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Testing for *ESR1* Mutations to Guide Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer

ASCO Guideline Rapid Recommendation Update

Burstein & DeMichele et al.

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1 Background & Methodology

Introduction

- Two previous ASCO guidelines discussed the role of testing for activating, gain-of-function mutations in the estrogen receptor gene ligand binding domain (*ESR1* mutation) to guide therapy for hormone receptor-positive, HER2-negative metastatic breast cancer (MBC)[1,2] and concluded that data were insufficient to recommend routine testing.[3]
- The EMERALD trial, an international, open-label, randomized phase III trial that evaluated the efficacy and safety of the oral selective estrogen receptor degrader, elacestrant, versus endocrine monotherapy (SOC) in patients with previously treated ER-positive, HER2-negative advanced breast cancer, including patients with *ESR1*-mutated tumors, provides a strong signal for updating prior ASCO MBC guidelines.

Development Methodology

- A targeted electronic literature search was conducted to identify any additional phase III randomized controlled trials in this patient population. No additional randomized controlled trials were identified.
- The Expert Panel reconvened to assess evidence and to review and approve the amended guideline.
- The ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

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2 Rapid Recommendation Update

Rapid Recommendation Update

Recommendation

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- To aid in treatment selection, the Expert Panel recommends routine testing for emergence of *ESR1* mutations at recurrence or progression on ET (with or without CDK4/6 inhibitor) in patients with ER-positive, HER2-negative MBC. Testing with a CLIA-certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor;[4] blood-based ctDNA is preferred owing to greater sensitivity.[5] If not performed earlier, testing for *PIK3CA* mutations should also be performed to guide further therapy. Patients whose tumor or ctDNA tests remain *ESR1* wildtype may warrant retesting at subsequent progression(s) to determine if an *ESR1* mutation has arisen.

Rapid Recommendation Update

Recommendation

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- Patients previously treated with ET and a CDK4/6 inhibitor for advanced breast cancer have several therapeutic options if choosing to continue endocrine-based approaches. For patients with prior CDK4/6 inhibitor treatment and *ESR1* wildtype tumors, appropriate subsequent ET options include fulvestrant, aromatase inhibitor, or tamoxifen monotherapy, or ET in combination with targeted agents such as alpelisib (for *PIK3CA* mutated tumors), or everolimus. For patients with prior CDK4/6 inhibitor treatment and a detectable *ESR1* mutation, options include elacestrant, or other ET either alone or in combination with targeted agents such as alpelisib (for *PIK3CA* mutated tumors) or everolimus. Elacestrant has comparable or greater activity than SOC ET monotherapy. Currently, there are no data on safety or clinical efficacy to support the use of elacestrant in combination with targeted agents.

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Summary of Previous *Endocrine Treatment and Targeted Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer: ASCO Guideline Update* Recommendations

Summary of Previous Recommendations

- Recommendations that are unchanged are provided in the following slides

Summary of Previous Recommendations

Clinical Question 1

- Should alpelisib be given to postmenopausal women, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced, or metastatic breast cancer?

Recommendation 1.1

- Alpelisib in combination with endocrine therapy should be offered to postmenopausal patients in combination with fulvestrant, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following prior endocrine therapy including an aromatase inhibitor, with or without a CDK4/6 inhibitor. Careful screening for and management of common toxicities are required.

Evidence-based
benefits outweigh harms

Evidence Quality	Strength of Recommendation
High	Moderate

Summary of Previous Recommendations

Clinical Question 2

- What is the role of biomarkers in treatment selection for patients with HR-positive metastatic breast cancer?

Recommendation 2.1

- To guide the decision to use alpelisib in combination with fulvestrant in postmenopausal patients, and in male patients, with HR-positive metastatic breast cancer, clinicians should use next generation sequencing in tumor tissue or cell-free DNA in plasma to detect *PIK3CA* mutations. If no mutation is found in cell free DNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 2.2

- **See updated recommendations.**

Summary of Previous Recommendations

Recommendation 2.3

- Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1* or *2* mutations who are no longer benefiting from endocrine therapy may be offered an oral PARP inhibitor in the first- through to third-line setting rather than chemotherapy.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Intermediate	Strong

Qualifying Statements

- Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in metastatic breast cancer 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.

Summary of Previous Recommendations

Clinical Question 3

- What is the role of CDK4/6 inhibitors in the treatment of patients with HR-positive metastatic breast cancer?

Recommendation 3.1

- A nonsteroidal AI and a CDK4/6 inhibitor should be offered to postmenopausal patients and to premenopausal patients combined with chemical ovarian function suppression, and to male patients (with a gonadotropin-releasing hormone analog), with treatment-naïve HR-positive MBC.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 3.2

- Fulvestrant and a CDK4/6 inhibitor should be offered to patients with progressive disease during treatment with AIs (or who develop a recurrence within one year of adjuvant AI therapy) with or without one line of prior chemotherapy for metastatic disease, or as first-line therapy. Treatment should be limited to those without prior exposure to CDK4/6 inhibitors in the metastatic setting.

Evidence-based
benefits outweigh harms

Evidence Quality	Strength of Recommendation
High	Strong

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4 Additional Information

Additional Resources

- More information, including clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines

- Patient information is available at www.cancer.net

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Abbreviations

- AI, aromatase inhibitor
- ASCO, American Society of Clinical Oncology
- ctDNA, circulating tumor DNA
- ER, estrogen receptor
- ET, endocrine therapy
- HER2, human epidermal growth factor receptor 2
- HR, hormone receptor
- MBC, metastatic breast cancer
- PARP, poly (ADP-ribose) polymerase
- SOC, standard-of-care

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5. Turner NC, Kingston B, Kilburn LS, et al: Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. Lancet Oncol 21:1296-1308, 2020

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