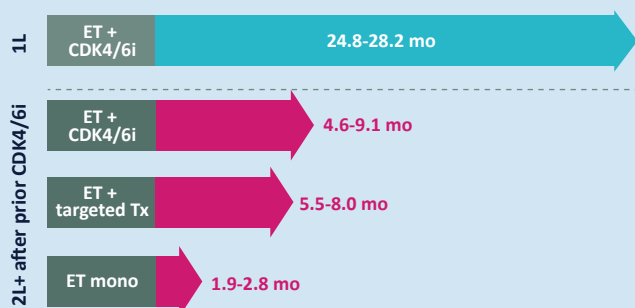


The **UNMET NEED** in 1L HR+/HER2- Advanced Breast Cancer (aBC)

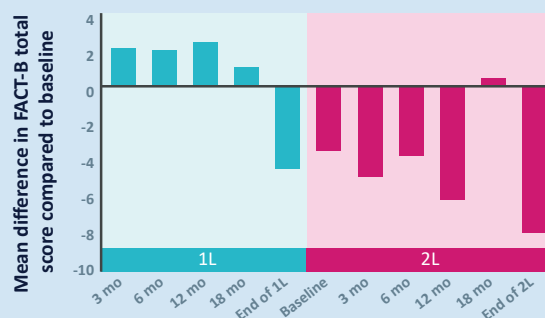
After 1L treatment with an endocrine therapy plus a CDK4/6 inhibitor, mPFS typically decreases with the next line of therapy.¹⁻¹⁰ Health-related quality of life may also deteriorate, potentially including worsened rates of depression, anxiety, or physical and functional well-being.^{11,12} This suggests that each patient should receive the treatment that provides the strongest benefit in the 1L setting.

mPFS in HR+/HER2- aBC*,1-10



Adapted from: Hortobagyi GN, et al. 2018; Tripathy D, et al. 2018; Jhaveri K, Marmé F. 2024; Kalinsky K, et al. 2025; Jhaveri KL, et al. 2025; Mayer EL, et al. 2022; Kalinsky K, et al. 2023; Turner NC, et al. [supplementary appendix] 2023; Rugo HS, et al. 2024; Bidard FC, et al. 2022.

HRQoL in 1L vs 2L HR+/HER2- aBC¹¹



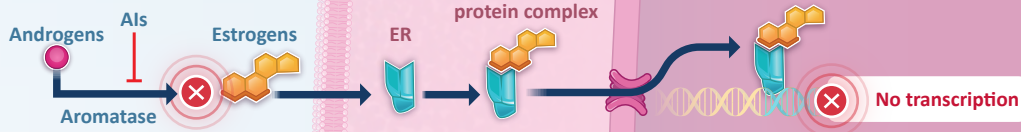
Adapted from: Sonke GS, et al. 2024.

*Cross-trial comparisons do not constitute substantial evidence, as varying study designs, methodology, and patient populations limit the ability to draw conclusions of comparative efficacy and safety.

Current Standard-of-Care Endocrine Therapies in 1L HR+/HER2- aBC^{13,14}

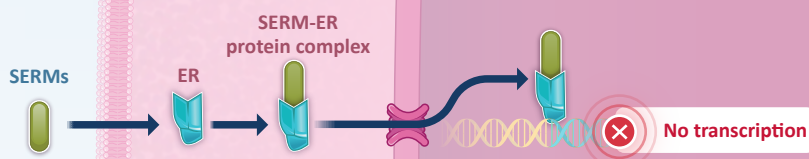
AROMATASE INHIBITORS (AIs)

block the production of estrogen by inhibiting the enzyme aromatase, which converts androgens to estrogens.¹³



SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

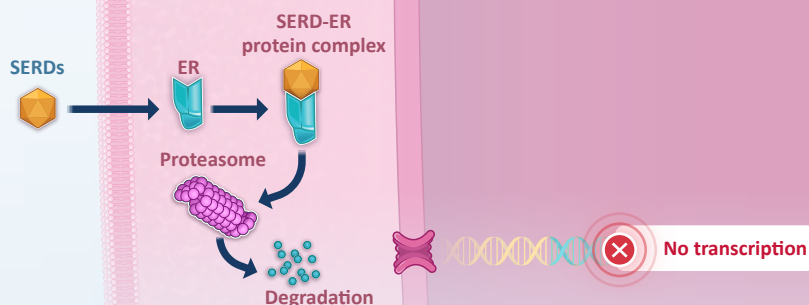
competitively bind to the estrogen receptor (ER) and inhibit ER-related transcription in the breast, while allowing that activity in other tissues like bone and endometrium.¹³



SELECTIVE ESTROGEN RECEPTOR DEGRADERS (SERDs)

competitively bind to the ER too, but in addition to blocking ER signaling, they also target the ER for degradation by the proteasome.¹⁴

» Fulvestrant, the first approved SERD, has limitations, such as intramuscular injections every month and a lower effectiveness against certain mutant forms of the ER¹⁴



Adapted from: Patel R, et al. 2023; Turner N, Huang-Bartlett C, et al. 2023.

Abbreviations: 1L, first line; 2L, second line; aBC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; mo, month; mono, monotherapy; mPFS, median progression-free survival; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; Tx, treatment.

References: 1. Hortobagyi GN, et al. *Ann Oncol.* 2018;29(7):1541-1547. 2. Tripathy D, et al. *Lancet Oncol.* 2018;19(7):904-915. 3. Jhaveri K, Marmé F. *Cancer Treat Rev.* 2024;123:102670. 4. Kalinsky K, et al. *J Clin Oncol.* 2025;43(9):1101-1112. 5. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202. 6. Mayer EL, et al. Presented at: 2022 SABCS, December 6-10, 2022. 7. Kalinsky K, et al. *J Clin Oncol.* 2023;41(24):4004-4013. 8. Turner NC, et al [supplementary appendix]. *N Engl J Med.* 2023;388(22):2058-2070. 9. Rugo HS, et al. *Lancet Oncol.* 2024;25(12):e629-e638. 10. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 11. Sonke GS, et al. *Nature.* 2024;636(8042):474-480. 12. Marschner N, et al. *JAMA Netw Open.* 2020;3(3):e200643. 13. Patel R, Klein P, Triersten A, Sparano JA. *NPI Breast Cancer.* 2023;9(1):20. 14. Turner N, et al. *Future Oncol.* 2023;19(8):559-573.

Investigational Endocrine Therapies in 1L HR+/HER2- aBC¹⁻³

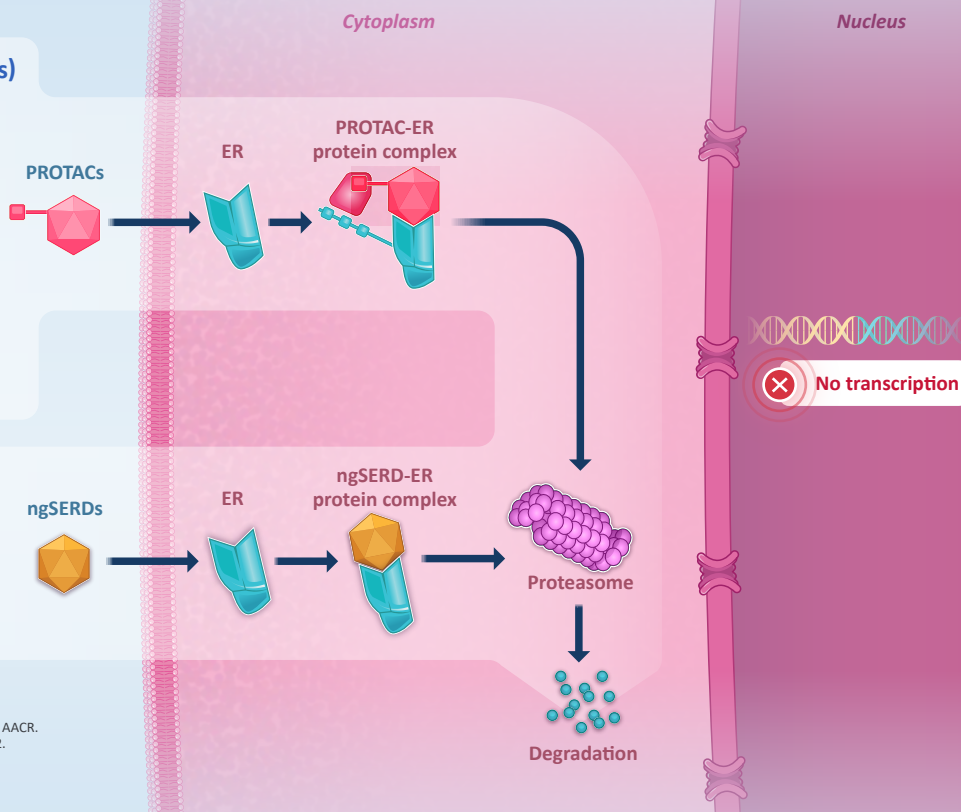
NEXT-GENERATION ORAL SERDs (ngSERDs)

are being developed to target the ER for degradation but also be orally available and potentially more effective than fulvestrant.^{1,2}

- Some ngSERDs are called complete ER antagonists due to their ability to inhibit the ER in all tissues^{1,2,4}
- Other ngSERDs only act as ER antagonists at high doses^{1,2,4}

PROTEOLYSIS-TARGETING CHIMERAS (PROTACs)

are being developed to bind to the ER and contain a domain that can mark the ER for degradation.¹

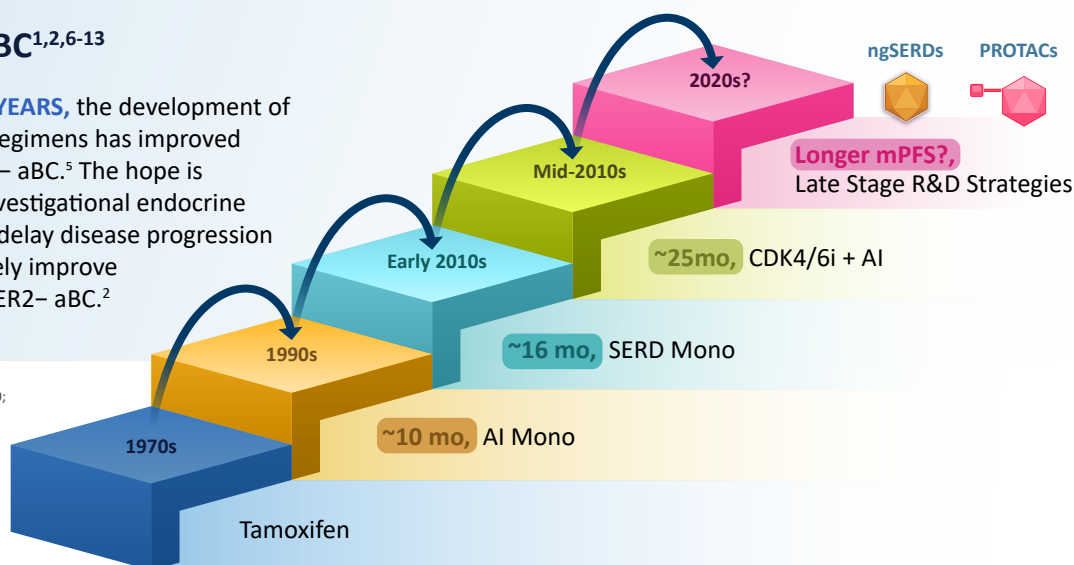


Adapted from: Patel R, et al. 2023; Turner N, Huang-Bartlett C, et al. 2023; AACR. Endocrine therapy in breast cancer: making sense of the 'word salad'. 2022.

mPFS in HR+/HER2- aBC^{1,2,6-13}



OVER THE PAST 50 YEARS, the development of endocrine therapy regimens has improved mPFS for HR+/HER2- aBC.⁵ The hope is that one or more investigational endocrine therapies may help delay disease progression further and ultimately improve outcomes in HR+/HER2- aBC.²



Adapted from: Jordan VC. 2021; Bonnetterre J, et al. 2000; Nabholz JM, et al. 2000; Mouridsen H, et al. 2001; Robertson JFR, et al. 2016; Hortobagyi GN, et al. 2018; Tripathy D, et al. 2018; Jhaveri K, Marmé F. 2024.

Abbreviations: 1L, first line; aBC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mo, month; mono, monotherapy; mPFS, median progression-free survival; ngSERD, next-generation selective estrogen receptor degrader; PROTAC, proteolysis-targeting chimera; R&D, research and development; SERD, selective estrogen receptor degrader.
References: 1. Patel R, Klein P, Tiersten A, Sparano JA. *NPI Breast Cancer*. 2023;9(1):20. 2. Turner N, Huang-Bartlett C, et al. *Future Oncol*. 2023;19(8):559-573. 3. AACR. Endocrine therapy in breast cancer: making sense of the 'word salad'. Published July 18, 2022. Accessed May 29, 2025. <https://www.aacr.org/blog/2022/07/18/endocrine-therapy-in-breast-cancer-making-sense-of-the-word-salad/> 4. Lawson M, et al. *Cancer Res*. 2023;83(23):3989-4004. 5. Turnbull AK. *Future Oncol*. 2015;11(20):2795-2798. 6. Jordan VC. *Endocr Relat Cancer*. 2021;28(1):R11-R30. 7. Bonnetterre J, et al. *J Clin Oncol*. 2000;18(22):3748-3757. 8. Robertson JFR, et al. *Lancet*. 2016;388(10063):2997-3005. 9. Nabholz JM, et al. *J Clin Oncol*. 2000;18(22):3758-3767. 10. Mouridsen H, et al. *J Clin Oncol*. 2001;19(10):2596-2606. 11. Hortobagyi GN, et al. *Ann Oncol*. 2018;29(7):1541-1547. 12. Tripathy D, et al. *Lancet Oncol*. 2018;19(7):904-915. 13. Jhaveri K, Marmé F. *Cancer Treat Rev*. 2024;123:102670.