Time-to-progression patterns during first and second-line endocrine therapy across clinical features and liquid biopsy-defined mutational profiles in HR+/HER2- metastatic breast cancer

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Background

- Monitoring strategies for HR+/HER2- metastatic breast cancer (MBC) remain largely based on fixed, trial-derived, schedules.
- Emerging evidence from the SERENA-6 and INAVO120 studies underscore the limitations of this approach and the need for a risk-adjusted, biomarker-guided strategy incorporating adaptive treatment escalation to optimize treatment sequencing

Aim

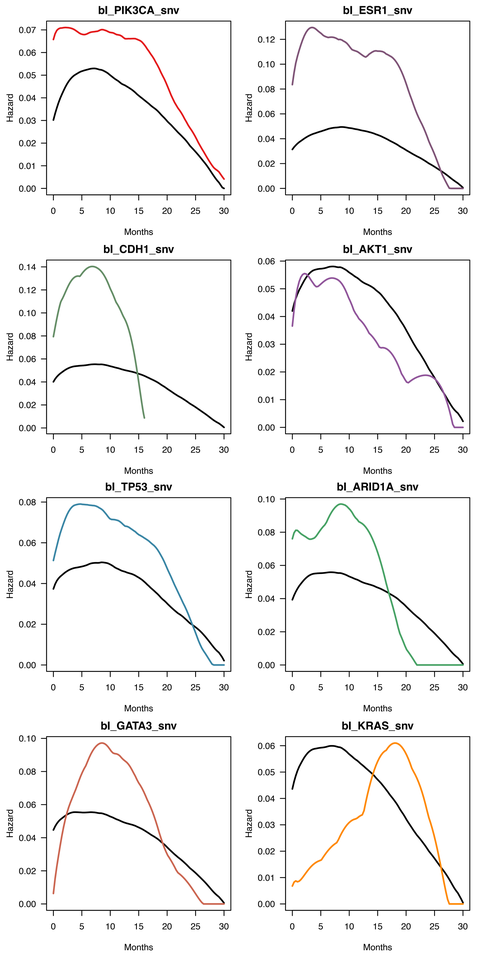
.This study investigated the impact of clinical and liquid biopsy-based features on time-to-progression during first and second-line endocrine therapy (ET) in HR+/HER2- MBC.

Methods

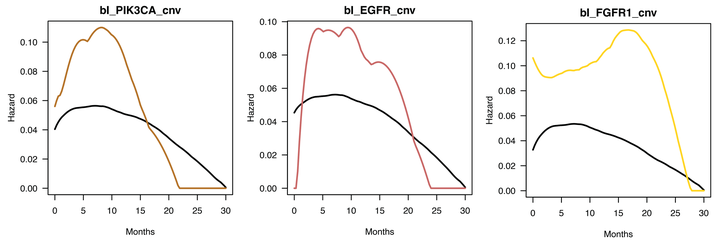
- We retrospectively analyzed a cohort of 909 patients with HR+/HER2- MBC who underwent circulating tumor DNA (ctDNA) profiling through the Guardant360 next-generation sequencing (NGS) panel within the multi-institutional “Precision Medicine Action for Cancer” (PMAC) academic consortium.
- Single nucleotide (SNVs) and copy number variations (CNVs), as well as clinical variables were evaluated.
- Oncogenic pathways were defined according to Sanchez-Vega et al. (Cell, 2018).
- Prognostic impact on progression-free survival (PFS), measured from the time of ctDNA collection, was investigated through log-rank test.
- Associations were evaluated using chi-square with false discovery rate correction (q value). Temporal patterns of disease progression were modeled through smoothed hazard function estimated up to 30 months.

Results

- A subset of 264 patients treated with 1st or 2nd-line ET was selected from the overall PMAC cohort of 909 HR+/HER2- MBC cases.
- The majority of patients were treated in 1st line (n=157, 59.5%), while 107 (40.5%) were treated in 2nd line. De novo MBC was present in 54 patients (20.5%).
- The majority received ET combined with CDK4/6 inhibitors (n=187, 70.8%), with visceral involvement in 115 cases (43.7%) and bone metastases in 208 (79.1%).
- Time-dependent hazard estimates revealed distinct temporal patterns of progression across baseline genomic alterations.
- SNVs in ESR1, PIK3CA, and TP53 were associated with early hazard peaks.
- ESR1 mutations displayed the steepest initial peak of PFS events at 3.6 months, followed by a plateau and a second peak at 15.3 months.
- PIK3CA had an early peak at 2.1 months and remained stable until 16 months.
- TP53 peaked at 4.8 months and steadily declined thereafter.

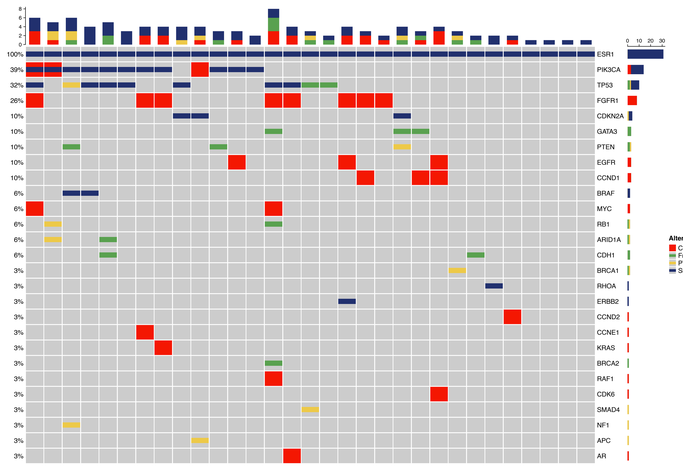


▲ **Figure 1** – Smoothed hazard functions for progression free survival across genomic subgroups. Kernel-smoothed hazard estimates have distinct temporal patterns across SNVs



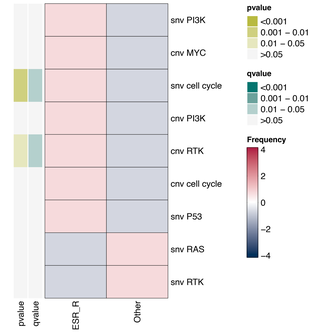
▲ **Figure 2** – Smoothed hazard functions for progression free survival across genomic subgroups. Kernel-smoothed hazard estimates have distinct temporal patterns across CNVs

- Delayed hazard peaks were observed for SNVs in GATA3 (8.4 months), ARID1A (8.4 months), and RB1 (11.4 months) (**Figure 1**), as well as for CNVs in FGFR1 (16.8 months) and PIK3CA (8.1 months), suggesting a delayed risk of progression (**Figure 2**).

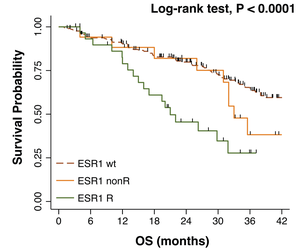


▲ **Table 3** – Oncoprint of genomic alterations across the ESR1 R cohort (patients captured within the early ESR1 hazard peak). The landscape of somatic mutations and copy-number changes across key cancer-related genes highlights heterogeneous but recurrent events across pathways involved in cell cycle regulation, PI3K/AKT signaling and RTK signaling.

- A significantly higher frequency of cell cycle pathway SNVs was observed in patients within the early ESR1 hazard peak (16% vs. 2.1%; p=0.003, q=0.013) (**Figure 3 - 4**) (**Table 1**).
- RTK pathway CNVs were also significantly enriched in this subgroup (p=0.013, q=0.044) (**Table 1**).
- No significant differences were found for the PI3K, TP53, RAS, or MYC pathways.



▲ **Figure 4** - Heatmap summarizing the frequency of key genomic alterations—single-nucleotide variants (SNVs) and copy-number variations (CNVs)—across major oncogenic pathways (PI3K, MYC, cell-cycle, RTK, P53, and RAS), stratified by ESR1-R status (patients captured within the early ESR1 hazard peak). Annotation bars display the corresponding p-values and q-values for enrichment tests.



► **Figure 5** - Kaplan–Meier curves for overall survival (OS) comparing ESR1 wild-type (wt), ESR1 nonR, and ESR1-R groups. The ESR1-R group is characterized by a distinct early decline in survival. This group shows substantially worse outcomes compared with wt and nonR patients (log-rank p < 0.0001).

	OR	95%C.I.		P>z
RTK CNVs	2.63	1.11	6.26	0.029
Cell cycle SNVs	8.16	2.15	30.97	0.002

▲ **Table 1** – Multivariable multinomial logistic regression for factors associated with ESR1-R. Model outputs showing variables independently associated with the ESR1-R subgroup, defined by patients clustering within the early ESR1 hazard peak.

- The ESR1-R subgroup exhibited a markedly worse overall survival compared with both ESR1-wild-type and ESR1-nonR groups (log-rank p < 0.0001) (**Figure 5**).
- The separation of the curves emerges early and remains consistent over time, supporting the presence of a biologically distinct high-risk trajectory within the ESR1-R subgroup.

Conclusions

- The temporal analysis of progression for patients with HR+/HER2- MBC revealed distinct patterns associated with specific genomic alterations.
- Early peaks in PIK3CA and TP53 mutations suggest intrinsic resistance, while delayed peaks in RB1, ARID1A, and FGFR1 indicate acquired mechanisms to ET +/- CDK4/6i therapy.
- The bimodal pattern observed in ESR1-mutant tumors, along with the enrichment of cell cycle and RTK pathway alterations in patients with early progression, further supports their role in endocrine resistance.
- If validated, these data may have important implications for both disease monitoring using ctDNA and rationale clinical trial design to overcome intrinsic and acquired resistance.

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