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HEALTH TECHNOLOGY BRIEFING
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177Lu-PSMA-617 for metastatic castration-resistant prostate cancer - third line

NIHRIO ID	17270	**NICE ID**	10445
Developer/Company	Advanced Accelerator Applications (AAA)	**UKPS ID**	656545

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

SUMMARY

177Lu-PSMA-617 is in clinical development for patients with metastatic castration-resistant prostate cancer (mCRPC) who have been previously treated with androgen receptor-directed therapy (ARDT) and a taxane-based chemotherapy. Prostate cancer is a cancer of the prostate gland and mCRPC is when the cancer has spread to parts of the body other than the prostate, and it is able to grow and spread even though drugs or other treatments to lower the amount of male sex hormones are being used to manage the cancer. The symptoms of prostate cancer may vary depending on the stage but can include pain, tiredness, and problems emptying the bladder and the bowels. Treatment options for mCRPC are currently limited in patients that have progressed following treatment with ARDT and a taxane-based chemotherapy.

177Lu-PSMA-617 delivered via intravenous infusion. It works by releasing an energetic beta particle to precisely deliver cell-killing radiation to the site of disease to kill cancer cells. Earlier studies indicate that 177Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in the third-line setting, where patients have no clear standard of care, having exhausted all key treatment options. If licensed, 177Lu-PSMA-617 will provide a treatment option for patients in this setting.

PROPOSED INDICATION

Treatment of patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy (ARDT) and a taxane-based chemotherapy- third line and beyond.[a]

TECHNOLOGY

DESCRIPTION

Lutetium-177 prostate-specific membrane antigen-617 (177Lu-PSMA-617) is a human PSMA-targeting ligand that is conjugated to the beta-emitting radioisotope lutetium (177Lu). It has potential antineoplastic activity against PSMA-expressing tumour cells due to the delivery of beta particle radiation specifically to the tumour cells. The PSMA-617 moiety targets and binds to any type of PSMA-expressing neoplastic tissue-both soft tissue and bone. Upon binding, PSMA-expressing tumour cells are destroyed by 177Lu through the specific delivery of beta particle radiation.[1]

177Lu-PSMA-617 is currently in clinical development for the treatment of patients with PSMA-positive mCRPC who have been treated with androgen receptor-directed therapy (ARDT) and a taxane-based chemotherapy. In the phase III clinical trial (VISION, NCT03511664), patients are administered 7.4 gigabecquerel (GBq) ±10% 177Lu-PSMA-617 intravenously over a period of 2 to 10 minutes every 6 weeks (±1 week) for a maximum of 6 cycles.[2]

INNOVATION AND/OR ADVANTAGES

There are currently no radioligand therapies recommended to treat castration-resistant, metastatic prostate cancer. If approved, 177Lu-PSMA-617 would represent a novel target therapy which offers an alternative choice of therapy for patients on their third-line (or beyond) of treatment.[3]

Preclinical data demonstrated high binding affinity and internalization, prolonged tumour uptake, rapid kidney clearance and high tumour-to-background ratio. Further, preliminary results indicate that 177Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients have no clear standard of care, having exhausted all key treatment options (i.e. chemotherapy and ARDT).[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

177Lu-PSMA-617 does not currently have Marketing Authorisation in the EU/UK or any indication. The ongoing trial phase III clinical trial (VISION, NCT03511664) has an estimated primary completion date of Q4 2020.[a]

177Lu-PSMA-617 is also in phase II clinical development for various other prostate cancer indications.[5]

[a] Information provided by AAA on UK PharmaScan

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 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] 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 metastatic castration-resistant prostate cancer (mCRPC).[10] Prostate-specific membrane antigen (PSMA), a transmembrane protein, is expressed by virtually all prostate cancers, and its expression is further increased in poorly differentiated, metastatic, and hormone-refractory carcinomas.[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 years 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).[6,12]

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 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 – including metastatic hormone-sensitive, mCRPC pre-taxane treatment, and mCRPC post-taxane treatment).[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]

The annual number of people eligible for third-line treatment in mCRPC is expected to be a smaller proportion of the overall prostate cancer population. According to the latest NICE review in mCRPC, an estimated 5,960 people would develop mCRPC annually. Of these mCRPC patients, 2,980 would receive docetaxel, with a further 1,640 being eligible for

subsequent therapy.[21] It is expected that a proportion of these patients would be eligible for treatment with 177-Lu-PSMA-617.

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).[22]

CURRENT TREATMENT OPTIONS

Drugs recommended by NICE for treating mCRPC after chemotherapy with a docetaxel regimen are cabazitaxel, enzalutamide and abiraterone according to specific criteria listed in the NICE pathway.[22] However, treatment options beyond third-line are currently limited, i.e. in patients who have been treated with a taxane-based chemotherapy (including cabazitaxel) and androgen receptor-directed therapy (including both enzalutamide, abiraterone).

PLACE OF TECHNOLOGY

If licensed, 177Lu-PSMA-617 will provide a treatment option for patients with PSMA-positive mCRPC who have been treated with androgen receptor-directed therapy (ARDT) and a taxane-based chemotherapy.[b]

CLINICAL TRIAL INFORMATION

Trial	**VISION,** NCT03511664; An international, prospective, open label, multicenter, randomized phase 3 study of 177Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) **Phase III-** Ongoing **Location(s)**: EU (including UK) USA and other countries
Trial design	Randomised, parallel assignment, open label
Population	N= 814 ; 18 years and older; male; ECOG status 0 to 2; life expectancy> 6 months; 68Ga-PSMA-11 PET/CT scan positive; serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L); at least one novel androgen axis drug (such as enzalutamide and/or abiraterone); previously treated with at least 1, but no more than 2 previous taxane regimens; progressive mCRPC.[2,4]
Intervention(s)	177Lu-PSMA-617 plus best supportive/best standard of care (BS/BSOC) • Patients randomized to receive the investigational product will receive 7.4 GBq (±10%) 177Lu-PSMA-617 intravenously every 6 weeks (±1 week) for a maximum of 6 cycles. + BS/BSOC

[b] Information provided by AAA on UK PharmaScan

Comparator(s)	BS/BSOC alone • Patients randomized to this arm will receive BS/BSOC as determined by the investigator
Outcome(s)	Designated co-primary endpoints:[c] • Overall survival and • Radiographic progression-free survival See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of 177Lu-PSMA-617 is not yet known.

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 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.[23]
- Public Health England. Prostate Cancer Risk Management Programme. January 2015. Updated March 2016.[24]

[c] Information provided by AAA

- Parker C., Gillessen S., Heinderich A. et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[25]
- European Association of Urology. Prostate Cancer Guidelines. 2015.[26]
- Canadian Urologic Oncology Group (CUOG) and the Canadian Urological Association (CUA). Guidelines for the management of castrate-resistant prostate cancer. 2010.[27]

ADDITIONAL INFORMATION

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