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Pembrolizumab (Keytruda) for metastatic castration-resistant prostate cancer – second or third line following treatment with docetaxel and at least one second-generation anti-androgen therapy

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LAY SUMMARY

Prostate cancer is cancer of the prostate gland (a small organ in a man's pelvis) and is the second most common cancer in the UK. There are three stages: localised, locally-advanced and advanced prostate cancer. About half of men diagnosed with locally-advanced prostate cancer will see their cancer spread to other body organs (i.e. becoming metastatic). The symptoms may vary but can include pain, tiredness, problems emptying the bladder and the bowels. These organs normally are lymph nodes in other parts of the body or the bones. When the cancer has become metastatic and has spread to the bones there is no cure and treatments aim to alleviate symptoms, pain and increase quality of life.

Pembrolizumab is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein allows the T-cells to find and kill the cancer cells. It is administered as a drip into a vein every three weeks for up to 35 cycles. If approved, pembrolizumab will offer an alternative treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC) in those that have received prior treatment with docetaxel and at least one second-generation anti-androgen therapy.

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TARGET GROUP

Metastatic castration-resistant prostate cancer (mCRPC) – second or third line following treatment with docetaxel and at least one second-generation anti-androgen therapy.

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda®; MK-3475; SCH-900475) is a humanized monoclonal immunoglobulin (Ig) G4 antibody directed against human cell surface receptor PD-1 (programmed death-1 or programmed cell death-1) with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, pembrolizumab binds to PD-1, an inhibitory signalling receptor expressed on the surface of activated T-cells, and blocks the binding to and activation of PD-1 by its ligands, which results in the activation of T-cell-mediated immune responses against tumour cells. The ligands for PD-1 include programmed cell death ligand 1 (PD-L1), overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen-presenting cells. Activated PD-1 negatively regulates T-cell activation and plays a key role in tumour evasion from host immunity.[1]

In the ongoing phase II trial (NCT02787005), five cohorts of participants with mCRPC will be allocated to different treatment regimens. Subjects previously treated with docetaxel-based chemotherapy in Cohorts 1 to 3 will receive monotherapy with pembrolizumab (by intravenous injection); chemotherapy-naïve subjects with mCRPC either having failed or showing signs of failure with enzalutamide in Cohorts 4 and 5 will receive pembrolizumab monotherapy in addition to their current regimen of enzalutamide.

Pembrolizumab is currently licensed in the EU under its commercial name Keytruda for the following indications[2]:

- Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Keytruda as monotherapy is indicated for the 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.
- Keytruda as monotherapy is indicated for the treatment of 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 Keytruda.
- Keytruda as monotherapy is indicated for the treatment of 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.
- Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

The most common side effects with Keytruda (which may affect more than 1 in 10 people) are diarrhoea, nausea (feeling sick), itching, rash, joint pain and tiredness, most of which are mild to moderate in severity. Other common side effects of Keytruda related to the activity of the immune

system causing inflammation of body organs. Most will resolve following appropriate treatment or on stopping Keytruda.[3]

Additional Phase III clinical trials of pembrolizumab are registered for the following indications:

- Head/Neck 1L: NCT02358031
- Head/Neck 2L: NCT02252042
- 2L Gastric/Gastroesophageal NCT02370498
- Colorectal 1L: NCT02563002
- Oesophageal/Oesophagogastric 2L: NCT02564263
- Bladder/Renal 1L: NCT02853305
- Bladder/Renal 2L: NCT02256436
- Mesothelioma 2L: NCT02991482
- Small Cell Lung Cancer 1L: NCT03066778
- Non-Small Cell Lung Cancer: NCT02220894

INNOVATION and/or ADVANTAGES

If licensed for this indication, Keytruda will offer an additional treatment option for men with mCRPC that have been previously treated with docetaxel and anti-androgen therapy for which there are limited treatment options available.

DEVELOPER

Merck Sharp & Dohme Ltd

AVAILABILITY, LAUNCH or MARKETING

Pembrolizumab was designated as a breakthrough therapy and given priority review designation for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumours express PD-L1 by FDA in 2016.[4]

No estimated license are available.

PATIENT GROUP

BACKGROUND

Prostate cancer is the most common male cancer in the UK. It affects the prostate gland which produces some of the fluid in the semen and plays a role in urine control in men. The cancer starts in the glandular cells in the prostate and are known as acinar adenocarcinomas. It is more common in black Caribbean and black African men than in white men, and very rare in Asian men. More than half of those diagnosed are aged 70 years and over.[5] There are three stages of prostate cancer; non-metastatic or localised (confined to the prostate gland), locally-advanced (spread outside the capsule of the gland) and advanced (spread to other body organs).[6] At an advanced stage the cancer most commonly spreads to lymph nodes in other parts of the body or to the bones. It can also spread to other organs.[7] About 50% of men diagnosed with localised prostate cancer will get metastatic cancer during their lifetime. Finding cancer early and treating it can lower that risk.[8]

Because the cancer develops slowly, people often have no signs in the early stages and symptoms only become apparent when the prostate is large enough to affect the urethra. General symptoms of prostate cancer include: urinary tract infection, urinary frequency, sensation of incomplete emptying, haematuria (presence of blood in urine), dysuria (painful urination), haematospermia (blood in sperm), symptoms of acute kidney injury or chronic kidney disease and impotence.[8] Various risk factors for prostate cancer have been identified, including ageing, black ethnic origin and a family history.[9] Other factors include diet, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure. [8]

CLINICAL NEED and BURDEN OF DISEASE

The number of men diagnosed with prostate cancer has been increasing over the last 10 years. This might be because more men are having the Prostate-specific Antigen (PSA) tests and the population is getting older. In adults, prostate cancer is the second most common cancer in the UK. In men, it is the most common cancer in the UK. In 2014, around 46,700 men were diagnosed with prostate cancer.[10] More than 11,000 deaths from prostate cancer were recorded that same year. Almost nine in 10 (85%) men diagnosed with prostate cancer in England and Wales survived their disease for five years or more (2010-11).[11]

The Hospital Episodes Statistics for 2015/2016 recorded 68,578 finished consultant episodes (FCE), 63,964 admissions and 102,107 FCE bed days for malignant neoplasm of the prostate (ICD-10 code C61). 41,665 of these admissions were day cases.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Radium–223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE technology appraisal guidance. Cabazitaxel for the second-line treatment of hormone refractory, metastatic prostate cancer treated with docetaxel (TA391). August 2016.
- NICE technology appraisal guidance. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA259). July 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE technology appraisal guidance. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). July 2014.
- NICE clinical guideline in development. Prostate cancer: diagnosis and management (update) (GID-NG10057). Expected January 2019.
- NICE clinical guideline. Prostate cancer: diagnosis and management (CG175). January 2014.

- NICE quality standard. Prostate cancer (QS91). June 2015.
- NICE diagnostic guidance. Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index (DG17). June 2015.

NHS ENGLAND and POLICY 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.
- NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer. B15/PS/a. January 2016.

OTHER GUIDANCE

- Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *European Urology*. 2017 Apr 30;71(4):618-29.
- Gnanapragasam VJ, Payne H, Syndikus I, Kynaston H, Johnstone T. Primary radical therapy selection in high-risk non-metastatic prostate cancer. *Clinical Oncology*. 2015 Mar 31;27(3):136-44.
- 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 Jul 22;26 (suppl 5): v69-77.

CURRENT TREATMENT OPTIONS

Treatment options for patients with mCRPC will depend on the nature and extent of the metastases and include some of the following strategies:[13]

- bilateral orchidectomy for all men with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy
- anti-androgen monotherapy with bicalutamide (to retain sexual function)
- androgen deprivation therapy only in cases when sexual function has not been maintained satisfactorily
- docetaxel as a treatment option for men with metastatic hormone-refractory disease who have a Karnofsky performance status score of 60% or more
- dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy to men with hormone-relapsed prostate cancer
- bisphosphonates for pain relief may be considered for men with hormone-relapsed prostate cancer when other treatments (including analgesics and palliative radiotherapy) have failed
- strontium-89 should be considered for men with hormone-relapsed prostate cancer and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy

Furthermore, for mCRPC NICE technology appraisal guidance 101 recommends docetaxel as a treatment option for men with metastatic hormone-refractory disease who have a Karnofsky

performance status score of 60% or more.[14] In clinical practice, after progression during or after a docetaxel-based treatment, patients may receive a further chemotherapy treatment or a combination of palliative treatments. Management options include mitoxantrone with or without steroids such as prednisolone.[15] NICE technology appraisal 259 recommends abiraterone in combination with prednisone or prednisolone as an option for the treatment of mCRPC which has progressed on or after one docetaxel-containing chemotherapy.[16]

EFFICACY and SAFETY

Trial	NCT02787005; MK-3475-199/KEYNOTE-199; EudraCT number: 2015-003644-40
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial registry[17]
Location	8 EU countries (incl UK), USA, Canada, Japan, Australia and other countries
Design	Non-randomized, parallel assignment, open label
Participants	n=370 (planned); aged 18-65 years; males; confirmed adenocarcinoma of the prostate without small cell histology; metastatic or locally confined inoperable and documented prostate cancer progression within 6 months prior to screening that have been either treated with at least 1 targeted endocrine therapy and one regimen/line of chemotherapy that contained docetaxel or patients showing signs of failure on current pre-chemotherapy enzalutamide treatment.
Schedule	5 intervention cohorts in total. Cohort 1 to 3 will receive pembrolizumab 200 mg via intravenous infusion on Day 1 of every 3-week cycle for up to 2 years; note that patient cohorts are defined as PD-L1 positive with measurable disease, PD-L1 negative with measurable diseases, or bone metastases with non-measurable disease. Cohorts 4 and 5 will receive pembrolizumab 200 mg via intravenous infusion on Day 1 of every 3-week cycle and enzalutamide via oral capsules once daily for up to 2 years; note that cohort 4 reports a patients population with RECIST 1.1 measureable disease and cohort 5 reports a population with bone metastases only or bone predominant disease. The dose of enzalutamide will be the same dose each participant was receiving before the start of pembrolizumab treatment.
Follow-up	Active treatment every 3-week cycle for up to 2 years.
Primary Outcomes	Objective Response Rate (ORR) using RECIST 1.1 assessed by central imaging vendor
Secondary Outcomes	Disease Control Rate (DCR); Prostate-specific Antigen (PSA) response rate; Percentage of participants who experience an adverse event (AE); Percentage of participants who discontinue study drug due to an AE.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study estimated primary completion date December 2018

ESTIMATED COST and IMPACT

COST

The current medicinal product price registered in the NHS is for Keytruda 100mg/4ml concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial at £2,630[18] and for Keytruda 50mg powder for concentrate for solution for infusion vials (Merck Sharp & Dohme Ltd) 1 vial is £1,315.[18]

The cost (list price) of enzalutamide is £2,735 for a 112-capsule pack of 40 mg enzalutamide. The daily dose of enzalutamide is 160 mg and costs £98 per day. The company has agreed a patient access scheme with the Department of Health.[19]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *pending of trial results*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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