NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
OCTOBER 2020

Ipatasertib in combination with abiraterone and prednisone for metastatic castrate resistant prostate cancer – first line

NIHRIO ID	15117	**NICE ID**	10491
Developer/Company	Roche Products Ltd	**UKPS ID**	645058

Licensing and market availability plans	Currently phase III clinical trials.

SUMMARY

Ipatasertib in addition to abiraterone and prednisone is in clinical development for the first line treatment of metastatic castrate resistant prostate cancer (mCRPC). Prostate cancer is a cancer of the prostate gland and mCRPC is when the cancer has spread to parts of the body other than the prostate, and it is able to grow and spread even though drugs or other treatments to lower the amount of male sex hormones are being used to manage the cancer. The symptoms of prostate cancer may vary depending on the stage but can include pain, tiredness, and problems emptying the bladder and the bowels. Treatment options for mCRPC are currently limited.

Ipatasertib is an oral, highly specific medicine designed to target and bind to all three forms of protein called AKT. By binding to AKT, ipatasertib blocks the PI3K/AKT signalling pathway and may prevent cancer cell growth and survival. If licensed, ipatasertib in addition to abiraterone and prednisone will provide a new regimen for mCRPC.

PROPOSED INDICATION

First line treatment of adult male patients with asymptomatic or mildly symptomatic, previously untreated, metastatic castrate-resistant prostate cancer.[1]

TECHNOLOGY

DESCRIPTION

Ipatasertib (GDC-0068; RG-7440) is an investigational, orally administered, adenosine triphosphate (ATP)-competitive, selective AKT inhibitor. Aberrant AKT signalling is associated with resistance to apoptosis and increased cell growth, proliferation, and metabolism. Ipatasertib is designed to target and bind to the ATP binding pocket of the three activated isoforms of AKT, potentially inhibiting downstream signalling. By inhibiting AKT serine/threonine kinase activity, ipatasertib may inhibit tumour growth and proliferation as well as activate apoptotic signalling.[2]

In the phase III clinical trial (NCT03072238), ipatasertib and abiraterone were administered orally, in 28-day cycles. Patients received ipatasertib, 400 mg, given once daily beginning on day 1 of cycle 1 and abiraterone acetate, 1000 mg once daily, taken on an empty stomach and swallowed whole with water, plus prednisone/prednisolone, 5 mg twice daily until disease progression or intolerable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Abiraterone acetate delays disease progression and improves overall survival in mCRPC; however, resistance and disease progression usually occur, highlighting a need for improved treatments.[3] PTEN loss (occurring in 40%-50% of mCRPC) results in activation of AKT, the target of ipatasertib, and worse outcomes.[4] In mCRPC, combined blockade with abiraterone and ipatasertib has shown superior antitumor activity to abiraterone alone, especially in patients with PTEN-loss tumors.[3]

Ipatasertib would also be the first ATP – competitive AKT inhibitor available for this indication.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ipatasertib is not approved for any indication in the EU/UK.

Abiraterone and prednisone in combination is a recommended treatment for mCRPC.[6]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is the most common cancer in older men in the UK.[7] It affects the prostate, a small gland in the pelvis found only in men which is located between the penis and the bladder and surrounds the urethra. The main function of the prostate is to help in the production of semen.[8] Advanced prostate cancer means the cancer has spread from the

prostate to other parts of the body (metastatic prostate cancer). It most commonly spreads to lymph nodes in other parts of the body or to the bones. It can also spread to other organs.[9]

Prostate cancer cells usually need testosterone to grow.[10] Prostate cancer that has spread to other parts of the body and which keeps growing even when the amount of testosterone in the body is reduced to very low levels (via testosterone suppression therapy) is identified as mCRPC.[11]

Prostate cancer is more common in black Caribbean and black African men than in white men and is less common in Asian men. Around 35% of the men diagnosed with prostate cancer in the UK each year are aged 75 years and over.[7] Additional factors which increase the risk of developing prostate cancer include having a family history of the condition, and lifestyle factors (e.g. consuming a lot or red meat and foods that are high in fat).[7,12]

Prostate cancer does not usually 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).[8] Advanced prostate cancer can cause symptoms, such as fatigue (extreme tiredness), bone pain, and problems urinating. The symptoms depend on where the cancer has spread to.[13] Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts on their daily lives, particularly physical and emotional health, relationships and social life.[14]

CLINICAL NEED AND BURDEN OF DISEASE

Prostate cancer is the most common cancer amongst males in the UK, accounting for 26% of all new cancer cases in this population (2017 data).[15] In England in 2017 there were 41,201 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD-10 code C61). Of these, 8,490 cases were diagnosed at stage 4.[16] European age standardised rates of prostate cancer in the UK are expected to increase from 208 per 100,000 in 2014 to 232.5 in 2035 (11.79% increase).[17] According to the latest NICE review in mCRPC (2016), an estimated 5,960 people develop mCRPC annually.[18]

According to Hospital Episode Statistics (HES) data, in 2018-19 there were 81,227 admissions with a primary diagnosis of neoplasm of the prostate (ICD-10 code C61), resulting in 86,487 finished consultant episodes (FCE), 92,702 FCE bed days and 57,193 day cases.[19]

In England and Wales in 2019, there were 10,872 deaths where malignant neoplasm of prostate (ICD-10 code C61) was recorded as the underlying cause.[20] Latest published survival statistics (patients diagnosed in 2013-2017) report a 1-year net survival rate of 88.3% and a 5-year net survival rate of 49% for men diagnosed with stage 4 prostate cancer.[21]

According to a 2011 systematic review in mCRPC, an estimated 5,960 people develop mCRPC annually.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of prostate cancer depends on the stage of the cancer and the general health of the patient. At advanced stage prostate cancer treatment aims to control the cancer and relieve symptoms. Treatment generally includes chemotherapy, hormone therapy, radiotherapy, steroids and symptom control - for example treatments to help with bone pain.[22] Hormone therapy, also known as androgen suppression therapy, aims to lower androgen levels and make the prostate cancer shrink or grow more slowly.[10]

CURRENT TREATMENT OPTIONS

NICE recommends docetaxel chemotherapy be offered to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities.[6]

As an option for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated NICE recommends:[6]

- Abiraterone in combination with prednisone or prednisolone
- Enzalutamide

Additionally, cabazitaxel has a UK marketing authorisation for use in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.[23]

PLACE OF TECHNOLOGY

If licenced, ipatasertib in combination with abiraterone and prednisone could provide a first line treatment of adult male patients with asymptomatic or mildly symptomatic, previously untreated, metastatic castrate-resistant prostate cancer.

CLINICAL TRIAL INFORMATION

Trial	**IPATential150;** NCT03072238**;** A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Testing Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients With Asymptomatic or Mildly Symptomatic, Previously Untreated, Metastatic Castrate-Resistant Prostate Cancer **Phase III**- Active, not recruiting **Location(s):** EU (incl UK), USA, Canada and other countries. **Primary completion date**: March 2020
Trial design	Randomised, parallel assignment, double masking
Population	N = 1101, histologically confirmed asymptomatic or mildly symptomatic form of metastatic prostate cancer, males aged 18 years and older.
Intervention(s)	Oral tablets, 400mg of ipatasertib, given once daily (QD) beginning on day 1 of cycle 1 until disease progression or intolerable toxicity. Oral tablets of abiraterone, 1000mg QD, taken on an empty stomach and swallowed whole with water, plus prednisone/prednisolone, 5mg twice daily (BID) until disease progression or intolerable toxicity.

Comparator(s)	Oral tablets of abiraterone, 1000 mg QD, taken on an empty stomach and swallowed whole with water, plus prednisone/prednisolone, 5mg BID and matched ipatasertib placebo.
Outcome(s)	Primary outcome: Investigator-Assessed Radiographic Progression-Free Survival (rPFS) [Time frame: up to approximately 31 months] See trial record for full list of other outcomes.
Results (efficacy)[4]	Ipatasertib in combination with abiraterone as first-line treatment for mCRPC resulted in significantly improved rPFS and antitumor activity vs placebo and abiraterone in patients with PTEN-loss mCRPC, but not in the intention to treat.
Results (safety)[4]	Serious adverse events (AEs) occurred in 40% and 23% of ipatasertib and placebo patients, respectively; AEs leading to discontinuation of ipatasertib/placebo occurred in 21% and 5%. The safety profile was in line with known and potential risks.

ESTIMATED COST

The cost of ipatasertib is not yet known.

The cost of abiraterone acetate on the NHS is £2735.00 for 500mg tablets supplied by Janssen-Cilag Ltd.[24]

For prednisolone, the NHS indicative price varies between suppliers and according to the concentration/administration. For example, the cost of prednisolone 5mg tablets (28 tablets POM) supplied by A H Pharmaceuticals Ltd is £1.48.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). August 2016
- NICE technology appraisal guidance. 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). April 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE technology appraisal guidance. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). July 2014.
- NICE technology appraisal guidance. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006.
- NICE guideline. Prostate cancer: diagnosis and management (NG131). May 2019

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

OTHER GUIDANCE

- Cassinello J, Arranz J.A., Piulats J.M. et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer. 2017.[26]
- Parker C., Gillessen S., Heinderich A. et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2015.[27]
- European Association of Urology. Prostate Cancer Guidelines. 2015.[28]
- Canadian Urologic Oncology Group (CUOG) and the Canadian Urological Association (CUA). Guidelines for the management of castrate-resistant prostate cancer. 2010.[29]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients With Metastatic Castrate-Resistant Prostate Cancer (IPATential150). *ID: NCT03072238*. 2017;Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03072238.

2 Genentech. *Ipatasertib (GDC-0068, RG7440)*. 2020. Available from: https://www.genentechoncology.com/pipeline-molecules/ipatasertib.html [Accessed 07 August 2020].

3 de Bono JS, De Giorgi U, Rodrigues DN, Massard C, Bracarda S, Font A, et al. Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss. *Clinical Cancer Research*. 2019;25(3):928. Available from: https://doi.org/10.1158/1078-0432.CCR-18-0981.

4 de Bono JS, Bracarda S, Sternberg CN, Chi KN, Olmos D, Sandhu S, et al. LBA4 IPATential150: Phase III study of ipatasertib (ipat) plus abiraterone (abi) vs placebo (pbo) plus abi in metastatic castration-resistant prostate cancer (mCRPC). *Annals of Oncology*. 2020;31:S1153-S4. Available from: https://doi.org/10.1016/j.annonc.2020.08.2250.

5 Saura C, Roda D, Rosello S, Oliveira M, Macarulla T, Perez-Fidalgo J, et al. A first-in-human phase I study of the ATP-competitive AKT inhibitor ipatasertib demonstrates robust and safe targeting of AKT in patients with solid tumors. *Cancer Discovery*. 2018;7:102 - 13. Available from: https://doi.org//10.1158/2159-8290.CD-16-0512.

6 National Insitute for Health and Care Excellence. *Prostate cancer: diagnosis and management* 2019. Available from: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133 [Accessed 16 September 2020].

7 Cancer Research UK. *About prostate cancer*. 2019. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 15 September 2020].

8 NHS. *Prostate Cancer*. 2018. Available from: https://www.nhs.uk/conditions/prostate-cancer/ [Accessed 15 September 2020].

9 Cancer Research UK. *What is advanced prostate cancer?* . 2019. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/about-advanced-cancer [Accessed 15 September 2020].

10 Prostate Cancer UK. *Hormone therapy.* 2016. Available from: https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy [Accessed 15 September 2020].

11 National Cancer Institute. *Clinical Trials Using Enzalutamide.* Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/intervention/enzalutamide [Accessed 15 September 2020].

12 American Cancer Society. *Prostate cancer risk factors.* 2019. Available from: https://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html [Accessed 17 September 2020].

13 Prostate Cancer UK. *Advanced prostate cancer.* Available from: https://prostatecanceruk.org/prostate-information/just-diagnosed/advanced-prostate-cancer [Accessed 17 September 2020].

14 Appleton L, Wyatt D, Perkins E, Parker C, Crane J, Jones A, et al. The impact of prostate cancer on men's everyday life. *European journal of cancer care*. 2015;24(1):71-84. Available from: https://doi.org/10.1111/ecc.12233.

15 Cancer Research UK. *Prostate cancer statistics,* . Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero [Accessed 17 September 2020].

16 National Cancer Registration and Analysis Service (NCRAS). *Survival by stage. Cancer breakdown by stage: 'stage breakdown by CCG 2017'.* 2019. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 17 September 2020].

17 Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed 17 September 2020].

18 National Insitute for Health and Care Excellence. *Resource impact report: Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391).* Available from: https://www.nice.org.uk/guidance/ta391/resources/resource-impact-report-pdf-2492881885 [Accessed 15 September 2020].

19 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 17 September 2020].

20 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality.* 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 17 September 2020].

21 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 16 September 2020].

22 Cancer Research UK. *Making decisions about treatment for advanced cancer.* 2019. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/advanced-treatment/making-decisions-about-treatment [Accessed 9 October 2020].

23 National Insitute for Health and Care Excellence. *Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel.* 2016. Available from: https://www.nice.org.uk/guidance/ta391 [Accessed 9 October 2020].

24 British National Formulary. *ABIRATERONE ACETATE.* 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/abiraterone-acetate.html [Accessed 9 October 2020].

25 British National Formulary. *PREDNISOLONE.* 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/prednisolone.html [Accessed 9 October 2020].

26 Cassinello J, Arranz JA, Piulats JM, Sanchez A, Perez-Valderrama B, Mellado B, et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017). *Clin Transl Oncol*. 2018 Jan;20(1):57-68. Available from: https://doi.org/10.1007/s12094-017-1783-2.

27 Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015 Sep;26 Suppl 5:v69-77. Available from: https://doi.org/10.1093/annonc/mdv222.

28 European Association of Urology. *Prostate cancer*. 2020. Available from: https://uroweb.org/guideline/prostate-cancer/ [Accessed 17 June 2020].

29 Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. *Canadian Urology Association Journal*. 2010 Dec;4(6):380-4. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC2997826/.

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