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Health Technology Briefing
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Niraparib with abiraterone acetate and prednisone for treating homologous recombination repair-mutated metastatic castration-sensitive prostate cancer

Company/Developer	Janssen-Cilag Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30385	NICE ID: Not available	UKPS ID: 665921

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Niraparib with abiraterone acetate and prednisone is in clinical development for patients with prostate cancer which is metastatic (has spread to other parts of the body) and hormone-sensitive, meaning the cancer is being controlled by keeping the testosterone level as low as would be expected if the testicles were removed. Prostate cancer is the most common type of cancer in men in the UK. Alterations to the homologous recombination repair (HRR) pathway (a mechanism by which DNA damage is repaired) may be associated with poorer outcomes. There is therefore a need to develop new treatment options for this population.

Niraparib is taken orally. It works by blocking the action of proteins called poly (adenosine diphosphate-ribose) polymerase (PARP)-1 and PARP-2, which help to repair damaged DNA when the cells divide to make new cells. This inhibition prevents cancer cells from repairing damaged DNA and as a result the cancer cells die. By combining drugs, multiple cancer-causing mechanisms are targeted. If licensed, niraparib with abiraterone acetate and prednisone will provide an additional treatment option for patients with HRR gene-mutated metastatic castration-sensitive prostate cancer.

Proposed Indication

Treatment of adults with homologous recombination repair (HRR) gene-mutated castration-sensitive prostate cancer (mCSPC).[1]

Technology

Description

Niraparib (Zejula, MK-4827) is an inhibitor of the poly(ADP-ribose) polymerase (PARP) enzymes PARP-1 and PARP-2.[2] PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, and cell death. The homologous recombination repair (HRR) pathway is a DNA damage repair mechanism and is the most frequently mutated pathway in advanced prostate cancer.[3-5] PARP inhibitors (PARPi) have shown antitumour activity with an improvement in overall survival in metastatic castration-resistant prostate cancer (mCRPC) carrying somatic and/or germline alterations of HHR.[4] PARPi exert cytotoxic effects on cancer cells by two mechanisms: inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, preventing DNA repair, replication, and transcription, thereby resulting in apoptosis and/or cell death.[6] *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis and cell death.[2]

Niraparib with abiraterone acetate and prednisone is in clinical development for the treatment of HRR-mutated mCSPC. In the phase III clinical trial (AMPLITUDE, NCT04497844), patients receive niraparib (200 mg), abiraterone acetate (1000 mg) and prednisone (5 mg) orally once daily for each 28-day treatment cycle.[1,7]

Key Innovation

Despite improvements in the treatment of advanced prostate cancer, metastatic prostate cancer remains incurable, and is also associated with therapy resistance.[8,9] Additional therapeutic options are needed for patients with HRR gene alterations, which are associated with worse outcomes in mCSPC.[3]

Abiraterone acetate selectively inhibits the enzyme CYP17 which is expressed in testicular, adrenal, and prostatic tumours and required for androgen biosynthesis.[10] This inhibition stops the body producing testosterone. Because the cancer needs a supply of testosterone to survive and grow, abiraterone acetate helps slow the growth of the prostate cancer.[11] By combining niraparib with abiraterone acetate, two oncogenic drivers may be targeted.[12] The fixed dose combination of niraparib (a PARP inhibitor) with abiraterone acetate (an androgen biosynthesis inhibitor) is known as AKEEGA and is given with prednisone as an authorised treatment for adult patients with mCRPC who have BRCA 1/2 genetic mutations and who cannot have chemotherapy.[11,13] If licensed, niraparib with abiraterone acetate and prednisone will offer an additional treatment option for patients with HRR gene mutated mCSPC.

Regulatory & Development Status

Niraparib with abiraterone acetate has Marketing Authorisation in the EU/UK in combination with prednisolone or prednisone, which is converted into prednisolone, for treating mCRPC in adults who have BRCA 1/2 genetic mutations and who cannot have chemotherapy, and when medical or surgical treatment to lower testosterone levels (castration) has not worked.[11]

Niraparib currently has Marketing Authorisation in the EU/UK as a monotherapy for:[2]

- The maintenance treatment of advanced epithelial (stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer in adults who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
- The maintenance treatment of platinum-sensitive relapsed high grade serious epithelial ovarian, fallopian tube or primary peritoneal cancer in adults who are in response (complete or partial) to platinum-based chemotherapy

Abiraterone acetate currently has Marketing Authorisation in the EU/UK as a monotherapy for:[10]

- The treatment of newly diagnosed high risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy
- The treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- The treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen

Prednisolone currently has Marketing Authorisation in the EU/UK as a monotherapy for:[14]

- Acute exacerbation of chronic obstructive pulmonary disease (if increased breathlessness interferes with daily activities)
- Severe croup (before transfer to hospital), mild croup that might cause complications (before transfer to hospital)
- Mild to moderate acute asthma, severe or life-threatening acute asthma
- Local treatment of inflammation (short-term), suppression of inflammatory and allergic disorders
- Idiopathic thrombocytopenic purpura
- Eczematous inflammation in otitis externa
- Ulcerative colitis, crohn's disease
- Neuritic pain or weakness heralding rapid onset of permanent nerve damage (during reversal reactions multibacillary leprosy)
- Generalised myasthenia gravis, ocular myasthenia
- Reduction in rate of joint destruction in moderate to severe acute rheumatoid arthritis
- Polymyalgia rheumatica
- Giant cell (temporal) arteritis
- Polyarteritis nodosa, polymyositis, systemic lupus erythematosus
- Symptom control of anorexia in palliative care
- Pneumocystis pneumonia in moderate to severe infections associated with HIV infection
- Short-term prophylaxis of episodic cluster headache as monotherapy or in combination with verapamil during verapamil titration
- Proctitis
- COVID-19 requiring supplemental oxygen (when dexamethasone cannot be used or is unavailable)

Patient Group

Disease Area and Clinical Need

Prostate cancer is cancer of the prostate gland, which is part of the male reproductive system. Prostate cancer is characterised by abnormal cells starting to divide and grow in an uncontrolled way.[15] Prostate cancer usually does not 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). Symptoms of prostate cancer can include a frequent need to urinate, straining while urinating, and blood in urine or in semen.[16] Although the exact cause of prostate cancer is unknown, it is more common in men over 50, obese men, and men with a family history of prostate cancer or breast cancer.[17] The growth of castration-sensitive prostate

cancer (CSPC), also known as hormone-sensitive prostate cancer (HSPC), depends on androgens (male hormones) and therefore inhibition of androgens stops growth.[18] In CSPC, the cancer is controlled by keeping the testosterone level as low as what would be expected if the testicles were removed by castration.[19] In mCSPC, the cancer has spread from the prostate to other parts of the body, such as distant lymph nodes, the bones, or other organs such as the lungs.[5,20]

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 (2016-18). The age-standardised incidence rate of prostate cancer in England is 186.4 per 100,000.[21] In England (2022-23), there were 86,381 finished consultant episodes (FCEs) and 81,717 admissions for malignant neoplasm of prostate (ICD-10 code C61), which resulted in 61,419 day cases and 78,764 FCE bed days.[22] In England (2020), there were 36,016 patients diagnosed with malignant neoplasm of the prostate and 10,268 deaths registered where malignant neoplasm of the prostate was the underlying cause.[23] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates were 96.6% and 86.6% respectively.[24] Prostate cancer has a 5 year survival rate of over 95% when diagnosed at stage 1 to 3. Although, for the 1 in 5 people diagnosed with stage 4 prostate cancer (metastatic), the 5 year survival rate drops to just 49%.[25] 9,972 men are diagnosed with stage 4 prostate cancer every year in the UK.[26]

Recommended Treatment Options

NICE guidelines recommend the following treatment options for metastatic hormone-sensitive prostate cancer in adults:[27-29]

- Enzalutamide plus androgen deprivation therapy
- Darolutamide plus androgen deprivation therapy with docetaxel
- Apalutamide plus androgen deprivation therapy, only if docetaxel is not suitable

Clinical Trial Information

Trial	**AMPLITUDE; NCT04497844; EudraCT 2020-002209-25;** A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC) **Phase III** – Active, not recruiting **Location(s):** Thirteen EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2024
Trial Design	Randomised, parallel assignment, triple blind
Population	N=696 (actual); aged 18 years and older; male; pathological diagnosis of prostate adenocarcinoma with HRR gene alteration; metastatic disease; androgen deprivation therapy started ≥14 days prior to randomisation
Intervention(s)	Niraparib 200mg + abiraterone acetate 1000mg + prednisone 5mg once daily in each 28-day treatment cycle
Comparator(s)	Abiraterone acetate 1000mg + prednisone 5mg + matching placebo once daily for 28-day treatment cycle

Outcome(s)	Primary outcome measure: radiographic progression-free survival [Time Frame: up to 47 months]. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative cost of niraparib is £4500.00 for 56 capsules (100 mg).[30] The NHS indicative cost of abiraterone acetate is £2735.00 for 120 tablets (250 mg).[31] The cost of prednisone is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab with enzalutamide and androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA11202). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Relugolix for treating hormone sensitive prostate cancer (TA11141). Expected date of issue to be confirmed.
- NICE technology appraisal. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (TA903). June 2023.
- NICE technology appraisal. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA741). October 2021.
- NICE technology appraisal. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (TA721). August 2021.
- NICE technology appraisal. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712). July 2021.
- NICE clinical guideline. Prostate cancer: diagnosis and management (NG131). December 2021.
- NICE quality standard. Prostate cancer (QS91). December 2021.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- European Association of Urology. Guidelines on Prostate Cancer. 2023.[32]
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Additional Information

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