# Health Technology Briefing
# September 2023

# Cabozantinib with atezolizumab for treating metastatic castration-resistant prostate cancer after one novel hormonal therapy

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

| NIHRIO ID: 29556 | NICE ID: Not available | UKPS ID: 668641 |
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## Licensing and Market Availability Plans

In phase III clinical development.

## Summary

Cabozantinib in combination with atezolizumab is in clinical development for the treatment of cancer that started in the prostate, has spread to another part of the body (metastatic), and no longer responds to hormone treatment options (castration-resistant). The prostate is a small gland in a man's pelvis and is involved in the male reproductive system. Symptoms of prostate cancer include an increased need and difficulty urinating and a feeling that the bladder is not fully empty. The castration-resistant form of metastatic prostate cancer is particularly hard to treat with limited options and has a high mortality rate so new and additional treatment options are needed.

Cabozantinib is administered orally. It works by blocking the activity of enzymes known as tyrosine kinases. These enzymes can be found in cancer cells. By blocking the activity of these enzymes in cancer cells, the medicine reduces the growth and spread of the cancer. If licensed cabozantinib with atezolizumab will offer an additional treatment option for patients with metastatic-castration resistant prostate cancer who have been previously treated with a novel hormone therapy.

## Proposed Indication

Treatment of metastatic castration-resistant prostate cancer (mCRPC) in men who have been previously treated with one novel hormonal therapy.[1]

## Technology

### Description

Cabozantinib (Cometriq, Cabometyx) is a tyrosine kinase inhibitor.[23] It inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib is an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, it inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.[4] By blocking the activity of these receptors in cancer cells, cabozantinib reduces the growth and spread of the cancer.[2]

Cabozantinib in combination with atezolizumab is in clinical development as a second line treatment for mCRPC in men who have been previously treated with one novel hormonal therapy. In the phase III clinical trial (NCT04446117), CONTACT-02, participants receive 40mg cabozantinib as oral tablets once daily and 1200mg atezolizumab administered intravenously (IV) once every 3 weeks.[1]

### Key Innovation

Despite advances in treatment, the prognosis for patients with mCRPC is poor, particularly for those who have progressed on treatment with a novel hormonal therapy. Although treatment with a second novel hormonal therapy is another option for patients who have received one previous novel hormonal therapy, several studies have documented low activity of sequential novel hormonal therapy, showing the need for new treatment options.[5] In the phase Ib (NCT03170960) study, cabozantinib plus atezolizumab demonstrated clinical activity and an acceptable safety profile in patients with previously treated metastatic castration-resistant prostate cancer including those with high-risk clinical features. These results suggest cabozantinib in combination with atezolizumab holds promise as a potential new treatment option in mCRPC, a difficult-to-treat tumour type that typically has a poor prognosis.[6] Preclinical studies have suggested that cabozantinib and atezolizumab work synergistically on tumour responses, attacking a large number of pathways to reduce cancer cell proliferation. The strong safety profile of the drugs in combination could also provide a new treatment option for those deemed unable to tolerate chemotherapy-associated toxicities.[7]

If licensed, cabozantinib in addition to atezolizumab will offer an additional second-line treatment option for patients with mCRPC who currently have few effective therapies available.

### Regulatory & Development Status

Cabozantinib in combination with atezolizumab does not currently have Marketing Authorisation in the EU/UK for any indication.
In the EU/UK, cabozantinib as a monotherapy has Marketing Authorisation for the following:[4]

- advanced renal cell carcinoma (and in combination with nivolumab)
- hepatocellular carcinoma.
- differentiated thyroid carcinoma.

Cabozantinib in combination with atezolizumab is in phase II/III clinical development for the treatment of:[8]

- neoplasms of the endocrine system
- pancreatic cancer

- metastatic oesophageal squamous cell carcinoma
- bladder cancer
- non-small cell lung cancer
- renal cell carcinoma
- recurrent glioblastoma
- locally advanced/metastatic solid tumours
- hepatocellular carcinoma
- advanced papillary kidney cancer
- advanced solid tumours involving the abdomen or thorax

## Patient Group

### Disease Area and Clinical Need

Prostate cancer is cancer of the prostate gland. The prostate gland is part of the male reproductive system.[9] Metastatic prostate cancer refers to cancer that has spread from the prostate to other parts of the body. It most commonly spreads to lymph nodes in other parts of the body or to the bones. It can also spread to other organs such as the lungs.[10] The exact cause of prostate cancer is unknown however some risk factors have been identified including; advanced age (men 50 years and older), African descent, family history, obesity, and diet.[11] Symptoms of metastatic prostate cancer include: bone pain, fatigue, malaise, and weight loss for no known reason.[12] Castrate-resistant prostate cancer is defined by disease progression despite androgen depletion therapy and may present as either a continuous rise in serum prostate-specific antigen levels, the progression of pre-existing disease, and/or the appearance of new metastases.[13]

Prostate cancer is the most common cancer in males in the UK, accounting for 27% of all new cancer cases in males (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 (2016-2018). The age standardised incidence rate of prostate cancer in England (2016-18) is 186.4 per 100,000 males.[14] About 50% of men diagnosed with metastatic prostate cancer will survive their cancer for 5 years or more after they are diagnosed.[15] Over 90% of people with metastatic prostate cancer initially respond to hormonal therapy but eventually become resistant to it.[16] In England (2021-22), there were 77,547 finished consultant episodes (FCEs) and 73,256 admissions for malignant neoplasm of prostate (ICD-10 code C61), which resulted in 54,896 day cases and 71,095 FCE bed days.[17] In England (2017), there were 41,201 patients diagnosed with malignant neoplasms of prostate and 10,146 deaths registered where prostate cancer was the underlying cause.[18] For patients diagnosed with stage 4 (metastatic) prostate cancer between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 88.3% and 49% respectively.[19]

### Recommended Treatment Options

For the treatment of mCRPC before chemotherapy is indicated, the National Institute for Health and Care Excellence (NICE) recommends abiraterone in combination with prednisone or prednisolone, or enzalutamide as monotherapy. Docetaxel is also recommended as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more.[20]

## Clinical Trial Information

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| Trial | **CONTACT-02,** NCT04446117; A Phase 3, Randomized, Open-Label, Controlled Study of Cabozantinib (XL184) in Combination With Atezolizumab vs Second |

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| | Novel Hormonal Therapy (NHT) in Subjects With Metastatic Castration-Resistant Prostate Cancer<br>**Phase III –** Active, not recruiting<br>**Locations:** 11 EU countries, UK, USA, Canada, and other countries<br>**Primary completion date:** June 2023 |
| Trial Design | Randomised, parallel-assignment, open label, active-comparator controlled |
| Population | N=575; men aged 18 years and older with histologically or cytologically confirmed metastatic, castration-resistant, adenocarcinoma of the prostate, previously treated with one, and only one novel hormonal therapy |
| Intervention(s) | • Cabozantinib (oral), 40mg daily<br>• Atezolizumab (IV), 1200mg every three weeks |
| Comparator(s) | • Abiraterone Acetate (oral), 1000mg daily with prednisone (oral), 5mg twice daily<br>• Enzalutamide (oral), 160mg daily |
| Outcome(s) | Primary outcomes:<br>• Duration of progression free survival per response evaluable criteria in solid tumours version 1.1 (RECIST 1.1) [Time frame: Approximately 21 months after the first subject is randomized.]<br>• Duration of overall survival (OS) [Time frame: Approximately 37 months after the first subject is randomized]<br><br>See trial record for secondary outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | NCT03170960; A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination with Atezolizumab to Subjects with Locally Advanced or Metastatic Solid Tumours<br>**Phase I/II -** Active, not recruiting<br>**Locations:** 6 EU countries, UK, USA, and Australia<br>**Primary completion date:** July 2023 |
| Trial Design | Non-randomised, sequential assignment, open label |
| Population | N=1,732; Subjects with cytologically or histologically and radiologically confirmed solid tumour that is inoperable, locally advanced, metastatic, or recurrent aged 18 years and older |
| Intervention(s) | • Cabozantinib (oral), various doses<br>• Atezolizumab (IV), various doses |
| Comparator(s) | - |
| Outcome(s) | Primary outcomes:<br>Dose escalation: maximum tolerated dose (MTD)/recommended dose [Time frame: up to 6 months] |

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| | Dose expansion: objective response rate (ORR) [Time Frame: Up to 31 months]<br><br>See trial record for secondary outcomes |
| Results (efficacy) | ORR was 23% (95% CI 17–32; 31 of 132 patients), with three (2%) confirmed complete responses and 28 (21%) confirmed partial responses.[5] |
| Results (safety) | 72 (55%) of 132 patients had grade 3–4 treatment-related adverse events, with the most common being pulmonary embolism (11 [8%] patients), diarrhoea (nine [7%]), fatigue (nine [7%]), and hypertension (nine [7%]). There was one grade 5 treatment-related adverse event (dehydration). 74 (56%) of 132 patients had serious adverse events of any causality. 28 (21%) of 132 patients had treatment-related adverse events leading to discontinuation of either study drug.[5] |

## Estimated Cost

The NHS indicative price of 30 tablets of 20, 40 or 60mg cabozantinib is £5,143.[21]
The NHS indicative price of 1 vial of atezolizumab (1200mg/20ml) is £3,807.69; (840mg/14ml) is £2,665.38.[22]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Abemaciclib with abiraterone acetate and prednisone for treating hormone-relapsed metastatic prostate cancer (TA11252). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ipatasertib with abiraterone and prednisone for hormone-relapsed metastatic prostate cancer (TA10779). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with enzalutamide for treating metastatic hormone-relapsed prostate cancer (TA11004). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Atezolizumab with cabozantinib for treating hormone-relapsed metastatic prostate cancer after 1 therapy (TA11163). Expected date of issue to be confirmed.
- NICE technology appraisal. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). July 2016.
- NICE technology appraisal. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE technology appraisal. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006.
- NICE clinical guideline. Prostate cancer: diagnosis and management (NG131). May 2019. Last updated: December 2021.
- NICE quality standard. Prostate cancer (QS91). June 2015. Last updated: December 2021.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Proton Beam Therapy for Cancer of the Prostate. 16020/P. July 2016.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Prostate Cancer. 16031/P. July 2016.

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

### Other Guidance

- European Association of Urology (EAU) – European Society for Radiotherapy & Oncology (ESTRO) –European Society of Urogenital Radiology (ESUR) – International Society of Geriatric Oncology (SIOG) Guidelines on Prostate Cancer. 2023.[23]
- Public Health England. Prostate Cancer Risk Management Programme. January 2015. Updated March 2016.[24]
- ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2015.[25]

## Additional Information

## References

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