NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING
# NOVEMBER 2020

# Olaparib in addition to abiraterone for metastatic castration-resistant prostate cancer – First line

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| **NIHRIO ID** | 26993 | **NICE ID** | 10303 |
| **Developer/Company** | AstraZeneca UK Ltd | **UKPS ID** | 653570 |

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| **Licensing and market availability plans** | Currently in phase III clinical trials |

## SUMMARY


Olaparib in combination with abiraterone acetate is in clinical development for patients with metastatic castrate-resistant prostate cancer (mCRPC). Prostate cancer is the most common type of cancer in men in the UK. The cancer is called advanced (metastatic) prostate cancer when the cancer cells have spread to other parts of the body like bones, lymph nodes outside the pelvis or rarely to the liver or lungs. It is not possible to cure metastatic prostate cancer but is possible to keep it under control. Prostate cancers that continue to grow despite hormonal therapies are called "castration-resistant" prostate cancer.

Olaparib is administered orally in tablet form and can lead to cancer cell death by blocking DNA repair by an enzyme (protein) called PARP. By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and the cells die. Abiraterone works by stopping the body making testosterone which subsequently stops the cancer growing. If licensed, this combination would provide a first-line treatment for men with mCRPC.

# PROPOSED INDICATION

First-line treatment for men with metastatic castration resistant prostate cancer (mCRPC).[a]

# TECHNOLOGY

## DESCRIPTION

Olaparib (Lynparza) is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies. PARPs are required for the efficient repair of DNA single-strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as breast cancer 1 and 2 (BRCA1 or 2), DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells.[1]

Abiraterone acetate (Zytiga) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumours. Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels.[2]

Olaparib in addition to abiraterone is currently in clinical development for patients with mCRPC. In the phase III clinical trial (PROpel, NCT03732820), participants receive olaparib 300 mg (2 x 150mg) orally twice daily plus abiraterone acetate 1000mg orally once daily. Patients also receive prednisone or prednisolone 5mg twice daily.[3]

## INNOVATION AND/OR ADVANTAGES

This is a novel combination of a PARP inhibitor and an androgen biosynthesis inhibitor for the treatment of prostate cancer.

Olaparib in combination with abiraterone provided clinical efficacy benefit for patients with mCRPC compared with abiraterone alone in a phase II trial (NCT01972217).[4]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Olaparib in combination with abiraterone does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by AstraZeneca UK Ltd on UK PharmaScan

Olaparib monotherapy is indicated for: [1,5]

- Ovarian cancer: BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; and, platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
- Breast cancer: treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2 negative locally advanced or metastatic breast cancer
- Adenocarcinoma of the pancreas: maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas
- Prostate cancer: treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

Abiraterone acetate in combination with prenisone or prednisolone is indicated for the treatment of metastatic castration resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel-containing chemotherapy regimen, or who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. It is also indicated in combination with androgen deprivation therapy for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer.[2,6]

The most commonly reported adverse events (≥ 10%) among patients receiving olaparib monotherapy were: nausea, vomiting, diarrhoea, dyspepsia, upper abdominal pain, neutropenia, thrombocytopenia, leukopenia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.[1]

The most commonly reported adverse events (≥ 10%) among patients receiving abiraterone monotherapy were: urinary tract infection, hypokalaemia, hypertension, diarrhoea, alanine aminotransferase increased and/or aspartate aminotransferase increased and peripheral oedema. [2]

# PATIENT GROUP

## DISEASE BACKGROUND

Prostate cancer is the most common cancer in 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-specific membrane antigen (PSMA), a transmembrane protein, is expressed by virtually all prostate cancers, and its expression is further increased in poorly differentiated, metastatic, and hormone-refractory carcinomas.[12]

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).[7,13]

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.[14] 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.[15]

## 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).[16] 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 (advanced – including metastatic hormone sensitive, mCRPC pre-taxane treatment, and mCRPC post-taxane treatment).[17] 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).[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 2017, there were 10,755 deaths where malignant neoplasm of prostate (ICD-10 code 61) 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]

The company estimates that the eligible population will be between 25 and 50 per 100,000.[b]

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

The decision about the best approach to treat and care for cancer should be discussed among a multidisciplinary team and the choice of treatment depends on several factors such as where the cancer is, how far it has grown or spread (the stage), type of cancer, how abnormal the cells look under a microscope (the grade), and general health and level of fitness of the patient. The aim of treatment for advanced prostate cancer is to control it, relieve symptoms and maintain quality of life. The main treatments are chemotherapy, hormone therapy, radiotherapy, steroids and symptom control.[22]

## CURRENT TREATMENT OPTIONS

For men with mCRPC, before chemotherapy is indicated, NICE recommends: [23]

**Abiraterone**

Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

[b] Information provided by AstraZeneca on UK PharmaScan

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

**Enzalutamide**

Enzalutamide is recommended, within its marketing authorisation, 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
- when the company provides it with the discount agreed in the patient access scheme.

If the above treatments are not preferred:[24]

**Docetaxel**

Docetaxel is recommended, within its licensed indications, as a treatment option for people with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more.

It is recommended that treatment with docetaxel should be stopped:

- at the completion of planned treatment of up to 10 cycles **or**
- if severe adverse events occur **or**
- in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies.

Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.

## PLACE OF TECHNOLOGY

If licensed, olaparib in combination with abiraterone will provide a first line therapy for men with mCRPC.

# CLINICAL TRIAL INFORMATION

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| **Trial** | **PROpel;** NCT03732820; 2018-002011-10**;** A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer<br>**Phase III** - Active, not recruiting**Location(s):** US, Canada, EU (incl UK) and other countries<br>**Primary completion date:** April 2021 |
| **Trial design** | Randomised, parallel assignment, quadruple-blinded, placebo-controlled |
| **Population** | N=720 (planned); 18-99 years old; male; histologically or cytologically confirmed prostate adenocarcinoma; metastatic status defined as at least 1 documented metastatic lesion on either a bone scan or a computed tomography(CT)/ magnetic resonance imaging (MRI) scan; first-line mCRPC; ongoing androgen deprivation with gonadotropin-releasing hormone analogue or bilateral orchiectomy, with serum testosterone <50 nanograms per decilitre (ng/dL) (<2.0 nanomoles per litre (nmol/L)) within 28 days before randomisation. Patients receiving androgen deprivation therapy (ADT) at study entry should continue to do so throughout the study; candidate for |

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| | abiraterone therapy with documented evidence of progressive disease. |
| **Intervention(s)** | - Olaparib; orally; 300mg twice daily<br>- Abiraterone acetate; orally; 1000mg once daily, in combination with prednisone or prednisolone 5 milligrams (mg) administered orally twice daily. |
| **Comparator(s)** | Placebo plus abiraterone acetate; orally; 1000mg once daily, in combination with prednisone or prednisolone 5 milligrams (mg) administered orally twice daily. |
| **Outcome(s)** | Radiological progression free survival (rPFS) [Time frame: from date of randomisation to study completion (up to 4 years)]<br><br>See trial record for full list of other outcomes |
| **Results (efficacy)** | - |
| **Results (safety)** | - |

# ESTIMATED COST

Olaparib tablet:[25]

- 100mg - £2317.50
- 150mg - £2317.50

Abiraterone acetate:[26]

- 500mg - £2735.00

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal guidance. Radium–223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE Technology Appraisal guidance. Abiraterone for treating metastatic hormone relapsed prostate cancer before chemotherapy (TA387). April 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (NG131). May 2019.
- NICE quality standard. Prostate cancer (QS91). June 2015. (Last updated: May 2019).

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Prostate Cancer. 16031/P. July 2016.
- NHS England. Clinical Commissioning Policy: Proton Beam Therapy for Cancer of the Prostate. 16020/P. July 2016.

## OTHER GUIDANCE

- European Society for Medical Oncology. Cancer of the Prostate: ESMO Clinical Practice Guidelines. 2015. (Updates: 2016, 2017). [27]
- 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. 2017.[28]

# ADDITIONAL INFORMATION

# REFERENCES


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