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Health Technology Briefing
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Rucaparib for metastatic castration-resistant prostate cancer associated with homologous recombination deficiency

Company/Developer	Clovis Oncology UK Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 12429	NICE ID: 10764	UKPS ID: 664965

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Rucaparib is currently in clinical development for the treatment of metastatic prostate cancer (cancer that has spread beyond the prostate) that is resistant to hormone therapy and associated with a homologous recombination deficiency (HRD), which is when your body is unable to repair double strand breaks in DNA. Metastatic prostate cancer that is resistant to hormone therapy is known as metastatic castration-resistant prostate cancer (mCRPC). Patients can progress on initial treatment such as androgen receptor–directed therapy and taxane chemotherapy, and subsequent treatment options are limited, thus more effective treatments are needed.

Rucaparib is a PARP inhibitor; PARP enzymes play a role in DNA repair, thus inhibition of this has shown increased DNA damage and cell death. Rucaparib will be administered orally. In clinical trials, rucaparib has demonstrated meaningful antitumour activity and a manageable safety profile in patients with mCRPC, including in those that have an HRD. If approved, rucaparib will provide an additional treatment option for patients with mCRPC that have HRD.

Proposed Indication

Metastatic, castration-resistant prostate cancer (mCRPC).[1]

Technology

Description

Rucaparib (Rubraca, CO-338) is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. *In vitro* studies have shown that rucaparib-induced cytotoxicity involves inhibition of PARP enzymatic activity and the trapping of PARP-DNA complexes resulting in increased DNA damage, apoptosis, and cell death.[1,2]

Rucaparib is currently in clinical development for the treatment of patients with mCRPC with HRD. In the phase III trial (NCT02975934), 600mg oral rucaparib is administered twice a day.[1,3,4]

Key Innovation

Therapies such as androgen receptor (AR)–directed therapy and taxane chemotherapy have led to improved outcomes for men with mCRPC. However, patients will eventually progress, and subsequent treatment options are limited, highlighting the need for additional effective therapies. Men with a germline Breast Cancer gene (BRCA) alteration have an increased risk for prostate cancer and more commonly have nodal involvement and/or distant metastases. PARP inhibitors can induce cytotoxicity via synthetic lethality in tumour cells that are deficient in homologous recombination–directed DNA damage repair (DDR), including those carrying loss-of-function alterations in BRCA genes.[5]

In a phase II trial (NCT02952534), rucaparib demonstrated meaningful antitumour activity and a manageable safety profile in patients with mCRPC, as well as a deleterious germline or somatic BRCA alteration.[5]

Regulatory & Development Status

Rucaparib is currently licensed in the UK as monotherapy 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. It is also indicated as monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.[2]

Rucaparib is currently in phase II and III trials for the treatment of ovarian cancer, epithelial ovarian cancer, fallopian tube cancer, peritoneal cancer, solid tumours, leiomyosarcoma, endometrial cancer, uterine carcinoma, biliary tract cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, cervical cancer, breast cancer, urothelial carcinoma, stomach cancer, oesophageal cancers, gastric cancers, mesothelioma and clear cell carcinoma.[6]

Patient Group

Disease Area and Clinical Need

The prostate is a small gland in the pelvis and is part of the male reproductive system. The causes of prostate cancer are largely unknown, but certain things can increase the risk of developing it. The chances of developing prostate cancer increase with age - most cases develop in men aged 50 or older. For reasons not yet understood, prostate cancer is more common in black men and less common in Asian men. Men whose father or brother were affected by prostate cancer are at slightly increased risk themselves. Recent research also suggests that obesity increases the risk of prostate cancer. Symptoms of prostate cancer do not usually appear until the prostate is large enough to affect the tube that carries urine from the bladder out of the penis (urethra), which can result in feeling an increased need to pee, straining while peeing, and a feeling that the bladder has not fully emptied.[7] Other key symptoms include blood in urine and blood in semen.[8] mCRPC refers to a cancer that has spread (metastasised) beyond the prostate gland and for which hormone therapy is no longer effective in stopping or slowing the disease.[9]

In males in the UK, prostate cancer is the most common cancer, with around 52,300 new cases every year (2016-2018). Prostate cancer accounts for 27% of all new cancer cases in males in the UK (2016-2018).[10] The age-standardised incidence rate of prostate cancer in England is 186.4 per 100,000 amongst males.[11] In the 2020-21 Hospital Episode Statistics (HES) data, there were 55,799 admissions with a primary diagnosis of neoplasm of the prostate (ICD-10 code C61), resulting in 60,023 finished consultant episodes (FCE), 58,293 FCE bed days and 39,040 day cases.[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 (castration-resistant prostate cancer).[13] Applying these estimated to the Cancer Research UK (CRUK) statistic of 52,3000 new cases of prostate cancer annually, we can predict that of that, 28,765-33,995 cases result in metastatic cancer, with 25,888-30,595 developing mCRPC yearly. Approximately 12% of men with mCRPC harbour a deleterious BRCA alteration, equating to approximately 3,107-3671 men per year.[5]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following treatment option for mCRPC before chemotherapy is indicated:

- Corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy (ADT) and anti-androgen therapy to people with hormone-relapsed prostate cancer.[14]
- Abiraterone in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer: in people who have no or mild symptoms after ADT has failed, and before chemotherapy is indicated.[15]
- Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer, in people who have no or mild symptoms after ADT has failed, and before chemotherapy is indicated.[16]

Clinical Trial Information

Trial	**TRITON 3;** NCT02975934; 2016-003163-20; A Multicenter, Randomized, Open Label Phase 3 Study of Rucaparib Versus Physician's Choice of Therapy for Patients With Metastatic Castration Resistant Prostate Cancer Associated With Homologous Recombination Deficiency. **Phase III –** Active, not recruiting **Locations** – 7 countries in EU, US, Australia, Canada, Asia and the UK **Estimated primary completion date:** June 2022

Trial Design	Randomised, parallel assignment, open label
Population	N = 405 (estimated); have a histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate that is metastatic; 18 years and older, male
Intervention(s)	Rucaparib, oral
Comparator(s)	Abiraterone acetate (with prednisone) and enzalutamide orally daily, intravenous docetaxel (with prednisone or prednisolone) every three weeks.
Outcome(s)	Primary outcome measures: Radiographic Progression-free Survival (rPFS) [Time Frame: From enrollment to primary completion of study (up to approximately 5 years)] See trial registry for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost oral rucaparib tablets is not yet known.[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 publication date to be confirmed.
- NICE technology appraisal guidance. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). July 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- 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. 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

- European Association of Urology. Prostate Cancer. 2022.[18]
- Spanish Society for Medical Oncology. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). May 2021.[19]
- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2020.[20]

- American Urological Association (AUA). Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2018. December 2018.[21]

Additional Information

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