NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
September 2022

Atezolizumab with cabozantinib for previously treated metastatic castration-resistant prostate cancer

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30124	NICE ID: 11799	UKPS ID: 665156

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Atezolizumab in combination with cabozantinib is in clinical development for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in male patients previously treated with one novel hormonal therapy (NHT). Prostate cancer is cancer of the prostate gland, which is part of the male reproductive system. When prostate cancer spreads to other parts of the body, it is called metastatic. Castration-resistant refers to when prostate cancer does not respond to initial treatments, which include surgery and/or a standard hormone treatment called androgen-deprivation therapy that lowers testosterone levels in the body to slow cancer growth. There is a significant unmet need for effective therapies in patients with mCRPC who have received prior NHT.

Atezolizumab is a monoclonal antibody designed to attach to a protein called PD-L1, which is present on many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effects, atezolizumab increases the immune system's ability to attack cancer cells, thereby slowing down progression of the disease. Cabozantinib blocks the activity of enzymes known as tyrosine kinases which are involved in the growth and spread of cancer. Atezolizumab will be administered as an intravenous infusion and cabozantinib as an oral tablet. If licensed, atezolizumab in combination with cabozantinib would offer an additional treatment option for mCRPC patients who have had prior treatment with one NHT.

Proposed Indication

Treatment of male patients with metastatic castration-resistant prostate cancer (mCRPC), who have had prior treatment with one novel hormonal therapy (NHT).[1]

Technology

Description

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.[2]

Cabozantinib (Cabometyx, XL184) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib 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.[3]

Atezolizumab in combination with cabozantinib is currently in clinical development for the treatment of mCRPC in male patients who have previously received a NHT for their prostate cancer disease. In the phase III clinical trial (CONTACT-02; NCT04446117), subjects will receive cabozantinib 40mg orally daily, in addition to atezolizumab 1200mg as an intravenous (IV) infusion once every 3 weeks.[1]

Key Innovation

Metastatic prostate cancer is a leading cause of cancer-related death in men worldwide. There remains a significant unmet need for efficacious therapies in patients with mCRPC who have received prior NHT with extrapelvic disease. Preclinical studies have shown that cabozantinib promotes an immune-permissive environment and may work synergistically with immune checkpoint inhibitors (ICIs) such as atezolizumab to improve tumour responses.[4] In a phase I/II clinical trial (NCT03170960), cabozantinib plus atezolizumab showed promising antitumour activity in patients with metastatic castration-resistant prostate cancer after NHT with an acceptable safety profile, supporting further evaluation of this combination.[5]

If licensed, cabozantinib in combination with atezolizumab will offer an additional treatment option for patients with mCRPC patients who have had previous treatment with an NHT.

Regulatory & Development Status

Atezolizumab has Marketing Authorisation in the EU/UK as a monotherapy and in combination for the following indications:[2]

- Urothelial carcinoma
- Early-stage non-small cell lung cancer (NSCLC)
- Metastatic NSCLC
- Small cell lung cancer (SCLC)

- Triple-negative breast cancer
- HCC

Cabozantinib has Marketing Authorisation in the EU/UK as a monotherapy and in combination for the following indications:[3]

- RCC
- HCC
- Differentiated thyroid carcinoma (DTC)

Cabozantinib in combination with atezolizumab is currently in phase II and III clinical trials for the following indications:[6]

- Osteosarcoma
- HCC
- Neoplasms of the endocrine system
- Pancreatic cancer
- Esophageal cancer
- Bladder cancer
- RCC
- NSCLC

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.[7] Metastatic prostate cancer means that the cancer has spread from the prostate to other parts of the body. It is sometimes called advanced prostate cancer. It most commonly spreads to lymph nodes in other parts of the body or to the bones, and can also spread to other organs.[8] Castration-resistant prostate cancers are a class of cancer that do not respond to first-line treatments, which include surgery and/or a standard hormone treatment called androgen-deprivation therapy (ADT). ADT works by lowering testosterone levels in the body, which can be achieved by either removing the testicles or employing drugs which lower the production of testosterone.[9] In castration-resistant prostate cancer, prostate cancer keeps growing even when the amount of testosterone in the body is reduced to very low levels.[10] Symptoms of metastatic prostate cancer can include bone pain, fatigue, feel generally unwell and weight loss for no known reason.[11]

Around 52,300 men are diagnosed with prostate cancer in the UK each year. In men, it is the most common cancer in the UK.[7] Prostate cancer accounts for 27% of all new cancer cases in males in the UK (2016-2018). Incidence rates for prostate cancer in the UK are highest in males aged 75 to 79 (2016-2018). There are around 12,000 prostate cancer deaths in the UK every year, that is 33 every day (2017-2019). Almost 9 in 10 (86.6%) of men diagnosed with prostate cancer in England survive their disease for five years or more (2013-2017).[12] Around 55–65% of people with prostate cancer develop metastatic disease. Over 90% of people with metastatic prostate cancer initially respond to hormonal therapy but eventually become resistant to it (mCRPC).[13] Using these statistics, it can be estimated that around 28,765-33,995 men are diagnosed with metastatic prostate cancer in the UK every year, with 25,888-30,595 having mCRPC.[7,13] In England (2020-21), there were 60,023 finished consultant episodes (FCEs) and 55,799 admissions for a primary diagnosis of malignant neoplasm of prostate (ICD-10 code C61), which resulted in 39,040 day cases and 58,293 FCE bed days.[14]

Recommended Treatment Options

NICE recommends the following treatment options for mCRPC:[15]

- abiraterone acetate (in combination with prednisone or prednisolone) and enzalutamide
- chemotherapy with docetaxel
- corticosteroid such as dexamethasone

Clinical Trial Information

Trial	**CONTACT-02, NCT04446117, 2020-000348-77;** A Phase 3, Randomized, Open-Label, Controlled Study of Cabozantinib (XL184) in Combination With Atezolizumab vs Second Novel Hormonal Therapy (NHT) in Subjects With Metastatic Castration-Resistant Prostate Cancer **Phase III –** Recruiting **Location(s) –** 11 EU countries, UK, USA, Canada and other countries **Primary completion date –** March 2022
Trial Design	Randomised, parallel assignment, open label
Population	N = 580 (estimated); Male subjects with histologically or cytologically confirmed adenocarcinoma of the prostate, who have received prior treatment with one, and only one, NHT; 18 years and older
Intervention(s)	Cabozantinib 40mg (oral) daily with 1200 mg atezolizumab (IV) once every 3 weeks
Comparator(s)	• Abiraterone acetate 1000mg (oral) daily with prednisone 5 mg (oral) twice a day; OR • Enzalutamide 160mg (oral) daily
Outcome(s)	Primary outcome measures: • 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] • Duration of Overall Survival (OS) [Time Frame: Approximately 37 months after the first subject is randomized]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Atezolizumab is already marketed in the UK; a 1200mg/20ml vial costs £3,807.69.[16]

Cabozantinib is already marketed in the UK; a pack of 30 x 20mg tablets cost £5,143.00.[17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Nivolumab in combination for treating hormone relapsed metastatic prostate cancer before chemotherapy (GID-TA10490). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab with docetaxel for treating hormone-relapsed metastatic prostate cancer untreated with chemotherapy (GID-TA10668). Expected date of issue to be confirmed.
- NICE technology appraisal. Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE technology appraisal. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). August 2016.
- NICE technology appraisal. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA259). July 2016.
- NICE technology appraisal guidance. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). July 2016.
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- NICE technology appraisal. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006.
- NICE guideline. Prostate cancer: diagnosis and management (NG131). December 2021.
- NICE quality standard. Prostate cancer (QS91). December 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised kidney, bladder and prostate cancer services (adults); Service specification. 170114S. February 2019.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Prostate Cancer. 16031/P. July 2016.
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Other Guidance

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- International Society of Geriatric Oncology. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. July 2019.[20]
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Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.