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Apalutamide in addition to abiraterone and prednisone/prednisolone for metastatic castration-resistant prostate cancer – first line

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LAY SUMMARY

Prostate cancer is a 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 (or metastatic) prostate cancer. The symptoms may vary depending on the stage of cancer but can include pain, tiredness, and problems emptying the bladder and the bowels. About half of men diagnosed with locally-advanced prostate cancer will see their cancer spread to other body organs (i.e. become metastatic). Prostate cancer growth and spread depends on the hormone, testosterone. Cancer that does not respond to hormonal treatments to reduce the level of testosterone is known as castration-resistant prostate cancer.

Apalutamide is an oral tablet in development for the treatment of metastatic castration-resistant prostate cancer, when used in addition to abiraterone acetate and prednisone/prednisolone. Apalutamide acts by blocking the androgen receptor (target binding site of various steroid hormones including testosterone) to prevent the effects of testosterone in the prostate and the body. If licensed, apalutamide in addition to abiraterone and prednisone/prednisolone will offer an additional treatment for metastatic castration-resistant prostate cancer in those who are not yet recommended to receive chemotherapy.

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TARGET GROUP

Prostate cancer (castration-resistant, metastatic) – pre-chemotherapy; in combination with abiraterone acetate and prednisone/prednisolone – first line

TECHNOLOGY

DESCRIPTION

Apalutamide (Erleada; JNJ56021927; ARN-509) is a nonsteroidal antiandrogen agent that is under development for the treatment of prostate cancer. Exerting an antitumor action, apalutamide blocks the effect of androgens that promote tumour growth.[1] Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription.[2]

Abiraterone acetate (Zytiga) is an androgen biosynthesis inhibitor and in combination with prednisone/prednisolone is indicated to treat metastatic castration-resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Abiraterone acetate in combination with prednisone/prednisolone is also licensed for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen and the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).[3]

Apalutamide is in development in addition to abiraterone acetate and prednisone/prednisolone for the treatment of mCRPC, in those who are not yet recommended chemotherapy. In the phase III trial (NCT02257736), participants receive 240 mg tablet of apalutamide and 1000 mg (four 250 mg tablets) of abiraterone acetate once daily on an empty stomach and 5 mg prednisone, twice daily, until disease progression, unacceptable toxicity, or end of treatment, whichever occurs first.[4]

Apalutamide in addition to abiraterone and prednisone/prednisolone does not currently have Marketing Authorisation in the EU for any other indication.

INNOVATION and/or ADVANTAGES

One of the main challenges in developing drugs that can benefit CRPC is being able to identify active drugs and understand how to best use these in combination or in sequence. In previous clinical studies, apalutamide was safe, well-tolerated and demonstrated clinical activity in mCRPC in both patients with and without prior abiraterone acetate and prednisone.[5]

If licensed, apalutamide in combination with abiraterone acetate and prednisone/prednisolone will offer an additional treatment for mCRPC in those who are not yet recommended chemotherapy.

DEVELOPER

Janssen-Cilag Ltd

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 originates in the glandular cells in the prostate, known as acinar adenocarcinomas. Various risk factors for prostate cancer have been identified, including ageing, black ethnic origin and a family history of the condition.[6] Prostate cancer 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 above.[7] Other factors include diet, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure.[10]

The development of prostate cancer is often slow, with people displaying no signs in the early stages and symptoms only becoming apparent when the prostate is large enough to affect the urethra.[8] 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 semen), symptoms of acute kidney injury or chronic kidney disease and impotence.[10]

There are three stages of prostate cancer: localised (confined to the prostate gland), locally-advanced (spread outside the capsule of the gland) and advanced or metastatic (spread to other body organs).[9] At an advanced stage, the cancer most commonly spreads to lymph nodes in other parts of the body or to the bones, but can also spread to other organs.[10] Approximately 50% of men diagnosed with locally-advanced prostate cancer will develop metastatic cancer during their lifetime. Early detection and treating the cancer can lower that risk.[11] Prostate cancer depends on testosterone to proliferate. Castration-resistant prostate cancer (CRPC) is a stage of the disease when progression occurs despite castrate levels of testosterone, induced for example by androgen deprivation therapy (ADT).[12]

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 prostate specific antigen (PSA) tests and the population is getting older. In adults, prostate cancer is the second most common type of cancer, and is the most common cancer in the UK.[13] In 2016, 40,484 men were newly diagnosed with prostate cancer and 10,178 deaths from prostate cancer were recorded.[14,15] About 9 in 10 (85%) men diagnosed with prostate cancer in England and Wales survived their disease for five years or more (2010-11).[16]

NICE estimates 55–65% of people with prostate cancer will develop metastatic disease. Over 90% of people with metastatic prostate cancer initially respond to hormonal therapy but eventually become resistant to it. This clinical condition is described as CRPC, but is alternatively referred to as hormone-relapsed prostate cancer, hormone-refractory prostate cancer and androgen-independent prostate cancer.[22] For CRPC, the disease epidemiology is hampered by the varying terminology, definition and disease management which may explain why there is a paucity of prevalence and incidence data currently available.[17]

In 2016-17 there were 70,295 admissions (of which 48,567 were day cases) for malignant neoplasm of the prostate (ICD-10 code C61) in England which resulted in 75,276 finished consultant episodes (FCE) and 97,382 FCE bed days.[18]

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 April 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 et al. TB. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. 2017[19]
- Parker C et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015[20]

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:[21]

- 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

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.[22]

Abiraterone acetate in combination with prednisone or prednisolone is also recommended as an option for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated and in mCRPC which has progressed on or after one docetaxel-containing chemotherapy.[23] Additionally abiraterone is recommended for the treatment of metastatic hormone-relapsed prostate cancer (mHRPC) before chemotherapy is indicated.[24] Enzalutamide has been recommended for mHRPC before chemotherapy is indicated[25] and also in those who have been previously treated with a docetaxel-containing regimen.[26]

EFFICACY and SAFETY

Trial	NCT02257736, EudraCT 2014-001718-25; apalutamide in combination with abiraterone acetate and prednisone vs abiraterone in combination with prednisone and placebo
Sponsor	Janssen-Cilag Ltd
Status	Ongoing
Source of Information	Registry[4,27]
Location	EU (incl UK), USA, Canada and countries in South America, Asia and Africa
Design	Randomised, placebo-controlled, double-blind study
Participants	n=983; aged ≥18 years old; male; metastatic disease castration-resistant prostate cancer
Schedule	Randomised to receive either: • 240 mg tablet of apalutamide and 1000 mg (four 250 mg tablets) of abiraterone acetate once daily on an empty stomach and 5 mg prednisone, twice daily, until disease progression, unacceptable toxicity, or end of treatment, whichever occurs first Or • Matching placebo of apalutamide and 1000 mg (four 250 mg tablets) of abiraterone acetate once daily on an empty stomach and 5 mg prednisone, twice daily, until disease progression, unacceptable toxicity, or end of treatment, whichever occurs first
Follow-up	Active treatment for up to 5 years
Primary Outcomes	Radiographic Progression-free Survival from randomisation until death or lost to follow-up or withdrawal of consent or study termination (whichever occurs first up to 5 years)
Secondary Outcomes	• Overall survival from randomization until death or lost to follow-up or withdrawal of consent or study termination (whichever occurs first up to 5 years) • Time to chronic opioid use (up to 5 years) • Time to initiation of cytoxic chemotherapy (up to 5 years) • Time to pain progression (up to 5 years)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as March 2018

ESTIMATED COST and IMPACT

COST

The cost of apalutamide is not yet known.

The NHS Indicative price for abiraterone (Zytiga) is listed as £2735.00 for 56 x 500mg tablets.[28]

The NHS Indicative price for prednisone (Lodotra) is listed as £89.00 for 100 x 5mg modified-release tablets.[29]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ 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: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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