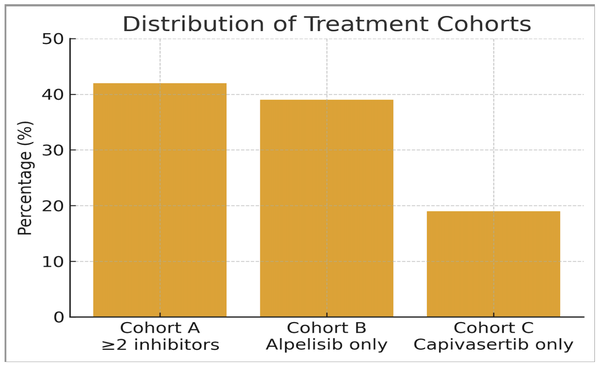
Sequencing PIK3CA, AKT and mTOR Inhibitors in HR+/HER2- Metastatic Breast Cancer: A Real-World Retrospective Analysis

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Introduction

- PIK3CA activating mutations comprise up to 40% of hormone receptor-positive (HR$^+$), human epidermal growth factor receptor 2-negative (Her2$^-$) breast cancer (BC) patients.
- Approved agents (everolimus, alpelisib, capivasertib) improve median PFS by ~5.5–7.3 mo post-CDK4/6i, but pivotal trials excluded prior PI3K/AKT/mTOR inhibitor use, limiting sequencing data.
- In real-world practice, these agents are often prescribed sequentially despite the lack of prospective evidence.
- We evaluated whether sequential use of these inhibitors provides sustained disease control compared to single-agent therapy in a post-CDK4/6i real-world cohort.



Methods and Materials

• 72 patients treated with everolimus, alpelisib, or capivasertib (2019–2025) were identified at our institution

•Collected baseline demographic, clinical and disease variables.

•We assigned the following cohorts--Cohort A: sequential therapy; B: alpelisib only; C: capivasertib only.

•In Cohort A, PFS1 (time from start of first targeted therapy to progression) and PFS2 (time from start of sequential agent to progression) were measured independently, and PFS1+PFS2 calculated to reflect cumulative disease control.

•ANOVA, log-rank, univariate analysis, and McNemar tests were used for survival comparisons.

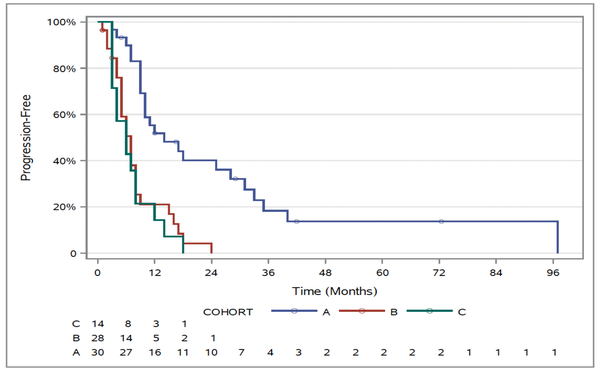


Chart 1. Kaplan–Meier Curve of Progression-Free Survival (PFS) by Treatment Cohort

Results

Demographics	Value
Median Age	66 years (46–81)
Median Prior Lines of therapy	2
Prior CDK4/6 Inhibitor Use	100% (unique to our study)
Median Number of Pathway Inhibitors Used	2 (range 2–3)
Most Common Treatment Sequence	Everolimus → Alpelisib (50%)
Next Most Common Sequences	Alpelisib → Capivasertib (20%); Everolimus → Capivasertib (15%)

Table 1. Baseline clinical and disease characteristics

- mPFS1+2 was 14.0 months in Cohort A (95% CI: 9–28),compared with 7.0 months in Cohort B (95% CI: 5–8) and 6.0 months in Cohort C (95% CI: 3–8), with a hazard ratio of 0.428 who received ≥2 versus a single agent ($p<0.0001$, log-rank).
- No association was found between progression or toxicity on the first drug and outcomes on the second drug within Cohort A ($p=0.366$).

Discussion/Conclusion

- In this real-world, post-CDK4/6i cohort of HR+/HER2– MBC patients, sequential use of PI3K/AKT/mTOR pathway inhibitors was associated with significantly longer disease control compared to single-agent use.
- Notably, measurable disease status and mutation profile (e.g., ESR1,PIK3CA subtype) did not predict benefit from sequential therapy.
- Furthermore, toxicity from one agent did not preclude benefit from subsequent agents.
- Our findings support that the practice of sequencing pathway inhibitors should be considered regardless of tolerance to the first agent, though prospective studies needed for validation.

Clinical Practice Impact

- Consider sequential pathway inhibition even after drug-specific intolerance.
- Mutation subtype should not preclude sequencing
- Supports continued PI3K/AKT/mTOR targeting post-progression.

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