Health Technology Briefing
July 2022

Enzalutamide for treating non-metastatic prostate cancer after radical prostatectomy and/or radiotherapy

Company/Developer	Astellas Pharma Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 17172	NICE ID: 9716	UKPS ID: 646209

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Enzalutamide is currently in clinical development for the treatment of high-risk non-metastatic prostate cancer (cancer that has not spread beyond the prostate) that has been previously treated with a radical prostatectomy (surgery to remove the prostate gland) and/or radiotherapy. Prostate cancer develops in the prostate gland and is the most common cancer in men in the UK. The symptoms may vary depending on the stage of cancer but can include pain, tiredness, and problems emptying the bladder and the bowels. There are currently limited non-hormonal treatment options available for patients with non-metastatic prostate cancer that has progressed after standard care treatment, therefore more effective treatments are needed.

Enzalutamide is an oral drug that works by blocking the action of testosterone and other male hormones known as androgens. Because prostate cancer needs testosterone to survive and grow, enzalutamide slows down the growth of the prostate cancer. Enzalutamide is already approved for use either alone or in combination with other treatments for different types of prostate cancer. If licenced, enzalutamide will provide an additional treatment option for patients with high-risk non-metastatic prostate cancer who have progressed following radical prostatectomy and/or radiotherapy.

Proposed Indication

High-risk non-metastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both.[1]

Technology

Description

Enzalutamide (Xtandi) 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 is currently in phase III clinical development for the treatment of high-risk non-metastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both (EMBARK: NCT02319837). In this trial, enzalutamide is administered as four 40mg capsules orally once daily, with or without leuprolide administered as a single intramuscular or subcutaneous injection once every 12 weeks.[1]

Key Innovation

Current treatments are limited to androgen deprivation therapy (ADT) for patients with high-risk non-metastatic castration-sensitive prostate cancer (nmCSPC) with evidence of disease recurrence by prostate-specific antigen (PSA) following definitive therapy (radical prostatectomy and/or radiotherapy).[3] There is therefore an unmet need for more safe and effective treatment options that target nmCSPC.

In a phase 2 study of patients with nmCSPC and metastatic CSPC (mCSPC), treatment with enzalutamide monotherapy was shown to be effective and well tolerated, with 92.5% of patients having a PSA decline of ≥80% at 25 weeks.[4]

If licenced, enzalutamide would provide an additional treatment option for patients with high-risk non-metastatic prostate cancer that has progressed following definitive therapy.

Regulatory & Development Status

Enzalutamide has Marketing Authorisation in the EU/UK for the treatment of adult men with:[2]

- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.
- High-risk non-metastatic castration-resistant prostate cancer (CRPC).
- Metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- Metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Enzalutamide is currently in phase II and III clinical trials for the treatment of various cancer indications including:[5]

- Breast cancer
- Hepatocellular carcinoma
- Ovarian cancer
- Peritoneal cancer
- Fallopian tube cancer
- Salivary cancer

- Endometrial cancer

Patient Group

Disease Area and Clinical Need

Prostate cancer develops in the prostate gland. The causes of prostate cancer are largely unknown. But certain things can increase the risk of developing the condition.[6] Risk factors for developing prostate cancer include increasing age, black ethnicity and family history of prostate cancer. Symptoms of prostate cancer can include lower back or bone pain, lethargy, erectile dysfunction, haematuria, anorexia/weight loss and lower urinary tract symptoms such as frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder.[7] Non-metastatic prostate cancer is cancer that has not spread to another part of the body and it includes localised and locally advanced cancer.[8,9] Locally advanced cancer has broken through the capsule of the prostate gland and may have spread into areas such as the tissue around the prostate.[8]

Prostate cancer is the most common cancer in males in the UK, accounting for 27% of all new cancer case in males (2016-18). In females and males combined, prostate cancer is the 2nd most common cancer in the UK, accounting for 14% of all new cancer cases (2016-2018). The age standardised incidence rate of prostate cancer in England is 186.4 per 100,000 amongst males.[10] In England (2020-21), there were 60,023 finished consultant episodes (FCEs) and 55,799 admissions for malignant neoplasm of prostate (ICD-10 code C61), which resulted in 39,040 day cases and 58,293 FCE bed days.[11]

In England (2017), there were 41,201 patients diagnosed with malignant neoplasm of prostate and 10,146 deaths registered where malignant neoplasm of prostate was the underlying cause.[12] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for prostate cancer in men were 96.6% and 86.6% respectively.[13]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends active surveillance, radical prostatectomy or radical radiotherapy for the treatment of localised prostate cancer.[14]

The following therapies may also be offered to people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer:[14]

- A combination of radical radiotherapy and androgen deprivation therapy
- 6 months of androgen deprivation therapy before, during or after radical external beam radiotherapy
- Brachytherapy in combination with external beam radiotherapy

Clinical Trial Information

Trial	**EMBARK, NCT02319837, 2014-001634-28;** A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy **Phase III** – Active, not recruiting **Locations:** 10 EU countries, UK, USA, Canada and other countries **Primary completion date:** August 2022
Trial Design	Randomized, parallel assignment, quadruple-blinded, active-controlled

Population	N=1068 (actual); Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features; Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent; Aged 18 years and older
Intervention(s)	- Enzalutamide (160mg) monotherapy administered as four 40-mg capsules by mouth once daily - Enzalutamide (160 mg) administered as four 40-mg capsules by mouth once daily in combination with leuprolide administered as as a single intramuscular or subcutaneous injection once every 12 weeks
Comparator(s)	Enzalutamide placebo (placebo) capsules (identical in appearance to enzalutamide) administered as 4 capsules by mouth once daily in combination with leuprolide administered as a single intramuscular or subcutaneous injection once every 12 weeks
Outcome(s)	**Primary outcome:** - Metastasis-free survival (MFS) [Time frame: up to approximately 90 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Enzalutamide is already marketed in the UK; a pack of 112 x 40mg tablets costs £2,734.67.[15]

Relevant Guidance

NICE Guidance

- NICE guideline. Prostate cancer: diagnosis and management (NG131). May 2019.
- NICE quality standard. Prostate cancer (QS91). June 2015.
- NICE interventional procedures guidance. Focal therapy using cryoablation for localised prostate cancer (IPG423). April 2012.
- NICE interventional procedures guidance. Cryotherapy for recurrent prostate cancer (IPG119). May 2005.

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

- European Association of Urology. Prostate Cancer. 2022.[16]
- Spanish Society for Medical Oncology. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). May 2021.[17]
- European Society for Medical Oncology (ESMO). Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2020.[18]

Additional Information

References

1 Clinicaltrials.gov. *Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer (EMBARK)*. *Trial ID: NCT02319837*. 2014. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02319837 [Accessed 7 June 2022].

2 Electronic Medicines Compendium. *Xtandi 40 mg film coated tablets (Great Britain).* 2022. Available from: https://www.medicines.org.uk/emc/product/10318/smpc [Accessed 7 June 2022].

3 Freedland SJ, De Giorgi U, Gleave M, Rosbrook B, Shen Q, Sugg J, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design. *BMJ Open*. 2021;11(8):e046588. Available from: https://doi.org/10.1136/bmjopen-2020-046588.

4 Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol*. 2014;15(6):592-600. Available from: https://doi.org/10.1016/s1470-2045(14)70129-9.

5 Clinicaltrials.gov. *Search of: Enzalutamide.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?cond=&term=enzalutamide&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 9 June 2022].

6 National Health Service. *Prostate cancer: overview.* 2021. Available from: https://www.nhs.uk/conditions/prostate-cancer/ [Accessed 7 June 2022].

7 National Institute for Health and Care Excellence. *Prostate cancer.* 2022. Available from: https://cks.nice.org.uk/topics/prostate-cancer/ [Accessed 7 June 2022].

8 Cancer Research UK. *Locally advanced prostate cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/stages/locally-advanced-prostate-cancer [Accessed 9 June 2022].

9 Cancer Research UK. *Localised prostate cancer.* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/stages/localised-prostate-cancer [Accessed 9 June 2022].

10 Cancer Research UK. *Prostate cancer incidence statistics.* 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence [Accessed 7 June 2022].

11 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 7 June 2022].

12 Office for National Statistics. *Cancer registration statistics, England.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsa

nddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 7 June 2022].

13 Office for National Statistics. *Cancer survival in England - adults diagnosed.* 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 9 June 2022].

14 National Institute for Health and Care Excellence. *Prostate cancer: diagnosis and management* (*NG131)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng131/resources/prostate-cancer-diagnosis-and-management-pdf-66141714312133 [Accessed 9 June 2022].

15 National Institute for Health and Care Excellence. *Enzalutamide: Medicinal forms.* Available from: https://bnf.nice.org.uk/drugs/enzalutamide/medicinal-forms/ [Accessed 7 June 2022].

16 European Association of Urology. *Prostate Cancer.* 2022. Available from: https://uroweb.org/guidelines/prostate-cancer/chapter/introduction [Accessed 9 June 2022].

17 González del Alba A, Méndez-Vidal MJ, Vazquez S, Castro E, Climent MA, Gallardo E, et al. SEOM clinical guidelines for the treatment of advanced prostate cancer (2020). *Clinical and Translational Oncology*. 2021;23(5):969-79. Available from: https://doi.org/10.1007/s12094-021-02561-5.

18 Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2020;31(9):1119-34. Available from: https://doi.org/10.1016/j.annonc.2020.06.011.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.