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Clinical Relevance of ctDNA-Guided Molecular Profiling After Progression on CDK4/6 Inhibitor plus Endocrine Therapy in HR+/HER2- Metastatic Breast Cancer

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BACKGROUNG

- Circulating tumor DNA (ctDNA)-based molecular profiling is used to guide therapeutic decision-making in hormone receptor-positive/HER2-negative (HR+/HER2–) metastatic breast cancer (mBC) following progression on cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) and endocrine therapy (ET).
- The predictive value of post-progression genomic alterations for subsequent lines of treatment remains unclear.

METHODS

- We analyzed all consecutive patients with HR+/HER2– mBC cancer with ctDNA testing at our Institution after progression on CDK4/6i-based therapy between November 2023 and June 2025.
- ctDNA sequencing was performed using a 77-gene liquid biopsy next-generation sequencing assay.
- Oncogenic alterations were assessed both individually and by oncogenic pathways, as described by Sanchez-Vega et al. (Cell, 2018).
- Real-world progression-free survival (PFS) was defined as the time from each treatment initiation to disease progression or death, whichever occurred first.
- The log-rank test was used to compare PFS among groups, and Cox proportional-hazards models were applied to compute hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS

Table 1. Study cohort characteristics

	N = 256
Age, median (IQR)	**49 (43, 57)**
Menopausal Status	
Postmenopausal	123 (49%)
Premenopausal	130 (51%)
Not Available	3
Histology	
IDC NST	192 (76%)
ILC	44 (17%)
MIDLC	12 (4.7%)
Other	6 (2.4%)
Not Available	2
De Novo Stage IV	
No	185 (72%)
Yes	71 (28%)
CDK4/6 Inhibitor Line	
1	195 (81%)
2	38 (16%)
≥3	9 (3%)
Not Available	14
CDK4/6 Inhibitor Partner	
AI	123 (51%)
SERD	119 (49%)
Not Available	14
Duration of CDK4/6 Inhibitor	
<6 Months	27 (11%)
6-24 Months	111 (47%)
>24 Months	98 (42%)
Not Available	20
Lines Before ctDNA Testing	
1	127 (52%)
2	62 (26%)
3	28 (12%)
≥4	24 (10%)
Not Available	15

Figure 1. Oncoprint summarizing ctDNA-detected somatic alterations following progression on CDK4/6 inhibitor + ET

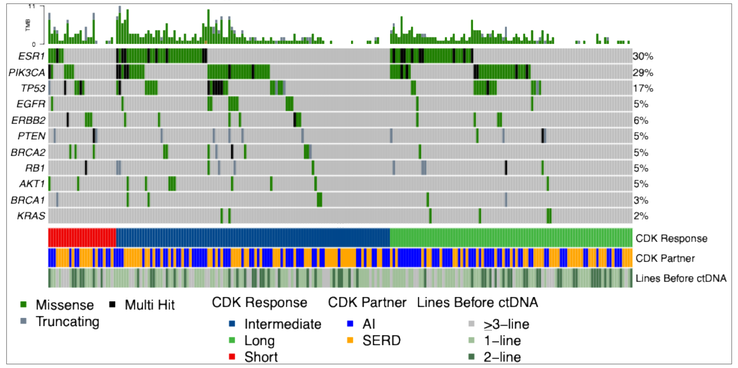


Figure 2. Kaplan Meier curves of patients with short, intermediate, and prolonged PFS on CDK4-6 inhibitor + ET

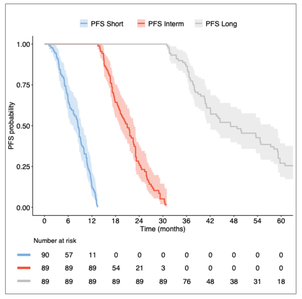


Figure 3. Association of individual genes with long term PFS (>24 mo) vs intermediate-short PFS (<24 mo) with CDK4/6 inhibitor + ET

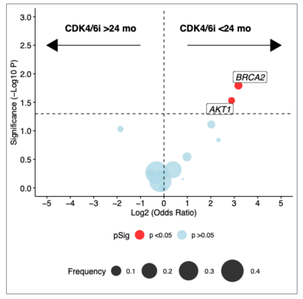


Figure 4. Post-CDK4/6 inhbitor treatment strategies

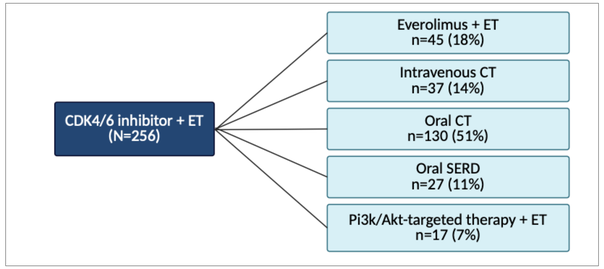
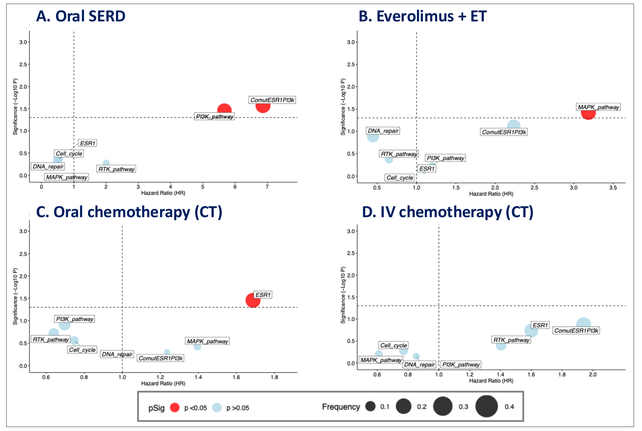


Figure 5. Impact of ctDNA-detected somatic genetic alterations (assessed at pathway level) on PFS of post-CDK4/6 inhbitor treatment strategies



CONCLUSIONS

- ctDNA-guided molecular profiling after progression on CDK4/6i + ET reveals clinically-relevant genomic alterations that may influence subsequent treatment outcomes in HR+/HER2– mBC.
- These findings further support integrating ctDNA analysis into treatment planning beyond first-line in HR+/HER2- mBC.

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