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HEALTH TECHNOLOGY BRIEFING
APRIL 2019

Olaparib for BRCAm or ATM mutated metastatic castration-resistant prostate cancer

NIHRIO ID	10339	**NICE ID**	9660
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	645825

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Olaparib is in clinical development as a monotherapy for the treatment of metastatic castrate-resistant prostate cancer with breast cancer mutated (BRCAm) gene or ataxia telangiectasia mutated (ATM). 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 to the liver or lungs. It is not possible to cure metastatic prostate cancer but is possible to keep it under control. Over time, many prostate cancers continue to grow despite hormonal therapies (and are called "castration-resistant" prostate cancer).

Olaparib is taken orally and works by blocking a protein called poly [adenosine diphosphate-ribose] polymerase (PARP). PARP is an important protein which tries to fix damaged deoxyribonucleic acid (DNA). By blocking PARP from fixing damaged DNA, the tumour cells may die. If licensed, olaparib will offer an additional treatment option for men with metastatic castrate-resistant prostate cancer with BRCAm or ATM mutations who have progressed following a prior new hormonal agent.

PROPOSED INDICATION

Monotherapy for patients with metastatic BRCAm or ATM mutated, castration-resistant prostate cancer who have progressed following a prior new hormonal agent.[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.[1]

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.[1,2]

Olaparib is in clinical development for the treatment of patients with metastatic BRCAm or ATM mutated castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent.[a] In the phase III clinical trial (PROfound; NCT02987543), participants receive oral tablet of olaparib, 300 mg (2 x 150mg) twice daily, with 100 mg tablets used to manage dose reductions. Treatment duration was not reported on the trial registry.[3]

INNOVATION AND/OR ADVANTAGES

Given the lack of curative intent provided by existing treatment options, there is a significant push for development of novel therapeutic approaches for addressing metastatic castration-resistant disease particularly for those patients whose options may be limited due to rapid progression or predicted lack of hormonal responsiveness. One emerging strategy involves the use of PARP inhibitors in patients exhibiting alterations in the homologous recombination repair pathway, which are most commonly associated with BRCA1/BRCA2-deficient tumours.[4]

Olaparib is an innovative oral PARP inhibitor that exploits tumour DNA repair pathway deficiencies to preferentially kill cancer cells. This mode of action gives olaparib the potential for activity in a range of tumour types with DNA repair deficiencies.[5] Findings from a phase II trials demonstrated that treatment with olaparib in patients whose prostate cancers were no longer responding to standard treatments and who had defects in DNA-repair genes led to a high response rate.[6]

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

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Olaparib is licensed as monotherapy in the EU/UK for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.[2]

The most commonly reported adverse events (≥ 10%) among patients receiving olaparib monotherapy were: nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.[2]

Olaparib is currently in development for the treatment of various types of cancers including: recurrent platinum-sensitive ovarian cancer, breast cancer, renal cell cancer, and advanced solid tumours.[7]

Olaparib was granted a Breakthrough Therapy designation by the US FDA for treatment of BRCA1/2 or ATM gene mutated metastatic Castration Resistant Prostate Cancer in January 2016.[5]

PATIENT GROUP

DISEASE BACKGROUND

Usually, prostate cancer grows slowly so there may be no signs for many years.[8] Some prostate cancers grow faster and need to be treated to stop them spreading. Advanced cancer means the cancer cells have spread to other parts of the body (also called of metastatic prostate cancer). The most common place for prostate cancer to spread to is the bones. It may also spread to lymph nodes outside the pelvis or rarely to the liver or the lungs. It is not possible to cure metastatic prostate cancer. Metastatic prostate cancer may develop in men who have previously been treated for prostate cancer. In some men, prostate cancer is first diagnosed when cancer has already reached an advanced stage.[8,9]

Prostate cancer growth and proliferation are primarily dependent on androgens, and androgen deprivation therapy (ADT) is an effective means of controlling the disease. However, some men develop resistance to androgen deprivation, resulting in the development of castration-resistant prostate cancer (CRPC).[10]

Inherited mutations in several genes involved in DNA damage repair have been reported to predispose men to prostate cancer.[11-14] Normal cells are less subjected to DNA damage than tumour cells and, therefore, less influenced by inhibitors of DNA repair mechanisms. DNA damage can be acquired in cells over time through exposure to exogenous chemicals and physical agents or endogenous reactive metabolites including reactive oxygen and nitrogen species. The nuclear PARP enzymes are physiologically involved in multiple aspects of DNA repair and transcription regulation. Efficient and correct repair of DNA damage is critical for cellular survival.[15]

Although the cause of prostate cancer is unknown, a man's risk of developing prostate cancer depends on many factors such as age, ethnicity, being overweight or obese, genetics and family history, lifestyle factors, and other medical conditions.[9] Patients might have specific symptoms depending on where cancer has spread. Prostate cancer does not usually cause any symptoms until cancer has grown large enough to put pressure on the urethra. Symptoms of prostate cancer can include: needing to pee more frequently, often during the night, needing to rush to the toilet, difficulty in starting to pee, straining or taking a long time while peeing, weak flow, feeling that your bladder has not emptied fully, blood in urine or in semen, fatigue, feeling generally unwell, and have weight loss for no known reason.[16,17]

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.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Genetic sequencing studies have shown that deleterious germline mutations in damaged DNA repair genes are present in 8% to 12% of patients with metastatic prostate cancer.[19-21] In the UK, there are over 47,000 new cases of prostate cancer every year. Prostate cancer accounted for 26% of all new cancer cases among males in the UK. In England, around 4 in 10 patients with prostate cancer are diagnosed at a late stage (2014 data).[22] According to statistical analysis, the incidence rates for prostate cancer are projected to rise by 12% in the UK between 2014 and 2035, from 208 cases per 100,000 males in 2014 to 233 cases per 100,000 males by 2035.[23]

Prostate cancer is predominantly a disease of older men (aged 65 – 79 years) but around 25% of cases occur in men younger than 65.[24] In 2017-18 there were 71,071 admissions (of which 49,309 were day cases) for malignant neoplasm of the prostate (ICD-10 code C61) in England which resulted in 76,218 finished consultant episodes (FCE) and 90,683 FCE bed days.[25]

There are around 11,500 prostate cancer deaths every year, accounting for 13% of all cancer deaths in males in the UK.[22] Prostate cancer mortality rates are projected to fall by 16% in the UK between 2014 and 2035, from 57 cases per 100,000 males in 2014 to 48 deaths per 100,000 males in 2035.[26]

Men diagnosed with prostate cancer in England and Wales have shown high survival rates. More than 8 in 10 (84%) men diagnosed with prostate cancer survive their disease for ten years or more. Around 85% of men diagnosed with prostate cancer survive for five years or more and 94% of men survive their disease for one year or more (2010-2011 data). Prostate cancer survival in England is higher for men diagnosed aged 60-69 years old, probably because of prostate-specific antigen (PSA) testing detecting latent, earlier, slow-growing cancers (2009-2013 data).[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The decision about the best approach to treat and care for prostrate cancer patient should be discussed among a multidisciplinary team and the choice of treatment depends on several factors such as where the cancer is, how far 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 patient. In general, there might not be immediate treatment but close monitoring of the cancer depending on the situation. The main treatments are surgery, external radiotherapy, brachytherapy, hormone therapy (androgen deprivation or anti-androgens), chemotherapy, and symptom control treatment.[27]
Bilateral orchiectomy should be offered to all patients with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone (LHRH) agonist treatment.Spinal MRI is offered to men with hormone-relapsed prostate cancer with extensive metastases in the spine (for example, on a bone scan) if they develop any spinal-related symptoms.[28,29]

CURRENT TREATMENT OPTIONS

For men with metastatic castrate-resistant prostate cancer, NICE recommends:[28,29]

- Anti-androgen monotherapy with bicalutamide (to retain sexual function);
- Docetaxel for men with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more;
- A corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer;
- Bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed.

PLACE OF TECHNOLOGY

If licensed, olaparib will offer an additional treatment option as a monotherapy for patients with metastatic BRCAm or ATM mutated, castrate resistant prostate cancer who have progressed following a prior new hormonal agent.

CLINICAL TRIAL INFORMATION

Trial	PROfound; NCT02987543; olaparib vs enzalutamide or abiraterone acetate; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[3,30]
Location	9 EU (including the UK), USA, Canada and other countries
Design	Randomized, parallel assignment, open label
Participants	N=340 (estimated); males aged ≥18 years; progressed on prior new hormonal agent (e.g. abiraterone acetate and/or enzalutamide) for metastatic prostate cancer and/or CRPC, qualifying homologous recombination repair mutation in tumour tissue.
Schedule	Subjects will be randomised in ratio 2:1 (olaparib: investigator choice of enzalutamide or abiraterone acetate). Subjects will receive: • Olaparib 300 mg oral tablet twice daily. The planned dose of 300 mg bid will be made up of two x 150 mg tablets twice daily, with 100 mg tablets used to manage dose reductions, or • Enzalutamide oral capsules, 160mg once daily available 40 mg per capsule, or • Abiraterone acetate oral tablets at a dose of 1,000 mg once daily in combination with oral prednisone 5 mg twice daily.
Follow-up	Patients continued in the treatment until radiographic progression or lack of treatment tolerability.[30]
Primary Outcomes	Change in radiographic progression free survival (rPFS) [Time Frame: During study period (up to 3 years)]
Secondary Outcomes	• Confirmed Objective Response Rate (ORR) by blinded independent central reader [Time Frame: During study period (up to 3 years)] • Time to Pain progression [Time Frame: To be completed by subject daily for 7 consecutive days before each respective 4-week visit/assessment date with Day 1 as the baseline visit date (not required to be at site)]

	• Overall Survival (OS) [Time Frame: During study period (up to 4 years)] • rPFS [Time Frame: During study period (up to 3 years)] • Adverse events (AEs)/Serious adverse events (SAEs) and Collection of clinical chemistry/hematology parameters [Time Frame: From the time of signature of informed consent throughout the treatment period up to and including the 30-day follow-up period]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as March 2020.

ESTIMATED COST

Olaparib is already marketed in the UK for the treatment of ovarian, fallopian tube, and peritoneal cancers; a pack of 56 x 100 mg or 150 mg tablets costs £2317.50, and a pack of 448 x 50 mg capsules costs £3550.[31]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- 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. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE technology appraisal. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). July 2014.
- NICE technology appraisal. Abiraterone for treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy TA259. June 2012 (Last updated: July 2016).
- NICE Clinical Guideline in development. Prostate cancer: diagnosis and management (update) (GID-NG10057). Expected publication: April 2019.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (CG175). Published: January 2014.
- NICE quality standard. Prostate cancer (QS91). June 2015.
- NICE diagnostic guidance. Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index (DG17). June 2015

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).[32]
- 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.[33]

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