

# The clinical utility of NGS panel testing: Identifying *PIK3CA*, *AKT1*, and/or *PTEN*- altered HR+/HER2- advanced breast cancers that may be eligible for treatment with TRUQAP™ (capivasertib) + fulvestrant following progression on or after ET ± CDK4/6i<sup>1</sup>

*PIK3CA*, *AKT1*, and/or *PTEN* alteration status in HR+/HER2- locally advanced and metastatic breast cancer may help determine treatment eligibility with TRUQAP + fulvestrant, following progression on or after ET ± CDK4/6i<sup>1</sup>

AKT1, serine/threonine protein kinase 1; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

#### **IMPORTANT PRODUCT INFORMATION**

##### **Select Safety Information About TRUQAP™ (capivasertib) tablets**

TRUQAP is contraindicated in patients with severe hypersensitivity to TRUQAP or any of its components.

Serious adverse reactions can include hyperglycemia, diarrhea, and cutaneous adverse reactions. May cause fetal harm when administered to a pregnant woman. Among the 355 patients who received TRUQAP in CAPitello-291, the most common (≥20%) adverse reactions, including laboratory abnormalities, were diarrhea (72%), cutaneous adverse reactions (58%), increased random glucose (57%), decreased lymphocytes (47%), decreased hemoglobin (45%), nausea and fatigue (35% each), increased fasting glucose (37%), decreased leukocytes (32%), increased triglycerides (27%), decreased neutrophils (23%), increased creatinine (22%), vomiting (21%), and stomatitis (20%).

##### **Indication and Usage**

TRUQAP in combination with fulvestrant is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more *PIK3CA*/*AKT1*/*PTEN* alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

**Please see full Prescribing Information, including Patient Information for TRUQAP.**

 **Truqap™**  
capivasertib  
160 mg • 200 mg tablets

# Course overview

## Key dates



- The live session took place on **Tuesday May 21<sup>st</sup> 2024**
- [Click here](#) for access to webinar information at the CAP Foundation webpage

## Speakers



### Fresia Pareja, MD, PhD

Pathologist, specializing in Breast Pathology.  
Assistant Attending, Department of Pathology,  
Memorial Sloan Kettering Cancer Center



### Erika P. Hamilton, MD

Director, Breast Cancer Research Program and  
Gynecologic Cancer Research Program,  
Sarah Cannon Research Institute

aBC, locally advanced breast cancer; AKT, serine/threonine protein kinase; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; NGS, next-generation sequencing; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog.

## Learning objectives



- Understand the importance of the PI3K/AKT/PTEN pathway in HR+/HER2- aBC/mBC
- Identify actionable biomarkers in the PI3K/AKT/PTEN pathway by NGS testing
- Recognize the clinical advancements in HR+/HER2- locally aBC/mBC, and an introduction to TRUQAP + fulvestrant:
  - Mode of Action
  - CAPItello-291 study overview, results, and adverse reactions
  - Case studies
- Discuss the role of pathologists in molecular biomarker testing

# Why is the PI3K/AKT/PTEN pathway important in context of HR+/HER2- aBC/mBC?

## The PI3K/AKT/PTEN pathway

- The PI3K/AKT/PTEN pathway mediates many cellular processes, including cell metabolism, cell proliferation, and cell survival<sup>2-6</sup>
- Hyperactivation of the PI3K/AKT/PTEN pathway leads to increased tumor growth, cell proliferation, and the suppression of apoptosis<sup>3,5,6</sup>

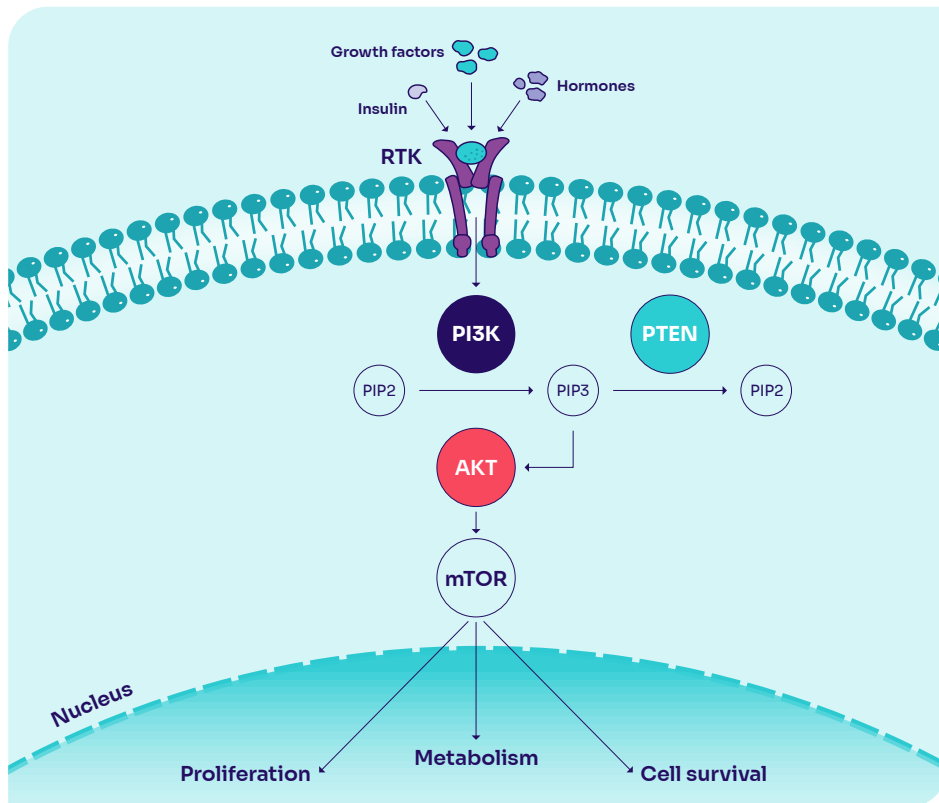


Figure adapted from Miricescu D, et al. *Int J Mol Sci.* 2020;22(1):173.<sup>3</sup>

aBC, locally advanced breast cancer; AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; *PTEN*, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

## The prevalence of *PIK3CA*, *AKT1*, and *PTEN* alterations in HR+ breast cancers

- *PIK3CA*, *AKT1*, and/or *PTEN* alterations occur in up to 50% of HR+ breast cancer cases<sup>5</sup>
- Activating mutations of *PIK3CA* and *AKT1* and loss of function of the *PTEN* protein can cause hyperactivation of this pathway<sup>3,5,7</sup>

	Activating <i>PIK3CA</i> Mutations	Activating <i>AKT1</i> Mutations	Inactivating <i>PTEN</i> Alterations
Description	Mutations in the <i>PIK3CA</i> gene, which encodes a specific subunit of the PI3K protein <sup>3</sup>	Mutations in the <i>AKT1</i> gene ( <i>AKT1</i> isoform is expressed in the majority of tissues) <sup>3,8</sup>	Multiple genomic alterations can cause <i>PTEN</i> to lose its regulatory function, including mutations, deletions and genomic rearrangements involving the <i>PTEN</i> gene <sup>3</sup>
Impact	Induces hyperactivation of PI3K resulting in pathway hyperactivation <sup>3</sup>	Promotes activation of AKT independent of PI3K resulting in pathway hyperactivation <sup>3,8,9</sup>	Enhances PI3K signaling resulting in pathway hyperactivation <sup>10</sup>

# Why is NGS panel testing recommended for patients with mBC?\*



- Biomarkers may provide valuable prognostic and predictive information about a patient's breast cancer and how they may respond to certain treatments, which may inform management decisions<sup>11</sup>



Actionable biomarkers are defined as functional genetic alterations that drive malignancy and may be targeted by an FDA-approved treatment regimen<sup>12</sup>

- Examples of these biomarkers are certain alterations in *PIK3CA*, *AKT1*, and/or *PTEN* genes in HR+/HER2- aBC/mBC<sup>13</sup>
- These clinically actionable biomarker alterations can be detected using different testing methods, including NGS<sup>13</sup>



NGS panel testing is recommended as it is more efficient and less expensive than single gene testing<sup>11</sup>

- Additionally, NGS testing results may guide clinical management, provide diagnostic and prognostic information, and may determine eligibility for therapies or clinical trials<sup>11,13</sup>

\*ASCO-CAP guidelines specify NGS testing for HR+/HER2- breast cancer patients when there are genomic biomarker-linked therapies approved for their tumor type.<sup>14</sup>

aBC, locally advanced breast cancer; *AKT1*, serine/threonine protein kinase 1; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; FDA, US Food and Drug Administration; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; qPCR, quantitative polymerase chain reaction.

# How is TRUQAP™ (capivasertib) advancing the treatment field of HR+/HER2- aBC/mBC?

TRUQAP + fulvestrant is the first and only combination to leverage dual power of AKT inhibition and endocrine receptor downregulation to reduce tumor growth<sup>1,15,16</sup>

## Mechanism of action of TRUQAP + fulvestrant

- TRUQAP is an oral, pan-AKT kinase inhibitor, that targets AKT and blocks amplified signaling driven by *PIK3CA*, *AKT1*, and/or *PTEN* gene alterations, inhibiting tumor growth<sup>1,15</sup>
- Fulvestrant is an injectable estrogen receptor antagonist that binds to and causes downregulation of ERs, reducing estrogen-driven tumor growth, and is used in combination with TRUQAP as an FDA-approved therapy for HR+/HER2-advanced/metastatic breast cancer<sup>16</sup>

aBC, locally advanced breast cancer; AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; E, estrogen; ER, estrogen receptor; FDA, US Food and Drug Administration; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; mBC, metastatic breast cancer; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; RTK; receptor tyrosine kinase.

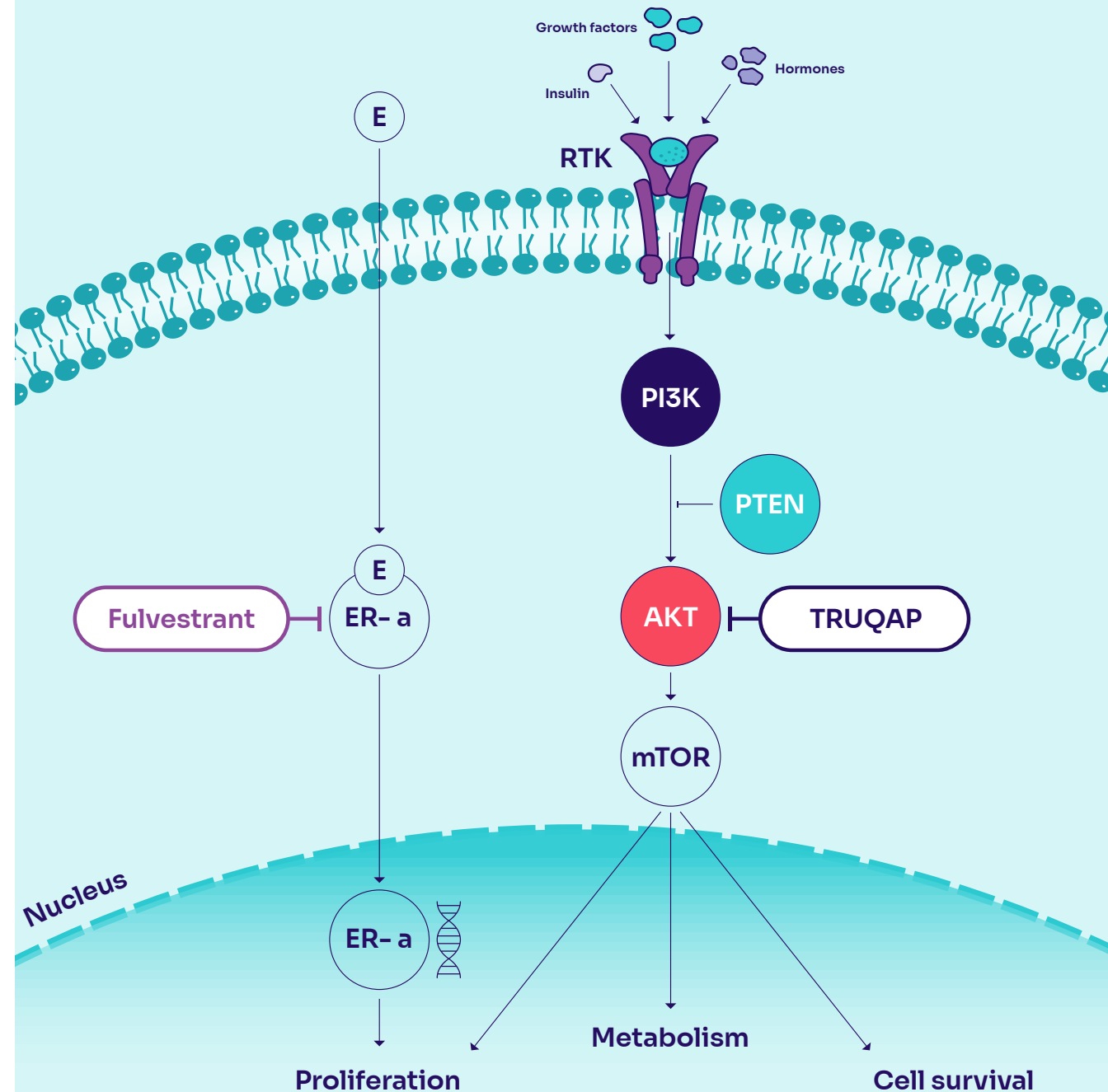


Figure adapted from Miricescu D, et al. *Int J Mol Sci.* 2020;22(1):173<sup>3</sup> and Alves C, et al. *Int J Mol Sci.* 2023;24:4522.<sup>17</sup>

# What were the results of the CAPItello-291 study in patients with HR+/HER2- aBC or mBC following progression on or after endocrine therapy?

## Investigator-assessed mPFS in patients with *PIK3CA*, *AKT1*, and/or *PTEN*-altered cancers (n=289)<sup>7</sup>

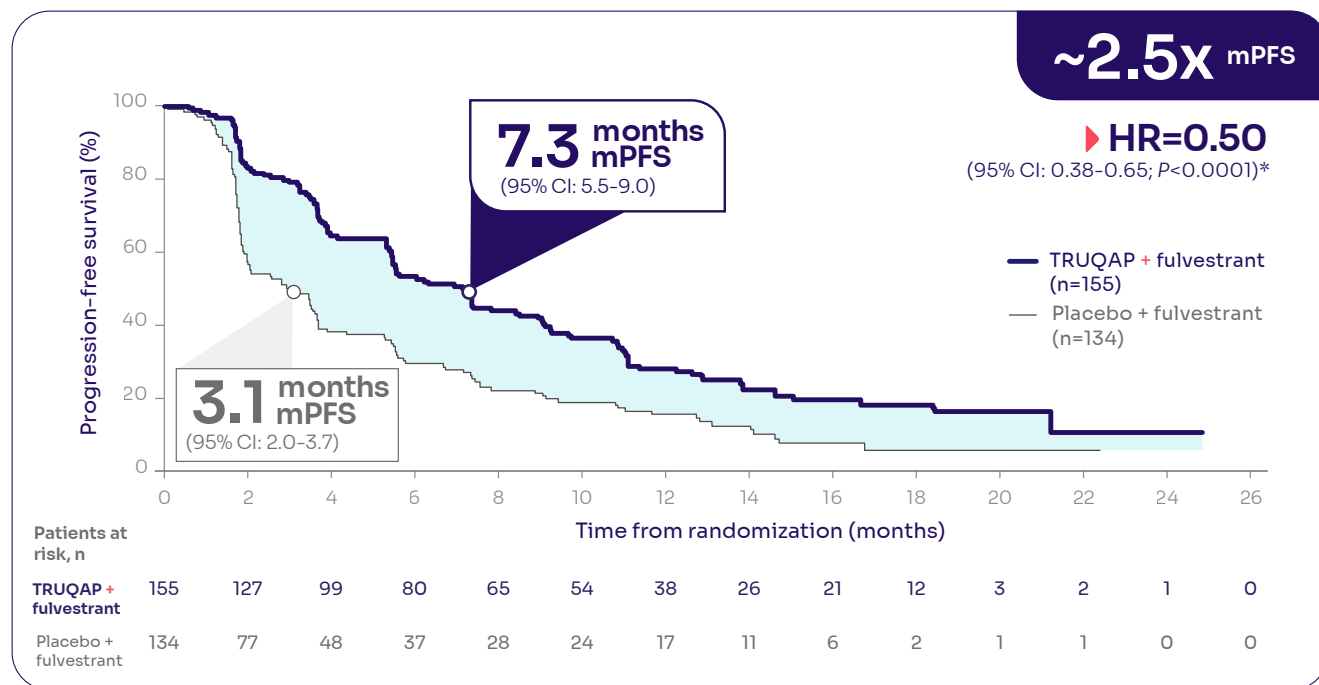


Figure adapted from Turner NC, et al. *N Engl J Med*. 2023;388:2058-2070.

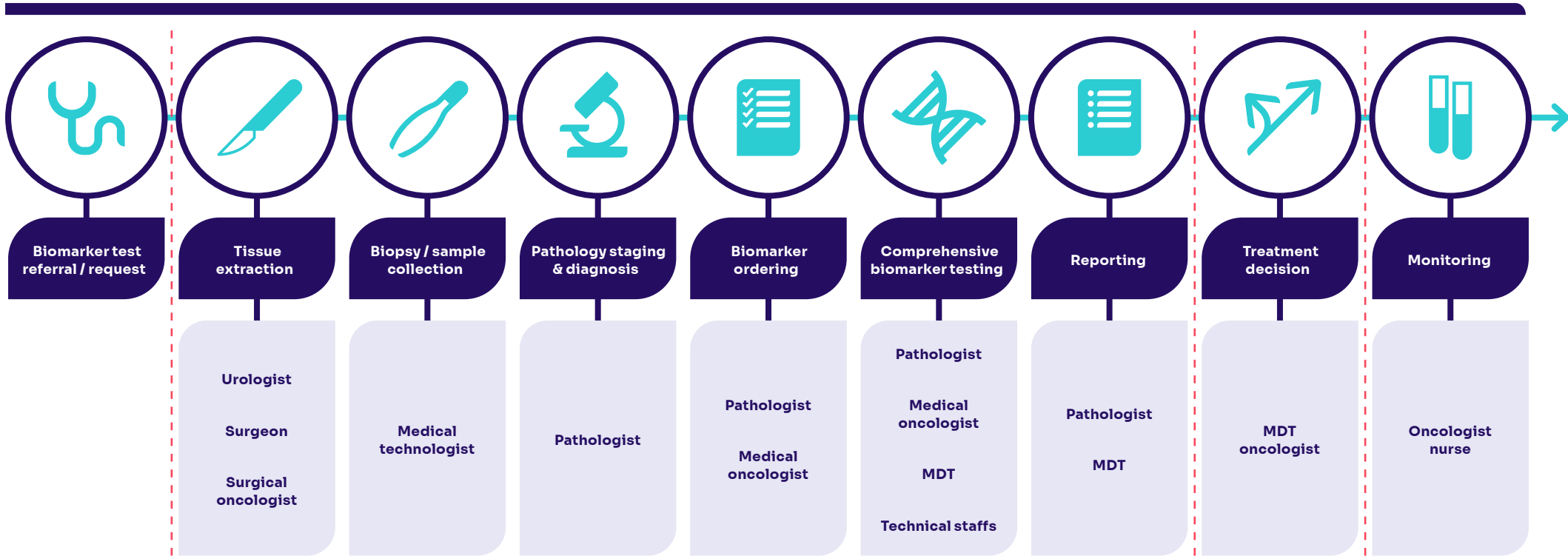
- Results demonstrated that TRUQAP™ (capiwasertib) + fulvestrant more than doubled mPFS vs placebo + fulvestrant in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors (7.3 months (5.5–9.0) vs 3.1 months (2.0–3.7), respectively)<sup>7</sup>
  - The most common ARs (≥20%, any grade), including laboratory abnormalities, in aBC patients with *PIK3CA*/*AKT1*/*PTEN* alterations receiving TRUQAP + fulvestrant were diarrhea (77%), increased random glucose (58%), cutaneous adverse reactions (56%), decreased lymphocytes (49%), decreased hemoglobin (47%), fatigue (38%), increased fasting glucose (37%), decreased leukocytes (35%), nausea (35%), increased triglycerides (30%), decreased neutrophils (25%), stomatitis (25%), and vomiting (21%)<sup>†</sup>
- CAPItello-291 was a Phase III, randomized, double-blind, placebo-controlled study (NCT04305496) with dual primary endpoints: progression-free survival (PFS) in the overall population and in patients whose tumors had *PIK3CA*, *AKT1*, and/or *PTEN* alterations<sup>7</sup>
  - In CAPItello-291, both primary endpoints, PFS in the overall population (N=708) and PFS in patients with *PIK3CA*, *AKT1*, and/or *PTEN* alterations (n=289), reached statistical significance<sup>1</sup>
  - An exploratory analysis of PFS in 313 (44%) patients who did not have *PIK3CA*, *AKT1*, and/or *PTEN* alterations showed an HR of 0.79 (95% CI: 0.61-1.02), indicating the improvement in PFS in the overall population was primarily due to the PFS results in patients with alterations. FDA approval of TRUQAP + fulvestrant was therefore based on the PFS results seen in patients with *PIK3CA*, *AKT1*, and/or *PTEN* alterations<sup>1</sup>
  - The safety population in the CAPItello-291 study included n=155 patients receiving TRUQAP plus fulvestrant, in which serious adverse reactions occurred in 18% of the population<sup>1,7</sup>
  - FoundationOne®CDx (F1CDx) was the tissue NGS test used in the clinical trial and is a clinically validated and FDA-approved NGS test<sup>7,18</sup>

\*Overall population (N=708); *PIK3CA*/*AKT1*/*PTEN*-altered population (n=289; TRUQAP + fulvestrant n=155; placebo + fulvestrant n=134).

<sup>†</sup>Please see additional Important Safety Information at the end of this summary and full Prescribing Information for TRUQAP.

aBC, locally advanced breast cancer; AKT, serine/threonine protein kinase; *AKT1*, serine/threonine protein kinase 1; AR, adverse reaction; CI, confidence interval; FDA, food and drug administration; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; mBC, metastatic breast cancer; mPFS, median progression-free survival; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog.

# Pathologists play an integral role in a patient's MDT<sup>19,20</sup>



**Pathologists should take a proactive role in advocating for NGS panel testing in the breast cancer diagnostic pathway**

## IMPORTANT SAFETY INFORMATION ABOUT TRUQAP™ (capivasertib) tablets

TRUQAP is contraindicated in patients with severe hypersensitivity to TRUQAP or any of its components.

### Hyperglycemia

Severe hyperglycemia, associated with ketoacidosis, has occurred in patients treated with TRUQAP. The safety of TRUQAP has not been established in patients with Type I diabetes or diabetes requiring insulin. Patients with insulin-dependent diabetes were excluded from CAPItello-291.

Hyperglycemia occurred in 18% of patients treated with TRUQAP (n=355). Grade 3 (insulin therapy initiated; hospitalization indicated) or Grade 4 (life-threatening consequences; urgent intervention indicated) hyperglycemia occurred in 2.8% of patients. Diabetic ketoacidosis occurred in 0.3% of patients and diabetic metabolic decompensation in 0.6% of patients. Dose reduction for hyperglycemia was required in 0.6% and permanent discontinuation was required in 0.6% of patients. The median time to first occurrence of hyperglycemia was 15 days (range: 1 to 367).

In the 65 patients with hyperglycemia, 45% required treatment with anti-hyperglycemic medication (insulin in 15% and metformin in 29%). Of the 29 patients who required anti-hyperglycemic medication during treatment with TRUQAP, 66% (19/29) remained on these medications at treatment discontinuation or last follow-up.

Evaluate fasting blood glucose (FG) and hemoglobin A1C (HbA1C) and optimize

blood glucose prior to treatment. Before initiating TRUQAP, inform patients about TRUQAP's potential to cause hyperglycemia and to immediately contact their healthcare professional if hyperglycemia symptoms occur (eg, excessive thirst, urinating more often than usual or greater amount of urine than usual, or increased appetite with weight loss). Evaluate FG at least every two weeks during the first month and at least once a month starting from the second month, prior to the scheduled dose of TRUQAP. Monitor HbA1C every three months. Monitor FG more frequently during treatment with TRUQAP in patients with a medical history of diabetes mellitus and in patients with risk factors for hyperglycemia such as obesity (BMI  $\geq$  30), elevated FG of  $>160$  mg/dL ( $>8.9$  mmol/L), HbA1C at or above the upper limit of normal, use of concomitant systemic corticosteroids, or intercurrent infections.

If a patient experiences hyperglycemia after initiating treatment with TRUQAP, monitor FG as clinically indicated, and at least twice weekly until FG decreases to normal levels. During treatment with anti-hyperglycemic medication, continue monitoring FG at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated. Consider consultation with a healthcare practitioner with expertise in the treatment of hyperglycemia and counsel patients on lifestyle changes. Withhold, dose reduce, or permanently discontinue TRUQAP based on severity.

### Diarrhea

Severe diarrhea associated with dehydration occurred in patients who received TRUQAP (n=355).

Diarrhea occurred in 72% of patients. Grade 3 or

4 diarrhea occurred in 9% of patients. The median time to first occurrence was 8 days (range: 1 to 519). In the 257 patients with diarrhea, 59% required antidiarrheal medications to manage symptoms. Dose reductions were required in 8% of patients and 2% of patients permanently discontinued TRUQAP due to diarrhea. In patients with Grade  $\geq$  2 diarrhea (n=93) with at least 1 grade improvement (n=89), median time to improvement from the first event was 4 days (range: 1 to 154).

Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start antidiarrheal treatment at the first sign of diarrhea while taking TRUQAP. Withhold, reduce dose, or permanently discontinue TRUQAP based on severity.

### Cutaneous Adverse Reactions

Cutaneous adverse reactions, which can be severe, including erythema multiforme (EM), palmar-plantar erythrodysesthesia, and drug reaction with eosinophilia and systemic symptoms (DRESS), occurred in patients who received TRUQAP (n=355).

Cutaneous adverse reactions occurred in 58% of patients. Grade 3 or 4 cutaneous adverse reactions occurred in 17% of patients receiving TRUQAP. EM occurred in 1.7% of patients and DRESS occurred in 0.3% of patients. Dose reduction was required in 7% of patients and 7% of patients permanently discontinued TRUQAP due to cutaneous adverse reactions.

Monitor patients for signs and symptoms of cutaneous adverse reactions. Early consultation with a dermatologist is recommended. Withhold, dose reduce, or permanently discontinue TRUQAP based on severity.





## Embryo–Fetal Toxicity

Based on findings from animals and mechanism of action, TRUQAP can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRUQAP and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRUQAP and for 4 months after the last dose.

TRUQAP is used in combination with fulvestrant. Refer to the full Prescribing Information of fulvestrant for pregnancy and contraception information.

## ADVERSE REACTIONS

Among the 355 patients who received TRUQAP in CAPitello-291, the most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were diarrhea (72%), cutaneous adverse reactions (58%), increased random glucose (57%), decreased lymphocytes (47%), decreased hemoglobin (45%), increased fasting glucose (37%), nausea and fatigue (35% each), decreased leukocytes (32%), increased triglycerides (27%), decreased neutrophils (23%), increased creatinine (22%), vomiting (21%), and stomatitis (20%).

In the 155 patients with *PIK3CA/AKT1/PTEN* alterations treated with TRUQAP + fulvestrant, dose reductions due to adverse reactions were

reported in 21% of patients. Permanent TRUQAP discontinuation due to an adverse reaction occurred in 10% of patients. Dose interruptions of TRUQAP occurred in 39% of patients.

## DRUG INTERACTIONS

**Strong CYP3A Inhibitors:** Avoid concomitant use with a strong CYP3A inhibitor. If concomitant use cannot be avoided, reduce the dose of TRUQAP and monitor patients for adverse reactions.


**Moderate CYP3A Inhibitors:** When concomitantly used with a moderate CYP3A inhibitor, reduce the dose of TRUQAP and monitor patients for adverse reactions.

**Strong or Moderate CYP3A Inducers:** Avoid concomitant use of TRUQAP with strong or moderate CYP3A inducers

## INDICATION AND USAGE

TRUQAP in combination with fulvestrant is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN* alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

Please see full [Prescribing Information](#), including [Patient Information](#) for TRUQAP.

You may [report side effects related to AstraZeneca products](#). 

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**References:** 1. TRUQAP™ (capivasertib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 2. Toss A, et al. *Int J Mol Sci.* 2017;18(1):85. 3. Miricescu D, et al. *Int J Mol Sci.* 2020;22(1):173. 4. Robertson JFR, et al. *Clin Cancer Res.* 2020;26(7):1574–1585. 5. Martorana F, et al. *Front Pharmacol.* 2021;12:662232. 6. Andrikopoulou A, et al. *Breast.* 2022;63:157–167. 7. Turner NC, et al. *N Engl J Med.* 2023;388:2058–2070. 8. Kalinsky K, Hong F, McCourt CK, et al. *JAMA Oncol.* 2021;7(2):217–278. 9. Mery B, et al. *Int J Mol Sci.* 2021;22:13512. 10. Castel P, et al. *Mol Cell Oncol.* 2014;1(3):e963447. 11. Li MM, et al. *J Mol Diagn.* 2017;19(1):4–23. 12. Li H, et al. *Cancers (Basel).* 2021;13(14):3517. 13. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer v2.2024. ©National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed March 21, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. 14. Henry NL, et al. *J Clin Oncol.* 2022;40(27):3205–3221. 15. Ribas R et al. *Mol Cancer Ther.* 2015;14(9):2035–2048. 16. FASLODEX® (fulvestrant) [prescribing information]. AstraZeneca Pharmaceuticals LP; 2020. 17. Alves CL, et al. *Int J Mol Sci.* 2023;24:4522. 18. FoundationOne®CDx. Technical Information. Accessed February 26, 2024. [https://www.foundationmedicine.com/sites/default/files/media/documents/2023-11/RAL-0003-24%20F1CDx%20Technical%20Label%20%28P170019\\_S048%29\\_Clean.pdf](https://www.foundationmedicine.com/sites/default/files/media/documents/2023-11/RAL-0003-24%20F1CDx%20Technical%20Label%20%28P170019_S048%29_Clean.pdf). 19. Memorial Sloan Kettering Cancer Center. The Role of Pathology in Diagnosing Breast Cancer. Accessed January 2024. <https://www.mskcc.org/cancer-care/diagnosis-treatment/diagnosing/role-pathology>. 20. Memorial Sloan Kettering Cancer Center. Your Cancer Care Team. Accessed January 31, 2024. <https://www.mskcc.org/cancer-care/diagnosis-treatment/your-care-team>.

This is a synopsis of the session, The clinical utility of NGS panel testing: Identifying *PIK3CA*, *AKT1*, and *PTEN*-altered HR+/HER2-advanced breast cancers that may be eligible for treatment with TRUQAP™ (capivasertib) + fulvestrant. Please visit the CAP Foundation website to view the full course in its entirety.

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