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HEALTH TECHNOLOGY BRIEFING MARCH 2019

Nivolumab in combination with rucaparib for chemotherapy naïve metastatic castration-resistant prostate cancer

NIHRIO ID	20603	**NICE ID**	10154
Developer/Company	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	650913

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Nivolumab in combination with rucaparib is in development for the treatment of chemotherapy naïve metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is a cancer of the prostate gland, a small organ in a man's pelvis. There are multiple stages: localised, locally-advanced and advanced (or metastatic) prostate cancer. The symptoms may vary depending on the stage of cancer but can include pain, tiredness, and problems empting the bladder and bowels. Prostate cancer growth and spread depends on the hormone, testosterone. Cancer that does not respond to hormonal treatments to reduce the level of testosterone is known as castration-resistant prostate cancer.

Nivolumab works by improving the activity of a type of white blood cells called T-cells thereby increasing the ability of the immune system to kill cancer cells. Rucaparib also has anti-tumour activity by blocking the effect of certain enzymes leading to the death of tumour cells. It is thought that when used in combination, both drugs may be more effective than each drug on its own. If licenced, nivolumab in combination with rucaparib may improve long-term outcomes in mCRPC patients who currently have limited treatment options.

PROPOSED INDICATION

Chemotherapy naïve metastatic castration-resistant prostate cancer (mCRPC)[a]

TECHNOLOGY

DESCRIPTION

Nivolumab (Opdivo; BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.[1]

Rucaparib (Rubraca) 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 may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cancer cell death. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes.[2]

Nivolumab in combination with rucaparib is in development for chemotherapy naïve mCRPC. In the phase II clinical trial (NCT03338790; CheckMate 9KD) subjects receive nivolumab at a concentration of 10 mg/mL solution for infusion and rucaparib 200, 250, or 300 mg film-coated tablets at a specified dose on specified days. Dosing specifics and duration of treatment were not reported on the trial registry.[3,4]

INNOVATION AND/OR ADVANTAGES

Despite the significant mortality associated with prostate cancer, there are a limited number of effective therapeutic options available after metastatic disease is no longer responsive to androgen deprivation therapy (ADT) via gonadotropin-releasing hormone (GnRH) agonism/antagonism.[5]

With advances in next-generation sequencing, the genomic landscape of prostate cancer is being defined more clearly. The burden of overall mutations and copy-number alterations appears higher in metastatic prostate cancer than in localized prostate cancer. Similarly, it has been shown that mutations leading to defective DNA repair appear to be enriched in later stages of the disease, perhaps speaking to an overall poorer prognosis for patients with these mutations.[6,7]

PARP inhibitors drive increased DNA damage, particularly in tumours with existing defects in DNA repair. This damage not only promotes immune priming through a range of molecular mechanisms, but also leads to adaptive upregulation of PD-L1 expression. In this context, PARP inhibition and programmed cell death PD-1/PD-L1–targeting antibodies represent a rationale combination and a novel mechanism of action for prostate cancer.[8]

[a] Information provided by Bristol-Myers Squibb on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Nivolumab in combination with rucaparib is currently in development for the treatment of various types of cancers including selected solid tumours, endometrial, biliary tract, and ovarian.[9]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is cancer that occurs in the prostate — a small walnut-shaped gland in men that produces the seminal fluid that nourishes and transports sperm.[10] The development of prostate cancer is often slow, with no signs in the early stages and symptoms only becoming apparent when the prostate is large enough to affect the urethra.[11] Although the cause of prostate cancer is not known, a number of risk factors have been identified including: increased age, ethnicity, family history, obesity, and diet.[12]

Advanced prostate cancer has been known under a number of names over the years, including androgen-insensitive prostate cancer (AIPC), and more recently, the terms castrate-resistant prostate cancer (CRPC) or castration recurrent prostate cancer.[13] In January 2013, the National Institute for Health and Clinical Excellence (NICE) agreed that the term 'castration resistant prostate cancer' should be replaced with 'hormone relapsed prostate cancer' (HRPC).[14] CRPC is defined by disease progression despite androgen depletion therapy (ADT) and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.[13]

A number system may be used to stage prostate cancer:[15]

- *Stage I*: Cancer in this early stage is usually slow growing.
- *Stage II:* The tumour is found only in the prostate.
- *Stage III:* Locally advanced cancer that is likely to grow and spread
- *Stage IV:* The cancer has spread (metastasized) beyond the prostate (may include regional or distant lymph nodes, other parts of the body, or to the bones)

Prostate cancer that is more advanced may cause signs and symptoms such as: trouble urinating, decreased force in the stream of urine, blood in semen, discomfort in the pelvic area, bone pain, and erectile dysfunction.[10] The most common place for prostate cancer to spread to is the bones. It can also spread to the lymph nodes, liver and lungs and other soft tissues of the body. [16]

Bone metastases will occur in 90% of men with CRPC and can produce significant morbidity, including pain, pathologic fractures, spinal cord compression and bone marrow failure.[13] The tumours of many patients with prostate cancer eventually become refractory to ADT with progression to metastatic castration-resistant disease.[17]

Paraneoplastic effects are also common, including anaemia, weight loss, fatigue, hypercoagulability and increased susceptibility to infection.[13] Prostate cancer impacts on the daily lives of men, particularly their physical and emotional health, relationships, and social life.[18]

CLINICAL NEED AND BURDEN OF DISEASE

Prostate cancer is the most common cancer among men in the UK.[19] There are over 40,000 new cases of prostate cancer diagnosed every year in the UK. [20] Prostate cancer is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65 years.[21]

In England in 2016 there were 40,489 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD-10 code C61). Of these, 8,153 cases (20%) were diagnosed at stage 4 (advanced).[22] Incidence rates are expected to increase from 208 per 100,000 in 2014 to 232.5 in 2035 (European age-standardised).[23]

According to Hospital Episode Statistics (HES) data, in 2017-18 there were 71,071 admissions with a primary diagnosis of neoplasm of the prostate (ICD-10 code C61), resulting in 90,683 finished consultant episodes (FCE) bed days. Of these admissions, 49,309 were day cases.[24]

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.[25] Latest published survival statistics (2016, patients diagnosed in 2011-2015) report a 1-year survival rate of 96.3% and a 5-year survival rate of 88.3% (age-standardised) for patients with prostate cancer.[26]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

When men with prostate cancer develop biochemical evidence of hormone-relapsed disease, NICE recommends their treatment options should be discussed by the urological cancer multidisciplinary team with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate. Additional treatment pathways for mCRPC may include: spinal MRI for men shown to have extensive metastases in the spine, bone-targeted therapies for pain relief, and management of obstructive uropathy. NICE recommends offering a corticosteroid such as dexamethasone (0.5 mg daily) as third-line hormonal therapy after ADT and anti-androgen therapy to men with hormone-relapsed prostate cancer.[27]

CURRENT TREATMENT OPTIONS

The following treatment options for hormone-relapsed metastatic prostate cancer before chemotherapy is indicated are recommended by NICE:[27]

- Abiraterone in combination with prednisone or prednisolone 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
    - only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England
- 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

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with rucaparib will offer an additional treatment option for chemotherapy naïve mCRPC patients who currently have few well-tolerated effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 9KD, NCT03338790, EudraCT 2017-001626-17; rucaparib vs docetaxel and prednisone vs enzalutamide, all in combination with nivolumab; phase II**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Abstract,[28] trial registry,[3,4] manufacturer
Location	EU (not UK), USA, Canada and other countries
Design	Non-randomised, parallel assignment, open label
Participants	n=330 (planned); males aged ≥18 years of age; histologic confirmation of adenocarcinoma of the prostate; evidence of stage 4 disease; ongoing ADT with a GnRH analogue or bilateral orchiectomy; mandatory plasma and fresh or archival tumour tissue must be submitted
Schedule	Patients are assigned to one of three experimental arms with a specified dose on specified days: **Arm A: Nivolumab + rucaparib** • Nivolumab at a concentration of 10 mg/mL solution for infusion and rucaparib 200, 250, or 300 mg film-coated tablets **Arm B: Nivolumab + docetaxel + prednisone** • Nivolumab at a concentration of 10 mg/mL solution for infusion and docetaxel at a concentration of 10mg/mL solution for infusion; prednisone specifics were not reported on the trial registry **Arm C: Nivolumab + enzalutamide** • Nivolumab at a concentration of 10 mg/mL solution for infusion and enzalutamide 40 mg capsule(s) Nivolumab, rucaparib and enzalutamide treatment will continue until disease progression/unacceptable toxicity (nivolumab treatment ≤2 years); docetaxel will be given for ≤10 cycles.
Follow-up	Throughout the study there will be tumour assessments, follow-up visits and survival follow up (survival analysis up to 5 years)
Primary Outcomes	• Objective Response Rate (ORR) [Time frame: Approximately 12 months] Assessed per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) • Prostate-specific antigen response rate (RR-PSA) [Time frame: Approximately 12 months] Assessed per the proportion of treated participants with a 50% or greater decrease in PSA from baseline to the lowest post-baseline PSA result
Secondary Outcomes	• Radiographic progression-free survival (rPFS) [Time frame: Approximately 12 months]

	Assessed per PCWG3 • Time to response (TTR) [Time frame: Approximately 12 months] Assessed per PCWG3 • Duration of response (DOR) [Time frame: Approximately 12 months] Assessed per PCWG3 • Time to prostate-specific antigen progression (TTP-PSA) [Time frame: Approximately 12 months] Assessed per PCWG3 • Overall Survival (OS) [Time frame: Up to 5 years] Time between treatment initiation and the date of death from any cause • Incidence of adverse events (AEs) [Time frame: Approximately 12 months] • Incidence of serious adverse events (SAEs) [Time frame: Approximately 12 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date February 2020. Estimate study completion date November 2020.

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg/10mL concentrate for solution for infusion vial costs £1,097, a 240mg/24mL concentrate for solution for infusion vial costs £2,633, and a 40mg/4ml concentrate for solution for infusion vial costs £439.[29]

The cost of rucaparib is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). April 2016. Last updated July 2016.
- NICE technology appraisal. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE clinical guideline. Prostate cancer: diagnosis and management (CG175). January 2014.
- NICE quality standard. Prostate cancer (QS91). June 2015.

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

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- Public Health England. Prostate Cancer Risk Management Programme. January 2015. Updated March 2016.[31]
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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.