Health Technology Briefing
February 2022

Pembrolizumab with enzalutamide for treating metastatic castration-resistant prostate cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27041	NICE ID:10326	UKPS ID: 653156

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab in addition to enzalutamide is in clinical development for patients with prostate cancer which has spread from its original site (metastatic), is untreatable via testosterone suppression therapy (castration resistant), and who are either abiraterone acetate naïve or have progressed on abiraterone acetate. 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. The symptoms may vary depending on the stage of cancer but can include pain, tiredness, and problems emptying the bladder and the bowels. The castration-resistant form of metastatic prostate cancer is particularly dangerous and leads to a very poor prognosis hence additional treatment options are needed.

Pembrolizumab is an immunotherapy drug administered by intravenous infusion. It works by improving the activity of white blood cells (T-cells) by blocking a protein, PD-L1, thereby increasing the ability of the immune system to kill cancer cells. Enzalutamide is an oral drug that works by blocking the action of testosterone and other androgens. Because prostate cancer needs testosterone to survive and grow, enzalutamide slows down the growth of the prostate cancer. If licenced, pembrolizumab in addition to enzalutamide could provide an additional treatment option for patients with metastatic castration-resistant prostate cancer who have not previously received chemotherapy.

Proposed Indication

Treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy for mCRPC, are abiraterone-naïve, or are intolerant to or progressed on abiraterone acetate.[1]

Technology

Description

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands programmed cell death ligand 1 and 2 (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.[2]

In the phase III clinical trial (NCT03834493) participants will receive 200 mg pembrolizumab by intravenous (IV) infusion administered on day 1 of each 21-day cycle for up to 35 cycles (approximately 2 years) and enzalutamide 160 mg administered orally once a day continuously until disease progression.[1]

Key Innovation

Treatment options for patients with mCRPC are noncurative, and life expectancy is only about 3 years.[3] Enzalutamide is licensed as monotherapy for the treatment of mCRPC, however the mechanism of action of pembrolizumab and enzalutamide might be synergistic, leading to increased antitumor activity, compared with either agent alone.[4]

Enzalutamide plus pembrolizumab has shown activity in abiraterone-pretreated patients with mCRPC in the phase 1b/2 KEYNOTE-365 (NCT02861573) study. In another study (NCT02312557) some patients had a profound anticancer response to pembrolizumab plus enzalutamide that lasted years.[3]

If licensed, pembrolizumab in addition to enzalutamide will offer an additional treatment option for mCRPC who currently have few effective therapies available.

Regulatory & Development Status

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

Enzalutamide is currently licenced as a monotherapy in the UK for the treatment of adult men with:[5]

- high-risk non-metastatic CRPC, mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- mCRPC whose disease has progressed on or after docetaxel therapy
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC)

Pembrolizumab is licensed in the UK as a combination therapy with:[2]

- Pemetrexed and platinum chemotherapy, 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, for the first-line treatment of metastatic squamous NSCLC in adults.
- Axitinib, for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.
- Platinum and 5-fluorouracil (5-FU) chemotherapy, for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Patient Group

Disease Area and Clinical Need

Prostate cancer is the most common cancer in older men in the UK.[6] It affects the prostate, a small gland in the pelvis found only in men which 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] In advanced prostate cancer, the cancer has spread from the prostate to other parts of the body (metastatic). It most commonly spreads to lymph nodes in other parts of the body or to the bones.[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 androgen deprivation 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.[6] Prostate cancer does not usually 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).[7] 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.[11]

Prostate cancer accounts for 27% of all new cancer cases in males in the UK (2017 data).[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.[13] 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 (metastatic).[14] According to Hospital Episode Statistics (HES) data, in 2020-21 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 bed days and 39,040 day cases.[15] In England and Wales in 2020, there were 10,971 deaths where malignant neoplasm of prostate (ICD-10 code C61) was recorded as the underlying cause.[16] 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.[17]

Recommended Treatment Options

As an option for treating metastatic hormone-relapsed prostate cancer after androgen deprivation therapy has failed, and before chemotherapy is indicated, NICE recommends:[18]

- Abiraterone in combination with prednisone or prednisolone
- Enzalutamide

Clinical Trial Information

Trial	**KEYNOTE-641, NCT03834493, 2018-004117-40;** A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus

	Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641) **Phase III** - Recruiting **Location(s):** 11 EU countries, United Kingdom, Canada, United States and other countries **Primary completion date:** November 2023
Trial design	Randomised, parallel assignment, triple masked
Population	N=1200 (planned), males aged 18 years and older, confirmed adenocarcinoma of the prostate without small cell histology, metastatic disease that has progressed on androgen deprivation therapy.
Intervention(s)	Participants receive 200 mg pembrolizumab by IV infusion administered and enzalutamide 160 mg administered orally.
Comparator(s)	Participants receive placebo by IV infusion and enzalutamide
Outcome(s)	Primary outcome(s); • Overall Survival (OS) [Time Frame: Up to approximately 52 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 52 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 (25 mg per 1 ml) is £2,630.00 (hospital only).[19]

The NHS indicative price for 112 tablets of enzalutamide (40 mg) is £2,734.67 (hospital only).[20]

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 in development. Pembrolizumab with docetaxel for treating hormone-relapsed metastatic prostate cancer untreated with chemotherapy (GID-TA10668). Expected publication date to be confirmed.
- NICE technology appraisal guidance. Radium−223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- 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.
- NICE quality standard. Prostate cancer (QS91). June 2015. Last updated: December 2021.

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

- Cassinello J, Arranz JÁ, Piulats JM, Sánchez A, Pérez-Valderrama B, Mellado B, et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer. 2017.[21]
- 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.[22]
- Public Health England. Prostate Cancer Risk Management Programme. January 2015. Updated March 2016.[23]
- ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[24]

Additional Information

References

1 Clinicaltrials.gov. Study of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-resistant Prostate Cancer (mCRPC) (MK-3475-641/KEYNOTE-641). *ID: NCT03834493*. 2019;Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03834493.

2 Electronic Medicines Compendium (eMC). *KEYTRUDA 25mg/ml concentrate for solution for infusion.* 2019. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 5 January 2022].

3 J.N. Graff JB, L.W. Liang, A. Stenzl,. 2241 - KEYNOTE-641: Phase 3 Study of Pembrolizumab (pembro) Plus Enzalutamide for Metastatic Castration-Resistant Prostate Cancer (mCRPC). *Annals of Oncology,*. 2019;20(v325-v355.). Available from: https://doi.org/10.1093/annonc/mdz248.049.

4 Urology Today. *ASCO 2019: Pembrolizumab plus Enzalutamide in Abiraterone-Pretreated Patients with Metastatic Castrate-Resistant Prostate Cancer: Cohort C of the Phase 1b/2 KEYNOTE-365 Study.* 2019. Available from: https://www.urotoday.com/conference-highlights/asco-2019-annual-meeting/asco-2019-prostate-cancer/112947-asco-2019-pembrolizumab-plus-enzalutamide-in-abiraterone-pretreated-patients-with-mcrpc-cohort-c-of-the-phase-1b-2-keynote-365-study.html [Accessed 5 January 2022].

5 electronic Medicines Compendium. *Xtandi Film-coated Tablets.* 2019. Available from: https://www.medicines.org.uk/emc/product/10318/smpc [Accessed 5 January 2022].

6 Cancer Research UK. *About prostate cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 5 January 2022].
7 NHS. *Prostate Cancer.* 2018. Available from: https://www.nhs.uk/conditions/prostate-cancer/ [Accessed 5 January 2022].
8 Cancer Research UK. *What is advanced prostate cancer? .* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/about-advanced-cancer [Accessed 5 January 2022].
9 Prostate Cancer UK. *Hormone therapy.* 2019. Available from: https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy [Accessed 5 January 2022].
10 Verywellhealth. *What Is Metastatic Castration-Resistant Prostate Cancer (mCRPC)?* 2020. Available from: https://www.verywellhealth.com/metastatic-castration-resistant-prostate-cancer-5073083 [Accessed 5 January 2022].
11 Appleton L, Wyatt D, Perkins E, Parker C, Crane J, Jones A, et al. The impact of prostate cancer on men's everyday life. *European journal of cancer care*. 2015;24(1):71-84. Available from: https://doi.org/10.1111/ecc.12233.
12 Cancer Research UK. *Prostate cancer statistics, .* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero [Accessed 5 January 2022].
13 National Insititute for Health and Care Excellence (NICE). *Draft scope for the proposed appraisal of cabazitaxel for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen (review of TA255)* 2015. Available from: https://www.nice.org.uk/guidance/ta391/documents/draft-scope-post-referral [Accessed 5 January 2022].
14 National Cancer Registration and Analysis Service (NCRAS). *Survival by stage. Cancer breakdown by stage: 'stage breakdown by CCG 2017'.* 2019. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 5 January 2022].
15 NHS Digital. *Hospital Admitted Patient Care Activity, 2020-21: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Downloaded 7 January 2022].
16 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 7 January 2022].
17 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 7 January 2022].
18 National Insititute for Health and Care Excellence (NICE). *Treating hormone-relapsed metastatic prostate cancer.* 2021. Available from: https://pathways.nice.org.uk/pathways/prostate-cancer/treating-hormone-relapsed-metastatic-prostate-cancer#content=view-node:nodes-treatment-options-before-chemotherapy-is-indicated [Accessed 5 January 2022].
19 National Insitute for Health and Care Excellence. *PEMBROLIZUMAB.* 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 5 January 2022].
20 British National Formulary. *ENZALUTAMIDE.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/enzalutamide.html [Accessed 5 January 2022].
21 Cassinello J, Arranz JÁ, Piulats JM, Sánchez A, Pérez-Valderrama B, Mellado B, et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017). *Clinical &*

translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2018;20(1):57-68. Available from: https://doi.org/10.1007/s12094-014-1225-3.

22 European Association of Urology. EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. 2017. Available from: https://uroweb.org/wp-content/uploads/09-Prostate-Cancer_2017_web.pdf.

23 Public Health England (PHE). *Prostate Cancer Risk Management Programme.* Available from: https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview [Accessed 5 January 2022].

24 Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2015;26(suppl_5):v69-v77. Available from: https://dx.doi.org/10.1093/annonc/mdv222.

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.