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Uncovering ctDNA-detected co-mutational patterns in HR+/HER2− metastatic breast cancer to inform treatment sequencing

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INTRODUCTION AND OBJECTIVES

- Endocrine resistance is a major challenge in hormone receptor-positive (HR+)/HER2– metastatic breast cancer (mBC), particularly after progression on endocrine therapy plus CDK4/6 inhibitors.
- Clinically actionable mutations in *ESR1* and the PI3K/AKT/PTEN pathway guide the use of selective estrogen receptor degraders (SERDs), PI3K, and AKT inhibitors.
- The prevalence of these mutations in circulating tumor DNA (ctDNA) varies across treatment types and lines.
- **AIM: Define co-occurring actionable mutations and assess their impact on treatment sequencing.**

METHODS

- Clinical and genomic data were retrospectively collected from patients with HR+/HER2− mBC who underwent ctDNA testing at the European Institute of Oncology (IEO) between November 2023 and June 2025, upon progression to endocrine therapy plus CDK4/6 inhibitors.
- Genomic profiling was performed using a 77-gene liquid biopsy (LB)-based next-generation sequencing (NGS) assay.
- Progression-free survival (PFS) and overall survival (OS) were compared between groups using Cox proportional hazards models.

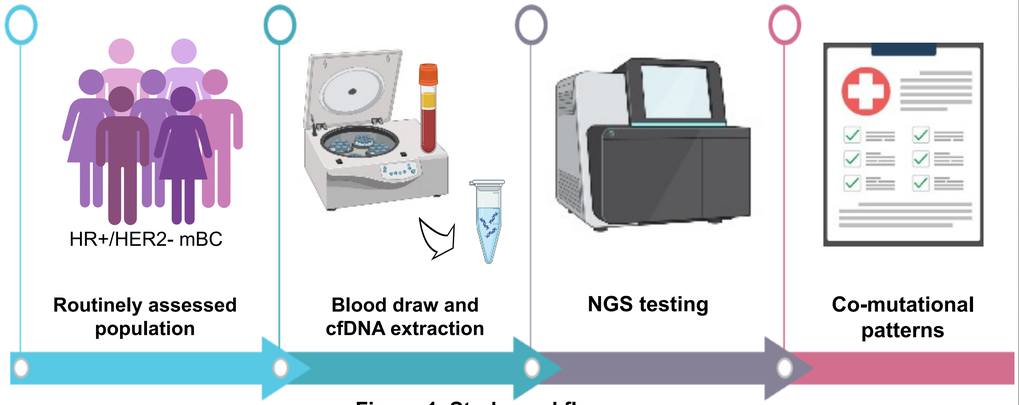


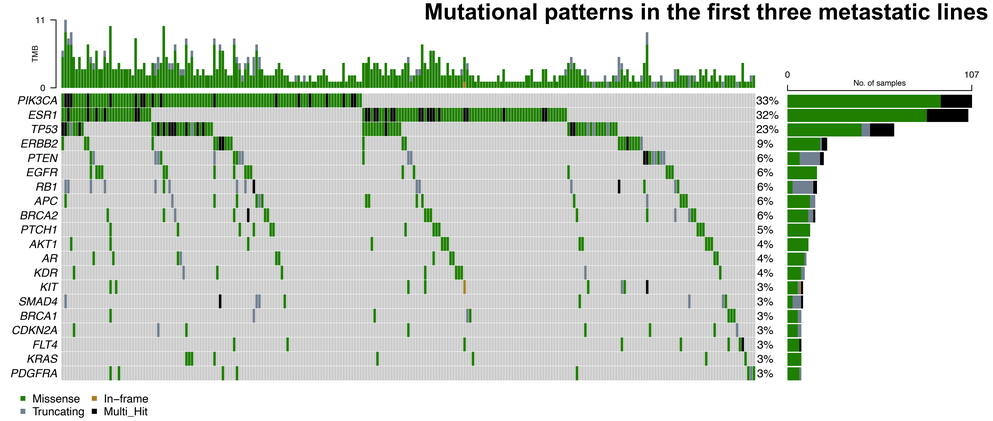
Figure 1. Study workflow

CONCLUSIONS

- ctDNA-guided molecular profiling is a fundamental tool for guiding clinical decisions among patients with HR+/HER2− who experience progression on ET.
- In our cohort, co-mutations occurred in almost 1/3 of patients and seems not to influence prognosis.

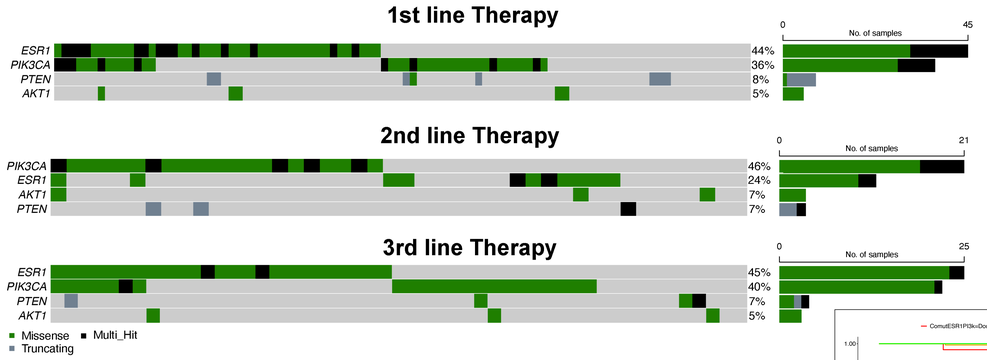
RESULTS

Mutational patterns in the first three metastatic lines of therapy



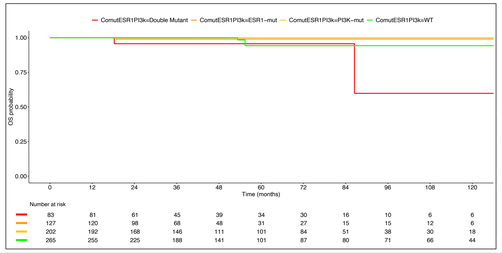
- A total of 256 patients underwent ctDNA testing
  - 53% were tested after (1L) therapy
  - 24% after (2L)
  - 23% after (≥3L)
- *PIK3CA* mutations were detected in 33% of pts, *ESR1* in 32% of pts , *PTEN* in 5.9% of pts, and *AKT1* in 3.9% of pts

Prevalence and co-mutations of *ESR1* and PI3K pathway gene alterations by lines of therapy



Line	Gene	ESR1mut Pts	N. of co-mutations	Co-mutation Rate
1-line	*PIK3CA*	48	15	31.2
1-line	*AKT1*	48	2	4.2
1-line	*PTEN*	48	2	4.2
2-line	*PIK3CA*	15	2	13.3
2-line	*AKT1*	15	2	13.3
2-line	*PTEN*	15	0	0
≥3-line	*PIK3CA*	19	8	42.1
≥3-line	*AKT1*	19	1	5.3
≥3-line	*PTEN*	19	1	5.3

- *PIK3CA* mutations were more common in patients tested after second-line therapy (2L)
- *ESR1* mutations were more frequently detected in patients tested at third line or beyond (≥3L)
- *PTEN* and *AKT1* alterations showed a similar distribution across treatment lines
- No association between co-mutations and clinical outcomes were found.



1 Giugliano, F. *et al*. Overcoming Resistance to CDK4/6 inhibitors in Hormone Receptor positive, HER2 negative breast cancer: Innovative Combinations and Emerging Strategies. Cancer Treat Rev **139:102980** (2025).
2 Dickinson, K., *et al*. Circulating Tumor DNA and Survival in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. JAMA Netw Open (2024).
3 Boscolo Bielo, L. *et al*. Genomic and clinical landscape of metastatic hormone receptors-positive breast cancers carrying ESR1 alterations. ESMO Open **10:103731** (2024).

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