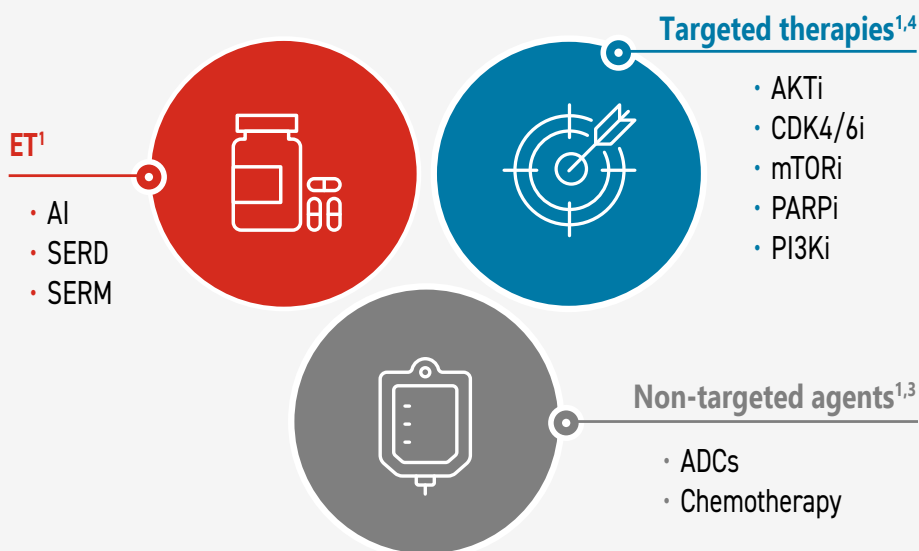


ER+, HER2-, Advanced Breast Cancer

After disease progression or recurrence on ET ± CDK4/6i, no consensus on an optimal treatment strategy for ER+, HER2-, ABC has been reached¹⁻³



ET is a tolerable strategy targeting the primary driver of ER+, HER2-, ABC, delaying time to non-targeted, less tolerable approaches

However, approved options have several limitations^{1,3,5-13}

| Limitations | AI | SERM | SERD |
|---|----|------|------|
| Exposure leads to <i>ESR1</i> mutations ⁵⁻⁷ | ✓ | | |
| <i>ESR1</i> mutation impacts efficacy ⁵⁻¹⁰ | ✓ | ✓ | ✓ IM |
| Partial ER agonism ^{9,10} | | ✓ | |
| Fluctuations in oral drug absorption due to GI physiology, possibly resulting in transient autocrine ER signaling ¹¹ | ✓ | ✓ | ✓ |
| Inferior PK and additional clinic visits ^{10,12} | | | ✓ IM |
| Additional toxicities and resistance mechanisms when combined with targeted therapies ^{1,3,13} | ✓ | ✓ | ✓ IM |

Novel therapeutic approaches are needed to overcome limitations of current ET options^{3,5-13}

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; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; GI, gastrointestinal; 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. 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. American Cancer Society. Accessed January 29, 2024. <https://www.cancer.org/cancer/types/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html>. 5. Vareslija D, et al. *Clin Cancer Res*. 2016;22(11): 2765-2777. 6. Allouchery V, et al. *Breast Cancer Res*. 2018;20(1):40. 7. Clatot F, et al. *Oncotarget*. 2016;7(46):74448-74459. 8. Brett JO, et al. *Breast Cancer Res*. 2021; 23(1):85. 9. Patel R, et al. *NPJ Breast Cancer*. 2023;9(20). 10. Patel HK, Bihani T. *Pharmacol Ther*. 2018;186:1-24. 11. Yu J, et al. *Pharmacol Ther*. 2022;236:108108. 12. Wardell SE, et al. *Breast Cancer Res Treat*. 2020;179(1):67-77. 13. Al-Qasem AJ, et al. *Cancers (Basel)*. 2021;13(21):5397.