ASCO Guidelines

Testing for *ESR1* Mutations to Guide Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update			
Recommendation	**Type**	**Evidence Quality**	**Strength**
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;[1] blood-based ctDNA is preferred owing to greater sensitivity.[2] 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.	EB	H	S
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.	EB	H	S

Abbreviations. ctDNA, circulating tumor DNA; EB, evidence based; ER, estrogen receptor; ET, estrogen therapy; H, high; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; S, strong; SOC, standard-of-care

References.

[1]Grinshpun A, Sandusky ZM, Jeselsohn R: The Clinical Utility of ESR1 Mutations in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer. Hematol Oncol Clin North Am 37:169-181, 2023

[2]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

ASCO® Guidelines

Endocrine Treatment and Targeted Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer: ASCO Guideline Update				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
Should alpelisib be given to postmenopausal women, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced, or metastatic breast cancer?	**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 (AI), with or without a CDK4/6 inhibitor. Careful screening for and management of common toxicities are required.	EB	H	M
What is the role of biomarkers in treatment selection for patients with HR-positive metastatic breast cancer?	**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.	EB	H	S
	2.2. See updated recommendations above.	-	-	-
	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.	EB	I	S
	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.			
What is the role of CDK4/6 inhibitors in the treatment of patients with HR-positive metastatic breast cancer?	**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 metastatic breast cancer.	EB	H	S

Endocrine Treatment and Targeted Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer: ASCO Guideline Update				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	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.	EB	H	S

Abbreviations. AI, aromatase inhibitor; EB, evidence based; H, high; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; I, intermediate; M, moderate; PARP, poly (ADP-ribose) polymerase; S, strong

Reference.

Burstein HJ, Somerfield MR, Barton DL, et al: Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959-3977, 2021