

Health Technology Briefing October 2022

Pembrolizumab with Enzalutamide and androgen deprivation therapy for the treatment of metastatic hormone sensitive prostate cancer

Company/Developer

Merck Sharp & Dohme Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 29598

NICE TSID: 11810

UKPS ID: 665569

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Pembrolizumab in addition to enzalutamide and androgen deprivation therapy (ADT) is in clinical development for patients with prostate cancer which has spread from its original site (metastatic), and who are hormone sensitive (mHSPC). 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 metastatic form of prostate cancer is particularly dangerous and leads to a very poor prognosis hence additional treatment options are needed. The combination of pembrolizumab and enzalutamide with ADT could lead to increased anti-tumour activity, compared to either substance alone.

Pembrolizumab is an immunotherapy drug administered via 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 combination with enzalutamide and ADT could provide an additional treatment option for patients with mHSPC.

Proposed Indication

For the treatment of patients with metastatic hormone sensitive prostate cancer (mHSPC).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 (NCT04191096, MK-3475-991/KEYNOTE-991) starting on day 1 of each 21-day cycle, participants will receive 200 mg pembrolizumab by intravenous (IV) infusion administered every 3 weeks (Q3W) for up to 35 cycles plus 160 mg enzalutamide taken orally once daily, while maintaining continuous androgen deprivation therapy (ADT) with a luteinizing-hormone releasing hormone (LHRH) agonist or antagonist during study treatment. Participants will continue to receive enzalutamide and ADT until criteria for discontinuation are met.¹

Key Innovation

Enzalutamide is licensed as a combination therapy with ADT for the treatment of mHSPC, however the mechanism of action of pembrolizumab and enzalutamide with ADT might be synergistic, leading to increased anti-tumour activity, compared with either agent alone.³ If licensed, pembrolizumab in addition to enzalutamide and ADT will offer an additional treatment option for patients with mHSPC who currently have few effective therapies available.

Regulatory & Development Status

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

Pembrolizumab currently has Market Authorisation in the EU/UK as a combination therapy with:²

- Pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung cancer (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 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 PDL1 with a CPS ≥ 1

Pembrolizumab is currently in phase in phase II and III clinical development for several indications, some of which include:⁵

- Adenocarcinoma of esophagogastric junction
- Unresectable hepatocellular carcinoma
- Urinary bladder cancer
- NSCLC

- Head and neck squamous cell carcinoma

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 When the metastatic prostate cancer can be treated using hormone therapy, this is termed mHSPC.⁹ Prostate cancer cells usually need testosterone to grow.¹⁰ In mHSPC androgens such as testosterone can be blocked or stopped to slow the cancer growth.⁹ 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. In England, in 2017 there were 41,201 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD10 code C61). Of these, 8,490 cases were diagnosed at stage 4 (metastatic).¹³ 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.¹⁴ 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.¹⁵ 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.¹⁶

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends active surveillance, radical prostatectomy or radical radiotherapy for the treatment of localised prostate cancer.¹⁷

NICE recommend the following treatment for adults with metastatic prostate cancer:¹⁷

- Docetaxel chemotherapy
- Bilateral orchidectomy

Clinical Trial Information

Trial

KEYNOTE-991; [NCT04191096](#); [EudraCT 2019-003633-41](#); A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)
Phase – Active, not recruiting
Location(s): 10 EU Countries, UK, USA, Canada and other countries
Primary completion date: July 2026

Trial Design	Randomised, double blind, parallel assignment
Population	N= 1232 (estimated); male patients aged 18 and older with histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology
Intervention(s)	Starting on day 1 of each 21-day cycle, participants receive oral 200 mg pembrolizumab Q3W for up to 35 cycles, plus 160 mg enzalutamide taken orally once daily, while maintaining continuous ADT with a luteinizing-hormone releasing hormone (LHRH) agonist or antagonist during study treatment.
Comparator(s)	Matched placebo
Outcome(s)	<ul style="list-style-type: none"> - 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 77 months] - Overall survival (OS) [Time frame: up to approximately 77 months] <p>See trial record for full list of other outcomes</p>
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).¹⁸ The NHS indicative price for 112 tablets of enzalutamide (40 mg) is £2,734.67 (hospital only).¹⁹

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 date of issue 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 date of issue 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). 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. 2017.²⁰
- Public Health England. Prostate Cancer Risk Management Programme. March 2016.²¹
- ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.²²

Additional Information

References

- 1 ClinicalTrials.gov. *Efficacy and Safety of Pembrolizumab (MK-3475) Plus Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (MK-3475-991/KEYNOTE-991)*. Trial ID: NCT04191096. 2019. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT04191096> [Accessed 6 September 2022].
- 2 Electronic Medicines Compendium (eMC). *Keytruda 25 mg/mL concentrate for solution for infusion*. Available from: <https://www.medicines.org.uk/emc/product/2498/smpc>.
- 3 Gratzke C, Niu C, Poehlein CH, Burgents JE. Pembrolizumab (pembro) plus enzalutamide (enza) and androgen deprivation therapy (ADT) for patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC): The phase III KEYNOTE-991 study. American Society of Clinical Oncology 2021.
- 4 Electronic Medicines Compendium (eMC). *Xtandi 40 mg film coated tablets (Great Britain)*. Available from: <https://www.medicines.org.uk/emc/product/10318/smpc>.
- 5 ClinicalTrials.gov. *Pembrolizumab*. Available from: https://www.clinicaltrials.gov/ct2/results?cond=pembrolizumab&age_v=&gndr=&type=&rslt=&Search=Apply.
- 6 Cancer Research UK. *What is prostate cancer?*. Available from: <https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about>.
- 7 National Health Services (NHS). *Prostate Cancer*. Available from: <https://www.nhs.uk/conditions/prostate-cancer/>.
- 8 Cancer Research UK. *What is advanced prostate cancer?* Available from: <https://www.cancerresearchuk.org/about-cancer/prostate-cancer/metastatic-cancer/what-is-metastatic-prostate-cancer>.

- 9 Urology Care Foundation. Metastatic hormone-sensitive prostate cancer (mHSPC): What you should know. 2020.
- 10 Prostate Cancer UK. *Hormone Therapy*. Available from:
<https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy>.
- 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.
<https://doi.org/10.1111/ecc.12233>.
- 12 Cancer Research UK. *Prostate cancer incidence*. 2017. Available from:
<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero>.
- 13 National Cancer Registration and Analysis Service (NCRAS). *Survival by Stage*. Available from:
http://www.ncin.org.uk/publications/survival_by_stage.
- 14 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from:
<https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21>.
- 15 Office for National Statistics (ONS). *Deaths registered in England and Wales – 21st century mortality*. 2022. Available from:
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset>.
- 16 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed*. 2019. Available from:
<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed>.
- 17 National Institute for Health and Care Excellence (NICE). *Prostate cancer: diagnosis and management*. 2019. Available from:
<https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133>.
- 18 British National Formulary (BNF). *Pembrolizumab - Medicinal forms*. Available from:
<https://bnf.nice.org.uk/drugs/pembrolizumab/medicinal-forms/>.
- 19 British National Formulary (BNF). *Enzalutamide - Medicinal forms*. Available from:
<https://bnf.nice.org.uk/drugs/enzalutamide/medicinal-forms/>.
- 20 Cassinello J, Arranz J, Piulats J, Sánchez A, Pérez-Valderrama B, Mellado B, et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017). *Clinical and Translational Oncology*. 2018;20(1):57-68. Available from:
<https://doi.org/https://doi.org/10.1007/s12094-017-1783-2>.
- 21 GOV.UK. *Prostate cancer risk management programme: overview*. 2015. Available from:
<https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview>.
- 22 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:v69-v77. <https://doi.org/10.1093/annonc/mdv222>.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.