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Truqap combination approved in the US as first and only targeted treatment for PTEN-deficient metastatic hormone-sensitive prostate cancer

Based on results of CAPItello-281 which prospectively defined PTEN-deficient disease and showed Truqap combination reduced risk of radiographic disease progression or death by 19%

First-in-class AKT inhibitor moves into second tumour type to address an aggressive form of prostate cancer associated with poor prognosis

AstraZeneca's *Truqap* (capivasertib) in combination with abiraterone and prednisone has been approved in the US as the first and only targeted treatment for adult patients with PTEN-deficient metastatic androgen pathway modulation-naïve or sensitive (mAPMN/S) prostate cancer, previously referred to as metastatic hormone-sensitive prostate cancer (mHSPC), as detected by a US Food and Drug Administration (FDA)-authorised test.[1]

The approval by the US FDA was based on positive results from the CAPItello-281 Phase III trial, presented at the 2025 European Society for Medical Oncology (ESMO) Congress and published in *Annals of Oncology*.[2]

Prostate cancer is the second most prevalent cancer in men and the fifth leading cause of male cancer death globally, with more than 1.4 million people diagnosed each year.[3] Of these, approximately 200,000 patients worldwide, including 35,000 in the US, are diagnosed with mAPMN/S prostate cancer annually.[4] One in four of these patients have PTEN-deficient tumours, which fuels the growth of cancer cells and defines an aggressive form of the disease associated with poor outcomes.[4-7] PTEN deficiency is an independent risk factor regardless of other clinical characteristics, and can be identified by immunohistochemistry testing at time of diagnosis.[7]

Daniel George, MD, Director of Genitourinary Oncology at Duke Cancer Institute and investigator for the CAPItello-281 trial, said: "Patients with PTEN-deficient metastatic hormone-sensitive prostate cancer, now called metastatic androgen pathway modulation-naïve or sensitive prostate cancer, experience faster progression and worse prognosis than those without PTEN deficiency. Keeping patients with this form of prostate cancer in remission and free from disease progression as long as possible is a high priority. Today's landmark approval of the capivasertib combination as the first and only targeted treatment option for these patients represents a significant clinical advance with the potential to improve their lives and change the course of disease."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "CAPItello-281 showed that for the first time, we can target a key driver of this disease to bring meaningful benefit to the one in four patients with this form of prostate cancer who urgently need biomarker-directed therapies. Today's approval makes clear the importance of testing for actionable biomarkers, including PTEN deficiency, in 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 *Truqap* in combination with abiraterone and androgen deprivation therapy (ADT) 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.[2] While overall survival (OS) data were immature at the time of the primary analysis, 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. Grade 3 or higher adverse events occurred in 67% of patients treated with the *Truqap* combination, with rash (12.3%) and hyperglycaemia (10.3%) the most frequently reported.[2]

Concurrently with this approval, the FDA also approved a companion diagnostic test to detect PTEN deficiency in tumours of patients with prostate adenocarcinoma.

A regulatory application for the *Truqap* combination in this setting is under review in the EU based on the CAPItello-281 Phase III trial.

Notes

Prostate cancer

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.[8]

Metastatic prostate cancer is associated with a significant mortality rate, with only one third of patients surviving five years after diagnosis.[9] Development of prostate cancer is often driven by male sex hormones called androgens, including testosterone.[10]

Metastatic androgen pathway modulation-naïve or sensitive prostate cancer

mAPMN/S prostate cancer, previously referred to as mHSPC or metastatic castration-sensitive prostate cancer (mCSPC) reflects new, redefined terminology for clinical trials and regulatory indications in prostate cancer.[1] In patients with mAPMN/S prostate cancer, prostate cancer cells need high levels of androgens to drive cancer growth.[5,10] Hormone therapies, such as androgen deprivation therapies, are widely used to block the action of male sex hormones and lower the levels of androgens in the body.[5,10] 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.[5,6,11]

mAPMN/S prostate cancer is an aggressive form of the disease associated with poor outcomes and survival.[5,6] Globally, approximately 200,000 patients are diagnosed with mAPMN/S prostate cancer each year, with 35,000 patients diagnosed with the disease in the US.[4] One in four of these patients have PTEN-deficient tumours.[4]

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.[12,13]

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 newly diagnosed PTEN-deficient mAPMN/S prostate cancer.

The global trial enrolled 1,012 adult patients with histologically confirmed newly diagnosed APMN/S 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 key 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 combination with established treatments for the 1st-line treatment of HR-positive breast cancer in the Phase III CAPItello-292 trial.

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

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Contacts

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