# Health Technology Briefing
# May 2024

# Capivasertib with abiraterone acetate for treating metastatic PTEN deficient hormone-sensitive prostate cancer

| Company/Developer | AstraZeneca UK Ltd |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 30225 | NICE ID: Not available | UKPS ID: 670181 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Capivasertib with abiraterone acetate is in clinical development for the treatment of prostate cancer which is metastatic (has spread to other parts of the body) and hormone-sensitive, meaning the cancer can be controlled by keeping the testosterone level as low as would be expected if the testicles were removed. Specifically, capivasertib with abiraterone acetate is indicated for patients who have phosphatase and tensin homolog (PTEN) deficiency, meaning the PTEN gene (a tumour suppressor gene) has been deleted. PTEN deficiency is associated with advanced prostate cancer development and poor clinical outcomes. Symptoms of advanced prostate cancer can include a frequent need to urinate, straining while urinating, and blood in urine or semen Metastatic prostate cancer is considered incurable. There is therefore a need to develop new treatment options for this population.

Capivasertib, taken orally, works by blocking a protein that stimulates cell growth and the spreading of tumours around the body. Abiraterone acetate is also taken by mouth and stops the body producing testosterone. Because the cancer needs a supply of testosterone to survive and grow, abiraterone acetate helps slow the growth. If licensed, capivasertib with abiraterone acetate will become the first treatment option specific for PTEN deficient metastatic hormone-sensitive prostate cancer and PTEN deficiency.

## Proposed Indication

Treatment of adults with metastatic hormone-sensitive prostate cancer (mHSPC) and phosphatase and tensin homolog (PTEN) deficiency.[1]

## Technology

### Description

Capivasertib (Truqap, AZD5363) is a selective protein kinase B (AKT) inhibitor. In tumour cells, AKT regulates cell proliferation, survival, migration, gene expression and metabolism. Loss of the tumour suppressor PTEN activates AKT signalling, through phosphatidylinositol 3 kinase (PI3K)-β.[2] Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α -hydroxylase/C17,20-lyase (CYP17), which is expressed in and is required for androgen biosynthesis in androgen biosynthesis in testicular, adrenal and prostatic tumour tissues.[3] In prostate cancer, targeting PI3K/AKT signalling by combining PI3Kβ or AKT inhibitors with inhibitors of androgen signalling increases anti-tumour effects in PTEN null tumour cell lines and tumour models due to reciprocal crosstalk between these two pathways.[2]

Capivasertib in combination with abiraterone acetate is in clinical development for the treatment of patients with PTEN deficient mHSPC. In the phase III clinical trial (CAPItello-281, NCT04493853), capivasertib (400 mg) is administered orally on days 1 to 4 and abiraterone acetate (1000 mg) is administered orally daily for each 28-day treatment cycle until disease progression or unacceptable toxicity.[1]

### Key Innovation

Despite advancements in the treatment of advanced prostate cancer, metastatic prostate cancer remains incurable, and is also associated with therapy resistance.[4,5] Loss of the PTEN tumour suppressor gene is observed in 20% to 30% of prostate cancers when first detected and the rate increases with prostate cancer progression and advanced disease.[6] Additional treatment options are needed for patients with PTEN deficiency, which is linked to advanced prostate cancer progression and poor clinical outcomes.[7]

Abiraterone acetate selectively inhibits the enzyme CYP17 which is expressed in testicular, adrenal, and prostatic tumours and required for androgen biosynthesis.[3] This inhibition stops the body producing testosterone. Because the cancer needs a supply of testosterone to survive and grow, abiraterone acetate helps slow the growth of the prostate cancer.[8] Enhanced activation of three AKT isoforms (AKT1, AKT2, and AKT3) can be implicated in tumour development and progression in cancers including prostate cancer.[9] Therefore, by combining capivasertib, a highly selective pan-AKT inhibitor, with abiraterone acetate, an androgen signalling inhibitor, anti-tumour effects in PTEN deficient prostate cancer may be increased.[2,10] If licensed, capivasertib with abiraterone acetate will become the first treatment option, and first AKT inhibitor, for patients with mHSPC that have a PTEN deficiency.

### Regulatory & Development Status

Capivasertib does not currently have marketing authorisation in the EU/UK for any indication.

Abiraterone acetate with prednisone or prednisolone currently has Marketing Authorisation in the EU/UK for:[3]

- The treatment of newly diagnosed high risk mHSPC in adult men in combination with androgen deprivation therapy

- The treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- The treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen

Capivasertib is also in phase III/II clinical development for lymphoma and breast cancer.[11]

Abiraterone aceteate is also in phase II/III clinical development for bladder cancer.[12]

## Patient Group

### Disease Area and Clinical Need

Prostate cancer is cancer of the prostate gland, characterised by abnormal cells starting to divide and grow in an uncontrolled way.[13] Prostate cancer usually does not cause any symptoms until the cancer has grown large enough to put pressure on the tube that carries urine from the bladder out of the penis (urethra). Symptoms of prostate cancer can include a frequent need to urinate, straining while urinating, and blood in urine or semen.[14] The exact cause of prostate cancer is unknown, however it is more common in men over 50, obese men, men who have a diet high in calcium, and men with a family history of prostate cancer or breast cancer.[15] Hormone-sensitive prostate cancer (HSPC) means the cancer is being controlled by keeping the testosterone level as low as what would be expected if the testicles were removed by castration. This can shrink the cancer or slow its growth for a time, but many cancers become resistant to this therapy with time.[16] With mHSPC, the cancer has spread from the prostate to other parts of the body such as lymph nodes, the bones, or other organs such as the lungs.[17] PTEN-deficient mHSPC means that the tumour suppressor gene PTEN has been deleted. PTEN is one of the most often deleted genes in prostate cancer. PTEN loss changes several pathways to promote prostate cancer development.[18]

Prostate cancer is the most common cancer in males in the UK, accounting for 27% of all new cancer cases (2016-18). In females and males combined, prostate cancer is the 2nd most common cancer in the UK, accounting for 14% of all new cancer cases (2016-18). The age standardised incidence rate of prostate cancer in England is 186.4 per 100,000 males.[19] In England (2022-23), there were 86,381 finished consultant episodes (FCEs) and 81,717 admissions for malignant neoplasm of prostate (ICD-10 code C61), which resulted in 61,419 day cases and 78,764 FCE bed days.[20] In England (2020), there were 36,016 patients diagnosed with malignant neoplasm of the prostate and 10,268 deaths registered where malignant neoplasm of the prostate was the underlying cause.[21] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates were 96.6% and 86.6% respectively.[22] Prostate cancer has a 5-year survival rate of over 95% when diagnosed at stage 1 to 3. Although, for the 1 in 5 people diagnosed with stage 4 prostate cancer (metastatic), the 5-year survival rate drops to 49%.[23] 9,972 men are diagnosed with stage 4 prostate cancer every year in the UK.[24] There are currently no treatment options recommended by NICE for PTEN-deficient mHSPC specifically.

### Recommended Treatment Options

NICE guidelines recommend the following treatment options for mHSPC in adults:

- Enzalutamide plus androgen deprivation therapy.[25]
- Darolutamide with docetaxel.[26]
- Apalutamide plus androgen deprivation therapy, only if docetaxel is not suitable.[27]

## Clinical Trial Information

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| Trial | **CAPItello-281;** NCT04493853; EudraCT 2020-000346-33; A Phase III Double-Blind, Randomised, Placebo-Controlled Study Assessing the Efficacy and Safety of Capivasertib+Abiraterone Versus Placebo+Abiraterone as Treatment for Patients With DeNovo Metastatic Hormone-Sensitive Prostate Cancer Characterised by PTEN Deficiency<br>**Phase III –** Active, not recruiting<br>**Location(s):** 9 EU countries, UK, USA, Canada, and other countries<br>**Primary completion date:** April 2025 |
| Trial Design | Randomised, parallel assignment, quadruple masking, placebo-controlled |
| Population | N=1000 (estimated); aged 18 years and over; histologically-confirmed de novo hormone-sensitive metastatic prostate adenocarcinoma. |
| Intervention(s) | Capivasertib (oral, 400mg days 1 and 4 each week of a 28-day treatment cycle) + abiraterone acetate (oral, 1000mg daily) |
| Comparator(s) | Matched placebo (oral) + abiraterone acetate (oral) |
| Outcome(s) | Primary outcome: radiographic progression-free survival [Time frame: up to approximately 55 months].<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of capivasertib is not yet known. The NHS indicative cost of abiraterone acetate ranges from £170.00 to £2735.00 for 56 tablets (500mg).[28]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Pembrolizumab with enzalutamide and androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA11202). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Relugolix for treating hormone sensitive prostate cancer (TA11141). Expected date of issue to be confirmed.
- NICE technology appraisal. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (TA903). June 2023.
- NICE technology appraisal. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA741). October 2021.
- NICE technology appraisal. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (TA721). August 2021.
- NICE technology appraisal. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712). July 2021.
- NICE clinical guideline. Prostate cancer: diagnosis and management (NG131). December 2021.
- NICE quality standard. Prostate cancer (QS91). December 2021.

| NHS England (Policy/Commissioning) Guidance |
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| • NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult), B15/S/a.<br>• NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a. |
| **Other Guidance** |
| • European Association of Urology. Guidelines on Prostate Cancer. 2023.[29]<br>• González del Alba A, Méndez-Vidal MJ, Vazquez S, Castro E, Climent MA, Gallardo E, et al. SEOM clinical guidelines for the treatment of advanced prostate cancer. 2020.[30]<br>• Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[31] |

## Additional Information

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