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AstraZeneca PLC
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Truqap recommended by FDA Advisory Committee for PTEN-deficient metastatic hormone-sensitive prostate cancer

ODAC overwhelming majority voted that Truqap plus abiraterone and ADT demonstrated a favourable benefit risk profile for patients based on the CAPItello-281 Phase III trial results

First and only targeted treatment combination to demonstrate benefit in this subtype of prostate cancer addresses significant unmet patient need

The US Food and Drug Administration's (FDA) Oncologic Drugs Advisory Committee (ODAC) has recognised a favourable benefit risk profile for AstraZeneca's *Truqap* (capivasertib) in combination with abiraterone and androgen deprivation therapy (ADT) for the treatment of patients with PTEN-deficient metastatic hormone-sensitive prostate cancer (mHSPC), based on the CAPItello-281 Phase III trial. The Committee voted 7 to 1, with 1 abstaining.

In August 2025, the FDA accepted the supplemental New Drug Application (sNDA) for *Truqap* in combination with abiraterone and ADT based on positive results from the CAPItello-281 Phase III trial, presented at the 2025 European Society for Medical Oncology (ESMO) Congress and simultaneously published in *Annals of Oncology*.[1]

Daniel George, MD, Director of Genitourinary Oncology at Duke Cancer Institute and investigator for the trial, said: "Patients identified to have PTEN-deficient metastatic hormone-sensitive prostate cancer have an aggressive form of the disease and currently experience poor outcomes. Their disease significantly impacts their quality of life and inevitably progresses to more advanced stages that are associated with high mortality rates. In addition to this poor prognosis, patients currently have limited treatment options, which is why today's recommendation of the capivasertib combination is welcome news for both patients and clinicians to address an urgent need for new treatments that delay progression."

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "CAPItello-281 is the first pivotal trial to prospectively define PTEN-deficient metastatic hormone-sensitive prostate cancer and its severe course of disease. The Committee's recognition of the unmet need in patients with PTEN-deficiency and of the benefit seen with the *Truqap* combination verifies its potential to address this significant need and optimise outcomes for patients. We are committed to working closely with the FDA to bring the first and only targeted treatment option to the one in four patients with this form of metastatic hormone-sensitive prostate cancer."

Results from the primary analysis of the CAPItello-281 Phase III trial showed a statistically significant 19% reduction in the risk of radiographic disease progression or death and a clinically meaningful improvement in median radiographic progression-free survival (rPFS) of 7.5 months with the *Truqap* combination versus treatment with abiraterone and ADT with placebo (based on a hazard ratio [HR] of 0.81; 95% confidence interval [CI] 0.66-0.98; p=0.034). Median rPFS was 33.2 months for the *Truqap* combination versus 25.7 months for the comparator arm.[1]

A consistent benefit was observed with the *Truqap* combination versus treatment with abiraterone and ADT with placebo in key secondary endpoints of the trial, including prolonged time to castration resistance (29.5 vs. 22.0 months [HR 0.77; 95% CI: 0.63-0.94]) and prostate-specific antigen (PSA) progression (HR 0.73; 95% CI: 0.52-1.01), and fewer and delayed events in terms of symptomatic skeletal event-free survival (SSE-FS) (42.5 vs. 37.3 months [HR 0.82, 95% CI: 0.66-1.02]).[1]

Overall survival (OS) data were immature at the time of primary analysis; however, subsequent interim results for OS numerically favoured the *Truqap* combination versus the comparator arm. The trial will continue as planned to further assess OS as a key secondary endpoint.

The safety profile of *Truqap* in combination with abiraterone and ADT in CAPItello-281 was broadly consistent with the known profile of each medicine. Consistent with the addition of a targeted treatment to background therapy, Grade 3 or higher adverse events occurred in 67% of patients treated with the *Truqap* combination versus 40.4% of patients treated with abiraterone and ADT with placebo. The most common Grade 3 or higher adverse events in the *Truqap* arm were rash (12.3%), hyperglycaemia (10.3%), hypokalaemia (8.7%), diarrhoea (6.2%), hypertension (5.8%) and anaemia (5.2%).[1]

The ODAC provides the FDA with independent, expert advice and recommendations on marketed and investigational medicines for use in the treatment of cancer. The FDA will consider the feedback as it reviews the submission and is not bound by the Committee's recommendation.

A regulatory application for *Truqap* in combination with abiraterone and ADT for the treatment of PTEN-deficient mHSPC is under review in the EU based on the CAPItello-281 Phase III trial.

Notes

Prostate cancer

Prostate cancer is the second most prevalent cancer in men and the fifth leading cause of male cancer death globally, with an incidence of more than 1.4 million and approximately 397,000 deaths in 2022.[2] In the US, prostate cancer is the most common cancer in men, with more than 300,000 new cases of the disease diagnosed annually, and more than 36,000 deaths.[3]

Metastatic prostate cancer is associated with a significant mortality rate, with only one third of patients surviving five years after diagnosis.[4] Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone.[5]

Metastatic hormone-sensitive prostate cancer

Metastatic hormone-sensitive prostate cancer
In patients with mHSPC, also known as metastatic castration-sensitive prostate cancer (mCSPC), prostate cancer cells need high levels of androgens to drive cancer growth.[5,6] Hormone therapies, such as ADT, are widely used to block the action of male sex hormones and lower the levels of androgens in the body.[6,7] However, resistance to these therapies is common and there is a need to extend their use to delay disease progression and castration resistance, where the prostate cancer grows and spreads to other parts of the body despite the use of these therapies.[6-8]

Newly diagnosed mHSPC is an aggressive form of the disease associated with poor outcomes and survival.[6,8] Globally, approximately 200,000 patients are diagnosed with mHSPC each year, with 35,000 patients diagnosed with the disease in the US.[9] One in four of these patients have PTEN-deficient tumours.[9]

PTEN-loss or deficiency fuels the growth of cancer cells, leading to dysregulation of the PI3K/AKT pathway, and is associated with poor outcomes in patients with prostate cancer.[10,11]

CAPItello-281
CAPItello-281 is a Phase III, double-blind, randomised trial evaluating the efficacy and safety of *Truqap* in combination with abiraterone and ADT versus abiraterone and ADT in combination with placebo in the treatment of patients with PTEN-deficient *de novo* mHSPC.

The global trial enrolled 1,012 adult patients with histologically confirmed *de novo* hormone-sensitive prostate adenocarcinoma and PTEN deficiency as confirmed by central testing. The primary endpoint of the CAPItello-281 trial is rPFS as assessed by investigator, with OS as a secondary endpoint.

Truqap
Truqap is a first-in-class, potent, adenosine triphosphate (ATP)-competitive inhibitor of all three AKT isoforms (*AKT1/2/3*). *Truqap* 400mg is administered twice daily according to an intermittent dosing schedule of four days on and three days off. This was chosen in early phase trials based on tolerability and the degree of target inhibition.

Truqap in combination with *Faslodex* (fulvestrant) is approved in the US, EU, Japan, China and a number of other countries for the treatment of adult patients with HR-positive (or estrogen receptor-positive), HER2-negative locally advanced or metastatic breast cancer with one or more biomarker alterations (*PIK3CA*, *AKT1* or *PTEN*) following recurrence or progression on or after an endocrine-based regimen based on the results from the CAPItello-291 trial. *Truqap* is also approved in Australia for the treatment of adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine based regimen based on these trial results.

Truqap is currently being evaluated in Phase III trials for the treatment of breast cancer (CAPItello-292) and prostate cancer (CAPItello-281) in combination with established treatments.

Truqap was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited).

AstraZeneca in oncology
AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Social Media @AstraZeneca.

Contacts
For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Matthew Bowden

Company Secretary
AstraZeneca PLC

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