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# New Oral Selective Estrogen Receptor Degraders Redefine Management of Estrogen Receptor–Positive Breast Cancer

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## Keywords

selective estrogen receptor degrader, SERD, breast cancer, estrogen receptor, elacestrant, camizestrant, giredestrant, imlunestrant, amcenestrant

## Abstract

Oral selective estrogen receptor degraders (SERDs) are pure estrogen receptor antagonists that have the potential to overcome common resistance mechanisms to endocrine therapy in estrogen receptor–positive breast cancer. There are currently five oral SERDs in published and ongoing clinical trials—elacestrant, camizestrant, giredestrant, imlunestrant, and amcenestrant—with more in development. They offer a reasonably well-tolerated oral therapy option with low discontinuation rates in studies. This review summarizes the currently available literature on this new class of drugs.

## BACKGROUND

The outcomes for breast cancer (BC) have improved, with a 5-year survival rate crossing 90% for the disease overall (1). Advancements in molecular categorization, directed treatments, and newer targeted therapeutic agents have contributed significantly to this progress (2). Endocrine therapy (ET) is the cornerstone of the management of estrogen receptor–positive (ER+)—and/or progesterone receptor–positive—BC, which constitutes ~75% of all BCs (3). Approved therapies targeting the endocrine/ER pathway include selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), the selective estrogen receptor degrader (SERD) fulvestrant, and, more recently, the oral SERD elacestrant. Additional oral SERDs, complete estrogen receptor antagonists (CERANs), proteolysis-targeting chimeras (PROTACs), and selective estrogen receptor covalent antagonists (SERCAs) have also entered clinical trials (4).

ERs are steroid hormone nuclear receptors that bind to estrogen, then dimerize and translocate to the nucleus (5). Thereafter, ER dimers bind to estrogen coactivators to form transcriptionally active ER complexes, which then bind to estrogen response elements (EREs) in the DNA. This results in cellular proliferation through the transcription of prosurvival genes and cellular signaling (5, 6). SERMs like tamoxifen bind to ERs; these complexes then bind to EREs and associate with corepressors in the breast to exert antiestrogenic effects. AIs inhibit the conversion of androgen, which is the main source of estrogen in postmenopausal women, to estrogen (4). Several mechanisms lead to resistance to conventional ET, particularly resistance to AIs. These mechanisms include ligand-independent activation of ERs, which may occur through mutations in the gene coding for ER alpha (*ESR1*); growth factor receptor amplification (e.g., HER2); and activation of oncogenic signaling pathways (e.g., *PI3K/AKT/mTOR*, *RAS/RAF/MEK/ERK*) (6). This resistance can be primary, defined as disease progression within 6 months of initiating ET in patients with metastatic breast cancer (MBC) and/or relapse within 2 years of initiating adjuvant ET for early breast cancer (EBC), or secondary, defined as disease progression after at least 6 months of ET in patients with metastatic BC and/or after at least 2 years of adjuvant ET or within 1 year of finishing adjuvant ET for EBC (7). Approximately 30–40% of patients with BC develop secondary resistance to ET, while 15–30% have primary resistance (8). While these definitions may be useful in clinical research, their utility is limited in clinical practice, as they apply mainly to treatment with single-agent ET and do not fully capture the variety of clinical scenarios involving patients with ER+ BC.

SERDs are pure ER antagonists that bind to ERs, which prevents ERs from translocating to the nucleus or binding to EREs, ultimately leading to their proteasomal degradation. Fulvestrant, a 7α-alkylsulphinyl analog of 17β-estradiol, was the first SERD developed; it showed no cross-reactivity to tamoxifen and demonstrated efficacy after AIs in metastatic ER+ BC (9). Fulvestrant is administered intramuscularly, which limits its bioavailability (10). Oral SERDs have the potential to overcome the pharmacological limitations of fulvestrant, and several are currently in development. This review summarizes the relevant literature on oral SERDs and future research directions.

## ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADERS: OVERVIEW AS A CLASS

Five oral SERDs are currently in various stages of evolution. One (elacestrant) was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in ER+ MBC with mutated *ERS1* (*ESR1*m). Most of the available data for these agents come from the metastatic setting, where endocrine resistance is a concern, especially after the current standard first-line therapy, which is a combination of a cyclin-dependent 4/6 kinase inhibitor (CDK4/6i) and ET.



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Approximately 45% of all patients exposed to AIs have *ESR1*m (11). Fulvestrant may have limited activity in tumors with *ESR1*m. This is partly due to the intramuscular route of administration, which limits its bioavailability (12). However, even with higher per-cycle doses of fulvestrant, such as those used in cohort A of the PlasmaMatch study in patients with identified *ESR1*m (500 mg on days 1, 8, and 15 in cycle 1 and on days 1 and 15 in cycle 2 onward), the activity of fulvestrant is limited (49). Oral SERDs may circumvent this limitation, and they have demonstrated efficacy in tumors with *ESR1*m, as shown below.

**Table 1** summarizes the available data on oral SERDs in the metastatic setting, while **Table 2** summarizes ongoing clinical trials. In the nonmetastatic realm, a number of ongoing studies are testing oral SERDs alone and/or combined with other agents (**Table 2**).

**Table 1 Comparison of oral selective estrogen receptor degraders based on largest available datasets**

| | EMERALD | SERENA-2 | AMEERA-3 | acelERA | EMBER |
|---|---|---|---|---|---|
| Phase | III | II | II | II | I |
| SERD, dose QD | Elacestrant, 400 mg (13) | Camizestrant, 75 mg/150 mg (21) | Amcenestrant, 400 mg (33) | Giredestrant, 30 mg (24) | Imlunestrant, 400 mg (30) |
| *n* | 477 | 240 | 290 | 303 | 114 |
| Control | PCET | F | PCET | PCET | NA |
| ESR1m | 47.8% | 36.7% | 41.3% | 39% | 49% |
| Visceral | 70% | 58.3% | 63.7% | NA | 63% |
| Prior F | 29% | 0% | 9.7% | 19% | 52% |
| Prior CDK4/6i | 100% | 51% | 79% | 42% | 93% |
| PFS, overall | 2.9 vs. 1.91 months (HR, 0.70; 95% CI, 0.55–0.88) | 75 mg: 7.2 vs. 3.7 months (HR, 0.58; 95% CI, 0.41–0.81)<br>150 mg: 7.7 vs. 3.7 months (HR, 0.67; 95% CI, 0.48–0.92 | 3.6 vs. 3.7 months (HR, 1.05; 95% CI, 0.79–1.4) | 5.6 vs. 5.4 months (HR, 0.81; 95% CI, 0.60–1.10) | 4.3 months (95% CI, 3.6–7.1)<br>Post-CDK4/6i: 6.5 months (95% CI, 3.7–8.3) |
| PFS, ESR1m | 3.8 vs. 1.9 months (HR, 0.55; 95% CI, 0.39–0.77) | 75 mg: 6.3 vs. 2.2 months (HR, 0.33; 95% CI, 0.18–0.58)<br>150 mg: 9.2 vs. 2.2 months (HR, 0.55; 95% CI, 0.33–0.89) | 3.7 vs. 2.0 months (HR, 0.9; 95% CI, 0.57–1.44) | 5.3 vs. 3.5 months (HR, 0.60; 95% CI, 0.35–1.03) | NA |
| ORR | NA | 16% vs. 20% | 5% vs. 3% (ESR1m) | 13% vs. 7% | 8% |
| Grade ≥3 AE (independent of causality) | 27% vs. 20.5%; nausea (2.5% vs. 0.9%), back pain (2.5% vs. 0.9%), increased alanine aminotransferase (2.1% vs. 0.9%) | 12.2% (75 mg) and 21.9% (150 mg) vs. 13.7% (F) | 26.7% vs. 16.3%; 2.4% discontinued due to AEs | 17% vs. 12% | 3.6% |

Abbreviations: AE, adverse event; CDK4/6i, cyclin-dependent 4/6 kinase inhibitor; CI, confidence interval; F, fulvestrant; HR, hazard ratio; ESR1m, mutated estrogen receptor 1; *n*, sample size; NA, not applicable; ORR, overall response rate; PFS, progression-free survival; QD, every day; SERD, selective estrogen receptor degrader; PCET, the physician's choice of endocrine therapy.



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## ELACESTRANT

Elacestrant was the first oral SERD approved by the FDA and EMA for use in patients with ER+ MBC with *ESR1*m. This was based on the results from the phase III EMERALD study (13), where 477 patients with ER+ MBC who had progressed on CDK4/6i were randomized between elacestrant and standard-of-care (SOC) ET (here, the physician's choice of ET was an

**Table 2 Selective list of ongoing studies of oral selective estrogen receptor degraders and similar agents**

| Trial, phase | Agent/control | Setting | Primary endpoint |
|---|---|---|---|
| **Adjuvant** | | | |
| NCT05512364, III; TREAT ctDNA | Elacestrant/SOC ET | Stage IIb–III or ≥ ypT1c and/or ypN+ ER+/HER2− BC with ctDNA monitoring; when ctDNA+ and no metastatic disease, randomized to elacestrant or same ET as before | Distant metastasis-free survival |
| NCT05774951, III; CAMBRIA-1 | Camizestrant/SOC ET | ER+/HER2− early BC after locoregional treatment, 2 years of ET +/− CDK4/6i, with intermediate/high risk of recurrence | Invasive breast cancer-free survival |
| NCT05952557, III; CAMBRIA-2 | Camizestrant/SOC ET | ER+/HER2− early BC after locoregional treatment, with intermediate/high risk of recurrence | Invasive breast cancer-free survival |
| NCT04961996, III; lidERA | Giredestrant/SOC ET | ER+/HER2− early BC after locoregional treatment | Invasive disease-free survival |
| NCT05514054, III; EMBER-4 | Imlunestrant/SOC ET | ER+/HER2− early BC after locoregional treatment, 2 years of ET +/− CDK4/6i, with increased risk of recurrence | Invasive disease-free survival |
| **Metastatic** | | | |
| NCT04711252, III; SERENA-4 | Camizestrant + palbociclib/ anastrozole + palbociclib | First-line treatment for advanced or metastatic ER+ (>10% immunohistochemistry)/HER2− BC | PFS |
| NCT04964934, III; SERENA-6 | Camizestrant + CDK4/6i/ continuing the same aromatase inhibitor + CDK4/6i | Patients with *ESR1*m identified while on first-line treatment with CDK4/6i + ET and no evidence or radiological disease progression | PFS |
| NCT04546009, III; persevERA | Giredestrant + palbociclib/ letrozole + palbociclib | First-line treatment for advanced or metastatic ER+/HER2− BC | PFS |
| NCT05306340, III; evERA | Giredestrant + everolimus/ exemestane + everolimus | ER+/HER2− MBC after prior CDK4/6i + ET in either the locally advanced/metastatic or adjuvant setting | PFS |
| NCT04975308, III; EMBER-3 | Imlunestrant or imlunestrant + abemaciclib/SOC ET | ER+/HER2− MBC after prior ET +/− CDK4/6i | PFS |

(*Continued*)



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**Table 2** (*Continued*)

| Trial, phase | Agent/control | Setting | Primary endpoint |
|---|---|---|---|
| **PROTAC** | | | |
| NCT05654623, III; VERITAC-2 | Vepdegestrant/fulvestrant | ER+/HER2− MBC after prior ET +/− CDK4/6i | PFS |
| NCT05909397, III; VERITAC-3 | Vepdegestrant + palbociclib/ letrozole + palbociclib | Treatment-naïve ER+/HER2− MBC | PFS |
| NCT05548127 substudy A and NCT05573555 substudy B, Ib/II umbrella study; TACTIVE-U | A: Vepdegestrant + abemaciclib<br>B: Vepdegestrant + ribociclib | ER+/HER2− MBC after prior ET +/− CDK4/6i, up to two prior lines of therapy | Phase Ib: dose-limiting toxicities<br>Phase II: overall response rate |
| **SERCA** | | | |
| NCT04288089, I | H3B-6545 + palbociclib | ER+ MBC after three lines of therapy | Median tolerated dose |
| **CERAN** | | | |
| NCT05508906, Ib/II | OP-1250 + ribociclib<br>OP-1250 + alpelisib | ER+ MBC; prior CDK4/6i and chemotherapy allowed | Safety and pharmacokinetics |
| **Novel SERM** | | | |
| NCT04432454, II; ELAINE II | Lasofoxifene + abemaciclib | ER+ MBC with *ESR1*m on ctDNA testing | Safety |

Abbreviations: BC, breast cancer; CDK4/6i, cyclin-dependent 4/6 kinase inhibitor; CERAN, complete estrogen receptor antagonist; ctDNA, circulating tumor DNA; ER, estrogen receptor; ET, endocrine therapy; MBC, metastatic breast cancer; PFS, progression-free survival; PROTAC, proteolysis-targeting chimera; SERCA, selective estrogen receptor covalent antagonist; SERM, selective estrogen receptor modulator; SOC, standard of care.

AI or fulvestrant). Elacestrant demonstrated a statistically significant benefit in the overall patient population, with a 30% reduction in the risk of progression or death (13) (**Table 1**) and a median progression-free survival (PFS) of 2.9 months (versus 1.9 months in the SOC arm). This small difference could potentially be explained by the fact that some patients likely had endocrine-resistant disease, a context where any ET, including elacestrant, would have limited benefit (14). In the *ESR1*m population, the gain in PFS exceeded that seen in the overall population [median 3.8 months versus 1.9 months; hazard ratio (HR), 0.55; 95% confidence interval (CI), 0.39–0.77]. The overall survival results were not statistically significant at interim analysis.

In the EMERALD study, the magnitude of benefit in PFS observed with elacestrant was different according to the duration of prior CDK4/6i, which may be a surrogate marker for endocrine sensitivity. Overall, in patients who were on prior CDK4/6i for at least 12 months, the median PFSs of elacestrant and SOC were 3.8 months and 1.9 months, respectively (HR, 0.613; 95% CI, 0.453–0.828); this increased to 5.5 months and 3.3 months, respectively, in patients on prior CDK4/6i for at least 18 months (15). Among patients with *ESR1*m, PFS was higher in the cohorts with longer durations of prior CDK4/6i; patients with ≥18 months of CDK4/6i exposure had a median PFS of 8.6 months with elacestrant versus 2.1 months with SOC (15).

Elacestrant was generally well tolerated, and most of the observed adverse events (AEs) were grade 1 or 2. Frequent AEs of all grades included nausea (35.0%), fatigue (19.0%), vomiting (19.0%), decreased appetite (14.8%), and arthralgia (14.3%). The most frequent grade 3/4 AEs included nausea (2.5%), back pain (2.5%), and increased alanine aminotransferase (2.1%) (**Table 1**). The rate of elacestrant discontinuation due to AEs was low (6.3% versus 4% in the control group).

Elacestrant can also be combined with other targeted drugs. ELEVATE is a phase I/IIb umbrella trial investigating the combination of elacestrant with alpelisib, a CDK4/6i, and



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everolimus at different doses, among others (16). Initial results were reported at the San Antonio Breast Cancer Symposium (SABCS) 2023. The 26 enrolled patients were given elacestrant in combination with alpelisib ($n = 8$), everolimus ($n = 6$), palbociclib ($n = 6$), or ribociclib ($n = 6$). Most adverse events were grade 1/2 and consisted of nausea, fatigue, and rash. Dose-limiting toxicities were observed in the alpelisib + elacestrant group in the form of a grade 3 rash. Lower doses of alpelisib in the combination are being explored (NCT05563220). The ELECTRA study (NCT05386108) is another phase I/IIb study evaluating elacestrant + abemaciclib in patients with ER+ MBC and brain metastases; neutropenia, diarrhea, and nausea were the most common all-grade toxicities, with neutropenia being the most common grade 3 side effect (17).

In the neoadjuvant setting, a preoperative trial demonstrated that 4 weeks of elacestrant before SOC treatment in 22 postmenopausal women with T1c–T3 N0 ER+ BC suppressed tumor proliferation in the surgical specimen (Ki-67 $\leq$ 2.7%, cell cycle arrest in $n = 6$) and rendered the tumor more endocrine sensitive and less proliferative on genetic testing (18). Ongoing trials with elacestrant are summarized in **Table 2**.

## CAMIZESTRANT

The phase I SERENA-1 study investigated camizestrant both as a single agent and in combination with palbociclib, abemaciclib, ribociclib, everolimus, or capivasertib in patients with ER+/HER2− MBC previously exposed to ET. Camizestrant showed a manageable safety profile with low-grade AEs (mainly asymptomatic sinus bradycardia and grade 1 visual alterations) and activity in heavily pretreated patients (19, 20).

SERENA-2 was a randomized phase II trial comparing different doses of camizestrant (75 mg, 150 mg, and 300 mg) with SOC fulvestrant in postmenopausal patients previously treated with ET (21). Among the 240 patients enrolled, approximately half had received prior CDK4/6i, according to the prespecified enrollment plan. In addition to prior treatment with CDK4/6i, patients were stratified by the presence of lung or liver metastasis. After 20 patients were included in the camizestrant 300 mg arm, the decision to discontinue treatment with this dose was made. The primary endpoint was PFS in all included patients, and the study was powered to detect differences between each of the camizestrant arms and fulvestrant, but it was not powered to compare camizestrant doses. Camizestrant at both 75 mg and 150 mg was superior to fulvestrant in terms of PFS, with HRs of 0.58 (95% CI, 0.41–0.81) and 0.67 (95% CI, 0.48–0.92), respectively. The median PFS was 7.2 months for camizestrant 75 mg, 7.7 months for camizestrant 150 mg, and 3.7 months for fulvestrant.

Camizestrant was superior to fulvestrant in all subgroups analyzed. In patients with detected *ESR1*m, the HRs for PFS were 0.33 (95% CI, 0.18–0.58) and 0.55 (95% CI, 0.33–0.89) for 75 mg and 150 mg, respectively. In patients with prior CDK4/6i, the median PFS was 5.5 months (HR, 0.49; 95% CI, 0.31–0.75) and 3.8 months (HR, 0.68; 95% CI, 0.44–1.04) in the 75 mg and 150 mg dose cohorts, respectively, versus 2.1 months in the control. Treatment was well tolerated, with a 2.7% discontinuation rate in the camizestrant 75 mg arm and no discontinuation in the other two arms. Photopsia (18.4%) and sinus bradycardia (13.6%) were distinct side effects and were more frequent with camizestrant 150 mg than with the 75 mg dose (24.7% versus 12.2% and 26% versus 5.4%, respectively). Camizestrant is being further studied in the advanced setting in the SERENA-4 (NCT04711252) and SERENA-6 (NCT04964934) trials (**Table 2**).

The preoperative window-of-opportunity SERENA-3 trial tested camizestrant at different doses (75 mg, 150 mg, and 300 mg) and durations (5–7 days and 12–14 days). The primary endpoint was the change in ER immunohistochemistry H-score in pre-/posttreatment biopsies, and secondary endpoints included Ki-67 and progesterone receptor changes, pharmacokinetics,



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and safety. A total of 135 patients were included; 76 received 5–7 days of camizestrant at 75 mg ($n = 30$), 150 mg ($n = 33$), and 300 mg ($n = 13$), and 59 received 12–15 days of camizestrant at 75 mg ($n = 30$) and 150 mg ($n = 29$). ER levels at baseline and degree of degradation on treatment were similar across the 75 mg, 150 mg, and 300 mg doses and across the different durations of exposure. Interestingly, different doses led to different Ki-67 decreases in patients exposed to 5–7 days of treatment, but for those receiving camizestrant for 12–15 days, Ki-67 decreases were similar, with an 82% reduction overall. This suggests that the 75 mg dose of camizestrant achieves maximal levels of ER degradation, antagonism, and downstream Ki-67 suppression, and, in fact, this dose has been selected for all ongoing camizestrant trials (22).

Currently, there are two ongoing adjuvant phase III trials testing camizestrant—CAMBRIA-1 and CAMBRIA-2 (**Table 2**)—with the primary endpoint of invasive BC-free survival in patients at intermediate to high risk of recurrence. CAMBRIA-1 (NCT05774951) assesses the addition of camizestrant to standard adjuvant ET after 2 years of ET +/− CDK4/6i. In the CAMBRIA-2 trial (NCT05952557), camizestrant is started within 12 weeks of ET initiation, concurrent with CDK4/6i if indicated. Ongoing trials with camizestrant are shown in **Table 2**.

## GIREDESTRANT

The phase Ia/b study by Jhaveri et al. (23) evaluated different doses of giredestrant as a single agent and in combination with palbociclib in patients with ER+ MBC who had progressed on ET. For single-agent giredestrant at different dose levels, the overall response rate (ORR) was 19.8% among 111 patients. All-grade toxicities were present in 65% of patients, and grade ≥3 AEs were present in 4.5% of patients. Common AEs were fatigue (16.2%), arthralgia (11.7%), nausea (9.9%), and bradycardia (8.1%). All bradycardia events were asymptomatic, clinically manageable, and reversible. Photopsia was described in 6.3% of patients (all grade 1 and transient).

The acelERA randomized phase II trial tested giredestrant as second-line therapy versus the ET of the physician's choice in the metastatic setting. In this trial, 303 pre- and postmenopausal women and men were included, with 28% of participants previously receiving two lines of treatment in the advanced setting. Giredestrant failed to demonstrate superiority over ET in terms of PFS and ORR both in the overall population and in the *ESR1*m population (24) (**Table 1**). Updated results were presented at SABCS 2022, and an exploratory biomarker analysis showed that patients whose tumors harbored *ESR1*m had a PFS benefit when given giredestrant over the ET of the physician's choice (HR, 0.55; 95% CI, 0.33–0.93), suggesting that this population could potentially benefit from giredestrant (25). In the acelERA trial, the side effects of giredestrant included fatigue, arthralgias, nausea, and grade 1/2 bradycardia (26).

In the window-of-opportunity phase II study cooPERA, giredestrant + palbociclib versus anastrozole + palbociclib was evaluated in patients with ER+ MBC with tumors ≥1.5 cm in size and baseline Ki-67 scores ≥5%. This study met its primary endpoint of geometric mean relative Ki-67 score change of –75% (95% CI, –80 to –70) versus –67% (95% CI, –73 to –59), $p = 0.043$ (27). These results suggest that giredestrant is more potent than standard ET in terms of antiproliferative effects in ER+ BC.

The recent MORPHEUS study demonstrated an impressive ORR of 47% with giredestrant + inavolisib (a PI3Kα-selective inhibitor) in patients with ER+ MBC after CDK4/6i. Similarly, giredestrant in combination with palbociclib had an ORR of 48.2% (23). The ongoing phase III double-blind randomized trial persevERA (NCT04546009) is comparing the efficacy and safety of giredestrant + palbociclib versus letrozole + palbociclib as first-line therapy in patients with ER+ MBC.

In the adjuvant setting, giredestrant is under evaluation through the ongoing lidERA study (NCT04961996), which is testing this agent against the physician's choice of ET for a minimum



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of 5 years in patients with protocol-defined medium- to high-risk ER+ BC. Ongoing studies with giredestrant are summarized in **Table 2**.

## IMLUNESTRANT

Imlunestrant is a potent antagonist and degrader of ERs and shows synergistic or additive inhibitory effects both in vitro and in vivo in combination with other drugs such as abemaciclib, everolimus, and alpelisib (28). The phase I EMBER study evaluated imlunestrant with or without abemaciclib, everolimus, alpelisib, trastuzumab, or an AI for ER+ MBC and endometrial endometrioid cancer after platinum therapy (29). A total of 141 patients were included (114 with BC) with a median age of 62 years and after a median of two lines of therapy, which could include a CDK4/6i and/or chemotherapy. Overall, the ORR of single-agent imlunestrant was 8%. In the subgroup of patients with prior CDK4/6i treatment (92% of the population), PFS was 6.5 months (95% CI, 3.6–8.3). Among the *ESR1*m population ($n = 53$), the median PFS was 5.4 months (95% CI, 3.7–7.5). The recommended phase II dose of imlunestrant was 400 mg every day. AEs were mostly grade 1/2, with nausea (33.3%), fatigue (27.5%), and diarrhea (23.2%) as the most frequent. Grade ≥3 AEs were infrequent (3.6% of patients), and there were no discontinuations due to AEs (29).

In the imlunestrant + abemaciclib +/− AI cohort, 85 patients with ER+ MBC were included. The documented ORR was 36% for imlunestrant + abemaciclib and 44% when AI was added (30). Although the incidence of AEs was higher, dose reductions occurred in <10% of patients, and no discontinuations due to AEs were observed (30).

In the preoperative setting, imlunestrant was given for 2 weeks to 100 patients with stage I–III ER+ BC and tumors ≥1 cm in size (the EMBER-2 trial). Imlunestrant induced a geometric mean percentage change of 81% for ERs and 73% for Ki-67 (31).

Phase II and III studies are in the pipeline for this agent. EMBER-3 (NCT04975308) is a three-arm study evaluating imlunestrant with or without abemaciclib versus SOC ET in patients with ER+ MBC after CDK4/6i. EMBER-4 (NCT05514054) is a phase III trial in the adjuvant setting evaluating the addition of imlunestrant to adjuvant ET in patients who have received at least 2 years of prior endocrine treatment (**Table 2**).

## AMCENESTRANT

Despite promising activity in the early clinical setting (32), negative results from subsequent trials led to the decision to discontinue amcenestrant development. The phase II study AMEERA-3 (33) randomized postmenopausal patients with ER+ MBC previously treated with a maximum of two lines of ET to receive either amcenestrant or SOC ET. Treatment with amcenestrant was not superior to SOC ET in terms of PFS, both in the overall population and the *ESR1*m subgroup (**Table 1**). The randomized phase III trial AMEERA-5 tested amcenestrant + palbociclib versus ET + palbociclib in the first-line setting. A prespecified interim analysis of this trial did not meet the study's prespecified boundary of continuation (34).

## ADDING NEWER AGENTS TO THE ARMAMENTARIUM

Additional oral SERDs are currently in the early phases of development. Rintodestrant (35) and D-0502 (36), for example, are oral SERDs with preliminary phase I data showing good tolerability. They have been evaluated in combination with palbociclib and have ORRs of 5% and 15%, respectively. Borestrant has demonstrated activity in xenograft models (37), and a phase I study (NCT04669587) is ongoing. Palazestrant is a unique combination of a CERAN and a SERD that inhibits both *ESR1*m and wild-type BC cell lines (38). This agent has shown activity



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in early results from ongoing phase I/II studies (39) and is being evaluated in combination with other agents (40), including TFX-06 and SIM0270, which had safety data presented at SABCS 2023, and FWD 1802, which has activity at the cellular level and is awaiting human study results.

Alongside the development of SERDs, other drugs that affect the ER pathway by different routes are in development and undergoing early testing. Comprehensive reviews of these novel molecules are outside the scope of this article and can be found elsewhere, but in summary they include:

- PROTACs. These are a unique set of heterobifunctional small molecules that have three parts: a ligand for the target protein, a linker, and a ligand to recruit E3 ligase. Because they result in complete degradation of ERs and destabilize ER complexes, it is hypothesized that they will retain activity despite resistance mutations such as *ESR1*m. Due to their catalytic activity and potential to be recycled, it is possible that low doses (which have fewer side effects) may be sufficient for effect. Vepdegestrant, or ARV-471, which targets ERs, is one such compound (41, 42). Vepdegestrant in two doses (200 mg and 500 mg once daily) was compared to fulvestrant in a phase I/II study (VERITAC) that included a heavily pretreated patient population, with a median of four lines of prior therapy in any setting (100% of patients were exposed to CDK4/6i, 79% to fulvestrant, and 45% to chemotherapy in the metastatic setting) (43). In the phase II cohort, which included 35 patients, vepdegestrant at 200 mg daily demonstrated a clinical benefit rate (primary endpoint) of 37% and a median PFS of 3.5 months. For the *ESR1*m population, the corresponding benefits were 47% and 5.5 months, respectively. Common AEs, which were mostly grade 1/2, were fatigue (40%), hot flushes (17%), nausea (14%), and arthralgia (11%). Only 2 of the 35 patients had a grade 3/4 event: one patient developed thrombocytopenia and hyperbilirubinemia, and the other developed $QT_C$ prolongation leading to treatment discontinuation (43). Ongoing phase III studies are evaluating vepdegestrant alone after CDK4/6i (VERITAC-2, NCT05654623) and as first-line therapy in combination with palbociclib (VERITAC-3, NCT05909397) (**Table 2**).
- SERCAs. These molecules covalently bind to the cysteine residue of ERs, which is not present in other receptors. Early-phase studies of H3B-6545 have shown initial evidence of efficacy and no dose-limiting side effects (44, 45).
- CERANs. These molecules are so named because they block both transcriptional domains of ERs, unlike SERMs, which block only one. Certain molecules, such as OP-1250, can act as both a CERAN and a SERD (46).
- SERMs. Lasofoxifene is a next-generation nonsteroidal SERM that has a greater binding affinity than conventional agents like tamoxifen. This agent demonstrated early efficacy; however, it did not improve PFS in comparison to fulvestrant in a phase II study (47). Lasofoxifene is currently under evaluation in additional prospective trials (**Table 2**).

## SUMMARY AND FUTURE DIRECTIONS

Oral SERDs are a fast-emerging ET with the potential to become the new SOC in patients with ER+/HER2− BC. Their activity can overcome resistance from *ESR1*m, which is seen in approximately 40–45% of patients exposed to AIs, and they are active in the post-CDK4/6i space, a current unmet clinical need. The side-effect profile of oral SERDs is acceptable, with low discontinuation rates in reported clinical trials.

Whether SERDs' activity is restricted to *ESR1*m tumors or relies on increased antiendocrine potency compared to currently approved drugs is now being tested in prospective trials. Reported responses to oral SERDs have been heterogeneous, with 30–50% of patients progressing at the



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first tumor assessment. Whether this is due to the presence of endocrine resistance or activation of alternative pathways (or a mixture of both) is currently a subject of research. Initial biomarker analysis results presented at SABCS 2023 suggest that tumors from patients with rapid progression may have enriched activation of alternative pathways such as RAS/MAPK and PI3K, and there is the potential to use combination therapies in this context. Patients with long-term benefit, in turn, have tumors that are more dependent on the ER pathway (48). Additional studies are needed to fully characterize the biomarkers of response and resistance to these agents.

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