

Review Article

New generation estrogen receptor-targeted agents in breast cancer: present situation and future prospectives

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ABSTRACT

Endocrine therapy that blocks estrogen receptor signaling has been effective for decades as a primary treatment choice for breast cancer patients expressing the estrogen receptor. However, the issue of drug resistance poses a significant clinical challenge. It is therefore critically important to create new therapeutic agents that can suppress ER α activity, particularly in cases of ESR1 mutations. This review highlights recent efforts in drug development of next generation ER-targeted agents, including oral selective ER degraders, proteolysis-targeting chimera ER degraders, and other innovative molecules, such as complete estrogen receptor antagonists and selective estrogen receptor covalent antagonists. The drug design, efficacy, and clinical trials for each compound are detailed herein.

Keywords: Estrogen receptor, endocrine-resistant breast cancer, SERD, PROTAC

1. INTRODUCTION

Breast cancer (BC) ranks as the leading malignant tumor in women and is a serious risk to women's health [1]. Being a highly heterogeneous disease, BC is typically classified into various subtypes based on immunohistochemical analysis. The classification mainly depends on the level of three biomarkers (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]). Genomic sequencing and transcriptomic profiling have classified BC into the following subtypes: luminal A; luminal B; and HER2-enriched and basal-like/triple negative (ER-/PR-/HER2-) [2]. The majority of luminal A and B BCs express ER, with approximately 70% of newly identified patients being ER+ (Figure 1) [3].

In patients with non-metastatic ER+ BC, endocrine therapy is advised as the primary treatment option [4]. Endocrine therapy consists of two types of drugs: aromatase inhibitors (AIs), which reduce the levels of estrogen in the body and reduce binding to the ER;

and anti-estrogens (AE), which reduce ER signaling and encompass selective estrogen receptor inhibitors (SERMs) that block ER function by blocking estrogen binding to ERs, and selective estrogen receptor degraders/downregulators (SERDs) that downregulate ER levels through protein degradation [5, 6].

Endocrine therapy has notably enhanced the survival rate of ER+ BC patients, yet drug resistance occurs in up to 50% of patients during long-term treatment, many of whom have metastases and relapses [7]. Moreover, the metastases and recurrences are often more aggressive than the primary cancer, resulting in lower survival and a poorer prognosis [8].

Since 2013 multiple research teams have found through deep gene sequencing that mutations in the ER α encoding gene, ESR1, are present in high levels in BCs that relapse and metastasize after endocrine therapy and are a genomic mechanism leading to endocrine resistance [9-11]. The full length of ER α is made up of 595 amino acids with a molecular weight of 66.2 kDa. As a typical nuclear receptor, ER α features a DNA-binding

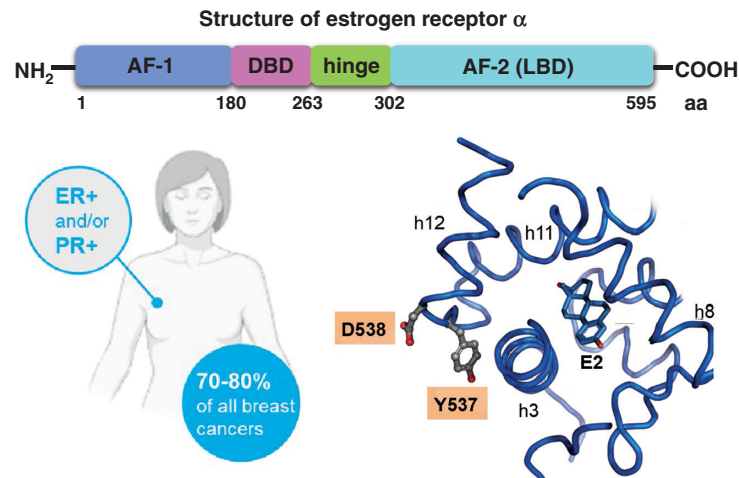


Figure 1 | Structure of ER α and hot spot ESR1 mutations.

domain (DBD) that is highly conserved and a ligand-binding domain (LBD) composed of 12 helices (**Figure 1**) [12]. ESR1 mutations are predominantly ER point mutations. Specifically, the ER point mutations, Y537S and D538G, are located on C-terminal helix 12 (h12) and are the most common ER point mutations in 50% of cases (**Figure 1**) [13]. Post-mutation the ER signaling pathway remains aberrantly activated and traditional ER inhibitors do not respond, leading to acquired resistance [14].

These acquired ESR1 mutations establish the clinical need to develop a new generation of ER-targeted agents. Amid overwhelming clinical demand, the pharmaceutical industry and academia have been investing in new-generation ER inhibitors to block the ER signaling pathway. Each class operates through a unique mechanism of action, as depicted in **Figure 2**.

From this viewpoint we will review the latest discoveries and advances in the new generation of anti-estrogens and how they set a new paradigm for treating ER+ BC.

2. SERDs

SERDs are viewed as a key strategy in overcoming endocrine resistance [15]. SERDs function as ER antagonists and trigger ER degradation to effectively block ER signaling [16]. Given the context of drug resistance, a number of oral SERDs have been identified to increase systemic exposure, thereby enhancing efficacy and clinical potency against ESR1 mutations [17].

The current active clinical trials of new oral SERDs are summarized in **Table 1**.

2.1 Fulvestrant and its analogue

Presently, fulvestrant is as the only SERD administered in treating endocrine-resistant metastatic BC in the first and subsequent lines [18]. However, the limited solubility and absence of oral bioavailability restricts the full clinical potential of fulvestrant, with ER blockade of < 75%, even with a monthly administration of 500 mg [19].

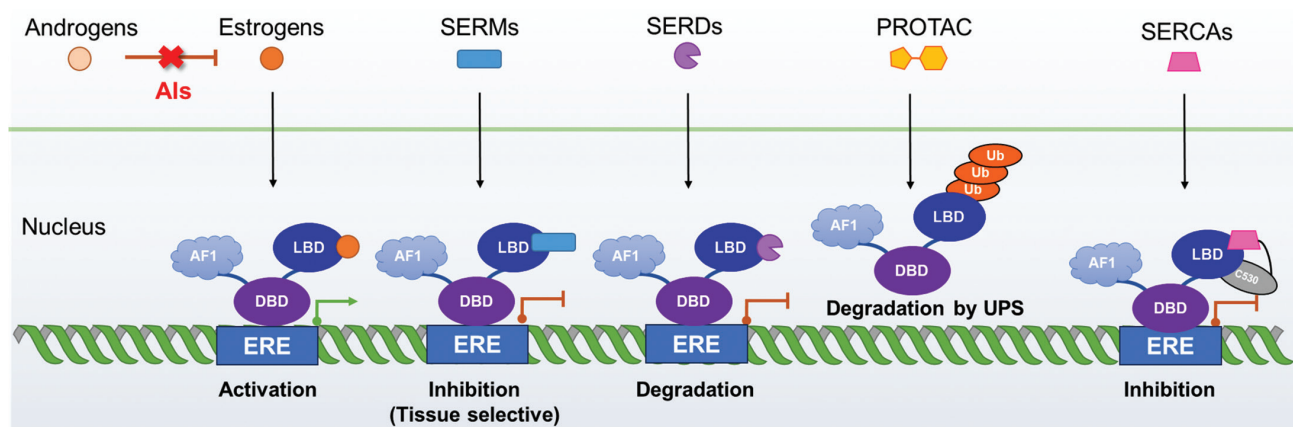


Figure 2 | Summary of the mechanism of action underlying the main classes of ER-targeted agents.

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Table 1 | Ongoing clinical trials of oral SERDs.

Oral SERD	Trial identifier	N	Study design	Patient characteristics
Borestrant (ZB716)	NCT04669587	106	Monotherapy and combined with palbociclib	ER+/HER2- Locally advanced or metastatic breast cancer
Rintodestrant (G1T48)	NCT03455270	107	Monotherapy and combined with palbociclib	ER+/HER2- Metastatic breast cancer
Taragarestrant (D-0502)	NCT03471663	200	Monotherapy and combined with palbociclib	ER+/HER2- Advanced or metastatic breast cancer
	CTR20190092	72	Monotherapy and combined with palbociclib	ER+/HER2- Advanced or metastatic breast cancer
ZN-c5	NCT03560531	181	Monotherapy combined with palbociclib	ER+/HER2- Advanced or metastatic breast cancer
	NCT04514159	14	Combined with abemaciclib	
LX-039	NCT04097756	44	Dose escalation and dose expansion	ER+/HER2- Locally advanced or metastatic breast cancer
Elacestrant (RAD1901)	NCT05386108	106	Combined with abemaciclib	Brain metastasis due to HR+/HER2- breast cancer
Imluestrant (LY3484356)	NCT04188548	500	Monotherapy and combined with abemaciclib/everolimus/alpelisib	ER+ Locally advanced or metastatic breast cancer and other select non-breast cancers
Camizestrant (AZD9833)	NCT04964934	300	Combined with CDK4/6 inhibitors vs. continue AI + CDK4/6 inhibitors	HR+/HER2- Metastatic breast cancer with detectable ESR1 mutation
Giredestrant (GDC9545)	NCT04546009	992	Combined with palbociclib vs. letrozole + palbociclib	ER+/HER2- Advanced or metastatic breast cancer

The introduction of a boronic acid component to substitute the C3 phenol led to the creation of borestrant (ZB716), the purpose of which is to inhibit first-pass metabolism while preserving the fulvestrant pharmacologic profile (Figure 3) [20]. Preclinical studies have shown that ZB716 is an orally bioavailable selective ER α degrader that exhibits complete ER antagonism and superior characteristics when compared to fulvestrant [21]. ZB716 was given orally in a phase I/II ENZENO trial (NCT04669587) alone and combined with palbociclib for patients with ER+/HER2- advanced or metastatic breast cancer (MBC) [22].

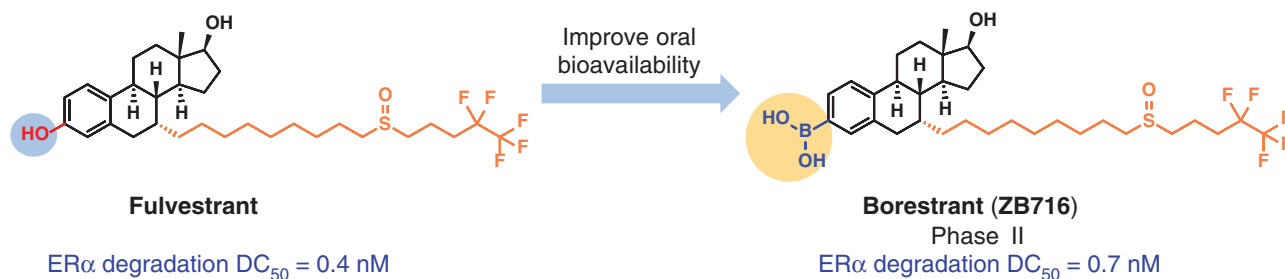
2.2 Oral SERDs with acrylic acid side chains

In addition to borestrant, pharmaceutical efforts have utilized non-steroidal scaffolds with two types of chemical

pendent moieties (an acid or basic side chain). These side chains perturb the ER LBD pocket and interfere with the co-activator binding site to drive antagonism [23].

An acrylic acid side chain was first employed in an early SERD (GW5638) from Glaxo-SmithKline (GSK) in 1994 [24]. During that period, tamoxifen had been successfully used as a selective estrogen receptor modulator (SERM) in adjuvant endocrine therapy for nearly 2 decades. However, while tamoxifen exhibits anti-estrogen effects in BC cells, tamoxifen functions as a partial agonist in certain tissues (uterus, bones, and endometrium), leading to side effects and drug resistance [25]. There was a demand for stronger anti-estrogens to fulfill the unaddressed clinical requirements of tamoxifen.

GW5638 was designed based on the tamoxifen core structure by substituting a basic piperidine side chain

**Figure 3** | Fulvestrant and its boric acid analogue, ZB716.

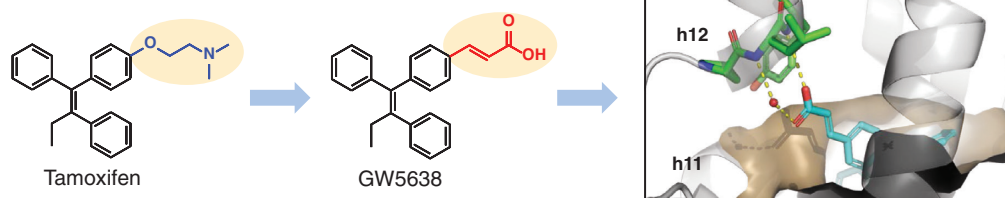
with an acrylic acid side chain. According to the crystal structure of GW5638 complexed with the ER LBD, this rigid acrylic acid moiety interacts with the N-terminus of h12 and shifts h12 to disrupt the co-activator binding site to induce protein degradation (Figure 4a) [26]. This rigid and acidic side chain was utilized in numerous newly developed SERDs, such as GDC-0810, G1T48, LSZ102, SHR9549, AZD9496, D-0502, ZN-c5, and LX-039 (Figure 4b).

Brilanestrant (GDC-0810) was developed by Seragon and derived from the structural design of GW5638 [27]. The benzene ring of GW5638 was replaced by indazole to improve pharmacokinetic properties [28]. A phase II trial (NCT02569801) demonstrated good safety and tolerability of GDC-0810. GDC-0810 also exhibited desirable anti-tumor potency in advanced ER+ or MBC patients

who had undergone extensive pretreatment, regardless of ESR1 mutations [29]. However, further development was discontinued owing to commercial consideration in contrast to other competitors under development, which showed early signs of complete ER antagonism and enhanced potency [30].

Rintodestrant (G1T48) was developed by G1 Therapeutics. The drug design was inspired by the typical 6-OH-benzothiophene scaffold used in arzoxifene and raloxifene [31, 32]. Rintodestrant acts as a potent oral SERD that selectively binds to the ER and inhibits ER signaling in endocrine-resistant tumors. A phase I trial (NCT03455270) of G1T48 alone and combined with the CDK4/6 inhibitor, palbociclib, generated excellent safety/tolerability profiles and potent anti-tumor activity in extensively pretreated ER+/HER2- advanced

a Design of GW5638



b New generation oral SERDs with acrylic acid side chain

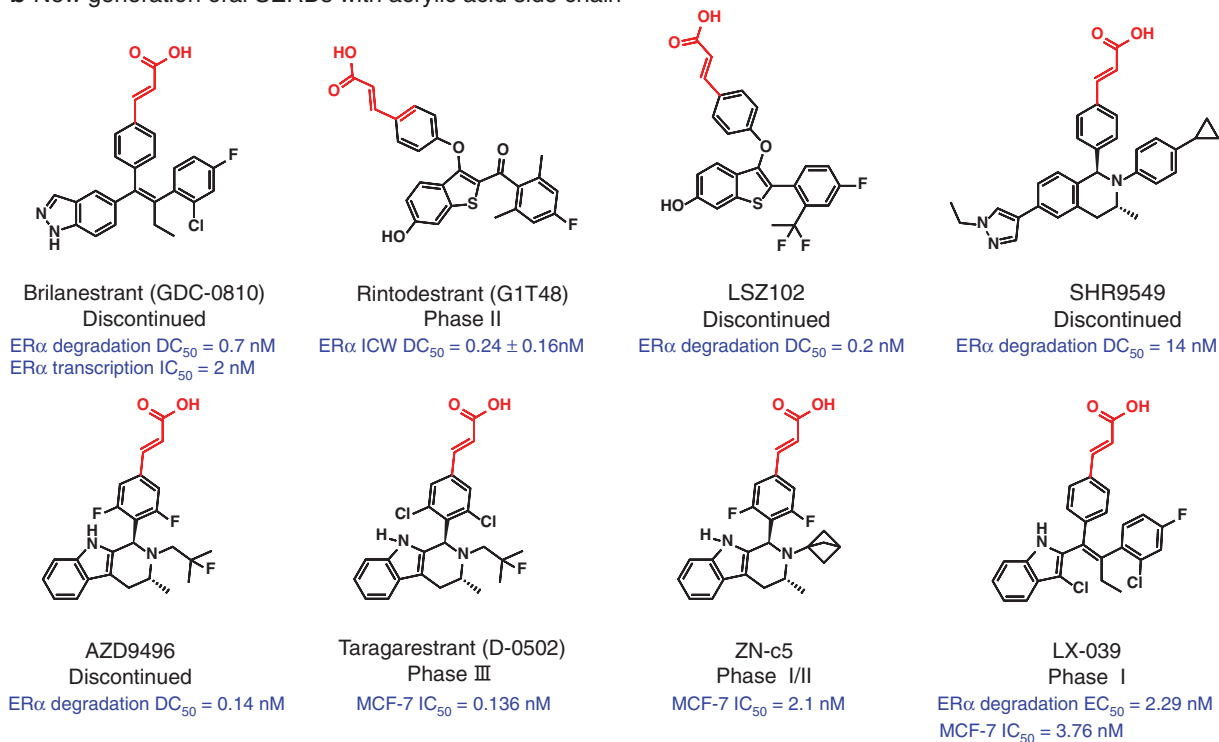


Figure 4 | Oral SERDs with acrylic acid side chains.

a. Design of the oral SERD, GW5638. The acrylic acid chain relocates h12 to block the co-activator binding site (PDB ID: 1R5K); **b.** Representative chemical structures of new generation oral SERDs with acrylic acid side chains.

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BC patients, especially those harboring ESR1 variants [33, 34].

LSZ102 is another benzothiophene scaffold oral SERD developed by Novartis with an acrylic acid side chain [35]. A phase I/II study (NCT02734615) reported encouraging activity of LSZ102 when combined with the CDK4/6 inhibitor, ribociclib, and the PI3K α inhibitor, alpelisib, for treating ER+ BC patients. However, Novartis terminated further clinical development due to the limited clinical potency of LSZ102 as a single treatment [36].

Compound SHR9549 was developed by Shanghai HengRui Medicine Co., Ltd. with a tetrahydroisoquinoline core. Rodents treated with SHR9549 revealed a potent (IC₅₀ = 14 nM) ER degrader with promising pharmacokinetic characteristics [37, 38]. A phase I trial involving SHR9549 (NCT03596658) was terminated because of dose-limited toxicity observed in one patient.

AZD9496 was developed by AstraZeneca based on a tricyclic tetrahydropiperidine core [39]. AZD9496 achieved sub-nanomolar degradation potency equal to fulvestrant and excellent oral bioavailability in mice [40]. However, AZD9496 exhibited weaker ER α degradation and partial agonism in various ER+ BC cell lines [41]. Further investment of AZD9496 was halted because of adverse toxicity and limited clinical benefits, paving the path for AZD9833, a more effective and well-tolerated successor [42].

Taragarestrant (D-0502) was created by Inventis Bio. It was noticed that taragarestrant has a very similar structure to AZD9496. This SERD, which can be taken orally, exhibits potent efficacy across multiple BC cell lines expressing ER and related xenograft models [43]. A phase I study (NCT03471663) involving D-0502 is ongoing in females with ER+/HER2- advanced BC or MBC [44]. D-0502 has shown good tolerability and considerable exposure, leading to preliminary clinical activity in patients when used alone and combined with palbociclib. Currently, D-0502 is under evaluation in a phase III clinical trial (CTR20190092) for patients with ER+/HER2- advanced BC or MBC in China [45].

ZN-c5 was developed by Zentalis with a tricyclic tetrahydropiperidine core similar to AZD9496 and D-0502 [46]. ZN-c5 represents an innovative, orally bioavailable ER degrader with high potency in estrogen-dependent tumor models. Preliminary clinical results showed that ZN-c5 is extremely safe and tolerable when used in combination with several CDK4/6 inhibitors [47]. A phase II trial involving ZN-c5 as monotherapy (NCT03560531) and a phase I trial involving ZN-c5 in combination with palbociclib (NCT03560531) and abemaciclib (NCT04514159) are ongoing [48].

LX-039 was developed by Luoxin Pharmaceuticals with a C-3 chlorine indole mimicking AZD9496 [49]. LX-039 demonstrated favorable physicochemical properties and potent biological activities *in vitro* [50]. LX-039 exhibited potent tumor inhibition in both wild-type and tamoxifen-resistant MCF-7 mouse xenograft models. The excellent pharmacokinetic profile and high

oral exposure of LX-038 facilitated its advancement into clinical trials. Currently, LX-039 is undergoing a phase I trial (NCT04097756) treating ER+/HER2- advanced BC or MBC patients [51].

2.3 Oral SERDs with basic side chains

Several clinical SERMs, such as tamoxifen, raloxifene, and lasofoxifene, contain a basic side chain that emerges from the ER LBD pocket and relocates h12 from the agonist conformation to the antagonist conformation (Figure 5a) [52, 53]. Early clinical data of new SERDs featuring acrylic acid side chains did not yield encouraging results with respect to efficacy and tolerability, leading to the termination of further development for most of these compounds [54]. Being a ligand-dependent receptor, ER exhibits sensitivity to minor structural changes of the ligand [55]. Consequently, a range of basic functionalities were screened in the drug design and ultimately utilized in oral SERDs (Figure 5b) [56].

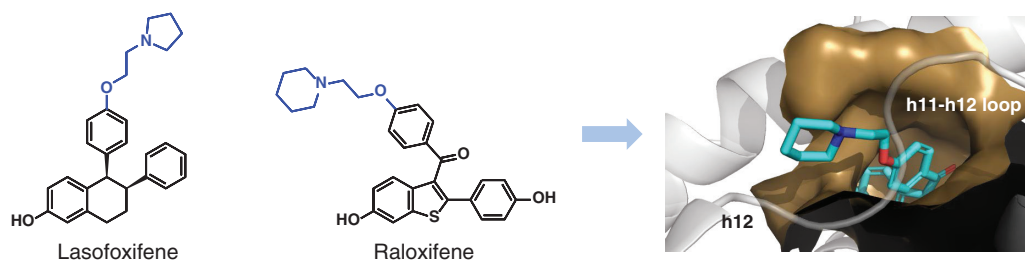
Elacestrant (RAD-1901) was the first new generation oral SERD approved by US FDA under the brand name, Orserdu[®], on 27 January 2023 [57]. Orserdu[®] was developed by Stemline Therapeutics, a branch of the Menarini Group [58]. The therapeutic indication for elacestrant is treatment of ER+/HER2- and ESR1-mutated advanced BC or MBC patients as a single agent [59]. When administered orally in a higher dose, elacestrant increases the receptor occupancy and triggers a conformational change, resulting in ER degradation and suppression of ER signaling pathways to prevent cancer progression [60]. The phase I/II ELECTRA trial (NCT05386108) involving elacestrant combined with abemaciclib is ongoing to treat patients with ER+/HER2- BC and brain metastases.

GDC-0927 was developed by Seragon Pharmaceuticals [61]. GDC-0927 has a chromene core with an azetidine base side chain and exhibits enhanced anti-tumor activity *in vivo* in two ER+ PDX models. A phase I trial (NCT02316509) showed that GDC-0927 consistently reduces ER availability regardless of the ESR1 mutation status [62]. Despite showing desirable features, the continued development of GDC-0927 was stopped based on the collective clinical data [63].

Bexirestrant (SCO-120) was developed by Sun Pharma [64]. Bexirestrant has a chromene core with an *E*-alkene linked to an azetidine base [65]. As a potent degrader in both wild-type and ESR1-mutated ER, bexirestrant showed notable efficacy in an MCF-7 ER-Y537S xenograft model [66]. Further clinical development of SCO-120 was terminated for commercial reasons.

Amcenestrant (SAR439859) was identified by Sanofi as a potent SERD [67]. Amcenestrant has a 6,7-dihydro-5*H*-benzo[7]annulene core with phenol attached to an O-linked fluoropropyl-pyrrolidine side chain. The reduction in ER α levels by amcenestrant was comparable to fulvestrant *in vitro* and amcenestrant demonstrated potent efficacy in BC xenograft murine models with significant tumor shrinkage [68]. Given the encouraging preclinical outcomes in wild-type and mutated

a Clinical SERMs lasofoxifene and raloxifene



b New generation oral SERDs with basic side chain

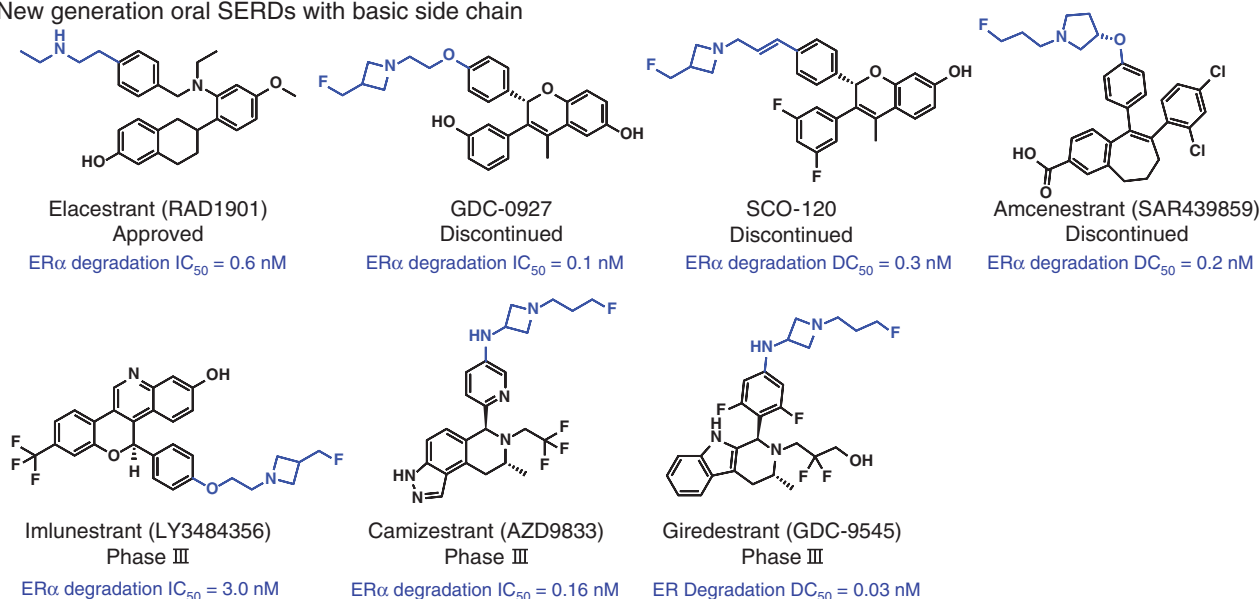


Figure 5 | SERMs and oral SERDs with basic side chains.

a. Chemical structures of lasofoxifene and raloxifene. The basic side chain of raloxifene relocates h12 from the agonist conformation to the antagonist conformation (PDB ID: 7KBS); **b.** Representative chemical structures of new generation oral SERDs with basic side chains.

ESR1 models, amcenenstrant has undergone assessment alone in the AMEERA-1 phase I/II trial (NCT03284957) in ER+/HER2- MBC patients, followed by AMEERA-3 trial (NCT04059484) in which the SERD was compared to the endocrine therapy (ET) selected by the physician [69]. Further clinical development of amcenenstrant was discontinued due to treatment-related toxicity observed in the AMEERA-5 (NCT04478266) and AMEERA-6 (NCT05128773) trials [70, 71].

Imlunestrant (LY3484356) was developed by Loxo Oncology of the Eli Lilly Corporation [72]. The core scaffold of imlunestrant mimics the ABCD ring of estradiol with a 7 β position phenyl appendant. Imlunestrant demonstrated potent efficacy in suppressing wild-type and ESR1-mutated mice xenograft BC tumor models. When imlunestrant was in combination treatment with the abemaciclib, everolimus, and alpelisib, synergistic effects were observed in suppressing multiple BC cell lines expressing ER and in corresponding xenograft or PDX models *in vivo* [73]. A phase I/II EMBER trial of LY3484356 (NCT04188548) is currently underway.

Camizestrant (AZD9833) was reported by AstraZeneca with a 3-(fluoromethyl)azetidino side chain replacing the acrylic acid chain of AZD9496 [74]. Among various ER+ BC cell lines, the maximal ER α degradation was similar to fulvestrant and exceeded AZD9496 [75]. The phase II SERENA-2 trial (NCT04214288) showed that camizestrant has enhanced efficacy and suppression in PDX models compared to fulvestrant [76, 77]. Furthermore, the phase III SERENA-6 trial (NCT04964934) showed that camizestrant has strong and broad anti-tumor potency as a single agent and when combined with CDK4/6 or PI3K/AKT/mTOR inhibitors in fulvestrant-resistant wide-type and ESR1-mutated PDX models [78].

Giredestrant (GDC9545) was developed by Genentech as a full ER antagonist and potent SERD [79]. Medicinal scientists from Genentech utilized the tricyclic tetrahydropiperidine core with a difluoropropyl alcohol side chain to enhance the physicochemical properties without sacrificing potency [80]. Giredestrant has potent oral bioavailability and superior degradation efficiency compared to fulvestrant in wild-type and mutant ER-Y537S

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MCF-7 cells [81]. The phase III persevERA (NCT04546009) and eVERA (NCT05306340) trials are ongoing to evaluate the efficacy and safety profiles of GDC-9545 combined with palbociclib and everolimus in ER+/HER2- MBC patients who are pretreated with CDK4/6 inhibitors and ET [82, 83].

3. ER PROTEOLYSIS-TARGETING CHIMERAS (PROTACs)

PROTAC technology has gained attention throughout the pharmaceutical industry in recent years. The PROTAC complex consists of three parts: a ligand of the target protein at one end; an E3 ubiquitin ligase binder at the other end; and a suitable linker connecting the two ends. Theoretically, only a catalytic dose of PROTAC is required to degrade nearly all of the proteins in the cell, which makes PROTACs safe, resistant, and promising for clinical application [84]. PROTACs can be used to overcome resistance to traditional therapeutic drugs on

their own, as well as a promising tool for future combination therapies. There have been numerous reports of ER PROTACs using the core structure of a SERM or SERD as an ER ligand, and von Hippel-Lindau (VHL), cerebron (CRBN), or inhibitors of apoptosis (IAPs) as an E3 ligase [85, 86].

The pioneering ER PROTAC, ARV-471 (vepedegestrant), was collaboratively developed by Pfizer and Arvinas. By targeting ER α and CRBN, vepdegestrant forms a heterobifunctional PROTAC that degrades wild-type and mutant ER (Figure 6). According to phase I/II trial data, ARV-471 was well-tolerated and clinically effective in extensively pretreated ER+/HER2- advanced BC or MBC patients [87]. The phase III VERITAC-2 trial (NCT05654623) is under assessment to compare vepdegestrant with fulvestrant. The phase III VERITAC-3 trial (NCT05909397), which involves vepdegestrant combined with palbociclib, is ongoing (Table 2) [88]. Other combination therapy studies with abemaciclib, ribociclib, samuraciclib, everolimus, and Pfizer's innovative CDK4

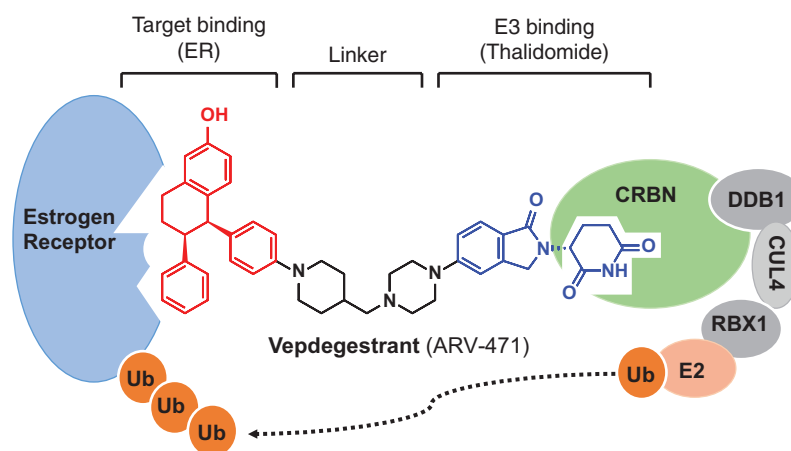


Figure 6 | Chemical structure of oral the ER-PROTAC, ARV-471.

Table 2 | Ongoing clinical trials of ER PROTACs, CERAN, and SERCA.

Drug name	Trial identifier	N	Study design	Patient characteristics
Vepdegestrant (ARV-471)	NCT05654623	560	Monotherapy vs. fulvestrant	ER+/HER2- Advanced or metastatic breast cancer
	NCT05909397	1180	Combined with palbociclib vs. letrozole + palbociclib	
AC0682	NCT05489679	6	Safety, tolerability, PK, and preliminary anti-tumor activity alone	ER+/HER2- Advanced or metastatic breast cancer
	NCT05080842	30	Side effects and effectiveness	
Palazestrant (OP-1250)	NCT05266105	30	Combined with palbociclib	ER+/HER2- Advanced or metastatic
	NCT05508906	90	Combined with ribociclib and alpelisib	
H3B-6545	NCT04288089	36	Combined with palbociclib	ER+/HER2- Locally advanced or metastatic breast cancer

inhibitor, PF-07220060, are also currently under assessment. On 6 February 2024, the US FDA approved a fast-track designation for vepdegestrant as monotherapy for treating ER+/HER2- MBC patients who were pretreated with ET. Granting fast-track designation underscores the promise of vepdegestrant as an innovative clinical choice for ER+ BC patients.

The other ER PROTAC undergoing clinical trial is AC0682. This oral chimeric ER degrader was created by Accutar Biotech on the basis of its artificial intelligence-empowered drug discovery platform using ACCU-Degron technology. The chemical structure of AC0682 has not been disclosed. Preclinical data showed that AC0682 degrades ER in wild-type and ER α Y537S/D538G MCF-7 cell lines with a sub-nanomolar DC50 [89]. The synergistic effect of AC0682 combined with palbociclib was evident in estradiol-dependent and tamoxifen-resistant MCF-7 models. AC0682 is ongoing in phase I clinical trials (NCT05489679 and NCT05080842) to assess its safety, tolerability, PK, and effectiveness for treating ER+/HER2- advanced BC or MBC patients (Table 2).

ERD-3111 was reported to be an orally efficacious ER PROTAC by Wang et al. [90] in 2023. This chimera has a tricyclic indazole core scaffold with a new CRBN ligand (TX-16) as an E3 ligase ligand (Figure 7). ERD-3111 showed tumor regression and completely inhibited tumor growth in the wild-type and two ESR1-mutated (Y537S and D538G) MCF-7 xenograft models. A significant reduction in ER α protein levels was also noted

in tumor tissues. Importantly, an *in vivo* murine study showed there was no animal weight loss or other toxicity with ERD-3111 treatment. These preclinical findings showed ERD-3111 to be a highly potent oral ER α PROTAC for further development.

In addition to CRBN ligands, the VHL tumor suppressor ligand is widely used as an E3 ligase in the development of ER PROTACs [91]. The ER PROTACs, ERD-308 and ERD-148, were also developed by Wang et al. Both PROTACs used a raloxifene core scaffold for ER ligands and compound 11 for the VHL ligand (Figure 7) [92, 93]. ERD-308 was first reported to show excellent inhibitory efficacy in suppressing MCF-7 and T47D BC cells and led to a more thorough ER degradation than fulvestrant. In the subsequent structure activity relationship (SAR) studies involving ERD-308, compound ERD-148 was shown to exhibit excellent ER degrading potency. The difference between ERD-308 and ERD-148 was the linker composition. Specifically, ERD-148 has a hydrophobic alkyl linker, while ERD-308 has an ether embedded in the linker. Preclinical data showed that ERD-148 suppresses the growth of estrogen-dependent wild-type and estrogen-independent ESR1-mutated (Y537S and D538G) MCF-7 cells. ERD-148 was more potent than fulvestrant in downregulating wild-type and mutant ER α expression in cell lines. Moreover, ERD-148 significantly downregulated the expression of an essential ER-regulated gene (GREB1) at 10 nM in various wild-type and mutant MCF-7 cell lines.

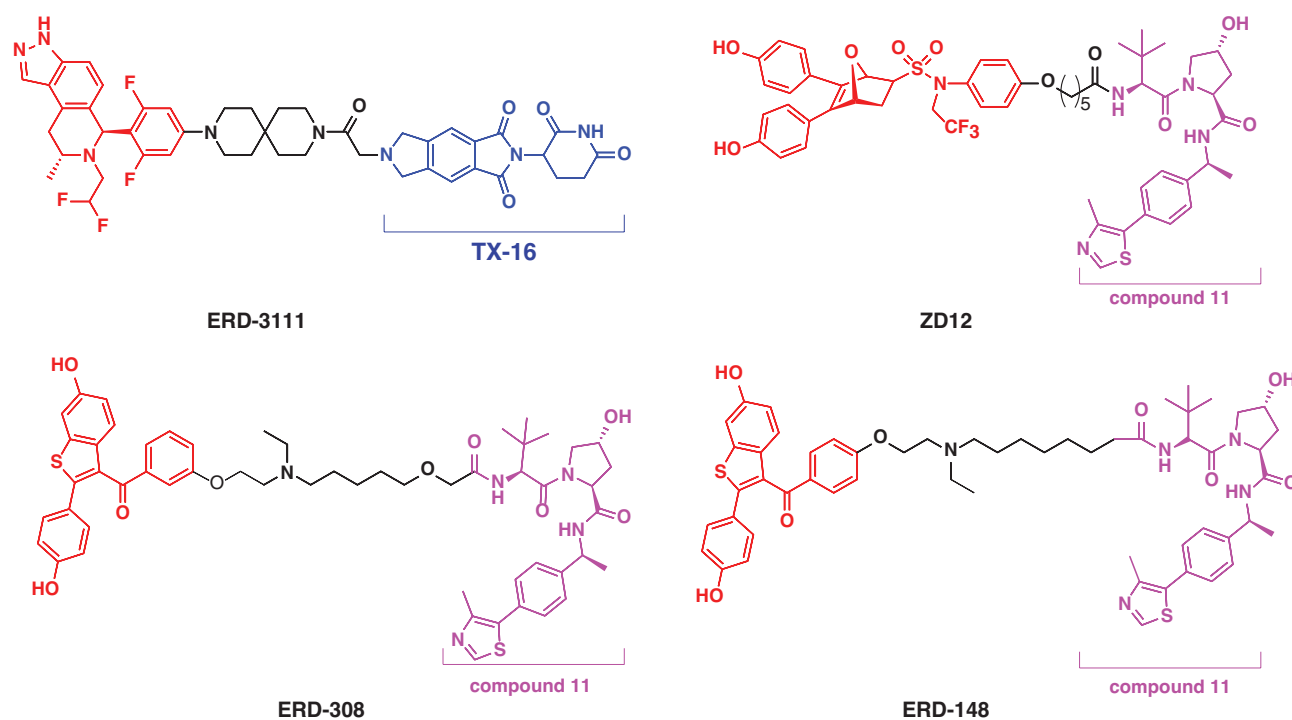


Figure 7 | Representative chemical structures of other ER-targeted PROTAC molecules.

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Compound ZD12 was reported by Zhou et al. [94] in 2023. Compound ZD12 was designed using a 7-oxabicyclo[2.2.1]heptane sulfonamide scaffold for ER, then attached to the VHL ligand through a five-carbon alkyl linker (Figure 7). In tamoxifen-sensitive and -resistant BC murine tumor models, compound ZD12 exhibited superior anti-tumor activity and ER α degradation potency than fulvestrant.

4. COMPLETE ESTROGEN RECEPTOR ANTAGONISTS (CERANs)

As shown in Figure 8a, the ER consists of two independent transcriptional activation function domains (AF1 and AF2). AF2 is located in the C-terminal of the ER-LBD and is activated by an endogenous estrogen. Unlike AF2, AF1 is located in the N-terminal A/B domain and activated by signaling pathways, such as mTOR, PI3K, and MAPK [95]. Activating AF1 and AF2 leads to gene transcription and cellular proliferation [96]. Traditional SERMs, such as tamoxifen, inhibit AF2 while not impacting AF1 agonist signaling pathways. It has been suggested that incomplete blockade of AF1 may be associated with endocrine resistance. Unlike SERMs, CERANs were developed to completely turn off both AF1 and AF2 (Figure 8b). Consequently, CERANs have been designated as complete ER antagonists.

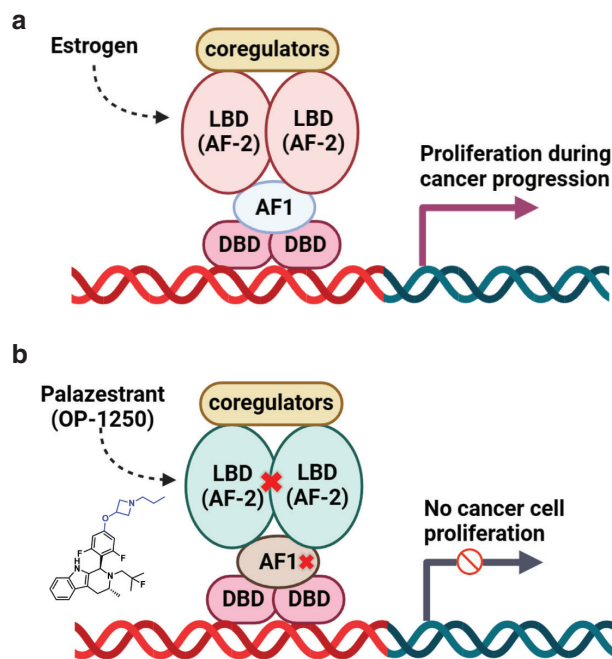


Figure 8 | Mechanism of action underlying the CERAN, OP-1250.

a. Estrogen activates both AF1 and AF2 domains to promote ER signaling; **b.** OP-1250 completely turns off both AF1 and AF2 transcriptional activation functions of ER α .

OP-1250 (palazestrant) was developed by Olema and is the only orally bioavailable CERAN in a clinical trial [97]. Additionally, palazestrant serves as a SERD for ER protein degradation. Preclinical trials revealed that OP-1250 effectively blocks wild-type and mutant ER and showed potent suppression in estrogen-stimulated BC cell lines. A phase I/II trial (NCT04505826) involving OP-1250 as monotherapy revealed acceptable safety, good tolerability, and a once-daily oral dosing PK profile in ER+/HER2- advanced BC or MBC patients. Combination therapy of OP-1250 with CDK4/6 inhibitors (palbociclib, ribociclib, and alpelisib) is also being assessed in phase I/II clinical trials (NCT05266105 and NCT05508906; Table 2) [98].

5. SELECTIVE ESTROGEN RECEPTOR COVALENT ANTAGONISTS (SERCAs)

Use of covalent inhibitors is a potent tactic to counteract drug resistance stemming from mutations in the gene encoding the target protein. In this metastatic setting, SERCAs have been designed by covalently interacting with a cysteine (C530) in the ER-LBD via an electrophilic warhead.

Compound H3B-6545 was developed by Eisai Co., Ltd. using a structure-based drug design strategy. A crystallography study involving H3B-6545 with the ER LBD confirmed that the covalent bond formed between the unique cysteine (C530) and the acrylamide warhead, as shown in Figure 9a [99]. A preclinical study revealed that H3B-6545 has beneficial drug-like characteristics and nanomolar anti-proliferation potency in wild-type and multiple clinically relevant ER α mutant MCF-7 cell lines. H3B-6545 also showed superior anti-tumor activity over fulvestrant in wild-type and mutant ER α BC tumor models. The encouraging outcomes led H3B-6545 into a phase I/II trial (NCT03250676) as a single agent and a phase I trial (NCT04288089) combined with palbociclib for the treatment of ER+/HER2- BC patients (Table 2) [100].

While H3B-6545 enforces an antagonist conformation without degrading ER α , compound **29c** disrupts ER α protein homeostasis by covalently targeting C530. The covalent bond formation was verified by crystallography and intact mass spectrometry. A crystallography study also suggested that compound **29c** has a strong hydrophobic interaction with helix 11, which promotes ER α degradation (Figure 9b) [101]. An *in vitro* study involving compound **29c** showed promising anti-tumor activity and ER α degradation potency in wild-type MCF-7, T47-D, and ESR1-mutated T47-D cell lines. An *in vivo* study involving compound **29c** in MCF-7 BC tumor xenograft models showed complete tumor growth inhibition comparable to fulvestrant with low toxicity.

6. CONCLUSIONS AND PERSPECTIVE

Reliance on ER signaling in ER+ BC is vital, establishing ER-targeted treatments as the cornerstone for this type

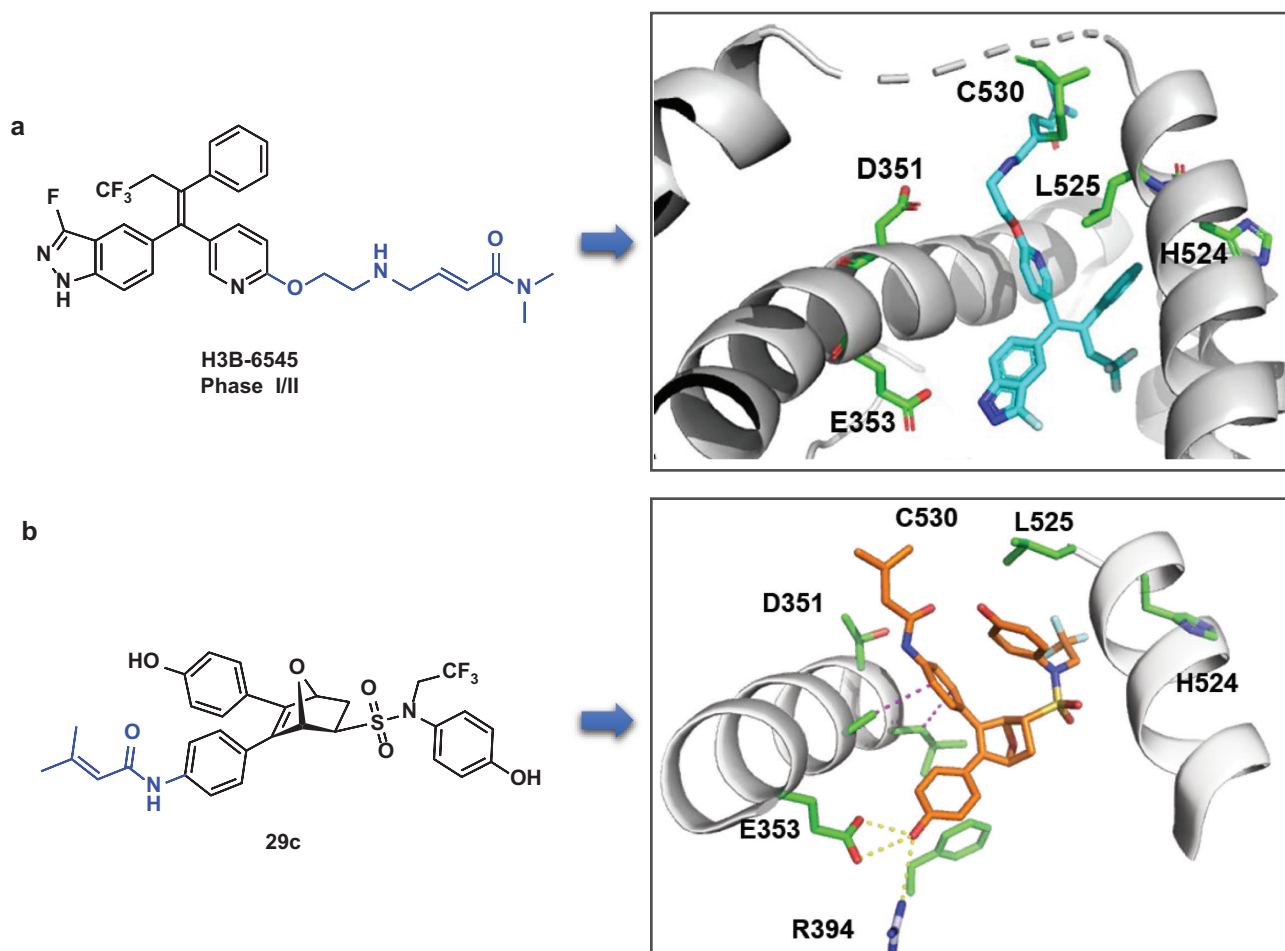


Figure 9 | a. Chemical structure of H3B-6465 (cyan) and its crystal structure complex with estrogen receptor (grey), PDB: 6OWC; **b.** Chemical structure of 29c (orange) and its crystal structure complex with estrogen receptor (grey), PDB: 7YMK.

of tumor. A major contributor to acquired resistance is the ESR1 mutation, suggesting that ER dependency persists through tumor progression. Therefore, tremendous efforts have been invested in identifying and developing new generations of ER-targeted agents, including new generation oral SERDs and other innovative agents, such as PROTACs, CERANs, and SERCAs [102]. Rigorous evaluations are underway for these new generation ER-targeted agents with multiple preclinical and clinical trials ongoing in primary and advanced BC cases.

The clinical outcomes of oral SERDs have been varied. Clinical developments of several new SERDs, such as GDC-0810, AZD9496, LSZ102, GDC-0927, SHR9549, and SAR439859, have been suspended for various reasons. Some oral SERDs, such as D-0502, LY3484356, AZD9833, and GDC9495, are presently being assessed in phase III trials for treating advanced BC or MBC patients alone or in combination therapy with CDK4/6, mTOR, and PI3K inhibitors. Importantly, the US FDA approval of elacestrant in 2023 delivered on its promise to provide an

effective endocrine blockade and verified the capacity of SERDs to counteract endocrine-resistant BC patients with ESR1 mutations. Current clinical data suggest that using SERDs alone has not been shown to offer prolonged and notable benefits following treatment with CDK4/6 inhibitors [103]. Improved clinical outcomes are expected when SERDs are used as a backbone in combination therapies [104].

In addition to orally administered SERDs, two ER PROTACs (ARV-471 and AC0682) have advanced to clinical trials. The early clinical observations of ARV-471 have shown favorable safety, desirable exposure, and clinical benefits for patients. The recent fast-track designation of ARV-471 from the US FDA are solidifying clinical proof of concept for PROTACs, demonstrating its ability to effectively degrade and remove target proteins by the ubiquitin-proteasome system [105]. Additional novel ER-targeted agents, such as CERANs and SERCAs, also hold considerable promise and are currently in the initial stages of clinical assessment.

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Despite the design and advancement of the new generation ER-targeted molecules tackling estrogen-independent ESR1 mutations, a critical question remains: Will these ER-targeted agents favor new ER reactivation mechanism or will they completely skew tumors towards ER independence? As primary or acquired resistance to therapy remains a major challenge, regimens that integrate ER-targeted therapy in combination with CDK4/6, PI3K, mTOR, and immunotherapy may have implications for ER+ BC treatment in the metastatic setting. The pharmaceutical and scientific communities await the results of current ongoing clinical trials, as well as the full analyses of tumor biopsies. Molecular tumor profiling and predictive biomarkers of response to therapy are expected to be crucial to adopt a more precision medicine strategy in the management of ER+ BC [106].

In conclusion, the development of new generation ER-targeted agents signifies a promising progression in drug discovery for BC. We hope these new molecules will eventually offer ER+ BC patients more effective and safer treatment options.

ABBREVIATIONS

BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; AI, aromatase inhibitor; ET, endocrine therapy; AE, anti-estrogen; DBD, DNA-binding domain; LBD, ligand-binding domain; SERD, selective estrogen receptor degrader/downregulator; PROTAC, proteolysis-targeted chimera; CERAN, complete estrogen receptor antagonist; SERCA, selective estrogen receptor covalent antagonist; MBC, metastatic breast cancer; PDX, patient-derived xenograft; SAR, structure activity relationship; FDA, Food and Drug Administration.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in this work.

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