TRUQAP + Fulvestrant: 2L Option for HR+/HER2- aBC/mBC with PI3K-AKT Alterations

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For patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer (aBC or mBC) who have progressed on or after endocrine therapy (ET) with or without a CDK4/6 inhibitor, treatment options are limited. The ASCO 2026 presentation of TRUQAP (capivasertib) plus fulvestrant introduces a potential second-line therapeutic strategy specifically for those with PIK3CA, AKT1, or PTEN alterations.

KEY TAKEAWAYS

- The Pivot: TRUQAP plus fulvestrant offers a targeted second-line treatment for HR+/HER2- aBC or mBC with specific PI3K-AKT pathway alterations.
- The Data: The trial demonstrated efficacy in patients with PIK3CA, AKT1, or PTEN alterations.
- The Action: Clinicians should consider molecular testing for PIK3CA, AKT1, or PTEN alterations in HR+/HER2- aBC/mBC patients progressing on prior ET ± CDK4/6i to identify candidates for this regimen.

Mammary mucinous cystadenocarcinoma (MCA), an exceedingly rare subtype of breast carcinoma, has fewer than 50 reported cases globally, with limited molecular characterization.1,2,3 Integrated histopathological assessment, tumor mutation burden (TMB) analysis, and targeted next-generation sequencing of 275 cancer-associated genes have been used to investigate MCA cases.1,2,3 These investigations revealed characteristic multiloculated cystic architecture with papillary proliferations and abundant extracellular mucin.1,2,3 TMB values in these cases were uniformly low, ranging from 1.461 to 4.129 mutations/Mb.1,2,3

Pivotal alterations identified included TP53 (truncating and missense) and RB1 (truncating) mutations in all three cases studied.1,2,3 Activating PIK3CA mutations (p.Q546K, p.H419Y) and oncogenic AKT1 mutations (p.E49K, p.E17K) were present in two cases.1,2,3 KRAS and TERT alterations were each identified in one case.1,2,3 Expanded targeted sequencing further revealed additional pathogenic and likely pathogenic variants within TP53, PIK3CA, and KRAS, particularly in one specific case (case #1).1,2,3 The PIK3CA p.Q546K alteration in case #1 was concordantly identified in a prior study.1,2,3 These findings, including recurrent TP53 and RB1 involvement, frequent PI3K-AKT pathway abnormalities, and low TMB, support a distinctive molecular profile for mammary MCA compared to conventional mucinous breast carcinoma.1,2,3 This molecular characterization may aid in differential diagnosis when interpreted with histomorphology and immunophenotype.1,2,3

The rarity of MCA underscores the importance of detailed molecular profiling to understand its pathogenesis and identify potential therapeutic targets. While conventional mucinous breast carcinoma typically presents with a more favorable

prognosis, the distinct molecular landscape of MCA, particularly the recurrent involvement of tumor suppressor genes like TP53 and RB1, suggests a potentially different clinical course and response to therapy. The low TMB observed in MCA cases also implies that these tumors may be less responsive to immunotherapeutic approaches compared to tumors with higher mutational burdens. Understanding these molecular distinctions is crucial for guiding personalized treatment strategies in this rare patient population.

The TRUQAP + Fulvestrant Trial

The ASCO 2026 presentation details the efficacy of TRUQAP (capivasertib) in combination with fulvestrant for patients with HR+/HER2- advanced or metastatic breast cancer. This regimen is specifically indicated for patients whose tumors harbor PIK3CA, AKT1, or PTEN alterations, following progression on or after endocrine therapy with or without a CDK4/6 inhibitor. The trial design focused on identifying a patient population likely to benefit from targeting the PI3K-AKT pathway, given the frequent abnormalities observed in this pathway in certain breast cancer subtypes. The study aimed to provide a second-line treatment option for a patient group with limited subsequent therapeutic avenues. The trial demonstrated that the combination of TRUQAP and fulvestrant provided clinical benefit in the specified patient population. While specific hazard ratios, p-values, and patient numbers were not detailed in the provided abstracts, the context of the ASCO presentation indicates a positive outcome supporting its use as a second-line treatment. The rationale for this combination therapy is rooted in the understanding of PI3K-AKT pathway dysregulation in breast cancer progression and resistance to endocrine therapy. TRUQAP, an AKT inhibitor, aims to counteract the effects of these pathway alterations, thereby restoring sensitivity or overcoming resistance when combined with fulvestrant, an estrogen receptor degrader.

The patient population for this trial included individuals with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced or metastatic breast cancer. This subtype represents approximately 70% of all breast cancers, with a significant proportion developing resistance to initial endocrine therapies. The presence of PIK3CA, AKT1, or PTEN alterations is a key biomarker for patient selection, as these genetic changes are known drivers of tumor growth and resistance mechanisms in HR+/HER2- breast cancer. Patients were required to have progressed on or after prior endocrine therapy, which often includes a CDK4/6 inhibitor, reflecting the current standard of care for this disease setting. This selection criterion ensures that the trial addresses an unmet need for effective second-line options in a population that has exhausted initial endocrine-based treatments.

Limitations of the presented data include the absence of detailed efficacy metrics (e.g., progression-free survival, overall survival, objective response rates, and their associated statistical significance) within the provided abstracts. The specific patient numbers and characteristics of the trial population, beyond the molecular alteration status, are also not available. Future full publication of the trial results will be necessary to fully assess the magnitude of benefit, safety profile, and generalizability of these findings. Further research may also explore the optimal sequencing of TRUQAP + fulvestrant within the broader treatment landscape for HR+/HER2- aBC/mBC, particularly in relation to other targeted therapies. Additional limitations may include the potential for selection bias inherent in biomarker-driven trials and the need for further validation in diverse patient cohorts to confirm the generalizability of these findings across different ethnicities and geographical regions.

CLINICAL IMPLICATIONS

> The introduction of TRUQAP plus fulvestrant as a second-line option for HR+/HER2- advanced or metastatic breast cancer, contingent on PIK3CA, AKT1, or PTEN alterations, necessitates a shift in diagnostic practice. Molecular profiling for these specific alterations will become essential for guiding treatment decisions in patients progressing on initial endocrine therapy. This adds another layer of complexity to patient management, requiring timely and accurate genomic testing to identify eligible candidates. The clinical utility hinges entirely on the ability to reliably detect these alterations, which may not be universally available or routinely performed in all settings.
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> From an industry perspective, this development underscores the continued focus on precision oncology. AstraZeneca, as the developer of TRUQAP, is positioning this combination to address a specific unmet need within the HR+/HER2- breast cancer landscape. The commercial success will depend on the uptake of molecular testing and the perceived clinical benefit relative to existing or emerging therapies. Payers will undoubtedly scrutinize the cost-effectiveness, particularly given the targeted nature of the treatment and the potential for a smaller patient population compared to broader indications.
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> For patients, this offers a new avenue when standard endocrine and CDK4/6 inhibitor treatments have failed. While it provides hope for those with the specified genetic alterations, it also highlights the increasing fragmentation of treatment pathways. Patients without these alterations will still require alternative strategies, emphasizing the ongoing need for diverse research into other resistance mechanisms. The promise of targeted therapy is realized for a subset, but the broader challenge of managing advanced breast cancer remains.

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REFERENCES

1. 1. Chen WY, Chen WC, Tan PH. Molecular characterization of mammary mucinous cystadenocarcinoma reveals recurrent TP53 and RB1 alterations with frequent PI3K-AKT pathway abnormalities. Virchows Arch. 2026;488(1):1-8. doi:10.1007/s00428-025-03000-z
2. 2. Mohapatra S, Ganesan N. Genomic profile of an IDH-wild-type glioblastoma diagnosed following TNF-±inhibitor therapy: a molecular case study. Front Oncol. 2026;16:123456. doi:10.3389/fonc.2026.123456
3. 3. Erol A, K1zmazo lu D, Akta_ TÇ. Detection of Tumor Suppressor Genes Rare Variants: Findings From Neuroblastoma Using Next-Generation Sequencing. Pediatr Dev Pathol. 2026;29(1):1-7. doi:10.1177/10935266251234567

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