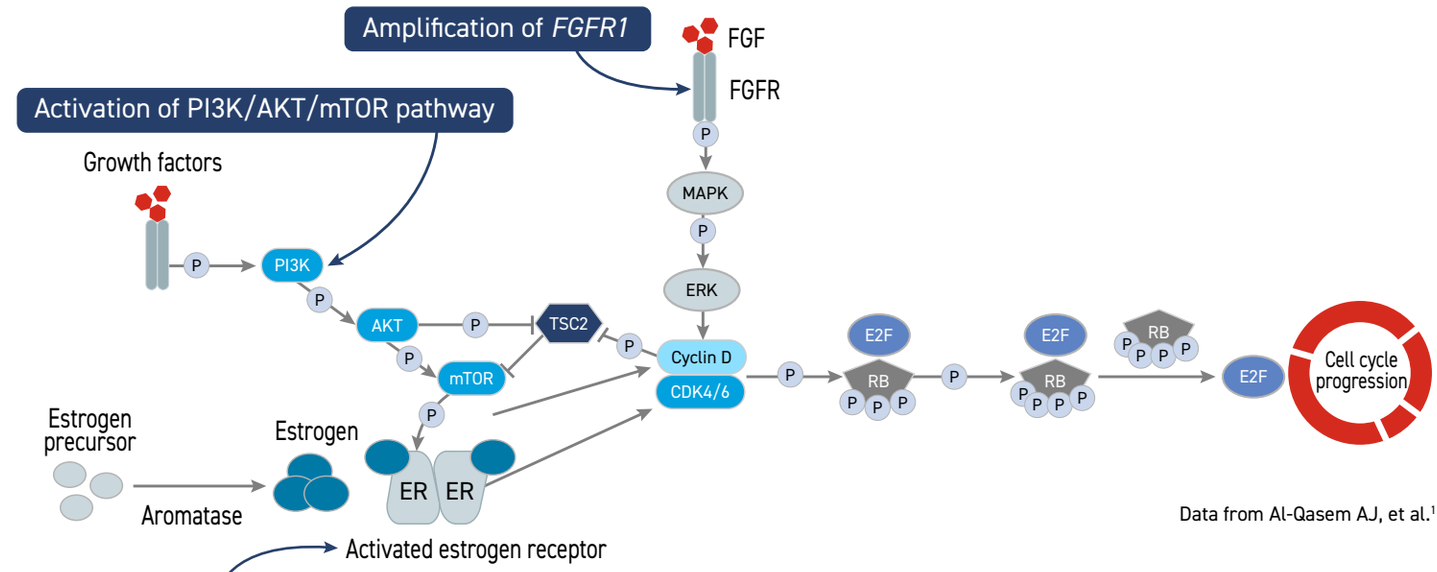
LOXO@Lilly

ER+, HER2-, Advanced Breast Cancer

There are multiple mechanisms of resistance to ET[1-5]

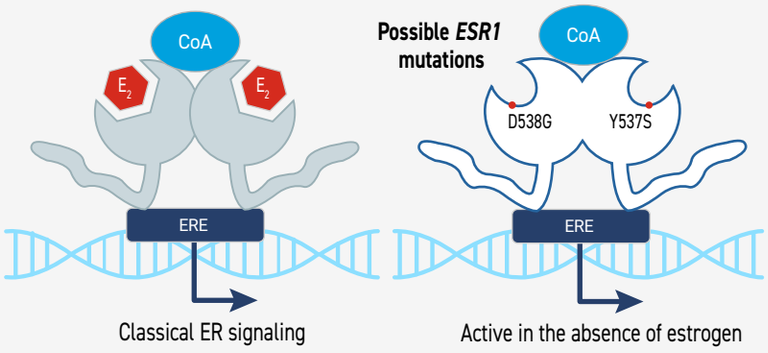


Data from Al-Qasem AJ, et al.[1]

Mutated *ESR1*

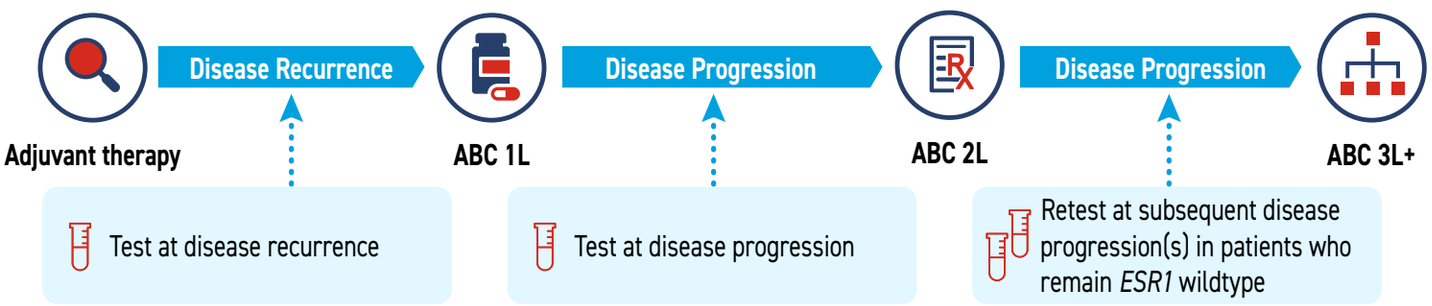
Approximately **20%-40%** of patients who have received AI for ABC develop *ESR1* mutations[6]

ESR1-mutated ER **auto activates** (even in the absence of estrogen), leading to constitutive ER signaling[6]



Data from Brett JO, et al.[6]

When and how to test for *ESR1* mutations[7]



ESR1 mutations are best detected with blood-based ctDNA analyses[1,7,8]

Guidelines recommend routine testing for emerging *ESR1* mutations at recurrence or progression on ET in ER+, HER2-, ABC to help identify the appropriate next line of therapy[1,7,8]

ABC, advanced breast cancer; AI, aromatase inhibitor; AKT1, serine/threonine kinase 1; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CoA, coactivator; ctDNA, circulating tumor DNA; E_2, estrogen; E2F, E2 transcription factor; ER, estrogen receptor; ER+, estrogen receptor positive; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; FGF, fibroblast growth factor; FGFR, fibroblast growth factor recetpor; HER2-, human epidermal growth factor receptor 2 negative; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphorylation; PI3K, phosphoinositide 3-kinase; RB, retinoblastoma tumor supressor; 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;30:2601-2608. 3. Hanker AB, et al. *Cancer Cell* 2020;37:496-513. 4. Clarke R, et al. *Mol Cell Endocrinol.* 2015;418:220-234. 5. Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24. 6. Brett JO, et al. *Breast Cancer Res.* 2021; 23(1):85. 7. Burstein HJ, et al. *J Clin Oncol.* 2023;31(18):3423-3425. 8. Clatot F, et al. *Oncotarget.* 2016;7(46):74448-74459.