

Next-generation selective estrogen receptor degraders and other novel endocrine therapies for management of metastatic hormone receptor-positive breast cancer: current and emerging role

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Ther Adv Med Oncol

2022, Vol. 14: 1–25

DOI: 10.1177/
17588359221113694

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Abstract: Endocrine therapy (ET) is a pivotal strategy to manage early- and advanced-stage estrogen receptor-positive (ER+) breast cancer. In patients with metastatic breast cancer (MBC), progression of disease inevitably occurs due to the presence of acquired or intrinsic resistance mechanisms. ET resistance can be driven by ligand-independent, ER-mediated signaling that promotes tumor proliferation in the absence of hormone, or ER-independent oncogenic signaling that circumvents endocrine regulated transcription pathways. Estrogen receptor 1 (*ESR1*) mutations induce constitutive ER activity and upregulate ER-dependent gene transcription, provoking resistance to estrogen deprivation and aromatase inhibitor therapy. The role *ESR1* mutations play in regulating response to other therapies, such as the selective estrogen receptor degrader (SERD) fulvestrant and the available CDK4/6 inhibitors, is less clear. Novel oral SERDs and other next-generation ETs are in clinical development for ER+ breast cancer as single agents and in combination with established targeted therapies. Recent results from the phase III EMERALD trial demonstrated improved outcomes with the oral SERD elacestrant compared to standard anti-estrogen therapies in ER+ MBC after prior progression on ET, and other agents have shown promise in both the laboratory and early-phase clinical trials. In this review, we will discuss the emerging data related to oral SERDs and other novel ET in managing ER+ breast cancer. As clinical data continue to mature on these next-generation ETs, important questions will emerge related to the optimal sequence of therapeutic options and the genomic and molecular landscape of resistance to these agents.

Keywords: breast cancer, endocrine therapy, estrogen, metastatic disease, SERD

Received: 27 May 2022; revised manuscript accepted: 28 June 2022.

Introduction: current endocrine therapies and mechanisms of action

Endocrine therapy (ET) is effective in the treatment of estrogen receptor-positive (ER+) breast cancer.¹ These breast tumors express estrogen receptor alpha (ER α) and are dependent on estrogen-mediated growth signaling. Collectively, ET works by depleting circulating estrogens available to bind to the estrogen receptor (ER),

targeting the ER directly and antagonizing or degrading, or a combination of the two. Anti-estrogen drugs are part of the standard armamentarium against early- and advanced-stage ER+ tumors, which accounts for close to 80% of newly diagnosed breast cancers and includes ER+/human epidermal growth factor receptor 2 (HER2-) and ER+/HER2+ disease.² Approved classes of ET can be broadly categorized into

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aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), and selective estrogen receptor degraders (SERDs), and can be used with or without ovarian suppression.

The AIs (letrozole, anastrozole, and exemestane) block the conversion of androgens to estrogens in non-ovarian tissues and decrease systemic estrogen levels in post-menopausal women.³ In hormone responsive tumors, adjuvant AIs effectively reduce the risk of recurrence after curative treatment,¹ and they are standard first-line therapy in metastatic disease, often in combination with a CDK4/6 inhibitor (CDK4/6i).^{4,5} AIs are oral medications with a side effect profile that includes exacerbating menopausal symptoms, vaginal dryness, arthralgias, and accelerated bone loss.

SERMs competitively bind the ER and have tissue-dependent antagonist or agonist properties.⁶ They potentiate an anti-estrogenic effect in breast tumors and prevent hormone-dependent proliferation.⁶ SERM-bound ER binds estrogen response elements (EREs) and downregulates transcriptional activity in breast tumors by associating with co-repressors.⁷ Tamoxifen is the most commonly used SERM in the clinical management of ER+ breast cancer; however, the development of newer agents in this class has demonstrated its exciting potential and is discussed in greater detail below. SERMs are oral and can be advantageous over AIs in terms of less sexual side effects and arthralgias, but can cause undesired adverse events such as endometrial hyperplasia and malignancy from agonist activity and deep venous thrombosis possibly due to their anti-estrogen effect in platelets.⁸

SERDs, such as fulvestrant, both antagonize ER transcriptional activity and promote its degradation.⁹ These agents bind ER causing immobilization and instability of the ER-SERD complex and facilitate ER degradation by the ubiquitin-proteasome pathway.^{10,11} More recent research suggests that SERDs exert an effect by slowing ER nuclear translocation, increasing ER turnover as a consequence of limited intracellular mobility.¹² In addition, SERD-bound ER undergoes conformational changes that reduce transcription of ER-modulated genes.¹² Clinical challenges with fulvestrant can be related to pharmacologic limitations, including the absence of oral bioavailability,¹³ but this drug can have a favorable side effect profile in terms of arthralgias. SERDs are also advantageous in the clinical setting of estrogen receptor 1 (*ESR1*)

mutation-related ET resistance, discussed in detail below. Several novel oral SERDs are in development and have shown exciting clinical results which are discussed later in this review.¹⁴

In premenopausal women, ovarian suppression with a luteinizing hormone releasing hormone agonist reduces circulating estrogen. Ovarian suppression is generally recommended in pre- or perimenopausal women with distant sites of disease or high-risk early stage breast cancer, where its combination with standard adjuvant therapy improves disease-free survival.¹⁵ Ovarian suppression also enables the use of AIs in high-risk younger women by blocking intrinsic hormonal production when AIs are advantageous over tamoxifen for added risk reduction.¹⁶

In this review, we will discuss the scientific rationale, current data, and upcoming clinical trials related to oral SERDs and other novel ET in management of ER+ breast cancer.

Emerging insights related to endocrine resistance

In the metastatic setting, ER+ breast cancer often responds initially to endocrine-directed therapy; however, the development of resistance and disease progression inevitably occur.⁴ Response to ET may depend on the presence of intrinsic or acquired drivers of endocrine resistance; acquired resistance emerges following an initial response to therapy (generally six or more months on treatment), whereas intrinsically resistant breast cancers may not respond at all (generally less than 6 months on treatment).⁷ Potential drivers of resistance have been elucidated through decades of efforts in the laboratory and clinic, a topic that has been extensively reviewed elsewhere.^{17,18} Endocrine resistance can be broadly subdivided into two categories including ER-mediated and ER-independent signaling, shown in Figure 1. This review will briefly highlight the mechanisms that have impacted emerging therapeutic strategies.

The ER itself is a ligand-dependent transcription factor that is activated by the steroid hormone estrogen and promotes proliferation through genomic and non-genomic mechanisms.⁷ The ligand-bound ER complex associates with DNA at ERE, generally recruiting coactivators in the process, and serves to mediate transcription of ER-controlled genes.⁷ Among a myriad of functions, these genes induce production of growth

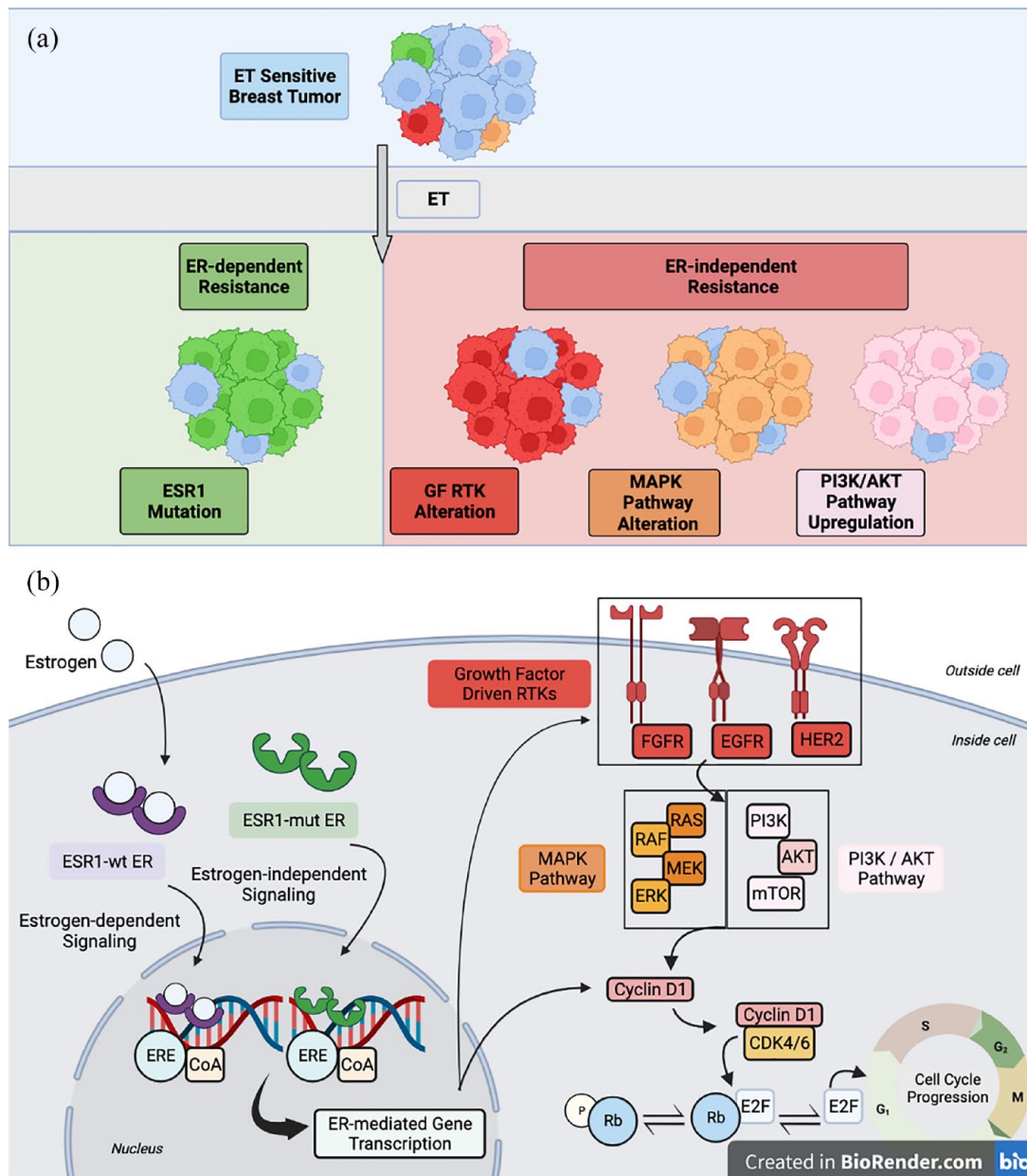


Figure 1. Drivers of ET resistance can be broadly subdivided into two categories of (i) ER-dependent and (ii) ER-independent mechanisms. (a) Ligand binding domain Estrogen Receptor 1 (*ESR1*) mutations mediate ligand-independent ER signaling and promote ET resistance via constitutive ER activity, upregulated coactivator binding, and stability against proteolytic degradation; ER remains a viable therapeutic target in these tumors. ER-independent resistance may be mediated by several mechanisms including mutations or amplifications in growth factor-driven RTKs (HER2, EGFR, and FGFR), alterations in MAPK pathway components including *KRAS*, *BRAF*, *MAP2K1*, and *NF1*, and upregulation in PI3K/AKT pathway signaling, though notably, *PIK3CA* and *AKT* mutations have not been shown to provoke resistance in the clinical setting. These alterations serve to upregulate mitogenic signaling and promote cell cycle progression and drug resistance. (b) At the cellular level, depicted are select pathways implicated in response and resistance to ET in *ESR1*-mut and *ESR1*-wt metastatic breast cancer. Note, while ER-dependent and ER-independent pathways are largely depicted separately for conceptualization, there is considerable intracellular crosstalk between these pathways. Purple factors are involved in estrogen-dependent signaling. Green factors facilitate estrogen-independent, ER-mediated signaling. Red, orange, and pink factors engage in ER crosstalk, and dysregulation in mitogenic signaling pathway components can contribute to ER-independent tumor growth and SERD resistance.

AKT, protein kinase B; CDK, cyclin-dependent kinase; CoA, coactivator; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; *ESR1*-mut, *ESR1* mutant; *ESR1*-wt, *ESR1* wild-type; ET, endocrine therapy; FGFR, fibroblast growth factor receptor; GF RTK, growth factor-driven receptor tyrosine kinase; HER2, human epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; MEK, meiotic chromosome-axis-associated kinase; mTOR, mammalian target of rapamycin; *p*, phosphate; PI3K, phosphoinositide 3-kinase; Rb, retinoblastoma; SERD, selective estrogen receptor degrader.

factors such as transforming growth factor alpha (TGF α) and insulin-like growth factor-1 (IGF1), regulate the expression of membrane receptor tyrosine kinases (RTKs) that promote cell survival, and increase cyclin D1 and MYC expression which drive cell cycle progression.^{18,19} Collectively, these functions can enhance pathologic breast cancer development when dysregulated.

In response to estrogen, cytoplasm- and membrane-associated ER also stimulates growth signaling directly, which is considered to be a non-genomic mechanism of regulation.⁷ ER interaction with growth factor-dependent RTKs, such as HER2, epidermal growth factor receptor (EGFR) and insulin-like growth factor-1 receptor (IGF1R), as well as other signaling molecules such as SRC kinase, activates downstream mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT oncogenic signal transduction pathways.²⁰ The MAPK and PI3K/AKT pathways are well characterized in cancer and play a role in tumor proliferation, invasive potential, and drug resistance.^{21,22}

ESR1 mutation as a clinical biomarker of AI resistance and ER pathway dependency

Mutated ER can provoke estrogen-independent ER activity and mediate resistance to estrogen deprivation.²³ Activating mutations in the ligand binding domain (LBD) of *ESR1*, the gene that codes for ER α , are rare in primary breast cancer but represent a commonly acquired mechanism of endocrine resistance in ER+ metastatic breast cancer (MBC).²⁴⁻²⁶ *ESR1* mutations are expressed in 4–8% of breast cancers that recur after adjuvant AI treatment and less than 1% of *de novo* metastatic tumors²⁷⁻²⁹; mechanisms beyond aberrant *ESR1* may play a more significant role in resistance to adjuvant ET.¹⁷ Aberrant *ESR1* emerges most often following prior AI exposure.^{27,30} After receiving a line of AI therapy in the metastatic setting, approximately 20–40% of tumors will acquire an *ESR1* mutation, with higher prevalence demonstrated on cell-free DNA (cfDNA) analyses than solid tumor biopsies.^{27,28,30} *ESR1* alterations were not readily apparent in The Cancer Genome Atlas due to sequencing of treatment-naïve MBC samples,³¹ but subsequent sequencing efforts characterizing ET-resistant tumors revealed *ESR1* as an acquired driver of resistance.^{25,32} The most common mutations seen in the *ESR1* gene are Y537S and D538G, with a prevalence of 14–21% and 32–36%, respectively;

several other activating mutations with lower rates of incidence have been implicated in resistance, including Y537C, E380Q, S463P, V534E, P535H, L536H, L536P, L536R, L536Q, and Y537N.³³⁻³⁵ Studies characterizing serial cfDNA in MBC demonstrate a relatively frequent polyclonal mutation burden and high levels of genetic heterogeneity in these tumors.^{28,36,37}

There are several implicated mechanisms by which *ESR1*-mutant (*ESR1*-mut) ER mediates resistance to ET. Activating *ESR1* mutations affect the LBD and stabilize an active receptor conformation.^{14,38,39} This promotes binding of coactivators and upregulates ER signal transduction in the absence of estrogen.^{14,38,39} Biochemical changes at the LBD of *ESR1*-mut confer a decreased affinity for ligands, including SERMs and SERDs, and greater stability against proteolytic degradation.^{24,25,32,38-40} Activity of *ESR1*-mut has neomorphic and hypermorphic regulatory effects as well, enhancing the transcription of genes not activated by *ESR1* wild-type (*ESR1*-wt) ER that promote a pro-metastatic phenotype.⁴⁰⁻⁴² Research also demonstrates mutation-specific variability in resistance patterns, where Y537S conveys greater resistance to ET^{33,40,42} while D538G carries greater metastatic potential.^{42,43}

ESR1 mutations in ER+ breast cancer have been shown to provoke resistance to AIs in both the preclinical and clinical setting.^{24,25,34,44} In laboratory-based models, higher doses of tamoxifen and fulvestrant are required to inhibit *ESR1*-mut transcriptional activity, suggesting *ESR1* mutations provoke dose-dependent resistance to these agents.^{24,25,32,38-40} The degree of resistance can be variable and highly mutant specific, ranging from as high as 50-fold dose increase in Y537S mutants, while a more modest 2- to 10-fold dose increase is required to inhibit models of most other *ESR1* mutants.^{24,25,32,38-40} However, the impact of *ESR1* mutations to SERD and SERM response remains controversial and likely context dependent.⁴⁴⁻⁴⁸

ESR1 fusions (*ESR1*-fus) represent rare but notable alterations that eliminate the LBD and drive ET resistance through constitutive ER transcriptional activity.^{49,50} Since *ESR1*-fus ER becomes completely independent of the LBD domain, these tumors are likely resistant to most current- and next-generation ETs that target the LBD. Data suggest that *ESR1*-fus represent about 0.5–1% of all *ESR1* alterations,^{26,51,52} although the frequency of fusion events may be underappreciated

as many of the breakpoints are intronic and not captured by conventional next-generation sequencing (NGS) assays.¹⁷ The use of RNA-based fusion detection methods has the potential to increase clinical recognition of *ESR1*-fus events, especially in post-SERD tumor samples as a mechanism of acquired secondary resistance.⁴⁹

Oncogenic signal transduction and ER pathway independence

Mutations and amplifications in oncogenic pathway components can drive ET resistance through upregulated mitogenic and survival pathway signaling. Laboratory and clinical data suggest that alterations in RTKs *HER2*,^{53–55} *EGFR*,^{26,56} and fibroblast growth factor receptors (*FGFRs*),^{57,58} provoke ET resistance by facilitating downstream growth signaling. Similar resistance is seen with loss-of-function mutations in the tumor suppressor *NF1*, leading to uncontrolled RAS activity.^{26,59–61} Activating alterations in other MAPK components *KRAS*, *BRAF*, and *MAP2K1* have been demonstrated in pre- and post-treatment matched tumor samples that acquired ET resistance.²⁶ Upregulation of the PI3K/AKT pathway provokes resistance to estrogen deprivation in laboratory-based models,⁶² and alterations in *PIK3CA*, *AKT*, and *PTEN* are often observed in ER+ MBC,⁶³ although mutations in these genes have not been shown to promote ET resistance in the clinical setting. Downstream mitogenic signaling increases cyclin D1 expression and facilitates cell cycle progression through the cyclin-dependent kinase 4/6 (*CDK4/6*)/*RB/E2F* pathway.^{64,65}

Overall, intracellular communication between these pathways is important in the development of resistance and is exploitable therapeutically. Endocrine resistance can be provoked by loss of ER; however, this mechanism is only seen in approximately 10% of cases.⁶⁶ Other mechanisms, including alterations in gene transcription regulators (*MYC*, *ARID1A*, *FOXA1*, *CTCF*, others), epigenetic changes, aberrant cofactor activity, and the tumor microenvironment, have been implicated in ET resistance and discussed elsewhere,¹⁷ but they are beyond the scope of this review.

Note, while the major mechanisms such as ER-dependent and ER-independent pathways have been highlighted for conceptual understanding, in reality, intracellular crosstalk is complex.

ER signaling is also regulated, in part, by oncogenic signal transduction in a ligand-independent manner.²⁰ In the absence of estrogen, MAPK and PI3K/AKT pathway activation increases the transcriptional function of ER through phosphorylation of the receptor,²⁰ and downregulates ER expression.⁶⁷ Cyclin D1 can activate ER directly and further promote ER-mediated gene transcription.⁶⁴ Thus, continued targeting of the ER will remain the cornerstone of management of ER+ breast cancer despite resistance. This has led to considerable interest in novel endocrine therapies, particularly those that will be active despite *ESR1* mutations. There are a number of next-generation ET drugs in clinical development and a list is summarized in Table 1; the mechanisms of action of several current and novel ETs are depicted in Figure 2.

Novel hormonal therapies and clinical opportunities

Selective estrogen receptor degraders

Fulvestrant. After the development of resistance to ET, breast cancers frequently continue to depend on estrogen-independent ER-mediated signaling, and the ER remains a viable therapeutic target.⁶⁸ Development of an endocrine agent with global ER antagonistic activity in the 1980s–1990s led to the creation of fulvestrant.^{69,70} As the first clinically impactful SERD, fulvestrant has been incorporated into the standard armamentarium for management of ER+ MBC. Fulvestrant antagonizes ER transcriptional activity by inhibiting nuclear translocation, promoting turnover through the ubiquitin-proteasome pathway, and inducing conformational change that downregulates ER signaling.¹² In MBC exposed to prior ET, a pair of clinical trials demonstrated non-inferiority of a 250 mg dose of monthly fulvestrant compared to anastrozole^{71,72}; the subsequent CONFIRM trial showed improved progression-free survival (PFS) and overall survival (OS) in patients receiving a 500 mg dose *versus* 250 mg dose of fulvestrant, which is the currently approved dose.^{73,74} The FALCON trial revealed that in treatment-naïve advanced breast cancer, patients treated with fulvestrant had significantly longer PFS compared to anastrozole (16.6 months *versus* 13.8 months), leading to its approval in the first-line setting.⁷⁵ *ESR1* mutations are a recognized mechanism of acquired resistance to AIs,⁷⁶ and these patients may retain some clinical sensitivity to SERDs,^{28,44,46} so the

Table 1. List of next-generation endocrine agents in development for the management of hormone receptor-positive breast cancer.

Endocrine agent	Developing company	ET class	Mode of delivery	Disease setting	Phase of development
Elacestrant (RAD1901)	Radius Health	SERD	Oral	Metastatic; neoadjuvant	3 complete
Amcenenstrant (SAR439859)	Sanofi	SERD	Oral	Metastatic; adjuvant	2–3
Camizestrant (AZD9833)	Astra Zeneca	SERD	Oral	Metastatic; neoadjuvant	2–3
Giredestrant (GDC-9545)	Genentech/Roche	SERD	Oral	Metastatic; adjuvant; neoadjuvant	2–3
Imlunestrant (LY3484356)	Eli Lilly	SERD	Oral	Metastatic; neoadjuvant	1
Rintodestrant (G1T48)	G1 Therapeutics	SERD	Oral	Metastatic	1–2
Borestrant (ZB-716)	Zeno Pharma	SERD	Oral	Metastatic	1 – 2
ZN-c5	Zentalis	SERD	Oral	Metastatic	1–2
D-0502	Inventisbio	SERD	Oral	Metastatic	1
Lasofloxifene	Sermonix	SERM	Oral	Metastatic	2
Bazedoxifene	Pfizer	SERM/SERD Hybrid	Oral	Metastatic; DCIS	2
H3B-6545	H3 Biomedicine	SERCA	Oral	Metastatic	1–2
OP-1250	Olema Oncology	CERAN	Oral	Metastatic	1–2
ARV-471	Arvinas	PROTAC	Oral	Metastatic	1–2
AC682	Accutar Biotech	Chimeric ER Degradar	Oral	Metastatic	1

AI, aromatase inhibitors; CERAN, complete estrogen receptor antagonist; ET, endocrine therapy; PROTAC, proteolysis targeting chimera; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

sequencing of ET lines for non-curative breast cancer treatment is an important clinical consideration.

Research has demonstrated conflicting results related to the impact of *ESR1* mutations on fulvestrant sensitivity in the laboratory and in the clinic. A robust body of preclinical work showed that *ESR1*-mut expressing breast cancer models demonstrate relative (dose-related) resistance to fulvestrant, requiring 10- to 50-fold greater concentrations of drug to inhibit ER signaling and tumor growth.^{24,25,39,40,77} However, clinical studies have demonstrated variable results regarding the efficacy of fulvestrant in the treatment of *ESR1*-mut MBC. Retrospective analysis of the FERGI, SoFEA, EFECT, and PALOMA-3 trials were performed to assess the impact of *ESR1*-mut on tumor response to fulvestrant.^{28,44–46} Combined analysis of the SoFEA and EFECT trials, which compared fulvestrant *versus*

exemestane in MBC after progression on an AI, demonstrated statistically significantly worse PFS (2.4 months *versus* 4.8 months) and 1-year OS in patients with *ESR1* mutations on the exemestane arm.⁴⁴ However, *ESR1*-mut and *ESR1*-wt MBC treated with fulvestrant had similar PFS (3.9 months *versus* 4.1 months) and 1-year OS.⁴⁴ In the metastatic setting after progression on an AI, the FERGI trial examined fulvestrant *versus* fulvestrant plus pictilisib⁷⁸ and the PALOMA-3 trial examined fulvestrant *versus* fulvestrant plus palbociclib.⁷⁹ Retrospective analysis of the fulvestrant arm in both clinical trials demonstrated the following: (a) no significant difference in PFS in *ESR1*-mut compared to *ESR1*-wt tumors; (b) similar prevalence of *ESR1* mutations at the start and end of treatment; and (c) that expression of multiple *ESR1* alterations or higher variant allele frequency (VAF) burden were not associated with worse outcomes.^{45,46} Notably, in the PALOMA-3 analysis, there was evidence for

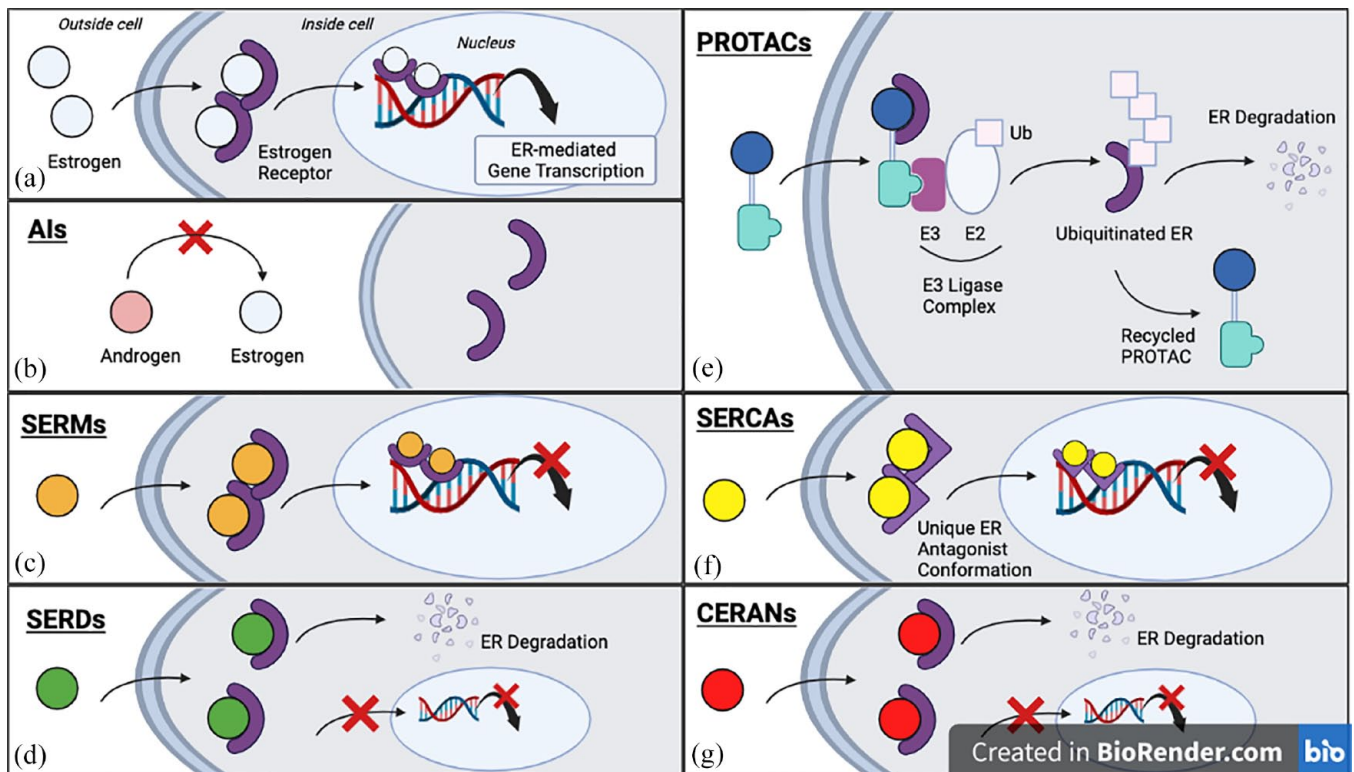


Figure 2. The mechanisms of action of different ETs, simplified for conceptualization. (a) Estrogen binds the ER, a ligand-dependent transcription factor, promoting ER dimerization and translocation to the nucleus. The estrogen-bound ER dimer regulates gene expression that facilitates cell growth and survival. (b) The AIs block the aromatization of androgens to estrogens. (c) SERMs competitively bind ER and mediate a tissue-dependent anti-estrogen effect. (d) SERDs slow ER nuclear translocation, increase receptor turnover, and reduce transcription of ER-regulated genes. (e) PROTACs mediate an interaction between ER and the E3 ligase complex, facilitating ubiquitination of ER and subsequent proteasomal degradation; the PROTAC molecule is recycled in this process. (f) SERCAs covalently bind the C530 residue in the ER ligand-binding domain and promote a unique antagonist conformation that decreases ER-regulated gene transcription. (g) CERANs bind ER and potentiate their effect by inducing ER degradation and blocking transcriptional activity.

AIs, aromatase inhibitors; CERANs, complete estrogen receptor antagonists; ER, estrogen receptor; ETs, endocrine therapies; PROTACs, proteolysis targeting chimeras; SERCAs, selective estrogen receptor covalent antagonists; SERDs, selective estrogen receptor degraders; SERMs, selective estrogen receptor modulators.

increased positive selection for Y537S mutation at time of progression.⁴⁵ Although limited by sample size ($n=19$), this specific *ESR1* mutation trended toward shorter PFS ($p=0.14$), highlighting the importance of further investigation into the impact of specific allelic variants on therapeutic resistance.⁴⁵

It is important to note that these analyses are retrospective and exploratory. Elucidating the true role of *ESR1*-mut in mediating response or resistance to SERDs requires large, prospective studies and the use of standardized methods for detecting *ESR1* mutations.⁸⁰ The importance of this is highlighted by clinical results presented from the plasmaMATCH trial.⁴⁷ Trial participants with MBC had cfDNA analyzed for mutations in

ESR1, *HER2*, *AKT*, and *PTEN* and were matched to concordant targeted therapies. In this heavily pretreated population, with a median of two prior lines of ET, high-dose fulvestrant monotherapy (500 mg biweekly dosing) was not effective in patients with *ESR1*-mut,⁴⁷ with a PFS of only 2.2 months. However, it is notable that tumors expressing a higher *ESR1* VAF (>50%) demonstrated rare responses to fulvestrant [overall response rate (ORR) 12%; $n=44$] compared to lower VAF (<50%) (ORR 0%; $n=30$), suggesting that mechanisms of resistance in these heavily pre-treated tumors are likely heterogeneous, and stratifying patients based on *ESR1* status alone may not be an optimal clinical approach to maximizing benefit.⁴⁷ In the first-line setting, the phase III PADA-1 trial is evaluating the clinical benefit

of switching from an AI to fulvestrant plus CDK4/6i upon detection of ESR1-mut on serial circulating tumor DNA (ctDNA) analysis prior to disease progression.⁸¹ Presented results demonstrated an improved median PFS of 11.9 months on the fulvestrant-CDK4/6i arm compared to 5.7 months on the AI-CDK4/6i arm; patients with progression on the AI arm could enroll in an optional crossover cohort, and this subgroup had a median second PFS of 3.5 months.²⁹ Compared with the standard strategy of starting fulvestrant after disease progression, this study highlights the potential benefit of targeting emerging ESR1-mut early in this patient population, although the OS data require more time to mature.

Pharmacologic limitations regarding the bioavailability of fulvestrant have prompted strong interest in an orally bioavailable alternative.⁸² A number of novel oral SERDs demonstrating preclinical and clinical efficacy in ER+ breast cancer are in varying stages of clinical development. These drugs could potentially replace fulvestrant, as monotherapy or as the ET backbone of combination treatment, in the management of ESR1-mut and ESR1-wt ER+ breast cancer.⁸³

Elacestrant. The oral SERD elacestrant (RAD1901) was developed by Radius Health for use in ER+ breast cancer and has demonstrated exciting clinical efficacy. Elacestrant selectively antagonizes ER, promoting ER turnover, and disrupting downstream signaling.⁸⁴ Laboratory-based studies demonstrate dose-dependent antitumor activity in ET-resistant breast cancer cells and patient-derived xenograft (PDX) models, including those expressing *ESR1* mutations^{84,85}; efficacy is retained in multiple *in vitro* models of CDK4/6i resistance as well.⁸⁶

Phase I evaluation of elacestrant showed single-agent activity in a heavily pretreated population of postmenopausal women with three median prior lines of therapy and a 50% rate of baseline *ESR1* mutation.⁸⁷ These encouraging results led to the multicenter phase III EMERALD trial which evaluated elacestrant *versus* ET SOC (fulvestrant or AI) in ER+ MBC following progression on 1–2 prior lines of ET and prior exposure to a CDK4/6i.⁸⁸ Around 477 patients were enrolled, and 228 of them harbored a baseline *ESR1* mutation (47.8%).⁸⁸ Recently published data from the EMERALD trial demonstrated that, compared with standard of care (SOC), elacestrant prolonged PFS in all patients [hazard ratio

(HR) = 0.70] and patients with ESR1-mut tumors (HR = 0.55), which were the primary endpoints of the study.⁸⁸ Improved 12-month PFS and median PFS were seen in the overall population (22.3% *versus* 9.4%; 2.8 months *versus* 1.9 months) and ESR1-mut cohort (26.8% *versus* 8.2%; 3.8 month *versus* 1.9 month).⁸⁸ In both arms, the modest difference in median PFS may be explained by an initial drop in the Kaplan–Meier curves, representing a subset of endocrine-resistant tumors in the second-/third-line ET setting, followed by survival curve separation between elacestrant and SOC in the endocrine-sensitive setting.⁸⁸ The interim OS analysis showed a trend toward favoring elacestrant in all patients (HR = 0.751) and those with ESR1-mut (HR = 0.592), with expectations for final OS reporting in 2022.⁸⁸ The most common treatment-related adverse events were nausea (25.3%), vomiting (11%), and fatigue (11%), primarily grade 1–2.⁸⁸

This is the first novel oral SERD in a phase III study to demonstrate a significant and clinically meaningful improvement over fulvestrant or AI in this population.⁸⁸ Pretreated patients harboring *ESR1* mutations had an even more pronounced clinical benefit with elacestrant and, based on this susceptibility, further efforts to assess the response of ESR1-mut metastatic tumors with novel oral SERDs remain ongoing.

Amcenestrant. Amcenestrant (SAR439859) is another oral SERD in development by Sanofi. Preclinical efficacy was demonstrated in breast cancer cells and PDX tumors, including ESR1-mut models which demonstrated relative (dose related) resistance to amcenestrant.⁷⁷ The phase I/II AMEERA-1 trial demonstrated antitumor activity of amcenestrant monotherapy in heavily pretreated ER+ MBC after progression on prior ET.⁸⁹ Single-agent amcenestrant conveyed a similar clinical benefit rate (CBR) in tumors expressing ESR1-mut (32.1%) and ESR1-wt (36.7%) ($n = 58$ for patients with *ESR1* status).⁸⁹

Based on these monotherapy results, amcenestrant is being evaluated in phase II and III trials characterizing its efficacy compared to SOC ET in MBC after progression on prior ET (AMEERA-3, NCT04059484) and first line in combination with palbociclib for treatment-naïve ER+ MBC (AMEERA-5, NCT04478266). Although the final data have not yet been presented, Sanofi announced that the AMEERA-3 trial did not meet its primary endpoint of

improving PFS.⁹⁰ The phase I AMEERA-1 trial is ongoing and examining targeted agent combinations of amcenestrant with palbociclib, alpelisib (a PI3K inhibitor), or everolimus [an mammalian target of rapamycin (mTOR) inhibitor] (NCT03284957). In the adjuvant setting, the phase III AMEERA-6 trial is evaluating amcenestrant *versus* tamoxifen in patients with early-stage ER+ breast cancer who discontinued AI therapy due to treatment-related toxicity (NCT0512877).

Camizestrant. The novel SERD camizestrant (AZD9833) is in development from AstraZeneca. In addition to promoting ER degradation, camizestrant's novel structure increases potency of the molecule and facilitates a pattern of gene regulation that is distinct when compared to fulvestrant.^{91,92} Camizestrant inhibits growth in pre-clinical breast cancer models, and unlike fulvestrant shows no relative (dose dependent) resistance in tumors expressing ESR1-mut.⁹³ In the phase I SERENA-1 trial, camizestrant showed single-agent activity treating ER+ MBC that had progressed on prior ET.^{94,95} ESR1 mutations were detected in baseline cfDNA samples in 26/56 (46%) of patients tested; 50% of tumors expressing ESR1-mut had a partial response or stable disease at 24 weeks on therapy, including 5/10 patients harboring Y537S alterations.⁹⁵

These encouraging findings have prompted phase II and III clinical trials examining camizestrant in several disease settings: (a) as monotherapy in ER+ MBC after progression on ET (SERENA-2, NCT04214288); (b) in combination with palbociclib as first-line treatment for advanced ER+ breast cancer (SERENA-4, NCT04711252) and ESR1-mut MBC (SERENA-6, NCT04964934); and (c) as neoadjuvant therapy in a window-of-opportunity study for early-stage disease (SERENA-3, NCT04588298). Similar to other oral SERDs, the SERENA-1 trial remains active in evaluating camizestrant in combination with CDK4/6, PI3K, or mTOR inhibitor, and recently presented data demonstrated efficacy and tolerability in combination with palbociclib.⁹⁵ Notable side effects of camizestrant documented during the SERENA-1 trial include sinus bradycardia and visual disturbances, neither of which prompted discontinuation of therapy.⁹⁵

Giredestrant. Giredestrant (GDC-9545) is under development by Roche/Genentech. This oral SERD induces tumor regression in ESR1-mut

PDX models in the laboratory.⁹⁶ Evidence of single-agent giredestrant antitumor activity was demonstrated in a phase I clinical trial enrolling patients with ER+ MBC after progression on two or fewer prior lines of ET, including patients harboring baseline ESR1 mutations (NCT03332797).^{97,98} It is notable that only 21% of patients in this cohort received prior fulvestrant, less than other phase I novel SERD trials reviewed here.⁹⁸ As with camizestrant, grade 1–2 sinus bradycardia was seen on therapy, though it appears to be dose dependent with low frequency at 30 mg dose.⁹⁸

Giredestrant efficacy data have led to the development of several clinical trials evaluating its use in the both advanced- and early-stage breast cancer at 30 mg dose. In the metastatic setting, first-line giredestrant combined with palbociclib for treatment-naïve MBC is being evaluated in the phase III persevERA trial (NCT04546009). Giredestrant monotherapy for MBC progressed on prior ET was the focus of the phase II accelERA trial (NCT04576455); however, Roche recently announced that the study did not meet its primary endpoint of improving PFS.⁹⁹ In early-stage disease, the phase II neoadjuvant window-of-opportunity coopERA study demonstrated superior efficacy of giredestrant over AI in terms of Ki67 suppression in ER+ breast tumors (NCT04436744).¹⁰⁰ The ongoing phase III lidERA trial is examining adjuvant giredestrant *versus* AI or tamoxifen for stage I–III ER+ breast cancer (NCT04961996).

Imlunestrant. Imlunestrant (LY3484356) is an oral SERD being developed by Eli Lilly and has demonstrated preclinical efficacy against wt- and ESR1-mut breast cancer models, both as a single-agent and in combination with several targeted therapies.¹⁰¹ The active phase I EMBER trial is characterizing imlunestrant alone or combined with abemaciclib, everolimus, alpelisib, trastuzumab, or AI for ER+ MBC (NCT04188548). Imlunestrant monotherapy data from the EMBER trial showed efficacy in a cohort of pretreated ER+ MBC patients.¹⁰² In the phase III setting, imlunestrant with or without abemaciclib is being compared against fulvestrant or exemestane for management of hormone-sensitive advanced breast cancer after progression on AI (EMBER-3, NCT04975308). In addition, the ongoing window-of-opportunity, phase I EMBER-2 trial is evaluating the pharmacodynamic effect of imlunestrant in the neoadjuvant setting (NCT04647487).

Rintodestrant. Rintodestrant (G1T48) is an oral SERD being developed by G1 therapeutics. Pre-clinical work showed dose-independent efficacy of this agent in breast cancer cells and ESR1-mut PDX tumors.¹⁰³ In a phase I clinical trial, rintodestrant conveyed antitumor activity in ER+ MBC after progression on prior lines of therapy.¹⁰⁴ Trial results demonstrated benefit in patients expressing *ESR1* mutations.¹⁰⁴ Evaluation of rintodestrant combined with palbociclib for ET-resistant MBC in the advanced disease setting is ongoing (NCT03455270).

Others. There are several additional next-generation SERDs that have demonstrated preclinical activity and are being evaluated in phase I–II clinical trials, including borestrant [ZB-716; ENZENO trial (NCT04669587)], ZN-c5 (NCT03560531), and D-0502 (NCT03471663).

While many of the current developments in oral SERDs have shown promise, maintaining a perspective on historical challenges is important in this growing field. After the advent of fulvestrant, initial attempts at creating an orally bioavailable SERD proved challenging.¹⁰⁵ Numerous iterations of ER-degrading compounds with chemically modified polarity and solubility were required to overcome bioavailability limitations.¹⁰⁵ Several candidate compounds showing preclinical antitumor activity have also been discontinued during various stages of clinical testing. One example is brilanestrant (GDC0810), an oral SERD that was removed from development by Roche after a phase II clinical trial failed to demonstrate comparable or superior efficacy to fulvestrant (NCT01823835). Another compound, LSZ102, had its phase I testing terminated by trial sponsor Novartis. Prior to discontinuation, interim single-agent results of LSZ102 in heavily pretreated ER+ MBC patients showed an ORR 1.3%, CBR 9.1%, and median PFS 1.8 months.¹⁰⁶ Notably, both of these drugs contain an acrylic acid side chain, whereas many of the novel oral SERDs discussed above were created with a basic amino side chain to optimize ER degradation across multiple breast cancer cell lines.¹⁰⁷ Similarly, clinical development of AZD9496 was discontinued in favor of AZD9833 that was optimized for absorption and activity. Differences in chemical structure, efficacy, and side effects between agents will likely play a significant role in determining which drugs ultimately enter clinical practice.

More broadly, the optimal use of SERDs and sequencing of ET in ER+ MBC remains uncertain. The PARSIFAL trial was conducted to assess the efficacy of fulvestrant compared to letrozole when combined with palbociclib for first-line management of ER+/HER2– MBC.¹⁰⁸ Although significant antitumor activity was demonstrated in the fulvestrant–palbociclib arm, an improvement in PFS over the letrozole–palbociclib regimen was not seen.¹⁰⁸ The results of several ongoing trials examining next-generation SERDs for first-line management of hormone-sensitive MBC will be informative in helping guide their clinical use (Table 3).

Other novel endocrine agents including SERMs, SERCAs, CERANs, and proteolytic activators

In addition to oral SERDs, several other novel endocrine-based therapies have emerged for the management of ER+ breast cancer.

SERMs and SERM/SERD hybrids. Lasofoxifene is a next-generation SERM with similar characteristics to tamoxifen in terms of ER binding and inhibition of coactivators, but with improved bioavailability.¹⁰⁹ Initially developed by Sermonix for osteoporosis, patients taking lasofoxifene in the PEARL trial were found to have a reduced incidence of breast cancer, and their risk of endometrial hyperplasia or endometrial cancer was not increased.¹¹⁰ Efficacy of this agent was demonstrated in preclinical breast cancer models, and notably, lasofoxifene was found to retain antagonist activity without evidence of resistance in cancer cells harboring ESR1-mut.⁴⁸ Based on laboratory evidence that lasofoxifene is not impacted by ESR1-mut status, clinical evaluation is underway in patients with ESR1-mut MBC. Currently, the ELAINE and ELAINE-2 trials are examining lasofoxifene, as monotherapy or in combination with abemaciclib, respectively, in patients with ESR1-mut advanced breast cancer after progression on prior ET and CDK4/6i (NCT03781063, NCT04432454).

Approved for the management of osteoporosis and postmenopausal hot flashes, bazedoxifene has also been studied for the treatment of breast cancer in preclinical and clinical settings. Developed by Pfizer, this SERM/SERD hybrid functions as a high affinity ER antagonist in breast tumors and promotes ER degradation.^{13,111,112} Bazedoxifene shows antitumor activity in

laboratory-based models of tamoxifen-resistant breast cancer,^{13,113} and is currently being studied in a phase II clinical trial in MBC after progression on prior ET (NCT02448771).

ER antagonists. Optimized by H3 Biomedicine, H3B-6545 is a selective estrogen receptor covalent antagonist (SERCA) which covalently inactivates wt- and ESR1-mut by targeting Cys530 and promoting an antagonist conformation.³⁹ A precursor drug (H3B-5942) showed dose-dependent growth inhibition of breast cancer cells and PDX models expressing *ESR1* mutations, and potency was improved in combination with a CDK4/6 or mTOR inhibitor.³⁹ Translating these results into the clinical space, H3B-6545 demonstrated single-agent antitumor activity in heavily pretreated patients with ER+ MBC.¹¹⁴ Sixty-one percent of patients harbored baseline *ESR1* mutations detected by ctDNA ($n=94$), and among patients with *ESR1* Y537S mutations ($n=10$), an ORR 40% and median PFS 7.3 months were demonstrated.¹¹⁴ Notable adverse events included asymptomatic sinus bradycardia and QTc prolongation.¹¹⁴ Ongoing clinical evaluation in the phase I and II settings includes H3B-6545 as monotherapy (NCT03250676) and combined with palbociclib (NCT04288089) for ER+ MBC progressed on prior ET.

OP-1250 is an orally bioavailable complete estrogen receptor antagonist (CERAN) that completely antagonizes ER, blocks transcriptional activity, and induces ER degradation.¹¹⁵ This agent is hypothesized to convey superior efficacy to agents with only partial antagonism.¹¹⁵ In laboratory-based studies, OP-1250 demonstrates antitumor efficacy in both *ESR1*-mut and *ESR1*-wt breast cancer models.¹¹⁵ These findings have prompted an active phase I–II clinical trials that is examining the activity of OP-1250 in ER+ MBC after progression on ET (NCT04505826).¹¹⁶ Reported phase I data showed benefit in heavily pretreated patients with an ORR 17% and CBR 46% at dose levels within the recommended phase II dose range.¹¹⁷

Proteolysis targeting chimer. ARV-471 facilitates interactions between ER and the intracellular E3 ligase complex, mediating degradation of ER by the proteasome.¹¹⁸ This compound, developed by Arvinas, shows tumor growth inhibition in laboratory-based breast cancer models, including those expressing *ESR1*-mut.¹¹⁸ An ongoing phase I–II clinical trial is evaluating ARV-471 alone or

in combination with palbociclib in ET-resistant MBC (NCT04072952). Presented trial data evaluating ARV-471 monotherapy in a heavily pretreated population demonstrated clinical benefit with ORR 5.2% and CBR 40%.¹¹⁹

AC682 is an oral chimeric ER degrader in development by Accutar Biotech that engages E3 ligase and ER to induce receptor degradation.¹²⁰ Preclinical data showed efficacy of this agent in ER+ breast cancer cells and tumor xenografts, including models harboring *ESR1* mutation.¹²⁰ A phase I trial examining AC682 activity in ER+ MBC is ongoing (NCT05080842).

The clinical efficacy and adverse effects of the different endocrine agents are summarized in Table 2. Note, Table 2 is meant to be a summary for easy reference and cross-study comparisons among different studies should be performed with caution. Patients enrolled in these studies will have differences related to multiple factors, including prior lines of therapy, baseline genomic alterations, and sensitivity to ET. For example, as mentioned above, phase I trial data from the oral SERDs demonstrates that prior fulvestrant exposure in participants ranges from 21% to 64%.^{87,89,95,98,102,104} This could have a marked impact on underlying ET resistance and subsequent measures of response to treatment. Active clinical trials designed to further evaluate the efficacy of these agents are summarized in Table 3.

Combination therapy and future directions

Several next-generation ET agents described above demonstrate efficacy in ER+ advanced breast cancers that can proliferate independent of estrogen. As a drug class, the oral SERDs have shown encouraging results in treating *ESR1*-mut MBC. *ESR1* mutations arise predominately following AI exposure, but often co-occur with other genomic drivers of resistance that upregulate ER-independent growth pathways.⁸³

Tumors that lose reliance on ER-mediated signaling may be less susceptible to even the most potent SERDs. For example, sensitivity to ET can be diminished by activating alterations in membrane RTKs (HER2, EGFR, FGFR), upregulation of oncogenic transduction pathways (MAPK, PI3K/AKT), and dysregulated cyclin D1/CDK4/6 pathway signaling.¹⁷ These features of ET resistance support a combination approach to therapy that concurrently abrogate

Table 2. Results from clinical trials of next-generation endocrine therapies in hormone receptor-positive MBC.

Endocrine agent	ET class	Trial description	Trial identifier	Median prior lines of therapy	Prior SERD exposure (%)	Prior CDK4/6i exposure (%)	Baseline ESR1 mutation rate (%)	ORR (%) and CBR (%)	Progression-free survival	Most frequent (>5%) treatment-related adverse events
Oral SERDs										
Elacestrant (RAD1901)	SERD	Phase III; n = 477 Elacestrant versus fulvestrant or AI for ER+ MBC progressed on 1–2 prior lines of ET and CDK4/6i	NCT03778931 (EMERALD)	1	Not reported	100%	48%	Not reported	12-month PFS rate of 22.3% versus 9.4%; 30% reduction in PD or death, HR 0.697	Nausea (25.3% G1–2), vomiting (11% G1–2), fatigue (11% G1–2)
Elacestrant (RAD1901)	SERD	Phase I; n = 50 Elacestrant for ER+ MBC progressed on ET	NCT02338349	3	52%	52%	50%	ORR 19.4% CBR 42.6%	Median 4.5 months	Nausea (33% G1–2), hypophosphatemia (25% G1–3), hypertriglyceridemia (25% G1–2), arthralgia (17% G1–2), fatigue (21% G1–2), diarrhea (12% G1–2), vomiting (17% G1–2), dyspepsia (21% G1–2), constipation (21% G1–2), anemia (12% G1–2), AST increased (12% G1–2), ALT increased (12% G1–2)
Amcnestrant (SAR439859)	SERD	Phase I–II; n = 62 Amcnestrant for ER+ MBC progressed on ET	NCT03284957 (AMEERA-1)	2	47%	63%	48%	ORR 8.5% CBR 33.9%	Not reported	Hot flush (16.1% G1–2); constipation (9.7% G1–2), arthralgia (9.7% G1–2), vomiting (8.1% G1–2), diarrhea (8.1% G1–2), nausea (8.1% G1–2), fatigue (6.5% G1–2)
Camizestrant (AZD9833)	SERD	Phase I; n = 98 Camizestrant for ER+ MBC progressed on ET	NCT04214288 (SERENA-1)	5	58%	69%	46%	ORR 10% CBR 35.3%	Median 5.4 months	Visual disturbances (51% G1–2, 2% G3), sinus bradycardia (45% G1–2), nausea (18% G1–2), fatigue (13% G1–2), dizziness (10% G1–2), vomiting (10% G1–3)

(Continued)

Table 2. (Continued)

Endocrine agent	ET class	Trial description	Trial identifier	Median prior lines of therapy	Prior SERD exposure (%)	Prior CDK4/6i exposure (%)	Baseline ESR1 mutation rate (%)	ORR (%) and CBR (%)	Progression-free survival	Most frequent (>5%) treatment-related adverse events
Giredestrant (GDC-9545)	SERD	Phase I; n = 111 Giredestrant for ER+ MBC progressed on ET	NCT03332797	1	21%	64%	Not reported	ORR 15% CBR 50%	Median 7.2 months	Sinus bradycardia (7% G1-2), fatigue (21% G1-2), arthralgia (17% G1-2), nausea (16% G1-2)
Imlunestrant (LY3484356)	SERD	Phase I; n = 35 Imlunestrant for ER+ MBC progressed on ET	NCT04188548 (EMBER)	2	60%	83%	37%	ORR 6% CBR 48%	Not reported	Nausea (32% G1-2), fatigue (25% G1-2), diarrhea (18% G1-2)
Rintodestrant (G1T48)	SERD	Phase I; n = 67 Rintodestrant for ER+ MBC progressed on ET	NCT03455270	2	64%	70%	41%	ORR 5% CBR 30%	Median 2.6-3.6 months	Hot flush (24% G1-2), fatigue (21% G1-2), nausea (19% G1-2), diarrhea (18% G1-2), vomiting (10% G1-2)
Other novel ET										
H3B-6545	SERCA	Phase I-II; n = 94 H3B-6545 for ER+ MBC progressed on ET	NCT03250676	3	72%	85%	61%	ORR 17% CBR 40%	Median 5.1 months	Sinus bradycardia (34% G1, 5% G2), QTcF prolongation (5% G2-3), anemia (19% G2+), fatigue (16% G2+), nausea (17% G2+), diarrhea (12% G2+), creatinine clearance decrease (38% G2+), hemoglobin decrease (37% G2+), bilirubin increase (12% G2+), ALT increase (14% G2+), AST increase (13% G2+)
P-1250	CERAN	Phase I; n = 41 OP-1250 for ER+ MBC progressed on ET	NCT04505826	3	68%	95%	49%	ORR 17% CBR 46%	Not reported	Nausea (49% G1-2), fatigue (34% G1-2), vomiting (22% G1-2), headache (17% G1-2)
ARV-471	PROTAC	Phase I; n = 50 ARV-471 for ER+ MBC progressed on ET	NCT04072952	Not reported	83%	100%	Not reported	ORR 5.2% CBR 40%	Not reported	Nausea (24% G1-2), fatigue (12% G1-2), vomiting (10% G1-2)

AI, aromatase inhibitors; ALT, alanine aminotransferase; AST, aspartate transaminase; CBR, clinical benefit rate; CDK4/6i, CDK4/6 inhibitor; CERAN, complete estrogen receptor antagonist; ER+, estrogen receptor positive; ET, endocrine therapy; G, grade; HR, hazard ratio; MBC, metastatic breast cancer; ORR, overall response rate; PD, progression of disease; PFS, progression-free survival; PROTAC, proteolysis targeting chimera; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulators; TRAE, treatment-related adverse event.

Table 3. Ongoing clinical trials of next-generation endocrine therapies in the metastatic, adjuvant, and neoadjuvant setting.

Endocrine agent	ET class	Combination therapy (drug class)	Disease setting	Trial description	Phase	Clinical trial identifier
First-line metastatic breast cancer trials						
Oral SERDs						
Amcnestrant (SAR439859)	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic; first line	Amcnestrant + palbociclib versus letrozole + palbociclib for treatment-naïve ER + MBC	Phase III	NCT04478266 (AMEERA-5)
Camizestrant (AZD9833)	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic; first line	Camizestrant + palbociclib versus AI + palbociclib for treatment-naïve ER + MBC	Phase II	NCT04711252 (SERENA-4)
Giredestrant (GDC-9545)	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic; first line	Giredestrant + palbociclib versus letrozole + palbociclib for treatment-naïve ER + MBC	Phase III	NCT04546009 (persevERA)
Second-line plus metastatic breast cancer trials						
Oral SERDs						
Amcnestrant (SAR439859)	SERD	None	Advanced/metastatic	Amcnestrant versus AI or fulvestrant or tamoxifen for ER + MBC progressed on ET	Phase II	NCT04059484 (AMEERA-3)
Amcnestrant (SAR439859)	SERD	Various	Advanced/metastatic	Amcnestrant + palbociclib, alpelisib, everolimus, or abemaciclib for ER + MBC progressed on ET	Phase I-II	NCT03284957 (AMEERA-1)
Camizestrant (AZD9833)	SERD	None	Advanced/metastatic	Camizestrant versus fulvestrant for ER + MBC progressed on ET	Phase II	NCT04214288 (SERENA-2)
Camizestrant (AZD9833)	SERD	Various	Advanced/metastatic	Camizestrant alone or in combination with palbociclib, abemaciclib, everolimus, or capivasertib for ER + MBC progressed on ET	Phase I	NCT04214288 (SERENA-1)
Camizestrant (AZD9833)	SERD	Abemaciclib/palbociclib (CDK4/6i)	Advanced/metastatic	Camizestrant + palbociclib or abemaciclib versus AI + palbociclib or abemaciclib for <i>ESR1</i> mutant ER + MBC before progression	Phase III	NCT04964934 (SERENA-6)
Giredestrant (GDC-9545)	SERD	None	Advanced/metastatic	Giredestrant versus fulvestrant or AI for ER + MBC progressed on ET	Phase II	NCT04576455 (aceLERA)
Imlunestrant (LY3484356)	SERD	Various	Advanced/metastatic	Imlunestrant alone or combined with abemaciclib, everolimus, alpelisib, trastuzumab, or AI for ER + MBC	Phase I	NCT04188548 (EMBER)
Imlunestrant (LY3484356)	SERD	Abemaciclib (CDK4/6i)	Advanced/metastatic	Imlunestrant with or without abemaciclib versus fulvestrant or exemestane for ER + MBC progressed on ET	Phase III	NCT04975308 (EMBER-3)
Rintodestrant (G1T48)	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic	Rintodestrant + palbociclib for ER + MBC progressed on ET	Phase I	NCT03455270
Borestrant (ZB-716)	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic	Borestrant alone or combined with palbociclib for ER + MBC	Phase I-II	NCT04669587 (ENZENO)

(Continued)

Table 3. (Continued)

Endocrine agent	ET class	Combination therapy (drug class)	Disease setting	Trial description	Phase	Clinical trial identifier
ZN-c5	SERD	Abemaciclib (CDK4/6i)	Advanced/metastatic	ZN-c5 + abemaciclib for ER + MBC	Phase I	NCT04514159
ZN-c5	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic	ZN-c5 alone or combined with palbociclib for ER + MBC	Phase I-II	NCT03560531
D-0502	SERD	Palbociclib (CDK4/6i)	Advanced/metastatic	D-0502 alone or combined with palbociclib for ER + MBC progressed on ET	Phase I	NCT03471663
SERMs + SERM/SERD hybrids						
Lasofixifene	SERM	Abemaciclib (CDK4/6i)	Advanced/metastatic	Lasofixifene + abemaciclib for <i>ESR1</i> mutant ER + MBC progressed on ET	Phase II	NCT04432454 (ELAINE-2)
Lasofixifene	SERM	None	Advanced/metastatic	Lasofixifene versus fulvestrant for <i>ESR1</i> mutant ER + MBC progressed on AI + CDK4/6i	Phase II	NCT03781063 (ELAINE)
Bazedoxifene	SERM/SERD hybrid	Palbociclib (CDK4/6i)	Advanced/metastatic	Bazedoxifene + palbociclib for ER + MBC progressed on prior ET	Phase II	NCT02448771
Other novel ET						
H3B-6545	SERCA	Palbociclib (CDK4/6i)	Advanced/metastatic	H3B-6545 + palbociclib for ER + MBC progressed on ET	Phase I	NCT04288089
H3B-6545	SERCA	None	Advanced/metastatic	H3B-6545 for ER + MBC progressed on ET + CDK4/6i	Phase I-II	NCT03250676
OP-1250	CERAN	None	Advanced/metastatic	OP-1250 for ER + MBC progressed on ET	Phase I-II	NCT04505826
OP-1250	CERAN	Palbociclib (CDK4/6i)	Advanced/metastatic	OP-1250 + palbociclib for ER + MBC	Phase I	NCT05266105
ARV-471	PROTAC	Palbociclib (CDK4/6i)	Advanced/metastatic	ARV-471 alone or combined with palbociclib for ER + MBC progressed on ET	Phase I-II	NCT04072952
AC682	Chimeric ER degrader	None	Advanced/metastatic	AC682 for ER + MBC	Phase II	NCT05080842
Adjuvant breast cancer trials						
Oral SERDs						
Amcnestrant (SAR439859)	SERD	None	Adjuvant	Amcnestrant versus tamoxifen for early ER + breast cancer after discontinuation of AI	Phase III	NCT05128777 (AMEERA-6)
Giredestrant (GDC-9545)	SERD	None	Adjuvant	Giredestrant versus AI or tamoxifen for early ER + breast cancer	Phase III	NCT04961996 (IuERA)

(Continued)

Table 3. (Continued)

Endocrine agent	ET class	Combination therapy (drug class)	Disease setting	Trial description	Phase	Clinical trial identifier
Neoadjuvant breast cancer trials						
Oral SERDs						
Elacestrant (RAD1901)	SERD	None	Neoadjuvant	Elacestrant for ER + early breast cancer prior to surgery	Phase I	NCT04797728
Camizestrant (AZD9833)	SERD	None	Neoadjuvant	Camizestrant for ER + early breast cancer prior to surgery	Phase II	NCT04688298 (SERENA-3)
Imlunestrant (LY3484356)	SERD	None	Neoadjuvant	LY3484356 for ER + early breast cancer prior to surgery	Phase I	NCT04647487 (EMBER-2)
SERM/SERD hybrids						
Bazedoxifene	SERM/SERD Hybrid	None	DCIS	Bazedoxifene + conjugated estrogens for DCIS	Phase II	NCT02694809 (PROMISE)

AI, aromatase inhibitors; CERAN, complete estrogen receptor antagonist; CDK4/6i, CDK4/6 inhibitor; DCIS, ductal carcinoma *in situ*; ER+, estrogen receptor positive; ET, endocrine therapy; MBC, metastatic breast cancer; PROTAC, proteolysis targeting chimera; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulators.

non-ER-mediated pathways of resistance. Indeed, therapeutic combinations are standard practice in the management of metastatic ER+ breast cancer, as reviewed below.

- (1) Combination with CDK4/6i: Several landmark clinical trials have demonstrated improved PFS and OS when ET is given with a CDK4/6i, leading to the approval of this combination as first-line SOC for ER+ MBC.^{121–127} Currently, the oral SERDs amcenestrant (AMEERA-5, NCT04478266), camizestrant (SERENA-4, NCT04711252), and giredestrant (persevera, NCT04546009) are being studied in combination with CDK4/6 blockade in treatment-naïve advanced breast cancer. Many other next-generation ET agents combined with a CDK4/6i are also being evaluated in varying phases of active clinical trials (see Table 3).
- (2) Combination with PI3K inhibitors: In the SOLAR-1 trial, patients with *PIK3CA* alterations demonstrated improved outcomes when receiving the PI3K inhibitor alpelisib, leading to the approval of alpelisib combined with fulvestrant in *PIK3CA* mutant, ER+ MBC.¹²⁸ The AMEERA-1 and EMBER clinical trials are evaluating the efficacy of amcenestrant and imlunestrant, respectively, combined with alpelisib (NCT03284957, NCT04188548).
- (3) Combination with AKT inhibitors: The AKT inhibitor capivasertib in combination with fulvestrant showed efficacy in the phase II FAKTION trial,¹²⁹ and capivasertib is now being combined with camizestrant in the SERENA-1 trial (NCT04214288). Results from these clinical efforts will inform future combination strategies and could impact the standard treatment of ER+ breast cancer.
- (4) Combination with mTOR inhibitors: The BOLERO-2 trial led to approval of the mTOR inhibitor everolimus, which acts downstream of the PI3K/AKT pathway, in combination with exemestane for MBC progressed on prior ET.¹³⁰ Antitumor activity of three novel SERDs (amcenestrant, camizestrant, and imlunestrant) are being assessed with everolimus in phase I trials (see Table 3).
- (5) Other combinations: Other regimens that exploit signaling pathway vulnerabilities could represent valuable areas for future

research. MEK and ERK inhibitors are under clinical investigation^{131–133}; these agents have the potential to abrogate ET resistance mediated by activating alterations in MAPK pathway components, such as *NF1* or *KRAS*. Resistance driven by membrane RTK mutations or amplifications could be circumvented by combining ET with a targeted RTK inhibitor.¹⁷ For example, in ER+ MBC harboring *HER2* mutations, the combination of neratinib, a *HER2* inhibitor, with fulvestrant has demonstrated clinical promise.¹³⁴ In the pre-clinical setting, breast cancer models harboring aberrant *FGFR* had endocrine resistance reversed with the use of an FGFR inhibitor,⁵⁷ and efficacy of this drug class is being studied in the clinic (NCT04024436). In *ESR1*-mut breast cancer, research demonstrates further genomic dysregulation and downstream signaling modulation that could be leveraged, including aberrant DNA bindings cofactors FOXA1 and CTCF,⁴¹ NOTCH signaling,⁴¹ and Wnt signaling.¹³⁵

Ongoing translational research efforts remain focused on the importance of modeling combination therapy resistance.¹³⁶ For example, alterations in *ESR1* and *PIK3CA* may convey resistance to ET, but these cancers remain sensitive to a CDK4/6i partner.¹³⁶ On the other hand, resistance may require multiple, synergistic driver events to occur. Tumor heterogeneity in pretreated MBC suggests simultaneous genomic and non-genomic resistance drivers can arise on therapy, and future research efforts characterizing their impact on drug sensitivity are important. Serial cfDNA samples collected on patients enrolled in the clinical trials detailed in Tables 2 and 3 could help elucidate high-value targets for translational study.

Conclusions

In the management of ER+ breast cancer, anti-estrogens are a critical component of all early therapeutic regimens. In post-menopausal patients with intact estrogen-ER signaling, AIs decrease systemic estrogen levels and can effectively treat early- and advanced-stage disease.¹ Patients with MBC inevitably progress secondary to acquired or intrinsic mechanisms of resistance.⁴ Disease progression on AI therapy is associated with the emergence of *ESR1* mutations^{27,30} that drive resistance via ligand-independent

ER-mediated growth signaling and proliferation.^{38,39} In these tumors, the ER still remains a viable therapeutic target.⁶⁸

Ongoing clinical development of next-generation ETs has demonstrated that these agents can effectively target both wt- and *ESR1*-mut breast cancer, promoting ER degradation and disrupting downstream signaling. These agents have a distinct pharmacologic advantage over fulvestrant in being orally bioavailable.⁸² Data from the phase III EMERALD trial demonstrate that, compared to SOC, the oral SERD elacestrant improves 12-month PFS in ER+ MBC following progression on prior ET, and clinical benefit was even more pronounced in patients with *ESR1*-mut.⁸⁸ This exciting result could signal the start of a shifting paradigm toward oral SERDs for ER+ breast cancer.

However, several questions around optimizing ET remain. *ESR1* mutation clearly enriches for patients more likely to respond to SERD therapy, possibly due to tumor dependence on ER-mediated signaling, but this association is not perfect or clinically reliable. In the EMERALD trial, about half of the patients demonstrated intrinsic ET resistance regardless of treatment arm, highlighting that some patients are unlikely to derive benefit from ET. Polyclonal resistance also poses a clinical challenge, and tumors with *ESR1*-mut often have subclones harboring concurrent genomic alterations that could mediate ER-pathway-independent resistance as well. Characterizing metastatic tumors by ER positivity or *ESR1* status is not enough, and we need better methodology to select post-CDK4/6i patients that remain endocrine sensitive. Possibilities include genomic profiling panels or novel biomarker identification that could more accurately characterize tumors that are likely to be susceptible. This remains an area of unmet need that future clinical and translation work could significantly impact.

Many of the next-generation ETs under development are being evaluated in ongoing clinical trials as single agents and in combination with targeted therapies (Table 3). Combined therapeutic strategies are important for the management of advanced breast cancer, with CDK4/6 inhibitors, PI3K inhibitors, and mTOR inhibitors already being part of approved combination regimens for MBC. Estrogen- and ER-independent resistance mechanisms can emerge that are not susceptible to Et alone and require one or more drug partners

to re-sensitize tumors. Several of these pathways have been implicated, including activating alterations in growth-factor-dependent kinases, upregulation in MAPK and PI3K/AKT signaling, and downstream dysregulation of the cyclin D1/CDK4/6 cell cycle pathway.¹⁷

Next-generation anti-estrogens have the potential to change how ER+ breast cancer is treated. As clinical trial data continue to mature, evaluating the efficacy and tolerability of these agents, as ET backbones in combination regimens and as monotherapy, will be important to determine how they impact outcomes and where they will be adopted into standard practice.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Maxwell R. Lloyd: Conceptualization; Writing – original draft; Writing – review & editing.

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Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing Interests

MRL: No disclosures. SAW: Consulting/Advisory Board – Foundation Medicine, Veracyte, Pfizer, Biovica, Hologic, Eli Lilly; Institutional Research Support – Genentech, Nuvation Bio, Regor Therapeutics, Eli Lilly. AB: Consultant/Advisory Board: Pfizer, Novartis, Genentech, Merck,

Radius Health, Immunomedics/Gilead, Sanofi, Daiichi Pharma/Astra Zeneca, Phillips, Eli Lilly, Foundation Medicine; Contracted Research/Grant (to institution): Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics/Gilead, Daiichi Pharma/Astra Zeneca, Eli Lilly. EH: Contracted Research/Grant (to institution): Abbvie, Acerta Pharma, Accutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Cullen-Florentine, Curis, CytomX, Daiichi Sankyo, Dana Farber Cancer Inst, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses Pharma, Elucida Oncology, EMD Serono, Fochon, FujiFilm, G1 Therapeutics, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals, InvestisBio, Jacobio, Karyopharm, Leap Therapeutics, Lilly, Lycera, Mabspace Biosciences, MacroGenics, MedImmune, Merck, Mersana, Merus, Millennium, Molecular Templates, Myriad Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Onconova Therapeutics, ORIC Pharmaceuticals, Orinove, Pfizer, Pharma Mar, Pieris Pharmaceuticals Pionyr, Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Relay Therapeutics, Repertoire, Immune Medicine, Rgenix, Roche/Genentech, SeaGen, Sermonix Pharmaceuticals, Shattuck Labs, Silverback, StemCentRx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, Zymeworks; Consulting Advisory Role (all to institution only): Arcus, Arvinas, AstraZeneca, Black Diamond, Boehringer Ingelheim, CytomX, Daiichi Sankyo, Dantari, Deciphera Pharmaceuticals, Eisai, Greenwich LifeSciences, H3 Biomedicine iTeosJanssen, Lilly, Loxo, Merck, Mersana, Novartis, Orum Therapeutics, Pfizer, Propella Therapeutics, Puma Biotechnology, Relay Therapeutics, Roche/Genentech, SeaGen, Silverback Therapeutics. PR: Contracted Research/Grant (to institution): Grail/Illumina, Tempus, Novartis, AstraZeneca, Guardant, Epic Sciences, Inivata, Invitae/ArcherDx, Biotheranostics, Biovica, Foundation Medicine; Consultant/Advisory board: Novartis, AstraZeneca, Pfizer, Daiichi, Guardant, Natera, Inivata, Biovica, Epic Sciences, Tempus, Foundation Medicine.

Availability of data and materials

Not applicable.

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