Endocrine and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer—Capivasertib-Fulvestrant: ASCO Rapid Recommendation Update

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ASCO Rapid Recommendation Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options. Guidelines and updates are not intended to substitute for independent professional judgment of the treating provider and do not account for individual variation among patients. See appendix for disclaimers and other important information (Appendix 1 and Appendix 2, online only).

ACCOMPANYING CONTENT

Articles, 10.1200/JCO.21.01392 and 10.1200/JCO.22.01063

Appendix

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BACKGROUND

Patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) have emerging therapeutic options including novel endocrine[1] and targeted agents, with treatment informed by genomic biomarker testing.[2] The CAPItello-291 phase III, double-blind, randomized controlled trial (RCT) evaluating fulvestrant with the AKT pathway inhibitor capivasertib[3] and subsequent US Food and Drug Administration approval of capivasertib and a companion diagnostic device on November 16, 2023, constituted strong signals for updating ASCO MBC guidelines.[1,2]

METHODS

A targeted electronic literature search was conducted to identify any additional RCTs in this patient population. The original guideline Expert Panel reconvened to review evidence and make revised recommendations.

EVIDENCE REVIEW

CAPItello-291 randomly assigned 708 premenopausal, perimenopausal, or postmenopausal women or men with hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer to either capivasertib + fulvestrant (n = 355) or placebo + fulvestrant (n = 353).[3] Patients had experienced disease progression or relapse during previous aromatase inhibitor therapy, with or without a CDK4/6 inhibitor. Capivasertib was administered on a unique schedule of 400 mg orally twice a day for 4 days, then 3 days off, each week. All patients had tumor tissue submitted for next-generation sequencing. Activating mutations in *PIK3CA* and *AKT1* and inactivating alterations in *PTEN* genes were determined centrally with the FoundationOneCDx assay in all countries except China (which used OncoScreen Plus). Analyses were stratified by prior CDK4/6 exposure. Progression-free survival (PFS) in all patients (N = 477) and in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors (n = 289) were the dual primary end

points. The median PFS in the overall population was 7.2 months with capivasertib + fulvestrant and 3.6 months for placebo + fulvestrant (hazard ratio [HR], 0.60; $P < .001$). The median PFS in the *PIK3CA/AKT1/PTEN*-altered tumor population was 7.3 months with capivasertib + fulvestrant and 3.1 months with placebo + fulvestrant (HR, 0.50; $P < .001$). Among those whose tumors were AKT pathway nonaltered, the median PFS was 5.3 months and 3.7 months for capivasertib-treated and placebo-treated patients, respectively (HR, 0.79; P = nonsignificant), suggesting greatest benefit when tumors harbored AKT pathway mutations. Capivasertib + fulvestrant improved PFS regardless of prior CDK4/6 exposure.

Patient-reported outcome measures of quality of life showed consistent overall global health status (GHS) for both groups from baseline and no clinically meaningful changes in functional or symptom scores apart from worse diarrhea in the capivasertib + fulvestrant arm. Time to deterioration of GHS was longer with capivasertib and numerically longer in functional and symptom domains apart from diarrhea.[4] Physician-reported grade ≥3 adverse events (AEs) were more frequent in the capivasertib + fulvestrant group, including rash (12.1% *v* 0.3% with placebo-fulvestrant), diarrhea (9.3% *v* 0.3%), and hyperglycemia (2.3% *v* 0.3%), and AEs more frequently led to treatment discontinuation (13% *v* 2.3%).

To our knowledge, to date, no survival benefit has been demonstrated. Appraisal of the trial report using the GRADE[5] instrument was performed as per ASCO's methodology and found a high certainty of the evidence.

The similar FAKTION study,[6] a randomized phase II comparison of fulvestrant with either capivasertib or placebo, showed qualitatively similar results as CAPItello-291 with benefit restricted to tumors harboring *PIK3CA/AKT1/PTEN* alterations.

TABLE 1. Treatment Options According to Prior Endocrine Therapy

Line of Therapy	Tumor Genomic Findings	Prior Endocrine Therapy[a]	
		None, tamoxifen only, or no prior recent AI therapy (anastrozole, exemestane, letrozole)	Recurrence on or within recent exposure to AI therapy
First-line treatment		AI + CDK4/6 inhibitor	Fulvestrant + CDK4/6 inhibitor
Tumor genomic testing[b]			
Second-line treatment	No targetable mutations	Fulvestrant or fulvestrant + everolimus	Fulvestrant + everolimus, or chemotherapy
	ESR1 mutation	Elacestrant, or fulvestrant + everolimus	Elacestrant
	PIK3CA mutation	Fulvestrant + capivasertib, fulvestrant + alpelisib,[d] or fulvestrant	Fulvestrant + capivasertib, or fulvestrant + alpelisib[d]
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib, or fulvestrant	Fulvestrant + capivasertib
Third-line treatment and beyond[c]	No targetable mutations or targeted therapy already given	Chemotherapy or further endocrine-based treatments	Chemotherapy or further endocrine-based treatments
	ESR1 mutation	Elacestrant[e] or chemotherapy	Elacestrant[e] or chemotherapy
	PIK3CA mutation	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib,[e] or chemotherapy	Fulvestrant + capivasertib,[e] or chemotherapy

NOTE. 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.

Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CLIA, Clinical Laboratory Improvement Amendments; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine treatment; PTEN, phosphatase and tensin homolog; SERD, selective estrogen receptor degrader.

[a]All contemporary studies for ER-positive advanced breast cancer have been based on outcomes in postmenopausal women or women who were premenopausal at the time of diagnosis of advanced cancer and then underwent medically induced menopause. For premenopausal women diagnosed with advanced, ER-positive breast cancer, ovarian function suppression should be initiated and then treatment proceeds as in the Table.

[b]Tumor genomic testing includes sequencing for targetable mutations, accomplished through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. In addition to selecting patients whose tumors have increased *PIK3CA* or *AKT1* activity because of the presence of activating mutations, it is also important to identify those whose tumors have inactivation of PTEN protein. PTEN inactivation can be identified based on the presence of premature stop codons, frameshift alterations, splice site mutations, *PTEN* homozygous deletion, *PTEN* rearrangements that disrupt protein function, or specific missense mutations (C124R, C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R, and R173C) on next-generation sequencing.

[c]There are few data on the value of older ET options after therapy with modern treatment regimens such as AIs, SERDs, CDK4/6 inhibitors, and/or other targeted agents. In select patients—typically those with indolent cancers, limited disease burden or symptoms, and demonstrated clinical benefit from prior ETs—therapies such as tamoxifen, megestrol acetate, or reintroduction of previously administered treatments may be of clinical value.

[d]Alpelisib is an option for patients with tumors harboring *PIK3CA*-activating mutations but not *AKT*1-activating mutations or PTEN inactivation.

[e]If not previously given.

UPDATED RECOMMENDATIONS

Recommendation 1.1

The Expert Panel recommends multiple lines of endocrine treatment (ET), frequently paired with targeted agents, with choices informed by prior treatments and by routine testing for activating mutations in *ESR1*, *PIK3CA*, or *AKT1* or inactivation of *PTEN* (Table 1). Panelists recommend inclusion of CDK4/6 inhibitor therapy with ET in the first line. Second- and third-line therapies reflect targeted options based on tumor genomics. Combining ET with the AKT pathway inhibitor capivasertib is appropriate for tumors harboring *PIK3CA* or *AKT1* mutations or *PTEN* inactivation while ET combined with the PI3 kinase inhibitor alpelisib is an option for tumors harboring *PIK3CA* mutations, but not *AKT1* mutations. Other options include ET with mammalian target of rapamycin inhibitor everolimus irrespective of tumor genomics (Table 1). Monotherapy with the oral selective estrogen receptor degrader elacestrant is an option for tumors with *ESR1* mutation (Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.2

There are no comparative efficacy data for choosing a *PIK3CA* targeted option for those who are potential candidates for capivasertib or alpelisib treatment. For such patients, the Panel recommends selecting the targeted agent based on perceived risk-benefit considerations such as hyperglycemia, diarrhea, or treatment discontinuation for AEs (Evidence quality: Low; Strength of recommendation: Weak).

Qualifying Statement for Recommendations 1.1 and 1.2

Both capivasertib and alpelisb can cause rash and/or diarrhea. Grade 3 or greater AEs included diarrhea (9.3% capivasertib *v* 6.7% alpelisib), rash (12.1% capivasertib *v* 9.9% alpelisib), and hyperglycemia (2.3% capivasertib *v* 36.6% alpelisib). Clinicians may mitigate symptoms with antihistamines, anti-diarrheal agents, or other supportive measures. Most patients with estrogen receptor–positive, HER2-negative breast cancers will be candidates for multiple lines of ET and/or targeted agents prior to chemotherapy or antibody-drug conjugate therapy. While newer agents have been added to the armamentarium, there remain few studies on the optimal timing or sequence of treatments, comparisons of targeted agents within a class, or studies that compare one class of agents against another. Such trials are an important clinical priority, as are studies to mitigate side effects of these agents.

Evidence supporting unchanged recommendations and sections on patient-clinician communication, gaps in the literature and directions for future research, and more are found in the full guideline publications[1,2] and apply to this Rapid Update. Additionally, for guideline tools and resources, including a complete summary table, visit www.asco.org/breast-cancer-guidelines.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline Recommendation Update provides a recommendation update, with review and analysis of the relevant literature for the recommendation. Additional information, including links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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