# Real world experience of PIK3CA, AKT inhibitor, and oral SERD in patients with hormone receptor-positive metastatic breast cancer

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## Background

- PIK3CA/AKT/mTOR(PAM) pathway alternation is the key cancer driver in approximately 30-40% hormone-positive(HR+) breast cancer, and accounts for the development of endocrine resistance. There are multiple PAM inhibitors received FDA approval. [1,2]
- ESR1 mutation is an acquired mutation that can be enriched in up to 40% of patients progressed after first line aromatase inhibitor (AI) and CDK4/6 inhibitor therapy in the metastatic setting.
- Oral selective estrogen receptor degraders (SERDs) are approved for ESR1 mutated HR+ metastatic breast cancer(MBC). Approximately 15% of patients develop co-mutation of PIK3CA and ESR1. [3]
- However, there is no guideline for optimal sequencing of these therapeutic choices. Therefore, we aim to analyze a real-world data of HR+ MBC receiving PAM inhibitors, including a small cohort of ESR1 and PAM co-mutation.

## Methods

- This retrospective study included patients with HR+/Her2- MBC receiving PIK3CA inhibitor (alpelisib, inavolisib, or an experimental drug in a clinical trial), and/or AKT inhibitor (capivasertib) from January 2019 to June 2025, through an IRB-approved protocol at Cedars-Sinai Medical Center.
- The genomic alterations were identified via commercially available Tempus XT, XR, or XF platforms, and clinical data were collected by retrospective chart review through the electronic medical record.
- Descriptive analysis was used for patients' characteristics, demographics, treatment history, and clinical results. Time to discontinuation(TTD) was defined from the start of a treatment to its end, which can be due to various reasons like lack of efficacy, adverse events, or death. Real-world progression-free survival(rwPFS) was defined from the initiation of cancer therapy to disease progression, death, or loss to follow-up, as determined by chart review. Median TTD and rwPFS data were summarized using Kaplan-Meier methods

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## Results

**Figure 1 & Table 1.** 107 patients with PAM pathway alteration who received PI3KCA/AKT inhibitors were identified

| Characteristics | Total No. = 107 |
|---|---|
| Median age | 66 (34-86) |
| Race | |
| White | 77 (72.0%) |
| African American | 11 (10.3%) |
| Asian | 9 (8.4%) |
| Other | 6 (5.6%) |
| Unknown | 3 (2.8%) |
| Declined | 1 (0.9%) |
| Pathology | |
| IDC | 96 (89.7%) |
| ILC | 11 (10.3%) |
| De Novo Stage IV | 31 (29.0%) |
| Metastatic site | |
| bone only | 42 (39.3%) |
| liver (+ others) | 65 (60.7%) |
| Prior lines of therapy | Median: 2 (0-9) |
| 0-2 | 71 (66.4%) |
| 3+ | 36 (33.6%) |
| Prior CDK4/6 inhibitor | 105 (98.1%) |

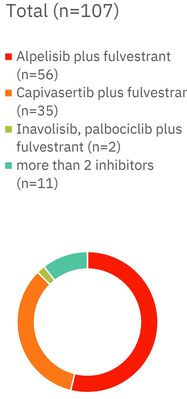
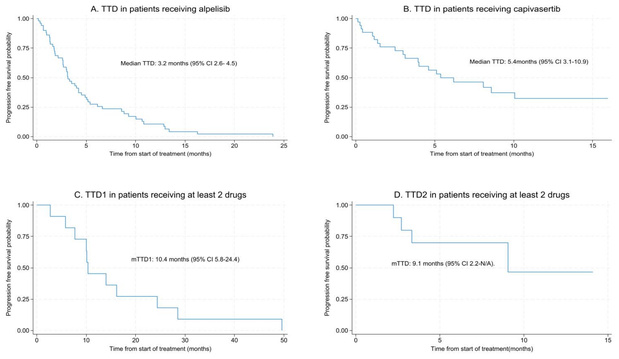



**Figure 2.** A. Median TTD were: alpelisib 3.2 months (95% CI 2.6- 4.5) and 5.4months (CI 3.1-10.9) for capivasertib-treated patients by survival analysis. In 11 patients receiving 2 PIK3CA/AKT inhibitors, mTTD1 was 10.4 months (95% CI 5.8-24.4) and mTTD2 was 9.1 months (95% CI 2.2-N/A).




- **Table 2. Summary of Treatment in Patients with PIK3CA and ESR1 co-mutations** (N=20). Among 20 patients, 8 patients received oral SERD and PIK3CA/AKT inhibitors sequentially. 3 patients started elacestrant first, and 5 patients received PIK3CA/AKT inhibitors first.

| Patient No. | Drugs sequence | No. of prior Tx line before the 1st drug | rwPFS1 (months) | No. of prior Tx (2nd drug) | rwPFS2 (months) | No. of prior Tx (3rd drug) | PFS3 (months) |
|---|---|---|---|---|---|---|---|
| 1 | Elacetrant → Capivasertib | 3 | 1.57 | 4.00 | 2.90 | | |
| 2 | Capivasertib → Elacetrant → Inavolisib | 4 | 12.90 | 6.00 | 16.10 | 9 | ongoing |
| 3 | Alpelisib → Elacetrant | 3 | 9.67 | 8.00 | 7.47 | | |
| 4 | Elacetrant first, adding Capivasertib later | 4 | 20.10 | | ongoing | | |
| 5 | Elacetrant and Capivasertib (part of ELEVATE trial) | 1 | 10.47 | | | | |
| 6 | Capivasertib → Elecetrant | 3 | 6.70 | 4.00 | 3.57 | | |
| 7 | Alpelisib → Elacestrant | 3 | 4.60 | 6.00 | 5.30 | | |
| 8 | Elacetrant → Trial drug (targeting PIK3CA mt) | 1 | 7.83 | 4 | ongoing | | |

- The median rwPFSs of 3 patients who received 1st line elacestrant followed by AKT inhibitors were 1.6, 7.8, and 20.1 months, respectively. Otherwise, the PFS of 1st line PIK3CA/AKT inhibitor patients were 4.6, 6.7, 9.7, and 12.0 months.
- PFS2 was not mature and most patient are on treatment.
- One patient with alpelisib experienced treatment interruption and dose reduction due to Gr3 skin toxicity, while elacestrant was well-tolerated without major adverse effects.

- Regarding other co-mutations, the most frequent alteration is CDH1 (no.=12), which is known to be a hallmark in ILC. 8 of 11 in ILC patients had CDH1 mutation.
- ATM mutation was the 2nd common alteration (4 of 107), and BRCA1/CHEK2 mutation was observed in 2 patients.

## Conclusion

- In this retrospective single center analysis, 15% of patients with PIK3CA/AKT mutation reported ESR1 co-mutation, which is consistent with the reported literature.
- Some patients received alpelisib as a later line (especially before 2024) after receiving endocrine therapies or chemotherapy. It might affect efficacy of alpelisib.
- We observed that most patients with ESR1 and PIK3CA pathway co-mutation were able to benefit from sequential therapy of oral SERD or PIK3CA pathway inhibitors, whichever treatment comes first and showed a favorable response to either treatments.
- The current study is limited by its small sample size. Future effort for a multi-institutional study is planned.

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