ESR1-Mutation Testing at First Progression in ER-Positive, HER2-Negative Advanced Breast Cancer

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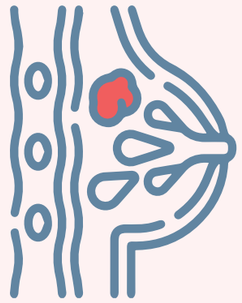
Background

- Resistance to endocrine therapy in ER+/HER2- advanced breast cancer can be classified as intrinsic or acquired [2,3]
- Intrinsic mutations include alterations to the PI3K/AKT/MTOR, RAS-MAPK, or FGFR1 pathways; RB1 loss; and TP53 activation[4]
- Mutations of the ER ligand-binding domain (*ESR1* mutations) are acquired predominantly during endocrine therapy in the metastatic setting, and result in constitutively active ER signalling, which promotes tumour growth and resistance to aromatase inhibitors or fulvestrant (Figure 1)[1,5,7]

- *ESR1* mutations are detected in up to 40% of patients with ER+/HER2- advanced breast cancer following initial endocrine therapy[8]
  - *ESR1* mutations emerge during endocrine therapy in the metastatic setting, becoming drivers of resistance, and are associated with poor outcomes in advanced breast cancer[9]
- Longer exposure to endocrine therapy in the metastatic setting increases the chance of developing an ESR1 mutation during treatment (Figure 1)[8-17]



- *ESR1* mutations are a predictive biomarker of response to treatment with elacestrant[8]
- Testing for *ESR1* mutations is recommended at each progression during the metastatic treatment course to identify patients who are most likely to respond to targeted treatments[10,12,14,18]
  - ASCO, NCCN, and ESMO guidelines recommend testing for *ESR1* mutations at each progression, if not detected previously[19-21]
  - Data suggest that greater progression-free survival benefit is achieved in biomarker-selected patient subgroups with targeted agents than with standard-of-care treatment[8,22,23]

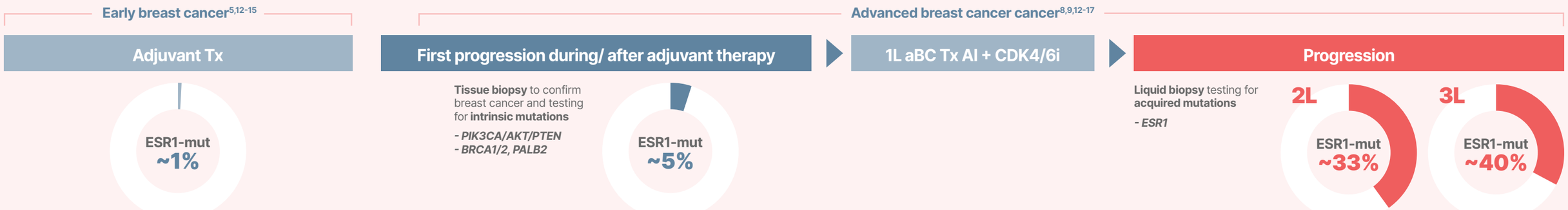


Figure 1: *ESR1*-mutation prevalence rate by treatment line.

As *ESR1* mutations occur almost exclusively after ET in the aBC setting,[14] testing for *ESR1*-mut should occur at each progression if not detected previously[2,19]

- Guidelines suggest testing for ESR1 mutations at each progression, preferably in ctDNA (liquid biopsy). Testing in primary archived tissue is not recommended given the acquired nature of ESR1 mutations during aBC treatment.[20,21]
- Since acquired *ESR1* mutations are subclonal, they are not always detected with tissue biopsy[24,25]
- Liquid biopsy confers more sensitivity to identify ESR1 mutations, especially if ctDNA tumor fraction is >1% (Figure 2)[17]
- Archival tissue from the primary tumour should not be used to identify *ESR1* mutations, as they develop mainly during treatment of advanced breast cancer[18]

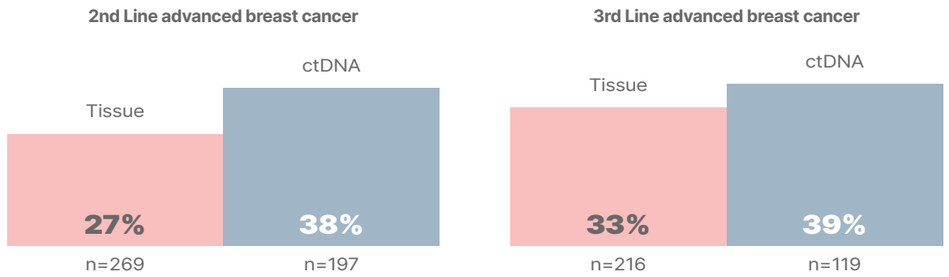


Figure 3: *ESR1*-mutation prevalence rate by treatment line in tissue and liquid biopsy.[17]
Percentages have been rounded to the nearest whole number.
ctDNA (TF≥1%) showed a markedly higher prevalence of any of the genomic alterations assessed.

ESR1-mutation testing, preferably by blood-based ctDNA, is recommended at each progression during the metastatic treatment course to identify patients who are most likely to respond to targeted treatments[19-21]

Abbreviations

2L: second line; 3L: third line; aBC: Advanced Breast Cancer; AKT: protein kinase B; ASCO: American Society of Clinical Oncology; ctDNA: circulating tumour DNA; ER: oestrogen receptor; ER+: oestrogen receptor positive; *ESR1*: oestrogen receptor 1; ERα: estrogen receptor-alpha; ESMO: European Society for Medical Oncology; FGFR1: fibroblast growth factor receptor 1; HER2: human epidermal growth factor receptor 2; HER2- human epidermal growth factor receptor negative; MTOR: mechanistic target of rapamycin; mut: mutation; NCCN: National Comprehensive Cancer Network; PI3K: phosphoinositide 3-kinase; RAS-MAPK: rat sarcoma-mitogen-activated protein kinase; RB1: retinoblastoma protein; TF: tumour fraction; TP53: tumour protein p53.

References

1. Bardia A et al. Case 35-2018: A 68-year-old woman with back pain and a remote history of breast cancer. N Engl J Med. 2018;379(20):1946-53.
2. Gennari A et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95.
3. Rasha F et al. Mechanisms of endocrine therapy resistance in breast cancer. Mol Cell Endocrinol. 2021;532:111322.
4. Rani A et al. Endocrine resistance in hormone receptor positive breast cancer - from mechanism to therapy. Front Endocrinol. 2019;10:245.
5. Jeselsohn R et al. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015;12(10):573-83.
6. Belachew EB, Sewasew DT. Molecular mechanisms of endocrine resistance in estrogen-positive breast cancer. Front Endocrinol. 2021;12:599586.
7. Lei JT et al. Endocrine therapy resistance: new insights. Breast. 2019;48(Suppl 1):S26 - 30.
8. Bidard FC et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized Phase III EMERALD trial. J Clin Oncol. 2022;40(28):3246-56.
9. Brett JO et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021;23(1):85.
10. Jeselsohn R et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor positive breast cancer. Clin Cancer Res. 2014;20(7):1757-67.
11. Jeselsohn R et al. Allele-specific chromatin recruitment and therapeutic vulnerabilities of ESR1 activating mutations. Cancer Cell. 2018;33(2):173-86.e5.
12. Allouchery V et al. Circulating ESR1 mutations at the end of aromatase inhibitor adjuvant treatment and after relapse in breast cancer patients. Breast Cancer Res. 2018;20(1):40.
13. Schiavon G et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med. 2015;7(313):313ra182.
14. Toy W et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet. 2013;45(12):1439-45.
15. Jhaveri K et al. 383MO - Imlunestrant with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): results from the phase Ia/b EMBER study. Ann Oncol. 2023;34(Suppl 2):S338-9.
16. Lin NU et al. 382MO - Updated results from the phase I/II study of OP-1250, an oral complete estrogen receptor (ER) antagonist (CERAN) and selective ER degrader (SERD) in patients (pts) with advanced or metastatic ER-positive, HER2-negative breast cancer. Ann Oncol. 2023;34(Suppl 2):S338.
17. Bhave M et al. Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+)HER2(-) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. Breast Cancer Res Treat. 2024. doi: 10.1007/s10549-024-07376-w.
18. Gradishar WJ et al. NCCN Guidelines® insights: breast cancer, version 4.2023. J Natl Compr Canc Netw. 2023;21(6):594-608.
19. Burstein HJ et al. Testing for ESR1 mutations to guide therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol. 2023;41:3423-5.
20. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guidelines®) breast cancer version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Last accessed 14 May 2024.
21. European Society for Medical Oncology (ESMO). ESMO metastatic breast cancer living guideline – ER-positive HER2-negative breast cancer. Available at:https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer. Last accessed: 11 September 2024.
22. Turner NC et al. Capivasertib in hormone receptor-positive advanced breast cancer. N Engl J Med. 2023;388(22):2058-70.
23. Turner N et al. Impact of ESR1 mutations on endocrine therapy (ET) plus alpelisib benefit in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA-mutated, advanced breast cancer (ABC) who progressed on or after prior cyclin-dependent kinase inhibitor (CDK4/6i) therapy in the BYLieve trial. Cancer Res. 2022;82(Suppl 4):PD15-01.
24. Turner NC et al. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. Lancet Oncol. 2020;21(10):1296-308.
25. Pascual J et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2022;33(8):750-68.