OVERVIEW OF ER+, HER2–, ADVANCED BREAST CANCER

The safety and efficacy of camizestrant, giredestrant, imlunestrant, inavolisib, lasofoxifene, palazestrant, and vepdegestrant uses under investigation have not been established. There is no guarantee that pipeline molecules will receive regulatory approval and become commercially available for the uses being investigated. The information provided about new disease states being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit https://www.lilly.com/discovery/clinical-development-pipeline, or www.lillyloxooncologypipeline.com. This presentation was commissioned by Loxo@Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

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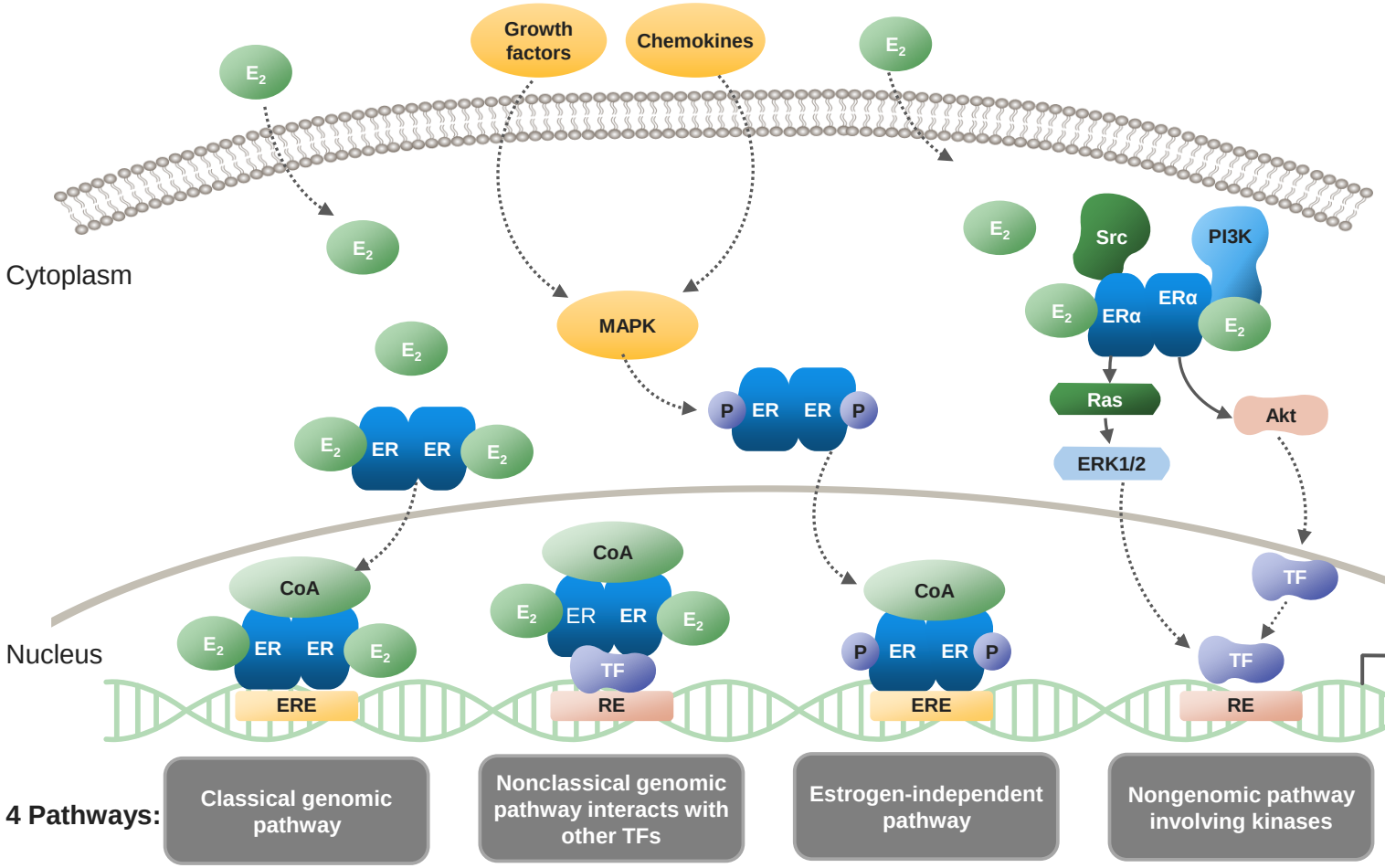
Learning Objectives

This disease state education slide deck provides HCPs with an overview of key concepts in ER+, HER2- MBC

- Review the clinical unmet need after disease progression on an AI ± CDK4/6i
- Investigate the impact of mechanisms of resistance to ET, including *ESR1* mutations
- Describe the current treatment landscape after AI ± CDK4/6i use, and ongoing clinical trials investigating next-generation oral ETs

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, estrogen receptor positive; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; HCP, healthcare professional; HER2−, human epidermal growth factor receptor 2 negative; MBC, metastatic breast cancer.

The Estrogen Pathway is the Primary Driver of ER+, HER2−, ABC[1]



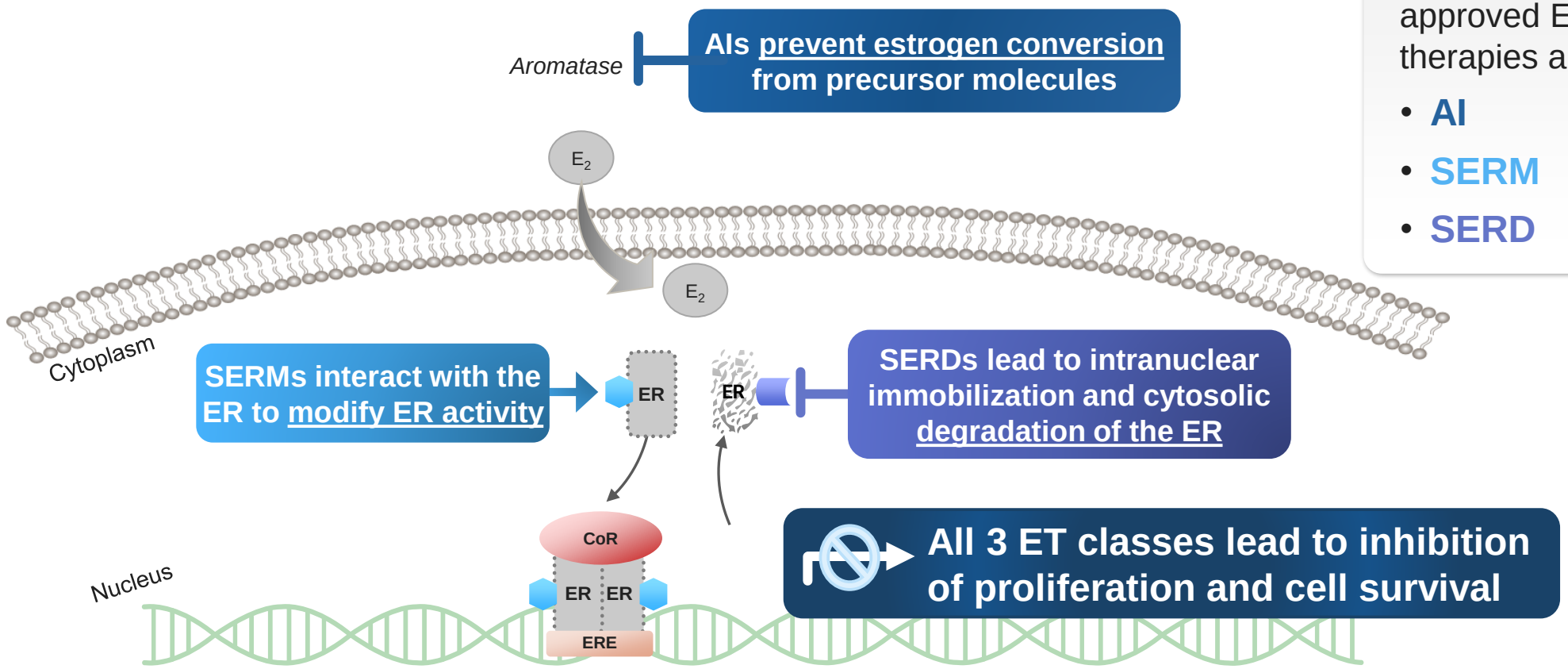
- Breast cancer is the most common cause of cancer mortality in women, with approximately 70% of cases classified as ER+[1,2]
- In these tumors, signaling through the ER controls multiple proliferation-promoting and anti-apoptotic pathways[1,3,4]

Proliferation
Cell survival

Le Romancer et al.[1]

ABC, advanced breast cancer; CoA, coactivator; E_2, estrogen; ER, estrogen receptor; ER+, estrogen receptor positive; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; HER2−, human epidermal growth factor receptor 2 negative; MAPK, mitogen-activated protein kinase; P, phosphorylation; PI3K, phosphoinositide 3-kinase; Ras, rat sarcoma virus; RE, response element; Src, sarcoma protein; TF, transcription factor. 1. Le Romancer M, et al. *Endocr Rev.* 2011;32(5):597-622. 2. Misganaw M, et al. *PLoS One*. 2023;18(1):e0279656. 3. Shanle EK, et al. *Adv Drug Deliv Rev*. 2010;62(13):1265-76. 4. Williams MM, et al. *Cell Death Dis*. 2018;9(21).

Three Main Classes of ER-Targeted Therapies Have Been Approved for Patients With ER+, HER2−, ABC[1-3]



The three main classes of approved ER-targeted therapies are:[1-3]

- AI
- SERM
- SERD

Le Romancer M, et al.[1], Chen YC, et al.[2], Patel HK, Bihani T. 2018.[3]

ABC, advanced breast cancer; AI, aromatase inhibitor; CoR, corepressor; E_2, estrogen; ER, estrogen receptor; ER+, estrogen receptor positive; ERE, estrogen response element; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

1. Le Romancer M, et al. *Endocr Rev.* 2011;32(5):597-622. 2. Chen YC, et al. *Expert Opin Investig Drugs*. 2022;31(6):515-529. 3. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24.

ET Remains the Backbone of Therapy for ER+, HER2−, ABC Following 25 Years of Therapeutic Advancement

AI	SERM	SERD
Nonsteroidal Inhibitor • Anastrozole[19] • Letrozole[17] **Steroidal Inhibitor** • Exemestane[21]	• Tamoxifen[23] • Toremifene[24]	• Elacestrant[3] • Fulvestrant[25]

Combined with endocrine therapies:

Targeted therapies

AKTi
- Capivasertib[2]

CDK4/6i
- Abemaciclib[5]
- Palbociclib[14]
- Ribociclib[6]

mTORi
- Everolimus[13]

PI3Ki
- Alpelisib[4]

Ongoing research and clinical trials are investigating novel approaches to block the ER pathway[1]

Note: SERM approvals occurred prior to 1998.[22]
References, links to USPI and abbreviations on slide 18.

AI + CDK 4/6i is the First-Line Standard of Care in ER+, HER2−, ABC[1]

Key Clinical Trials Combining ET With CDK4/6 Inhibitors Include:

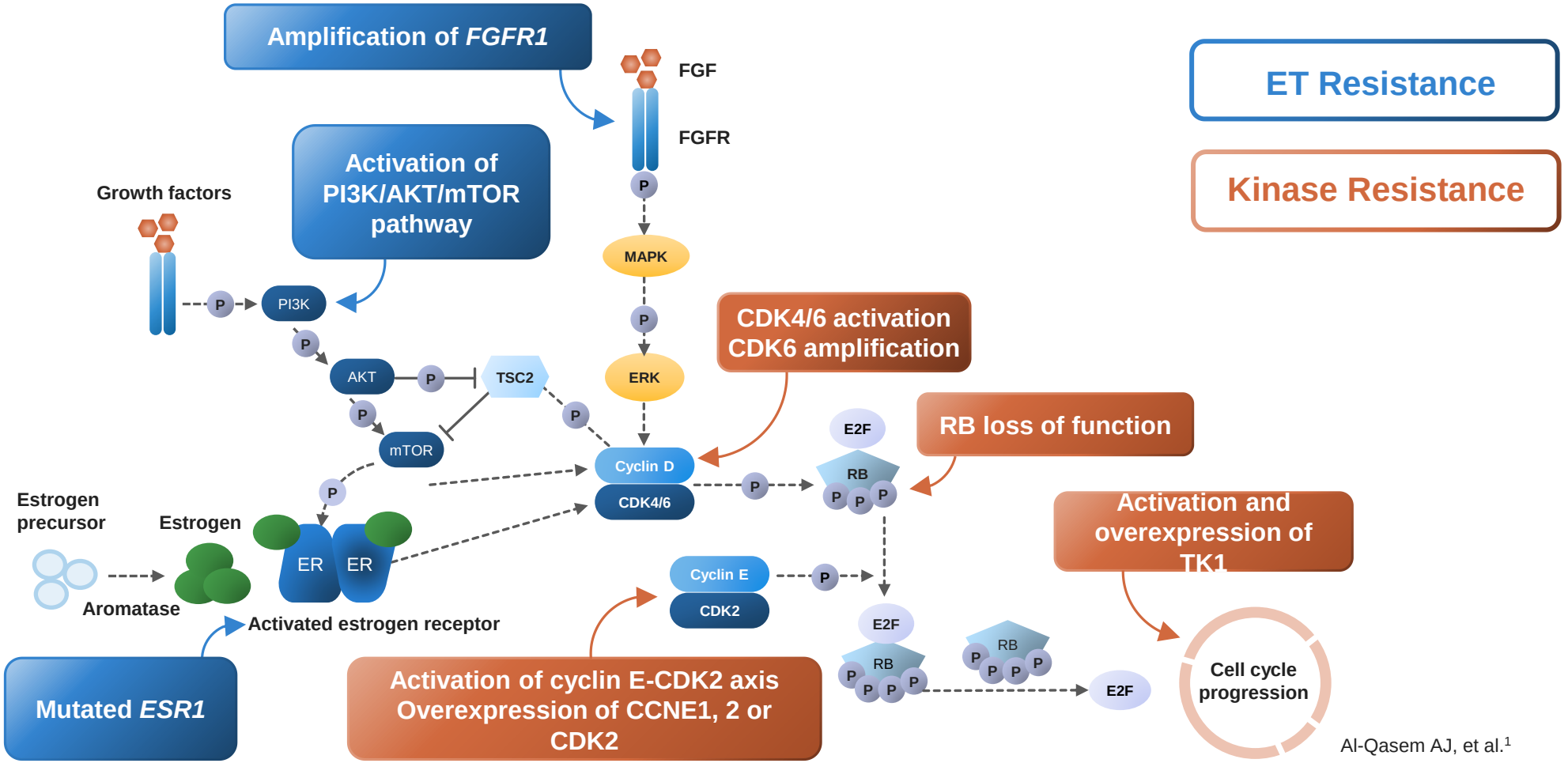
AI + CDK4/6i	**MONALEESA-2 and -7**[2,3] Ribociclib + AI	**MONARCH-3**[4] Abemaciclib + AI	**PALOMA-2**[5] Palbociclib + AI
SERD + CDK4/6i	**MONALEESA-3**[6] Ribociclib + Fulvestrant	**MONARCH-2**[7] Abemaciclib + Fulvestrant	**PALOMA-3**[8] Palbociclib + Fulvestrant

Despite treatment with AI + CDK4/6i, disease progression inevitably occurs[9,10]

ABC, advanced breast cancer; AI, aromotase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, estrogen receptor positive; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; SERD, selective estrogen receptor degrader.

1. Gradishar WJ, et al. *J Natl Compr Canc Netw.* 2023;21(6):594-608. 2. Lu YS, et al. *Clin Cancer Res.* 2022;28(5):851-859. 3. Hortobagyi GN, et al. *N Engl J Med*. 2022;386(10):942-950. 4. Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646. 5. Finn RS, et al. *N Engl J Med.* 2016;375(20):1925-1936. 6. Neven P, et al. *Ann Oncol.* 2022;33(suppl 3):Abstact LBA4. 7. Sledge GW Jr, et al. *J Clin Oncol.* 2017;35:2875-2884. 8. Turner NC, et al. *N Engl J Med.* 2018;379(20):1926-1936. 9. Chen YC, et al. *Expert Opin Investig Drugs.* 2022;31(6):515-529. 10. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792.

There Are Multiple Mechanisms of Resistance to ET ± CDK4/6i[1-5]



Al-Qasem AJ, et al.[1]

AI, aromatase inhibitor; AKT, serine/threonine kinase; CCNE1,2, cyclin E1,2; CDK2, cyclin-dpendent kinase 2; CDK4/6, cyclin-dependent kinase 4/6; E2F, E2 transcription factor; E-CDK2, cyclin E-cyclin-depdendent kinase 2; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; *ESR1*, estrogen receptor 1 gene; FGF, fibroblast growth factor; FGFR, fibroblast growth factor recetpor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphorylation; RB, retinoblastoma tumor supressor; PI3K, phosphoinositide 3-kinase; TK1, thymidine kinase; TSC2, tuberous sclerosis 2 protein.

1. Al-Qasem AJ, et al. *Cancers (Basel).* 2021;13(21):5397. 2. Lindström LS, et al. *J Clin Oncol.* 2012;30:2601-8. 3. Hanker AB, et al. *Cancer Cell.* 2020;37:496-513. 4. Clarke R, et al. *Mol Cell Endocrinol.* 2015;418:220-34. 5. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24.

The Treatment Goal for Patients With ER+, HER2−, ABC is to Extend Survival, Alleviate Symptoms, and Improve Quality of Life[1]

ER+, HER2−, ABC Unmet Needs

Despite the utility of first-line treatment, patients still experience **progression**[1-3]

There are **limitations** with **second-line therapies** and **no defined treatment strategy**[1]

Within the incurable disease setting of ABC, research is ongoing[2,4]

ABC, advanced breast cancer; ER+, estrogen receptor positive; HER2−, human epidermal growth factor receptor 2 negative.

1. Gradishar WJ, et al. *J Natl Compr Canc Netw.* 2023;21(6):594-608. 2. Chen YC, et al. *Expert Opin Investig Drugs.* 2022;31(6):515-529. 3. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792. 4. Patel R, et al. *NPJ Breast Cancer*. 2023;9(20).

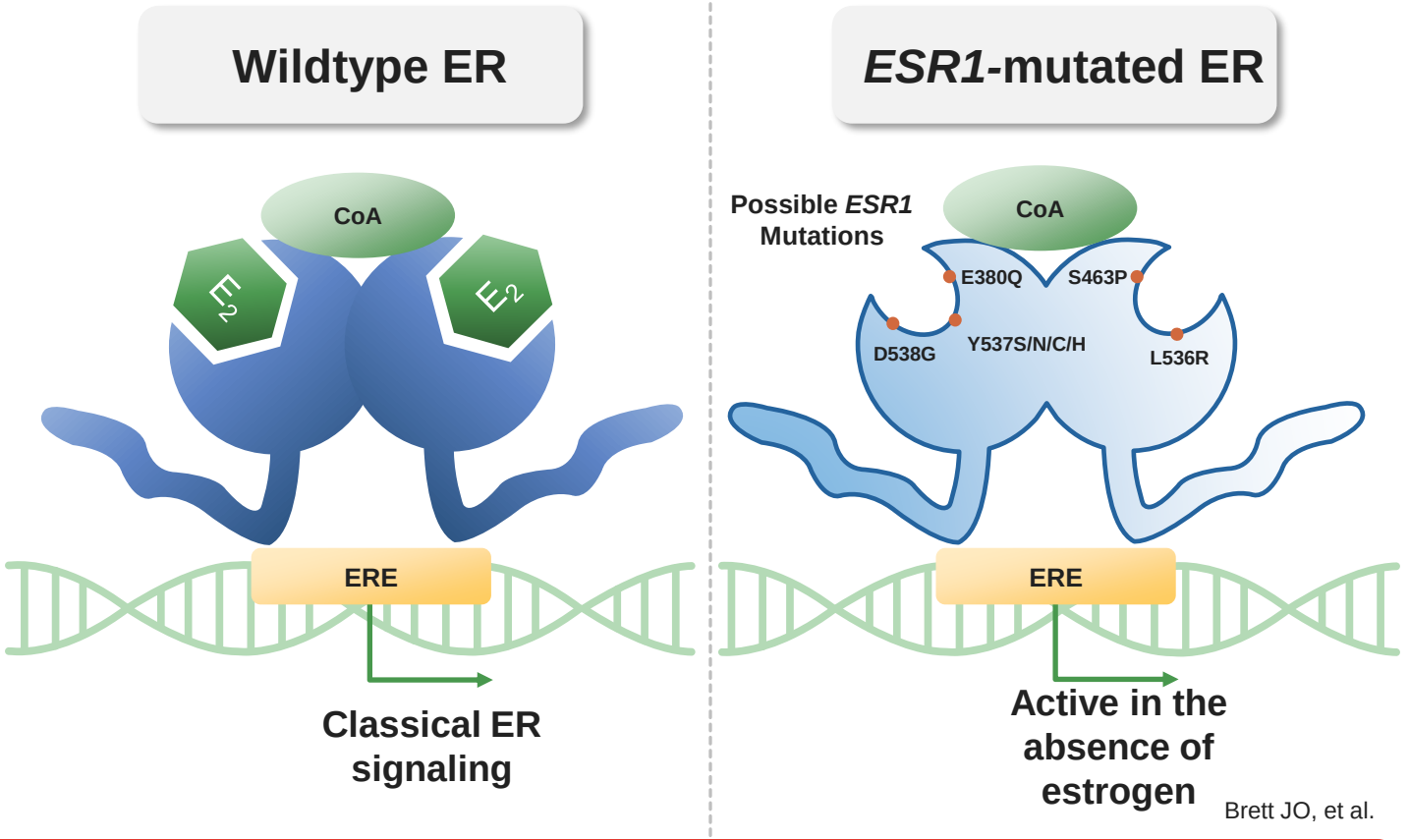
After Progression on ET ± CDK4/6i, No Consensus on an Optimal Treatment Strategy in ER+, HER2−, ABC Has Been Reached[1-3]

Endocrine therapies[1]	Targeted therapies[1,4]	Nontargeted agents[1,5]
Aromatase inhibitors **Selective Estrogen Receptor Modulators** **Selective Estrogen Receptor Degraders**	**AKT inhibitors** **CDK 4/6 inhibitors** **mTOR inhibitors** **PARP inhibitors** **PI3K inhibitors**	**Antibody Drug Conjugates** **Chemotherapy**
Targets the **primary driver of ER+, HER2-, ABC**, delaying time to nontargeted, less tolerable approaches[1,6]	Subject to **tolerability concerns**[2,4]	**Significant toxicities** and **poor quality of life** are associated with chemotherapy[1,5,9]
The efficacy of AI, SERM, and SERD (IM) are **impacted by prior ET** and **blunted in the contemporary therapeutic landscape**[1-3,6-8]	Efficacy is **dependent on prior treatment history** and may be limited to specific **biomarker-selected subgroups**[1,2]	Reserved until patients become **endocrine-refractory** and/or for patients with specific **disease characteristics**[1]

Note: Only approved therapies presented.
ABC, advanced breast cancer; ADC, antibody-drug conjugates; AI, aromatase inhibitor; AKTi, serine/threonine kinase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, estrogen receptor positive; HER2−, human epidermal growth factor receptor 2 negative; IM, intramuscular; mTORi, mammalian target of rapamycin inhibitor; PARPi, poly-ADP ribose polymerase inhibitor; PI3Ki, phosphatidylinositol 3-kinase inhibitor; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.
1. Gradishar WJ, et al. *J Natl Compr Canc Netw.* 2023;21(6):594-608. 2. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792. 3. Chen YC, et al. *Expert Opin Investig Drugs.* 2022;31(6):515-529. 4. American Cancer Society. Accessed January 29, 2024. https://www.cancer.org/cancer/types/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html. 5. American Cancer Society. Accessed January 5, 2024. https://www.cancer.org/cancer/types/breast-cancer/treatment/chemotherapy-for-breast-cancer.html. 6. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24. 7. Kaminska K, et al. *Breast Cancer Res.* 2021;23:26. 8. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. 9. Mayer E. *Am Soc Clin Oncol Educ Book*. 2013:9-14.

ESR1 Mutations Induce Ligand-Independent Activation, Causing Resistance to ET

- Approximately 50% of endocrine resistance cases have an *ESR1* mutation
  - ≈20%-40% of patients who have received AI for ABC develop *ESR1* mutations
- All ESR1 mutations form in the receptor ligand-binding domain
- ESR1 mutations decrease the binding affinity of SERMs and SERDs



Brett JO, et al.

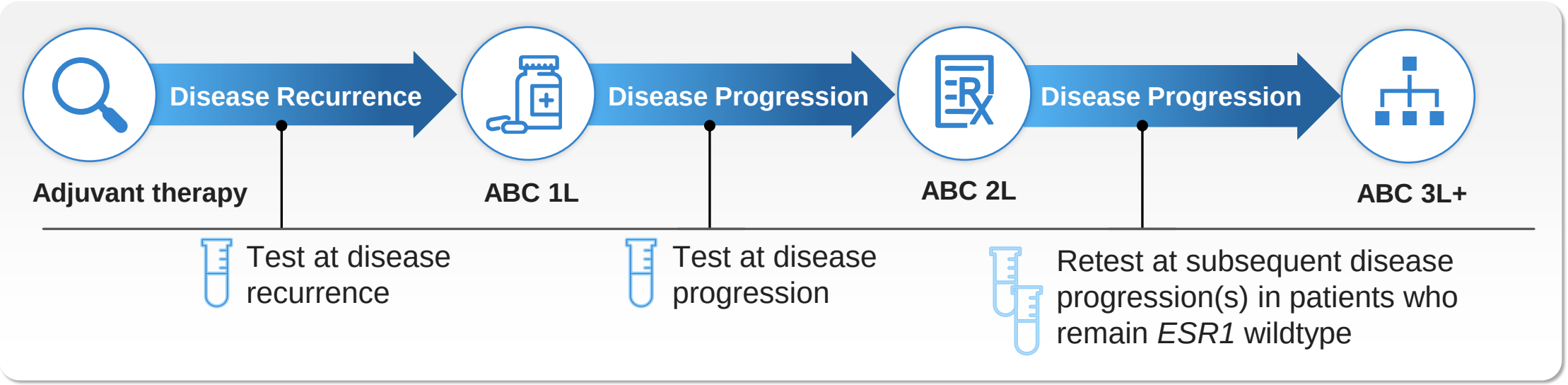
→ *ESR1* mutated ER auto activates (even in the absence of estrogen), leading to constitutive ER signaling

ABC, advanced breast cancer; AI, aromatase inhibitor; E_2, estrogen; ER, estrogen receptor; ERE, estrogen response element; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85.

Guidelines Recommend Routine Testing for Emerging *ESR1* Mutations at Recurrence or Progression on ET in ER+, HER2−, ABC[1]

ESR1 mutation testing[1]



- *ESR1* mutations emerge while on treatment (typically AI) and are not usually detected prior to treatment[1-3]
- *ESR1* mutations are best detected by blood-based ctDNA analyses, which have greater sensitivity and are less invasive than tissue-based testing[a,1-4]

Biomarker testing at progression can help identify the appropriate next line of therapy[2,3]

[a]Disadvantages of tissue-based testing include: impractical to repeat, longer turnaround time for analysis, may not reveal tumor heterogeneity, and/or biopsy of metastaic sites.[3,4]

ABC, advanced breast cancer; AI, aromatase inhibitor; ctDNA, circulating tumor DNA; ER+, estrogen receptor positive; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative. 1. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423-3425. 2. Clatot F, et al. *Oncotarget*. 2016;7(46):74448-74459. 3. Al-Qasem AJ, et al. *Cancers (Basel).* 2021;13(21):5397. 4. Lone SN, et al. *Mol Cancer.* 2022;18;21(1):79.

Several Limitations Exist for All 3 Main Classes of Approved ET

Approved ET limitations	AI	SERM	SERD
Resistance	Longer AI exposure increases the prevalence of *ESR1* mutations, a resistance mechanism that constitutively activates ER signaling in the absence of estrogen[1-3]	Partial ER agonism through coactivator proteins leads to drug resistance and inferior efficacy[8,9]	SERDs administered IM have reduced efficacy in patients with certain *ESR1* mutations[9,10]
Drug administration	Oral ETs may have fluctuations in drug absorption due to GI physiology, possibly resulting in transient autocrine ER signaling[4]		IM route demonstrates inferior pharmacokinetics and requires in-person clinic visits, restricting utility in the adjuvant setting[9,10]
Combination therapies	Typically administered with kinase inhibitors in the ABC setting, which may result in additional toxicities and acquired resistance mechanisms[5-7]		

Novel therapeutic approaches are being investigated[8]

ABC, advanced breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; GI, gastrointestinal; IM intramuscular; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.
1. Vareslija D, et al. *Clin Cancer Res.* 2016;22(11): 2765–2777. 2. Allouchery V, et al. *Breast Cancer Res.* 2018;20(1):40. 3. Clatot F, et al. *Oncotarget.* 2016;7(46):74448-74459. 4. Yu J, et al. *Pharmcol Ther.* 2022:236:108108. 5. Gradishar WJ, et al. *J Natl Compr Canc Netw.* 2023;21(6):594-608. 6. Al-Qasem AJ, et al. *Cancers (Basel).* 2021;13(21):5397. 7. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792. 8. Patel R, et al. *NPJ Breast Cancer.* 2023;9(20). 9. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24. 10. Wardell SE, et al. *Breast Cancer Res Treat.* 2020; 179(1): 67–77.

Scientific Advancements in ETs Seek to Maximize Antagonizing the Estrogen Pathway, the Primary Driver of ER+, HER2−, ABC[1-3]

Next-generation oral ETs are enabling more potent endocrine pathway antagonism while conferring alternative drug-like properties including:

Exposure[1-3]

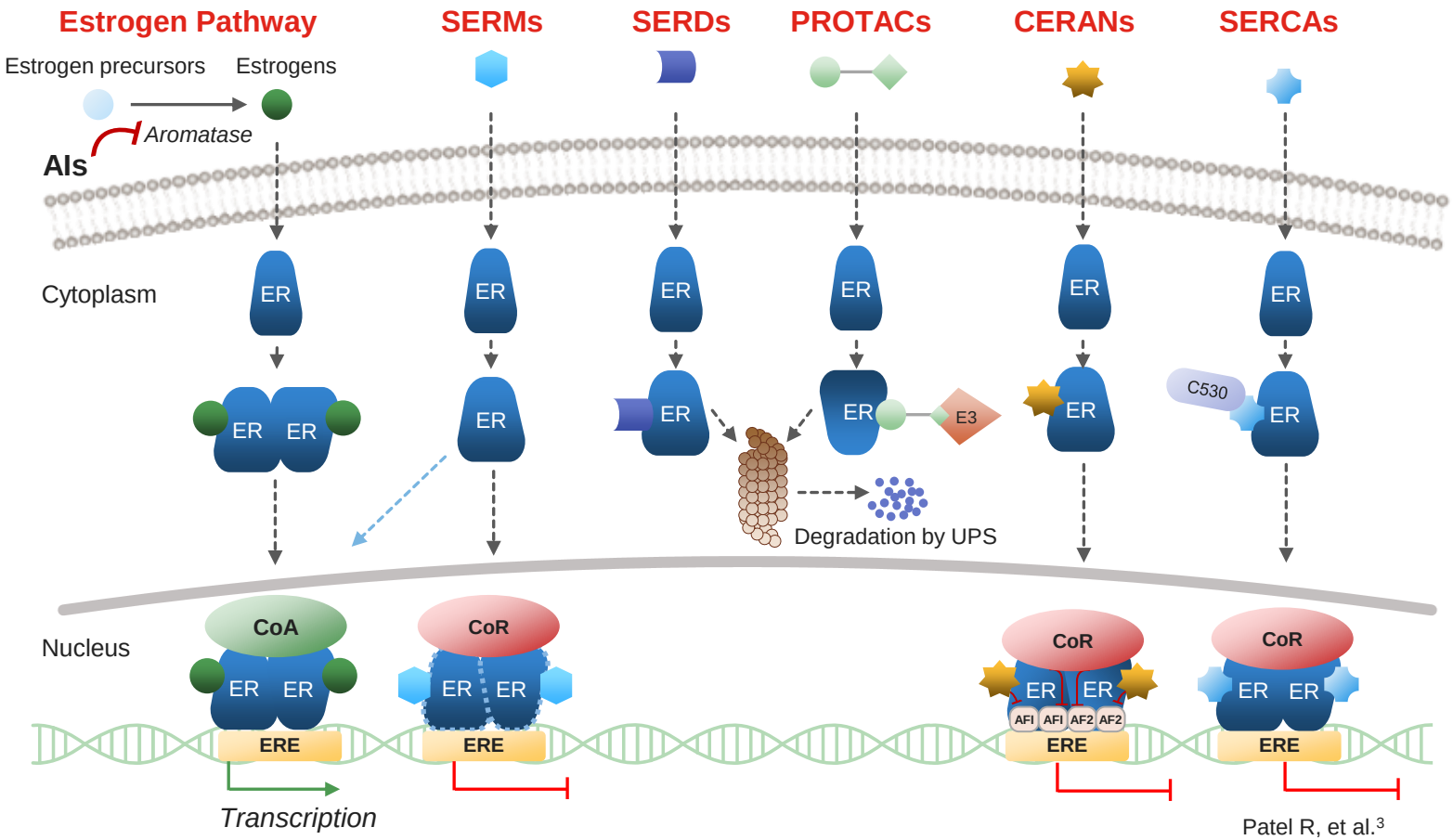
- Sustained high, dose-dependent exposure

Binding[1-3]

- Potent and highly specific binding to both wildtype and mutated ER
- Maintain activity in AI-resistant and ESR1-mutant models

Degradation[1-3]

- SERDs and PROTACs have potent ER degradation and suppression of ER-dependent signaling



ABC, advanced breast cancer; AF1/2, activation function 1/2; AI, aromatase inhibitor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CERAN, complete estrogen receptor antagonist; CoA, coactivator; CoR, corepressor; ER, estrogen receptor; ER+, estrogen receptor positive; ERE, estrogen response element; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative; PROTAC, proteolysis targeting chimera; SERCA, selective estrogen receptor covalent antagonist; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; UPS, ubiquitin-proteasome system. 1. Lloyd MR, et al. *Ther Adv Med Oncol.* 2022;14:17588359221113694. 2. Mittal A, et al. *Cancers (Basel).* 2023;15(7):2015. 3. Patel R, et al. *NPJ Breast Cancer*. 2023;9(20).

Registrational Phase 3 Trials of the Next-Generation ETs as Monotherapy or in Combination with a CDK4/6i[1]

ELAINE-3[2]
Lasofoxifene + Abemaciclib vs Fulvestrant + Abemaciclib

EMBER-3[3]
Imlunestrant vs ET vs Imlunestrant + CDK4/6i

EMERALD[4]
Elacestrant vs ET

persevERA[5]
Giredestrant + Palbociclib vs Letrozole + Palbociclib

pionERA Breast Cancer[6]
Giredestrant + CDK4/6i vs Fulvestrant + CDK4/6i

SERENA-4[7]
Camizestrant +Palbociclib vs Anastrozole + Palbociclib

SERENA-6[8]
Camizestrant + CDK4/6i vs AI + CDK4/6i

VERITAC-2[9]
Vepdegestrant vs Fulvestrant

VERITAC-3[10]
Vepdegestrant + Palbociclib vs Letrozole + Palbociclib

OPERA-01[11]
Palazestrant vs ET

KEY

EMERALD outcomes led to approval of elacestrant in 2023[12-14]

SERM | SERD | PROTAC | CERAN

Next-generation ETs are also being investigated in combination with targeted therapies[1]

AI, aromatase inhibitor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; 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.

1. Patel R, et al. *NPJ Breast Cancer.* 2023;9(20). 2. ClinicalTrials.gov Accessed January 18, 2024. https://classic.clinicaltrials.gov/ct2/show/results/NCT05696626?view=results. 3. ClinicalTrials.gov Accessed January 18, 2024. https://clinicaltrials.gov/study/NCT04975308. 4. ClinicalTrials.gov Accessed January 18, 2024. https://www.clinicaltrials.gov/study/NCT03778931. 5. ClinicalTrials.gov Accessed January 18, 2024. https://clinicaltrials.gov/study/NCT04546009. 6. ClinicalTrials.gov Accessed January 18, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT06065748. 7. ClinicalTrials.gov Accessed January 18, 2024. https://www.clinicaltrials.gov/study/NCT04711252. 8. ClinicalTrials.gov Accessed January 18, 2024. https://www.clinicaltrials.gov/study/NCT04964934. 9. ClinicalTrials.gov Accessed January 18, 2024. https://clinicaltrials.gov/study/NCT05654623. 10. ClinicalTrials.gov Accessed January 18, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT05909397 11. ClinicalTrials.gov Accessed January 18, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT06016738. 12. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 13. FDA.gov. Accessed January 18, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer. 14. ORSERDU™ (elacestrant). Stemline Therapeutics, Inc. 2023.

Summary of Ongoing Combination Trials of Next-Generation ETs

Class	Next-Generation ET	Combination Partner	CT.gov (Study Name)
AKTi	Camizestrant (Oral SERD)	Capivasertib	NCT03616587 (SERENA-1)[1]
	Giredestrant (Oral SERD)	Ipatasertib	NCT04802759[2]
CDK4/6i	Vepdegestrant (PROTAC) Elacestrant (Oral SERD) Imlunestrant(Oral SERD) Lasofoxifene (SERM) Camizestrant (Oral SERD)	Abemaciclib	NCT05548127 (TACTIVE-U)[3] NCT05386108 (ELECTRA)[4]; NCT05563220 (ELEVATE)[5] NCT04975308 (EMBER-3)[6] NCT05696626 (ELAINE-3)[7] NCT04964934 (SERENA-6)[8]
	Vepdegestrant (PROTAC) Camizestrant (Oral SERD) Elacestrant (Oral SERD)	Ribociclib	NCT05573555 (TACTIVE-U)[9] NCT03616587 (SERENA-1)[1] NCT05563220 (ELEVATE)[5]
	Vepdegestrant (PROTAC) Camizestrant (Oral SERD) Elacestrant (Oral SERD) Giredestrant (Oral SERD)	Palbociclib	NCT04072952 (VERITAC-3)[10] NCT03616587 (SERENA-1)[1]; NCT04711252 (SERENA-4)[11] NCT05563220 (ELEVATE)[5] NCT04546009 (persevERA)[12]
CDK7i	Giredestrant (Oral SERD)	Samuraciclib	NCT04802759[13]
Checkpoint inhibitor	Giredestrant (Oral SERD)	Atezolizumab	NCT04802759[13]
ET combinations	Camizestrant (Oral SERD)	Anastrazole	NCT03616587 (SERENA-1)[1]
	Imlunestrant (Oral SERD)	Letrozole/Anastrazole/ Exemestane	NCT04188548 (EMBER)[14]

Note: Investigational ETs being evaluated in this section have positive Phase 2 or beyond data.

AKTi, serine/threonine kinase inhibitor; CDK4/6/7i, cyclin-dependent kinase 4/6/7 inhibitor; ET, endocrine therapy; PROTAC, proteolysis targeting chimera; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator. See references on slide 19.

Summary of Ongoing Combination Trials of Next-Generation ETs (continued)

Class	Next-Generation ET	Combination Partner	CT.gov (Study Name)
HER2 antibody	Giredestrant (Oral SERD)	Pertuzumab, Trastuzumab, and rHuPH2	NCT05296798 (heredERA)[15]
	Imlunestrant (Oral SERD)	Pertuzumab and Trastuzumab	NCT04188548 (EMBER)[16]
	Imlunestrant (Oral SERD)	Trastuzumab	NCT04188548 (EMBER)[16]
mTORi	Camizestrant (Oral SERD) Elacestrant (Oral SERD) Giredestrant (Oral SERD) Imlunestrant (Oral SERD) Vepdegestrant (PROTAC)	Everolimus	NCT03616587 (SERENA-1)[17] NCT05563220 (ELEVATE)[18] NCT05306340 (evERA)[19] NCT04188548 (EMBER)[16] NCT05501769[20]
PI3Ki	Elacestrant (Oral SERD) Imlunestrant (Oral SERD)	Alpelisib	NCT05563220 (ELEVATE)[18] NCT04188548 (EMBER)[16]
	Giredestrant (Oral SERD)	Inavolisib	NCT04802759[21]
	Imlunestrant (Oral SERD)	LOXO-783	NCT05307705 (PIKASSO-01)[22]
Progesterone receptor antagonist	Elacestrant (Oral SERD)	Onapristone	NCT05618613 (ELONA)[23]

Note: Investigational ETs being evaluated in this section have positive Phase 2 or beyond data.

ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mTORi, mammalian target of rapmycin inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor; PROTAC, proteolysis targeting chimera; SERD, selective estrogen receptor degrader. See references on slide 19.

Key Takeaways

- Despite treatment with ET + CDK4/6i, medical unmet needs remain for patients with ER+, HER2−, ABC[1,2]
- There are multiple mechanisms of resistance to ET ± CDK4/6i[3-7]
- Several limitations exist with the second-line therapies along with no defined optimal treatment strategy[1,2,8]
- Ongoing clinical trials are investigating novel approaches to ET[9,10]

ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+, estrogen receptor positive; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2 negative.

1. Chen YC, et al. *Expert Opin Investig Drugs.* 2022;31(6):515-529. 2. Zhou FH, et al. *Front Cell Dev Biol.* 2023;11:1148792. 3. Al-Qasem AJ, et al. *Cancers (Basel).* 2021;13(21):5397. 4. Lindström LS, et al. *J Clin Oncol.* 2012;30:2601-8. 5. Hanker AB, et al. *Cancer Cell.* 2020;37:496-513. 6. Clarke R, et al. *Mol Cell Endocrinol*. 2015;418:220-34. 7. Patel HK, Bihani T. *Pharmacol Ther*. 2018;186:1-244. 8. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608. 9. Patel R, et al. *NPJ Breast Cancer.* 2023;9(20). 10. ORSERDU™ (elacestrant). Stemline Therapeutics, Inc. 2023.

References

References for Slide #5

Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; AKTi, AKT inhibitor; CDK4/6i, cyclin-dependent kinases 4/6 inhibitor; ET, endocrine therapy; ER+, estrogen receptor positive; HER2−, human epidermal growth factor receptor 2 negative; mTORi, mammalian target of rapamycin inhibitor; SERDs, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

References:

1. Patel R, et al. *NPJ Breast Cancer.* 2023;9(20).
2. Truqap™ [US PI]. Wilmington, DE, USA: AstraZeneca, 2023.
3. Orserdu™ [US PI]. New York, NY, USA: Stemline Therapeutics, 2023.
4. Piqray® [US PI]. East Hanover, NJ, USA: Novartis, 2024.
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Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; AKTi, AKT inhibitor; CDK4/6i, cyclin-dependent kinases 4/6 inhibitor; ET, endocrine therapy; ER+, estrogen receptor positive; HER2−, human epidermal growth factor receptor 2 negative; mTORi, mammalian target of rapamycin inhibitor; SERDs, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

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