Current Breast Cancer Reports (2024) 16:402–416
https://doi.org/10.1007/s12609-024-00563-0

REVIEW

Selective Estrogen Receptor Degraders (SERDs)

Melissa Taylor[1] · Adriana Kahn[1] · Julia Foldi[2]

Accepted: 14 July 2024 / Published online: 26 July 2024

Abstract

Purpose of Review Update on the most recent clinical evidence on selective estrogen receptor degraders (SERDs) in the treatment of hormone receptor (HR)-positive (HR +), human epidermal growth factor receptor 2 (HER2)-negative (HER2-) breast cancer.

Recent Findings Despite effective endocrine therapies, resistance commonly develops during treatment of HR + breast cancer and mutations in *ESR1* account for a large proportion of resistance mechanisms. After demonstration of the superior efficacy of fulvestrant in *ESR1*-mutated tumors, recent advances allowed the development of a novel class of orally bioavailable selective estrogen receptor degraders (SERDs), which are beginning to revolutionize the field. The first approved oral SERD, elacestrant, is currently used in the second-line treatment of HR + /HER2- metastatic breast cancer, and a number of other oral SERDs are undergoing clinical evaluation in both the metastatic and early-stage settings.

Summary SERDs are a rapidly developing class of antiestrogens that show activity in treatment of tumors harboring *ESR1* mutations associated with resistance to earlier generations of endocrine therapy, but knowledge gaps remain, and further research is necessary to better define their optimal use.

Keywords Hormone receptor positive breast cancer · Endocrine therapy · Estrogen receptor · Selective estrogen receptor degraders

Introduction

Breast cancer is the most common type of cancer affecting women and the second leading cause of cancer death for women in the US (not accounting for skin cancers). It is estimated that in 2024 there will be 310,720 new cases of female breast cancer. The most common type of breast cancer is hormone receptor (HR)-positive (HR +) and human epidermal growth factor receptor 2 (HER2)-negative (HER2-), which makes up about 70% of all female breast cancer cases [1]. The mainstay of systemic treatment for HR + breast cancers is endocrine therapy (ET), which aims to slow tumor growth by starving tumors of estrogen either by reducing the levels of circulating estrogen or by acting at its receptor. Until recently, the only oral ET options available in routine clinical practice were aromatase inhibitors (AIs) and the selective estrogen receptor (ER) modulator (SERM), tamoxifen. A major clinical challenge in the treatment of HR + breast cancers is the development of endocrine resistance, which has been driving the development of novel treatments with differing mechanisms of action. Fulvestrant, an injectable selective ER degrader (SERD), a newer class of ET that targets the ER for proteasome-dependent degradation, thereby is able to overcome resistance mechanisms to AIs and tamoxifen. In the metastatic breast cancer (mBC) setting, fulvestrant has been shown to improve outcomes compared to AIs [2–4]; however, its major limitation is its availability as an injectable formulation only. Thus, there has been considerable effort to develop novel orally bioavailable SERDs for the treatment of both early-stage and metastatic HR + breast cancers. The first oral SERD to be approved by the United States Food and Drug Administration (FDA) for

✉ Julia Foldi
foldij@upmc.edu

Melissa Taylor
m.taylor@yale.edu

Adriana Kahn
Adriana.kahn@yale.edu

[1] Section of Medical Oncology, Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA

[2] Division of Hematology/Oncology, University of Pittsburgh School of Medicine and UPMC Hillman Cancer Center, 300 Halket Street, Suite 3524, Pittsburgh, PA 15213, USA

the second-line and beyond treatment of HR + /HER2- mBC in January 2023 was elacestrant [5]. This review aims to provide a comprehensive overview focusing on the clinical aspects of SERDs in the treatment of HR + breast cancers.

Estrogen and Estrogen Receptor as Targets for *Cancer* Treatment

Estrogens are steroid hormones synthesized in the ovaries, adrenal glands, and adipose tissue. In pre-menopausal women, estrogen is predominantly synthesized in the ovaries while in post-menopausal women estrogen is largely produced in the adipose tissue and adrenal glands by peripheral conversion from testosterone via the enzyme aromatase. The predominant form of circulating estrogen is E2 or estradiol, which crosses the cellular membrane to bind the intranuclear ER alpha (ERα) [6] (Fig. 1). ERα is a transcription factor that dimerizes when bound by E2 and functions through two pathways: the nuclear pathway and the non-nuclear pathway. In the nuclear pathway, dimerized ERα interacts with various coregulator proteins at specific DNA sequences known as estrogen response elements (EREs), promoting transcription of genes involved in cell cycle regulation, DNA replication, cellular differentiation, apoptosis, and angiogenesis. In the non-nuclear pathway, E2 binding to ERα recruits coregulators for growth factors and G-protein signaling such as insulin-like growth factor 1 (IGF-1), fibroblast growth factor receptor (FGFR), HER2, phosphoinositide 3-kinase (PI3K), protein kinase B (PKB, also known as AKT), mammalian target of rapamycin (mTOR), and cyclin dependent kinases (CDKs) [7, 8].

Systemic treatment for HR + /HER2- breast cancer exploits its dependence on E2 and the ERα pathway by using

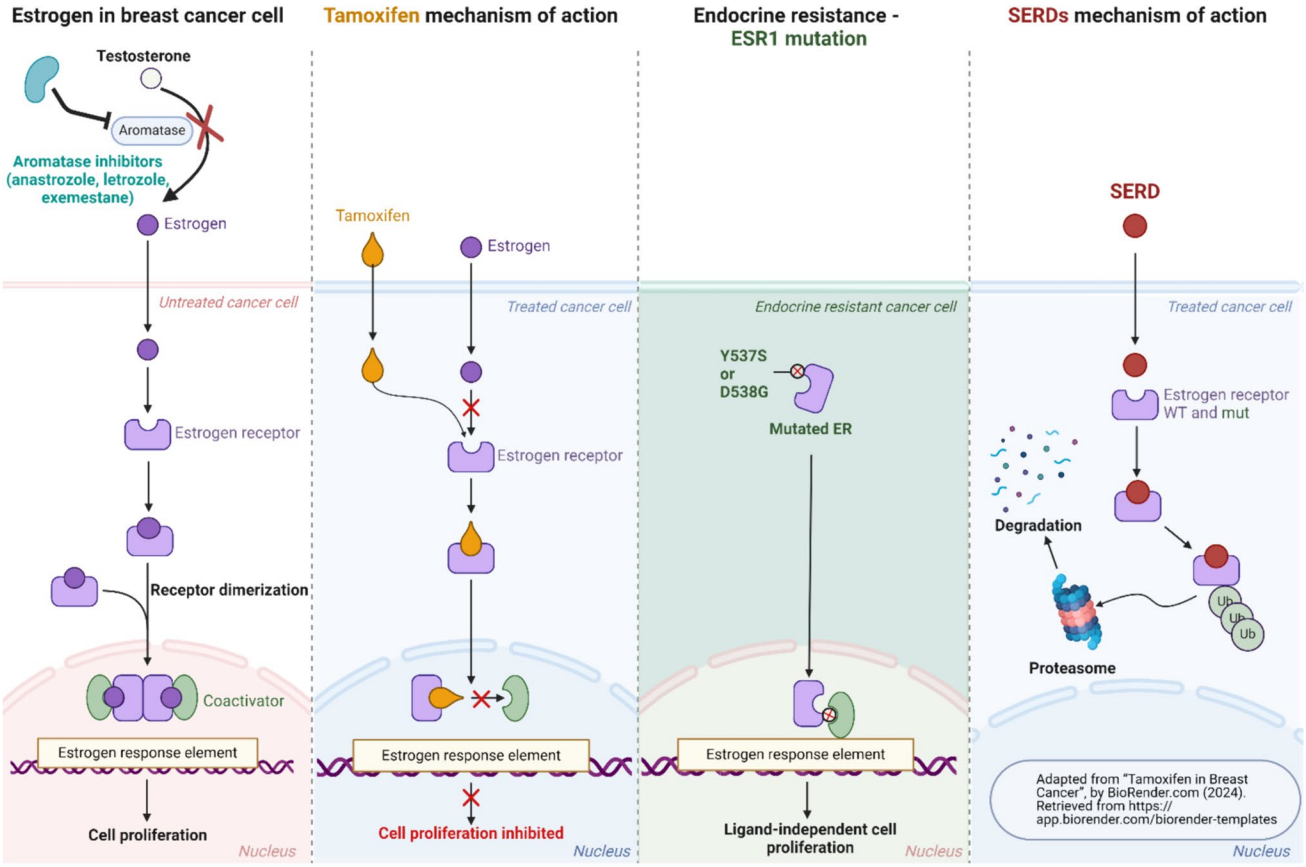

Fig. 1 Mechanism of action for estrogen, aromatase inhibitors, tamoxifen and SERDs. (**a**) Mechanism of action of estrogen in breast cancer; aromatase inhibitors (AIs: anastrozole, letrozole and exemestane) inhibit the enzyme, aromatase, which convers testosterone to estrogen in the periphery. (**b**) Tamoxifen, a selective estrogen receptor modulator (SERM) prevents binding of estrogen to the estrogen receptor (ER), thereby preventing recruitment of co-activators and biding to estrogen response elements on the DNA and inhibiting its downstream actions on cell proliferation. (**c**) A mutation in the estrogen receptor 1 gene (*ESR1*) causes constitutive ER activity and enhanced transcription of ER-dependent genes in a ligand-independent manner, resulting in resistance to estrogen deprivation using AIs or modulation of ER by tamoxifen. (**d**) SERDs bind to the ER, activating E3 ubiquitin ligases ubiquitinating ER, thereby marking it for proteasomal degradation. (Adapted from "Tamoxifen in Breast Cancer," by BioRender.com [2024]; https://app.biorender.com/biorender-templates)

therapies targeted specifically at the ER pathway. Figure 1 summarizes the mechanisms of action of the major classes of antiestrogens. Tamoxifen is an oral SERM taken for at least 5 years and can be used in pre- and post-menopausal women. Tamoxifen competitively inhibits the binding of estrogen to the ER. Tamoxifen prevents the conformational change of the receptor required for dimerization and downstream activation of coregulator proteins and when taken in the adjuvant setting for the treatment of HR + /HER2- early-stage breast cancer (eBC)it reduces the risk of distant and local recurrence by up to 50% [9, 10]. Aromatase inhibitors (AIs) are another class of antiestrogens that block the conversion of androgens into estrogen by the enzyme aromatase in the periphery. When taken for at least 5 years, AIs reduce the risk of distant and local recurrence by about 50% and can be used in post-menopausal women or in pre-menopausal women who are concurrently on ovarian function suppression [10, 11].

Mechanisms of Endocrine Resistance

Despite antiestrogen treatment being highly effective, distant metastatic recurrence occurs in 15–20% of patients with surgically resected HR + /HER2- eBC and this recurrence risk persists for multiple decades after diagnosis [12]. In the metastatic setting, the current treatment paradigm is to employ sequential ETs combined with targeted agents – such as CDK4/6 inhibitors (CDK4/6i) – however, endocrine resistance inevitably develops. There are multiple known mechanisms of resistance to antiestrogen treatment, the detailed discussion of which is beyond the scope of this review. Some examples include loss of ER expression, which occurs in about 10% of patients with recurrent disease who had HR + primary breast cancers [13]. In 30–40% of patients with recurrent disease, the selective pressure from antiestrogen treatment result in acquired gain-of-function mutations [14] often occurring in the *ESR1* gene, which enables the ER to be constitutively activated even in the absence of estrogen, promoting ongoing ligand-independent transcription and cell cycle activation [15]. Another mechanism of ET resistance is through the PI3K-AKT-mTOR and RAS/RAF/MEK/ERK pathways which can reactivate ER-mediated transcription in the absence of E2 binding. Mutations in the CDK4/6/Cyclin D1 axis also frequently occur in HR + breast cancer as a mechanism of resistance through the inactivation of Rb resulting in unchecked progression through the cell cycle [16].

Targeting these mechanisms of estrogen resistance have been a focus for the development of novel therapeutics for HR + /HER2- breast cancer. For example, CKD4/6i, when used in combination with ET, have been shown to improve invasive disease-free survival (iDFS) in patients with eBC [17] and progression-free survival (PFS) and in some cases overall survival (OS) in the metastatic setting [18–22], and they have become standard first-line treatment in the latter disease setting. Additional targeted therapies such as alpelisib [23] and inavolisib [24] (PI3K inhibitors), capivasertib (AKT inhibitor) [25], and everolimus (mTOR inhibitor) [26, 27] have been shown to be effective in HR + /HER2- mBC after progression on first-line ET with a CDK4/6i. Because of the high incidence of *ESR1* mutations arising under therapeutic pressure with antiestrogen treatment, developing specific therapeutics targeting *ESR1*-mutated breast cancers has been an active and promising area of drug development. The remainder of this review will focus on the clinical evidence that has begun to establish SERDs as the most promising novel class of endocrine-based therapies. Table 1 summarizes completed phase II and III trials of novel oral SERDs and Table 2 summarizes ongoing clinical trials evaluating them.

Steroidal SERDs

Fulvestrant

Fulvestrant was the first SERD to be approved by the FDA in 2002 – and remained the only FDA-approved SERD until January 2023 – for its use in patients with HR + /HER2- mBC who have progressed on prior antiestrogen therapy. Fulvestrant is administered as an intramuscular (IM) injection and acts as a pure antagonist of ER with higher affinity for the receptor than tamoxifen. When binding to the ER, it prevents its dimerization and inhibits its translocation into the nucleus. Fulvestrant-bound ER forms an unstable complex resulting in the degradation of the complex through the ubiquitin–proteasome pathway [28, 29]. Interestingly, the anticancer effect of fulvestrant is not primarily mediated through proteasome-mediated ER degradation; rather, prior to receptor degradation, fulvestrant induces transient binding of ERα to DNA, followed by SUMOylation of the receptor and rapid dissociation from ER-target regions, which prevents transcription [29–32].

Trials 0020 and 0021 [33, 34] were pivotal studies for fulvestrant in the second-line setting after progression or relapse while on tamoxifen treatment. Combined analysis of the two trials showed that fulvestrant, at a dose of 250 mg once monthly, was at least as effective as the AI, anastrozole, in 851 postmenopausal women, with time to progression of 5.5 months versus 4.1 months [35] and OS of 27.4 months versus 27.7 months, respectively, for fulvestrant and anastrozole [36]. These studies led to the initial approval of fulvestrant at 250 mg. A meta-analysis of 11 trials with a total of 5808 patients included showed that fulvestrant was more effective at prolonging PFS at 500 mg compared to

Table 1 Completed phase II/III trials of novel oral SERDs

SERD	Clinical Trial (phase; ref; NCT#)	N	Patients	Study Design	Primary endpoints	Main Results
Metastatic BC						
Elacestrant	Phase III EMERALD [49, 51] (NCT03778931)	477	Metastatic HR + /HER2- BC with 1–2 prior lines of ET, including CDK4/6i	Elacestrant vs. standard of care (SOC) endocrine monotherapy (fulvestrant/AI)	PFS -Overall population -Subset with *ESR1* mutations	mPFS in overall population (n = 477) • 2.8 vs. 1.9 mos (HR 0.70; 95% CI: 0.55–0.88; p = 0.002) • 6-month PFS rates: 34.3% (elacestrant) vs. 20.4% (SOC) mPFS in *ESR1*-mutated population (n = 228) • 3.8 vs. 1.9 mos (HR 0.55; 95% CI: 0.39–0.77; p = 0.0005) • 6-month PFS rates: 40.8% vs. 19.1%
Giredestrant	Phase II acelRA [58] (NCT04576455)	303	Metastatic HR + /HER2- BC with 1–2 prior lines of therapy, including at least 1 ET	Giredestrant vs. physicians' choice ET	PFS -Overall population -Subset with *ESR1* mutations	mPFS in overall population (n = 303) • 5.6 vs. 5.4 mos (HR 0.81; 95% CI: 0.60–1.10; p = 0.18) mPFS in ESR-mutated population (n = 118) • 5.5 vs. 3.5 mos (HR 0.60; 95% CI: 0.35–1.03; p = 0.06)
Camizestrant	Phase II SERENA-2 [68] (NCT04214288)	240	Metastatic HR + /HER2- BC 2nd line and beyond ET (1 line of CT allowed)	Camizestrant (at 75 and 150 mg) vs. fulvestrant	PFS	mPFS in overall population (n = 240) • 7.2 mos (C 75 mg) vs. 7.7 mos (C 150 mg) vs. 3.7 mos (fulvestrant) - C 75 mg versus fulvestrant HR 0.67; 95% CI 0.41–0.81; p = 0.0124 mPFS in *ESR1*-mutated population (n = 83) • 6.3 mos (C 75 mg) vs. 9.2 mos (C 150 mg) vs. 2.2 mos (fulvestrant) - C 75 mg versus fulvestrant HR 0.33; 95% CI 0.18–0.58 Camizestrant favored in patients with visceral metastases
Early-stage BC						

Table 1 (continued)

SERD	Clinical Trial (phase; ref; NCT#)	N	Patients	Study Design	Primary endpoints	Main Results
Giredestrant	Phase II coopERA [62] (NCT04436744)	221	Untreated HR + /HER2- early-stage BC and Ki-67 ≥ 5%	Window-of-opportunity phase with 14 days of giredestrant vs. anastrozole followed by 16 weeks of continued ET (as randomized in phase I) plus palbociclib	Geometric mean change in Ki-67 from baseline to 2 weeks	Ki-67 reduction from baseline to week 2: • Higher with giredestrant (mean reduction of 75% vs. 67%); p = 0.043 Other outcomes • Ki-67 reduction from baseline to surgery higher in giredestrant arm (-81% vs. -74%) • ORR similar in both arms: 50% giredestrant vs. 49% anastrozole

Abbreviations: BC: breast cancer; HR: hormone receptor/ hazard ratio; HER2: human epidermal growth factor receptor 2; ET: endocrine therapy; CT: chemotherapy; E: elacestrant; C: camizestrant; PFS: progression-free survival; ORR: objective response rate; CI: confidence interval

250 mg dose and was also more effective when compared to anastrozole and megestrol acetate [37]. The phase III FALCON trial (NCT01602380) randomized 524 patients with HR + /HER2- mBC to fulvestrant at a dose of 500 mg versus anastrozole as first-line therapy. Median PFS (mPFS) was significantly longer in the fulvestrant group (16.6 versus 13.8 months; hazard ratio [HR] 0.797, 95% confidence interval [CI] 0.637–0.999; p = 0.0486) [4]. More recently, fulvestrant has also shown excellent efficacy in combination with targeted agents such as CDK4/6i [19, 38, 39], alpelisib [23] and everolimus [26]. Because of the inconvenience of IM administration of fulvestrant, limiting its long-term use, there has been great interest in the development of orally bioavailable SERDs, many of which are currently under evaluation in clinical trials in both the metastatic and eBC settings.

Borestrant

ZB716, or borestrant, is an orally bioavailable form of fulvestrant. Preclinical data demonstrated that it had superior properties compared to fulvestrant with improved ER antagonism. Borestrant is currently being investigated in an ongoing multicenter phase I/II open label trial, ENZENO (NCT04669587), both as monotherapy and in combination with palbociclib in patients with HR + /HER2- mBC. Results have not yet been released.

Non-steroidal SERDs with Acrylic Acid Side Chains

Brilanestrant (GDC-0810/ARN-810)

Brilanestrant is a second generation non-steroidal SERD that acts as an ERα binder with full transcriptional antagonism and no agonism. In vitro studies showed that it was active in tamoxifen- and fulvestrant-resistant models of breast cancer [40]. In a phase I/II clinical trial (NCT01823835), brilanestrant was shown to be safe and tolerable and with preliminary anti-tumor activity in heavily pretreated patients with HR + /HER2- mBC [41]. In the follow-up phase II trial, HydranGea (NCT02569801), brilanestrant was compared to fulvestrant and failed to show comparable or superior efficacy. Its development was discontinued in April 2017.

AZD9496

AZD9496 is an oral non-steroidal small molecule that acts as a potent and selective antagonist and degrader of ERα in vitro including in *ESR1*-mutated models. Preclinical studies also demonstrated further tumor growth inhibition when combined with PI3K inhibitors and CDK4/6i compared to monotherapy

Table 2 Ongoing phase II/III trials of novel oral SERDs

SERD	Clinical Trial (phase; ref; NCT#)	N (est)	Patients	Study Design	Primary endpoints	Status
Metastatic BC						
Elacestrant	Phase Ib/II ELEVATE [52] (NCT05563220)	310 (Ph II)	Metastatic HR + /HER2- BC with 1–2 prior lines of ET, including CDK4/6i	Umbrella study evaluating multiple combinations: • E + alpelisib • E + everolimus • E + abemaciclib/ribociclib/palbociclib • E + capivasertib	PFS (Ph II) Safety (Ph I)	Actively recruiting
Elacestrant	Phase Ib/II ELECTRA (NCT05386108)	106	Pre-treated HR + /HER2- metastatic BC with brain metastases (Ph II)	Single arm study of E plus abemaciclib	RP2D ORR	Actively recruiting
Giredestant	Phase III persevERA (NCT04546009)	992	Metastatic HR + /HER2- BC first-line treatment	Giredestrant + palbociclib (± LHRH agonist) vs. letrozole + palbociclib (± LHRH agonist)	PFS	Actively recruiting
Giredestrant	Phase III evERA [59] (NCT05306340)	320	Metastatic HR + /HER2- BC with 1–2 prior lines of ET including CDK4/6i	Giredestrant + everolimus (± LHRH agonist) vs. exemestane + everolimus (± LHRH agonist)	PFS	Actively recruiting
Giredestrant	Phase Ib/II MORPHEUS [60] (NCT04802759)	510	Metastatic HR + /HER2- BC after progression on prior CDK4/6i and metastatic HR + /HER2 + BC on anti-HER2 therapies	Giredestrant as monotherapy or in combination with multiple therapies (abemaciclib, palbociclib, ribociclib, samuraciclib, ipatasertib, inavolisib, everolimus, atezolizumab, trastuzumab, pertuzumab)	ORR Safety PK	Actively recruiting
Camizestrant	Phase III SERENA-4 [69] (NCT04711252)	1370	Metastatic HR + /HER2- BC first-line treatment	Camizestrant + palbociclib vs. anastrozole + palbociclib	PFS	Actively recruiting
Camizestrant	Phase III SERENA-6 [70] (NCT04964934)	3000 screened for *ESR1* mutation; 300 randomized	Metastatic HR + /HER2 BC on first-line ET + CDK4/6i, in patients with detectable *ESR1* mutation in ctDNA before clinical disease progression	Switch from AI to camizestrant while maintaining the same CDK4/6i vs. continued AI + CDK4/6i	PFS	Actively recruiting
Imlunestrant	Phase III EMBER-3 [74] (NCT04975308)	860	Metastatic breast cancer 2nd line and beyond	Imlunestrant monotherapy vs imlunestrant + abemaciclib + investigators choice ET	PFS	Actively recruiting
Early-stage BC						

Table 2 (continued)

SERD	Clinical Trial (phase; ref; NCT#)	N (est)	Patients	Study Design	Primary endpoints	Status
Elacestrant	Phase III EORTC-2129-BCG/TREAT ctDNA (NCT05512364)	220	Early-stage HR + /HER2- BC after 2–7 yrs of adjuvant ET and have a ctDNA relapse by the Signatera assay	Switch ET to elacestrant vs. continue physician's choice ET	Distant metastasis free survival (DMFS)	Actively recruiting
Giredestrant	Phase III lidERA [61] (NCT04961996)	4200	Intermediate- and high-risk early-stage HR + /HER2- BC	Giredestrant (± LHRH agonist) vs. physician's choice ET (± LHRH agonist) Substudy: giredestrant plus abemaciclib for 2 yrs, followed by giredestarnt	Invasive disease-free survival (IDFS)	Completed accrual
Camizestrant	Phase III CAMBRIA-1 (NCT05774951)	4300	Intermediate- and high-risk early-stage HR + /HER2- BC after 2–5 yrs of standard adjuvant ET	Switch ET to camizestrant vs. continue physician's choice ET	Invasive breast cancer free survival (IBCFS)	Actively recruiting
Camizestrant	Phase III CAMBRIA-2 (NCT05952557)	5500	Intermediate- and high-risk early-stage HR + /HER2- BC starting initial adjuvant ET	Camizestrant vs. physician's choice ET	IBCFS	Actively recruiting
Imlunestrant	Phase III EMBER-4 (NCT05514054)	6000	Intermediate- and high-risk early-stage ER + HER2 BC after 2–5 yrs of standard adjuvant ET	Switch to imlunestrant vs. continue physician's choice ET	IDFS (excluding second primary non-breast primary invasive cancers)	Actively recruiting

Abbreviations: Est: estimated; BC: breast cancer; ET: endocrine therapy; Ph: phase; E: elacestrant; C: camizestrant; PFS: progression-free survival; ORR: objective response rate; IDFS: invasive disease-free survival; IBCFS: invasive breast cancer free survival; DMFS: distant metastasis free survival

[42]. In phase I studies of patients with heavily pretreated HR + /HER2- mBC, AZD9496 showed good tolerability and safety. More than half of the patients had previously received fulvestrant and the most common adverse events (AEs) were diarrhea, nausea, and fatigue. [43]. A phase II randomized, open-label, presurgical, window-of-opportunity trial compared AZD9496 with fulvestrant in 46 postmenopausal patients with HR + /HER2- eBC and found that reduction in ER H-score, PR H-score, and Ki-67 proliferation index were not superior to fulvestrant at the tested dose [44].

LSZ102

LSZ102 is an oral SERD and in preclinical models it showed a high potency and efficient degradation and induced significant tumor regression [45]. A phase I, multicenter, open-label dose-escalation study (NCT02734615) of heavily pretreated patients with HR + mBC examined LSZ102 monotherapy, as well as in combination with ribociclib and alpelisib. LSZ102 was well tolerated as monotherapy and in combination with ribociclib and alpelisib. Objective response rate (ORR) was low as a single agent (1.3%) but higher response rates were seen in combination with ribociclib (17%) and alpelisib (7%) [46]. Mutations in *ESR1*, *PIK3CA*, and *TP53* did not correlate with response to treatment. The limited clinical activity as a single agent resulted in the decision to discontinue further development of LSZ102.

G1T48 (Rintodestrant)

Rintodestrant is an orally bioavailable non-steroidal SERD that effectively suppresses ERα activity in multiple endocrine therapy resistant in vitro models including those with *ESR1* mutations. Preclinical data also demonstrated that rintodestrant in combination with the CDK4/6i, lerociclib, inhibited tumor growth in animal models of endocrine-resistant breast cancer [47]. Phase I dose-escalation and expansion studies showed that rintodestrant had a favorable safety profile and antitumor activity in patients with heavily pre-treated HR + /HER2- mBC. Rintodestrant combined with palbociclib was also demonstrated to be safe and tolerable with antitumor activity with 68% of patients having stable disease at median treatment duration of 3 months. The most common AEs were cytopenias including neutropenia and leukopenia [48].

Non-steroidal SERDs with Basic Amino Acid Side Chains

Elacestrant

Elacestrant is the first FDA approved orally bioavailable SERD for the use in HR + /HER2- mBC based on the results of the EMERALD study [49]. Elacestrant selectively binds to ER and induces its degradation leading to inhibition of downstream signaling. Phase I (NCT02338349) data showed that in heavily pretreated postmenopausal women with HR + /HER2- mBC, 50% of whom had tumors harboring *ESR1* mutations, there was single agent activity with ORR of 19.4% and a clinical benefit rate (CBR) of 42.6% [50]. The ORR was 16.7% in patients with prior CDK4/6i and 33.3% in patients with tumors harboring *ESR1* mutations. These results led to the phase III randomized, open-label, multicenter EMERALD trial (NCT03778931) which randomized patients to receive elacestrant versus physicians' choice standard of care (SOC) ET. The trial cohort consisted of 477 postmenopausal women with HR + /HER2- mBC, 228 of whom had tumors harboring a mutation in *ESR1*, who progressed on 1–2 prior lines of ET including a CDK4/6i and ≤ 1 chemotherapy. The results demonstrated a statistically significant improvement in PFS in patients with *ESR1* mutations with mPFS of 3.8 months in the elacestrant arm and 1.9 months in the SOC arm (HR 0.55; 95% CI 0.39–0.77; p = 0.0005) as well as in the overall population (HR 0.7; 95% CI 0.55–0.88; p = 0.002) [49]. In an updated analysis presented at the 2023 San Antonio Breast Cancer Symposium, duration of prior CDK4/6i therapy in the metastatic setting was associated with PFS, with longer duration of prior CDK4/6i resulting in longer PFS on elacestrant versus SOC: all patients with ≥ 18 months on prior CDK4/6i had mPFS of 5.5 months with elacestrant versus 3.3 months with SOC ET (HR 0.70; 95% CI 0.48–1.020), while those with *ESR1*-mutated tumors who had ≥ 18 months on prior CDK4/6i had mPFS of 8.6 months with elacestrant versus 2.1 months with SOC ET (HR 0.47; 95% CI 0.20–0.79) [51]. Elacestrant is also well tolerated with the most common AEs observed with elacestrant versus SOC ET being nausea, fatigue, vomiting, decreased appetite and arthralgias, with the most frequent grade 3 or higher AEs being nausea, back pain and increased liver function tests [49]. Based on these data, elacestrant received FDA-approval in January 2023, for the second-line and beyond treatment of HR + /HER2- mBC harboring *ESR1* mutations [5].

Currently, elacestrant is being evaluated in the ELEVATE study (NCT05563220), an open-label umbrella study of elacestrant in various combinations in the metastatic setting (in combination with alpelisib, everolimus, palbociclib, abemaciclib, and ribociclib) [52]. The ELECTRA trial is examining the combination of abemaciclib with elacestrant in patients with brain metastases (NCT05386108). In the eBC setting, the TREAT ctDNA trial (NCT05512364; EORTC-2129-BCG) is currently evaluating switching to elacestrant versus continuation of standard ET in patients with HR + /HER2- eBC and ctDNA molecular relapse, measured by the tumor-informed Signatera minimal residual disease (MRD) test, in the absence of clinical relapse.

GDC-0927

GDC-0927 is a novel, potent, non-steroidal, orally bioavailable SERD that had promising preclinical data showing that it induced tumor regression in ER + breast cancer xenograft models [53]. In an open label phase I study of GDC-0927 (NCT02316509) in 42 postmenopausal women with HR + /HER2- mBC, it appeared to be well tolerated with preliminary evidence of antitumor activity in heavily pretreated patients with 12 patients (29%) achieving clinical benefit and 17 patients (41%) with confirmed best overall response of stable disease, with no correlation between response and the presence of *ESR1* mutations [54]. On-treatment biopsies showed reduction in ER and PR levels and reduced Ki-67. Despite these positive early results, the development of GDC-927 was discontinued due to suboptimal properties.

Giredestrant (GDC-9545)

Giredestrant is a highly potent E2 agonist and reduces levels of ER protein through proteasome mediated degradation. It also induces ER turnover and suppresses ER transcriptional activity, thereby reducing tumor proliferation. In preclinical models there was activity in both *ESR1* wild-type (WT) and *ESR1*-mutated breast cancer models [55]. In a phase Ia/b trial (NCT03332797) of patients with HR + /HER2- mBC, single agent giredestrant (with or without a ± luteinizing hormone-releasing hormone [LHRH] agonist) at four dose levels (10, 30, 90 and 250 mg) was well tolerated at all doses with relatively low-grade AEs (grade 3 or higher AEs were observed in 5% of patients) [56]. In a separate cohort, patients also received giredestrant 100 mg in combination with palbociclib ± LHRH agonists if pre-menopausal. In the single agent cohorts, ORR in patients with measurable disease at baseline was 19.8% and CBR was 48.6%. In the combination cohort, ORR in patients with measurable disease at baseline was 48.2% and CBR was 81.3% [57]. Detailed cardiovascular assessment was included in the study, which did not identify significant cardiac-related toxicities in terms of heart rate, blood pressure or exercise duration [57]. A phase II randomized, open label, multicenter trial, acelERA (NCT04576455) was evaluating the efficacy and safety of giredestrant versus physician's choice ET in patients with previously treated HR + /HER2- mBC. Although it did not reach statistical significance for its primary endpoint of investigator assessed PFS, there was a consistent treatment effect with giredestrant across most key subgroups. At a median follow-up of 7.9 months, the HR favored giredestrant versus SOC ET in the overall population (HR 0.81; 95% CI 0.60–1.10; p = 0.1757) as well as in patients whose tumors harbored an *ESR1* mutation (HR 0.60; 95% CI 0.35–1.03) [58]. It is also being evaluated in a phase III, randomized, double-blind, placebo controlled multicenter study of giredestrant plus palbociclib versus letrozole plus palbociclib as first-line treatment of patients with HR + /HER2- mBC (persevERA; NCT04546009), as well as the phase III evERA trial (NCT05306340) in combination with everolimus versus exemestane plus everolimus in patients who progressed on 1–2 prior lines of ET including a CDK4/6i [59]. MORPHEUS-BREAST CANCER is a phase Ib/II randomized umbrella trial (NCT04802759) evaluating the safety and efficacy of giredestrant as a single agent and in multiple combinations, including with CDK4/6i, in patients with HR + /HER2- mBC with primary endpoint of ORR and safety. Interim results of giredestrant monotherapy as well as the combination arms with abemaciclib and ribociclib were presented at the 2023 ASCO Annual Meeting [60]: three patients had a partial response with one in the giredestrant plus abemaciclib and two in the giredestrant plus ribociclib arm and stable disease seen in 19 patients (5 in giredestrant monotherapy, and 7 each in the combination arms). Grade 3–4 AEs were seen in ~ 40% of patients in the combination arms with no unexpected safety signals, suggesting that giredestrant can be safely combined with CDK4/6i.

In the eBC setting, the lidERA trial (NCT04961996), which recently completed accrual, randomized patients with HR + /HER2- intermediate- or high-risk eBC to giredestrant versus SOC ET in the adjuvant setting [61], while the neoadjuvant window-of opportunity trial, coopERA (NCT04436744) randomized women with previously untreated eBC to palbociclib plus giredestrant versus anastrozole [62]. The primary endpoint of coopERA was geometric mean relative reduction of Ki-67 proliferation index from baseline to week 2, which was evaluated after a lead-in period of patients receiving single agent giredestrant versus anastrozole. Reduction in Ki67 was -75% with giredestrant and -67% with anastrozole (p = 0.043), meeting the primary endpoint, showing encouraging anti-proliferative activity [62].

Amcenestrant (SAR439859)

Amcenestrant is a potent orally bioavailable SERD. It acts as an antagonist for the binding of E2 to the ER and promotes the transition of ERα to the inactive confirmation. This leads to a deeper inhibition of the downstream ERα pathways and is effective in decreasing proliferation in preclinical WT and *ESR1*-mutated breast cancer models [63]. The phase I/II AMEERA-1 trial (NCT03284957) evaluated amcenestrant in heavily pretreated postmenopausal women with HR + /HER2- mBC. The study showed an overall CBR of 28.3%, and CBRs among patients with baseline WT tumors and tumors with mutated *ESR1* were 34.6% and 21.1%, respectively [64]. Notably, there were no dose limiting or grade 3 or higher toxicities nor cardiac/eye toxicities reported. The main side effects were hot flashes, constipation, arthralgias,

and fatigue [64]. AMEERA-3 (NCT04059484) was a randomized phase II trial of amcenestrant versus SOC ET monotherapy in HR + /HER2- mBC. The study did not meet its primary objective of improved PFS with amcenestrant compared to physician's choice ET (mPFS 3.6 versus 3.7 months; HR 1.051; 95% CI 0.789–1.4; p = 0.643) [65]. Among patients with an *ESR1* mutation there was a numerical improvement in mPFS from 2.0 to 3.7 months (HR 0.9; 95% CI 0.565–1.435). In the amcenestrant group, 21.7% of patients experienced treatment-emergent grade 3 or higher AEs. AMEERA-5 (NCT04478266) was a phase III trial evaluating amcenestrant in combination with palbociclib versus letrozole plus palbociclib in first-line treatment of patients with HR + /HER2- mBC that did not meet the prespecified boundary for continuation; therefore, clinical development of the drug was discontinued in 2022.

Camizestrant (AZD9833)

Camizestrant is a next-generation oral SERD and pure ERα antagonist with potent in vivo activity superior to that of fulvestrant and when combined with CDK4/6i, PI3K-, AKT-, and mTOR-inhibitors [66]. The SERENA-1 (NCT03616587) study was a phase I dose escalation and expansion trial of camizestrant in women with HR + /HER2- mBC that demonstrated a tolerable safety profile in patients who had been heavily pretreated [67]. The phase II randomized SERENA-2 trial (NCT04214288) compared camizestrant to fulvestrant in patients with previously treated HR + /HER2- mBC. mPFS on the camizestrant arm was double that of fulvestrant – mPFS 7.2 months with camizestrant 75 mg, 7.7 months with 150 mg, versus 3.7 months with fulvestrant (camizestrant 75 mg versus fulvestrant HR 0.67; 95% CI 0.41–0.81; p = 0.0124) – and was heavily favored in patients with visceral metastases and detectable *ESR1* mutations [68]. SERENA-4 (NCT04711252) and SERENA-6 (NCT04964934) are ongoing phase III trials evaluating combinations of camizestrant with CDK4/6i. In SERENA-4, first-line treatment with camizestrant plus palbociclib versus anastrozole plus palbociclib is being evaluated [69], while SERENA-6 is evaluating the efficacy of switching from an AI to camizestrant while maintaining the same CDK4/6i versus continuing on same AI plus CDK4/6i in patients with an *ESR1* mutation detected from circulating tumor DNA (ctDNA) before clinical disease progression on first-line therapy [70].

In the eBC setting, camizestrant is being evaluated in two large phase III randomized trials CAMBRIA-1 (NCT05774951) and CAMBRIA-2 (NCT05952557). CAMBRIA-2 will randomize 5,500 patients with intermediate- and high-risk HR + /HER2- eBC to camizestrant versus SOC ET of physician's choice with a primary endpoint of invasive breast cancer-free survival, while CAMBRIA-1 is evaluating camizestrant as extended ET in patients who already completed 2–5 years of adjuvant SOC ET.

An adverse event of interest for camizestrant has been ocular toxicity [71], also observed with other SERDs, mostly giredestrant [55]. These include visual distortions such as floaters and flashes of light, which were seen in 12.2% of patients on the SERENA-2 study [68]. Because of these effects, the FDA has mandated that all patients enrolling on clinical trials of camizestrant get formal ophthalmology evaluations prior to randomization as well as at regular intervals while on treatment with camizestrant.

Imlunestrant (LY3484356)

Imlunestrant is an orally bioavailable SERD with pure ER antagonistic properties that inhibits ER-dependent gene transcription and cell proliferation. In the phase Ia/b EMBER trial (NCT04188548), imlunestrant demonstrated a favorable safety profile in patients with pretreated HR + /HER2- mBC: most treatment related AEs were grade 1; across all doses, the incidence of grade 3 AEs was low at 3.6% [72]. ORR and CBR were 8.0% and 40.4%, respectively and clinical benefit was seen regardless of baseline *ESR1* mutation status as determined by ctDNA sequencing [72]. EMBER-2 (NCT04647487) was a neoadjuvant window-of-opportunity study evaluating the biological effects of imlunestrant in postmenopausal women with stage I-III HR + /HER2- eBC. Primary endpoint was change in ER expression by IHC: in the 75 patients evaluable for ER expression, there was an overall -81% mean geometric percent change in ER expression and in the 59 patients evaluable for Ki-67, there was a -73% mean geometric percent change [73], suggesting consistent and robust target engagement. This led to the phase III adjuvant EMBER-4 trial (NCT05514054), which is currently randomizaing patients with high-risk HR + /HER2- eBC who already completed between 2 and 5 years of standard adjuvant ET to imlunestrant versus SOC ET. Imlunestrant is also being tested in combination with abemaciclib in the EMBER-3 trial (NCT04975308), which is enrolling patients with HR + /HER2- mBC who have received and progressed on AI (± CDK4/6i) in the first-line and randomizing to three arms: imlunestrant monotherapy versus imlunestrant plus abemaciclib versus SOC ET (exemestane or fulvestrant) [74].

ZN-c5

ZN-c55 is a novel potent and oral SERD that is a small molecule with antagonism and degradative effect against the ER. In vitro, ZN-c5 in combination with CDK4/6i and PI3K inhibitors resulted in enhanced anti-proliferative effects [75]. ZN-c5 is currently being studied in a phase I/II open-label multicenter, dose-escalation and expansion study

(NCT03560531) in patients with HR + /HER2- mBC both as a monotherapy and in combination with palbociclib [76]. Another phase Ib study (NCT04514159) is also ongoing, evaluating the safety and preliminary antitumor activity of ZN-c5 in combination with abemaciclib [77].

D-0502

D-0502 is another orally bioavailable SERD that has been shown to have activity in HR + /HER2- breast cancer cell lines in vitro. In combination with CKD4/6i there was greater suppression of tumor growth in *ESR1*-mutated cell lines. It is currently being studied in a phase I trial (NCT03471663) as monotherapy and in combination with palbociclib in women with HR + /HER2- mBC [78].

Safety concerns Associated with SERDs

With the increasingly widespread use of SERDs in clinical practice including the recently approved elacestrant and many ongoing clinical trials of various other medications, an important consideration is how the safety profiles of these novel agents compare to other endocrine agents we currently have available. SERDs tend to cause more gastrointestinal (GI) toxicity with patients experiencing nausea, vomiting and diarrhea, which is not typically seen with AIs or tamoxifen. For example, in the EMERALD trial of elacestrant, 35% of patients experienced all grade nausea with 2.5% being grade 3–4 compared to 25% and 2.9 of patients in the control arm, respectively [49]. Elacestrant is also associated with fatigue and arthralgias but to a similar extent as SOC ET. Vomiting was also more common, 19% all grade and 0.8% grade 3–4 in the elacestrant and 10.3% and 0% in the control arm, respectively. In the acelERA study of giredestrant, any grade and grade 3–4 diarrhea were more common with giredestrant (8.7% and 0.7%, respectively) than with SOC ET (3.9% and 0%, respectively) [58]. Camizestrant has also been associated with sinus bradycardia with up to 40% of patients experiencing it in SERENA-2 as well as visual disturbances in approximately 12% of patients [68]. Vasomotor symptoms such as hot flashes are also common with SERDs [49]. We are awaiting results of large, randomized phase III adjuvant studies (lidERA, CAMBRIA-1 and -2, EMBER-4) to better understand AEs in the largest patient population with the potential for experiencing benefit of SERDs, namely, those who are taking adjuvant ET for 5–10 years after an eBC diagnosis.

An important consideration, particularly in the adjuvant setting, is the bone loss associated with AIs, which are currently most commonly used as adjuvant ET in postmenopausal women with HR + /HER2- eBC. At this time, there is scarce data in the literature addressing how oral SERDs impact bone health. For example, in the EMERALD trial, bone-related events were not reported. Based on the mechanism of action of SERDs, and the fact that ER is present at the bone, it is likely that they could lead to decrease in bone density over time, similarly to AIs. Many postmenopausal patients with preexisting bone loss diagnoses already receive a bisphosphonate such as zoledronic acid to help prevent further bone loss, and this may be important also in patients receiving SERDs.

Future Directions

Besides the presence of *ESR1* mutations, there are currently no standardized biomarkers to predict response to therapy with SERDs. In general, identifying patients who benefit from ET beyond the first-line in mBC is a significant clinical challenge. One interesting observation is the sharp drop in PFS observed on both the EMERALD [49] and SERENA-2 [68] trials after ~ 2 months of treatment, representing rapid progression of disease at the first assessment timepoint – this is regardless of which arm patients were randomized to. For example, in EMERALD, although less patients progressed at this early timepoint on the elacestrant arm compared to SOC ET, there were up to 40% of patients whose tumors harbored *ESR1* mutations who still derived no benefit from second-line elacestrant (~ 50% versus ~ 60% of the overall population with elacestrant versus SOC ET, and ~ 40% versus ~ 60% of those with an *ESR1* mutation) [49]. This phenomenon is not unique to SERDs; it was also observed in other studies of novel agents evaluated as second-line ET after progression on first-line CDK4/6i plus ET in this patient population, including CAPItello-291 [25] and represents endocrine resistance developing on first-line CDK4/6i. A major challenge in the field is elucidating which patients benefit from further endocrine-based therapies such as SERDs in the second-line and which patients have endocrine-resistant tumors by the time of starting second-line therapy and therefore, would likely benefit from non-endocrine approaches such as earlier administration of cytotoxic chemotherapy or antibody–drug conjugates. Studies are being planned to evaluate earlier administration of effective cytotoxic therapy in HR + /HER2- mBC; a crucial aspect of those studies will be evaluating biomarkers of endocrine resistance that may be able to predict which patients benefit from moving to cytotoxic therapies before exhausting all endocrine options. Another interesting question is whether cytotoxic therapies may be able to eradicate or reduce endocrine-resistant subpopulations of tumor cells, which could allow for endocrine-based therapies to be re-introduced at a later timepoint in a patient's disease course.

Identifying and overcoming mechanisms of resistance to SERDs will be critical as these become more widely used

in clinical practice. Continuing to explore the synergistic potential of SERDs in combination with targeted agents, such as CDK4/6i, PI3K inhibitors, and potentially even immunotherapy, will be crucial in the near future. As the number of endocrine targeted treatments increases, sequencing of various agents will have to be explored. Additionally, as more SERDs are evaluated in the curative setting in patients with eBC, understanding their long-term toxicities such as their effects on bone and cardiovascular health will be even more important. Furthermore, SERDs that may work on specific *ESR1* mutations or may work better on a specific mutation versus others will have to be clinically evaluated. There are also an increasing number of other endocrine agents that target the ER using various mechanisms such as proteolysis-targeting chimeras (PROTACs) [79], selective ER covalent antagonists (SERCAs), and complete ER antagonists (CERANs) [80]. Finally, as oral SERDs become more widely used it will be critical to gather real-world evidence to validate clinical trial findings, determine efficacy in a diverse patient population, identify toxicities, and inform future research [81].

Conclusions

SERDs have been recently added to our therapeutic armamentarium for patients with HR + /HER2- breast cancers. Orally bioavailable members of the SERD family provide an advantage over fulvestrant in terms of route of administration and convenience and studies suggest that they are also more effective. Beyond effective antitumor activity, SERDs are generally well tolerated with manageable safety profiles. They also have the potential to overcome resistance to currently available older generation endocrine therapies such as AIs and tamoxifen and offer a superior treatment option as monotherapy or in combination with targeted agents, such as CDK4/6i and PI3K inhibitors. There are many emerging oral SERDs currently in early-stage clinical trials that have the potential to change the current landscape of HR + / HER2- breast cancer treatment options for both the advanced and early-stage settings. Developing biomarkers, beyond the presence of *ESR1* mutations, to predict which patients derive benefit from several lines of endocrine-based therapies in the metastatic setting is going to be a major challenge in the field.

Author Contributions M.T. and A.K. prepared the initial draft of the manuscript text and tables 1-2. J.F. edited and finalized manuscript text and tables and prepared figure 1. All authors reviewed the final manuscript.

Funding The authors did not receive support from any organization for the submitted work.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest Dr. Foldi reports personal fees from OncLive, personal fees from Research To Practice Inc., outside the submitted work; and has received research funding (paid to her institution) from Conquer Cancer/ASCO Foundation and the Pennsylvania Breast Cancer Coalition. The other authors declare that they have no conflicts of interest.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA A Cancer J Clin. 2024;74:12–49. https://doi.org/10.3322/caac.21820.
2. Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol. 2015;33:3781–7. https://doi.org/10.1200/JCO.2015.61.5831.
3. Robertson JFR, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol. 2009;27:4530–5. https://doi.org/10.1200/JCO.2008.21.1136.
4. Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016;388:2997–3005. https://doi.org/10.1016/S0140-6736(16)32389-3.
5. FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. In: FDA [Internet]. FDA; 27 Jan 2023 [cited 21 Jun 2024]. Available: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer
6. Clusan L, Ferrière F, Flouriot G, Pakdel F. A Basic Review on Estrogen Receptor Signaling Pathways in Breast Cancer. Int J Mol Sci. 2023;24:6834. https://doi.org/10.3390/ijms24076834.
7. Brufsky AM, Dickler MN. Estrogen Receptor-Positive Breast Cancer: Exploiting Signaling Pathways Implicated in Endocrine Resistance. Oncologist. 2018;23:528–39. https://doi.org/10.1634/theoncologist.2017-0423.
8. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen Receptors Alpha (ERα) and Beta (ERβ): Subtype-Selective Ligands and Clinical Potential. Steroids. 2014;90:13–29. https://doi.org/10.1016/j.steroids.2014.06.012.
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771–84.
10. Burstein HJ. Systemic Therapy for Estrogen Receptor-Positive, HER2-Negative Breast Cancer. N Engl J Med. 2020;383:2557–70. https://doi.org/10.1056/NEJMra1307118.
11. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. 2019;321:288–300. https://doi.org/10.1001/jama.2018.19323.
12. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping

Endocrine Therapy at 5 Years. N Engl J Med. 2017;377:1836–46. https://doi.org/10.1056/NEJMoa1701830.
13. Shiino S, Kinoshita T, Yoshida M, Jimbo K, Asaga S, Takayama S, et al. Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clin Breast Cancer. 2016;16:e133-140. https://doi.org/10.1016/j.clbc.2016.05.014.
14. Gnant M, Turner NC, Hernando C. Managing a Long and Winding Road: Estrogen Receptor-Positive Breast Cancer. Am Soc Clin Oncol Educ Book. 2023;43:e390922. https://doi.org/10.1200/EDBK_390922.
15. Reinert T, Saad ED, Barrios CH, Bines J. Clinical Implications of ESR1 Mutations in Hormone Receptor-Positive Advanced Breast Cancer. Front Oncol. 2017;7:26. https://doi.org/10.3389/fonc.2017.00026.
16. Malorni L, Piazza S, Ciani Y, Guarducci C, Bonechi M, Biagioni C, et al. A gene expression signature of retinoblastoma loss-of-function is a predictive biomarker of resistance to palbociclib in breast cancer cell lines and is prognostic in patients with ER positive early breast cancer. Oncotarget. 2016;7:68012–22.
17. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020;38:3987–98. https://doi.org/10.1200/JCO.20.02514.
18. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017;35:3638–46. https://doi.org/10.1200/JCO.2017.75.6155.
19. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36:2465–72. https://doi.org/10.1200/JCO.2018.78.9909.
20. Tripathy D, Im S-A, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19:904–15. https://doi.org/10.1016/S1470-2045(18)30292-4.
21. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25–35. https://doi.org/10.1016/S1470-2045(14)71159-3.
22. Cristofanilli M, Rugo HS, Im S-A, Slamon DJ, Harbeck N, Bondarenko I, et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2− ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer Res. 2022;28:3433–42. https://doi.org/10.1158/1078-0432.CCR-22-0305.
23. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380:1929–40. https://doi.org/10.1056/NEJMoa1813904.
24. Jhaveri K, Im S-A, Saura C, Juric D, Loibl S, Kalinsky K, et al. GS03–13: Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with PIK3CA-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis. San Antonio Breast Cancer Symposium 2023; 2023 Dec 8; San Antonio, TX. Available: https://aacr.ent.box.com/s/im3djx6fp13rad4kr3fmaf5ijj251pni
25. Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023;388:2058–70. https://doi.org/10.1056/NEJMoa2214131.
26. Kornblum N, Zhao F, Manola J, Klein P, Ramaswamy B, Brufsky A, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. J Clin Oncol. 2018;36:1556. https://doi.org/10.1200/JCO.2017.76.9331.
27. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2012;366:520–9. https://doi.org/10.1056/NEJMoa1109653.
28. Osborne CK, Wakeling A, Nicholson RI. Fulvestrant: an oestrogen receptor antagonist with a novel mechanism of action. Br J Cancer. 2004;90(Suppl 1):S2-6. https://doi.org/10.1038/sj.bjc.6601629.
29. Long X, Nephew KP. Fulvestrant (ICI 182,780)-dependent interacting proteins mediate immobilization and degradation of estrogen receptor-alpha. J Biol Chem. 2006;281:9607–15. https://doi.org/10.1074/jbc.M510809200.
30. Traboulsi T, El Ezzy M, Dumeaux V, Audemard E, Mader S. Role of SUMOylation in differential ERα transcriptional repression by tamoxifen and fulvestrant in breast cancer cells. Oncogene. 2019;38:1019–37. https://doi.org/10.1038/s41388-018-0468-9.
31. Vallet A, El Ezzy M, Diennet M, Haidar S, Bouvier M, Mader S. The AF-2 cofactor binding region is key for the selective SUMOylation of estrogen receptor alpha by antiestrogens. J Biol Chem. 2023;299:102757. https://doi.org/10.1016/j.jbc.2022.102757.
32. Wang Q, Zhang N, Yang X, Feng S, Wang F, Zhang W, et al. ERα promotes SUMO1 transcription by binding with the ERE and enhances SUMO1-mediated protein SUMOylation in breast cancer. Gland Surg. 2023;12:963–73. https://doi.org/10.21037/gs-23-39.
33. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol. 2002;20:3386–95. https://doi.org/10.1200/JCO.2002.10.058.
34. Howell A, Robertson JFR, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, et al. Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment. J Clin Oncol. 2002;20:3396–403. https://doi.org/10.1200/JCO.2002.10.057.
35. Robertson JFR, Osborne CK, Howell A, Jones SE, Mauriac L, Ellis M, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women. Cancer. 2003;98:229–38. https://doi.org/10.1002/cncr.11468.
36. Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma. Cancer. 2005;104:236–9. https://doi.org/10.1002/cncr.21163.
37. Cope S, Ouwens MJNM, Jansen JP, Schmid P. Progression-free survival with fulvestrant 500 mg and alternative endocrine therapies as second-line treatment for advanced breast cancer: a network meta-analysis with parametric survival models. Value Health. 2013;16:403–17. https://doi.org/10.1016/j.jval.2012.10.019.
38. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had

Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35:2875–84. https://doi.org/10.1200/JCO.2017.73.7585.
39. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373:209–19. https://doi.org/10.1056/NEJMoa1505270.
40. Lai A, Kahraman M, Govek S, Nagasawa J, Bonnefous C, Julien J, et al. Identification of GDC-0810 (ARN-810), an Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) that Demonstrates Robust Activity in Tamoxifen-Resistant Breast Cancer Xenografts. J Med Chem. 2015;58:4888–904. https://doi.org/10.1021/acs.jmedchem.5b00054.
41. Bardia A, Mayer I, Winer E, Linden HM, Ma CX, Parker BA, et al. The oral selective estrogen receptor degrader GDC-0810 (ARN-810) in postmenopausal women with hormone receptor-positive HER2-negative (HR + /HER2 -) advanced/metastatic breast cancer. Breast Cancer Res Treat. 2023;197:319–31. https://doi.org/10.1007/s10549-022-06797-9.
42. Weir HM, Bradbury RH, Lawson M, Rabow AA, Buttar D, Callis RJ, et al. AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res. 2016;76:3307–18. https://doi.org/10.1158/0008-5472.CAN-15-2357.
43. Hamilton EP, Patel MR, Armstrong AC, Baird RD, Jhaveri K, Hoch M, et al. A First-in-Human Study of the New Oral Selective Estrogen Receptor Degrader AZD9496 for ER+/HER2- Advanced Breast Cancer. Clin Cancer Res. 2018;24:3510–8. https://doi.org/10.1158/1078-0432.CCR-17-3102.
44. Robertson JFR, Evans A, Henschen S, Kirwan CC, Jahan A, Kenny LM, et al. A Randomized, Open-label, Presurgical, Window-of-Opportunity Study Comparing the Pharmacodynamic Effects of the Novel Oral SERD AZD9496 with Fulvestrant in Patients with Newly Diagnosed ER+ HER2− Primary Breast Cancer. Clin Cancer Res. 2020;26:4242–9. https://doi.org/10.1158/1078-0432.CCR-19-3387.
45. Tria GS, Abrams T, Baird J, Burks HE, Firestone B, Gaither LA, et al. Discovery of LSZ102, a Potent, Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) for the Treatment of Estrogen Receptor Positive Breast Cancer. J Med Chem. 2018;61:2837–64. https://doi.org/10.1021/acs.jmedchem.7b01682.
46. Jhaveri K, Juric D, Yap Y-S, Cresta S, Layman RM, Duhoux FP, et al. A Phase I Study of LSZ102, an Oral Selective Estrogen Receptor Degrader, with or without Ribociclib or Alpelisib, in Patients with Estrogen Receptor-Positive Breast Cancer. Clin Cancer Res. 2021;27:5760–70. https://doi.org/10.1158/1078-0432.CCR-21-1095.
47. Andreano KJ, Wardell SE, Baker JG, Desautels TK, Baldi R, Chao CA, et al. G1T48, an oral selective estrogen receptor degrader, and the CDK4/6 inhibitor lerociclib inhibit tumor growth in animal models of endocrine-resistant breast cancer. Breast Cancer Res Treat. 2020;180:635–46. https://doi.org/10.1007/s10549-020-05575-9.
48. Maglakelidze M, Bulat I, Ryspayeva D, Krastev BM, Gogiladze M, Crijanovschi A, et al. Rintodestrant (G1T48), an oral selective estrogen receptor degrader, in combination with palbociclib for ER+/HER2– advanced breast cancer: Phase 1 results. J Clin Oncol. 2021;39:1063–1063. https://doi.org/10.1200/JCO.2021.39.15_suppl.1063.
49. Bidard F-C, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, 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;40:3246–56. https://doi.org/10.1200/JCO.22.00338.
50. Bardia A, Kaklamani V, Wilks S, Weise A, Richards D, Harb W, et al. Phase I Study of Elacestrant (RAD1901), a Novel Selective Estrogen Receptor Degrader, in ER-Positive, HER2-Negative Advanced Breast Cancer. J Clin Oncol. 2021;39:1360–70. https://doi.org/10.1200/JCO.20.02272.
51. Bardia A, Bidard F-C, Neven P, Streich G, Montero AJ, Forget F, et al. Abstract GS3–01: GS3–01 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. Cancer Res. 2023;83. https://doi.org/10.1158/1538-7445.SABCS22-GS3-01.
52. Rugo H, Bardia A, Cortés J, Curigliano G, Hamilton E, Hurvitz S, et al. Abstract OT2–01–03: ELEVATE: A phase 1b/2, open-label, umbrella study evaluating elacestrant in various combinations in women and men with metastatic breast cancer (mBC). Cancer Research. 2023;83: OT2–01–03. https://doi.org/10.1158/1538-7445.SABCS22-OT2-01-03
53. Kahraman M, Govek SP, Nagasawa JY, Lai A, Bonnefous C, Douglas K, et al. Maximizing ER-α Degradation Maximizes Activity in a Tamoxifen-Resistant Breast Cancer Model: Identification of GDC-0927. ACS Med Chem Lett. 2019;10:50–5. https://doi.org/10.1021/acsmedchemlett.8b00414.
54. Chandarlapaty S, Dickler MN, Perez Fidalgo JA, Villanueva-Vázquez R, Giltnane J, Gates M, et al. An Open-label Phase I Study of GDC-0927 in Postmenopausal Women with Locally Advanced or Metastatic Estrogen Receptor-Positive Breast Cancer. Clin Cancer Res. 2023;29:2781–90. https://doi.org/10.1158/1078-0432.CCR-23-0011.
55 Metcalfe C, Ingalla E, Blake R, Chang J, Daemen A, De Bruyn T, et al. Abstract P5–04–07: GDC-9545: A novel ER antagonist and clinical candidate that combines desirable mechanistic and pre-clinical DMPK attributes. Cancer Res. 2019;79:P5.
56. Jhaveri KL, Boni V, Sohn J, Villanueva-Vásquez R, Bardia A, Schmid P, et al. Safety and activity of single-agent giredestrant (GDC-9545) from a phase Ia/b study in patients (pts) with estrogen receptor-positive (ER+), HER2-negative locally advanced/metastatic breast cancer (LA/mBC). J Clin Oncol. 2021;39:1017–1017. https://doi.org/10.1200/JCO.2021.39.15_suppl.1017.
57. Jhaveri KL, Bellet M, Turner NC, Loi S, Bardia A, Boni V, et al. Phase Ia/b Study of Giredestrant ± Palbociclib and ± Luteinizing Hormone-Releasing Hormone Agonists in Estrogen Receptor-Positive, HER2-Negative, Locally Advanced/Metastatic Breast Cancer. Clin Cancer Res. 2024;30:754–66. https://doi.org/10.1158/1078-0432.CCR-23-1796.
58. Martín M, Lim E, Chavez-MacGregor M, Bardia A, Wu J, Zhang Q, et al. Giredestrant for Estrogen Receptor-Positive, HER2-Negative, Previously Treated Advanced Breast Cancer: Results From the Randomized, Phase II acelERA Breast Cancer Study. J Clin Oncol. 2024;42:2149–60. https://doi.org/10.1200/JCO.23.01500.
59. Mayer EL, Tolaney SM, Brufsky A, Gradishar WJ, Jhaveri KL, Martin M, et al. evERA Breast Cancer (BC): Phase III study of giredestrant + everolimus vs exemestane + everolimus in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced or metastatic BC (ER+, HER2– LA/mBC). J Clin Oncol. 2023;41:TPS1119. https://doi.org/10.1200/JCO.2023.41.16_suppl.TPS1119.
60. Oliveira M, Sonnenblick A, Rugo HS, Jung KH, Yam EG, Hurvitz SA, et al. Interim analyses (IA) of the giredestrant (G), G + abemaciclib (A), and G + ribociclib (R) arms in MORPHEUS Breast Cancer (BC): A phase I/II study of G treatment (tx) combinations in patients (pts) with estrogen receptor-positive, HER2-negative locally advanced/metastatic BC (ER+, HER2– LA/mBC). J Clin Oncol. 2023;41:1061–1061. https://doi.org/10.1200/JCO.2023.41.16_suppl.1061.
61. Geyer C, Bardia A, Harbeck N, Rimawi MF, Hurvitz SA, Martin M, et al. lidERA Breast Cancer (BC): Phase III adjuvant study of

giredestrant vs. physician's choice of endocrine therapy (PCET) in patients (pts) with estrogen receptor-positive, HER2-negative early BC (ER+, HER2– eBC). J Clin Oncol. 2023;41:616.
62. Hurvitz SA, Bardia A, Quiroga V, Park YH, Blancas I, Alonso-Romero JL, et al. Neoadjuvant palbociclib plus either giredestrant or anastrozole in oestrogen receptor-positive, HER2-negative, early breast cancer (coopERA Breast Cancer): an open-label, randomised, controlled, phase 2 study. Lancet Oncol. 2023;24:1029–41. https://doi.org/10.1016/S1470-2045(23)00268-1.
63. Shomali M, Cheng J, Sun F, Koundinya M, Guo Z, Hebert AT, et al. SAR439859, a Novel Selective Estrogen Receptor Degrader (SERD), Demonstrates Effective and Broad Antitumor Activity in Wild-Type and Mutant ER-Positive Breast Cancer Models. Mol Cancer Ther. 2021;20:250–62. https://doi.org/10.1158/1535-7163.MCT-20-0390.
64. Bardia A, Chandarlapaty S, Linden HM, Ulaner GA, Gosselin A, Cartot-Cotton S, et al. AMEERA-1 phase 1/2 study of amcenestrant, SAR439859, in postmenopausal women with ER-positive/HER2-negative advanced breast cancer. Nat Commun. 2022;13:4116. https://doi.org/10.1038/s41467-022-31668-8.
65. Tolaney SM, Chan A, Petrakova K, Delaloge S, Campone M, Iwata H, et al. AMEERA-3: Randomized Phase II Study of Amcenestrant (Oral Selective Estrogen Receptor Degrader) Versus Standard Endocrine Monotherapy in Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer. J Clin Oncol. 2023;41:4014–24. https://doi.org/10.1200/JCO.22.02746.
66. Lawson M, Cureton N, Ros S, Cheraghchi-Bashi A, Urosevic J, D'Arcy S, et al. The Next-Generation Oral Selective Estrogen Receptor Degrader Camizestrant (AZD9833) Suppresses ER+ Breast Cancer Growth and Overcomes Endocrine and CDK4/6 Inhibitor Resistance. Cancer Res. 2023;83:3989–4004. https://doi.org/10.1158/0008-5472.CAN-23-0694.
67. Oliveira M, Hamilton EP, Incorvati J, Bermejo de la Heras B, Calvo E, García-Corbacho J, et al. Serena-1: Updated analyses from a phase 1 study (parts C/D) of the next-generation oral SERD camizestrant (AZD9833) in combination with palbociclib, in women with ER-positive, HER2-negative advanced breast cancer. J Clin Oncol. 2022;40:1032–1032. https://doi.org/10.1200/JCO.2022.40.16_suppl.1032.
68. Oliveira M, Pominchuck D, Nowecki Z, Hamilton E, Kulyaba Y, Andabekov T, et al. Abstract GS3–02: GS3–02 Camizestrant, a next generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial. Cancer Res. 2023;83:GS3. https://doi.org/10.1158/1538-7445.SABCS22-GS3-02.
69. Im S-A, Hamilton EP, LlombartCussac A, Baird RD, Ettl J, Goetz MP, et al. SERENA-4: A phase 3 comparison of AZD9833 (camizestrant) plus palbociclib, versus anastrozole plus palbociclib, for patients with ER-positive, HER2-negative advanced breast cancer who have not previously received systemic treatment for advanced disease. J Clin Oncol. 2021;39:TPS1101. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS1101.
70. Turner N, Huang-Bartlett C, Kalinsky K, Cristofanilli M, Bianchini G, Chia S, et al. Design of SERENA-6, a phase III switching trial of camizestrant in ESR1-mutant breast cancer during first-line treatment. Future Oncol. 2023;19:559–73. https://doi.org/10.2217/fon-2022-1196.
71. Baird R, Oliveira M, Gil EMC, Patel MR, Bermejo de las Heras B, Ruiz-Borrego M, et al. Abstract PS11–05: Updated data from SERENA-1: A Phase 1 dose escalation and expansion study of the next generation oral SERD AZD9833 as a monotherapy and in combination with palbociclib, in women with ER-positive, HER2-negative advanced breast cancer. Cancer Res. 2021;81:PS11. https://doi.org/10.1158/1538-7445.SABCS20-PS11-05.
72. Jhaveri KL, Jeselsohn R, Lim E, Hamilton EP, Yonemori K, Beck JT, 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. J Clin Oncol. 2022;40:1021–1021. https://doi.org/10.1200/JCO.2022.40.16_suppl.1021.
73. Neven P, Stahl N, Losada MJV, Jimenez MM, Kaufman PA, Harbeck N, et al. 273P A preoperative window-of-opportunity (WOO) study of imlunestrant in ER+, HER2- early breast cancer (EBC): Final analysis from EMBER-2. Ann Oncol. 2023;34:S292–3. https://doi.org/10.1016/j.annonc.2023.09.470.
74. Jhaveri K, Harbeck N, Aftimos P, Kim S-B, Pivot X, Saura C, et al. Abstract OT2-11-01: EMBER-3: A randomized phase 3 study of LY3484356, a novel, oral selective estrogen receptor degrader vs investigator's choice of endocrine therapy of either fulvestrant or exemestane, in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer previously treated with endocrine-based therapy. Cancer Res. 2022;82. https://doi.org/10.1158/1538-7445.SABCS21-OT2-11-01.
75. Samatar AA, Li J, Hegde S, Huang P, Ma J, Bunker K, et al. Abstract 4373: Discovery of ZN-c5, a novel potent and oral selective estrogen receptor degrader. Can Res. 2020;80:4373. https://doi.org/10.1158/1538-7445.AM2020-4373.
76. Abramson V, Linden HM, Crew K, Mortimer J, Alidzanovic J, Nangia J, et al. 565TiP A phase I/II dose-escalation and expansion study of ZN-c5, an oral selective estrogen receptor degrader (SERD), as monotherapy and in combination with palbociclib in patients with advanced estrogen receptor (ER)+/HER2- breast cancer. Ann Oncol. 2021;32:S619. https://doi.org/10.1016/j.annonc.2021.08.1087.
77. Keogh GP, Papish S, Piskorski W, Ulanska M, Jackson B, Suster M, et al. 564TiP A phase Ib dose-escalation study of ZN-c5, an oral selective estrogen receptor degrader (SERD), in combination with abemaciclib in patients with advanced estrogen receptor (ER)+/HER2- breast cancer. Ann Oncol. 2021;32:S618–9. https://doi.org/10.1016/j.annonc.2021.08.1086.
78 Osborne C, Richards DA, Wilks ST, Diab S, Juric D, Lathrop K, et al. Abstract PS11–26: A phase 1 study of D-0502, an orally bioavailable SERD, for advanced or metastatic HR-positive and HER2-negative breast cancer. Cancer Res. 2021;81:PS11. https://doi.org/10.1158/1538-7445.SABCS20-PS11-26.
79. Sincere NI, Anand K, Ashique S, Yang J, You C. PROTACs: Emerging Targeted Protein Degradation Approaches for Advanced Druggable Strategies. Molecules. 2023;28:4014. https://doi.org/10.3390/molecules28104014.
80. Lloyd MR, Wander SA, Hamilton E, Razavi P, Bardia A. Next-generation selective estrogen receptor degraders and other novel endocrine therapies for management of metastatic hormone receptor-positive breast cancer: current and emerging role. Ther Adv Med Oncol. 2022;14:17588359221113694. https://doi.org/10.1177/17588359221113694.
81. Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ Breast Cancer. 2023;9:20. https://doi.org/10.1038/s41523-023-00523-4.