Innovation Observatory

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EVIDENCE BRIEFING
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Apalutamide in addition to androgen deprivation therapy for metastatic hormone-sensitive prostate cancer

NIHRIO ID	13634	**NICE ID**	9573
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	644129

Licencing and market availability plans	Apalutamide in addition to androgen deprivation therapy is currently in phase III clinical trials for the treatment of metastatic hormone-sensitive prostate cancer

SUMMARY

Apalutamide in addition to androgen deprivation therapy (ADT) is in clinical development for the treatment of metastatic hormone-sensitive prostate cancer as first or second-line therapy before or after chemotherapy. Prostate cancer is the second most common cancer in the UK and is classified into localised (confined to the prostate gland), locally-advanced (spread outside the capsule of the prostate gland) and advanced (spread to other parts of the body). Advanced prostate cancer that still responds to ADT is identified as metastatic hormone-sensitive prostate cancer. Current treatment options at this stage often involves either ADT alone (surgery and hormone therapy) or ADT in combination with chemotherapy.

Apalutamide is an oral tablet that works by blocking the androgen receptor to prevent the effects of the hormone testosterone in the prostate and, thereby, reducing the growth of the cancer cells. If licensed, apalutamide in addition to ADT will increase the treatment options available for patients with metastatic. Apalutamide is also currently being considered for use in hormone-resistant prostate cancer which has not yet spread.

PROPOSED INDICATION

Prostate cancer (metastatic, hormone-sensitive)[1]

TECHNOLOGY

DESCRIPTION

Apalutamide (Erleada; JNJ56021927; ARN-509) is a non-steroidal anti-androgen agent that is under development for the treatment of prostate cancer. Exerting an anti-tumour action, apalutamide blocks the effect of androgens that promote tumour growth.[2] Apalutamide binds directly to the ligand binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription.[3]

Apalutamide is in clinical development, in addition to androgen deprivation therapy (ADT), for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). In the phase III trial (TITAN; NCT02489318), participants receive 240 mg (four 60 mg tablets) of apalutamide once daily in 28-day treatment cycles and a stable regimen of ADT (gonadotropin releasing hormone analog or surgical castration) until disease progression or the progression of unacceptable treatment related toxicity.[1]

INNOVATION AND/OR ADVANTAGES

The addition of apalutamide to ADT may allow for an additional, more efficacious treatment option for patients with mHSPC. In UK clinical practice, people with newly diagnosed mHSPC are offered either ADT or docetaxel plus ADT.[4] As such, apalutamide + ADT may also meet an unmet need for alternative treatment options for patients who cannot receive or do not respond to docetaxel plus ADT.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Apalutamide does not currently have Marketing Authorisation in the EU/UK for any indication, though a Market Authorisation Application (MAA) has been submitted for its use in non-metastatic castration-resistant prostate cancer.[5]

The most common adverse reactions (≥10%) associated with treatment are: fatigue, hypertension, rash, diarrhoea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral oedema.[6]

Apalutamide is also in Phase III development for:[7,8,9]

- High-risk, biochemically relapsed prostate cancer
- High risk, localised or locally advanced prostate cancer
- Chemotherapy-naïve, metastatic castration-resistant prostate cancer

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is the second most common cancer in men in the UK after non-melanoma skin cancer.[10] It affects the prostate, a small gland in the pelvis found only in men. It 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.[11] 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 is very rare in Asian men. More than half the men (50%) diagnosed with prostate cancer in the UK each year are aged 70 and over.[12]

Early prostate cancer often has no symptoms at all. When symptoms occur, these include increased urinary frequency, nocturia, urinary hesitancy, urgency, post-void dribbling, blood in urine or semen, erectile dysfunction (uncommon) and poor stream.[11,13] Symptoms indicating that the cancer may have spread include bone and back pain, a loss of appetite, pain in the testicles and unexplained weight loss.[11] Although the cause of prostate cancer is not known, a number of risk factors have been identified which include (increased) age, ethnicity, family history, obesity, lack of exercise, high calcium diet, being taller, high levels of insulin like growth factor (IGF-1), having had a previous cancer, vasectomy, prostatitis and being exposed to cadmium and cadmium compounds. .[10,11]

Prostate cancer can be classified into localised (confined to the prostate gland), locally advanced (spread outside the capsule of the prostate gland), and advanced cancer (spread to other parts of the body).[14] Prostate cancer that has spread to other parts of the body (advanced) but still responds to androgen deprivation therapy (ADT) is identified as metastatic hormone-sensitive prostate cancer.[15]

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.[16]

CLINICAL NEED AND BURDEN OF DISEASE

There are over 40,000 new cases of prostate cancer diagnosed every year in the UK.[11] Prostate cancer is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65.[17] More than 50% of prostate cancer diagnoses in the UK each year are in men aged 70 years and over (2012 data), and the incidence rate is highest in men aged 90 years and over (2012–2014 data).

Out of every 10 prostate cancer cases, 4 (40%) are only diagnosed at a late stage in England (2014 data) and Northern Ireland (2010– 2014 data). Incidence rates are projected to rise by 12% between 2014 and 2035 in the UK to 233 cases per 100,000 in 2035.[18]

In England in 2016, there were 40,489 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD-10 code C61).[19] Considering that 40% of patients have late stage cancer at the time of diagnosis, the number of patients in 2016 out of 40,489 cases of prostate cancer with late stage prostate cancer would be around 16,196.

In UK in 2016, there were 11,631 deaths where malignant neoplasm of prostate (ICD-10 code C61) was recorded as the underlying cause.[20]

Latest published survival statistics (2016, patients diagnosed in 2011-2015) report stated 1-year survival rate of 96.3% and 5-year survival rate of 88.3% (age-standardised) for patients with prostate cancer.[19]

According to the Hospital Episode Statistics (HES) data, in 2016-17 there were 70,295 admissions due to neoplasm of the prostate which resulted in 97,382 FCE bed days (ICD-10 code C61).[21]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Depending on the stage and prognostic risk of the person's disease, treatment options for prostate cancer include: watchful waiting and active surveillance, surgery, radiotherapy, androgen deprivation therapy (ADT), novel agents (e.g. abiraterone and enzalutamide) and chemotherapy.

As the androgen receptor is involved in the growth and spread of prostate cancer, prostate cancer can be treated hormonally using ADT. ADT treatments include surgical castration (bilateral orchidectomy) and medical castration using luteinising-hormone-releasing hormone (LHRH) agonists, and LHRH antagonists.[22]

ADT alone was long considered the standard-of-care for mHSPC. Following recent clinical studies, however, the addition of docetaxel to ADT has become standard care for patients with high-risk mHSPC. Newer trials involving abiraterone have also shown improvement in survival with the addition of abiraterone plus prednisone to ADT. As such, abiraterone plus prednisone in addition to ADT has emerged as an alternative standard-of-care to docetaxel plus ADT.[23,24]

In the UK clinical practice, people with newly diagnosed mHSPC have ADT or docetaxel plus ADT. NICE's guideline for prostate cancer recommends ADT, specifically: continuous luteinising hormone-releasing hormone agonists, bilateral orchidectomy (removal of the testicles), or bicalutamide monotherapy. According to clinical experts, orchidectomy and bicalutamide monotherapy are rarely used in this way in the NHS. It understood that, although docetaxel is not licensed for use with ADT for mHSPC, NHS England commissions 6 cycles of docetaxel with ADT.[4]

CURRENT TREATMENT OPTIONS

For men with hormone-sensitive metastatic prostate cancer, NICE recommends:[17, 22]

- bilateral orchidectomy or continuous LHRH agonist therapy;
- anti-androgen therapy with bicalutamide; or
- combined androgen blockade (not first-line)

Although not currently recommended by NICE, abiraterone (Zytiga) is licensed for the treatment of newly diagnosed, high risk metastatic hormone sensitive prostate cancer in adult men in combination with ADT plus prednisone or prednisolone.[25]

PLACE OF TECHNOLOGY

If licensed, apalutamide in addition to ADT will increase the treatment options available for patients with metastatic hormone-sensitive prostate cancer.

CLINICAL TRIAL INFORMATION

Trial	TITAN, NCT02489318, CR107614; adults, apalutamide vs placebo, in combination with androgen deprivation therapy (ADT); phase III
Sponsor	Janssen-Cilag Ltd
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (including UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled
Participants	n=1052; aged 18-65 years; prostate cancer; hormone-sensitive; metastatic; progression despite first line chemotherapy.
Schedule	Participants are randomised to one of two treatment arms: 1. Apalutamide 240mg orally (as 4 60mg tablets) once daily in each 28 day treatment cycle plus ADT (gonadotropin releasing hormone analog or surgical castration) until disease progression or the occurrence of unacceptable treatment related toxicity. 2. Placebo taken orally once daily in each 28 day treatment cycle plus ADT (gonadotropin releasing hormone analog or surgical castration) until disease progression or the occurrence of unacceptable treatment related toxicity.
Follow-up	Approx. 54 months
Primary Outcomes	• Radiographic Progression-Free Survival (rPFS) [Time frame: Up to 54 months] • Overall Survival (OS) [Time frame: Up to 54 months]
Secondary Outcomes	• Time to pain progression [Time frame: Up to 54 months] • Time to Skeletal-Related Event (SRE) [Time frame: Up to 54 months] • Time to chronic opioid use [Time frame: Up to 54 months] • Time to Initiation of cytotoxic chemotherapy [Time frame: Up to 54 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as November 2020.

ESTIMATED COST

The cost of apalutamide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal. Degarelix for treating advanced hormone-dependent prostate cancer (TA404). August 2016.
- NICE Technology Appraisal. Abiraterone for treating newly diagnosed high risk metastatic hormone-naïve prostate cancer (ID945). *In development*. Expected publication: October 2018.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (update)(GID-NG10057). *In development*. Expected publication: April 2019.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (CG175). January 2014.
- NICE quality standard. Prostate cancer (QS91). June 2015.
- NICE Evidence Summary. Hormone-sensitive metastatic prostate cancer: docetaxel (ESUOM50). January 2016.
- NICE interventional procedures guidance. Laparoscopic radical prostatectomy (IPG193). November 2006.NICE interventional procedures guidance. Cryotherapy as a primary treatment for prostate cancer (IPG145). November 2005.

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. 2016. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer. B15/PS/a.

OTHER GUIDANCE

- American Society of Clinical Oncology (ASCO). Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline. 2018.[26]
- European Association of Urology (EAU) - European Society for Radiotherapy & Oncology (ESTRO) - International Society of Geriatric Oncology (SIOG). Guidelines on screening, diagnosis, and local treatment with curative intent of clinically localised prostate cancer. 2017.[27]
- European Society for Medical Oncology. Cancer of the Prostate: ESMO Clinical Practice Guidelines. 2015. (*Updates*: 2016, 2017).[28]

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