

Methods: 59 HR+/HER2— breast cancer patients who relapsed after standard-of-care therapies were evaluated through targeted NGS of tumor DNA. Patients were stratified by treatment modality & PFS (<2 years vs >2 years). Genetic alterations potentially correlating with therapeutic resistance were documented, with emphasis on PIK3CA alterations.

Results: Comprehensive tumor DNA NGS from foci of disease recurrence revealed that the most frequent alteration was in PIK3CA, observed in 49% cases. Additional recurrent alterations included ESR1 & TP53 (8% each), FGFR1/2 (7%), DDR pathway genes (5%), ERBB2 & PTEN (3% each); while 12% had no detectable alterations. Compliant therapeutic details were available for 46/59 patients of which 61% received CDK4/6i in combination with endocrine therapy (Gr.1), 26% received endocrine therapy alone (Gr.2), and 13% received either chemo or surgery (Gr.3). In Gr.1, 75% had disease progression within 2 years, among them, 81% had PIK3CA mutations, predominantly in Ex.20. The remaining 25% who progressed beyond 2 years also exhibited PIK3CA mutations in 57% of cases. In Gr.2, 58% progressed within 2 years, with a lower incidence of PIK3CA mutations (14%); in contrast, other genetic alterations accounted for 43%. In Gr.3, 2/6 patients progressed within 2 years, one had a PIK3CA mutation & the other ESR1 mutation, while 4 patients progressed after 2 years, with PIK3CA mutations present in 50%. Overall, PIK3CA mutations were detected in 33% of HR+/HER2— breast cancers at progression. Ex.20 mut were predominant, accounting for 59% followed by Ex.9 mut in 27%. Of these, 54% demonstrated disease progression within 2 years, with the majority carrying Ex.20 mut, while the remaining 46% had longer PFS, associated more frequently with exon 9 or non-hotspot variants.

Conclusions: PIK3CA Ex 20 mut, particularly p.H1047L/R is significantly associated with early resistance (<2 years) to CDK4/6i plus ET. This suggests that PIK3CA profiling at baseline or progression may enable risk stratification and early incorporation of PIK3/AKT inhibitors.

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525P Efficacy and safety of post-CDK4/6 inhibitor treatment options for HR-positive, HER2-negative advanced breast cancer: A network meta-analysis of randomized controlled trials

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Background: In patients with HR-positive, HER2-negative advanced breast cancer who have progressed after CDK4/6 inhibitors, the optimal selection of subsequent therapies remains uncertain. This study employs a Bayesian network meta-analysis to evaluate the efficacy and safety of different treatment options.

Methods: We conducted a comprehensive literature search in the PubMed, Embase, and Cochrane databases, as well as abstracts from the San Antonio Breast Cancer Symposium, European Society for Medical Oncology, and American Society of Clinical Oncology, covering the past five years, with the search cutoff date of April 1, 2025. Only randomized controlled trials were included in the final analysis. Our analysis focused on several key outcomes, including progression-free survival (PFS) in the overall population, PFS in the ESR1 mutations, PFS in those with PIK3CA mutations population, overall survival, objective response rate and the incidence of grade 3 or higher adverse events.

Results: We identified a total of 7,860 publications, ultimately including 16 studies involving 2,972 patients, all of whom experienced disease progression following treatment with CDK4/6 inhibitors. mTOR inhibitors demonstrated superior PFS. Oral-SERD were preferred in ESR1-mutant patients (vs endocrine therapy: HR 0.66, 95% CI 0.44–0.99), while CDK4/6 inhibitor rechallenge showed benefit in PIK3CA-mutant cases (vs endocrine therapy: HR 0.56, 95% CI 0.32–0.98). SERM and oral-SERD achieved optimal efficacy-safety balance.

Conclusions: Our findings demonstrate that mTOR inhibitors represent a viable therapeutic option for patients with good performance status, while Oral-SERD may be more suitable for elderly patients or those with multiple comorbidities. Future research should focus on addressing existing evidence gaps and optimizing therapeutic strategies to further improve long-term patient outcomes.

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526P

Capivasertib plus fulvestrant as first and second-line endocrine-based therapy in PIK3CA/AKT1/PTEN-altered hormone receptor-positive advanced breast cancer: Subgroup analysis from the phase 3 CAPitello-291 trial

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Background: CDK4/6 inhibitor (i) + endocrine therapy (ET) is the recommended first-line (1L) treatment for patients with hormone receptor-positive (HR+)/HER2— advanced breast cancer (ABC). Capivasertib (C) + fulvestrant (F) is recommended for patients with PIK3CA/AKT1/PTEN-altered HR+/HER2— ABC that has progressed after at least one line of ET-based treatment; here we report a subgroup analysis by line of ET from the phase III CAPitello-291 trial.

Methods: Eligible patients with HR+/HER2— ABC had disease progression on or ≤12 months of (neo)adjuvant aromatase inhibitor (AI) treatment (1L ET), or whilst receiving prior AI-based treatment for ABC (2L or 3L ET). Alteration status was determined by central testing of tumour tissue collected prior to enrolment. Patients were randomised 1:1 to C (400 mg BD; 4 days on, 3 days off) + F (500 mg intramuscularly on Days 1 and 15 of Cycle 1, and Day 1 of each subsequent 28-day cycle) or placebo (pbo) + F. Progression-free survival (PFS) was analysed using Cox regression for each subgroup of ET line in which treatment was given.

Results: Among 236 patients with PIK3CA/AKT1/PTEN-altered HR+ ABC and who had received no prior chemotherapy for ABC, 32 were randomised to treatment as 1L ET (n=12 C + F; n=20 pbo + F) and 185 as 2L ET (n=106 C + F; n=79 pbo + F; including 155 post-CDK4/6i + AI: n=88 C; n=67 pbo). Baseline characteristics were broadly balanced between treatment arms, with some exceptions in the 1L ET subgroup (C; pbo): Asian race (50%; 35%); visceral metastases (42%; 65%); bone-only metastases (42%; 20%). PFS by line of ET is reported in the Table. The safety profile with C + F across subgroups was broadly consistent with the overall population.

Table: 526P of PFS by line of ET

Line of ET	PIK3CA/AKT1/PTEN-altered population (N=236) ^a		
	C + F, median PFS, months (95% CI)	Pbo + F, median PFS, months (95% CI)	Hazard ratio (95% CI)
1L (n=32)	14.3 (5.4–NC)	3.7 (1.7–11.7)	0.43 (0.17–1.01)
2L (n=185)	7.2 (5.4–9.1)	3.1 (2.0–3.7)	0.56 (0.40–0.77)
2L post-CDK4/6i for ABC (n=155)	7.0 (5.4–8.5)	2.6 (1.8–3.5)	0.5 (0.35–0.71)

CI, confidence interval; NC, non-calculable. 3L not reported due to small n. ^aNo prior chemotherapy for ABC.

Conclusions: Although limited by the small 1L ET population, the PFS benefit of C + F vs pbo + F was consistent when administered as 1L, 2L or 2L post-CDK4/6i ET for ABC.

Clinical trial identification: NCT04305496.

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527P

Real-world study on rates of positivity for ESR1, PIK3CA, PTEN, and ATK1 among ER+/HER2- metastatic breast cancer patients

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Background: The National Comprehensive Cancer Network and European Society of Medical Oncology recommend testing to assess the prevalence of ESR1, PIK3CA, PTEN, and AKT1 biomarkers at the time of progression following endocrine therapy. Using real-world data, a study was conducted to assess test results of the respective biomarkers, positivity rates, and co-mutations, specifically among ER+/HER2- metastatic breast cancer patients (pts) who experienced disease progression on endocrine therapy.

Methods: This real-world study was conducted using the IntegraConnect PrecisionQ de-identified database comprising of pts aged 18 or older, diagnosed with ER+/HER2- metastatic breast cancer, who were all assessed via manual chart curation. These patients began a subsequent line of therapy between February 1, 2023, and December 31, 2024, after prior exposure to endocrine therapy, including AI, CDK4/6i, SERM, or SERDs, in the metastatic setting. The analysis assessed the testing rate and positivity rates for ESR1, AKT1, PTEN, or PIK3CA signaling pathways. The study exclusively included pts who received NGS genetic test results regardless of time-frame. Descriptive statistics were utilized to compute proportions.

Results: The cohort consisted of 636 ER+/HER2- pts, 98% female and 2% male participants, with a median age of 68 years at the start of their initial treatment following endocrine therapy. The positivity rates for the respective biomarkers were as follows: ESR1 only 24% (155/636), PIK3CA only 37% (238/636), PTEN only 18% (112/636), and AKT1 only 4% (27/636). Among the pts, 15% (94/636) were found positive for ESR1 and either PIK3CA, PTEN, or AKT1 positive. Among the pts, 48% (306/636) harbored either a PIK3CA, PTEN, or AKT1 mutation irrespective of ESR1 mutation status.

Conclusions: The real-world analysis shows that nearly 50% of pts harbor either PTEN, AKT1, or PIK3CA mutations with nearly a third of those pts also harboring an ESR1 mutation. The results underscore the importance for healthcare providers to implement routine Next Generation Sequencing testing at disease progression to identify relevant biomarkers to direct guideline concordant care.

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Visual symptom questionnaire results from SERENA-6, a phase 3 study of switch to camizestrant (CAMI) + CDK4/6 inhibitor (CDK4/6i) at emergence of ESR1m during first-line (1L) therapy for patients (pts) with HR+/HER2- advanced breast cancer (ABC)

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Background: In SERENA-6, switching treatment to CAMI + CDK4/6i at emergence of ESR1m during 1L aromatase inhibitor (AI) + CDK4/6i in pts with HR+/HER2- ABC resulted in a statistically significant and clinically meaningful improvement in PFS, was well tolerated, and reduced the risk of deterioration in quality of life vs AI +