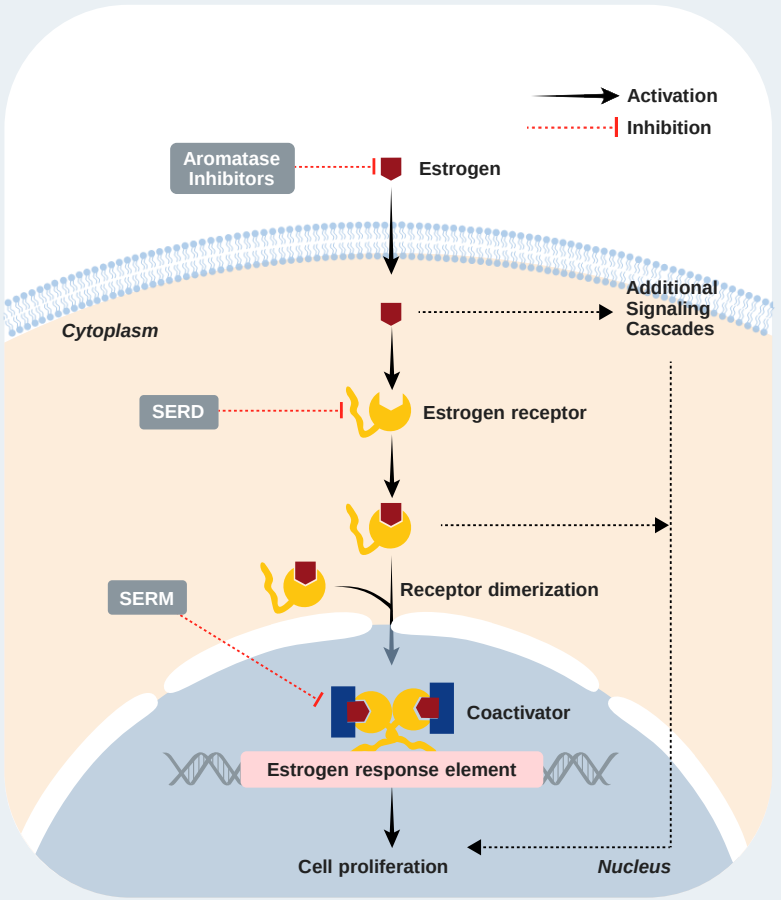
UNDERSTAND THE ROLE *ESR1* MUTATIONS PLAY IN MEDIATING RESISTANCE TO ESTROGEN THERAPY IN ER+, HER2- ADVANCED BREAST CANCER

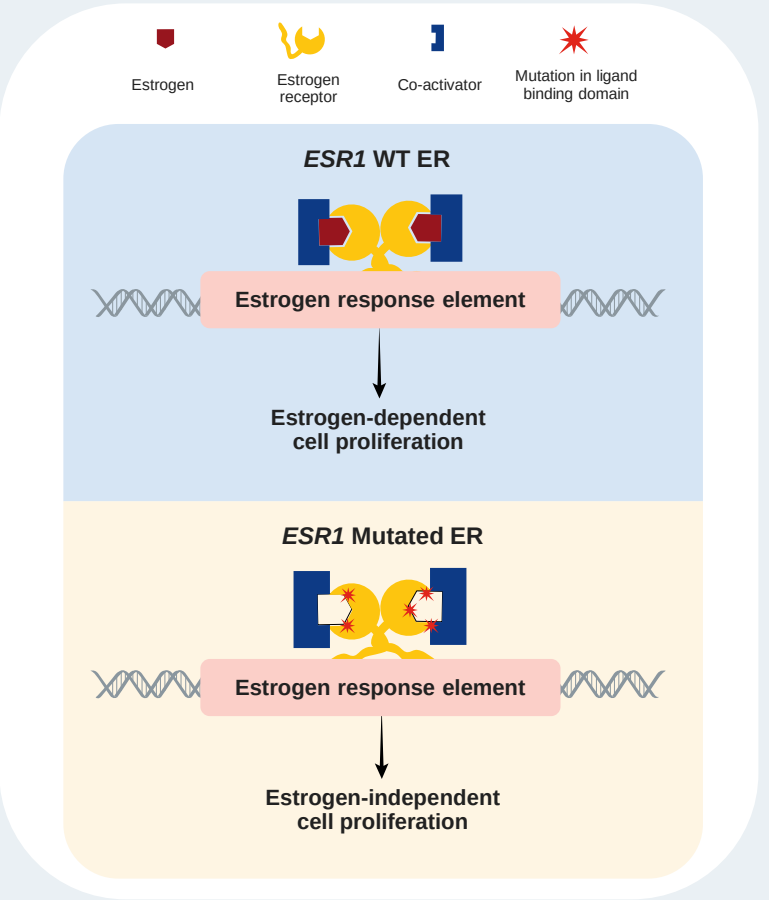
Targeting the Estrogen Pathway in ER+, HER2- mBC[1]

- Breast cancer is the most common cause of cancer mortality in women,[1] with approximately 70% of cases classified as ER+[2]
- The 3 main classes of approved ER-targeted therapies, which lead to inhibition of proliferation and cell survival, are AIs, SERMs, and SERDs[2-4]

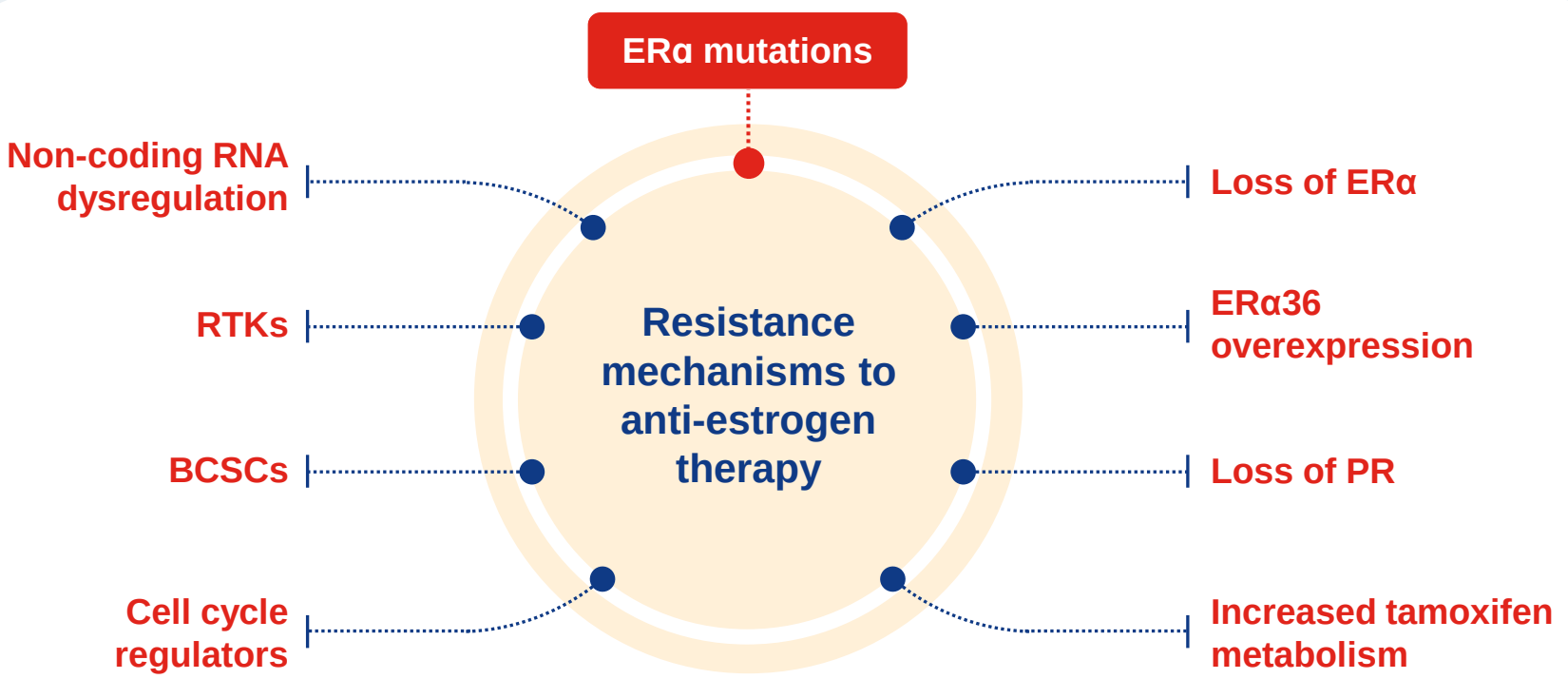


ESR1 Mutations Mediate Resistance to ET in ER+, HER2- mBC[5]

- *ESR1* mutations predict poor response to single agent AI and can blunt response to combination therapies using AI[5]
- *ESR1*-mutated ER autoactivates, even in the absence of estrogen, leading to constitutive ER signaling[5]



Resistance to Estrogen Therapy in ER+, HER2-, mBC[6]



AF=Activation Function; AI=Aromatase Inhibitor; AKT1=Ak Strain Transforming 1; BCSC=Breast Cancer Stem Cell; DBD=DNA-binding Domain; CDK4/6=Cyclin-dependent Kinase 4/6; ET=Endocrine Therapy; ESR1=Estrogen Receptor 1; HER2=Human Epidermal Growth Factor Receptor 2; i=Inhibitor; LBD=Ligand-binding Domain; mBC=Metastatic Breast Cancer; PIK3CA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PI3K/AKT=Phosphatidylinositol 3-Kinase/Protein Kinase B pathway; PR=Progesterone Receptor; PTEN=Phosphatase and Tensin Homolog; RTK=Receptor Tyrosine Kinase; SERD=Selective Estrogen Receptor Degrader; SERM=Selective Estrogen Receptor Modifier; WT=Wild-type; 1L=First Line.

1. Misganaw M, et al. *PLoS One*. 2023;18(1):e0279656. 2. Le Romancer M, et al. *Endocr Rev.* 2011;32(5):597-622. 3. Chen YC, et al. *Expert Opin Investig Drugs*. 2022;31(6):515-529. 4. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24.5. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. 6.Ozyurt R, Ozpolat B. *Cancers*. 2022;14(21):5206.

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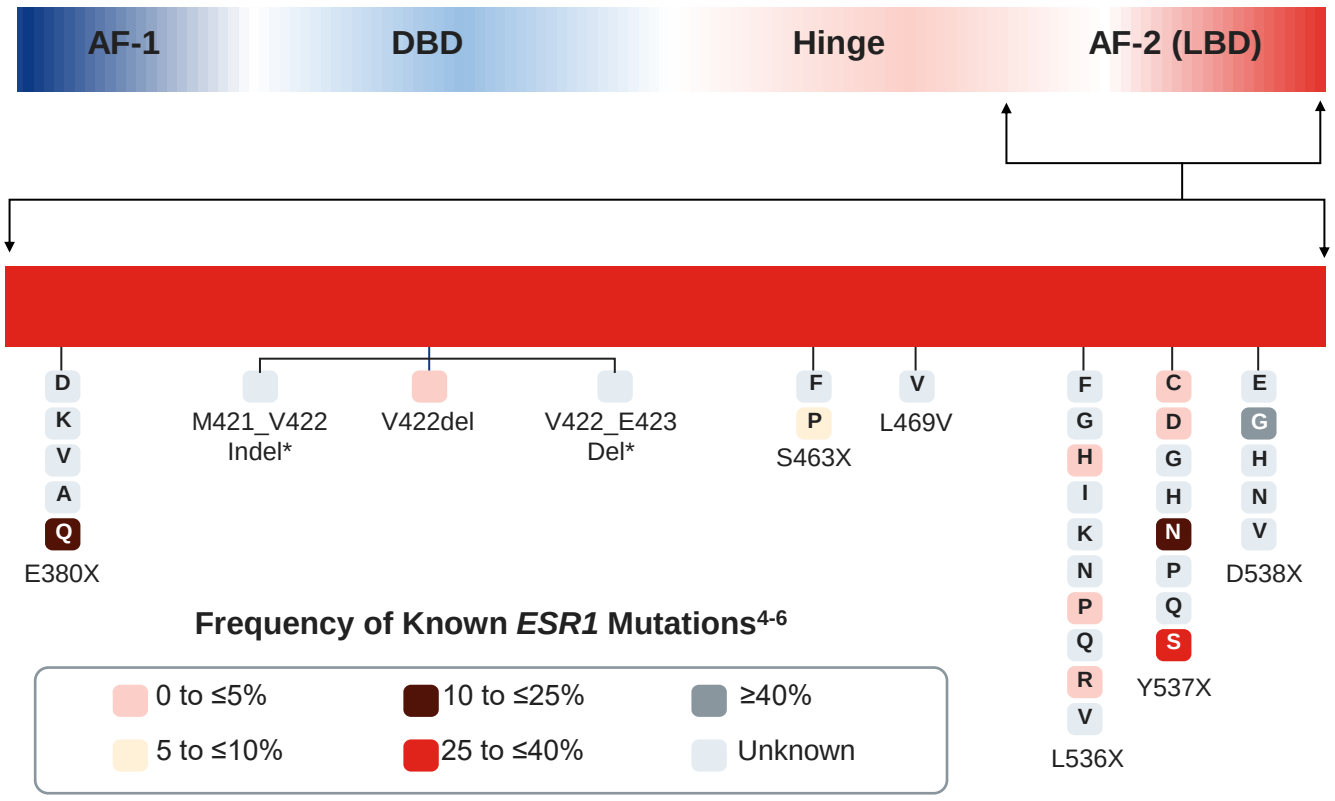
Clinical Impact of *ESR1* Mutations

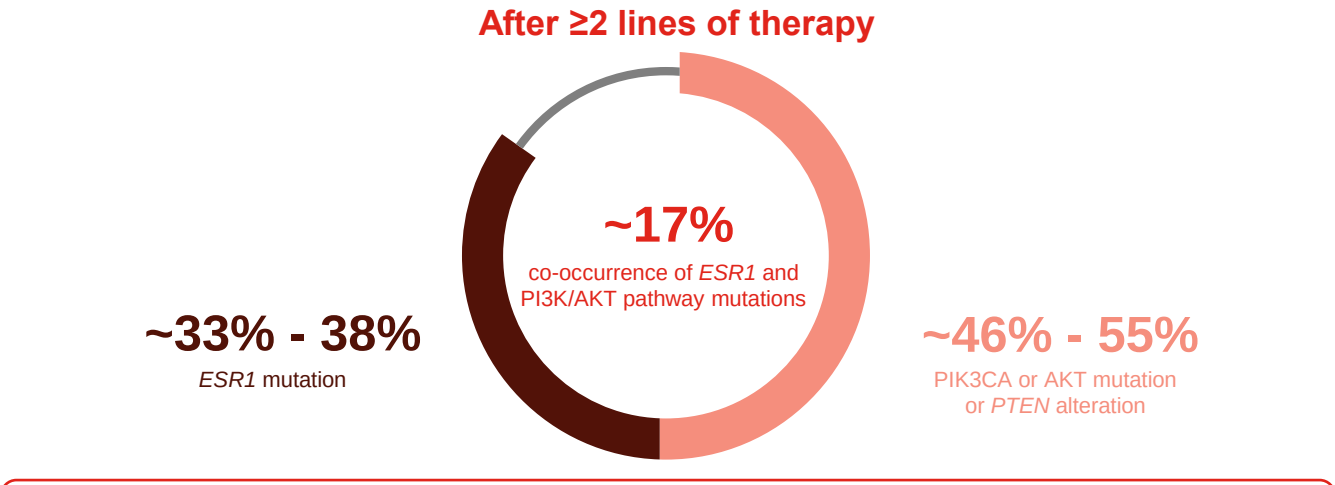
Most identified mutations are found in the LBD[1]

- The most frequent mutations occur at Y537 and D538, but ≥51 have been identified[1]
  - Unique *ESR1* alterations may still occur
- Mutations have different clinical implications for patients[1,2]
  - Compared to D538G, Y537S has greater resistance to traditional estrogen deprivation and some new SERMs and SERDs
  - D538G produces greater metastatic potential, especially to the liver[3]



Co-Occurrence of *ESR1* and *PI3K/AKT* Pathway Mutations[7]

- **38%-55%** of patients with mBC have a genomic alteration in *PIK3CA*, *AKT1,* and *PTEN* at the time of 1L treatment
  - The frequency of *ESR1* mutations increases from <5% in *de novo* mBC to >40% after ET



Comprehensive genomic profiling at the time of diagnosis/recurrence and at the start of each line of therapy can identify actionable mutations and help optimize treatment selection

*The frequency of this specific mutation is presumed to be unknown as it could not be verified in the current literature. AF=Activation Function; AI=Aromatase Inhibitor; AKT1=Ak Strain Transforming 1; BCSC=Breast Cancer Stem Cell; DBD=DNA-binding Domain; CDK4/6=Cyclin-dependent Kinase 4/6; ET=Endocrine Therapy; ESR1=Estrogen Receptor 1; HER2=Human Epidermal Growth Factor Receptor 2; i=Inhibitor; LBD=Ligand-binding Domain; mBC=Metastatic Breast Cancer; PIK3CA=Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PI3K/AKT=Phosphatidylinositol 3-Kinase/Protein Kinase B pathway; PR=Progesterone Receptor; PTEN=Phosphatase and Tensin Homolog; RTK=Receptor Tyrosine Kinase; SERD=Selective Estrogen Receptor Degrader; SERM=Selective Estrogen Receptor Modifier; 1L=First Line.

1. Dustin D, Gu G, Fuqua SAW. *Cancer*. 2019;125(21):3714-3728. 2. Bardia A, et al. *J Clin Oncol.* 2021;39(12):1360-1370. 3. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85. 4. Corné J, et al. *Clin Chim Acta*. 2023;545:117366. 5. Kingston B, et al. *Cancer Discov*. 2024;14(2):274-289. 6. Grinshpun A, et al. *Biochim Biophys Acta Rev Cancer*. 2023;1878(1):188830. 7. Bhave MA, et al. *Breast Cancer Res Treat*. 2024; 207(3):599-609.