Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING JANUARY 2019

Enzalutamide in addition to androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer

NIHRIO ID	12596	**NICE ID**	10113
Developer/Company	Astellas Pharma Ltd	**UKPS ID**	650658

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Enzalutamide in addition to androgen deprivation therapy (ADT) is in clinical development for the treatment of metastatic hormone-sensitive prostate cancer. 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 involve either ADT alone (surgical removal of the testes or hormone therapy) or ADT in combination with chemotherapy.

Enzalutamide is an oral capsule that works by blocking the androgen receptor to modify the effects of androgens on the prostate, stopping the growth of the cancer cells. Enzalutamide in addition to ADT may offer an alternative option for people that cannot receive or do not respond to chemotherapy plus ADT. If licensed, enzalutamide in addition to ADT will increase the treatment options available for patients with metastatic hormone-sensitive prostate cancer.

PROPOSED INDICATION

The treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in addition to androgen deprivation therapy (ADT)[1,a]

TECHNOLOGY

DESCRIPTION

Enzalutamide (Xtandi; MDV 3100) is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.[2]

Enzalutamide in addition to androgen deprivation therapy (ADT) is in clinical development for the treatment of mHSPC as a first-line therapy. In the phase III clinical trial (ARCHES; NCT02677896), enzalutamide is administered as oral capsules at 160mg taken once daily. Duration of treatment is not reported.[1]

INNOVATION AND/OR ADVANTAGES

The addition of enzalutamide to ADT may allow for an additional treatment option for patients with mHSPC. In UK clinical practice, people with mHSPC are offered either ADT or docetaxel plus ADT.[3] In addition, enzalutamide may 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

Enzalutamide is licensed in the UK for the treatment of:[4]

- adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)
- adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated
- adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy

Common or very common side-effects include anxiety, asthenia, fatigue, ischaemic heart disease, bone fracture, impaired concentration, fall, gynaecomastia, headache, hot flush, hypertension, memory loss, restless legs, or skin reactions.[4]

Enzalutamide is also in phase III clinical development for the treatment of high-risk non-metastatic hormone-sensitive prostate cancer.[5]

[a] Information provided by Astellas 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. 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.[7] The cancer starts in the glandular cells in the prostate and is known as acinar adenocarcinoma. It 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.[6]

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.[7,8] 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.[7] 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, 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.[7,9]

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. This is also known as metastatic prostate cancer).[10] Prostate cancer that has spread to other parts of the body (advanced) but still responds to ADT is identified as metastatic hormone-sensitive prostate cancer (mHSPC).[11]

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.[12]

CLINICAL NEED AND BURDEN OF DISEASE

There are over 40,000 new cases of prostate cancer diagnosed every year in the UK.[13] Prostate cancer is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65 years.[14]

In England in 2016 there were 40,489 registrations of newly diagnosed cases of malignant neoplasm of prostate (ICD-10 code C61). Of these, 8,153 cases (20%) were diagnosed at stage 4 (advanced).[15] Incidence rates are expected to increase from 208 per 100,000 in 2014 to 232.5 in 2035 (European age-standardised).[16]

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.[17] Latest published survival statistics (2016, patients diagnosed in 2011-2015) report a 1-year survival rate of 96.3% and a 5-year survival rate of 88.3% (age-standardised) for patients with prostate cancer.[18]

According to Hospital Episode Statistics (HES) data, in 2017-18 there were 71,071 admissions with a primary diagnosis of neoplasm of the prostate (ICD-10 code C61), resulting in 90,683 finished consultant episodes (FCE) bed days. Of these admissions, 49,309 were daycases.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatment for metastatic prostate cancer is to control the cancer, prolong life, relieve symptoms and maintain quality of life.[7,20] Hormone therapy will be a life-long treatment for many men with metastatic prostate cancer, and will shrink the cancer and slow down its growth.[21]

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] First-line treatment with ADT, although palliative, can normalise serum levels of prostate-specific antigen (PSA) in over 90% of patients and can produce objective tumour responses in 80-90%. This anti-tumour activity can improve quality of life by reducing bone pain as well as the rates of complications including spinal cord compression or ureteral obstruction.[23]

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.[24,25]

CURRENT TREATMENT OPTIONS

For men with mHSPC, NICE guidelines recommend:[14]

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

NICE has also published an evidence summary for the off-label use of docetaxel (in combination with ADT) for the treatment of mHSPC. Docetaxel is licensed in the UK for the treatment of metastatic hormone-resistant prostate cancer.[22] A draft of an update to the NICE guideline for prostate cancer recommends offering docetaxel to people who do not have significant comorbidities, starting treatment within 12 weeks of starting ADT, to be administered in six 3-weekly cycles with or without daily prednisolone.[26]

Although not currently recommended by NICE, abiraterone (Zytiga) is licensed for the treatment of newly diagnosed, high risk mHSPC in adult men in combination with ADT plus prednisone or prednisolone.[27]

PLACE OF TECHNOLOGY

If licensed, enzalutamide in addition to ADT will increase the treatment options available for adult men with mHSPC.

CLINICAL TRIAL INFORMATION

Trial	ARCHES, NCT02677896, EudraCT2015-003869-28; enzalutamide vs placebo, both in combination with androgen deprivation therapy (ADT); phase III
Sponsor	Astellas Pharma Global Development, Inc.
Status	Ongoing

Source of Information	Trial registry[1], Press release[5,28]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled
Participants	n=1,150; aged 18 yrs and older; males; prostate cancer; hormone-sensitive; metastatic; first-line therapy
Schedule	Randomised to enzalutamide 160mg take orally once daily; or matching placebo taken orally once daily; both in combination with ADT (either bilateral orchiectomy or LHRH agonist/antagonist) maintained during study treatment as per standard of care
Follow-up	Active treatment time not reported, follow-up for 4 yrs
Primary Outcomes	Radiographic progression-free survival [Time frame: up to 4 yrs]
Secondary Outcomes	• Overall survival [Time frame: up to 7 yrs] Time frame up to 4 yrs: • Time to first symptomatic skeletal event • Time to castration resistance • Time to deterioration of quality of life • Time to initiation of a new antineoplastic therapy • Time to PSA progression • PSA undetectable rate • Objective response rate • Time to pain progression
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as October 2018. This was brought forward from April 2020 in August 2018.

ESTIMATED COST

Enzalutamide is already marketed in the UK; a pack of 112 x 40mg capsules costs £2,735.[29]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Apalutamide with androgen deprivation therapy for treating metastatic hormone-sensitive prostate cancer (ID1534, GID-TA10423). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Abiraterone for treating newly diagnosed high risk metastatic hormone-naïve prostate cancer (ID945, GID-TA10122). Expected date of issue to be confirmed.

- NICE clinical guideline in development. Prostate cancer: diagnosis and management (update) (GID-NG10057). 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.

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

OTHER GUIDANCE

- European Association of Urology. Guidelines on Prostate Cancer. 2018.[30]
- European Society for Medical Oncology. Cancer of the prostate ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[31]

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