

SERDs and Breast Cancer Therapy

Subjects: Oncology

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New SERDs are currently under development capable of reducing ER α protein expression and blocking estrogen-dependent and independent ER signaling. SERDs are therefore considered a significant therapeutic approach to treat ER+ BC in both early stage and more advanced drug-resistant cases.

Keywords: SERD ; breast cancer ; endocrine therapy ; hormone therapy ; luminal breast cancer

1. Introduction

Breast cancer (BC) is a heterogeneous disease comprising different subtypes, which can be identified through molecular biomarkers that also act as predictive factors. Luminal BC is characterized by the expression of estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+), HER2-positive BC is defined by overexpression of human epidermal growth factor 2 (HER2) oncogene and conversely, triple-negative BC is characterized by lack of expression of ER/PR and HER2.

Among these, luminal is the most common BC subtype. In the case of metastatic breast cancer, luminal subtype accounts for more than sixty-five percent of all cases. Recommended treatment is endocrine-based systemic therapy, since multiple publications and consensus recommendations conclude that chemotherapy would not be the best option for endocrine sensitive disease, except in situations such as visceral crisis ^[1].

Endocrine therapy (ET) comprises different strategies as suppression of estrogen production or directly targeting the estrogen receptor (ER). For example, aromatase inhibitors (AIs) (letrozole, anastrozole and exemestane) are potent inhibitors of the aromatase enzyme, which catalyzes the last step in estrogen biosynthesis. These agents decrease estrogen production by blocking androgen conversion to estrogens ^{[2][3]}.

Direct targeting of ER α is achieved by selective estrogen receptor modulator (SERM) (e.g., tamoxifen) and selective estrogen receptor degrader (SERD) (e.g., fulvestrant). SERMs compete with estrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion. Meanwhile, SERDs create an unstable protein complex that induces ER protein degradation via proteasome ^[4]. Fulvestrant is a first-generation SERD approved by the FDA in 2007 for treatment of metastatic luminal BC in postmenopausal patients following progression on prior ET with AI or tamoxifen ^{[5][6]}.

2. Antiestrogen Therapy: Basic Concepts Regarding Old and New Agents

Two major isoforms of the estrogen receptor have been identified, ER α and ER β : however, the role of ER β in cancer remains unclear ^{[7][8]}. The two isoforms are encoded by two genes located on different chromosomes (ESR1 on chromosome 6 and ESR2 on chromosome 14), and regulate different specific genes ^{[9][10]}. Both isoforms are structurally organized in six different functional domains (A to F). The receptor contains two activation functions (AF) regions (AF-1: domains A/B and AF-2 domains E/F) , responsible for the transcriptional activation of the receptor. C domain is the DNA-binding region, while D domain is a flexible hinge region containing the nuclear localization signal and links the C to E domain. Finally, E domain harbors the hormone-binding site ^[11].

While ESR1 alterations, such as amplifications, can be identified in up to 30% of ER+ BC patients ^{[12][13]}, it is still uncertain whether this alteration has clinical significance in terms of ET resistance: while some studies have found that ESR1 amplifications were associated with improved disease-free survival ^{[14][15]} several others studies report an association between ESR1 amplifications and tamoxifen resistance ^{[16][17]}.

Similarly, clinical outcomes for ESR1 fusions require further investigation and efforts, since to this date conclusion cannot be drawn regarding their implications ^[18]. Fusions and rearrangements are estimated to have an incidence of 1%, mainly involving the first two noncoding exons of ESR1 binding to various C-terminal sequences from the coiled-coil domain-

containing 170 genes (CCDC170) (ESR1 -e2 > CCDC170), consequently conferring endocrine resistance to tamoxifen [19].

A retrospective analysis of the SoFEA phase III trial showed that median PFS in fulvestrant-containing regimens was significantly better than those treated with exemestane (HR = 0.52; 95% CI 0.30–0.92; p = 0.02) for metastatic BC (MBC) and ESR1 mutations [20]. This data may suggest that fulvestrant could be a potentially more adequate ET for ESR1 mutated patients. Conversely, ESR1 Y735S mutations may reflect higher resistance to fulvestrant [21][22].

3. Novel Strategies

PROTACs are heterobifunctional molecules made up of a ligand for ER (target protein) and another ligand, serving as the E3 ubiquitin ligase complex substrate. Once PROTACs bind to ER, recruit the E3 ubiquitin ligase complex, leading to a polyubiquitilation of ER ending on a proteasomal degradation [23]. PROTACs produce a rapid and complete elimination of intracellular receptor and inhibition of ER signaling [24][25]. PROTACs action is pure antagonism of ER realized by elimination of the receptor, rather than conformational changes of ER to block transcriptional activation. Only a transient binding event is required for degradation, and the PROTAC molecules can cycle through multiple rounds of activity, removing substoichiometric quantities of proteins. (**Figure 4**)

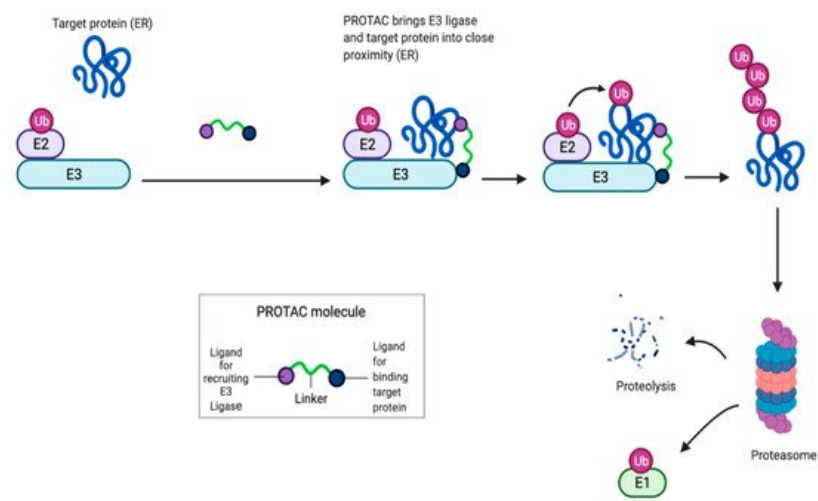


Figure 4. PROTACs: proteolysis targeting chimeras are heterobifunctional molecules made up of a ligand for ER (target protein) and another ligand, serving as the E3 ubiquitin ligase complex substrate. Once PROTACs bind to ER, recruit the E3 ubiquitin ligase complex, leading to a polyubiquitilation of ER ending on a proteasomal degradation.

The rapid progress in ER PROTACs development in preclinical studies lead to a first-in-class, orally bioavailable ER degrading agent, ARV-471, which entered clinical trials in 2019 (NCT04072952) (**Table 1**).

Table 1. Ongoing Trials: Numerous nonsteroidal SERDs are now being studied in clinical trials. Here we summarize the orally available SERDs currently in clinical development.

AGENT	TREATMENT	DISEASE SETTING	PHASE	NAME (INDICATOR)
SERMs				
LASOFOXIFENE	vs. FULVESTRANT +ABEMACICLIB	Previously treated advanced/metastatic disease with <i>ESR1</i> mutations	2	ELAINE: NCT03781063
		Previously treated advanced/metastatic disease with <i>ESR1</i> mutations	2	ELAINE 2: NCT04432454
BAZEDOXIFENE	+PALBOCICLIB	Previously treated advanced/metastatic	1/2	NCT02448771
SERDs				
LSZ102	SINGLE AGENT/+ RIBOCICLIB/+ ALPELISIB	Previously treated advanced/metastatic	1/1b	NCT02734615
G1T48 (RINTODESTRANT)	SINGLE AGENT+/- PALBOCICLIB	Previously treated advanced/metastatic	1	NCT03455270
RAD1901 (ELACESTRANT)	vs. SOC (standard of care)	Previously treated advanced/metastatic	3	EMERALD: NCT03778931

AGENT	TREATMENT	DISEASE SETTING	PHASE	NAME (INDICATOR)
GDC-9545 (GIREDESTRANT)	GDC-9545 vs. LETROZOLE + PALBOCICLIB GDC-9545 vs. ANASTROZOLE + PALBOCICLIB vs. physician's choice of endocrine therapy +/- PALBOCICLIB and LHRH agonist Monotherapy	Advanced/metastatic	3	persevERA: NCT04546009
		Treatment-naïve early breast cancer (window-of-opportunity -> neoadjuvant)	2	coopERA: NCT04436744
		Previously treated advanced/metastatic	2	aceIERA: NCT04576455
		Advanced/metastatic	1	NCT03332797
		Treatment-naïve early breast cancer (window-of-opportunity)	1	NCT03916744
SAR439859 (AMCENESTRANT)	SAR439859 vs. LETROZOLE + PALBOCICLIB vs. physician's choice of endocrine therapy vs. LETROZOLE +/- PALBOCICLIB OR ALPELISIB	Advanced/metastatic	3	AMEERA-5: NCT04478266
		Previously treated advanced/metastatic	2	AMEERA-3: NCT04059484
		Newly diagnosed advanced/metastatic	2	AMEERA-4: NCT04191382
		Advanced/metastatic	1/2	AMEERA-1 NCT03284957
AZD9833 (CAMIZESTRANT)	AZD9833 vs. LETROZOLE + PALBOCICLIB MONOTHERAPY vs. FULVESTRANT +/- PALBOCICLIB, EVEROLIMUS OR ABEMACICLIB	Treatment-naïve advanced/metastatic	3	SERENA-4: NCT04711252
		Neoadjuvant treatment	2	SERENA-3: NCT04588298
		Previously treated advanced/metastatic	2	SERENA-2: NCT04214288
		Previously treated advanced/metastatic	1	SERENA-1: NCT03616587
LY3484356	+/- other anticancer therapies MONOTHERAPY	Advanced/metastatic	1	EMBER: NCT04188548
		Neoadjuvant treatment	1	EMBER 2: NCT04647487
Zn-c5	SINGLE AGENT +/- PALBOCICLIB	Previously treated advanced/metastatic	1/2	NCT03560531
D-0502	SINGLE AGENT +/- PALBOCICLIB	Previously treated advanced/metastatic	1	NCT03471663
NOVEL THERAPIES				
ARV-471 (PROTAC)	+/- PALBOCICLIB	Previously treated advanced/metastatic	1/2	NCT04072952
H3B-5942 (SERCA)	MONOTHERAPY + PALBOCICLIB	Previously treated advanced/metastatic	1/2	NCT03250676
		Previously treated advanced/metastatic	1	NCT04288089

Abbreviations: ORR: overall response rate; CBR: clinical benefit rate; PFS: progression-free survival; AEs: adverse events; AAT: aspartate aminotransferase; DLT: dose-limiting toxicities; SD: stable disease.

ARV-471 is a PROTAC in which E2 is linked to a small-molecule ubiquitin E3 ligase-binding moiety, facilitating the interaction between the ER and an E3 ligase complex that will tag the ER for degradation by the ubiquitin-proteasome system [26].

A total of 130 patients were enrolled (47 in the phase I part and 83 in the phase II part of the trial) and 105 (58% ER1-mutated) were response-evaluable. The phase I evaluated once daily doses from 100 to 600 mg and the dose of 450 mg was selected as the RP2D. Median age was 62 years and in MBC, the median number of prior therapies was three. Prior CDK4/6i, fulvestrant, and chemotherapy were received by 87%, 71%, and 54% of the patients, respectively. Regarding toxicities, grade 2 or higher adverse events reported in ≥10% were anemia (20%), fatigue (16%), nausea (14%), diarrhea (11%) and AST increase (11%). In the response-evaluable group, 13 confirmed PR (12%). SD and CBR (≥23 weeks) were 45% and 33% respectively at 450 mg. Three PRs (25%) and four SDs were observed in 12 patients in whom clonal ESR1 Y537S was present. Median PFS in all patients was 3.7 months and in ESR1 -mutated patients (Y537S) was 7.3 months [27] (Table 2).

Table 2. Reported efficacy and toxicity: Efficacious ER target engagement and promising clinical activity was shown in early-phase clinical trials with a good toxicity profile but clinical efficacy needs to be confirmed in larger patient populations.

LSZ102	Phase I/Ib (NCT02734615) (65) Arm A: Monotherapy Arm B: Combination with Arm B: Combination with Alpelisib	Arm A (n: 78): ORR (1.3%), CBR (9.1%), PFS (1.8 m) Arm B (n: 76): ORR (15.8%), CBR (35.5%), PFS (6.2 m) Arm C (n: 39): ORR (5.4%), CBR (18.9%), PFS 3.5m	Arm A, B, C: Grade 3/4: Nausea (3.1%) and Diarrhea (6.7%) Arm B (Grade 3 AEs): Neutropenia (13.2%) and Increased AAT (3.9%) Arm C (Grade 3 AEs): Hyperglycemia (10%), Skin Rashes (15.4%)
RAD1901 (ELACESTRANT)	Phase I (NCT02338349) (73)	N: 50 (dose- escalation) ORR 19.4% N: 47 (dose expansion) CBR 42.6%	No DLTs Grade 1/2: nausea (33.3%), increased triglycerides (25%), decreased blood phosphorus (25%)
GDC-9545 (GIREDESTRANT)	Phase Ib/II (NCT03332797) (88) Dose expansion: Cohort A: monotherapy Cohort B: combination with palbociclib	N: 88 Cohort A, n: 39 ORR (13%), PFS (7.8 m) Cohort B, n:43 ORR (33%), PFS (9.3 m)	Cohort A: Grade 1/2 fatigue, arthralgia. Grade 3: Fatigue (1), diarrhea (1), transaminase increased (1) Cohort B: Grade 1/2: neutropenia, fatigue, bradycardia, diarrhea, constipation, dizziness, nausea, anemia, asthenia, pruritus and visual impairment. Grade 3: neutropenia (50%)
SAR439859 (AMCENESTRANT)	Phase I: AMEERA-1 (NCT03284957). (84) Monotherapy dose- escalation (Part A)	Part A: n: 59 ORR 8.5%, CBR (33.5%)	Part A: hot flushes (16.1%), constipation (9.7%), arthralgia (9.7%), decreased appetite (8.1%), vomiting (8.1%), diarrhea (8.1%), nausea (8.1%), and fatigue (6.5%)
AZD9833 (CAMIZESTRANT)	Phase I: SERENA-1 (NCT03616587) (87) Part A and B: monotherapy Part C and D: Combination with palbociclib	Part A and B, n: 98 ORR (10%), CDR (35.3%), PFS (5.4m) Part B and C, n: 48 ORR (6.3%), CBR (50%)	5 dose-limiting toxicities (3 for monotherapy and 2 for combination therapy) Monotherapy (≥Grade 2 instances of AZD9833- related adverse events): fatigue (9%), bradycardia (3.1%), nausea (3%), visual disturbances (1.1%) Combination: grade 1–2: anemia, fatigue, lymphopenia, nausea, neutropenia, thrombocytopenia, and reduced white blood cell count
LY3484356	Phase I/Ib (89) EMBER (NCT04188548)	N: 28	Grade 1–2: nausea (32%), fatigue (25%), and diarrhea (18%)
H3B-5942 (SERCA)	Phase 1/2 (NCT03250676) (97)	N: 130 (phase I n: 47/phase II n: 83) PR (12%). SD (45%) and CBR (33%), PFS (3.7m)	Grade 2 or higher adverse: anemia (20%), fatigue (16%), nausea (14%), diarrhea (11%) and AST increase (11%).

4. Summary

ER is involved in the initiation of BC tumorigenesis and in the progression of disease after ET. Targeting, modulating, and degrading ER is the goal of new drugs development, including ESR1 gene mutations identified after ET. Fulvestrant is the only approved SERD and can be used in first-line treatment or after AI or tamoxifen progression. Overcoming fulvestrant's limitations, new SERDs are currently in early-phase clinical development and some of them in phase III clinical trials. New SERDs have demonstrated improved pharmacokinetic and bioavailability compared to fulvestrant in preclinical and early studies, with a potentially higher clinical benefit rate. In this line, PROTACs and SERCAs open new paths to degrade ER, and are still in early clinical studies.

All the currently available results need to be confirmed in phase III clinical trials with larger patient population, exploring the activity of ET plus CDK4/6i combination progression disease setting.

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