NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2020

Pembrolizumab in combination with olaparib for anti-hormone and chemotherapy failure metastatic castration-resistant prostate cancer – third line

NIHRIO ID	27037	**NICE ID**	10258
Developer/Company	Merck Sharp & Dohme Ltd	**UKPS ID**	653154

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Pembrolizumab in combination with olaparib is in clinical development for patients with metastatic and castration-resistant prostate cancer. 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. Prostate cancer can be localised, locally advanced or advanced (metastatic). The symptoms of prostate cancer may vary depending on the stage but can include pain, tiredness, and problems emptying the bladder and the bowels.

Pembrolizumab delivered via intravenous infusion is a type of immunotherapy. It stimulates the body's immune system to fight cancer cells by targeting specific proteins that stimulate an immune response. Olaparib is administered orally in tablet form and can lead to cancer cell death by blocking DNA repair by an enzyme (protein) called PARP. If licensed, pembrolizumab in combination with olaparib will provide a therapy option for a heavily pre-treated patient population with limited remaining treatments available.

PROPOSED INDICATION

Treatment of anti-hormone and chemotherapy failure metastatic castration-resistant prostate cancer patients – third line.[a,1]

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda; MK-3475) is a humanised monoclonal antibody which binds to the programmed cell death receptor PD-1, blocking its interaction with ligands PD-L1 and PD-L2.[2] Upon binding to PD-L1 and PD-L2, the PD-1 receptor transmits inhibitory signals to T cells, downregulating their activity and preventing them from killing cancer cells.[3] Through blockade of this interaction between PD-1 and PD-L1 and PD-L2, pembrolizumab potentiates T-cell activity, including anti-tumour responses.[2]

Olaparib (Lynparza) is a potent inhibitor of human PARP enzymes (PARP-1, PARP-2, and PARP-3). PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. Olaparib has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo either as a standalone treatment or in combination with established chemotherapies.[4]

Pembrolizumab in combination with olaparib is currently in clinical development for the treatment of anti-hormone and chemotherapy failure metastatic and castration-resistant prostate cancer. In the phase III clinical trial (NCT03834519), patients are administered olaparib 600 mg as two 150 mg oral tablets twice daily continuously until progression plus on day 1 of each 21-day cycle and pembrolizumab 200 mg by intravenous infusion for up to 35 cycles (approximately 2 years).[1]

INNOVATION AND/OR ADVANTAGES

Therapeutic options for patients with docetaxel-pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients are limited. Pembrolizumab and olaparib have shown anti-tumour activity as monotherapies in patients previously treated for mCRPC. In the phase 1b/ 2 study (NCT02861573), pembrolizumab plus olaparib showed activity in docetaxel-pre-treated patients who previously received hormone therapy for mCRPC. The safety and tolerability profile of pembrolizumab plus olaparib was consistent with the individual profiles of each agent.[5]

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

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Pembrolizumab is currently licenced as a monotherapy in the UK for:[2]

- The treatment of 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 epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive tumour mutations.
- 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 pembrolizumab.
- The treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.
- The treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.
- The treatment of 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.
- The treatment of 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:[2]

- 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 in adults.

The most common adverse events of pembrolizumab monotherapy or in combination with chemotherapy or other anti-tumour medicines 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. [2]

Olaparib is currently licenced as a monotherapy in the UK as follows:[4]

- As maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

- As maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

- The treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments (see section 5.1). Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy ($\geqslant$ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.[4]

Pembrolizumab in combination with olaparib is currently in phase II clinical trials for solid tumours, cholangiocarcinoma and triple negative breast neoplasms. [2]

Pembrolizumab in combination with olaparib is currently in phase III clinical trials for non-small cell lung cancer; ovarian cancer, fallopian tube cancer and peritoneal neoplasms; and triple negative breast neoplasms.[6]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is the most common cancer in men in the UK.[7] 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.[8] 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.[9] Prostate cancer cells usually need testosterone to grow.[10] 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.[11]

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.[7] 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).[7,12]

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.[13]

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.[14]

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 (2017 data).[15] 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).[16] European age-standardised rates of prostate cancer in the UK are expected to increase from 208 per 100,000 in 2014 to 232.5 in 2035 (11.79% increase).[17]

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.[18]

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.[19]

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.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment options after chemotherapy with a docetaxel regimen are drug-based, outlined below (see Current Treatment Options section). The treatment used depends on factors including the patient's Eastern Cooperative Oncology Group (ECOG) performance status, docetaxel dosage received, whether the disease has progressed following treatment with docetaxel, and funding arrangements (if the manufacturer provides the treatment in accordance with the commercial access arrangement as agreed with NHS England).[21]

CURRENT TREATMENT OPTIONS

Drugs recommended by NICE for treating chemotherapy failure metastatic castration-resistant prostate cancer are cabazitaxel, enzalutamide and abiraterone according to the following drug combinations and criteria:[21]

Cabazitaxel in combination with prednisone or prednisolone in people whose disease has progressed during or after docetaxel chemotherapy, only if:

- The person has an ECOG performance status of 0 or 1
- The person has had 225 mg/m2 or more of docetaxel
- Treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

In addition, cabazitaxel is recommended only if:

- The company provides cabazitaxel with the discount in the patient access scheme agreed with the Department of Health, and

- NHS Trusts purchase cabazitaxel in accordance with the commercial access agreement between the company and NHS England, either: pre-prepared intravenous-infusion bags, or in vials, at a reduced price that includes a further discount reflecting the average cost of waste per patient.

When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

Enzalutamide is recommended within its marketing authorisation as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if:
their disease has progressed on or after one docetaxel-containing chemotherapy regimen and the manufacturer provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

People currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet the criteria described above should be able to continue therapy until they and their clinician consider it appropriate to stop.

PLACE OF TECHNOLOGY

If licensed, pembrolizumab in combination with olaparib will offer an additional third-line therapeutic option for patients with mCRPC who have not responded to chemotherapy treatment.

CLINICAL TRIAL INFORMATION

Trial	NCT03834519, Eudra CT 2018-004118-16; A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants With Metastatic Castration-resistant Prostate Cancer (mCRPC) Who Are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment With One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010) **Phase III - ongoing** **Locations: EU (including the UK), Canada, United States and other countries**
Trial design	Randomised, active comparator, parallel assignment, open label
Population	N=780 (planned); aged 18 years and older; has histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology; has prostate cancer progression while receiving androgen deprivation therapy (or post bilateral orchiectomy) within 6 months prior to screening; has current evidence of metastatic disease documented by bone lesions on bone scan and/or soft tissue disease shown by computed

	tomography/magnetic resonance imaging (CT/MRI); has received prior treatment with abiraterone acetate OR enzalutamide, but not both; have received docetaxel chemotherapy regimen for mCRPC and have had progressive disease during or after treatment with docetaxel
Intervention(s)	Subjects will receive olaparib 600 mg as two 150 mg oral tablets twice daily continuously until progression plus on day 1 of each 21-day cycle, pembrolizumab 200 mg by intravenous infusion for up to 35 cycles (approximately 2 years).
Comparator(s)	Participants receive abiraterone acetate (participants previously treated with enzalutamide) 1000 mg as two 500 mg or four 250 mg oral tablets once daily (QD) PLUS prednisone 10 mg as one 5 mg tablet BID until progression OR Participants receive enzalutamide (participants previously treated with abiraterone acetate) 160 mg as four 40 mg oral tablets or capsules QD until progression.
Outcome(s)	Primary outcomes [Time frame: up to approximately 29 months]: • Overall Survival (OS) • 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 See trial record for full list of other outcomes.
Results (safety)	-
Results (efficacy)	-

ESTIMATED COST

The NHS indicative price for a vial of pembrolizumab (50 mg) is £1315.00 (hospital only).[22] For olaparib, the NHS indicative price is £2317.50 for 56 x 100 and 150mg tablets and £3,550 for 448 x 50 mg capsules.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Cabazitaxel for hormone-relapsed 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 metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). July 2014.
- NICE 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

- Cassinello J, Arranz J.A., Piulats J.M. et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer. 2017.[24]
- Public Health England. Prostate Cancer Risk Management Programme. January 2015. Updated March 2016.[25]
- Parker C., Gillessen S., Heinderich A. et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[26]
- European Association of Urology. Prostate Cancer Guidelines. 2015.[27]
- Canadian Urologic Oncology Group (CUOG) and the Canadian Urological Association (CUA). Guidelines for the management of castrate-resistant prostate cancer. 2010. [28]

ADDITIONAL INFORMATION

REFERENCES

1 Clinical Trials.gov. *Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Metastatic Castration-resistant Prostate Cancer (mCRPC) (MK-7339-010/KEYLYNK-010) (KEYLYNK-010).* 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03834519 [Accessed 25 October 2019]

2 Electronic Medicines Compendium (emc). *KEYTRUDA 25 mg/mL concentrate for solution for infusion.* 2020. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 16 April 2020]

3 Lee HT, Lee SH, Heo Y-S. Molecular Interactions of Antibody Drugs Targeting PD-1, PD-L1, and CTLA-4 in Immuno-Oncology. Molecules (Basel, Switzerland). 2019;24(6):1190. Available from: https://www.mdpi.com/1420-3049/24/6/1190

4 Electronic Medicines Compendium (eMC). *Lynparza 100mg Film-Coated Tablets.* 2019. Available from: https://www.medicines.org.uk/emc/product/9204/smpc [Accessed 25 October 2019]

5 Urotoday. *ASCO GU 2020: KEYNOTE-365 Cohort A Updated Results: Pembrolizumab Plus Olaparib in Docetaxel-Pretreated Patients with mCRPC* 2020. Available from:

https://www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-prostate-cancer/119160-asco-gu-2020-keynote-365-cohort-a-updated-results-pembrolizumab-plus-olaparib-in-docetaxel-pretreated-patients-with-mcrpc.html [Accessed 21 April 2020]
6 Clinicaltrials.gov. *5 Studies found for: olaparib pembrolizumab | Phase 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=olaparib+pembrolizumab&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 16 April 2020]
7 Cancer Research UK. *About prostate cancer*. 2019. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 29 November 2019]
8 NHS. *Prostate cancer*. 2018. Available from: https://www.nhs.uk/conditions/prostate-cancer/ [Accessed 29 November 2019]
9 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 21 April 2020]
10 Prostate Cancer UK. *Hormone therapy*. 2016. Available from: https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy [Accessed 21 April 2020]
11 National Cancer Institute. *Clinical Trials Using Enzalutamide*. Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/intervention/enzalutamide [Accessed 21 April 2020]
12 American Cancer Society. *Prostate cancer risk factors*. 2019. Available from: https://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html [Accessed 29 November 2019]
13 Prostate Cancer UK. *Advanced prostate cancer*. Available from: https://prostatecanceruk.org/prostate-information/just-diagnosed/advanced-prostate-cancer [Accessed 21 April 2020]
14 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|
15 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 29 November 2019]
16 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 29 November 2019]
17 Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed 29 November 2019]
18 Office for National Statistics. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis*. 2018-19. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 15 November 2019]
19 Office for National Statistics. *Death Registrations Summary Statistics, England and Wales*. 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 29 November 2019]
20 Office for National Statistics. *Cancer survival in England - adults diagnosed* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 29 November 2019]
21 National Institute for Health and Care Excellence. *Treating hormone-relapsed metastatic prostate cancer*; 2019. Available from: https://pathways.nice.org.uk/pathways/prostate-cancer#path=view%3A/pathways/prostate-cancer/treating-hormone-relapsed-metastatic-prostate-cancer.xml&content=view-index [Accessed 29 November 2019]
22 NICE. *PEMBROLIZUMAB*. 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/pembrolizumab.html [Accessed 29 November 2019]
23 National Institute for Health and Care Excellence. *Olaparib*. 2020. Available from: https://bnf.nice.org.uk/medicinal-forms/olaparib.html [Accessed 16 April 2020]

24 Cassinello J, Arranz JA, Piulats JM, Sanchez A, Perez-Valderrama B, Mellado B, et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017). Clin Transl Oncol. 2018 Jan;20(1):57-68. Available from: https://link.springer.com/article/10.1007/s12094-017-1783-2

25 GOV.UK. *Prostate cancer risk management programme: overview*. 2019. Available from: https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview [Accessed 21 May 2020]

26 Parker C, Gillessen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v69-77. Available from: https://doi.org/10.1093/annonc/mdv222

27 European Association of Urology. *Prostate cancer*. 2020. Available from: https://uroweb.org/guideline/prostate-cancer/ [Accessed 22 April 2020]

28 Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2010;4(6):380-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2997826/

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.