Selective estrogen receptor degraders and their effect on the breast cancer immune microenvironment

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One in eight women will be diagnosed with breast cancer in their lifetime. Most breast cancers express estrogen receptor α (ERα) and depend on its signaling, which promotes tumor growth, survival, and metastatic spread through hormone-dependent transcriptional reprogramming. Selective estrogen receptor degraders/downregulators (SERDs), such as fulvestrant (faslodex), which was FDA approved in 2002, are second-line endocrine therapies for the treatment of advanced metastatic disease. Tumors containing activating hotspot mutations in *ESR1* (the gene encoding ERα) retain some sensitivity to fulvestrant but require higher doses to achieve inhibition of the mutant receptor. Substantial efforts to develop next-generation SERDs with improved pharmacology over fulvestrant have led to the FDA approval of the first-in-class orally available SERD elacestrant (Orserdu), followed by imlunestrant (Inluriyo), and the anticipated approval of several more therapies. Excitingly, recent studies show that in addition to their previously described antitumoral mechanisms, SERDs also act by increasing antitumor immunity. In this Review, we detail the current SERD clinical landscape and our emerging understanding of the interplay among SERDs, breast cancer cells, and the tumor immune microenvironment.

Introduction

In the United States, breast cancer (BC) is the leading cause of cancer-related deaths among women under 50, with more than 40,000 deaths projected in 2026 (1). Unique molecular features classify BCs into three main subtypes: estrogen receptor α positive (ER^+), human epidermal growth factor-2 positive ($HER2^+$), and triple-negative BC (TNBC) (2). Most BCs (about 70%–80%) are ER^+; this classification denotes that they overexpress the oncogenic nuclear transcription factor (3, 4). ER^+ BCs are stimulated by the hormone estrogen; 17β-estradiol (E2) as the most potent endogenous estrogen; it elicits a robust upregulation of tumor-promoting genes (5). Endocrine therapy (ET) refers to a class of drugs that aim to slow tumor growth by blocking proproliferative E2-driven signaling. Here, we focus mainly on ET's effect on the canonical ERα66, but it should be noted that other receptors are E2-responsive and may also be affected by ET. Another isoform, ERβ, also binds E2, and there are variants of ERα, including ERα46 and ERα36, whose distribution and function are detailed in a recent review (6). G protein–coupled estrogen receptor (GPER, also known as GPR30) also acts as an E2 agonist in syngeneic BC murine studies and binds anti-estrogens (7, 8).

First-line ERα-targeted ETs belong to two drug classes, which have distinct mechanisms of action. Aromatase inhibitors (AIs) starve ERα of its endogenous hormone by preventing the conversion of androgens into E2 (9, 10). AIs are the standard of care (SOC) in postmenopausal patients who have not received prior ET (11). In premenopausal patients, the first-line ET is the selective estrogen receptor modulator (SERM) tamoxifen, which is prescribed with or without ovarian suppression (12). The major active metabolite of tamoxifen is 4-hydroxytamoxifen (4OHT), which is a competitive allosteric ER antagonist in BC cells that acts as a weak estrogen in other tissues such as the uterus and bone (13, 14). These first-line ETs are administered for 5–10 years in the adjuvant setting to reduce the risk of recurrence (15–17).

Nearly half of all patients with BC with high nodal involvement at the time of primary diagnosis will relapse in their lifetime (18). This recurrent disease has often metastasized to distant organs at the time of diagnosis, most commonly to the bone, liver, lung, and brain (19, 20). Over 95% of BCs retain their ER^+ or ER^- status in the metastatic setting, as measured by immunohistochemistry (21). However, approximately 40% of patients with metastatic ER^+ BC present with hotspot somatic mutations to the gene encoding ERα, *ESR1*, with the most prevalent being a tyrosine-to-serine missense mutation at position 537 (Y537S) and a glutamate-to-glycine missense mutation at position 538 (D538G) (22–25). These mutations are highly enriched in metastatic lesions, but less than 1% of ET-naive patients have detectable *ESR1* mutations, suggesting that they arise over time from a dormant disease state (26). These mutations stabilize a constitutively active receptor, enabling ERα to stimulate gene transcription in the absence of E2 (27, 28).

Beyond promoting a constitutively active receptor, *ESR1* mutations increase the oncogenicity of ER^+ BCs. Mutant ERα recruits transcriptional coactivator proteins to drive both canonical and pathogenic transcriptional programs (29). BC cells that harbor *ESR1* mutants display increased Histone H3 Lysine 27 acetylation (H3K27ac), corresponding to enhanced chromatin accessibility, which enables the expression of additional genes associated with metastatic aggres-

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Table 1. Current approved and late-stage clinical trials for ERα degraders

Name of drug	Approval date/ clinical trial stage	Current indications (in ER$^+$ BC)	MOA	*ESR1* mutant disease activity	BBB penetration
Fulvestrant (Faslodex)	2002	Late-stage ER$^+$/HER2$^-$ endocrine therapy for postmenopausal women (40), frequently combined with CDK4/6i (164).	SERD	Decreased efficacy in *ESR1*-mutant patients (50).	No
Elacestrant (Orserdu)	2023	Late-stage ER$^+$/HER2$^-$ endocrine therapy for postmenopausal patients with detectable *ESR1* mutation (53, 155).	SERD	Prolonged survival in patients and in patients with *ESR1* mutation (58, 61).	Yes (64)
Imlunestrant (Inluriyo)	2025	Late-stage endocrine monotherapy for postmenopausal patients with detectable *ESR1* mutation (66).	SERD	Increased activity in *ESR1* mutant compared with fulvestrant (67, 69).	Yes (69)
Giredestrant	Phase III (lidERA, evERA, pionERA, heredERA)	lidERA: first-line (NCT04961996) (165). evERA: locally advanced or metastatic breast cancer combined with mTOR inhibitor (NCT05306340). pionERA: combined with CDK4/6i versus fulvestrant with CDK4/6i for advanced endocrine therapy–resistant BC (NCT06065748). heredERA: ER$^+$/HER2$^+$ BC combined with HER2 blockade versus HER2 blockade alone (NCT05296798) (166).	SERD	Preclinical models show activity against *ESR1* mutants (71). No significant benefit in patients with *ESR1* mutations in clinical trials (74).	No evidence to date
Camizestrant	Phase III (CAMBRIA-1 and CAMBRIA-2)	Comparing camizestrant versus standard endocrine therapy in ER$^+$ patients who have already received at least 2 years of endocrine therapy (CAMBRIA-1) or 7 years of upfront camizestrant versus standard endocrine therapy (CAMBRIA-2) (NCT05774951, NCT05952557) (81).	SERD	Significant benefit over fulvestrant in *ESR1*-mutant patients (77, 80).	Limited evidence
Vepdegestrant (Veppanu)	2026	ER$^+$/HER2$^-$ advanced mutant *ESR1* BC (83).	PROTAC	Specific efficacy in the population with *ESR1* mutations (83).	Likely no, interacts with p-glycoprotein at the BBB (86, 167).
Palazestrant	Phase III (OPERA-02)	ER$^+$/HER2$^-$ advanced BC in combination with CDK4/6i versus AI in combination with CDK4/6i (88).	CERAN/ SERD	Slightly improved survival in *ESR1*-mutant population in phase I/II study (89).	Yes (90)

siveness (29). *ESR1* mutants upregulate genes associated with cell-cell adhesion and downregulate genes related to the extracellular matrix, which cumulatively enhances tumor extravasation, cell clumping in circulation, and invasion and survival in distant organs (30).

The most prevalent *ESR1* mutations, Y537S and D538G, also impact ET efficacy in BC cells. Both mutations decrease the ligand-binding affinity of ERα's ligand-binding domain (LBD), requiring higher doses of ETs to achieve antiproliferative activities (27, 28, 31, 32). In the case of tamoxifen, maximal dosing does not fully suppress Y537S ERα transactivation within BC cells (27, 28). Reduced tamoxifen efficacy stems from mutational influences on the capacity of ETs to exert the allosteric structural rearrangements required to exert their antagonistic activities (27, 31, 33). Collectively, *ESR1* mutations confer ET resistance by engaging canonical and neomorphic biologic mechanisms of action, while also reducing the target engagement capacity of clinically approved first-line ETs.

Selective estrogen receptor degraders/downregulators (SERDs) were developed as second-line therapies for metastatic ER$^+$ BC. Classically, SERDs induce the antagonistic conformation of ERα to oppose estrogenic gene expression programs before destabilizing the receptor, leading to ubiquitination and proteasomal degradation (31, 34–37). In advanced disease, the SERD fulvestrant acts as a complete antiestrogen throughout the body (38). While fulvestrant demonstrates superior efficacy compared with tamoxifen in models harboring *ESR1* mutations in vitro, its utility is limited by its poor solubility (39–41). Next-generation SERDs have been developed to target mutant ERα across all metastatic sites with improved pharmacologic properties, especially solubility and oral availability. The past few years have brought tremendous advances in the development of next-generation SERDs and, with them, an improved understanding of how to target ERα in complex tumor microenvironments. Here, we summarize the current clinical landscape of SERDs for the treatment of BC (Table 1) and highlight recent advances in our understanding of how they reshape the tumor microenvironment to enhance anticancer immunity.

Current FDA-approved SERDs for ER$^+$ BC

Fulvestrant. Fulvestrant was the first SERD to receive FDA approval and is a complete ERα antagonist throughout the body, administered via an intramuscular injection owing to its poor solubility and lack of oral bioavailability (39, 40). Fulvestrant has been shown to have the same efficacy as anastrozole (a common AI) in advanced ER$^+$ BCs (42). Initially, AIs were used as second-line therapy after tamoxifen treatment for recurrent disease in postmenopausal patients with ER$^+$ BC. However, in the early 2000s, third-generation AIs (anastrozole, letrozole, and exemestane) were approved for first-line ET, demonstrating improved disease-free survival and reduced recurrence compared with tamoxifen in this patient population (43). Tamoxifen remains the SOC ET in premenopausal patients owing to its ability to prevent recurrence, with a disease-free 8-year survival rate of 78.9%–83.2% (44). While the phase III FALCON Trial reported a progression-free survival (PFS) benefit in ET-naive postmenopausal women receiving fulvestrant compared with anastrozole, there was no significant difference in overall survival (OS) (45). These data support the use of fulvestrant as a second- or later-line ET if other lines fail.

Fulvestrant represents a major innovation in the use of ERα-targeted ETs across disease stages. Although response rates between fulvestrant and tamoxifen are similar in patients with previously untreated advanced ER^+ disease, with objective response rates (ORRs) of 33.2% and 31.1%, respectively, fulvestrant shows increased efficacy in in vitro models and in patients with tamoxifen resistance (46–48). However, fulvestrant also has common life-impacting side effects, including injection site reactions, gastrointestinal adverse events, and joint pain (42, 49). In addition, BC cells harboring the most common *ESR1* mutations require elevated doses of fulvestrant to achieve complete transcriptional antagonism, exposing its poor solubility as a major liability in this setting (28, 32). Indeed, in metastatic clinical cohorts, patients with the Y537S *ESR1* mutation had a PFS of only 1.8 months on fulvestrant versus 3.5 months in patients with other detected *ESR1* mutations, and the median PFS with fulvestrant monotherapy, regardless of mutational status, is 3.18 months (50, 51). Responses are also nondurable, with a median OS of 26.4 months for the 500 mg dose reported in the CONFIRM trial (52). While fulvestrant remains an essential second-line ET, these studies showed the need for continued SERD development.

Elacestrant. Elacestrant (Orserdu) is the first orally available SERD to be FDA approved for $ER^+/HER2^-$ advanced BC (53). Elacestrant is a chemically unconventional SERD, as its side arm attaches to a distinct ring, allowing a unique interaction with helix 8 of ERα, whereas SERD side arms are usually attached to the steroidal ring (33). Elacestrant exposes a unique protein-binding surface when bound to ERα, affecting the repertoire of coregulators that drive ligand-specific gene expression programs, thus leading to a neomorphic transcriptional program (33, 54). Using a library of other unconventional SERD scaffolds, the Nettles and Katzenellenbogen laboratories showed that targeting unique combinations of structural features allows ERα to bind unique transcriptional coregulator proteins (55). In addition, our group showed that perturbing other ERα structural motifs allows it to engage new and therapeutically relevant transcriptional programs in hormone-sensitive and -resistant BC cells (33, 56). Accordingly, an x-ray cocrystal structure of elacestrant with the ERα LBD shows an unconventional ligand-binding pose that interacts with some structural features unique to the molecule (57), allowing it to maintain antiproliferative activities in models of CDK4/6 inhibitor–resistant (CDK4/6i-resistant) BCs (58).

The therapeutic potential of elacestrant was first described in mammary xenograft murine tumor studies in 2015 (54). These studies ultimately led to the EMERALD phase III clinical trial, in which elacestrant demonstrated a significant increase in 6-month PFS compared with SOC ET (34.3 versus 20.4 months, respectively) and specifically showed a benefit in patients who harbored a detectable *ESR1* mutation (40.8 versus 19.1 months, respectively) (59, 60). This clinical trial required patients to have prior exposure to a CDK4/6i and at least one chemotherapy (60). In *ESR1* D538G- and Y537S/N-mutated tumors that received prior ET and CDK4/6i for at least 12 months, the median PFS for elacestrant was 8.6 months versus 1.9 months for SOC (AI or fulvestrant) (61). Mechanistically, elacestrant has notable antitumoral effects in murine mammary xenograft and subcutaneous patient-derived xenograft (PDX) tumor models and downregulates ERα levels through receptor degradation; however, it does show weak endometrial stimulation in uterine wet weight studies, suggesting that it is not a complete ERα antagonist (54, 62). Maintenance of at least some tissue-specific ERα pharmacology may have bone-sparing effects (63). Furthermore, elacestrant crosses the blood-brain barrier (BBB) in healthy postmenopausal women (64). The ability of a systemic SERD to cross the BBB is promising in combating brain metastases, but more studies are needed to understand how these molecules affect ERs throughout this complex environment (65).

Together, these studies suggest that elacestrant can engage neomorphic anticancer transcriptional activities by forming new coregulator complexes, raising the exciting possibility of an expanded ERα pharmacology that could improve treatment options for specific, molecularly defined patient populations, including those with detectable *ESR1* mutations.

Imlunestrant. Imlunestrant (Inluriyo) recently became the second orally available SERD to be FDA approved. It is specifically indicated for patients with advanced $ER^+/HER2^-$ BC with a detectable *ESR1* mutation (66). Molecular docking shows imlunestrant binds with high affinity to the Y537S ERα LBD, but unlike other SERDs, there is no predicted binding to D351 of ERα, and it is predicted to perturb the loop preceding helix 12 rather than the helix itself (67). Imlunestrant harbors a steroidal core, similar to fulvestrant but antagonizes ERα more efficiently. Imlunestrant is a pure antagonist at all concentrations, causing ER degradation in BC cells (67).

In the EMBER-3 phase III study, imlunestrant was administered with or without a CDK4/6i in pre- and postmenopausal patients who had progressed after starting an AI and had $ER^+/HER2^-$ disease (68). As seen with elacestrant, the greatest benefit was in patients with detectable *ESR1* mutations, with a median PFS of 5.5 months compared with 3.8 months with SOC (68). Data on imlunestrant's benefits in patients with specific *ESR1* mutants was not specified. Notably, the EMBER-3 phase III study did not demonstrate a benefit for imlunestrant over SOC in the overall patient population, with a median 6-month PFS of 5.6 months versus 5.5 months with SOC (68). Imlunestrant can cross the BBB and markedly increases survival in a preclinical model of immunocompromised mice with ER^+ intracranial tumors (69). It does not show tissue-specific partial agonist activities in immunocompromised PDX models (67). To this end, the characterization of bone-sparing activities of imlunestrant thus far is limited.

SERDs in clinical trials for late-stage disease

Giredestrant. Several more SERDs are nearing FDA approval. Among these, giredestrant is a nonsteroidal oral SERD currently in phase III clinical trials (lidERA trial, NCT04961996). Preclinical in vitro studies showed that giredestrant has a potent antiproliferative IC_{50} and improved binding affinity to ERα compared with fulvestrant (70). In murine uterine wet weight studies, giredestrant was confirmed as an ERα degrader in the endometrium (70, 71). Furthermore, giredestrant reduced ERα levels in mouse mammary tissue in transgenic murine models with inducible WT or mutant *ESR1*, whereas fulvestrant exhibited varying results (71). Additionally, in an in vitro functional luciferase assay that quantified the interaction between ERα and steroid receptor coactivator-3 (SRC-3), giredestrant showed superior potency toward WT ERα, while retaining activity in the presence of the *ESR1* mutant compared with other clinically relevant molecules (56).

Important clinical trials are also underway to test whether giredestrant, and therefore other next-generation SERDs, could be used at earlier disease stages. These trials are anticipated to be completed in 2026 (72). In the early-stage trials, giredestrant is being compared with the physician's choice ET for 5 years in the adjuvant setting (72). The phase II clinical trial coopERA compared giredestrant versus AI (anastrozole) in ET-naive, postmenopausal women for 2 weeks followed by 16 weeks of the same therapy with addition of a CDK4/6i (73). The Ki67 (proliferative) index of the tumor was reduced in the giredestrant versus the anastrozole group, and both groups had an increased benefit with the addition of CDK4/6i, with comparable adverse events (73). In the phase II aceIERA clinical trial, giredestrant was compared with SOC (fulvestrant or AI) in patients with advanced ER^+ BC who had progressed after 1–2 lines of therapy, including patients treated with fulvestrant (74). There was no significant increase in PFS from this clinical trial in patients receiving giredestrant versus SOC (74). Furthermore, there was no statistical benefit in patients with detectable *ESR1* mutations; however, it should be noted that this cohort was smaller than that of patients with WT *ESR1* (90 patients versus 142, respectively) (74). In the phase III persevERA study in patients with locally advanced or metastatic $ER^+/HER2^-$ BC, giredestrant with CDK4/6i was compared with AI with CDK4/6i as a first-line therapy, but primary statistical endpoints were not met (75). However, in the lidERA study, giredestrant in the adjuvant setting significantly improved patient outcomes compared with SOC (tamoxifen or AI), although the data are still immature (76). This shows that giredestrant has promise as the first SERD that could be used consistently in the first-line setting.

Camizestrant. Camizestrant is also under clinical investigation for advanced $ER^+/HER2^-$ BC with detectable *ESR1* mutations (77). In mechanistic studies, camizestrant can block ER transcriptional pathways in fulvestrant-insensitive immunocompromised PDX murine tumor models, showing retained ER antagonism (78). Structurally, camizestrant disrupts helix 12 stabilization like other SERDs; however, it retains activity in *ESR1*-mutant PDX murine models (78, 79). In the phase II SERENA-2 study, three doses of camizestrant were compared with fulvestrant in postmenopausal patients with metastatic or recurrent $ER^+/HER2^-$ BC who have progressed on no more than one ET in the advanced setting (80). A significant increase in median PFS was observed with the two lower doses of monotherapy (75 mg and 150 mg camizestrant) compared with fulvestrant (7.2 months, 7.7 months, and 3.7 months, respectively) in patients with WT and *ESR1* mutant BC, with superior efficacy over fulvestrant in patients with ESR1 mutations (median PFS, 6.3, 9.2, and 2.2 months, respectively) (80). In the phase III (SERENA-6) clinical trial, treatment with camizestrant is initiated upon detectable *ESR1* mutation (measured from circulating tumor DNA [ctDNA]) after receiving at least 6 months of AI and CDK4/6i, and the CDK4/6i is maintained during treatment (77). So far, median PFS has been significantly higher in the camizestrant arm than the SOC AI treatment arm (16.0 versus 9.2 months) (77).

In the CAMBRIA-1 and CAMBRIA-2 phase III clinical trials, camizestrant is compared with AI or tamoxifen therapy in patients with $ER^+/HER2^-$ early BC, as a first-line ET (81). CAMBRIA-1 compares 5 years of camizestrant versus standard ET for patients who have already received 2–5 years of standard adjuvant ET and have a high risk of recurrence, and prior CDK4/6i use is allowed (82). CAMBRIA-2 compares camizestrant as a first-line adjuvant ET versus standard ET for 7 years with CDK4/6i treatment for the first 2 years in both treatment arms (81). Preliminary findings for these studies will be completed in 2027.

Vepdegestrant. Vepdegestrant is a proteolysis-targeting chimera (PROTAC) rather than a traditional SERD and was recently FDA approved after its phase III trial, the VERITAC-2 study, in patients with advanced $ER^+/HER2^-$ BC harboring *ESR1* mutations that have received prior CDK4/6i and ET (83). Like SERDs, the greatest benefit of the PROTAC was seen in the PFS of the patient population harboring *ESR1* mutations (median PFS of 5.0 months versus 2.1 months with fulvestrant, $n = 270$), while no significant change was observed between the general population on vepdegestrant versus fulvestrant (3.8 months versus 3.6 months median PFS, respectively) (83).

PROTACs are heterobifunctional molecules that work by conjugating the protein of interest, in this case ERα, with a ubiquitin-ligase (E3) ligand, which directs ERα for degradation by the ubiquitin-proteasome system (84). Preclinical studies showed that vepdegestrant achieved a maximal degradation of ERα of greater than 90% in most WT *ESR1* ER^+ cell lines (85). Further characterization showed a dose-dependent, antiproliferative effect with vepdegestrant in vitro in WT and mutant *ESR1* cell models, with more potent antiproliferative effects in the hormone-dependent WT models (85). In *ESR1*-mutant PDX murine models, treatment with vepdegestrant induced tumor regression, whereas fulvestrant only slowed tumor growth relative to vehicle (85). Furthermore, synergy was observed with the treatment of vepdegestrant in orthotopic xenograft murine models with the addition of CDK4/6i, alpelisib (PI3-kinase inhibitor), or evorlimus (mTOR inhibitor) (85). One consideration with vepdegestrant is liver metabolism, which may affect combination therapies due to drug-drug interactions (86). These preclinical and clinical trial results for the compound show that vepdegestrant is efficacious in advanced *ESR1*-mutant BC (similar to SERDs) (87).

Palazestrant. Palazestrant (OP-1250) is a SERD currently in phase III clinical trials in combination with a CDK4/6i as a first-line therapy for advanced ER^+ BC (88). In the phase III study, which began recruitment in late 2025, palazestrant and CDK4/6i will be compared with an AI with a CDK4/6i (88). In the phase I/II study, the median PFS was 4.8 months overall and 5.6 months for patients with *ESR1* mutants with the 120 mg/d dose of palazestrant (89). Palazestrant is a complete estrogen receptor antagonist (CERAN), with brain penetrance and superior kinetics to fulvestrant in cell-line and PDX mammary and intracranial models (90). Furthermore, in vivo PDX studies show a greater benefit of palazestrant in combination with CDK4/6i (90). Palazestrant is characterized as a CERAN because of its ability to completely antagonize the AF-1 and AF-2 domains of ERα (34).

Differential gene regulation and degradation patterns by SERDs. Although all SERDs antagonize ERα, transcriptional responses arising from induced conformational changes to ERα are also critical for SERD efficacy. As such, in vitro studies show that, when fulvestrant binds to ERα, it induces conformational changes that blunt E2-driven transcription without requiring proteasomal degradation (37). Mechanistically, fulvestrant decreases the nuclear mobility of

ERα, increasing ERα replacement (91). Unlike fulvestrant, which is a pure ERα degrader, elacestrant has partial agonistic effects on tumor growth in mammary PDX murine studies at low concentrations (54, 92). At higher concentrations in vitro, elacestrant downregulates the *ESR1* target genes *TFF1*, *PGR*, and *FHL1*, but at low concentrations in MCF7 mammary xenografts, it induces genes associated with tamoxifen resistance, such as *AGR2* and *KRT13* (54). In contrast, imlunestrant shows increased ERα degradation at low levels compared with elacestrant, and superior progesterone receptor (PR) inhibition compared with elacestrant in vitro (69). Interestingly, transcriptomic studies with Y537S *ESR1* PDX murine tumors show that imlunestrant more significantly downregulates estrogen response late genes, Myc targets, and cell cycle pathways and uniquely upregulates NF-κB and IFN-γ responses compared with fulvestrant (67). These data show that SERDs can engage distinct therapeutic mechanisms of action to achieve therapeutic efficacy in the *ESR1* mutant setting.

Genome-wide analyses further distinguish distinct SERD transcriptional effects. MCF7 cells treated with giredestrant show differential expression of over 2,400 genes, reduced accessibility of transcription start sites of E2 genes and H3K27ac, and increased expression of tumor suppressors, furthering the concept that ERα immobilization may be as important as degradation in antitumor control (93). Similarly, camizestrant specifically downregulates ER-early and -late gene signatures more robustly than fulvestrant, leading to utility in fulvestrant-resistant PDX murine models (78). The superior antagonism of ERα is the major contributor to camizestrant's efficacy in the ESR1-mutant and fulvestrant-resistant settings (78).Thus, in addition to ERα antagonism, specific transcriptome changes are associated with the efficacy of SERDs. Together, these studies suggest that through engaging different therapeutic mechanisms of action, precision oncology approaches could improve efficacy by matching the patient with the SERD best suited to act in their unique molecular landscape. However, more work is needed to understand the SERD-specific ERα complexes that drive therapeutic response.

SERDs and the tumor immune microenvironment

The immune landscape of ER⁺ tumors. Immune cells are critical mediators of both pathogenic and antitumor responses. Immunotherapies, which aim to reinvigorate antitumor immunity, have revolutionized care across multiple cancer types (94). These immunotherapies predominantly target programmed death-ligand 1 (PD-L1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), which suppress/exhaust immune cells (95, 96). Therapeutic anti–PD-L1 antibodies bind to the suppressive ligand on tumor cells and allow improved recognition of tumor cells by cytotoxic T cells (97, 98).

Immune checkpoint blockade (ICB) has reduced benefit in patients with ER⁺ BC compared with patients with TNBC, where anti–PD-L1 therapy has shown increased pathological complete response (pCR) and event-free survival with neoadjuvant chemotherapy (99–101). In the phase Ib KEYNOTE-028 trial, the ORR of PD-L1⁺ patients with ER⁺/HER2⁻ advanced BC treated with pembrolizumab (anti–PD-L1 therapy) was 12%, and no pCR effect was reported (102). However, in patients with TNBC in the KEYNOTE-012 study, the ORR was 18.5% (103). Furthermore, PD-L1 positivity in patients with TNBC is significantly higher than in patients with ER⁺ BC, at 58.6% versus 19.4%, respectively, illustrating the immune-cold landscape of ER⁺ tumors (102, 103).

T cell–directed therapies face many challenges in ER⁺ BC thanks to their low mutational rate, reduced neoantigen expression, and the immune-suppressive actions of ERα (104–107). Moreover, PD-L1 expression is downregulated by ERα in tumor cells (108, 109), whereas PD-L1 expression is higher in ER⁻ tumors (110, 111), and tumors with lower ER positivity (1%–50% positivity) show more robust responses to ICB (112). In transgenic murine *ESR1*-mutant tumors, immune pathway activation and cytokine expression are decreased, emphasizing the aggressive, immunosuppressive nature of these tumors (113). In contrast, in vitro characterization and clinical studies show increased immune pathway activation in *ESR1*-mutant tumors, revealing model-dependent differences and suggesting a potential therapeutic vulnerability (114, 115). Together, these studies suggest that increased *ESR1* expression correlates with reduced sensitivity to ICB, but distinct *ESR1*-mutant immune signatures represent a promising therapeutic opportunity.

The role of estrogen signaling in the ER⁺ tumor immune microenvironment. In the ER⁺ BC tumor immune microenvironment (TIME), E2 exerts direct and indirect immunosuppressive influences (Figure 1). A preclinical study with transgenic mice and ex vivo coculture showed that E2-stimulated ERα in the myeloid compartment prevented the proliferation of CD4⁺ and CD8⁺ T cells (116). Furthermore, E2 promotes proliferation of immunosuppressive Tregs (117, 118). Early studies investigating B cells suggest that high B cell activity in patients with ER⁺ BC correlates with a better prognosis, and genes upregulated by E2 signaling in B cells decrease their receptor signaling (119, 120). Furthermore, E2 promotes IgG and IgM production in healthy human PBMCs, and ERα activation with E2 triggers autoimmunity in B cells in transgenic murine models (121, 122). The role of E2 in autoimmunity is under investigation.

E2 signaling is also immunosuppressive in innate immune compartments. ERα is expressed in NK cells and monocytes, though some cite lower levels of ERα in CD8⁺ T cells and monocytes compared with CD4⁺ T cells (123). Myeloid-derived suppressor cells (MDSCs) are innate immune cells that inhibit lymphocyte anticancer function in the immune microenvironment (124). E2 signaling increases the abundance of MDSCs via activation/phosphorylation of STAT3 in BC patient–derived bone marrow samples (125). In a syngeneic murine melanoma model, E2 signaling through ERα in myeloid cells fosters an immunosuppressive TIME that confers resistance to ICB (116). Eosinophils, which are innate granulocytes that interact with T cells, decrease in abundance upon E2 treatment and correspond with decreased expression of CCL11, CCL24, and CCL5, and ERα depletion within eosinophils decreases tumor growth in syngeneic mammary tumors and transgenic murine models (126, 127).

NK cells are innate immune lymphocytes that are critical for host defense and anticancer activities (128–130). Engagement of NK cell receptors, including NKG2D, NKp46, and CD16, can trigger direct cell killing (131, 132). Upon recognition, NK cells secrete cytokines, notably perforin and granzyme B, to kill cancer cells (129, 133). In BC, lower amounts of cytotoxic immune activity, including lower infiltrating NK effector activity and gene signatures, are observed in larger tumors with nodal involvement

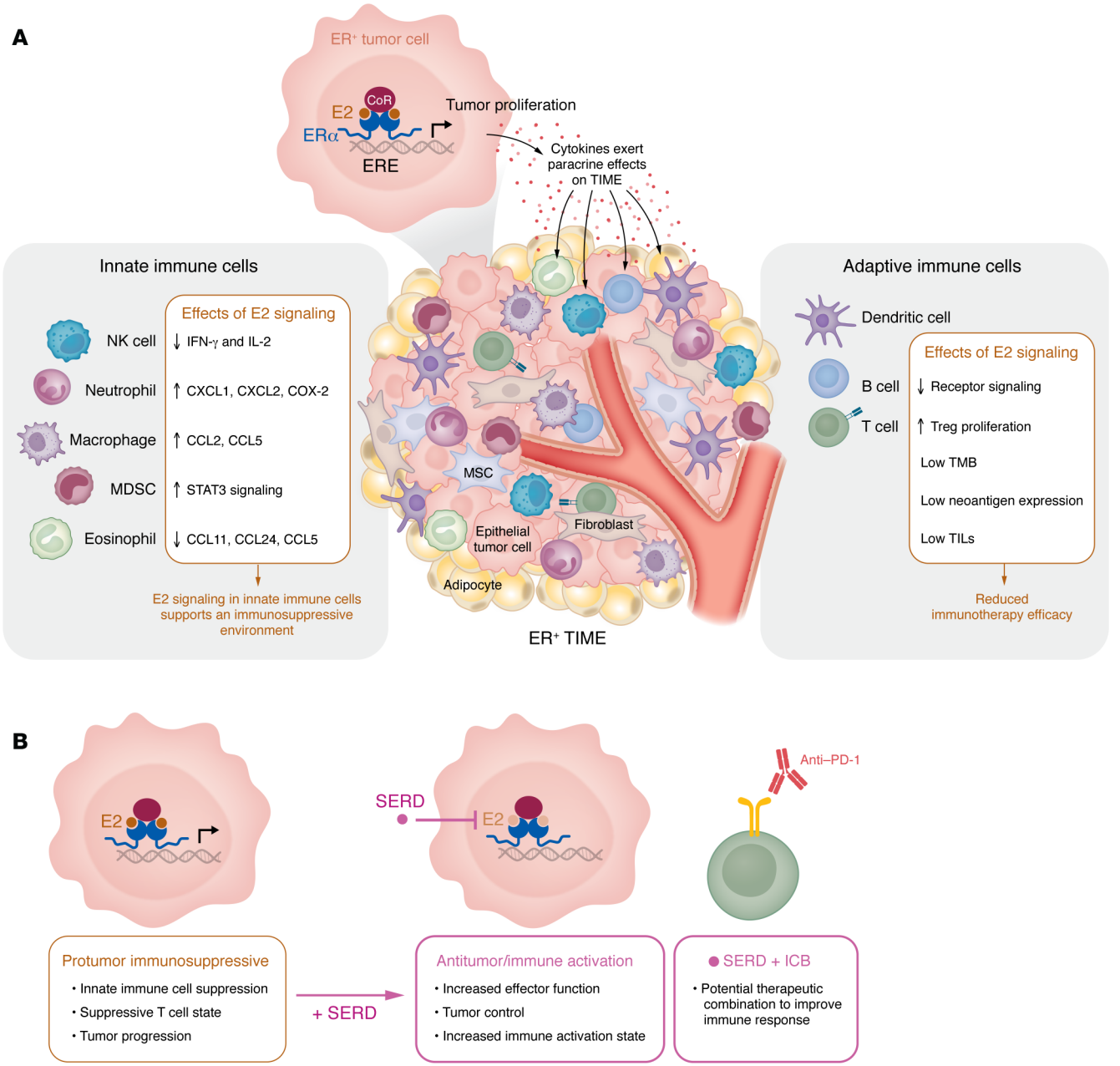


Figure 1. ERα signaling contributes to the immunosuppressive phenotype in ER⁺ breast cancer. ERα signaling contributes to the immunosuppressive phenotype in ER⁺ breast cancer. (**A**) In addition to the direct effects of E2 on tumor cell proliferation, the hormone also acts on the TIME. In innate immune cells (left), ERα signaling downregulates IFN-γ signaling and inflammatory chemokines. In the adaptive immune compartment (right), E2 signaling promotes Treg proliferation and decreases B cell receptor signaling. These effects contribute to the reduced efficacy of immunotherapy in ER⁺ BC. (**B**) SERDs can act on both tumor cells and the TIME. In addition to blocking the proliferative effect of E2 signaling in tumor cells, SERDs may make the TIME more immunogenic, increasing the efficacy of immunotherapy. ERE, estrogen response element; MSC, mesenchymal stem cell; TMB, tumor mutational burden; TIL, tumor-infiltrating lymphocyte.

(134). In ER⁺/HER2⁻ BCs, NK cells are underactive, and, while higher infiltration is correlated with improved OS, low functionality and infiltration is noted in ER⁺/PR⁺ subtypes (135–137). The role of estrogen has been under investigation in NK cell biology. In NK cells from the uterus of human first-trimester decidua, treatment with E2 increased migration and proangiogenic vascular remodeling, which was blocked by fulvestrant administration (138). Estrogen suppresses NK cell–mediated cytotoxicity in vitro, and, perhaps accordingly, NK cells have lower activation levels in patients with ER⁺ BC compared with TNBC (135, 139). Specifically, E2 suppresses IFN-γ and IL-2 expression in murine NK cells and human PBMCs (140, 141). IFN-γ is critical for a robust NK cell–mediated antitumor response (142, 143).

Neutrophils and macrophages are phagocytic innate immune cells that have both tumor-promoting and killing activities. In murine ER⁺ xenograft and syngeneic BC models, E2 increases the

abundance of tumor-associated neutrophil recruitment, which is opposed by fulvestrant (144). The influx of neutrophils is caused by an E2-dependent secretion of TGFβ1, an immunosuppressive cytokine, from the cancer cells, which attracts integrin lymphocyte function-associated antigen-1–positive (LFA-1$^+$) neutrophils to the TIME (144). In immunocompetent postpartum mammary involution murine models supplemented with E2, neutrophils show increased expression of COX-2 and protumoral cytokines, including CXCL1, CXCL2, and S100A8 (145). E2 also increases recruitment and activation of protumor macrophages through CCL2 and CCL5 signaling in syngeneic murine mammary models, and these macrophages may be associated with enhanced cancer cell dissemination in a zebrafish model (146). In BC clinical datasets, inflammatory M1 polarization is associated with more aggressive, immunogenic cancer (147), and in preclinical melanoma murine models, E2 treatment promotes immunosuppressive M2 macrophage polarization (116). However, ER$^+$ BC cells can induce inflammatory responses when cocultured with monocytes in full media (148). This discordance shows the context-dependent nature of macrophage polarization, suggesting that a spectrum of inflammatory and suppressive macrophage programs may exist in the ER$^+$ TIME, which may be delineated as further immune-inclusive ER$^+$ models are developed.

The effect of SERDs on the TIME. SERDs reinvigorate antitumor immunity in adaptive and innate immune compartments. Since fulvestrant is the longstanding SOC, most studies of the BC TIME have investigated this drug. In an ER$^+$ syngeneic fulvestrant-resistant murine model, the combination of fulvestrant with ICB showed greater tumor regression than the single-agent alone, indicating that SERDs can affect the TIME to improve ICB efficacy (149). In an ER$^-$ murine BC model, SERDs can act on ERα in MDSCs, blocking their accumulation and permitting influx of cytotoxic T cells (125). Furthermore, in immunocompetent murine models of ER$^-$ BC, ICB in combination with fulvestrant or the SERM lasofoxifene increased antitumor activity, further suggesting that targeting ERα in nontumor cells enhances immunotherapy efficacy (126). Moreover, emerging sequencing data from the SOLTI-ELIPSE trial (NCT04797728) investigating adjuvant elacestrant treatment in early BC found that elacestrant induced genes related to immune activation, including *CD8A*, *IGJ*, *CD4*, and *GZMB* (150). This, combined with the finding that imlunestrant increases IFN-γ response, shows that antagonizing ERα in the TIME with SERDs improves the immunogenicity of ER$^+$ tumors to improve ICB efficacy (67, 125, 149).

In vitro, pretreatment of BC cells with tamoxifen or fulvestrant increases NK cell–mediated killing of both ER$^+$ and ER$^-$ cell lines, an effect involving increased GPR30 signaling in the tumor cells (151). Similar results have been shown in cocultures of NK cells and lung cancer cells (152). This suggests that modulation of ERα in NK cells improves their cancer-killing capacities, but further studies are needed to define the complexity of ERα signaling in NK cells (151, 152).

In syngeneic murine models of melanoma, M2 polarization can be reversed by fulvestrant treatment (116). In addition, fulvestrant decreases the number of neutrophils in mammary tissue and the invasive margin of ER$^+$ tumors compared with tamoxifen in normal mice as well as syngeneic and xenograft BC murine models, corresponding with an improved antitumor response (153, 154). Reduced macrophage infiltration in tumors was also observed with fulvestrant treatment (153). This indicates that antagonizing ER in these cells increases antitumor immunity by decreasing the prevalence of immunosuppressive cells in ER$^+$ TIME.

Discussion

While SERDs have historically been used as second-line ERα-targeted ETs, current clinical trials with giredestrant and camizestrant are testing whether SERDs can be moved to earlier disease stages. Next-generation SERDs have shown improved efficacy in the *ESR1* mutant setting and are orally available, thereby overcoming persistent limitations of fulvestrant (60). In 2023, elacestrant marked a major milestone, becoming the first orally available SERD that improved PFS in patients with metastatic BC, while specifically showing utility in patients harboring an *ESR1* mutation (54, 60, 155). Although a marked breakthrough, 6-month PFS is only extended by 13.9 months in the overall population (60). This highlights the aggressive nature of metastatic ER$^+$ BC and the need for therapies that antagonize tumor cells and reengage the immune system to fight the disease.

Excitingly, some SERDs are brain penetrant, such as imlunestrant and elacestrant (64, 69). The role of E2 in ER$^+$ brain metastasis is an active area of investigation. While studies in immunocompromised mice with intracranial tumors show decreased tumor burden when treated with a brain-penetrant SERD, and cocultures with TNBC cells and astrocytes show that E2 promotes brain metastatic colonization, there is also evidence that agonists for ERβ may increase BBB integrity (69, 156, 157). Therefore, further understanding of the complex relationship between E2, ERα, ERβ, and immune cells in the brain niche is needed. It should be noted as well that the SERM lasofoxifene is currently in phase III clinical trials in combination with a CDK4/6i for advanced ER$^+$ *ESR1*-mutant BC (158). This is a competing strategy to SERDs in advanced ER$^+$ BC, because lasofoxifene reinforces the inactive conformation of the Y537S ERα, leading to inhibition of xenograft tumor growth and metastasis in murine models (159, 160).

The roles of distinct immune cell compartments in ER$^+$ BC remain difficult to resolve, as there is a paucity of ER$^+$ syngeneic models. Therefore, immune-oncology studies typically use ER$^-$ murine models or coculture systems. Furthermore, many preclinical ER$^+$ models primarily focus on mammary tumors rather than metastatic progression and tumor cell colonization. Recently, a study utilizing matched patient ER$^+$ biopsies from metastatic sites revealed trends in tumor-associated macrophages after treatment with ET$^+$CDK4/6i that correlate with improved survival (161). Studies such as this that utilize next-generation sequencing techniques, such as single-cell RNA sequencing, are critical to delineate the TIME in advanced ER$^+$ disease. Further research into the impact of SERDs on different cell types will enhance our understanding of their utility in patients and reveal new targets to combat the disease, and the emergence of next-generation SERDs provides more options to combat ER$^+$ BC.

Future therapeutic implications, directions, and outstanding questions. Emerging preclinical evidence suggests that antagonizing the immune cell ER with SERDs enhances the antitumor response. Excitingly, studies in murine models of metastatic TNBC and colorectal cancer show that combining ICB with fulvestrant increases tumor-infiltrating lymphocytes and decreases M2 macrophages in the TIME (125, 162). In a rat ER$^+$ BC model, fulvestrant alone promoted tumor regres-

sion, and in combination with ICB it reduced the emergence of more tumors (163). This illustrates the potential of combining ER degradation in the TIME with ICB to limit cancer spread.

As noted above, most of the experimental models investigating the role of SERDs on the TIME utilize fulvestrant, leaving a sizeable gap in our understanding of how different SERDs impact the TIME and different immune populations. However, state-of-the-art technologies including single-cell and spatial transcriptomics and imaging mass cytometry promise to improve our understanding of SERD influences on the TIME. As clinically relevant ER^+ models continue to develop, beneficial combinations of SERDs with immunotherapies that have been revolutionary for other cancers may be illuminated for better disease management. This remains an exciting future direction in personalized medicine for ER^+ BC.

Conflict of interest

The authors have declared that no conflict of interest exists.

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