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New steps on an old path: Novel estrogen receptor inhibitors in breast cancer

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ABSTRACT

Estrogen receptor (ER) signaling represents the main driver of tumor growth and survival in hormone receptor positive (HR+) breast cancer (BC). Thus, endocrine therapy (ET) alone or in combination with targeted agents constitutes the mainstay of the treatment for this BC subtype. Despite its efficacy, intrinsic or acquired resistance to ET occurs in a large proportion of cases, mainly due to aberrant activation of ER signaling (i.e. through ligand-independent ER activation, in the presence of estrogen receptor 1 (*ESR1)* gene aberration or ER protein phosphorylation) and/or the upregulation of escape pathways, such as the PI3K/AKT/mTOR pathway.

Therefore, the development of new ER pathway targeting agents remains essential to delay and overcome ET resistance, enhance treatment efficacy and tolerability, and ultimately prolong patient survival and improve their quality of life.

Several novel ER targeting agents are currently under investigation. Among these, the oral selective ER degraders (SERDs) represent the pharmacological class at the most advanced stage of development and promise to enrich the therapeutic armamentarium of HR+ BC in the next few years, as they showed promising results in several clinical trials, either as single ET agents or in combination with targeted therapies.

In this manuscript, we aim to provide a comprehensive overview on the clinical development of novel ER targeting agents, reporting the most up-to-date evidence on oral SERDs and other compounds, including new selective ER modulators (SERMs), ER proteolysis targeting chimera (PROTACs), selective ER covalent antagonists (SERCAs), complete ER antagonists (CERANs), selective human ER partial agonists (ShERPAs). Furthermore, we discuss the potential implications of introducing these novel treatment strategies in the evolving and complex therapeutic scenario of HR+ BC.

1. Introduction

Breast Cancer (BC) represents a heterogeneous disease embracing different molecular subtypes. Luminal BC, which is depicted by the expression of hormone receptors (HR) - namely estrogen receptor α (ER) and progesterone receptor (PR), is the most prevalent subtype (Dai et al., 2016). ER signaling represents the main driver of tumor growth and survival in HR positive (HR+) BC. Thus, ER-targeting endocrine therapy

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(ET) alone or in combination with targeted agents represents the mainstay of the treatment for HR+ BC subtype.

Two different genes encode for isoforms α and β of ER; ERα supports BC cell survival and proliferation, whereas the role played by ERβ is still unclear in BC. In this review, we will use 'ER' to indicate 'ERα', if not otherwise specified. Estrogen binding to ER protein determines its dimerization, with subsequent translocation to the nucleus and assembling of the active transcriptional complex, together with ER coactivators (CoA) (Osborne et al., 2001). This "classical" genomic ER activity induces the transcription of several genes, involved in cell signaling, survival and cycle progression through binding to estrogen response element (ERE) sequences of deoxyribonucleic acid (DNA) (Nilsson et al., 2001). Moreover, activated ER also upregulates growth factors transcription. On the other hand, overactivity of receptor tyrosine kinases (RTKs), and their downstream pathway intermediates, such as phosphatidylinositol 3-kinases (PI3K) and mitogen-activated protein kinase (MAPK), leads to phosphorylation of ER and its ligand-independent activation. This "alternative" genomic signalling is also known as the non-classical ER nuclear genomic pathway and is thought to be important in the development of endocrine resistance (Giuliano et al., 2013). Many strategies have therefore been developed to block the described pathways.

Several ER signalling inhibitors have proven to be effective in HR+ BC and thus have been introduced in the clinical practice in the last five decades. Direct targeting of ER is achieved through selective ER modulators (SERMs) and selective ER degraders (SERDs) (Awan and Esfahani, 2018). SERMs compete with estrogen for ER binding and exert agonist/antagonist activities, depending on the target tissue. Tamoxifen, approved in the 1970 s (Rondón-Lagos et al., 2016), competes for binding the ER and still represents a recommended therapeutic option, mostly as adjuvant treatment in premenopausal patients with early stage HR+ BC (Jordan, 1993). SERDs antagonize ER activity with much higher binding affinity and induce ER degradation/downregulation. These agents create an unstable protein complex that induces ER degradation via proteasome complex (Shagufta et al., 2020). SERDs activity is purely antiestrogenic, with none of the agonist effects of SERMs. Currently, fulvestrant is the only first-generation SERD approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for clinical use in HR+ metastatic BC (mBC), alone or in combination with cyclin-dependent kinases 4 and 6 inhibitors (CDK 4/6i) (Nathan and Schmid, 2017). Another therapeutic strategy developed to effectively inhibit ER signalling is reducing estrogen levels. Third-generation aromatase inhibitors (AIs) including the nonsteroidal inhibitors anastrozole and letrozole, and the steroidal inhibitor exemestane impede cancer cell growth by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens.

Despite the efficacy of the aforementioned endocrine agents, a critical challenge for the treatment of HR+ BC is the development of endocrine resistance. Several molecular mechanisms of primary (*de novo*) and acquired endocrine resistance have been identified and extensively reviewed elsewhere (Hanker et al., 2020). Endocrine resistance can be driven by somatic alterations in drug targets (ER and aromatase), in key components of cellular pathways (i.e., receptor tyrosine kinases, PI3K, MAPK), and in gene expression modulators or by loss-of-function changes in DNA-repair genes (Hanker et al., 2020). A potential role in determining endocrine resistance is also exerted by non-genetic mechanisms and epigenetic modifications, comprising of metabolic reprogramming, epithelial-to-mesenchymal transition and cofactors activity (Dagogo-Jack and Shaw, 2017; Hanker et al., 2020). Notably, a significant contribution to ET inefficacy is also related to tumor microenvironment, through several cell factors potentially leading to endocrine resistance, such as hypoxia, inflammation and immunomodulation (Hanker et al., 2020). Understanding these escape pathways in HR+ BC has led the development of new treatment strategies aiming at overcoming and delaying endocrine resistance. Exploiting cross talk between ER signaling and other intracellular pathways, inhibitors of CDK4/6i and PI3K are now approved by the FDA for the treatment of patients with HR+ BC (Shen et al., 2020).

Activating mutations in the estrogen receptor 1 gene (*ESR1*), which encodes the main form of ER in the breast, represent a major mechanism of acquired resistance to currently available ETs (Jeselsohn et al., 2015). *De novo ESR1* mutations are found at low frequencies in patients with newly diagnosed disease, but acquired alterations arise in up to 40% of patients previously treated with ET (Toy et al., 2017). As a matter of the fact, *ESR1* mutations were discovered in BC in 1997 (Zhang et al., 1997) however, its role in sustaining ET resistance was only established after genomic sequencing of mBC was accomplished in 2013 (Li et al., 2013; Robinson et al., 2013). The prevalence of *ESR1* mutations in patients depends on prior duration and setting of ET and the ET agent. Approximately 20–40% of patients who have received AI for mBC have *ESR1* mutations, with prevalence varying by sites of metastatic disease. In contrast, *ESR1* mutation prevalence is only 4–5% in recurrent BC after prior adjuvant AI (including recurrence while on adjuvant AI), 1.5–7% after neoadjuvant AI and less than 1% in ET-naïve mBC (Brett, 2021). Although *ESR1* mutations promote some level of resistance to all currently available ETs, fulvestrant appears to be the least affected. However, its bioavailability is believed to be limited by its intramuscular administration, accordingly, an oral SERD may result more effective and less susceptible to endocrine resistance. Several novel ER signaling inhibitors are currently under development and have the potential to improve treatment armamentarium for HR+ BC.

The aim of this manuscript is to provide a comprehensive overview on up-to-date evidence and ongoing research about new ER signaling inhibitors in HR+ BC, focusing on the most recent molecules that showed promising anti-tumor activity in early clinical trials, through different mechanism of action (Fig. 1).

2. New-generation SERDs

In 2001, Wijayaratne and McDonnell identified that fulvestrant, a 17β-estradiol derivative carrying an alkyl chain on the 7α-position, that induced the reduction of intracellular ERα leading to its degradation through the ubiquitin–proteasome system (Wijayaratne and McDonnell, 2001). Nevertheless, the clinical effectiveness of fulvestrant is limited by its poor oral bioavailability, that forces its intramuscular use, which in turn determines a non-optimal occupation of the ER (van Kruchten et al., 2015). This led to the development of new orally bioavailable SERDs obtaining by refining side chain substitution, with better polarity and solubility and upholding the antiestrogenic activity (Jiang et al., 2013). The next-generation SERDs are described below:

2.1. Elacestrant (RAD1901)

Elacestrant is an oral non-steroidal SERM/SERD with amino basic side chain, which demonstrated to inhibit ER signaling and exert antitumor activity in HR+ BC cell lines and patient derived xenografts (PDX), both as monotherapy and in combination with palbociclib or everolimus (Bihani et al., 2017). Moreover, elacestrant was evaluated in in vitro and in vivo models of CDK4/6i resistant BC, showing to inhibit tumor growth, also in the presence of *ESR1* mutations (Patel et al., 2019). Elacestrant is characterized by a peculiar pharmacodynamic since it acts as a SERM at low dose and as a SERD at higher doses (Wardell et al., 2015a; Garner et al., 2015). This unique pharmacologic properties, together with its ability to cross blood-brain barrier and activity toward both wild-type (WT) and mutated ER (including Y537S and D538G variant, usually associated with substantial resistance to ET), could be attributed to the unique binding mode of elacestrant with ER (Fanning et al., 2020). In two first-in-human (FIH) phase I studies enrolling 140 postmenopausal healthy subjects elacestrant confirmed high ER occupancy (75–90%) in the dose range of 200–500 mg, good oral bioavailability and long half-life supporting the feasibility of a single daily administration, blood-brain barrier penetration, and overall

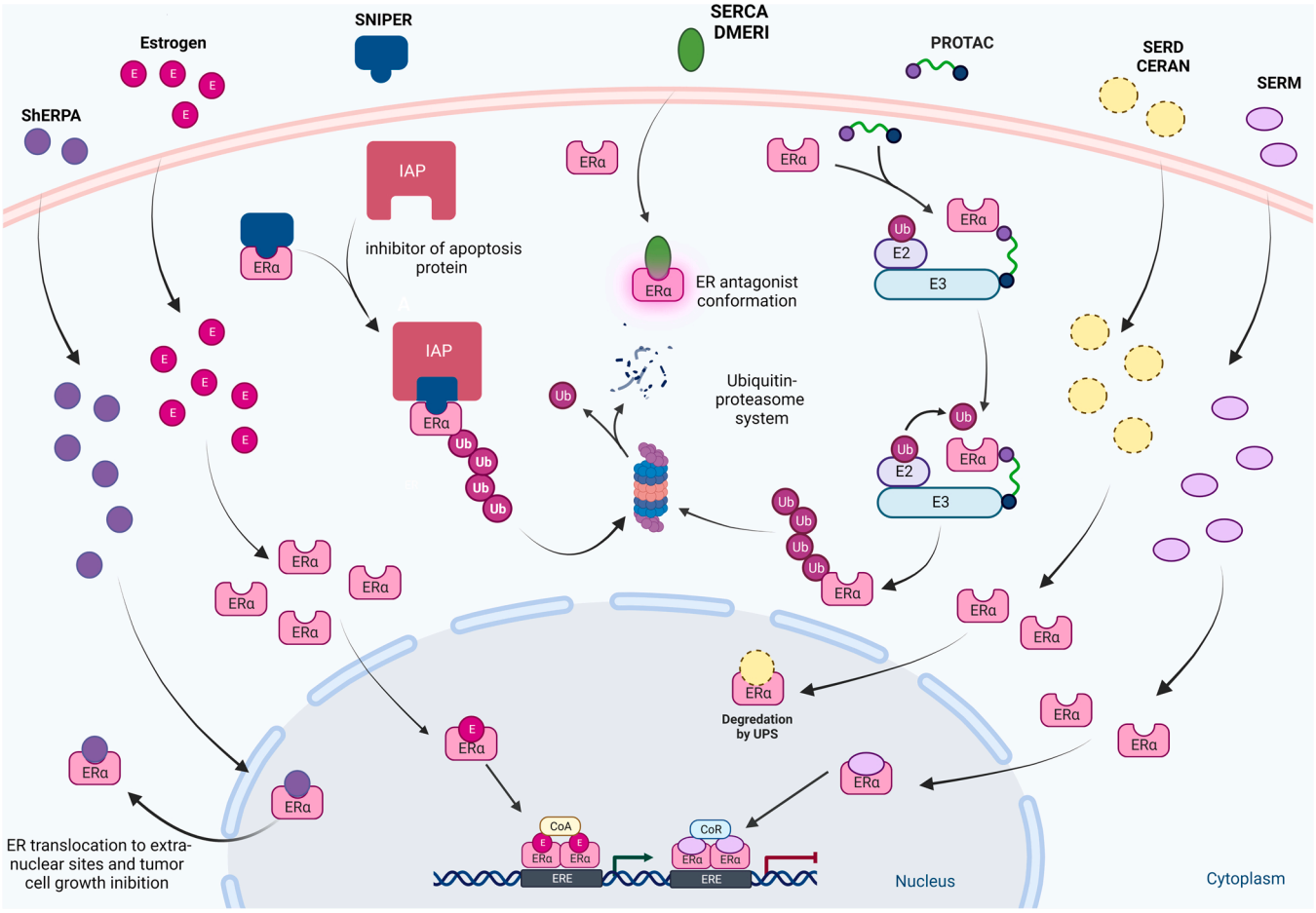

Fig. 1. Schematic representation of the mechanisms of action of drugs acting on estrogen receptor signaling. CERAN complete estrogen receptor antagonist; CoA co-activator; CoR corepressor; DMERI dual-mechanism estrogen receptor inhibitor; E estrogen; E2 ubiquitin-conjugating enzyme; E3 ubiquitin-protein ligase; ERα estrogen receptor α; ERE estrogen response element; IAP inhibitor of apoptosis protein; PROTAC proteolysis targeting chimera; SERCA selective estrogen receptor covalent antagonist; SERD selective estrogen receptor degrader; SERM selective estrogen receptor modulator; ShERPA selective human estrogen receptor partial agonist; SNIPER specific non-genetic IAP-dependent protein eraser; Ub ubiquitin; UPS ubiquitin-proteasome system. Created with BioRender.com.

favorable safety profile (Conlan et al., 2020). The most commonly reported treatment-related adverse events (TRAEs) were gastrointestinal disorders, such as nausea, vomiting, diarrhea, and headache. In the phase I study RAD1901–005 (NCT02338349), the recommended phase II dose (RP2D), was identified in 400 mg once daily. In this phase I study, elacestrant showed promising activity as monotherapy also in patients with *ESR1* mutation, previously treated with SERD or CDK4/6i. A decline in *ESR1* mutant allele fraction (MAF) was observed in patient reporting partial response, whereas a mounting MAF was evidenced at progressive disease (PD) (Table 1) (Bardia et al., 2021a). In a phase Ib study (NCT02650817) elacestrant was reported to reduce ER expression assessed by 18-F fluroestradiol (FES) positron emission tomography (PET)/computed tomography (CT) (Jager et al., 2020). Recently, elacestrant monotherapy was investigated in the randomized (1:1), multicenter, open-label phase III EMERALD study versus investigator's choice ET in men and postmenopausal women with HR+ human epidermal growth factor receptor negative (HER2-) advanced/mBC who progressed after prior ET in combination with CDK4/6i. Primary endpoint was median progression-free survival (mPFS), which was 2.79 months with elacestrant and 1.91 months with standard of care (SOC) in the intention to treat (ITT) population (30% reduction in the risk of PD or death, hazard ratio (HR) 0.697, 95% confidence interval (CI): 0.552–0.880; p = 0.0018). In patients with tumor harboring *ESR1* mutation mPFS was 3.78 months in experimental arm versus 1.87 months in the control group (45% reduction in the risk of PD or death, HR 0.546, 95%CI: 0.387–0.768; p = 0.0005). Elacestrant was the first oral SERD to provide statistically significant improvement in mPFS as compared to SOC ET in a randomized phase III trial in patients with HR+ /HER2- mBC as second- or third-line treatment after CDK4/6i. In a recent subgroup analysis, elacestrant showed prolonged PFS at 6, 12, 15 and 18 months compared to fulvestrant as well as AIs in both overall population and in patients with *ESR1* mutations, underlining its higher efficacy regardless of type of ET (Aftimos et al., 2022). Elacestrant was confirmed to have a manageable toxicity profile and was overall well tolerated (Bardia, 2019; Bardia et al., 2021b) Further investigations of elacestrant in combination with different drugs or in earlier disease setting are ongoing (Tables 1 and 2) (Vidal et al., 2022; https://clinicaltrials.gov/ct2/show/record/NCT04791384).

2.2. *Camizestrant (AZD9833)*

AZD9833 is a new generation oral non-steroidal SERD, which exerts pure ER antagonism and degradation similar to fulvestrant in several cancer cell lines. In patient-derived xenografts (PDX) model, including those with *ESR1* mutations (e.g. D538G, Y537S), camizestrant completely inhibited tumor growth (Scott et al., 2020aScott et al., 2020b). To date, multiple clinical studies investigating this agent are ongoing. SERENA-1 (NCT03616587) is a FIH phase I, open-label, dose escalation and dose expansion trial to evaluate tolerability and safety of camizestrant alone (parts A/B) or in combination with palbociclib (parts C/D) or everolimus (parts E/F) or abemaciclib (parts G/H) or capivasertib (parts I/J) in pretreated women with HR+ /HER2- advanced

Table 1
Phase I-II clinical trials including SERDs as monotherapy. ABC advanced breast cancer; BC breast cancer; BID bis in die; CBR clinical benefit rate; CDK4/6i cyclin-dependent kinase 4 and 6 inhibitors; CT chemotherapy; D1 day 1; DLT dose limiting toxicity; DR disease relapse; ER estrogen receptor; ET endocrine therapy; ful fulvestrant; G grade; HER2 human epidermal growth factor receptor 2; HR hormone receptor; ITT intention-to-treat; LABC locally advanced breast cancer; mBC metastatic breast cancer; mESR1 estrogen receptor 1 gene mutated; mo months; mPFS median progression-free survival; MTD maximum tolerated dose; mTORi mammalian target of rapamycin inhibitors; n/a not available; ORR objective response rate; PCET physician's choice ET; PD progression of disease; PFS progression-free survival; PR progesterone receptor; SERD selective estrogen receptor degrader; WT wild-type.

Identifier	Phase	Status	Study drugs	Study desing	Disease setting	Study population	N (enrolled)	Prior treatment	*ESR1*m (%)	Results	Safety	References
RAD1901–005 (NCT02338349)	I	completed	elacestrant (400 mg daily)	single group, open-label	LABC or mBC	women with HR+/ HER2- BC	57	median n° of prior lines: 3 (1–7); ful: 52%; CDK4/6i: 52%	50	ORR 19.4% (33.3% m*ESR1*; 15% prior SERD; 16.7% prior CDK4/6i), CBR 42.6% (56.5% m*ESR1*; 33.3% prior SERD), mPFS 4.5 mo (7.4 mo m*ESR1*; 3.7 prior SERD; 3.8 prior CDK4/6i)	No DLT. G1/2: nausea (33.3%), increased triglycerides (25%), decreased plasma phosphorus (25%)	(Bardia et al., 2021)
RAD1901–106 (NCT02650817)	Ib	completed	elacestrant (200–400 mg daily)	two cohort, open-label	LABC or mBC	postmenopausal women with HR+/ HER2- BC	16	median n° of prior lines: 3 (2–3); ful: 37.5%; CDK4/6i: 0%	56.3	ORR 11.1%, CBR 30.8%	G1/2: nausea (68.8%), fatigue (50%), dyspepsia (43.8%), vomiting (37.5%), decreased appetite (31.3%), dysphagia (31.3%), hot flush (31.3%)	(Jager et al., 2020)
SERENA-1 part A (NCT03616587)	I	ongoing	camizestrant (25–450 mg daily)	multi-parts, open label	LABC or mBC	women with HR+/ HER2- BC	305 (60)	after $\geq$ 1 ET and $\leq$ 2 CT lines median n° of prior line: 5 (1–9); ful: 82%; CDK4/6i: 68%	46	ORR 16.3%, CBR 42.3% (50% m*ESR1*), mPFS 5.5 mo	DLT at 300 mg and 450 mg. G1: Visual disturbances, bradycardia, nausea, fatigue, dizziness, vomiting, asthenia	(Hamilton et al., 2020a)
SERENA-2 (NCT04214288)	II	active, not recruiting	camizestrant (75–300 mg) vs fulvestrant	randomized, open-label	LABC or mBC	postmenopausal women with HR+/ HER2- BC	288	ET (CDK4/6i allowed, ful or other SERDs not permitted)	n/a	n/a	n/a	(Oliveira et al., 2021)
GO39932 cohort A (NCT03332797)	I	active, not recruiting	giredestrant (10–250 mg daily, fasting status)	single group, open-label	LABC or mBC	ER+/HER2-BC	111	$\leq$ 2 lines for ABC; PD during adjuvant ET ($\geq$24 mo) or ET ($\geq$6 mo); median n° of prior lines: 1 (0–3); ful: 21%; CDK4/6i: 64%	47	ORR 20% (30 mg group), CBR 55% (30 mg group), mPFS 7.8 mo	No MTD. No DLT. G1/2: fatigue (21%), arthralgia (17%), nausea (16%)	(Jhaveri et al., 2021a; Turner et al., 2022; Lim et al., 2020)
acelERA BC (NCT04576455)	II	active, not recruiting	giredestrant (30 mg daily) vs fulvestrant/ AI	randomized, open-label	LABC or mBC	ER+/HER2- BC	303	1–2 prior lines, at least 1 ET prior ful: 20% giredestrant arm, 18% PCET arm; CDK4/6i: 43% giredestrant arm, 41% PCET arm; CT: 31%	44 giredestrant arm vs 34 PCET arm	ORR 12.6% giredestrant arm, 7.2% PCET arm; CBR 31.8% giredestrant arm, 21.1% PCET arm; mPFS 5.6 mo giredestrant arm, 5.4 mo PCET arm	G5: 1 giredestrant (ischaemic stroke), 1 PCET (pulmonary embolism). All G ($\geq$10%): hepatotoxicity, musculoskeletal pain, arthralgia, fatigue, nausea.	(Martin et al., 2021)

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Table 1 (*continued*)

								giredestrant arm, 32% PCET arm.				
AMEERA-1 arm 1, parts A-B (NCT03284957)	I/II	ongoing	amcenestrant (20–600 mg daily, part A; 400 mg daily, part B)	randomized, open-label	LABC or mBC	postmenopausal women with HR+/HER2- BC	62 (≥150 mg)	after ≥ 6 mo of ET (mBC) or DR ≤ 1 y after adjuvant ET completion ≥ 3 prior lines (48.4%)	n/a	ORR 10.9% (15.4% WT *ESR1*, 5.3% m*ESR1*), CBR 28.3% (34.6% WT *ESR1*; 21.1% m*ESR1*)	G1/2: hot flush (part A 31.3%, part B 10.2%), diarrhoea (part A 25%), nausea (part A 25%), constipation (part A 18.8%), decreased appetite (part A 18.8%), asthenia (part A 18.8%), night sweat (part A 18.8%), fatigue (part A 12.5%), arthralgia (part A 12.5%).	(Bardia et al., 2021c)
AMEERA-3 (NCT04059484)	II	active, not recruiting	amcenestrant (400 mg daily) vs PCET (tamoxifen, AI, fulvestrant)	randomized, open-label	LABC or mBC	postmenopausal women with HR+/HER2- BC	290	prior ≤ 2 ET lines and ≤ 1 CT or targeted therapy (including CDK4/6i) for metastatic setting permitted prior ful: 10.4% amcenestrant arm, 10.2% PCET arm; CDK4/6i: 79.7% amcenestrant arm, 78.2% PCET arm; CT: 9.8% amcenestrant arm, 12.9% PCET	46.4 amcenestrant arm vs 39.3 PCET arm	mPFS ITT population: 3.6 mo amcenestrant arm vs 3.7 mo PCET arm; mPFS m*ESR1* population: 3.7 mo amcenestrant arm vs 2.0 mo PCET arm)	All G: nausea (20.3% amcenestrant, 8.8% PCET), vomiting (19.6% amcenestrant, 3.4% PCET), arthralgia (14% amcenestrant, 9.5% PCET), back pain (13.3% amcenestrant, 10.9% PCET), headache (12.6% amcenestrant, 9.5% PCET), fatigue (11.2% amcenestrant, 11.6% PCET), diarrhea (10.5% amcenestrant, 6.1% PCET).	(Tolaney et al., 2021)
EMBER (NCT04188548)	I	ongoing	imlunestrant (200–1200 mg daily) ± everolimus, abemaciclib, alpelisib, trastuzumab	multi-cohort, open-label	LABC or mBC	HR+/HER2- BC	500 (114)	median n° of prior lines: 2 (0–8); ful: 50.9%; CDK4/6i: 92.1%	49	ORR 8%, CBR 40.4%, mPFS 6.5 mo (after CDK4/6i)	No DLT. G1/2: nausea (32%), fatigue (25%), diarrhea (18%)	(Jhaveri et al., 2022a)
NCT02248090	I	completed	AZD9496 (20–600 mg BID)	single group, open label	LABC or mBC	women (84% postmenopausal) with HR+/HER2- BC	45	median n° of prior ET: 3 (1–6); ful: 55.6%; CDK4/6i: 15.6%; mTORi: 40%	n/a	n/a	MTD not reached. DLT in 3 patients (abnormal hepatic function at 150 mg BID; elevated liver function tests and diarrhea at 400 mg BID; diarrhea at 600 mg BID). G1/2: Diarrhea (35.6%), fatigue (31.1%), nausea (22.2%), upper abdominal pain (13.3%)	(Hamilton et al., 2018)

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Table 1 (*continued*)

NCT03560531	I/II	active, not recruiting	ZN-c5 (50–300 mg daily)	single group, open label	LABC or mBC	ER+/HER2- BC	181 (56)	median n° of prior lines: 2 (0–9); ful: 46%; 68% CDK4/6i;	38	CBR 31%, mPFs 3.8 mo	No DLT. G1/2: Nausea (30%), fatigue (25%), arthralgia (20%), hot flushes (14%)	(Kalinksy et al., 2022)
Identifier	**Phase**	**Status**	**Study drugs**	**Study design**	**Disease setting**	**Study population**	**N (enrolled)**	**Results**			**Safety**	**References**
SOLTI-1905 ELIPSE (NCT04797728)	I	ongoing	elacestrant (400 mg daily for 4 weeks)	single group, open label	early stage BC neoadjuvant	postmenopausal women with ER+/HER2- resectable early BC	24 (7)	n/a			n/a	(Vidal et al., 2022)
SERENA-3 (NCT04588298)	II	ongoing	camizestrant (75–150 mg daily)	randomized, open-label	early stage BC neoadjuvant	postmenopausal women with treatment-naïve ER+/HER2- BC	92	n/a			n/a	(Robertson et al., 2021)
AMEERA-4 (NCT04191382)	II	terminated (by sponsor)	amcenestrant 400 mg vs amcenestrant 200 mg vs letrozole (2.5 mg daily) for 14 days	randomized, open-label	early stage BC neoadjuvant	postmenopausal women with resectable stage I-III ER+/HER2- BC Ki-67 $\geq$ 15%	105	Ki-67 reduction 75.9% vs 68.2% vs 77.7%; ER H-score reduction 65.3% vs 68.3% vs 9.5%			All G: anemia (18% 400 mg; 11.4% 200 mg), white blood cell decreased (15.6% 400 mg; 17.1% 200 mg)	(Campone et al., 2022)
EMBER-2 (NCT04647487)	I	ongoing	imlunestrant	randomized, open-label	early stage BC neoadjuvant	postmenopausal women with stage I-II ER+/HER- BC	90	n/a			n/a	(https://clinicaltrials.gov/ct2/show/NCT04647487)
NCT03236974	I	completed	AZD9496 (250 mg BID, D1 → biopsy) vs fulvestrant (500 mg single dose D1)	randomized, open-label	early stage BC neoadjuvant	postmenopausal patients with resectable treatment-naïve HR+/HER2- BC	49	Ki-67 reduction 39.9% vs 75.4%; ER H-score reduction 24% vs 36%; PR H-score reduction 33.3% vs 68.7%			G1/2: nausea (18.2%)	(Robertson et al., 2020)

Table 2
Phase I-II clinical trials including combination therapy with SERDs. 1 L first line; 2 L second line; 3w/1w 3 weeks on treatment, followed by 1 week off treatment; ABC advanced breast cancer; AKTi protein kinase B inhibitors; BC breast cancer; CBR clinical benefit rate; CCCA complete cell cycle arrest; CDK4/6i cyclin-dependent kinase 4 and 6 inhibitors; CT chemotherapy; DLT dose limiting toxicity; DR disease relapse; ER estrogen receptor; ET endocrine therapy; G grade; HER2 human epidermal growth factor receptor 2; HR hormone receptor; LABC locally advanced breast cancer; mBC metastatic breast cancer; mESR1 estrogen receptor 1 gene mutated; mo months; mPFS median progression-free survival; mPI3Ki phosphoinositide 3-kinase inhibitors; mTORi mammalian target of rapamycin inhibitors; n/a not available; ORR objective response rate; pCR pathologic complete response; PD progression of disease; PFS progression-free survival; PH PDC SC fixed-dose combination of P (pertuzumab) and H (trastuzumab) for subcutaneous injection; SERD selective estrogen receptor degrader; WT wild-type.

Identifier	Phase	Status	Study drugs	Study design	Disease setting	Study population	N (enrolled)	Prior treatment	m*ESR1* (%)	Results	Safety	References
NCT04791384	Ib/II	ongoing	elacestrant + abemaciclib	single group, open-label	mBC	ER+/HER2- brain metastatic BC	44	≤ 2 lines for mBC (use of CDK4/6i other than abemaciclib was allowed)	n/a	n/a	n/a	(https://clinicaltrials.gov/ct2/show/NCT04791384)
SERENA-1 parts C/D (NCT03616587)	I	ongoing	camizestrant + palbociclib	multi-parts, open-label	LABC or mBC	women with ER+/HER2- BC	305 (75 mg parts C/D 25)	prior ET and ≤ 2 CT lines 75 mg group median n° of prior lines: 2 (1–5); ful: 68%; CDK4/6i: 80%; CT: 48%	44	ORR 12%, 24 weeks-CBR 28%	DLT at 150 mg dose. 75 mg cohorts G ≥ 3: neutropenia (68%). 75 mg cohorts all G: neutropenia (80%), visual disturbances (44%), fatigue (20%), infections (20%), anemia (20%), bradycardia (16%), nausea (16%), decreased appetite (12%), diarrhea (12%), vomiting (12%)	(Oliveira et al., 2022)
GO39932 Cohort B (NCT03332797)	I	active, not recruiting	giredestrant (100 mg daily) + palbociclib (125 mg 3w/1w)	single group, open-label	LABC or mBC	women with ER+/HER2- BC	181 (cohort B 48)	≤ 2 lines for ABC; PD during adjuvant ET (≥24 mo) or ET in LABC/mBC (≥6 mo) median n° of prior lines: 1 (0–2); ful 7%, CDK4/6i 0 (not allowed)	29	ORR 47.7%, CBR 81.3% (100% m*ESR1*), mPFS 9.3 mo	G ≥ 3: neutropenia (50%). All G: neutropenia (77%), diarrhea (33%), bradycardia (31%), fatigue (29%), cough (21%), constipation (21%), nausea (21%), dizziness (19%), anemia (17%), asthenia, thrombocytopenia (17%), pruritus, visual impairment	(Turner et al., 2022; Lim et al., 2020)
MORPHEUS -BREAST CANCER (NCT04802759)	Ib/II	ongoing	giredestrant (30 mg daily) ± abemaciclib/ipatasertib/	randomized, open-label	LABC or mBC	women with ER+/HER2- BC	510	cohort 1: HER2- BC progressed during or after	n/a	n/a	n/a	(https://www.clinicaltrials.gov/ct2/show/study/NCT04802759)

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Table 2 (*continued*)

Identifier	Phase	Status	Study drugs	Study design	Disease setting	Study population	N (enrolled)	Prior treatment	m*ESR1* (%)	Results	Safety	References
			inavolisib/ ribociclib/ everolimus/ samuraciclib/ PH FDC SC/ PH FDC SC + abemaciclib/ PH FDC SC + palbociclib					treatment with CDK4/ 6i in 1 L or 2 L setting. cohort 2: HER2 + BC presenting PD on trastuzumab-taxane or T-DM1 containing therapies				
AMEERA-1 (NCT03284957)	I/II	ongoing	amcenestrant (200–400 mg daily) + palbociclib (125 mg 3w/ 1w) arm 2 (parts C-D)/ alpelisib arm 3/ everolimus arm 4/ abemaciclib arm 5	randomized, open-label	LABC or mBC	women with ER+/HER2- BC	251 (39 arm 2)	≥ 6 mo ET for advanced disease mandatory; arm 2 prior ≤ 1 line of CT, ≤ 2 lines of ET (part D), ≤ 1line of CDK4/6i (part C) allowed for advanced disease; no prior CDK4/ 6i, PI3Ki, mTORi, AKTi allowed in part D arm 2 ful:7.7%; CDK4/6i: 5.1%, mTORi 2.6%, CT 23.1%	8 patients arm 2	ORR 31.4% arm 2 (37.5% m*ESR1*; 30.8% WT *ESR1*), CBR 74.3% arm 2 (87.5% m*ESR1*; 69.2% WT *ESR1*)	No DLT. Neutropenia: 56% G3, 95% all G. Amcenestrant related G1/2: nausea (17.9%), fatigue (17.9%), hot flush (10.3%), arthralgia (10.3%), asthenia (10.3%). Palbociclib related G1/2: fatigue (30.8%), nausea (25.6%), asthenia (10.3%), dysgeusia (10.3%), stomatitis (10.3%).	(Chandarlapaty et al., 2021a; Chandarlapaty, 2021b)
NCT03455270 part 3	I	active, not recruiting	rintodestrant (800 mg daily) + palbociclib (125 mg 3w/ 1w)	single group, open-label	LABC or mBC	women with ER+/HER2- BC	107 (40)	median n° of prior lines: 1 (0–2); ET: 73%; ful: 15%; CT: 48%; CDK4/ 6i: 0 (not allowed)	41	ORR 5% (4% WT *ESR1*, 6% m*ESR1*), CBR 60% (61% WT *ESR1*, 56% m*ESR1*), mPFS 7.4 mo	G ≥ 3: neutropenia (53%), leukopenia (18%). All G: neutropenia (90%), leukopenia (45%), anemia (15%), thrombocytopenia (10%), asymptomatic bacteriuria (10%)	(Maglakelidze et al., 2021)
ENZENO (NCT04669587)	I/II	ongoing	borestrant ± palbociclib	single group, open-label	LABC or mBC	ER+/HER2- BC	106	n/a	n/a	n/a	n/a	(https://clinicaltrials.gov/ct2/show/NCT04647487)
NCT04514159	Ib	active, not recruiting	ZN-c5 + abemaciclib	single group, open-label	LABC or mBC	ER+/HER2- BC	14	≤ 1 line of ET for ABC/	n/a	n/a	n/a	(Fu et al., 2021)

(*continued on next page*)

Table 2 (*continued*)

Identifier	Phase	Status	Study drugs	Study design	Disease setting	Study population	N (enrolled)	Prior treatment	m*ESR1* (%)	Results	Safety	References
								mBC (CDK4/6i not allowed), no prior CT allowed for ABC/mBC				
NCT03560531	I/II	active, not recruiting	ZN-c5 ± palbociclib	single group, open-label	LABC or mBC	ER+/HER2- BC	181	prior response to ET for mBC (>6 mo) or DR after ≤ 24 mo of adjuvant ET	n/a	n/a	n/a	(Abramson et al., 2021; https://clinicaltrials.gov/ct2/show/NCT03560531)
NCT03471663	I	Active, not recruiting	D-0502 ± palbociclib	multi-parts, open-label	LABC or mBC	omen with ER+/HER2- BC	200	≥ 1 ET (≥6 months) for ER+ mBC rior SERD: 38%; CDK4/6i: 75%.	n/a	n/a	No DLT.	(Osborne et al., 2021; https://clinicaltrials.gov/ct2/show/NCT03471663)
Identifier	**Phase**	**Status**	**Study drugs**	**Study design**	**Disease setting**	**Study population**	**N (enrolled)**	**Results**			**Safety**	**References**
CoopERA (NCT04436744)	II	completed	giredestrant (2w) (30 mg daily)→ giredestrant + palbociclib (16w) (125 mg standard schedule) vs anastrozole (2w)→ anastrozole (1 mg daily) + palbociclib (16w)	randomized, open-label	early stage BC neoadjuvant	women with ER+/HER- cT1-cT4 Ki-67 ≥ 5% BC	221	ORR 50% vs 49%, pCR rate 4.5% vs 4.6%, Ki-67 reduction 81% vs 74%, CCCA 20% vs 14%			G1/2: fatigue (9% vs 17%), anemia (11% vs 6%), arthralgia (11% vs 19%), diarrhea (7% vs 17%).	(Fasching et al., 2022)
I-SPY2 EOP (NCT01042379)	II	ongoing	amcenestrant (200 mg daily) ± abemaciclib/ letrozole for 6 mo	randomized, open-label	early stage BC neoadjuvant	clinical high-risk and molecular low-risk (MammaPrint® low-risk score) ER+/HER2- BC (≥2.5 cm)	120	n/a			n/a	(Chien et al., 2022)

BC. Patients received camizestrant monotherapy at different doses (Table 1). Forty six percent of patients were carrier of *ESR1* mutations at baseline, for whom samples were available for subsequent analyses, and 85% presented a reduction or loss of *ESR1* mutant on AZD9833 treatment (Hamilton et al., 2020a). With camizestrant 75 mg daily dose administered in combination with palbociclib neither grade ≥ 3 TRAEs nor dose reduction or treatment interruption/discontinuation were reported (Table 2) (Oliveira et al., 2022). When administered at 150 mg or 300 mg once daily together with palbociclib, most common TRAEs were visual disturbances, bradycardia (only grade 1), asthenia, anemia, nausea, prolonged corrected QT interval according to Fridericia formula (QTcF), neutropenia, vomiting and leucopenia (Table 2) (Baird et al., 2021). Several additional clinical trials investigating camizestrant are ongoing (Tables 1 and 3) (Oliveira et al., 2021; Robertson et al., 2021; André et al., 2022; Im et al., 2021). Of note, SERENA-6 (NCT04964934) is an ongoing phase 3 study evaluating an early circulating tumoral DNA (ctDNA)-guided treatment switch. Patients with detectable *ESR1* mutation are randomized 1:1 to continue the same treatment (AI) or switch to camizestrant (Table 3) (Bidard et al., 2022a).

2.3. Giredestrant (GDC-9545)

Giredestrant is an orally administered non-steroidal SERD with capability to totally antagonize ER and induce its degradation (Metcalfe et al., 2019). In both WT and mutant *ESR1* cell line and PDX models, it demonstrated to elicit tumor regression alone or in combination with CDK4/6i (Liang et al., 2021). Giredestrant also acts through immobilization of ER, preventing its activation, and altering chromatin accessibility (Metcalfe et al., 2020). Safety, pharmacokinetic (PK) and pharmacodynamic activity of giredestrant is evaluated in the ongoing phase Ia/Ib GO39932 study (NCT03332797) (Table 1). Pharmacodynamic activity was assessed with both FES-PET/CT, showing > 90% of FES uptake in 78% of evaluable patients (including those harboring mutant *ESR1*), and using paired biopsies to evaluate biomarkers pre- and on-study treatment, reduced ER, PR and Ki-67 immunohistochemistry (IHC) values and ER activity signature were observed. Clinical benefit (CB) and objective response (OR) were observed at all doses including patients with *ESR1* mutations or those undergone prior treatment with fulvestrant or CDK4/6i (Jhaveri et al., 2020; Jhaveri et al., 2021a). In cohort B, including patients not previously treated with CDK4/6i, giredestrant was evaluated in combination with palbociclib (Table 2). None of patients discontinued treatment due to TRAEs, although 57% of study participants experienced grade 3 or higher toxicity. CB and partial response were observed also in patients with *ESR1* mutations or those who had undergone prior treatment with fulvestrant. Decreased *ESR1* MAF was reported in ctDNA in both cohorts (Lim et al., 2020). The reduction in ER, PR and Ki-67 level on paired biopsies were reported in both cohort but the decrease was deeper when giredestrant was combined with palbociclib (Turner et al., 2022; Neilan et al., 2022). In advanced disease settings, persevERA BC (NCT04546009) trial is ongoing and acelERA BC (NCT04576455) trial (Table 3) (Turner et al., 2021; Martin et al., 2021) missed to reach primary endpoint (investigator-assessedPFS) (https://www.roche.com/media/releases/med-cor-2022-04-25). Phase II acelERA BC study compared giredestrant versus physician's choice ET for HR+/HER2- locally advanced (LA) or mBC in second- or third-line setting. mPFS was similar between the two arms of the trial (5.6 months with giredestrant versus 5.4 months with physician's choice ET; HR 0.8, p = 0.17), while a numerical improvement was seen in *ESR1* mutation cohort (5.3 months in investigational arm versus 3.5 months in control arm; HR 0.6, p = 0.06). Giredestrant toxicity profile was consistent with known ET one (Jimenez et al., 2022). CoopERA BC is a phase II trial conducted in preoperative setting. Patients were randomized to receive anastrozole or GDC-9545 for 14 days (window of opportunity (WoO) phase) followed by addition of palbociclib 125 mg standard schedule in both arms for 4 × 28-days cycles (neoadjuvant phase; 16 weeks)(Moore et al., 2021; Hurvitz et al., 2022). Reduction in Ki-67 from baseline was superior with giredestrant + palbociclib than with anastrozole + palbociclib, complete cell cycle arrest (CCCA) was also greater in the experimental arm (Bardia et al., 2022a). The two groups showed similar OR rates, pathological complete response (CR) rate, as well as TRAEs and therapy interruption rate due to toxicity. Overall, GDC-9545 appears to be well tolerated in the preoperative setting. Thus, coopERA was the first randomized trial showing higher antiproliferative activity of an oral SERD over an AI in HR+/HER2- early-stage BC (eBC) (Table 2) (Fasching et al., 2022). Giredestrant is currently evaluated in additional trials (Tables 2 and 3) (https://www.clinicaltrials.gov/ct2/show/study/NCT04802759; Bardia et al., 2022b; https://www.clinicaltrials.gov/ct2/show/NCT05306340; https://clinicaltrials.gov/ct2/show/NCT05296798).

2.4. Amcenestrant (SAR439859)

Amcenestrant is an orally bioavailable potent ER antagonist and also causes its degradation and transcriptional inhibition, with optimized pharmacological and PK properties (Campone et al., 2020). It elicited tumor regression in both WT and mutant *ESR1* in HR+ BC models (El-Ahmad et al., 2020; Shomali et al., 2021). Synergistic antitumor activity was demonstrated in combination with palbociclib (Shomali et al., 2022). ER occupancy was further demonstrated with FES-PET in vivo (Besret et al., 2020). The phase I/II AMEERA-1 trial (NCT03284957) evaluates amcenestrant as monotherapy (arm 1, parts A-B) or in combination with palbociclib (2, C-D), alpelisib (3, F-G), everolimus (4, H-I) or abemaciclib (5, J-K) in HR+/HER2- mBC. Sixty-two patients received amcenestrant monotherapy ≥ 150 mg, 93.5% had visceral disease, 48.4% had received ≥ 3 prior lines in advanced setting. CB rate (CBR) (rate of confirmed CR or partial response or stable disease (SD) ≥ 24 weeks) was similar in *ESR1* wt and mutant BC. Neither TRAEs leading to discontinuation nor grade ≥ 3 toxicitis were observed (Table 1) (Bardia et al., 2022b; Linden et al., 2021). In 93% of patients with *ESR1* mutation, *ESR1* MAF was decreased by amcenestrant treatment (Chandarlapaty et al., 2020; Chandarlapaty et al., 2021a). AMEERA-3 (NCT04059484) was a phase II trial to investigates safety and efficacy of amcenestrant versus physician's choice ET in HR+/HER2- LA or mBC progressed on ET (Table 1) (Tolaney et al., 2021), it did not meet primary endpoint of improved PFS with amcenestrant as monotherapy in the investigated setting (https://www.sanofi.com/en/media-room/press-releases/2022/2022-03-14-07-00-00-2402216). Similar mPFS was observed between the two arms (3.6 months with amcenestrant versus 3.7 months with physician's choice treatment; HR 1.051, p = 0.6437) in patients with endocrine-resistant HR+/HER2- BC. Common TRAEs were mostly grade 1/2: nausea, vomiting, hot flish, asthenia, and fatigue (Tolaney et al., 2022). AMEERA-4 (NCT04191382) was a WoO trial to evaluate pharmacodynamic effects of amcenestrant on tumor cell proliferation with a pre-surgery treatment in patients with untreated HR+/HER2- eBC. Primary endpoint was change in Ki-67 levels after 14-day treatment (last dose received the day before surgery) compared to baseline (Campone et al., 2021). Enrollment was early discontinued based on sponsor decision not concerning safety (Campone et al., 2022). AMEERA-5 (NCT04478266) was a phase III trial assessing efficacy and safety of amcenestrant and palbociclib co-administration compared to letrozole plus palbociclib as first line treatment in patients with ER+/HER- mBC (Bardia et al., 2021c). In August 2022, the pharmacological industry Sanofi announced the discontinuation of the entire global clinical development program of amcenestrant following AMEERA-5 trial negative results at the interim analysis. Specifically, amcenestrant in combination with palbociclib did not meet the pre-specified boundary for continuation in comparison with the control arm. All the other ongoing studies of amcenestrant, including those in early-stage disease (AMEERA-6 - NCT05128773) were also discontinued (https://www.clinicaltrials.gov/ct2/show/record/NCT05128773; Meyskens et al., 2022; https://www.clinicaltrials.gov/ct2/show/NCT05101564; https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668).

Table 3
Phase III clinical trials including SERDs as single or combination therapy. * Study results of EMERALD trial included in the full text. 1 L first line; 3w/1w 3 weeks on treatment, followed by 1 week off treatment; AI aromatase inhibitors; BC breast cancer; CDK4/6i cyclin-dependent kinase 4 and 6 inhibitors; CT chemotherapy; DR disease relapse; ECOG Eastern Cooperative Oncology Group performance status; ER estrogen receptor; ESR1-mut estrogen receptor 1 gene mutated; ET endocrine therapy; DFI disease-free interval; HER2 human epidermal growth factor receptor 2; IDFS invasive disease-free survival; LABC locally advanced breast cancer; mBC metastatic breast cancer; mo months; mTORi mammalian target of rapamycin inhibitor; PD progression of disease; PFS progression-free survival; PI3Ki phosphoinositide 3-kinase inhibitor; SERD selective estrogen receptor degrader; SoC standard of care.

Identifier	Status	Study drugs	Study desing	Disease setting	Study population	N	Prior treatment	Primary endpoint	References
EMERALD* (NCT03778931)	active, not recruiting	elacestrant vs SoC (fulvestrant, anastrozole, letrozole, exemestane)	randomized, open-label	LABC or mBC	ER+/HER2 + BC. Postmenopausal women or men who must not allow pregnancy.	477	Prior treatment with at least one line of ET in the advanced setting and prior treatment with CDK4/6i + fulvestrant or AI (mandatory), one line treatment with CT. Prior ET: 100%; CDK4/6i: 100%; CT: 20.1% elacestrant arm, 24.4% SoC arm; mTORi: 4.2% elacestrant arm, 2.5% SoC arm; PI3Ki: 1.3% elacestrant arm, 0.4% SoC arm.	PFS in all subjects (elacestrant arm 2.79 mo vs SoC arm 1.91 mo), PFS in *ESR1*-mut subject (elacestrant arm 3.78 mo vs SoC arm1.87 mo)	(Bardia et al., 2021b)
SERENA-4 (NCT04711252)	ongoing	camizestrant (75 mg daily) + palbociclib (125 mg 3w/1w) vs anastrozole (1 mg daily) + palbociclib Men and premenopausal patient receive LHRH agonist in addition to study treatment	randomized, double-blind	LABC or mBC	*De novo* or recurrent ER+/HER2- BC.	1402	No prior systemic treatment in the advanced setting. Patients with recurrent disease: adjuvant treatment with at least 24 mo of AI or tamoxifen and without DR after 12 mo of the last dose.	PFS	(André et al., 2022)
SERENA-6 (NCT04964934)	ongoing	camizestrant + CDK4/6i (palbociclib or abemaciclib) vs ongoing treatment with AI (anastrozole or letrozole) + CDK4/6i	randomized, double-blind	LABC or mBC	ER+/HER2- BC on current 1 L SOC. Detectable ESR1 mutation.	302	1 L treatment with at least 6 mo of AI (letrozole or anastrozole) + CDK4/6i (palbociclib or abemaciclib) ± LHRH without PD.	PFS	(Bidard et al., 2022a)
evERA (NCT05306340)	ongoing	giredestrant + everolimus vs exemestane + everolimus	randomized, open-label	LABC or mBC	ER+/HER2- BC	224	Prior treatment with CDK4/6 and ET. PD > 6 mo after initiating CDK4/6i + ET in the advanced setting. Adjuvant treatment with at least 12 mo of ET + at least 6 mo in combination with a CDK4/6i.	PFS	(https://www.clinicaltrials.gov/ct2/show/NCT05306340)
heredERA (NCT05296798)	not yet recruiting	giredestrant + subcutaneous double anti-HER2 therapy phesgo (pertuzumab, trastuzumab, hyaluronidase-zzxf) vs investigator's choice ET + phesgo after induction therapy with a taxane plus the same anti-HER2 treatment in 1 L setting	randomized, open-label	LABC or mBC	ER+/HER2 + BC. LVEF ≥ 50%	812	DFI since completion of adjuvant or neoadjuvant non-hormonal treatment > 6 mo.	PFS	(https://clinicaltrials.gov/ct2/show/NCT05296798)
persevERA (NCT04546009)	ongoing	giredestrant (30 mg daily) + palbociclib (125 mg 3w/1w) vs letrozole (2.5 mg daily) + palbociclib	randomized, double-blind	LABC or mBC	ER+/HER2- BC.	978	No prior systemic treatment in the advanced setting. Adjuvant tamoxifen ≥ 24 mo without DR and DFI since completion of the neo/adjuvant ET (AI included) ≥ 12 mo. Prior	PFS	(Turner et al., 2021)

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Table 3 (*continued*)

Identifier	Status	Study drugs	Study desing	Disease setting	Study population	N	Prior treatment	Primary endpoint	References
							therapy with fulvestrant or CDK4/6i represents exclusion criterion.		
lidERA (NCT04961996)	ongoing	giredestrant (30 mg daily) vs physician's choice ET (tamoxifen or AIs) for at least 5 years	randomized, open-label	early stage BC adjuvant	ER+/HER2- medium/ high risk stage I-III resected BC enrolled within 12 mo following definitive surgery of the primary tumor.	4100	neoadjuvant or adjuvant CT + surgery	IDFS	(Bardia et al., 2022b)
AMEERA-5 (NCT04478266)	active, not recruiting	amcenestrant (200 mg daily) + palbociclib vs letrozole + palbociclib	randomized, double-blind	LABC or mBC	ER+/HER2- BC. ECOG 0–2	1068	No prior systemic treatment in the advanced setting. No prior neo/adjuvant treatment with any SERD. Prior neo/adjuvant ET with AI, fulvestrant or CDK4/6i (DFI >12 mo).	PFS	(Bardia et al., 2021a)
AMEERA-6 (NCT05128773)	ongoing	amcenestrant vs tamoxifen 5 years	randomized, double-blind	early stage BC adjuvant	stage IIB or III ER+/ HER2± BC undergone surgery and adjuvant RT if indicated.	3738	Adjuvant anti-HER2 + CT in HER2 + BC. Adjuvant treatment with AI > 6mo discontinued within 30 mo due to TRAE.	IDFS	(Meyskens et al., 2022)
EMBER-3 (NCT04975308)	ongoing	imlunestrant ± abemaciclib vs physichian's choice ET (fulvestrant or exemestane)	randomized, open-label	LABC or mBC	ER+/HER2- BC.	800	PD on or after AI ± CDK4/6i. Neoadjuvant or adjuvant CT, 1 L treatment with AI ± CDK4/6i.	PFS	(Jhaveri et al., 2022b)

2.5. Rintodestrant (G1T48)

Rintodestrant (G1T48) is a novel orally bioavailable compound with SERD activity developed from the raloxifene structure, chosen for its favorable toxicity profile, with the addition of an acrylic acid side chain. Rintodestrant was created through structure-guided studies driven by activity in cancer cell lines (Andreano et al., 2020a). G1T48 is able to downregulate ER more effectively than other SERDs (fulvestrant, AZD9496) and has demonstrated inhibition of ER+ BC cell growth ((Andreano et al., 2020a)). In BC models, it has been found to interfere with estrogen signaling with both WT ER and endocrine-refractory ER mutants (e.g. D538G) (Wardell et al., 2017). An ongoing clinical study (NCT03455270) aims to investigate the CB of rintodestrant alone (parts 1 and 2) or combined with palbociclib (part 3) in patients with HR+/HER2- mBC progressed on previous ET. The dose escalation and the dose expansion parts (1 and 2) has demonstrated a favorable safety profile (Dees et al., 2019; Aftimos et al., 2021a; Aftimos et al., 2021b; Beelen et al., 2021). The addition of palbociclib doubled the CBR from 28% of rintodestrant alone up to 60% (Table 2) (Aftimos et al., 2021a; Maglakelidze et al., 2021). Although based on preliminary data, the antitumor activity of the combination seems encouraging also in patients with *ESR1* and PI3K catalytic subunit alpha gene (*PIK3CA*) variants (Maglakelidze et al., 2021).

2.6. Imlunestrant (LY3484356)

Imlunestrant also exerts pure antagonist activity for ER. It inhibits cell proliferation in WT ER and *ESR1* Y537N mutant BC cell lines (Bhagwat et al., 2021). It has shown robust tumor growth inhibition in combination with abemaciclib, everolimus and alpelisib, which led to its study in the phase I EMBER trial, with the aim to assess its incorporation into the actual treatment landscape (NCT04188548) (Lim et al., 2021). Imlunestrant showed a CBR $\geq$ 48%, irrespective of *ESR1* mutations status, in patients who had been heavily pretreated. No dose-limiting toxicities (DLTs) were observed, but the only G3 TRAE was diarrhea (Jhaveri et al., 2021b). mPFS was 6.5 months with second-line imlunestrant in patients previously treated with CDK4/6i. In patients with *ESR1* mutation at baseline (n = 44), decline ($\geq$50%) or clearance in *ESR1* ctDNA level were observed.(Jhaveri et al., 2022a) A phase I preoperative WoO study evaluating the biological effects of imlunestrant in women with HR+/HER2- eBC (EMBER-2; NCT04647487) (https://clinicaltrials.gov/ct2/show/NCT04647487), and a phase III trial comparing imlunestrant with investigator's choice of ET are ongoing (EMBER-3; NCT04975308) (Jhaveri et al., 2022b; https://clinicaltrials.gov/ct2/show/NCT04975308). Finally, a phase III study of adjuvant imlunestrant vs standard ET in patients with HR+/HER2- eBC at high risk of recurrence, who have been treated with adjuvant ET for 2–5 years is planned (EMBER-4).

2.7. Other SERDs in active clinical development

AZD9496 is a first-generation non-steroidal SERD with acrylic acid side and oral administration (Willson et al., 1994; Connor et al., 2001) that demonstrated ability to antagonize and downregulate ER, even in presence of *ESR1* mutations (Lai et al., 2015). Furthermore, AZD9496 inhibits cellular aromatase expression and, consequently, activity mediated by ER signaling (Liu et al., 2016). Hamilton and colleagues conducted the FIH phase I study of AZD9496 on advanced HR+/HER2- BC patients (Liu et al., 2017). AZD9496 demonstrated a manageable safety profile. In a WoO presurgical trial, patients with naïve HR+/HER2- resectable BC were assigned to receive AZD9496 or fulvestrant (Table 1). AZD9496 was no superior to fulvestrant (Kahraman et al., 2019).

The insertion of a boronic acid side on the C-3 position of fulvestrant molecule allowed to develop a new compound, ZB716 (borestrant), that was as effective as fulvestrant but with enhanced oral bioavailability

(Zhang et al., 2017). ZB716 demonstrated promising antitumor activity in the preclinical setting (Guo et al., 2018). The first phase I/II clinical trial of ZB716 is ongoing (ENZENO study) (https://clinicaltrials.gov/ct2/show/NCT04669587). Another SERD, ZN-c5, is being studied in a phase I/II trial in patients with HR+/HER2- LA or mBC with a documented prior response to ET (https://clinicaltrials.gov/ct2/-show/NCT03560531). The interim analysis from phase I monotherapy dose escalation and expansion part showed no dose limiting toxicities (DLTs), an overall manageable toxicity profile and a promising CBR (Kalinksy et al., 2022). The phase I investigation of ZN-c5 in combination with palbociclib and the phase II monotherapy parts of the same trial, as well as another study of ZN-c5 in combination with abemaciclib are currently ongoing (Tables 1 and 2) (Abramson et al., 2021; Fu et al., 2021).

D-0502 is another oral SERD being evaluated as monotherapy or in combination with palbociclib in ER+ BC cell lines (Wang et al., 2018) as well as in a phase I clinical trial (NCT03471663) (https://clinicaltrials.gov/ct2/show/NCT03471663). Phase Ia has been completed with good tolerance and no DLTs. The most common TRAEs were gastrointestinal disorders such as nausea, vomiting and diarrhea. A CB response has been observed, in a heavily pretreated study population, including a 75% who received a prior CDK4/6i and a 38% a prior SERD (Osborne et al., 2021).

3. Novel SERMs

The acronym SERMs describes a class of ER binding molecules that mimic the activity of the natural hormone 17β-estradiol in some tissues (i.e., bone tissue) while exerting opposite effects on others (i.e., breast tissue). SERMs are designed to compete with estrogen and modulate ER activity by modifying its cofactors (Nilsson and Koehler, 2005).

3.1. Lasofoxifene

Lasofoxifene is a third-generation SERM, developed to treat post-menopausal vaginal atrophy and osteoporosis (Komm and Chines, 2012). A recent preclinical study showed that the antagonist activity of lasofoxifene on HR+ BC cells was not affected by the expression level of activating ER mutants as compared to WT, a property not observed for other clinically available agents, including tamoxifen, bazedoxifene, raloxifene, and fulvestrant (Andreano et al., 2020b). In mouse models of ET-resistant BC cell lines, a monotherapy with lasofoxifene was more effective than fulvestrant at inhibiting primary tumor growth and reducing metastases. The combination of lasofoxifene and palbociclib was generally more effective than fulvestrant plus palbociclib (Lainé et al., 2021). ELAINE 1 trial investigated lasofoxifene versus fulvestrant in women with HR+/HER2- mBC with *ESR1* mutations in a post-AI plus CDK4/6i second-line setting. mPFS was numerically greater with lasofoxifene 6.04 months (95% CI, 2.82–8.04) versus 4.04 months (95% CI, 2.93–6.04) with fulvestrant (p = 0.138; HR 0.699, 95% CI 0.445–1.125). Similar results were observed in visceral metastasis and Y537S *ESR1* mutation subgroups. Most common TRAEs were fatigue, nausea, arthralgias and hot flushes (Goetz et al., 2022). The ELAINE 2 study is a phase II single arm multicenter trial designed to evaluate the safety and efficacy of lasofoxifene combined with abemaciclib. Pre- and post-menopausal women with ER+ /HER2- mBC with acquired *ESR1* mutation (identified by ctDNA testing) were enrolled after progression on one or two lines of ET for metastatic disease, including or not a CDK4/6i. Twenty-nine patients were included; 80% of them had progressed after at least two previous ET. All except one patient had received prior CDK4/6i and 72% had prior fulvestrant; 48% had also received chemotherapy (CT) for metastatic disease. mPFS was 13.9 months, OR rate was 33.3% and CBR was 62.1% at the time of analysis. Tolerability was acceptable and most common adverse events were diarrhea, nausea, and leukopenia (Table 4) (Damodaran et al., 2022).

3.2. Z-endoxifen

Z-endoxifen is a tamoxifen metabolite with antiestrogenic activity. Tamoxifen is converted in endoxifen in liver by CYP2D6 enzyme. Thus, patients with low CYP2D6 enzyme activity could have lower drug concentrations when treated with tamoxifen. As matter of fact, pharmacogenetic analyses of tamoxifen trials showed an association between treatment efficacy and reduced cytochrome P450 2D6 (CYP2D6) metabolism or low endoxifen concentrations (Wu et al., 2009). Moreover, in vitro studies showed that Z-endoxifen inhibited tumor growth more potently than tamoxifen (Wu et al., 2009). The phase I study of endoxifen in women with endocrine refractory mBC revealed Z-endoxifene to be safe and well tolerated. Furthermore, it was unaffected by cytochrome P450 2D6 (CYP2D6) metabolism (Goetz et al., 2017). A randomized phase II clinical trial comparing Z-endoxifen with tamoxifen in women with mBC has been recently completed. Z-endoxifen was not significantly superior to tamoxifen, although a longer PFS was observed in the experimental arm for patients not previously treated with CDK4/6i (Table 4) (Goetz et al., 2020).

4. SERM/SERD hybrids

SERM/SERD hybrids (SSHs) act as agonists in bone, but also inhibit ER action in the reproductive system by inducing receptor degradation in these tissues (Wardell et al., 2015b).

Bazedoxifene contains a bulkier side chain than both tamoxifen and raloxifene, and its interaction distorts ER ligand binding domain (LBD) to enable its improved antagonist efficacy and decrease ER stability in BC cells (Haines et al., 2021). Bazedoxifene binding with ER prevents the association between ER and its co-regulators inducing receptor ubiquitination and subsequent proteosomal degradation (Fanning et al., 2018). Based on these unique properties, bazedoxifene is under clinical investigation in mBC as it showed promising results in the preclinical setting, both in treatment-sensitive and resistant models, alone or in combination with palbociclib (Wardell et al., 2013; Wardell et al., 2015b; Fanning et al., 2018). A phase Ib/II study investigated bazedoxifene in combination with palbociclib in patients with HR+/HER2- mBC who had progressed on at least one line of ET for metastatic disease or with tumor relapse within 12 months after the end of adjuvant ET (Table 4) (Jeselsohn et al., 2019). A whole-exome sequencing (WES) on serial ctDNA samples from endocrine resistant patients was collected at baseline, day 1 of cycle 2, and at the end of treatment. There was no association between *ESR1* mutations and PFS. In contrast, baseline *PIK3CA* mutations were only detected in patients who did not achieve CB, and were associated with worse PFS compared to patients with WT *PIK3CA* (Grinshpun et al., 2022).

5. PROTACs (PROteolysis TARgeting Chimera)

PROTACs are a group of small molecules including two active domains and a linker, which have the capability to eliminate target proteins. This class of agents represent a new pharmacological tool that employs the ubiquitin-protease system. The enzyme E3 ligase adds ubiquitin on the protein to be demolished so that it is recognized and degraded by the proteasome (Flanagan and Neklesa, 2019). The mechanism by which PROTACs degrade the ER protein is fast and transient. This allows PROTACs to cycle several times and eliminate a large amount of target protein.

ARV-471 is an orally bioavailable PROTAC designed to target and degrade ER (Snyder et al., 2021). In preclinical studies, this agent has shown the capability to degrade ER in HR+ BC cell lines. It decreases the expression of classically regulated ER-target genes, inhibits cell proliferation of ER-dependent cell lines (MCF7, T47D), degrades clinically relevant *ESR1* variants (i.e. Y537S and D538G) and impedes growth of cell expressing those variants in PDX. When it was combined with a CDK4/6i in the MCF7 xenograft model, it produced a more pronounced

Table 4
Completed and ongoing clinical trials testing ER signaling inhibitors other than SERDs. 3w/1w 3 weeks on treatment, followed by 1 week off treatment; ABC advanced breast cancer; AEs adverse events; AI aromatase inhibitors; AST aspartate transaminase; BC breast cancer; BID bis in die; CBR clinical benefit rate; CDK4/6i cyclin-dependent kinase 4 and 6 inhibitors; CT chemotherapy; d days; DE dose escalation; EC extended cohort; Endx endoxifen; ER estrogen receptor; ET endocrine therapy; eve everolimus; ful fulvestrant; G grade; GGT gamma-glutamyl transferase; HER2 human epidermal growth factor receptor 2; LABC locally advanced breast cancer; mBC metastatic breast cancer; mESR1 estrogen receptor 1 gene mutated; mPFS; median progression-free survival; mo months; n/a not available; ORR objective response rate; PD progression of disease; PFS progression-free survival; RP2D recommended phase 2 dose; tam tamoxifen; TRAEs Treatment related adverse events.

Identifier	Phase	Status	Study Drugs	Study design	Disease setting	Study population	N	Prior treatment	mESR1 (%)	Results	Safety	References
ELAINE 1 NCT03781063	II	Active, not recruiting	Lasofoxifene (5 mg daily) vs fulvestrant (standard schedule)	randomized	LABC or mBC	ER+/HER2- BC and *ESR1* mutation progressed on prior AI (≥12 mo) + CDK4/6i	103	CDK4/6i 100% both cohorts; CT 5.8% lasofoxifene arm, 5.9% ful arm	100%	ORR 13.2% lasofoxifene arm, 2.9% fil arm; CBR 36.5% lasofoxifene arm, 21.6% ful arm; PFS 6.04 mo lasofoxifene arm, 4.04 mo ful arm	Lasofoxifene: nausea (27.5%), fatigue (23.5%), arthralgia (21.6%), hot flush (21.6%), constipation (15.7%), dizziness (15.7%), hypertension (15.7%), cough (15.7%); Ful: fatigue (37.5%), arthralgia (22.9%), nausea (18.8%), hypertension (14.6%), constipation (12.5%), hot flush (10.4%), cough (10.4%).	(Goetz et al., 2022)
ELAINE 2 NCT04432454	II	active, not recruiting	Lasofoxifene (5 mg daily) + abemaciclib (300 mg daily)	single group	LABC or mBC	ER+/HER2- BC with detectable *ESR1* mutation.	29	median n° of prior lines: 2; ≤ 2 ET: 80%; CDK 4/6i: 96%; ful 72%; CT: 48%	100%	ORR 33.3%, CBR 62.1%, PFS 13.9 mo	No deaths. G1/2: diarrhea, nausea, leukopenia, muscle spasms and hot flashes.	(Damodaran et al., 2022)
NCT01327781	I	active, not recruiting	Z-Endoxifen (once daily at seven dose levels 20–160 mg)	single group, dose escalation	mBC	ER+/HER2 ± BC	22 (dose-escalation cohorts) 16 (dose-expansion cohorts)	Tam 22.8% DE, 18.8% EC; AI 72.7% DE, 75% EC; megestrol acetate 3.6% DE, 6.3% EC; ful 4.9% DE, 75% EC; CDK4/6i 0%	1.8%	ORR 12%, CBR 26%, PFS 110 d	No deaths, G4: hypertriglyceridemia (1 patient), G2/3: fatigue, nausea, sleep disorders	(Goetz et al., 2017)
NCT02311933	II	active, not recruiting	Z-Endoxifen (80 mg daily) vs tamoxifen (20 mg daily)	randomized	mBC	ER+/HER2- BC	77	PD during AI in any setting, ≤ 2 CT for mBC, no tam in mBC or PD ≤ 24 mo from adj tam. median n° of prior ET for mBC 2 (1–4); CDK4/6i: 42.5% vs 29.7%; eve: 35.0% vs 40.5%	n/a	mPFS 130 d vs 42 d	Endx: G3 hypertriglyceridemia (7.5%); tam: G3 hypertension with G2 stroke (2.7%), G3 thromboembolic event (2.7%), G3 abdominal, bone and liver pain (2.7%)	(Goetz et al., 2020)

(*continued on next page*)

Table 4 (*continued*)

Identifier	Phase	Status	Study Drugs	Study design	Disease setting	Study population	N	Prior treatment	mESR1 (%)	Results	Safety	References
NCT02448771	Ib/II	completed	Bazedoxifene (40 mg daily) + palbociclib (125 mg 3w/ 1w)	single group	mBC	ER+/HER2- BC	36	PD during or ≤ 24 mo from the end of adjuvant ET ≤ 1 line of ET for ABC ≤ 1 CT for for ABC. ≥ 1 ET (>80%), ≥ 2 ET (45%), 1–2 CT lines (52%)	n/a	ORR 8%, CBR (primary outcome) 36%, PFS 3.6 mo	No deaths. G1/2: fatigue, neutropenia.	(Jeselsohn et al., 2019; Grinshpun et al., 2022)
NCT04072952	I	completed	ARV-471 (30–700 mg daily)	single group, dose escalation	LABC or mBC	postmepausal ER+/HER2- BC	60	median n° of prior lines 4 (1–10); CDK4/6i: 100%; ful: 80%; other SERD: 10%; CT: 78%.	n/a	CBR 40%	6 G3 TRAEs in 4 patients: headache, asymptomatic increased amylase and lipase, nausea, asymptomatic QTc prolongation, venous embolism. G1/2: nausea (27%), fatigue (20%), vomiting (10%), AST increased (10%).	(Snyder et al., 2021; Hamilton et al., 2021b)
NCT04072952	I/II	ongoing	ARV-471 + palbociclib (125 mg 3w/ 1w)	single group	LABC or mBC	postmenopausal ER+/HER2- BC	n/a	≥ 1 ET (including CDK4/6i, fulv and AI), ≤ 2 CT for ABC	n/a	n/a	n/a	(Hamilton et al., 2022b)
NCT03250676	I/II	completed	H3B-6545 (450 mg daily)	single group	mBC	ER+/HER2- BC	84	median n° of prior lines 3 (1–8); CDK4/ 6i: 85%; AI: 80%; ful: 72%; CT: 50%.	62%	ITT: ORR 17%, CBR 32%, mPFS 5 mo Y537S m*ESR1*: ORR 30%, mPFS 7.3 mo	No deaths. All G: eGFR decrease (40%), anemia (39%), lymphocytes decreased (36%), nausea (18%), fatigue (16%), ALT increased (14%), AST increased (13%), creatinine increased (13%), diarrhea (12%), bilirubin increased (11%) Cardiological AEs: sinus bradycardia (G1 36%, G2 5%), corrected QT interval prolongation (G2 2 patients, G3 3 patients)	(Hamilton et al., 2021a)
NCT04288089	I	ongoing	H3B-6545 300 mg daily + palbociclib 100 mg daily cohort 1; H3B-6545 300 mg daily + palbociclib 125 mg daily cohort 2	single group	LABC or mBC	ER+/HER2- BC	10 (7 cohort 1, 3 cohort 2)	ET for ABC (including CDK4/6i and ful), CT	n/a	n/a	G3/4: neutropenia (40%) G3: trombocytopenia (10%), lipase increase (10%)	(Johnston et al., 2021)

(*continued on next page*)

Table 4 (*continued*)

Identifier	Phase	Status	Study Drugs	Study design	Disease setting	Study population	N	Prior treatment	mESR1 (%)	Results	Safety	References
NCT04505826	I/II	recruiting	OP-1250 (30–300 mg daily)	single group	LABC or mBC	ER+/HER2- BC	41	ET (including CDK 4/6i and ful), CT	n/a	All doses (24 pts): ORR 8%, CBR 29%. RP2D (12 pts): ORR 17%, CBR 46%	All G: nausea (49%), fatigue (34%), vomiting (22%), headache (17%).	(Hodges-Gallagher et al., 2020a)
NCT05266105	I	recruiting	OP-1250 (60–120 mg daily) + palbociclib (125 mg 3w/1w)	single group	LABC or mBC	ER+/HER2- BC	n/a	no specific inclusion/exclusion criteria	n/a	n/a	n/a	(https://www.clinicaltrials.gov/ct2/show/NCT05266105)
NCT03201913	I	completed	TTC 352 (180 mg BID)	single group, dose escalation	mBC	ER+ BC	15	≤2 lines of ET for ABC (1 line including CDK4/6i)	n/a	PFS 58 d	No deaths. G3: asymptomatic pulmonary embolism, diarrhea, AST elevation, and myalgia; G4: GGT elevation	(Dudek et al., 2020)

tumor growth inhibition accompanied by significant reductions in ER protein levels (Snyder et al., 2021).

A phase I/II, multicenter, open-label study of ARV-471 in patients with HR+ /HER2- BC (Snyder et al., 2021) had the primary objective to evaluate its safety and tolerability and to find the maximum tolerated dose (MTD). Moreover, the study focused on evaluating PK and pharmacodynamics and explore ARV-471 antitumor activity. CBR was analyzed in patients enrolled ≥ 24 weeks prior to the data cutoff. ARV-471 had a good safety profile and was well tolerated at all tested dose levels. ARV-471 showed robust signals of efficacy in a challenging population (all patients were previously treated with CDK4/6i, 80% received prior fulvestrant, and 78% received prior CT). Results are presented in Table 4. ER degradation (up to 89%) was observed at all doses up to 500 mg daily, irrespective of *ESR1* mutation status (Hamilton et al., 2022a). ARV-471 is currently being investigated as a treatment for mBC in a phase I dose escalation study, a phase Ib combination study with palbociclib, and a phase II monotherapy dose expansion study (Hamilton et al., 2022b).

Other PROTACs with interesting in vitro antitumor activity are under development in preclinical studies. These agents include ERD-148, ERD-308, AC682, SGK3-PROTAC1; they induce better ER degradation and are more effective than fulvestrant in inhibiting cell proliferation in MCF-7 cells.

6. SERCAs (Selective ER Covalent Antagonists)

SERCAs represents a group of small molecules which act as ER antagonists, binding covalently to and altering the function of the receptor protein.

H3B-6545, a selective, small covalent antagonist of ER has demonstrated preclinical and preliminary clinical activity against HR+ BC. H3B-6545 has a manageable safety profile and demonstrated single-agent antitumor activity in heavily pretreated HR+/HER2- mBC patients. Clinical activity was also observed in patients with *ESR1* mutations (Table 4) (Hamilton, 2020b; Hamilton et al., 2021a). A phase I trial testing H3B-6545 in combination with palbociclib is ongoing. H3B-6545 300 mg daily plus palbociclib is well-tolerated and has a manageable safety profile. Preliminary antitumor activity in previously treated patients with HR+/HER2- mBC is encouraging (Table 4) (Goetz et al., 2017; Johnston et al., 2021).

7. CERANs (complete ER antagonists)

CERANs are small molecules with complete ER antagonist function, which are able to degrade ER as a SERD but also block ER function.

OP-1250 is a CERAN acting as a complete antagonist of activation function 1 (AF1) and activation function 2 (AF2) of ER (Shang and Brown, 2002). It is an orally bioavailable drug with a favorable PK profile, once-daily dosing, and has shown robust central nervous system (CNS) penetration in preclinical brain metastasis model. In preclinical studies, it has been able to completely degrade and inactivate ER, block gene transcription and cell growth (Hodges-Gallagher et al., 2020a). It also showed anticancer activity in brain metastases and anti-tumor activity in both WT and mutant *ESR1* preclinical models. In additional preclinical studies where OP-1250 was compared to fulvestrant, it demonstrated a robust tumor shrinkage (Hodges-Gallagher et al., 2021).

The phase I dose-escalation portion of the ongoing phase I/II clinical trial of OP-1250, enrolled HR+/HER2- recurrent LA or mBC who received prior ET. Part 1 (dose escalation) aimed to identify the DLTs, MTD, RP2D and the PK of OP-1250. The part 2 (monotherapy dose expansion) objectives were to estimate the clinical activity of OP-1250 in subjects with HR+/HER2- mBC who showed no evidence of CNS metastases in the measurable disease cohort and to estimate the clinical activity in patients with CNS metastases. Within part 1, 41 heavily pretreated patients were enrolled across 7 dose cohorts. OP-1250 was generally well tolerated and safe, the majority of reported TRAEs were

grade 1 or 2 at all dose levels, and the most common were nausea, fatigue, vomiting and headache. Three partial responses were observed among 24 efficacy-evaluable patients. For dose levels within the RP2D range, the objective response rate (ORR) was 17% and the CBR was 46% (Table 4) (Hodges-Gallagher and Sun, 2020b). A phase Ib at 2 dose levels and a phase II efficacy evaluation study are ongoing (https://www.clinicaltrials.gov/ct2/show/NCT04505826). Moreover, a phase I study of OP-1250 in combination with palbociclib in HR+/HER2- BC patients is ongoing (https://www.clinicaltrials.gov/ct2/show/NCT05266105). In addition, OP-1250 in combination with tucatinib and trastuzumab proved to reduce proliferation and degrade ER protein in ER+/HER2 + cell line-derived xenografts and PDX models. When co-administered with trastuzumab and tucatinib it reduced ER+/HER2 + xenograft growth similar or better than capecitabine-based CT (Parisian et al., 2022). A clinical study evaluating the combination of OP-1250 and HER2 targeted agents will be started.

8. ShERPAs (Selective human ER Partial Agonists)

ShERPA are benzothiophene derivatives that mimics the β-estradiol. They target and bind to ER into the nucleus causing ER translocation to extra-nuclear sites. Nuclear export of ER causes ER+ tumor cells growth inhibition.

TTC-352 is a ShERPA in clinical development for the treatment of hormone-refractory HR+ BC. A phase I accelerated dose escalation study with the primary endpoint of MTD assessment, evaluated five dose levels of TTC-352 in BC progressing after at least two lines of ET including one in combination with a CDK4/6i. The secondary objectives were to determinate treatment tolerability, PK of TTC-352, best response, PFS, and protein kinase C alpha (PKCα) expression in tumors, since PKCα may be predictive of benefit from ET. Fifteen patients were enrolled. No DLTs were observed. TTC-352 demonstrated a favorable safety profile and early clinical evidence of antitumor activity against heavily pretreated hormone-refractory BC (Table 4) (Dudek et al., 2020).

9. Additional classes of ER inhibitors under preclinical development

A high number of molecules, which act with intriguing mechanisms of action, are currently moving their first steps into research. Notably, the following ones worth a mention:

- **Specific non-genetic inhibitor of apoptosis protein (IAP)-dependent protein erasers (SNIPERs)**: These hybrid molecules are designed based on IAP and used to degrade target proteins implicated in disease development (Ma et al., 2021).

- **Dual-mechanism ER inhibitors (DMERI)**: These antiestrogens cause alternate, non-canonical structural perturbations of the receptor LBD to antagonize proliferation in HR+ BC cells and in allele-specific resistance models (Min et al., 2021).

To date, no clinical information is available, nevertheless these drugs may expand the choice of therapeutic strategies in the future.

10. Discussion and perspective

Here, we have reviewed the most relevant preclinical and clinical available results regarding novel ER-targeting agents under investigation in order to provide an up-to-date state-of-the-art in this field of research. ER signaling represents the main driver of tumor growth and survival in HR+/HER2- BC, therefore ET-based treatments are still central for this disease subtype. As matter of the fact, several classes of new drugs with unique PK and pharmacodynamic features are being investigated with the purpose of blocking ER pathway more efficiently and potently than standard ET, and ultimately preventing or overcoming resistance to standard ET (Hanker et al., 2020). First of all, these new classes of agents include second generation SERDs, which are administered orally and inhibit ER more potently than fulvestrant. Besides oral SERDs, other classes of compounds such as novel SERMs, SSHs, PROTACs, SERCAs, ShERPAs and CERANs have reported promising preliminary results so far. In particular, PROTACs represent a new pharmacological technology, which could be developed to target and degrade different proteins involved in tumor growth and treatment resistance. This is particularly important as new PROTACs could be developed to specifically target key proteins which cannot be targeted by traditional anti-cancer agents. Notably, most of the aforementioned new agents, and particularly the new SERDs, are active also in the presence of *ESR1* mutations, that induce conformational change in the receptor with consequent ligand-independent constitutive activation. This is particularly important, considering that *ESR1* mutations represent the most common genomic mechanism of acquired ET resistance and are associated with poor prognosis (Brett et al., 2021b). Positive results in HR+/HER2- mBC harboring *ESR1* mutations were observed in preclinical and early phase clinical trials of different oral SERDs, the novel SERM lasofoxifene (Andreano et al., 2020b), the SSH basedoxifene (Fanning et al., 2018; Wardell et al., 2013), and the SERCA H3B-6545 (Hamilton et al., 2021a; Puyang et al., 2018).

All the unique pharmacological features of these new agents, together with the promising results observed in many phase I/II studies has led to further development in larger trials, both in the metastatic and early disease settings, with the aim of addressing different clinical questions. To date, one of most important unmet clinical needs is to develop new ET-based treatment strategies after failure of CDK4/6i. In this regard, the most solid evidence derives from the EMERALD trial. More than 20 years after the approval of the last ET agent (fulvestrant), EMERALD is the first pivotal phase III study of an oral SERD showing positive results in HR+/HER2- mBC patients previously treated with standard CDK4/6i-based first line therapy. In this trial, co-primary endpoints were PFS in the overall population and in patients with *ESR1* mutations, elacestrant demonstrated statistically significant improvement in both outcomes compared to SOC endocrine monotherapy. In patients with *ESR1* mutation the magnitude of benefit was even higher with an increase in median PFS from 1.9 to 3.8 months (HR 0.55) (Bardia et al., 2021b). Despite these positive results, it could be argued that the overall benefit of this treatment is marginal considering the limited mPFS observed in both the control and the experimental arm. Nevertheless, it should be considered that 70% of patients who were randomly assigned to standard arm received fulvestrant, which, according to the major international guidelines, represents a standard of care after failure of CDK 4/6i, in the absence of rapidly progressing disease and visceral crises (Gennari et al., 2021; Kumar et al., 2022). Thus, elacestrant represents a new treatment option, superior to the previous standard of care, also in a subset of patients particularly difficult to treat as 70% of the enrolled patients had visceral metastases, almost one third had already received one prior CT, and the rate of *ESR1* mutation was 48%. Among patients who had not received prior CT for mBC (77.8%), PFS was prolonged in both the overall population (mPFS 3.7 vs 2.0 months; HR 0.68, 95% CI: 0.52–0.89; $p = 0.004$) and in patients with *ESR1* mutations (mPFS 5.3 vs 1.9 months, HR 0.54, 95% CI: 0.36–0.80; $p = 0.002$) (Kaklamani et al., 2022). On the other hand, the early drop of PFS curves in both arms suggests that a large proportion of patients did not benefit at all from ET monotherapy and experienced rapid disease evolution. Timely identification of those patients using predictive markers may be crucial in order to define alternative treatment strategies, which, in turn, could substantially affect the natural history of disease. Similar to the results of the SOC arm in the EMERALD trial, ET monotherapy with fulvestrant after CDK4/6i-based therapy reached a mPFS of less than 2 months both in VERONICA (1.94 months) (Lindeman et al., 2021) and SOLAR-1 trials (1.8 months) (Juric et al., 2019), both including patients with poor prognosis. These results raise the question on whether single-agent ET constitutes the optimal strategy to treat these patients. Whether continued treatment with another CDK4/6i in combination with elacestrant is a clinically viable option warrants investigation based on the recent reports of clinical activity of

abemaciclib after progression with prior palbociclib or ribociclib (Wander et al., 2021).

Despite the favorable outcomes reported with elacestrant in EMERALD, as described above, there is some discrepancy in the clinical benefit of oral SERDs in general. For e.g., negative results have been observed for the acelERA trial testing giredestrant and the AMEERA-3 trial testing amcenestrant. In addition, results from the phase III EMBER-3 trial investigating imlunestrant and the phase II SERENA-2 study on camizestrant are awaited. While we wait for the final results of all of these studies, we speculate on the reasons for inconsistency among trials. For e.g., the proportion of patients who received prior CDK4/6i was different across the trials and was the highest in the EMERALD (100%), followed by AMEERA-3 (80%) and acelERA BC (42%). Another point to consider is the prevalence and type of *ESR1* mutations (EMERALD 48%, AMEERA-3 43% and acelERA BC 39%), which may have a potential role as a predictive biomarker of efficacy for oral SERDs. Furthermore, it is important to define the proportion of patients with prior sensitivity to ET included in each trial. Finally, a crucial aspect may be the mechanism of action. In particular, Elacestrant is a SERM/SERD while giredestrant and amcenestrant are pure oral SERDs, which may contribute to the observed differences.

Another emerging question about the new ER signaling inhibitors is related to their possible use as an improved ET backbone in combination with targeted agents (Tables 2, 3 and 4), in particular as first line therapy, in combination with CDK4/6i. Several, late-stage ongoing trials, including the SERENA-4 with camizestrant, the persevERA with giredestrant and the AMEERA-5 with amcenestrant, are testing this option. Negative results have been announced for the latter study.

A potential positioning of these new ET in the therapeutic landscape of mBC may be defined by the onset of the *ESR1* mutation. Indeed, the new generation SERDs may overcome ET resistance associated with the occurrence of *ESR1* mutation in patients treated with AIs and CDK4/6i. PADA-1 trial has established the concept of switching to a SERD (fulvestrant) upon the *ESR1* mutation emergence; this approach was shown to reduce the risk of progression or death and increase mPFS of more than 6 months as compared to SOC treatment (Bidard et al., 2022b). Currently, the SERENA-6 trial is investigating the switch from AI to camizestrant plus palbociclib or abemaciclib in presence of occurring ctDNA-based discovery of *ESR1* mutations.

Further challenges and open questions remain regarding the incorporation of oral SERDs and other novel ETs in the treatment algorithm of mBC. First, it would be very important to study the activity and efficacy of oral SERDs also in pre-menopausal women, as many trials, including the EMERALD, enrolled only postmenopausal patients. It is questionable whether all pre-menopausal women would need the concomitant therapy with luteinizing hormone-releasing hormone (LHRH) analogues. In addition, the effectiveness of combining these new agents with different targeted therapy has yet to be established. Many trials are ongoing (Tables 2, 3 and 4) and include: (1) evERA trial comparing giredestrant plus everolimus versus exemestane plus everolimus, (2) MORPHEUS umbrella trial testing giredestrant plus several different partners, including the PI3K inhibitor inavolisib in case of *PIK3CA* mutated tumors, (3) phase I EMBER trial testing imlunestrant plus alpelisib in presence of *PIK3CA* mutation or trastuzumab and pertuzumab in HER2-enriched diseases (https://clinicaltrials.gov/ct2/show/NCT04791384). Finally, the incorporation of novel ER signaling inhibitors within the treatment landscape of HR+/HER2- mBC may become even more complex as new treatment perspectives are emerging with the rise of antibody-drug conjugates (ADCs), in view of the results of DESTINY-Breast04 trial with trastuzumab deruxtecan (Modi et al., 2022) and TROPiCS-02 study with sacituzumab govitecan (Rugo et al., 2022).

Safety plays a fundamental role in establishing the possible use of new drugs in clinical practice. Each of these new agents shows a specific toxicity profile, although some TRAEs are common across different class of compounds. In addition to general TRAEs, traditionally reported with standard ET, such as hot flashes, arthralgia and fatigue, gastrointestinal effects (nausea, vomiting, constipation, dyspepsia, and diarrhea) are also common with the new ER inhibitors. Other emerging TRAEs were hematological toxicity detected with the SERCA H3B-6545 and other agents in combination with CDK4/6i, bradycardia, described with SERCAs and oral SERDs, and visual disturbance, reported with the oral SERDs camizestrant and giredestrant. Importantly, in phase I trials, the great majority of these TRAEs were low grade and very rarely led to dose reduction or drug discontinuation.

The toxicity profile is particularly important also considering that a potential use of these new ETs is already emerging even in the early disease stage. Indeed, similar to the metastatic setting, there are several trials evaluating the effectiveness of novel ER inhibitors in the neo/adjuvant setting, including SERENA-3, EMBER-2, ELIPSE, I-SPY2, lidERA, and AMEERA-6 (Table 3). Furthermore, medication adherence is a key challenge with long-term treatment with oral ET in BC patients (Partridge et al., 2002, 2003; Chlebowski et al., 2009; Van Herk-Sukel et al., 2010; Nekhlyudov et al., 2011; Murphy et al., 2012; Huiart et al., 2013). Lack of adherence to ET has shown to impact clinical outcomes (McCowan et al., 2008; Hershman et al., 2011; Markkula et al., 2012; Makubate et al., 2013; Pagani et al., 2013; Pistilli et al., 2020). The ongoing and future trials with emerging ET should evaluate adherence to these therapies and assess outcomes based on adherence behavior to understand its impact.

11. Conclusion

The treatment landscape for HR+/HER2- BC is particularly complex as many agents have been approved and many other novel compounds are under investigation (Fig. 1). One of the greatest challenges in our clinical practice is the choice of right treatment sequence for each patient, assuring an optimal balance between treatment efficacy and quality of life. Further evidence is needed to establish whether these new drugs can be implemented in clinical practice in the metastatic setting as an option for post-CDK4/6i treatment, or as novel backbone of front-line ET. In addition, the efficacy of these new endocrine agents is currently under evaluation also in the adjuvant setting.

Discovery of novel biomarkers predicting likelihood of response to each of these agents is also of utmost importance and may allow better selection of ET for individual patient. Moving forward, it would be very important to look at patients reported outcome (PRO), tolerability, and quality of life from all the trials in every treatment setting, in order to comprehensively define the magnitude of the benefit associated with each new treatment strategy.

CRediT authorship contribution statement

Martina Pagliuca: Conceptualization, Investigation, Resources, Writing – Original Draft. **Marco Donato**: Conceptualization, Investigation, Resources, Writing – Original Draft. **Agostina Lagodin D'Amato**: Conceptualization, Investigation, Resources, Writing – Original Draft. **Mario Rosanova**: Conceptualization, Investigation, Resources. **Anna Orsola Maria Russo**: Conceptualization, Investigation, Resources, Writing – Original Draft. **Roberta Scafetta**: Conceptualization, Investigation, Resources, Writing – Original Draft. **Carmine De Angelis**: Supervision, Writing – Review & Editing. **Meghna V. Trivedi**: Supervision, Writing – Review & Editing. **Fabrice André**: Supervision, Writing – Review & Editing. **Grazia Arpino**: Supervision, Writing – Review & Editing. **Lucia Del Mastro**: Supervision, Writing – Review & Editing. **Michelino De Laurentiis**: Supervision, Writing – Review & Editing. **Fabio Puglisi**: Supervision, Writing – Review & Editing. **Mario Giuliano**: Conceptualization, Methodology, Supervision, Writing – Review & Editing, Funding acquisition.

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