Addressing Unmet Need in the Management of Patients With ER+/HER2–, *ESR1*-Mutated Metastatic Breast Cancer: Clinician's Perspective

Hope S. Rugo, MD
University of California San Francisco Comprehensive Cancer Center

Corresponding author:
Hope S. Rugo, MD
Box 1710, UCSF
San Francisco, CA 94143
Tel: (415) 994-5436
Email: Hope.Rugo@ucsf.edu

Abstract: Approximately 70% of breast tumors are ER+ and HER2–. First-line treatment that combines endocrine therapy (AIs, SERMs, and SERDs) with a CDK4/6 inhibitor is the treatment of choice for many patients with ER+/HER2– metastatic breast cancer. However, *ESR1* mutations develop in up to 40% of patients—more than 90% of these in response to therapy. The presence of *ESR1* mutations is associated with a worse prognosis, including faster progression and poorer survival, underscoring the need for routine testing and the urgency of developing novel therapies that address *ESR1*-mutated breast cancer. For more than 20 years, fulvestrant (given as an intramuscular injection) was the only SERD approved by the US Food and Drug Administration for the treatment of ER+/HER2– metastatic breast cancer, and a standard second-line therapy following progression on an AI. This review discusses (1) the importance of routine testing for *ESR1* mutations after disease recurrence or progression and the role of liquid biopsy in this regard; (2) elacestrant, a novel oral SERD approved in 2023 for the treatment of postmenopausal women and adult men with ER+/HER2–, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following 1 or more lines of endocrine therapy (unlike other SERDs, elacestrant is not associated with cardiac or ocular toxicity); and (3) new agents in development, including SERDs and innovative molecules targeting the ER—PROTACs, SERCAs, and CERANs—currently being tested in early-phase trials in combination with targeted agents, including CDK4/6 inhibitors.

Keywords
ER+/HER2–, *ESR1*-mutated metastatic breast cancer, *ESR1* mutations, endocrine therapy resistance, testing for *ESR1* mutations, selective ER degraders (SERDs), elacestrant

Introduction

Breast cancer remains the most common malignancy detected in women worldwide. In 2020, an estimated 2.26 million cases of breast cancer were diagnosed, and 685,000 patients died of the disease.[1] Approximately 70% of breast tumors are estrogen recep-

tor–positive (ER+) and human epidermal growth factor receptor 2–negative (HER2–).[2,3] Because the ER drives tumor growth and progression, first-line therapy for postmenopausal patients with ER+ tumors is aimed at blocking the activity of the ER by means of endocrine therapy. The latter includes drugs that reflect 2 different strategies for inhibiting ER activity. Aromatase inhibitors (AIs) inhibit estrogen production and include anastrozole, letrozole, and exemestane. Agents in the second category directly inhibit the activity of the ER and include selective ER modulators (SERMs) and selective ER degraders (SERDs). SERDs bind directly to the ER, and instead of activating the ER signaling pathway, they cause degradation of the ER. Approved SERMs for the treatment of patients with breast cancer include tamoxifen and toremifene. Fulvestrant was the first SERD approved for the treatment of ER+ breast cancer, and it remained the only SERD approved for this tumor type for more than 2 decades. In early 2023, elacestrant [RAD1901] (Orserdu, Stemline Therapeutics) became the second SERD to receive approval for the treatment of ER+/HER2– metastatic breast cancer; however, its administration is restricted to those with *ESR1*-mutated disease.

An AI or fulvestrant can be effectively combined with a second agent that inhibits the activity of CDK4/6, and this combination is the preferred first-line therapy for postmenopausal patients with ER+/HER2– metastatic breast cancer.[4,5] Currently approved CDK4/6 inhibitors for the treatment of breast cancer include abemaciclib (Verzenio, Eli Lilly), palbociclib (Ibrance, Pfizer), and ribociclib (Kisqali, Novartis). All 3 drugs disrupt the kinase activity of CDK4/6, inhibiting cell cycle progression, but they have different dosing schedules and toxicity profiles. However, even with state-of-the-art therapy, the majority of patients with advanced or metastatic ER+ disease experience disease recurrence or progression due to resistance to endocrine therapy mediated by underlying genetic changes that allow reactivation of the ER signaling pathway.

ESR1 Mutations and Resistance to Therapy

The development of resistance to endocrine therapy remains a significant challenge to the successful treatment of ER+ breast cancer.[6,7] In up to 40% of patients, *ESR1* mutations develop in response to combined first-line treatment with endocrine therapy plus a CDK4/6 inhibitor.[8] Multiple mechanisms of resistance have been identified involving *ESR1*, arising from point mutations and fusions.[6,9-12] These genetic lesions can lead to activating mutations and changes to the ER protein structure that alter the functionality of the ER. An established mechanism of resistance to endocrine therapy has been found in mutations of the ligand-binding domain of the ER, most commonly Y537S and D538G, which result in hormone-independent activation of the ER, thus enabling tumor growth and metastasis. The presence of *ESR1* mutations is associated with a worse prognosis, including faster disease progression and poorer survival, underscoring the urgency of developing novel therapies that address *ESR1*-mutated breast cancer.[13-18]

The importance of *ESR1* mutations in breast cancer came to light only after the genomic sequencing of metastatic tumors because the vast majority of *ESR1* mutations—as many as 90% or more—develop in response to therapy.[19,20] In an analysis of circulating tumor DNA (ctDNA) from 171 patients with metastatic breast cancer, *ESR1* mutations were found only in patients with ER+ tumors (P=.0093); moreover, all patients had prior exposure to AI therapy (median prior exposure, 23 months; range, 5.9-141.4). Because only a small percentage of primary tumors present initially with lesions in the *ESR1* gene, the characterization of metastatic disease is crucial for determining the optimal selection of second and later lines of therapy in this patient population. Indeed, *ESR1* mutations have been observed in up to 40% of patients who have received treatment with an AI for their ER+/HER2– metastatic breast cancer.[12,13] Although next-generation sequencing of tumor biopsy samples can yield valuable information, liquid biopsy offers a noninvasive, rapid, easy, repeatable, and real-time test that may be superior to tissue biopsy with respect to its capability to capture tumor heterogeneity in patients with metastatic cancer.[21,22]

Patients with *ESR1* mutations may not benefit from continuing CDK4/6 inhibition following progression on endocrine therapy in combination with a CDK4/6 inhibitor. This was shown in the MAINTAIN study—an investigator-initiated, double-blind, randomized, placebo-controlled phase 2 trial of 119 patients with HR+/HER2– breast cancer. The study investigated maintaining treatment with a CDK4/6 inhibitor while switching patients to a different endocrine therapy at progression.[23] Enrolled patients had previously had disease progression while on treatment with a CDK4/6 inhibitor plus endocrine therapy, and the majority of them (87%) had received prior therapy with palbociclib. At progression, all patients were switched to treatment with a new endocrine therapy and were randomly assigned to receive concomitant ribociclib or placebo. After a median follow-up of 18.2 months, median progression-free survival (PFS) in the patients receiving ribociclib was significantly longer than that in the patients receiving placebo in combination with endocrine therapy (5.29 vs 2.76 months; hazard ratio [HR], 0.57; P=.006). In an exploratory analysis, ctDNA was evaluated for *ESR1* mutations among the patients

who received fulvestrant. Among the patients who were randomized to placebo, the median PFS was similar in those with wild-type *ESR1* (2.76 months) and those with mutated *ESR1* (3.02 months). In contrast, among the patients who were randomized to ribociclib, the median PFS was 8.32 months in those with wild-type *ESR1* and 2.96 months in those with mutated *ESR1*, suggesting that patients with *ESR1* mutations may not benefit from continuing CDK4/6 inhibition following progression on endocrine therapy in combination with a CDK4/6 inhibitor.

Elacestrant: A Novel SERD

For more than 20 years, fulvestrant was the only approved SERD for the treatment of ER+/HER2– metastatic breast cancer, and a standard second-line therapy following progression on an AI. However, fulvestrant treatment is burdened by the requirement for a monthly intramuscular injection for administration and low bioavailability.

Elacestrant (approved in early 2023) is an oral nonsteroidal SERD that binds selectively to the ER.[24] In early preclinical studies, the binding of elacestrant to the ER prevented estrogen-mediated signaling, induced receptor degradation, and thus reduced ER signaling.[25] Exposure to elacestrant led to a decreased expression of *ESR1* in breast cancer cell lines. In addition to inhibiting the estrogen-dependent growth of breast cancer cell lines, elacestrant inhibited the growth of MCF7 xenografts in mice. Although elacestrant exhibited complex pharmacokinetics, the drug displayed pharmacokinetic behavior expected of a SERD. Subsequently, elacestrant was shown to be effective in xenograft models of breast cancer, both as monotherapy and in combination with palbociclib or everolimus, and in xenograft tumors resistant to CDK4/6 inhibition.[26,27] In addition to the advantage of an oral route of administration, elacestrant has been shown to cross the blood-brain barrier.

A Phase 1 Trial of Elacestrant

The safety and efficacy of elacestrant were evaluated in a phase 1 trial that enrolled 57 heavily pretreated postmenopausal women with ER+/HER2– metastatic breast cancer, including women whose tumors had *ESR1* mutations.[28] The recommended phase 2 dose of elacestrant (400 mg, daily) was given to 50 patients whose median age was 63 years (range, 43-81). Of these, 70% had visceral disease and 20% had bone-only disease. The median number of prior lines of therapy was 3 (range, 1-7), and the median number of prior lines of endocrine therapy was 2.5 (range, 1-7). *ESR1* mutations were detected in half of the patients; the most common mutations were D538G and Y537S. More than one *ESR1* mutation was detected in 44% of the patients. Of note, the frequency of *ESR1* mutations increased as the number of lines of prior endocrine therapy increased, reflecting observations from other studies showing that *ESR1* mutations generally develop during endocrine therapy. Elacestrant yielded an acceptable safety profile, with no dose-limiting toxicities observed at doses of up to 600 mg once daily. However, upper gastrointestinal events such as vomiting, esophageal pain, and others were of concern with long-term use of the drug, leading to the recommended phase 2 dose of elacestrant (400 mg, daily). The most common treatment-emergent adverse events (AEs) of any grade were nausea (50%), dyspepsia (32%), and vomiting (30%).

The phase 1 trial yielded an objective response rate (ORR) of 19.4% among the patients treated with elacestrant (400 mg, once daily). Antitumor activity was observed in patients with prior exposure to CDK4/6 inhibitors, those with prior exposure to fulvestrant, and those with *ESR1* mutations. The authors further evaluated response rates in patients with *ESR1* mutations, and the results showed a superior benefit among patients with *ESR1* mutations (33.3%; 5/15) vs those with wild-type *ESR1* (6.3%; 1/16). Moreover, responses were noted in patients whose tumors harbored the ER mutations Y537S and D538G, both of which are associated with resistance to endocrine therapy. In addition, elacestrant yielded a superior clinical benefit rate in patients with mutated vs wild-type *ESR1* (56.5% vs 29.2%) as well as a superior median PFS (7.4 vs 2.8 months). The median duration of response in the overall study population was 24.9 weeks (range, 13.4-44.3). In summary, the phase 1 trial demonstrated the efficacy of elacestrant in a heavily pretreated population of patients with ER+/HER2– metastatic breast cancer, with a manageable safety profile. Elacestrant showed greater activity among patients with *ESR1* mutations.

A Phase 1b Trial of Elacestrant

A phase 1b study of postmenopausal women with ER+/HER2– advanced breast cancer investigated the ability of elacestrant to decrease estradiol binding activity of the ER by means of 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES) positron emission tomography.[29] This open-label, nonrandomized study enrolled 16 patients with previously treated advanced breast cancer whose disease had progressed after at least 6 months of treatment. Of these patients, 56% had *ESR1* mutations at baseline, reflecting extensive prior exposure to endocrine therapy. Study treatment consisted of elacestrant at a daily dose of 200 or 400 mg. In the cohort of patients receiving 200 mg of elacestrant, the dose was increased to 400 mg on day 14. On day 14, 16 patients showed a median reduction in the tumor uptake of ^{18}F-FES of 89.1% in comparison

Table 1. Progression-Free Survival Rate: Results From the Randomized Phase 3 EMERALD Trial[31]

All Patients			
	Elacestrant (n=239)	*SOC* (n=238)	*Fulvestrant* (n=165)
6-mo PFS, % (95% CI)	34.3 (27.2-41.5)	20.4 (14.1-26.7)	22.9 (15.15-30.57)
12-mo PFS, % (95% CI)	22.3 (15.2-29.4)	9.4 (4.0-14.8)	10.2 (3.4-16.9)
Patients With a Detectable *ESR1* Mutation			
	Elacestrant (n=115)	*SOC* (n=113)	*Fulvestrant* (n=83)
6-mo PFS, % (95% CI)	40.8 (30.1-51.4)	19.1 (10.5-27.8)	20.8 (10.68-30.83)
12-mo PFS, % (95% CI)	26.8 (16.2-37.4)	8.2 (1.3-15.1)	8.4 (0.2-16.6)

mo, months; PFS, progression-free survival; SOC, standard of care.

Table 2. Progression-Free Survival: Results From the Randomized Phase 3 EMERALD Trial[31]

All Patients		
	Elacestrant (n=239)	*Fulvestrant* (n=165)
HR (95% CI)	0.68 (0.52-0.90)	
P	.0049	
PFS, mo	2.8	1.9
Patients With a Detectable *ESR1* Mutation		
	Elacestrant (n=115)	*Fulvestrant* (n=83)
HR (95% CI)	0.50 (0.34-0.74)	
P	.0005	
PFS, mo	3.8	1.9

HR, hazard ratio; mo, months; PFS, progression-free survival.

with baseline, with both cohorts demonstrating a reduction in ^{18}F-FES uptake of approximately 89%. The ORR was 11.1% and the clinical benefit rate was 30.8%. In the cohort of patients treated with the lower vs the higher dose of elacestrant, the proportion of patients with a reduction in ER availability of at least 75% was 62.5% vs 88%, which compares favorably with comparable results observed with fulvestrant.

EMERALD: A Phase 3 Trial of Elacestrant

The international, open-label, phase 3 EMERALD trial evaluated elacestrant vs standard-of-care (SOC) endocrine monotherapy in men or postmenopausal women with previously treated, ER+/HER2– advanced or metastatic breast cancer.[30-32] The study included patients whose disease had progressed after first- or second-line therapy. Patients were required to have had disease progression on prior therapy with a CDK4/6 inhibitor in combination with either fulvestrant or an AI. One prior chemotherapy regimen for advanced or metastatic disease was allowed. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with measurable disease based on RECIST 1.1 criteria or evaluable bone-only disease with at least one lytic or mixed lytic-blastic bone lesion.[33] Exclusion criteria included symptomatic visceral disease and cardiovascular events within 6 months of enrollment. *ESR1* mutation status was determined by the evaluation of cell-free ctDNA in blood samples analyzed at a central laboratory, and *ESR1* mutations were defined as any missense mutation in codons 310 through 547. Note that the study sites were not informed of *ESR1* mutation status during treatment. Stratification factors included *ESR1* mutation status, visceral metastases, and prior treatment with fulvestrant.

Enrolled patients were evenly randomized to elacestrant or SOC. Per the phase 1 trial, the dose of elacestrant evaluated in the EMERALD trial was 400 mg given orally once daily. Dose reductions to 300 or 200 mg daily were allowed for toxicity. SOC therapy was based on the investigator's choice and included fulvestrant, anastrozole, letrozole, or exemestane monotherapy, with guidance to use a therapy that was different from prior treatment. The primary endpoint was PFS in the overall study population, as well as in patients with *ESR1* mutations, determined by blinded independent review.

The EMERALD trial randomized 239 patients to elacestrant and 238 to SOC. Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 63 years (range, 24-89), and 228 patients (47.8%) had a detectable *ESR1* mutation. In the elacestrant vs the SOC arm, the majority of patients had visceral metastasis (68.2% vs 71%) and had received prior adjuvant therapy (66.1% vs 59.2%), respectively. It is important to note that the EMERALD trial evaluated elacestrant vs SOC as second- or third-line therapy—approximately half of the patients had already received 1 line of therapy and half had received 2 prior lines of therapy. Endocrine resistance increases with each subsequent line of therapy. In addition, the majority of patients in this study had visceral metastasis, another indication of increasing endocrine resistance.

The trial results showed a benefit in terms of disease progression in both the overall study population and patients with an *ESR1* mutation (Tables 1 and 2). After a median follow-up of 15 months, the trial met its primary endpoint, demonstrating a superior median PFS

Table 3. Progression-Free Survival by Duration of Prior CDK4/6 Inhibitor in Metastatic Setting: Results From the Randomized Phase 3 EMERALD Trial[32]

	Duration of CDK4/6 Inhibitor in Metastatic Setting, mo					
	≥6.0		≥12.0		≥18.0	
All Patients						
	Elacestrant (n=202)	*SOC* (n=205)	*Elacestrant* (n=150)	*SOC* (n=160)	*Elacestrant* (n=98)	*SOC* (n=119)
HR (95% CI)	.69 (0.54-0.88)		0.61 (0.45-0.83)		0.70 (0.48-1.020)	
Median PFS, mo	2.8	1.9	3.8	1.9	5.5	3.3
Patients With a Detectable *ESR1* Mutation						
	Elacestrant (n=103)	*SOC* (n=102)	*Elacestrant* (n=78)	*SOC* (n=81)	*Elacestrant* (n=55)	*SOC* (n=56)
HR (95% CI)	0.52 (0.36-0.74)		0.41 (0.26-0.63)		0.47 (0.20-0.79)	
Median PFS, mo	4.1	1.9	8.6	1.9	8.6	2.1

HR, hazard ratio; mo, months; PFS, progression-free survival; SOC, standard of care.

with elacestrant vs SOC in the overall study population (HR, 0.70; 95% CI, 0.55-0.88; *P*=.0018) as well as in the subset of patients with an *ESR1* mutation (HR, 0.55; 95% CI, 0.389-0.77; *P*=.0005). This corresponds to 30% and 45% relative reductions in progression or death with elacestrant in the overall study population and in the subset of patients with an *ESR1* mutation, respectively. In the overall study population, the median 6-month PFS rate was 34.3% with elacestrant vs 20.4% with SOC, and the median 12-month PFS rate was 22.3% vs 9.4%, respectively. In the subset of patients with an *ESR1* mutation, the median 6-month PFS rate was 40.8% with elacestrant vs 19.1% with SOC, and the median 12-month PFS rate was 26.8% with elacestrant vs 8.2% with SOC. Thus, as in the phase 1 trial, the clinical effect of elacestrant was more pronounced in patients whose tumors expressed detectable *ESR1* mutations; however, elacestrant retained superior efficacy vs SOC among patients with wild-type *ESR1*. In this group of patients with pretreated HR+/HER2– metastatic breast cancer, approximately 40% had come off study treatment by the first study-mandated imaging procedure, reflecting the significant heterogeneity of the disease and affecting median differences between the 2 treatment arms. The HRs more accurately reflect the benefit of elacestrant over SOC endocrine therapy in the endocrine-sensitive population, with the PFS curves separated after the first imaging and remaining separated for the duration of follow-up.

Among 239 patients treated with elacestrant vs 165 treated with fulvestrant, elacestrant yielded a superior median PFS (2.8 vs 1.9 months; HR, 0.68; 95% CI, 0.52-0.90; *P*=.0049). Within the subset of patients with an *ESR1* mutation, elacestrant again showed a superior median PFS vs fulvestrant (3.8 vs 1.9 months; HR, 0.50; 95% CI, 0.34-0.74; *P*=.0005) and a superior 12-month PFS rate (26.8% vs 8.4%). The HR analysis reflects a 50% relative reduction in progression or death with elacestrant in the subset of patients with an *ESR1* mutation.

Elacestrant also yielded a statistically superior median PFS vs SOC in several prespecified subgroups, including patients with visceral metastasis (HR, 0.665; 95% CI, 0.507-0.869), patients who were at least 65 years of age (HR, 0.548; 95% CI, 0.386-0.773), patients who had received 1 prior line of endocrine therapy (HR, 0.705; 95% CI, 0.517-0.959), and patients who had received 2 prior lines of endocrine therapy (HR, 0.597; 95% CI, 0.423-0.841). Interim analysis of overall survival (OS) did not demonstrate a significant difference with elacestrant vs SOC in the overall population (HR, 0.75; 95% CI, 0.54-1.04, *P*=.0821) or in the subset of patients with an *ESR1* mutation (HR, 0.59; 95% CI, 0.36-0.96, *P*=.0325). In a post hoc analysis of data from EMERALD, the median PFS was superior with elacestrant in comparison with SOC in patients with prior exposure to a CDK4/6 inhibitor (Table 3).[32] The benefit with elacestrant was observed across patient subgroups based on duration of prior exposure to a CDK4/6 inhibitor ranging from 6 to 18 months or longer, although the differences were more pronounced in patients who had received more than 6 to 12 months of prior CDK4/6 inhibition, as a surrogate marker of endocrine sensitivity. Analysis of the latter subgroup yielded a median PFS of 8.61 months with elacestrant (n=55) vs 2.10 months with SOC (n=56).

AEs of any grade were observed in 92.0% of patients in the elacestrant arm vs 86.0% in the SOC arm, with grade 3/4 AEs occurring in 27.0% vs 20.5%, respectively.

In the elacestrant arm, serious AEs occurred in 12% of patients; serious AEs occurring in more than 1% of patients included musculoskeletal pain (1.7%) and nausea (1.3%). Grade 5 AEs occurred in 1.7% of patients in the elacestrant arm vs 2.6% in the SOC arm. In the elacestrant arm, fatal AEs included cardiac arrest, septic shock, diverticulitis, and unknown, each observed in 1 patient. None of the patient deaths was considered related to study treatment. AEs leading to dose reduction occurred in 3.0% of patients treated with elacestrant vs none with SOC. Treatment-related AEs leading to study drug discontinuation were reported in 3.4% vs 0.9% of patients, respectively.[32] In the elacestrant arm, the most common AEs of any grade were nausea (35.0%), fatigue (19.0%), and vomiting (19.0%), and the most common grade 3/4 AEs were nausea (2.5%), back pain (2.5%), and increased alanine aminotransferase (2.1%). In the SOC arm, the most common AEs of any grade were nausea (18.8%), fatigue (18.8%), and arthralgia (16.2%), and the most common grade 3/4 AEs were nausea, fatigue, diarrhea, and increased aspartate aminotransferase, each at 0.9%. It is notable that unlike other SERDs, elacestrant is not associated with cardiac or ocular toxicity. The most common toxicity associated with elacestrant therapy was nausea, and this is generally well managed with antiemetics. A striking outcome in the EMERALD trial was the low number of patients who needed antiemetics.

Many patients in this study had not received prior treatment with fulvestrant, and therefore these patients could receive fulvestrant as their study drug. Another point to note about the patient population is that all enrolled patients had received prior therapy with a CDK4/6 inhibitor, providing a relatively uniform study population in terms of prior exposure. This is helpful because first-line therapy that combines endocrine therapy with a CDK4/6 inhibitor is the treatment of choice for many patients with ER+/HER2– metastatic breast cancer and is included in international guidelines.

The results from the EMERALD trial led to the approval of elacestrant for the treatment of postmenopausal women and adult men with ER+/HER2–, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following 1 or more lines of endocrine therapy at a recommended dosage of 345 mg daily.[24] Along with elacestrant, the US Food and Drug Administration also approved the Guardant360 CDx assay as a companion diagnostic to identify the patients most likely to benefit from treatment with the novel SERD. Ongoing clinical trials are evaluating elacestrant in different patient populations, importantly are evaluating elacestrant safety and efficacy in combination with other agents, and are further validating the use of ctDNA as a diagnostic tool in this patient setting.

ELEVATE: An Ongoing Phase 1b/2 Trial of Elacestrant in Combination With Other Agents

The multicenter, open-label, phase 1b/2 ELEVATE trial (NCT05563220) is currently recruiting patients with locally advanced or metastatic breast cancer to evaluate elacestrant paired with other agents, including alpelisib (Piqray, Novartis), abemaciclib, palbociclib, ribociclib, and everolimus (Table 4).[34] Eligibility requirements include confirmed ER+/HER2– breast cancer; measurable disease by RECIST 1.1 or at least one lytic bone lesion; and an ECOG performance status of 0 or 1. Female patients may be premenopausal, perimenopausal, or postmenopausal. Patients who have received prior treatment with elacestrant or chemotherapy will be excluded. Other eligibility requirements pertain to specific treatment arms. The primary endpoint of the phase 1b portion of the trial is to determine the recommended phase 2 dose of elacestrant in combination with each of the other drugs; a standard 3 + 3 design will be used for elacestrant dose escalation, based on the dose-limiting toxicity outcomes of the novel SERD in combination with each of the other study drugs. Secondary endpoints include those associated with safety, efficacy, pharmacokinetics, and pharmacodynamics. The phase 2 portion of the trial has a planned recruitment of 250 patients into the 4 arms to evaluate the efficacy and safety of the five 2-drug combinations. The primary endpoint for each arm in phase 2 is PFS at 6 or 12 months, with secondary endpoints of ORR, duration of response, PFS, OS, and safety.

Testing for *ESR1* Mutations After Recurrence or Progression

Results from 2 phase 3 trials underscore the importance of repeat testing of patients, as well as the utility of ctDNA analysis.[35,36] Both the EFECT and SoFEA trials recruited patients with HR+ metastatic breast cancer that had progressed on prior therapy with a nonsteroidal AI. Patients were randomized to therapy with fulvestrant or exemestane. The combined analysis included 227 patients from EFECT and 161 from SoFEA. Patients from EFECT provided baseline serum samples, and those from SoFEA provided plasma. Analysis by digital polymerase chain reaction (PCR) revealed the presence of *ESR1* mutations in 30% of patients (115/383) at baseline—after first progression and before the initiation of study therapy. Among patients with *ESR1* mutations, the median PFS was prolonged with fulvestrant vs exemestane (3.9 vs 2.4 months; HR, 0.59; 95% CI, 0.38-0.89; *P*=.01). In contrast, among patients without *ESR1* mutations, the median PFS was similar in the 2 groups (4.1 months with fulvestrant vs 4.8 months with exemestane; HR, 1.05; 95% CI, 0.81-1.38; *P*=.69). In multivariate analysis, *ESR1* mutations were

Table 4. Elacestrant in Various Combinations in Patients With Metastatic Breast Cancer (ELEVATE): Study Arms[34]

Phase 1b arm A	Elacestrant 258 or 345 mg + alpelisib 250 or 300 mg
Phase 1b arm B	Elacestrant 258 or 345 mg + everolimus 5.0, 7.5, or possibly 10 mg
Phase 1b arm C	Elacestrant 86, 172, or 258 mg + ribociclib 400 or possibly 600 mg
Phase 1b arm D	Elacestrant 258 or 345 mg + palbociclib 100 or 125 mg **OR** Elacestrant 258 or 345 mg + the recommended phase 2 dose for the combination of elacestrant and abemaciclib (currently being evaluated in the ongoing ELECTRA trial [NCT04791384]) **OR** Elacestrant 86, 172, or 258 mg + ribociclib 400 or possibly 600 mg

significantly associated with a shortened PFS (HR, 1.96; 95% CI, 1.34-2.86; *P*=.001).

The multicohort, multicenter, open-label, phase 2 plasmaMATCH study provided validation for the use of ctDNA in place of solid tumor biopsy.[37] The study enrolled 1051 women with histologically confirmed, advanced breast cancer who had completed at least one line of treatment for their advanced disease and had experienced progression or relapse. ctDNA samples were evaluated for mutations in *PIK3CA*, *ESR1*, *ERBB2* (HER2), and *AKT1* by digital droplet PCR. In addition, the same samples were evaluated by targeted sequencing for mutations in the same 4 genes plus *PTEN* and *TP53*. The study revealed excellent agreement in the rates of mutation detection between digital droplet PCR and targeted sequencing for all 4 genes (Table 5). The most common mutations detected in the *ESR1* gene from plasma samples were at codons 538 (54%), 537 (37%), and 380 (35%). Targeted sequencing was performed on tissue biopsy samples from 77 patients. Results from digital PCR analysis of ctDNA showed a 93% rate of agreement with sequencing of tumor biopsy specimens, and this rate of agreement reached 98% when ctDNA results were compared with those from contemporaneous biopsy specimens.

In a recent update to its testing guidelines, the American Society of Clinical Oncology recommends routine testing for *ESR1* mutations for women with ER+/HER2– metastatic breast cancer who are receiving or have received endocrine therapy and experience recurrence or progression of their disease.[5] The guideline recommends testing with a Clinical Laboratory Improvement Amendments (CLIA)–certified assay of a blood or tissue sample

Table 5. Agreement Between Digital PCR and Sequencing in the plasmaMATCH Trial[37]

Gene	Kappa	95% CI
AKT1	0.93	0.87-0.99
ESR1	0.90	0.86-0.93
ERBB2 (HER2)	0.89	0.79-0.98
PIK3CA	0.92	0.89-0.95

PCR, polymerase chain reaction.

that is obtained at the time of recurrence or progression, on the basis of the observation that the vast majority of *ESR1* mutations emerge in response to treatment. Per findings from the plasmaMATCH study, the guideline further recommends testing of ctDNA in preference to tissue samples.[21,22,37] For patients whose ctDNA results show wild-type *ESR1*, subsequent retesting may be warranted. The guideline further recommends that for patients with *ESR1* mutations who have received prior treatment with a CDK4/6 inhibitor, elacestrant, either alone or in combination with another agent, may be an appropriate treatment.

For some patients, repeat testing with a tumor biopsy at some point in disease progression may be useful to assess whether ER or HER2 expression has changed. However, given the information that can be gleaned with blood biopsy, tumor biopsies can be performed less frequently than in the past for mutation testing, which is beneficial for patients and avoids the risks of and time required for serial biopsies.

Future Developments: Agents on the Horizon for the Treatment of ER+/HER2– Advanced or Metastatic Breast Cancer

Given the certain development of resistance to endocrine therapy, new agents that can turn off ER signaling in breast cancer cells while avoiding unacceptable toxicity are urgently needed.[8,38] New SERDs in development include camizestrant, imlunestrant, and giredestrant. Additional novel agents that have shown promise in ER-driven breast cancer include innovative molecules targeting the ER—proteolysis-targeting chimera molecules (PROTACs), selective ER covalent antagonists (SERCAs), and complete ER antagonists (CERANs).

SERDs

Camizestrant [AZD9833] is an oral nonsteroidal SERD that has been shown to induce degradation of the ER and inhibit the growth of xenograft tumors in mice and has since progressed to early-stage clinical trials.[39] In the randomized phase 2 SERENA-2 trial, camizestrant was

compared with fulvestrant in 240 postmenopausal women with ER+/HER2–metastatic breast cancer and at least one prior line of endocrine therapy.[40] At baseline, *ESR1* mutations were detected in 36.7% of patients. The study met its primary endpoint, demonstrating a median PFS of 7.2 months (*P*=.0124) with camizestrant (75 mg, daily) and of 7.7 months (*P*=.0161) with camizestrant (150 mg, daily) vs 3.7 months with fulvestrant. At both dose levels, camizestrant yielded a superior median PFS in prespecified subgroups representing patients with prior exposure to a CDK4/6 inhibitor, lung or liver metastasis, or *ESR1* mutations, although the benefit appeared primarily in patients with *ESR1* mutations. The investigational SERD was generally well tolerated and showed low rates of treatment-emergent AEs of grade 3 or higher, dose reduction, and drug discontinuation. Most treatment-emergent AEs included photopsia and bradycardia.

Imlunestrant [LY3484356] is another investigational SERD that has demonstrated efficacy in early clinical trials of patients with breast cancer. The phase 1a/1b EMBER trial enrolled 114 patients with ER+, previously treated, advanced breast cancer.[41] The dose of imlunestrant ranged from 200 to 1200 mg, administered once daily. No dose-limiting toxicities were observed. At the recommended phase 2 dose of 400 mg, daily, imlunestrant was generally well tolerated; the most common treatment-emergent AEs of any grade were nausea (33.3%), fatigue (27.5%), and diarrhea (23.2%). In addition to an ORR of 8%, the trial showed a clinical benefit rate of 47.1%.

Giredestrant [GDC-9545], an oral SERD, has demonstrated antitumor activity as a single agent and in combination with a CDK 4/6 inhibitor.[38] A phase 1a/b study evaluated giredestrant monotherapy and combination therapy with palbociclib in postmenopausal patients with ER+ metastatic breast cancer who had disease recurrence while on adjuvant endocrine therapy for 24 months or longer or progression after prior endocrine therapy for 6 months or longer and 2 or fewer lines of therapy. The dose of giredestrant was 30 mg, daily, as monotherapy and 100 mg, daily, in combination therapy. The most common AEs with giredestrant monotherapy were fatigue, arthralgias, and nausea. Notably, 7% of patients had bradycardia. The most common AE with giredestrant combination therapy was neutropenia. Interim analysis in a randomized phase 2 study evaluating the efficacy and safety of giredestrant vs physician's choice of endocrine therapy in postmenopausal and premenopausal women on ovarian function suppression with ER+/HER2– advanced/metastatic breast cancer who had received 1 or 2 prior lines of systemic therapy (at least one of which was endocrine therapy) showed no significant improvements in PFS in the overall population and a nonsignificant benefit in the *ESR1* mutation subgroup (median PFS, 5.3 vs 3.5 months; HR, 0.60 [95% CI, 0.35-1.03]; *P*=.06).

PROTACs

Proteolysis-targeting chimera molecules (PROTACs) comprise a target-binding domain linked to a ligase-binding moiety that recruits the enzyme E3 ligase, which catalyzes the addition of ubiquitin to the target protein, thus resulting in degradation of the target protein by the proteasome.[42] The PROTAC ARV-471 was investigated in a phase 1 trial of women with HR+/HER2– metastatic breast cancer who had received prior treatment with endocrine therapy and a CDK4/6 inhibitor.[43] Of these patients, 80% had received prior treatment with fulvestrant. The drug was generally well tolerated and showed a clinical benefit rate of 40% in 47 evaluable patients. With daily doses ranging from 30 to 700 mg, the maximum tolerated dose was not reached and no dose-limiting toxicity was observed. The most common treatment-related AEs of any grade were nausea (24%), fatigue (12%), and vomiting (10%). Only 2 grade 3 AEs were considered potentially related to the study therapy.

SERCAs

Selective ER covalent antagonists (SERCAs) inactivate the receptor by binding to the ER through C530, a unique cysteine residue. Covalent binding to C530 induces a conformational change in the receptor that blocks ER function without causing degradation. H3B-6545 is a first-in-class SERCA that showed promising activity in preclinical studies and in the first-in-human clinical study.[44,45] In the phase 2 portion of the trial, 83 patients with ER+/HER2– advanced breast cancer that was refractory to endocrine therapy received H3B-6545 (450 mg).[46] The phase 2 analysis included 11 patients who had received H3B-6545 at the same dose in the phase 1 portion of the trial. The patients had a median age of 62 years, 81% had metastasis to the lung and/or liver, and the median number of prior lines of therapy for metastatic disease was 3 (range, 1-8). The majority of patients had previously received therapy comprising CDK4/6 inhibition (85%), AIs (80%), and/or fulvestrant (72%). *ESR1* mutations were detected by blood biopsy in 62% of patients. The most common AEs of at least grade 2 included anemia (19%), nausea (17%), and fatigue (16%). Grade 3 QTcF prolongation occurred in 3 patients. Among 94 patients, the ORR was 17%, and the median duration of response was 7.6 months (95% CI, 5.4 months-not evaluable). The clinical benefit rate was 32%, and the median PFS was 5.1 months (95% CI, 3.2-6.2).

CERANs

OP-1250 is a complete ER antagonist (CERAN) that

blocks ER transcription and causes receptor degradation.[47] In a phase 1/2 trial of 68 patients with ER+/HER2– previously treated advanced breast cancer, OP-1250 was administered orally at either 60 or 120 mg, daily. Patients had a median age of 61 years, 82% had visceral disease, and 41% had received 3 or more prior lines of therapy. The most common AEs of any grade were nausea (53%), fatigue (35%), and vomiting (31%). AEs of grade 3 or higher included nausea, fatigue, and vomiting, each observed in 3% of study participants. The clinical benefit rate was 29%. On the basis of manageable toxicity, absence of dose-limiting toxicities, and preliminary evidence of efficacy, the recommended phase 2 dose of OP-1250 is 120 mg, daily. OP-1250 is being evaluated in combination with other agents.[48,49]

All of these novel agents are now being tested in early-phase trials in combination with targeted agents, including CDK4/6 inhibitors. Results from ongoing or planned phase 3 trials are eagerly awaited.

Disclosures

Dr Rugo has served as a consultant or advisor to Daiichi Sankyo, Mylan, Napo Pharmaceuticals, and Puma, and has received institutional research support from Astellas Pharma, AstraZeneca, Daiichi Sankyo, F. Hoffmann-La Roche AG/Genentech, Gilead Sciences, GlaxoSmithKline, Lilly, Merck, Novartis, Pfizer, Pionyr Immunotherapeutics, Sermonix Pharmaceuticals, Taiho Oncology, and Veru.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol*. 1999;17(5):1474-1481.
3. Hwang KT, Kim J, Jung J, et al. Impact of breast cancer subtypes on prognosis of women with operable invasive breast cancer: a population-based study using SEER database. *Clin Cancer Res*. 2019;25(6):1970-1979.
4. National Comprehensive Cancer Network. NCCN Guidelines: Invasive Breast Cancer. Version 4.2022.
5. Burstein HJ, DeMichele A, Somerfield MR, Henry NL; Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels. Testing for *ESR1* mutations to guide therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline rapid recommendation update. *J Clin Oncol*. 2023;41(18):3423-3425.
6. Lei JT, Anurag M, Haricharan S, Gou X, Ellis MJ. Endocrine therapy resistance: new insights. *Breast*. 2019;48(suppl 1):S26-S30.
7. Will M, Liang J, Metcalfe C, Chandarlapaty S. Therapeutic resistance to anti-oestrogen therapy in breast cancer. *Nat Rev Cancer*. 2023;23(10):673-685.
8. Pagliuca M, Donato M, D'Amato AL, et al. New steps on an old path: novel estrogen receptor inhibitors in breast cancer. *Crit Rev Oncol Hematol*. 2022;180:103861.
9. Nagy Z, Jeselsohn R. *ESR1* fusions and therapeutic resistance in metastatic breast cancer. *Front Oncol*. 2023;12:1037531.
10. Nagy Z, Jeselsohn R. Corrigendum: *ESR1* fusions and therapeutic resistance in metastatic breast cancer. *Front Oncol*. 2023;13:1155540.
11. Lei JT, Gou X, Ellis MJ. *ESR1* fusions drive endocrine therapy resistance and metastasis in breast cancer. *Mol Cell Oncol*. 2018;5(6):e1526005.
12. Razavi P, Chang MT, Xu G, et al. The genomic landscape of endocrine-resistant advanced breast cancers. *Cancer Cell*. 2018;34(3):427-438.e6.
13. Brett JO, Spring LM, Bardia A, Wander SA. *ESR1* mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*. 2021;23(1):85.
14. Chandarlapaty S, Chen D, He W, et al. Prevalence of *ESR1* mutations in cell-free DNA and outcomes in metastatic breast cancer: a secondary analysis of the BOLERO-2 clinical trial. *JAMA Oncol*. 2016;2(10):1310-1315.
15. Clatot F, Perdrix A, Beaussire L, et al. Risk of early progression according to circulating *ESR1* mutation, CA-15.3 and cfDNA increases under first-line anti-aromatase treatment in metastatic breast cancer. *Breast Cancer Res*. 2020;22(1):56.
16. Zundelevich A, Dadiani M, Kahana-Edwin S, et al. *ESR1* mutations are frequent in newly diagnosed metastatic and loco-regional recurrence of endocrine-treated breast cancer and carry worse prognosis. *Breast Cancer Res*. 2020;22(1):16.
17. Turner NC, Swift C, Kilburn L, et al. *ESR1* mutations and overall survival on fulvestrant versus exemestane in advanced hormone receptor-positive breast cancer: a combined analysis of the phase III SoFEA and EFECT trials. *Clin Cancer Res*. 2020;26(19):5172-5177.
18. Zundelevich A, Dadiani M, Kahana-Edwin S, et al. Correction to: *ESR1* mutations are frequent in newly diagnosed metastatic and loco-regional recurrence of endocrine-treated breast cancer and carry worse prognosis. *Breast Cancer Res*. 2020;22(1):28.
19. 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*. 2023;37(1):169-181.
20. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of *ESR1* mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. *Sci Transl Med*. 2015;7(313):313ra182.
21. Russano M, Napolitano A, Ribelli G, et al. Correction to: Liquid biopsy and tumor heterogeneity in metastatic solid tumors: the potentiality of blood samples. *J Exp Clin Cancer Res*. 2020;39(1):120.
22. Russano M, Napolitano A, Ribelli G, et al. Liquid biopsy and tumor heterogeneity in metastatic solid tumors: the potentiality of blood samples. *J Exp Clin Cancer Res*. 2020;39(1):95.
23. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN trial. *J Clin Oncol*. 2023;41(24):4004-4013.
24. Orserdu [package insert]. New York, NY: Stemline Therapeutics, Inc; 2023.
25. Wardell SE, Nelson ER, Chao CA, Alley HM, McDonnell DP. Evaluation of the pharmacological activities of RAD1901, a selective estrogen receptor degrader. *Endocr Relat Cancer*. 2015;22(5):713-724.
26. Bihani T, Patel HK, Arlt H, et al. Elacestrant (RAD1901), a selective estrogen receptor degrader (SERD), has antitumor activity in multiple ER(+) breast cancer patient-derived xenograft models. *Clin Cancer Res*. 2017;23(16):4793-4804.
27. Patel HK, Tao N, Lee KM, et al. Elacestrant (RAD1901) exhibits anti-tumor activity in multiple ER+ breast cancer models resistant to CDK4/6 inhibitors. *Breast Cancer Res*. 2019;21(1):146.
28. Bardia A, Kaklamani V, Wilks S, et al. Phase I study of elacestrant (RAD901), a novel selective estrogen receptor degrader, in ER-positive, HER2-negative advanced breast cancer. *J Clin Oncol*. 2021;39(12):1360-1370.
29. Jager A, de Vries EGE, der Houven van Oordt CWM, et al. A phase 1b study evaluating the effect of elacestrant treatment on estrogen receptor availability and estradiol binding to the estrogen receptor in metastatic breast cancer lesions using ^{18}F-FES PET/CT imaging. *Breast Cancer Res*. 2020;22(1):97.
30. Bardia A, Aftimos P, Bihani T, et al. EMERALD: phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer. *Future Oncol*. 2019;15(28):3209-3218.
31. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
32. Bardia A, Bidard FC, Neven P, et al. EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting [SABCS abstract GS3-01]. *Cancer Res*. 2022;82(4)(suppl).
33. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*.

2009;45(2):228-247.
34. ClinicalTrials.gov. Open-label umbrella study to evaluate safety and efficacy of elacestrant in various combination in patients with metastatic breast cancer (ELEVATE). https://classic.clinicaltrials.gov/ct2/show/NCT05563220. Identifier: NCT05563220. Updated August 31, 2023. Accessed October 13, 2023.
35. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol*. 2008;26(10):1664-1670.
36. Johnston SR, Kilburn LS, Ellis P, et al; SoFEA investigators. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. 2013;14(10):989-998.
37. 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*. 2020;21(10):1296-1308.
38. Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. *NPJ Breast Cancer*. 2023;9(1):20.
39. Scott JS, Moss TA, Balazs A, et al. Discovery of AZD9833, a potent and orally bioavailable selective estrogen receptor degrader and antagonist. *J Med Chem*. 2020;63(23):14530-14559.
40. Oliveira M, Pominchuk D, Hamilton EP, et al. Clinical activity of camizestrant, a next-generation SERD, versus fulvestrant in patients with a detectable *ESR1* mutation: exploratory analysis of the SERENA-2 phase 2 trial [ASCO abstract 1066]. *J Clin Oncol*. 2023;41(16)(suppl).
41. Jhaveri KL, Jeselsohn R, Lim E, et al. A phase 1a/b trial of imlunestrant (LY3484356), an oral selective estrogen receptor degrader (SERD) in ER-positive (ER+) advanced breast cancer (aBC) and endometrial endometrioid cancer (EEC): monotherapy results from EMBER [ASCO abstract 1021]. *J Clin Oncol*. 2022;40(16)(suppl).
42. Grinshpun A. Clinician's guide to targeted estrogen receptor degradation using PROTAC in patients with estrogen receptor-positive metastatic breast cancer. *Curr Opin Oncol*. 2023;35(6):472-478.
43. Hamilton E, Vahdat L, Han HS, et al. First-in-human safety and activity of ARV-471, a novel PROTAC estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer [SABCS abstract PD13-08]. *Cancer Res*. 2022;82(4)(suppl).
44. Furman C, Puyang X, Zhang Z, et al. Covalent ERα antagonist H3B-6545 demonstrates encouraging preclinical activity in therapy-resistant breast cancer. *Mol Cancer Ther*. 2022;21(6):890-902.
45. Hamilton EP, Wang JS, Pluard TJ, et al. Phase I/II study of H3B-6545, a novel selective estrogen receptor covalent antagonist (SERCA), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer [ASCO abstract 1018]. *J Clin Oncol*. 2021;39(15)(suppl).
46. Hamilton EP, Wang JS, Pluard TJ, et al. H3B-6545, a novel selective estrogen receptor covalent antagonist (SERCA), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer - a phase II study [SABCS abstract P1-17-10]. *Cancer Res*. 2022;82(4)(suppl).
47. Hamilton E, Meisel J, Alemany C, et al. Preliminary phase 1/2 results from OP-1250-001, a study of OP-1250, an oral CERAN/SERD, in patients with advanced and/or metastatic estrogen receptor-positive, HER2-negative breast cancer (NCT04505826). Presented at: EORTC-NCI-AACR Molecular Targets and Cancer Symposium; October 26-28, 2022; Barcelona, Spain. Abstract 101.
48. Chan A, Dinh P, Day D, et al. A phase 1b/2 study of OP-1250, an oral complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD) with palbociclib in patients with advanced or metastatic HR+/HER2- breast cancer [ESMO Breast Cancer Annual Congress abstract 202P]. *Ann Oncol*. 2023;8(suppl 4):101223.
49. Borges VF, Chan A, Lin NU, et al. A phase 1b dose escalation and expansion study of OP-1250 in combination with ribociclib or alpelisib in patients with advanced and/or metastatic estrogen receptor-positive (ER+)/HER2- breast cancer [ASCO abstract TSP1127]. *J Clin Oncol*. 2022;41(16)(suppl).