The emerging role of SERDs in HR+ breast cancer: Which patients may benefit most in clinical practice?

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Agenda

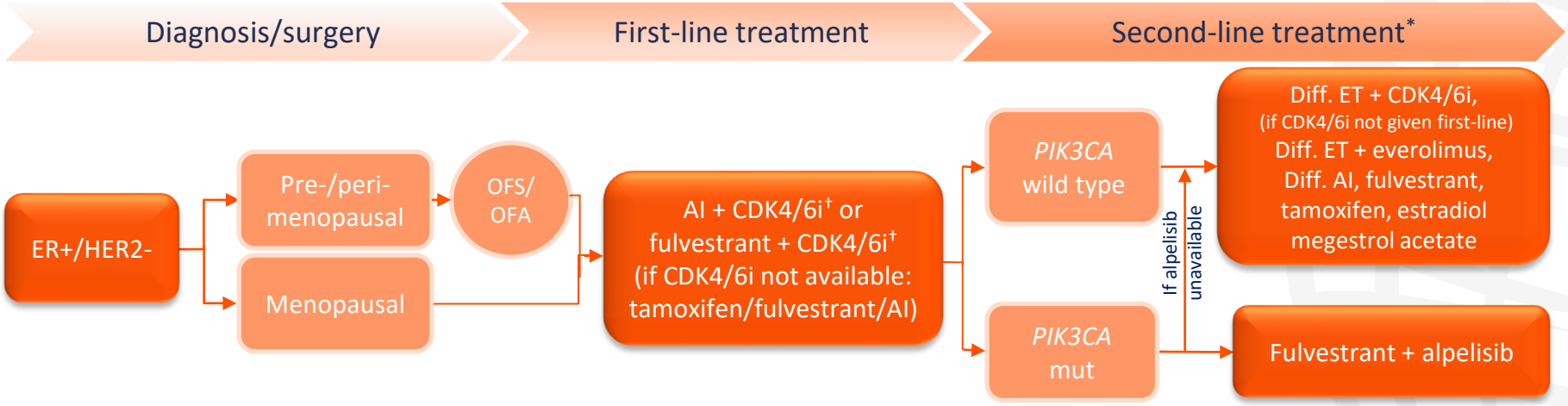
What are the key advances in HR+ breast cancer for 2021?

Which patient subgroups require specific considerations/treatments in the breast cancer setting?

Which patients would benefit most from the oral, second-generation SERD therapies in development?

HR, hormone receptor; SERD, selective estrogen receptor degrader/downregulator.

Latest guidelines: Choosing the best treatment for patients with advanced HR+ breast cancer[1,2]



There are no validated predictive biomarkers other than HR status to identify patients who will/will not benefit from the addition of a CDK4/6i or an mTORi to ET;[1] biomarkers like *ESR1* and *HER2* mutations may impact future clinical decision-making[3]

*PARPi are generally recommended for second-line treatment for patients with g*BRCA*. †Ribociclib is strongly recommended based on overall survival data; survival data are currently still required for other CDK4/6i in the first-line setting.[4]

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; diff, different; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine therapy; g*BRCA*, germline BReast CAncer gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mTORi, mechanistic target of rapamycin inhibitor; mut, mutation; OFS/OFA, ovarian function suppression/ovarian function ablation; PARPi, poly-adenosine diphosphate-ribose polymerase inhibitor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–49; 2. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 7.2021, August 23, 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 13 September 2021); 3. Nagaraj G, Ma CX. *Adv Ther*. 2021;38:109–36; 4. Neven P, et al. *Expert Rev Anticancer Ther*. 2021;21:93–106.

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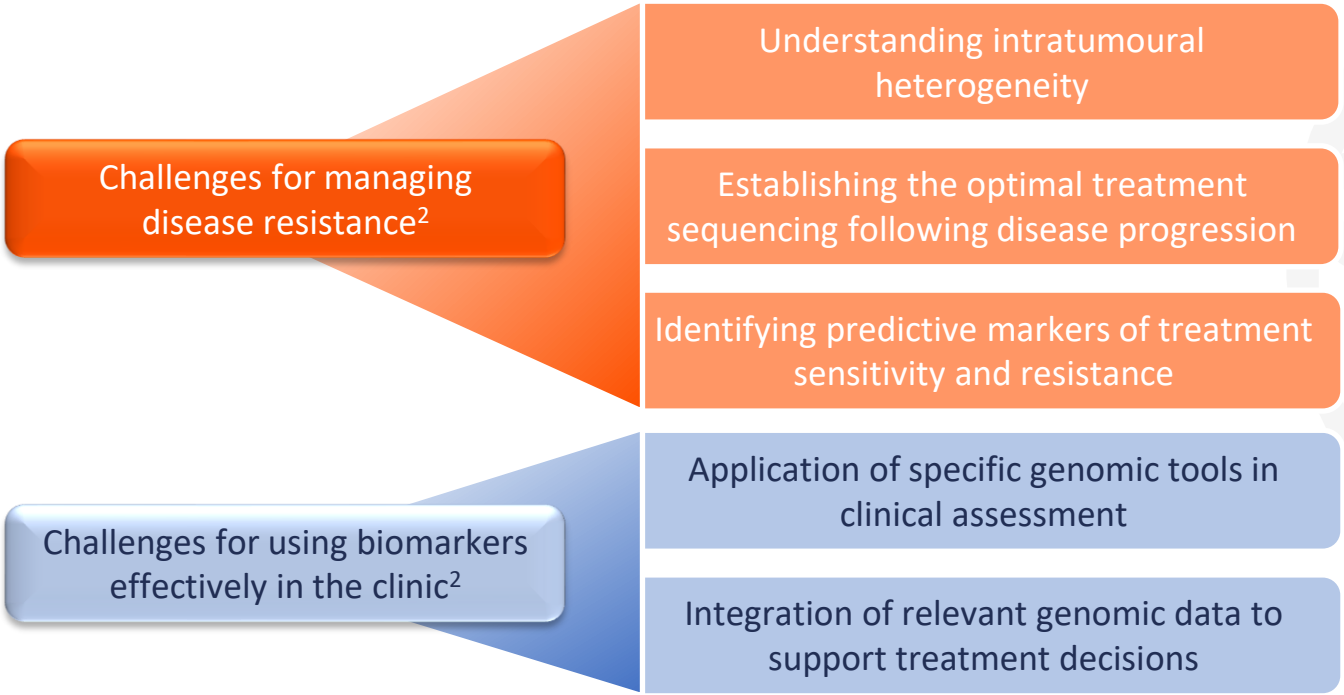
Acquired resistance to endocrine therapy in HR+ breast cancer represents a significant challenge[1]



HR, hormone receptor.

1. Hanker A.B. et al. *Cancer Cell.* 2020;37:496–513; 2. Nagaraj G, Ma CX. *Adv Ther*. 2021;38:109–36.

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Treatment choice should balance mutation status, patient-specific factors and clinical history

- HR and HER2 status
- *PIK3CA*
- Germline mutations e.g. g*BRCA*
- TNBC: PD-L1 expression

- Biological age
- Menopausal status (for ET)
- Socioeconomic and psychological factors
- Therapy availability and patient preference

- Previous therapies and toxicities
- Disease-free interval
- Tumour burden (number and site of metastases)
- Performance status
- Comorbidities
- Organ dysfunctions
- Need for rapid disease/ symptom control

ET, endocrine therapy; g*BRCA*, germline BReast CAncer gene; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD-L1, programmed death-ligand 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TNBC, triple-negative breast cancer.

Cardoso F, et al. *Ann Oncol*. 2020;31:1623–49.

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Newer SERDs vary in their MoAs, bioavailability and AEs

Fulvestrant[1–4]

Approved: 2002

MoA: ERα antagonist. Prevents ER dimerization and inhibits translocation of the receptor to the cell nucleus

PALOMA-3:
Pre/post-menopausal (n=521),
median age 57 y, ≥1 prior line of ET
PFS (fulv + palbo vs fulv + pbo) 11.2 vs 4.6 mo

Safety:
Injection site pain, nausea, bone pain, headache, fatigue, hot flush, increased hepatic enzymes (>15%)

Amcenestrant[3,5,6]

Ongoing trials:
AMEERA-3 (NCT04059484; ph II, Nov 2021)
AMEERA-5 (NCT04478266; ph III, Jan 2024)

MoA: Selective ERα inhibitor. Antagonizes the binding of E2 to ER and promotes the transition of ER to an inactive conformation

AMEERA-1 (NCT03284957, ph I/II):
Post-menopausal (n=35), median age 59 y,
≥6 mo prior ET or adjuvant ET resistance
Part C + D:* ORR, 31.4%; CBR, 74.3%

Safety:
Grade 1–2 nausea and fatigue (17.9% each), asthenia and hot flush (10.3% each)

Elacestrant[3,7,8]

Ongoing trial:
EMERALD (NCT03778931, ph III, Aug 2021)

MoA: Binds to ER inducing its degradation and inhibiting downstream signalling. Activity in *ESR1*-mutant and CDK4/6i-resistant models

RAD1901-005 (NCT02338349, ph I):
Post-menopausal (n=57), median age 63 y,
median 3 prior anticancer therapies
ORR (n=31), 19.4%; CBR (n=47), 42.6%

Safety:
Nausea (33.3%), increased blood triglycerides and decreased blood phosphorus (25.0% each)

*Part C, amcenestrant dose escalation; Part D, dose expansion amcenestrant + palbociclib. All dates reflect estimated primary completion.

AE, adverse event; CBR, clinical benefit rate; CDK6/4i, cyclin-dependent kinase 6/4 inhibitor; E2, estradiol; ER, estrogen receptor; *ERS1*, estrogen receptor 1; ET, endocrine therapy; fulv, fulvestrant; mo, months; MoA, mechanism of action; ORR, overall response rate; palbo, palbococlib; pbo, placebo; PFS, progression free survival; ph, phase; PI, prescribing information; SERD, selective estrogen receptor degrader/downregulator; SmPC, summary of product characteristics; y, years.

1. FDA. Fulvestrant PI, revised May 2019; 2. EMA. Fulvestrant SmPC, revised Oct 2020; 3. Hernando C, et al. *Int J Mol Sci*. 2021;22:7812; 4. Turner NC, et al. *N Engl J Med*. 2018;379:1926–36; 5. Chandarlapaty S, et al. *J Clin Oncol*. 2021;39 (Suppl. 15):1058; 6. Bardia A, et al. *J Clin Oncol*. 2021;39(Suppl. 15):TPS1104; 7. Bardia A, et al. *Future Oncol*. 2019;15:3209–18; 8. Bardia A, et al. *J Clin Oncol*. 2021;39:1360–70. All links, including trial information by NCT number available at: www.clinicaltrials.gov (accessed September 2021).

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Newer SERDs vary in their MoAs, bioavailability and AEs

Camizestrant[1–3]

Ongoing trial:
SERENA-4 (NCT04711252, ph III, Nov 2025)

MoA: Potent, selective, nonsteroidal, pure ERα antagonist. Significant antitumour effects in PDX models of ER+ BC, incl. *ESR1* mutations

SERENA-1 (NCT03616587, ph I):
Pts with ER+/HER2- aBC, ≥1 prior ET, ≤2 prior CT (n=60, median 5 prior therapies)
ORR, 16.3%; CBR, 42.3%

Safety:
Visual disturbances, nausea, bradycardia, fatigue, dizziness, asthenia

Giredestrant[1,4]

Ongoing trial:
PersevERA (NCT04546009, ph III, Apr 2026)

MoA: Competes against E2 for binding, driving an antagonist conformation within the ER ligand-binding domain. Induces ER turnover. Suppresses ER transcriptional activity. Has activity against *ESR1* mutations

CoopERA (NCT04436744, ph II):
Pts with ER+/HER2- eBC (n=83)
Reduction in Ki67 (proliferation biomarker), baseline to week 2: giredestrant + palbo, 80%; anastrozole + palbo, 67%

Safety:
Consistent with known profile for giredestrant

Emerging treatments (phase I)

SHR9549: NCT03596658, Dec 2019*

LY3484356: NCT04188548, Aug 2021†

LSZ102: NCT02734615, Oct 2021

D-0502: NCT03471663, Dec 2021

Rintodestrant: NCT03455270, Jan 2022

ZN-c5: NCT03560531, Dec 2023‡

*Status unknown. †Phase III recently initiated, NCT04975308. ‡Phase I/II. All dates reflect estimated primary completion.
aBC, advanced breast cancer; AE, adverse event; BC, breast cancer; CBR, clinical benefit rate; CT, chemotherapy; E2, estradiol; eBC, early breast cancer; ER, estrogen receptor; *ERS1*, estrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MoA, mechanism of action; ORR, overall response rate; palbo, palbociclib; PDX, patient-derived xenograft; ph, phase; pts, patients; SERD, selective estrogen receptor degrader/downregulator.

1. Hernando C, et al. *Int J Mol Sci*. 2021;22:7812; 2. Paige-Hamilton E, et al. *J Clin Oncol*. 2020;38(Suppl. 15):1024. 3. Im S-A, et al. *J Clin Oncol*. 2021;39 (Suppl. 15):TPS1101;
4. Hurvitz S, et al. LBA14. ESMO, Virtual platform. 16–21 September 2021. All trial information by NCT number available at: www.clinicaltrials.gov (accessed September 2021).

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ESMO 2021: Key SERD updates in ER+/HER2- BC

Amcenestrant

- Amcenestrant combined with palbociclib showed encouraging ORR and CB in aBC, irrespective of *ESR1* mutation status (AMEERA-1 subgroup analyses)[1]
- In the ongoing AMEERA-1 trial in aBC, Part F will confirm the recommended phase II dose of amcenestrant in combination with alpelisib, based on safety, and Part G, will assess safety and tolerability, PK and antitumour activity of the recommended phase II dose[2]

Giredestrant

- Interim analysis data demonstrated superior anti-proliferative activity of giredestrant compared with anastrozole in eBC in the neoadjuvant setting[3]

ZN-c5

- Phase Ib and phase I/II open-label, multicentre studies in aBC are evaluating the safety, PK, and anti-tumour activity of ZN-c5 in combination with abemaciclib, and alone and in combination with palbociclib, respectively[4,5]

aBC, advanced breast cancer; BC, breast cancer; CB, clinical benefit; eBC, early breast cancer; ER, estrogen receptor; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PK, pharmacokinetics; SERD, selective estrogen receptor degrader/downregulator.

1. Chandarlapaty S, et al. Abstract/presentation number: 264P; 2. Campone M, et al. Abstract/presentation number: 333TiP. 3. Hurvitz S, et al. Abstract/presentation number: LBA14; 4. Keogh GP, et al. Abstract/presentation number: 564TiP. 5. Abramson V, et al. Abstract/presentation number: 565TiP. All updates presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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