumab and were tTMB-high), 67 of 105 participants (64%) had at least one treatment-related AE; the most common AEs were

fatigue (16%), asthenia (12%), and hypothyroidism (12%). Serious treatment-related AEs occurred in 11 (10%) patients in the safety population. Twenty-six (25%) of the 105 patients in the safety population experienced immune-related AEs. Hypothyroidism (13%), hyperthyroidism (8%), colitis (2%), and pneumonitis (3%) were the most frequently occurring immune-related AEs. Nine patients had a grade 3 immune-mediated AE or an infusion reaction.

Alva et al[8] reported the results of an analysis of the efficacy and toxicity of single-agent pembrolizumab (either 2 mg/kg [n = 8] or 200 mg [n = 20] once every 3 weeks until disease progression) for a cohort of patients with previously treated MBC and high TMB (HTMB; range, 9-37 mutations/megabase) from the TAPUR study, a nonrandomized, open-label, phase II basket trial. The primary end point of the trial was DC, which was defined as OR or stable disease of at least 16 weeks' duration. PFS, OS, and safety were secondary end points. The DC rate was 37% (10 of 28 enrolled patients; 95% CI, 21 to 50); the OR rate was 21% (95% CI, 8 to 41). The median PFS and median OS were 10.6 weeks (95% CI, 77.7 to 21.1 weeks) and 30.6 weeks (95% CI, 18.3 to 103.3 weeks), respectively. The incidence of grade 3 and 4 treatment-related AEs was 11%; drug-related serious AEs were reported in 11% of patients.

Clinical interpretation. TMB describes the quantity of somatic mutations in the tumor. There are a variety of factors that influence assessment of TMB, including sample type, preanalytical factors, size of the panel of mutations that are tested, depth of the sequencing, type of the mutations included, and cutpoint variables.[32] In particular, assessment of TMB in cell-free DNA assays is an area of evolving evidence. To highlight a few examples, TMB precision is directly related to the size of the gene panel used and coverage of the genome. Caution should therefore be used when TMB is assessed using a ctDNA assay, given the limited subset of genes used to calculate TMB. In addition, the assessment of TMB can be influenced by the gene selection if a panel is biased toward inclusion of genes that are frequently mutated. In addition, there is the potential to both under-call TMB compared with tissue testing in cancers with low purity of cell-free DNA in plasma, and over-call TMB compared with tissue testing in cancers with subclonal mutations detected in cell-free DNA. At this time, HTMB assessed in cell-free DNA should not be used to direct treatment without confirmatory testing in tumor tissue. However, there are also potential concerns with testing tumor tissue. For example, formalin-fixed paraffin-embedded tissue that is more than 5 years old can cause artificially HTMB because of fixation artifacts related to deamination. Finally, some assays compare tumor mutations to matched normal tissue, whereas others compare to a population allele frequency database; selection of the comparison database is important, especially given differences in distribution of variant allele frequency by race for different genes.[33,34]

Therefore, there are important caveats to be aware of when selecting a TMB assay and assessing the results, and different assays can yield different results for the same tissue specimen. It is important to use the approved companion assay and the approved cutpoint when making decisions regarding a specific treatment. For example, pembrolizumab has been approved for treatment of patients with HTMB, defined as at least 10 mutations per megabase on the basis of the FoundationOne CDx assay. Importantly, this was the first approval by the FDA on the basis of the result of a biomarker that was not specific to a certain tumor histology.[35]

Clinical Question 8

What is the role of testing for *NTRK* fusions in treatment selection for patients with MBC to identify candidates for treatment with tyrosine kinase inhibitors (larotrectinib or entrectinib)?

Recommendation 8.1. Clinicians may test for *NTRK* fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The systematic review did not identify any studies, either RCTs or prospective-retrospective studies, that investigated the use of biomarker results to inform the recommendation for use of TRK inhibitors in patients with MBC and *NTRK* fusions. The *NTRK* testing recommendation is based on the results of phase I-II studies identified by the Expert Panel that evaluated the efficacy and safety of TRK inhibitors for the treatment of advanced solid tumors with *NTRK* gene fusions[9-12]; and on Expert Panel informal consensus in the absence of studies designed to test for clinical utility specifically for treatment of MBC that demonstrated a favorable balance of benefits and harms to patients.

Two of the four articles identified by the Expert Panel related to this clinical question evaluated the efficacy and safety of the TRK inhibitor, larotrectinib.[12,36] Drilon et al[9] reported the results of an integrated analysis of 55 patients with TRK fusion–positive unresectable or metastatic solid tumors, representing 17 unique tumor types, including one breast tumor. On the basis of independent (central) review, the ORR was 75% (95% CI, 61 to 85); on the basis of investigator assessment, the ORR was 80% (95% CI, 67 to 90). The antitumor effect of larotrectinib was durable, with 71% of responses ongoing at 1 year and 55% of patients still progression-free. Grade 3 or higher AEs were uncommon, and no grade 3 AEs related to treatment were seen in more than 5% of patients.

Hong et al[12] reported on an expanded efficacy population of patients with TRK fusion–positive, locally advanced or metastatic, non-CNS solid tumors (five breast tumors)

treated with larotrectinib. Of 153 evaluable patients, 129 (79%; 95% CI, 72 to 85) had an OR on the basis of investigator assessment; 24 (16%) had a CR, and 97 (63%) had a PR. The median duration of response in the overall population was 35.2 months (95% CI, 22.8 to not estimable [NE]). For the overall population, the median time to response was 1.8 months (interquartile range, 1.7-1.9 months; range, 0.9-6.1 months), the median PFS was 28.3 months (95% CI, 22.1 to NE), and the median OS was 44.4 months (95% CI, 36.5 to NE).

A safety population (n = 260) comprised all patients who enrolled in one of the trials (without regard to TRK fusion status) and who had received at least a single dose of larotrectinib. Grade 3 or grade 4 treatment-emergent AEs occurred in 39% (101/260) and 7% (17/260) patients, respectively. Grade 3-4 AEs attributed to larotrectinib were uncommon.

Two articles identified by the Expert Panel evaluated the efficacy and safety of the TRK inhibitor, entrectinib.[10,11] Doebele et al[10] reported efficacy and safety results from an integrated analysis of 54 patients with TRK fusion–positive metastatic or locally advanced solid tumors.

In the 54 patients in the efficacy-evaluable population, the ORR was 57% (95% CI, 43.2 to 70.8); four patients (7%) had a CR and 27 patients (50%) had a PR. The median duration of response was 10 months (95% CI, 7.1 to NE), the median PFS was 11 months (95% CI, 8.0 to 14.9), the median OS was 21 months (95% CI, 14.9 to NE), and the median time to CNS progression was 17 months (95% CI, 14.3 to NE). Weight increase and anemia were the most frequently occurring grade 3 or grade 4 AEs in both of the populations. Seven patients (10%) in the *NTRK* fusion–positive safety population and 30 patients (9%) in the overall safety population reported serious treatment-related AEs.

Demetri et al[11] recently reported the results of an updated, integrated efficacy and safety analysis of the pooled analysis of entrectinib phase I and II clinical trials (n = 121). Seventy-four of 121 patients (61.2%) had an OR, 19 patients (15.7%) had a CR, and 55 patients (45.5%) had a PR. The median duration of response was 20.0 months (95% CI, 13.0 to 38.2), the median PFS was 13.8 months (95% CI, 10.1 to 19.9), and the median OS was 33.8 months (95% CI, 23.4 to 46.4). Grade 3 or higher treatment-related AEs occurred in 41.5% of patients in the *NTRK* fusion–positive population (n = 193) and in 38.0% of patients in the overall safety population (n = 626).

Clinical interpretation. TRK gene fusions are rarely identified in non-secretory breast tumors.[37] A meta-analysis of evidence on *NTRK* gene fusion frequency reported a frequency of *NTRK* fusions in non-secretory breast carcinoma of 0.60% (95% CI, 0.00 to 1.50).[38] In an analysis of more than 295,000 patients with cancer from the FoundationCORE database, Westphalen et al[37] reported an *NTRK* fusion prevalence of 0.39% in adult patients with breast cancer (n = 30,075). Identification of positive *NTRK* gene fusion status in the original trials was prospectively determined in local laboratories using NGS, fluorescence in situ hybridization, or reverse transcriptase PCR methods. The FDA subsequently approved an NGS test as a companion diagnostic. Of note, because of analytic issues, not all available diagnostic tests will detect all *NTRK* fusions. If testing is negative or indeterminate, then RNA NGS for fusion analysis could be considered.

Clinical Question 9

What is the role of testing tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor–negative, HER2-negative MBC?

Recommendation 9.1. There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor–negative, HER2-negative MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The systematic literature review identified one prospective-retrospective study that evaluated the association between tumor TROP2 expression and clinical outcomes. Bardia et al[39] reported the results of a prespecified biomarker analysis from the phase III randomized ASCENT trial of the efficacy and safety of sacituzumab govitecan (SG) compared with single-agent, physician's-choice chemotherapy (capecitabine, eribulin, vinorelbine, or gemcitabine; TPC) in patients with metastatic, chemotherapy-pretreated TNBC.[40] The exploratory biomarker analysis assessed the association between efficacy outcomes and tumor TROP-2 expression and germline *BRCA1/2* mutation status via subgroup analyses of PFS, OS, and ORR by biomarker status. For the TROP-2 expression analyses, the following categories were used: H-score 0 to < 100: Trop-2 low; H-score 100-200: Trop-2 medium; and H-score > 200-300: Trop-2 high. Among patients treated with SG, 151 had TROP-2 expression data; 139 of TPC patients had TROP-2 expression data. The analyses by TROP-2 expression subgroups indicated that, in patients with high and medium TROP-2 expression, PFS and OS outcomes among TROP-2 subgroups were numerically higher with SG versus TPC. Patients treated with SG who had high, medium, or low TROP-2 scores had a median PFS of 6.9 months (95% CI, 5.8 to 7.4), 5.6 months (95% CI, 2.9 to 8.2), and 2.7 months (95% CI, 1.4 to 5.8), respectively. By contrast, patients treated with TPC who had high, medium, or low TROP-2 scores had a median PFS of 2.5 months (95% CI, 1.5 to 2.9), 2.2 months (95% CI, 1.4 to 4.3), and 1.6 months (95% CI, 1.4 to 2.7), respectively. Patients treated with SG who had high, medium, or low TROP-2 scores had a median OS of 14.2 months (95% CI, 11.3 to 17.5), 14.9 months (95% CI, 6.9 to not evaluable), and 9.3 months (95% CI, 7.5 to 17.8), respectively, compared with patients treated with TPC with

high, medium, or low TROP-2 scores who had a median OS of 6.9 months (95% CI, 5.3 to 8.9), 6.9 months (95% CI, 4.6 to 10.1), and 7.6 months (95% CI, 5.0 to 9.6), respectively.

Clinical interpretation. The Expert Panel reviewed the available data on TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate (SG) for hormone receptor–negative, HER2-negative MBC and concluded that there is no evidence for the clinical utility of testing of tumors for TROP2 expression. However, the existing data are based on small numbers of patients treated on a single clinical trial, and, in particular, only 20% had low TROP-2 scores. Additional studies are needed to address whether TROP-2 expression should be used to select patients who are candidates for treatment with SG.

Clinical Question 10

What is the role of using ctDNA for monitoring response to treatment?

Recommendation 10.1. There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The Expert Panel found no studies that met the inclusion criteria on the use of ctDNA to monitor response to therapy among patients with MBC and concluded that there is no evidence for the clinical utility of the routine use of ctDNA for this purpose.

Clinical Interpretation. ctDNA consists of mutated gene fragments that are shed by cancer cells into the blood, which are detected by digital PCR or sequencing. ctDNA technology holds promise in metastatic disease for its ability to potentially identify shed tumor-specific mutations that may be targetable. However, to date, neither the measurement of dynamic changes in ctDNA as a marker of treatment responsiveness nor identification of specific mutations to direct therapy has been prospectively shown to improve patient outcomes over standard imaging-based detection of tumor progression.

Clinical Question 11

What is the role of using CTCs for monitoring response to treatment?

Recommendation 11.1. There are insufficient data to recommend routine use of CTCs to monitor response to therapy among patients with MBC (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. The Expert Panel reviewed the available data on the use of CTCs to monitor response to therapy among patients with MBC and concluded that there is no evidence for the clinical utility of the routine use of CTCs for this purpose. The systematic literature review identified one RCT published since the 2015 guideline[1] that leads to the role of using CTCs for monitoring response to treatment. Cabel et al[41] reported on CirCe01, a prospective, open-label RCT of the clinical utility of CTC-based monitoring in patients with MBC who were starting the third line of chemotherapy. The trial was designed to assess whether CTC-guided changes in chemotherapy would provide a survival benefit. Patients with ≥ 5 CTC/7.5 mL before the start of the first cycle of third-line chemotherapy (n = 101) were randomly assigned to the CTC arm (n = 51) or to the standard arm (n = 50). In the CTC arm of the trial, CTC monitoring was repeated at each subsequent line of chemotherapy, starting from the third line of therapy; in the standard arm, CTC count was not repeated and patients were treated according to tumor imaging completed every three cycles of therapy. The trial did not demonstrate clinical utility of CTC monitoring. There were no statistically significant differences between the two study arms in PFS (HR, 0.9; 95% CI, 0.6 to 1.3; $P = .6$) or in OS (HR, 0.95; 95% CI, 0.6 to 1.4; $P = .8$). Study accrual was ultimately terminated because of slow accrual and lack of compliance with the CTC monitoring–guided chemotherapy changes. The results of any safety analyses were not reported.

Clinical interpretation. CTCs are tumor cells that are measured in the blood. Initial studies validated the prognostic significance of high CTC levels for poor OS, and a cutoff of > 5 CTC/7.5 mL was established.[42] Despite this, studies examining the clinical utility of this marker to determine the optimal time for therapy change have not led to improvements in outcomes in MBC.[43] OS using a CTC-guided strategy has not been prolonged, either when used early in the course of metastatic disease or in later lines of therapy.

GAPS IN THE LITERATURE AND FUTURE RESEARCH DIRECTIONS

Several areas have been identified by the Expert Panel as gaps in the existing literature. Given the excitement around the development and potential of ctDNA to guide therapy, much has yet to be determined about the utility of these tests in practice. Both bespoke tumor-derived and panel-based tests exist with important differences in the depth and breadth of information they provide. With improvements in technology, more sensitive bespoke assays are constantly emerging. Panel tests are available from several companies, with no available data on how they compare for different patient populations and tumor subtypes. In addition, when identifying specific mutations in ctDNA for the selection of treatment, there is little information on the relationship between allele frequency of a particular mutation and treatment response.

Regarding biomarker testing to determine the potential to benefit from specific therapies, the Panel limited recommendations to those assays that were evaluated by the FDA

in the course of drug approval. However, other assays may have comparable clinical utility for treatment selection, but a lack of comparative data limits the ability to recommend them. For example, in the case of pembrolizumab, as stated previously, there are numerous assays available to measure PD-L1, using a variety of different antibodies. But, information on the utility of these tests in identifying patients who may benefit from pembrolizumab is lacking, thereby limiting the Panel's recommendation.

NGS panel tests can be used to identify somatic mutations in tumors, many of which are not yet actionable. Clinical trials testing drugs that target specific mutations may be available and should be considered when appropriate. For example, small trials such as SUMMIT have demonstrated a possible benefit from neratinib for treatment of patients whose cancers have a mutation in HER2.[44] Larger randomized trials are ongoing that are investigating the role of other anti–HER2-directed therapies for treatment of breast cancers with HER2 somatic mutations that do not have concomitant HER2 amplification.

In addition, as noted above, there are preliminary data that suggest that next-generation oral SERDs may be more effective than both AIs and the currently available injectable SERD fulvestrant,[45-47] especially in patients whose tumors have *ESR1* mutations. For example, in the recently reported EMERALD trial, which enrolled patients with previously treated hormone receptor–positive, HER2-negative MBC, there was improved PFS with elacestrant compared with physician's choice endocrine therapy in both the overall study population and the patients whose tumors had *ESR1* mutations.[48] Once available, the published results from this and similar trials of oral SERD and other antihormone therapies are anticipated to affect both diagnostic testing and treatment recommendations for patients with hormone receptor–positive MBC.

There are no direct data leading to the question of how to manage patients whose tumors are found to harbor multiple actionable variants and/or who have inherited germline pathogenic variants. At this time, the clinician should make a therapy decision on the basis of the most active therapy available for the set of biomarkers identified, taking into consideration the toxicity profile of each therapy, the patient's comorbidities, as well as previously administered therapies. However, more research is needed to guide the appropriate management course and to determine how best to sequence or combine targeted therapies.

Finally, it has long been recognized that metabolism of some drugs can vary widely with different pharmacogenetic polymorphisms, leading to dramatically increased toxicity in some patients. Two drugs commonly used in MBC, capecitabine and sacituzumab, are metabolized by enzymes that have common variants that reduce enzymatic activity. For capecitabine, the *DPYD* gene encodes DPD, an enzyme that catalyzes the rate-limiting step in its metabolism. The FDA label states that there are insufficient data to recommend a specific dose in individuals with partial DPD activity. For sacituzumab, SN-38 is metabolized via *UGT1A1*, and the *28 allele leads to reduced enzyme activity. Although the FDA label acknowledges that patients with reduced *UGT1A1* activity should be monitored closely for severe neutropenia, specific dosing instructions on the basis of testing are lacking. Additional studies are needed to guide dosing for patients with MBC who are carriers of these genetic variants, and therefore at risk for severe, potentially life-threatening toxicity.

PATIENT AND CLINICIAN COMMUNICATION

MBC presents complicated and evolving treatment options. It is imperative that clinicians apply skills and tasks that optimize patient-provider communication around the goals of treatment and treatment options, and check for patient understanding. If practicable and acceptable to the patient, clinicians should include significant others in the conversation and reassess the patient's goals of care, QoL priorities, and tolerance for risk. See the Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline for recommendations and strategies to optimize patient-provider communication.[49]

With respect to biomarker testing in particular, clinicians should educate patients, and/or caregivers and family members about the results of pathology evaluations and specific genomic tests, including how the results of this testing are used to develop a treatment plan tailored to their cancer biology.[50] A White Paper from the Consistent Testing Terminology Working Group recommends using consistent terminology to maximize communication and understanding between patient and clinician.[51] The terminology around testing is complex; simplifying and explaining this terminology is essential to enhancing patient understanding of the role of biomarker testing in their cancer care. Clear definitions and understanding about known end points such as PFS are necessary to ensure patients have the information they need to participate in treatment decision making.[52] Asking patients to repeat back key pieces of information, providing written or recorded notes, and using visual aids can also help ensure information is effectively communicated.

Finally, patients should be provided with a copy of their pathology report and, if available, other test results when useful. Clinicians should review the individual results with patients and offer to discuss any questions about test interpretation or performance.[50] Conversations between the oncology team and the person with MBC need to include the caveat that NGS and biomarker testing is a rapidly evolving field; that shared decision making is paramount; and that, if there are questions about the role of or interpretation of NGS and/or biomarker testing, consultation with a molecular tumor board or MBC expert should be considered.

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 on the guideline panel is not only to assess the suitability of the recommendations for implementation in the community setting but also to identify any other barrier to implementation of which a reader should be aware. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate the 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.

OPEN COMMENT AND EXTERNAL REVIEW

The draft recommendations were released to the public for open comment from January 26, 2022, through February 9, 2022. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for each of the proposed recommendations with 35 written comments received across draft recommendations. A total of 79% of the respondents (19 of 24) either agreed or agreed with slight modifications with the recommendations, and 21% (five of 24) of the respondents disagreed with selected recommendations and offered comments, and suggested revisions. The Expert Panel reviewed comments from all sources and determined whether to maintain the original draft recommendations; revise with minor language changes; or consider major recommendation revisions. All changes were incorporated before Evidence Based Medicine Committee final review and approval.

ADDITIONAL RESOURCES

Additional information including a data supplement, evidence tables, and clinical tools and resources can be found at www.asco.org/breast-cancer-guidelines. Patient information is available there and at www.cancer.net.

RELATED ASCO GUIDELINES

- Patient-Clinician Communication[49] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Integration of Palliative Care into Standard Oncology Care[53] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer[50] (http://ascopubs.org/doi/10.1200/JCO.22.00069)
- Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer[54] (https://ascopubs.org/doi/10.1200/JCO.21.02767)

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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, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

EQUAL CONTRIBUTION

N.L.H. and A.D. were expert panel co-chairs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update

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APPENDIX

TABLE A1. Biomarkers for Systemic Therapy in Metastatic Breast Cancer Guideline Expert Panel

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TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits *v* harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on strong evidence for a true net effect (eg, benefits exceed harms); consistent results, with no or minor exceptions; minor or no concerns about study quality; and/or the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on good evidence for a true net effect (eg, benefits exceed harms); consistent results with minor and/or few exceptions; minor and/or few concerns about study quality; and/or the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on limited evidence for a true net effect (eg, benefits exceed harms); consistent results, but with important exceptions; concerns about study quality; and/or the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation

TABLE A3. Complete List of Recommendations

New Recommendations From 2022 Focused Guideline Update

Recommendation	Evidence Rating
Recommendation 1.1 Patients with locally recurrent unresectable or metastatic hormone receptor–positive and HER2-negative breast cancer who are candidates for a treatment regimen that includes a PI3K inhibitor and a hormonal therapy should undergo testing for *PIK3CA* mutations using NGS of tumor tissue or ctDNA in plasma to determine their eligibility for treatment with the PI3K inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations. See the Burstein et al[4] guideline for the corresponding recommendation concerning the use of alpelisib in patients with *PIK3CA*-mutated, advanced breast cancer or MBC.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Recommendation 2.1 There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for hormone receptor–positive, HER2-negative MBC. Existing data suggest reduced efficacy of AIs compared with the SERD fulvestrant in patients who have tumor or ctDNA with *ESR1* mutations	Type: informal consensus Evidence quality: insufficient Strength of recommendation: moderate
Recommendation 3.1 Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a PARP inhibitor should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib. See the Burstein et al[4] guideline for the corresponding recommendation concerning the use of the use of PARP inhibitors in the treatment of patients with HER2-negative MBC.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Recommendation 3.2 There is insufficient evidence to support a recommendation either for or against testing for a germline *PALB2* pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk *Qualifying Statements*: Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* pathogenic variants and somatic *BRCA1/2* 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[3,4]	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 4.1 There are insufficient data at present to recommend routine testing of tumors for HRD to guide therapy for MBC	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 5.1 Patients with locally recurrent unresectable or metastatic hormone receptor–negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for expression of PD-L1 in the tumor and immune cells with an FDA-approved test to determine eligibility for treatment with the ICI pembrolizumab plus chemotherapy	Type: evidence based; benefits outweigh harms Evidence quality: intermediate Strength of recommendation: strong
Recommendation 6.1 Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for dMMR/MSI-H to determine eligibility for dostarlimab-gxly or pembrolizumab	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 7.1 Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for TMB to determine eligibility for pembrolizumab monotherapy	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 8.1 Clinicians may test for NTRK fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 9.1 There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor–negative, HER2-negative MBC	Type: informal consensus Evidence quality: low Strength of recommendation: moderate
Recommendation 10.1 There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC	Type: informal consensus Evidence quality: low Strength of recommendation: moderate

(continued on following page)

TABLE A3. Complete List of Recommendations (continued)

New Recommendations From 2022 Focused Guideline Update

Recommendation	Evidence Rating
Recommendation 11.1 There are insufficient data to recommend routine use of CTCs to monitor response to therapy among patients with MBC	Type: informal consensus Evidence quality: low Strength of recommendation: moderate

Recommendations Unchanged From 2015 Guideline

At initial presentation of metastasis from breast cancer, it is standard of care to biopsy an accessible lesion to confirm MBC. When evaluating the metastatic site(s), it is important to note that the results of ER, PgR, and/or HER2 status may have changed from the primary tumor, and these results may inform treatment decisions. Therefore, this Panel recommends retesting for ER, PgR, and HER2 on ≥ one metastasis with careful attention to assay performance, particularly for bone metastases. However, for patients with documented changes in these biomarkers, data are lacking to determine whether outcomes from systemic therapy are altered when guided by biomarker test results from the metastases. The Panel informal consensus for the management of care when there is discordance of ER, PgR, or HER2 results between primary and metastatic tissues is to use the ER, PgR, or HER2 status from the metastasis to direct therapy, if supported by the clinical scenario and the patient's goals for care (Type: evidence based for biomarker change from primary to metastasis, but no evidence to demonstrate that systemic therapy choices affect health outcomes when biomarker change occurs; Evidence quality: insufficient; Strength of recommendation: moderate)
Recommendations for tissue biomarkers In patients who are already receiving systemic therapy for MBC, decisions on changing to a new drug or regimen or discontinuing treatment should be based on the patient's goals for care and clinical evaluation and judgment of disease progression or response, given that there is no evidence at this time that changing therapy solely on the basis of biomarker results beyond ER, PgR, and HER2 improves health outcome, QoL, or cost-effectiveness (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate)
Recommendations for circulating tumor markers In patients already receiving systemic therapy for MBC, decisions on changing to a new drug or regimen or discontinuing treatment should be based on clinical evaluation, judgment of disease progression or response, and the patient's goals for care. There is no evidence at this time that changing therapy based solely on circulating biomarker results improves health outcomes, QoL, or cost-effectiveness (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate) CEA, CA 15-3, and CA 27-29 may be used as adjunctive assessments to contribute to decisions regarding therapy for MBC. Data are insufficient to recommend use of CEA, CA 15-3, and CA 27-29 alone for monitoring response to treatment. The Panel acknowledges the lack of evidence of clinical utility in support of use of these circulating biomarkers; biochemical assessments of CEA, CA15-3, and CA27-29 were developed before the present standards for measuring clinical utility. The recommendation for use is based on clinical experience and Panel informal consensus in the absence of studies designed to evaluate the clinical utility of the markers. As such, it is also reasonable for clinicians to not use these markers as adjunctive assessments (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)

Abbreviations: AI, aromatase inhibitor; CA, cancer antigen; CEA, carcinoembryonic antigen; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; ER, estrogen receptor; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; ICI, immune checkpoint inhibitor; MBC, metastatic breast cancer; MSI-H, microsatellite instability; NGS, next-generation sequencing; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death ligand-1; PgR, progesterone receptor; PI3K, phosphatidylinositol 3-kinase; QoL, quality of life; SERD, selective estrogen receptor degrader; TMB, tumor mutational burden.