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Clinical and genomic biomarkers of capivasertib response in patients with hormone receptor-positive, HER2-negative metastatic breast cancer (HR+/HER2- MBC)

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BACKGROUND AND OBJECTIVES

- Hormone receptor-positive, HER2-negative metastatic breast cancer (HR+/HER2- MBC) remains incurable, with therapeutic resistance limiting treatment durability.
- Capivasertib, the first FDA-approved AKT inhibitor for MBC harboring a *PIK3CA / AKT1 / PTEN* alteration, is widely utilized in practice in combination with fulvestrant. However, predictors of response and resistance to this regimen remain poorly understood.
- This study retrospectively examined baseline genomic alterations and prior therapy exposures for associations with progression-free survival (PFS) in patients treated with capivasertib and fulvestrant as part of routine care.

METHODS

- This retrospective cohort included patients from three U.S. centers treated between November 2023 (capivasertib approval) and June 2025 (data cutoff). Follow up continued until progression, toxicity-related discontinuation, death, or data cutoff.
- Eligible patients had HR+/HER2- MBC treated with capivasertib plus fulvestrant and baseline next-generation sequencing, as defined by sequencing within 6 months of therapy start.
- Two cohorts were analyzed: 1) patients with baseline circulating tumor DNA (ctDNA) sequencing only, and 2) patients with baseline ctDNA or tumor tissue sequencing.
- Patients were identified via pharmacy claims for capivasertib exposure; clinical and sequencing data were extracted from charts of eligible patients and de-identified.
- Baseline oncogenic or likely oncogenic genomic alterations (*as defined in OncoKB)* were examined; variants of uncertain significance were excluded, as were genes altered in fewer than 3 patients for statistical robustness. Prior lines of metastatic therapy and prior PI3K inhibitor (PI3Ki) exposure were assessed.
- The primary outcome was PFS, analyzed using the Kaplan-Meier method and Cox regression, adjusting for relevant covariates as sample size allowed.

CORRESPONDENCE

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RESULTS

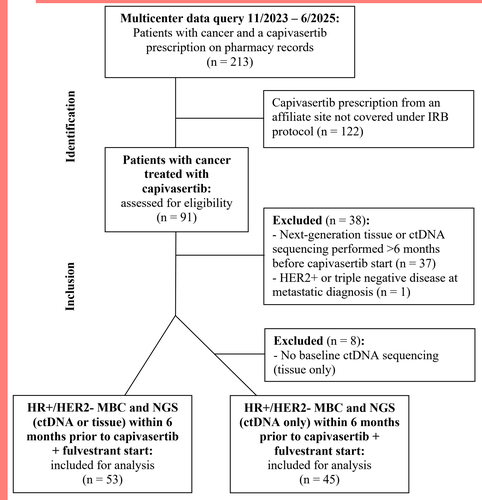


Figure 1: Inclusion flow diagram

Table 1. Cohort characteristics

	ctDNA seq only (cohort 1)	ctDNA + tissue seq (cohort 2)
	N = 45	**N = 53**
Age, median (range), years	67 (34 – 86)	67 (34 – 86)
Female sex, n (%)	45 (100%)	53 (100%)
Race, n (%)		
White	31 (69%)	36 (68%)
Black	9 (20%)	11 (21%)
Asian	4 (9%)	4 (8%)
Not reported	1 (2%)	2 (4%)
Menopausal status, n (%)		
Pre/Peri	2 (4%)	3 (6%)
Post	43 (96%)	50 (94%)
# prior lines for MBC, median (range)	2 (0-8)	2 (0-8)
Patients with prior CDK4/6 inhibitor, n (%)	43 (96%)	51 (96%)
Patients with prior fulvestrant, n (%)	27 (60%)	34 (64%)
Patients with prior PI3K inhibitor, n (%)	10 (22%)	11 (21%)
Patients with prior chemotherapy	23 (51%)	26 (49%)
Visceral metastases, n (%)	31 (69%)	38 (72%)
Median PFS on capiva, months (95% CI)	8.4 (4.9-13.1)	7.2 (4.9-13.1)

PFS by prior lines of therapy: ≤1 (black), 2-3 (red) or ≥4 (blue)

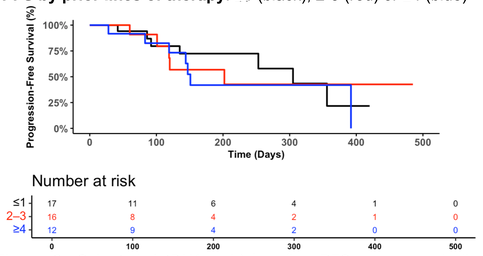


Figure 2: Cohort 1 (*ctDNA only*), median PFS was numerically longer in patients with ≤1 prior line of therapy (black) vs 2–3 prior lines (red) [305 vs 202 days; HR 1.17, 95% CI 0.36-3.53] or ≥4 prior lines (blue) [305 vs 151 days; HR 1.44, 95% CI 0.51-4.06]

PFS by PI3K inhibitor exposure: Prior PI3Ki (black) vs no prior PI3Ki (red)

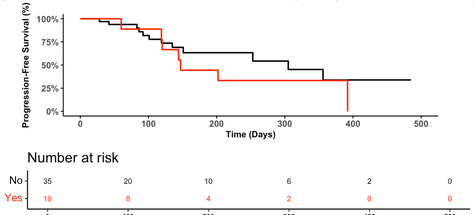


Figure 3: Cohort 1 (*ctDNA only*), median PFS in those with prior PI3Ki exposure (red) trended toward shorter PFS on capivasertib (147 vs 305 days; HR 1.67, 95% CI 0.64-4.07).

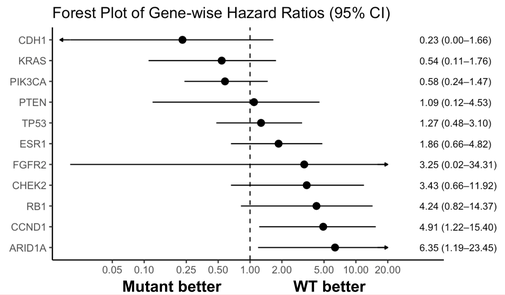


Figure 4: Cohort 1 (*ctDNA only*), forest plot for univariate gene analysis displaying the impact of single-gene alterations on capivasertib outcomes. All genes altered in 3 or more patients in the cohort are presented and organized by lowest to highest hazard ratio (HR).

PFS by ESR1 status: ESR1 mutant (red) vs no mutation (black)

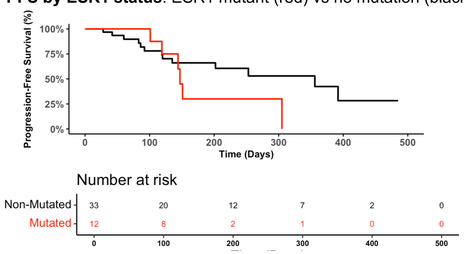


Figure 5: Cohort 1 (*ctDNA only*), dual *ESR1* and PI3K pathway alterations (n=12, red) trended toward worse PFS vs. no ESR1 mutation (black) (147 vs 356 days; HR 1.86, 95% CI 0.66-4.82).

PFS by CCND1 status: CCND1 altered (red) vs no alteration (black)

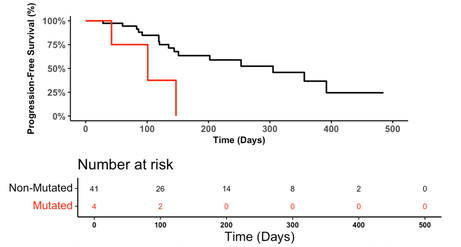


Figure 6: Cohort 1 (*ctDNA only*), *CCND1* alterations (n=4; red) were associated with shorter PFS (101 vs 305 days; HR 4.91, 95% CI 1.22-15.40)

PFS by ARID1A status: ARID1A altered (red) vs no alteration (black)

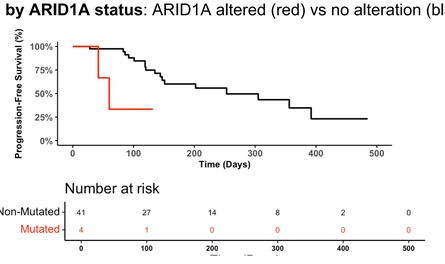


Figure 7: Cohort 1 (*ctDNA only*), *ARID1A* alterations (n=4; red) were associated with shorter PFS (HR 6.35, 95% CI 1.19-23.45)

PFS by FGFR1 status: FGFR1 altered (red) vs no alteration (black)

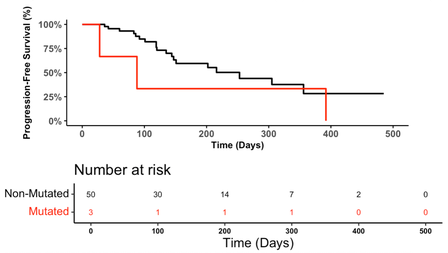


Figure 8: Cohort 2 (*ctDNA + tissue*), *FGFR1* alterations (n=3; red [*too few in cohort 1 to analyze*]) trended toward shorter PFS (88 vs 253 days; HR 2.33, 95% CI 0.58-6.92). Other clinical-genomic associations remained similar in cohort 2 compared to cohort 1.

CONCLUSIONS AND FUTURE DIRECTIONS

- In this study of patients with HR+/HER2- MBC treated with capivasertib and fulvestrant, alterations in *CCND1* and *ARID1A* in baseline ctDNA were associated with poorer PFS.
- Patients with dual *ESR1* and PI3K pathway co-mutations trended toward worse PFS compared to those without an *ESR1* mutation detected.
- Patients treated in the second-line or earlier metastatic setting, and those without prior PI3Ki exposure, may derive greater benefit on capivasertib therapy.
- These findings are exploratory and warrant additional clinical and preclinical validation but suggest specific biomarkers that may correlate with risk for early progression on an AKT inhibitor regimen.

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