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HEALTH TECHNOLOGY BRIEFING
FEBRUARY 2020

Pembrolizumab in addition to docetaxel for chemotherapy-naïve metastatic castration-resistant prostate cancer – second line

NIHRIO ID	27039	**NICE ID**	10259
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	653155

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

SUMMARY

Pembrolizumab in addition to docetaxel is in clinical development for patients with prostate cancer which has spread from its original site (i.e. is metastatic), is untreatable via testosterone suppression therapy (i.e. is castration resistant), and where the patient has not received chemotherapy (i.e. chemotherapy-naïve). Prostate cancer is a cancer of the prostate gland (a small organ in a man's pelvis) and is the most common cancer in men in the UK. There are three 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 emptying the bladder and the bowels.

Pembrolizumab is a drug that is already used for other types of cancer. It works by stimulating an immune response against cancer cells. Docetaxel adversely affects cancer cell function through disrupting cell division (mitosis), and inducing cancer cell death. Docetaxel is already licensed for treating men with hormone-resistant metastatic prostate cancer. If licensed, pembrolizumab in addition to docetaxel, both delivered via intra-venous infusion, will offer a novel treatment and an additional therapeutic option for men with metastatic castration-resistant prostate cancer.

PROPOSED INDICATION

Chemotherapy-naïve, metastatic, castration-resistant prostate cancer patients – second line.[a]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody (mAb) which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to 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.[1]

Pembrolizumab in addition to docetaxel is in clinical development for the treatment of metastatic castration-resistant prostate cancer in chemotherapy-naïve patients. In the phase III trial (NCT03834506; MK-3475-921/keynote-921), patients will receive pembrolizumab 200 mg by intravenous (IV) infusion on day 1 of each 21-day cycle for up to a maximum of 35 cycles (approximately 2 years). Patients also will receive docetaxel 75 mg/m^2 by IV infusion for up to a maximum of 10 cycles (approximately 7 months). Details of the dosing regimen and administration schedule assessed are detailed in the clinical trial table section of this briefing document.[2]

INNOVATION AND/OR ADVANTAGES

There is a need for the development of novel therapeutic approaches for addressing metastatic castration-resistant prostate cancer (mCRPC), particularly for those patients whose options may be limited due to rapid progression or predicted lack of hormonal responsiveness. The combination of pembrolizumab in addition to docetaxel is a novel approach to treatment and an additional therapeutic option for men with mCRPC.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab in addition to docetaxel does not currently have Marketing Authorisation in the EU/ UK for any indication.

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:[4]

- Advanced (unresectable or metastatic) melanoma in adults.
- Adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
- First-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- Locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

[a] Information provided by Merck Sharp & Dohme Ltd on UK PharmaScan

- Adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.
- Locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- Locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10.
- As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.
- Recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

Pembrolizumab is also licensed in the UK in combination with:[4]

- Pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- Carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- Axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

The most common adverse events of pembrolizumab as monotherapy and in combination with chemotherapy (affecting more than one in ten people) include anaemia, neutropenia, thrombocytopenia, hypothyroidism, hyperthyroidism, decreased appetite, hypokalaemia, headache, dizziness, peripheral neuropathy, dysgeusia, hypertension, dyspnoea, cough, dysphonia, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, alopecia, palmar-plantar erythrodysaesthesia syndrome, musculoskeletal pain, arthralgia, pain in extremity, fatigue, asthenia, oedema, pyrexia, blood creatinine increased, alanine aminotransferase increased, and aspartate aminotransferase increased.[1]

Pembrolizumab in addition to docetaxel is currently in phase II clinical trials for thyroid and salivary gland cancer and head and neck carcinoma.[5]

Pembrolizumab in addition to docetaxel is currently in phase III clinical trials for prostatic neoplasms.[5]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is the most common cancer in men in the UK.[6] It affects the prostate, a small gland in the pelvis found only in men. It 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.[7] 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.[8] Prostate cancer cells usually need testosterone to grow.[9] 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.[10]

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 and over.[6] 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).[6,11]

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.[12]

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.[13]

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 in this population (2016 data).[14] 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).[15] Incidence rates are expected to increase from 208 per 100,000 in 2014 to 232.5 in 2035 (European age-standardised).[16]

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.[17]

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.[18]

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.[19]

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.[20]

CURRENT TREATMENT OPTIONS

Treatment options before chemotherapy include the following: [20]

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.

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

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in addition to docetaxel will offer an additional second-line therapeutic option for chemotherapy-naïve men with mCRPC.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**NCT03834506, 3475-921, Eudra CT 2018-004116-22;** A phase 3, randomized, double-blind study of pembrolizumab (mk-3475) plus docetaxel plus prednisone versus placebo plus docetaxel plus prednisone in participants with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) who have progressed on a next generation hormonal agent (NHA) (KEYNOTE-921) **Phase III** **Location(s):** EU (including the UK), Canada, United States and other countries
Trial design	Randomised, placebo-controlled, triple-blind
Population	N=1,000; men with metastatic mCRPC who have not received chemotherapy for mCRPC but have progressed on or are intolerant to next generation hormonal agent; aged 18 years and older.
Intervention(s)	Pembrolizumab and docetaxel IV infusion and dexamethasone and prednisone oral tablets.
Comparator(s)	Placebo and docetaxel IV infusion and dexamethasone and prednisone oral tablets.
Outcome(s)	Primary outcomes: • Overall Survival (OS): time from randomisation to death due to any cause [time frame: up to approximately 28 months] • Radiographic Progression-free Survival (rPFS) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by blinded independent central review [time frame: up to approximately 28 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price for a vial of pembrolizumab (50 mg) is £1315.00 (hospital only).[21]
For docetaxel, the NHS indicative price varies between suppliers and according to the concentration. For example, the cost of docetaxel 20mg/2ml (10 mg per 1 ml) vial supplied by Pfizer Ltd is £162.75 (hospital only).[22]

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 clinical guideline. Prostate cancer: diagnosis and management (NG131). May 2019.

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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- European Association of Urology. Prostate Cancer Guidelines. 2015.[27]

ADDITIONAL INFORMATION

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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.