

**NIHR Innovation Observatory  
Evidence Briefing: September 2017****Enzalutamide (Xtandi) for non-metastatic  
castration resistant prostate cancer**

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**LAY SUMMARY**

Prostate cancer is 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 of prostate cancer; localised, locally-advanced and advanced prostate cancer. Non-metastatic prostate cancer is a type of localised cancer that has not spread to other parts of the body. Symptoms may not appear for many years because it develops slowly, however they can include difficulty or more frequent passing of urine, feeling of not completely emptying bladder and blood in urine or semen.

Enzalutamide (Xtandi) is a drug which blocks the effect of the hormone testosterone on the prostate and so slows down the growth of the cancer. Enzalutamide is taken as four capsules once a day. If licenced in the UK, it could provide an additional treatment option for patients with non-metastatic castration resistant prostate cancer.

*This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Castration resistant prostate cancer, non-metastatic.

## TECHNOLOGY

### DESCRIPTION

Enzalutamide (Xtandi) is a hormone therapy drug classed as a potent androgen receptor signalling inhibitor which blocks the effects of testosterone, a male hormone that cancer of the prostate depends on. It does this by targeting the androgen receptors to which the hormone attaches and prevents them from responding to natural testosterone. By blocking the action of testosterone, enzalutamide slows down the growth of the cancer.<sup>1</sup>

In the ongoing phase III trial, enzalutamide was administered orally in capsule formulation as four 40mg capsules once daily for up to 37 weeks.<sup>2</sup>

Enzalutamide is currently licensed in the EU for metastatic hormone refractory (castration resistant, androgen-independent) prostate cancer.<sup>3</sup> Recognised common adverse effects ( $\geq 10\%$ ) of enzalutamide are falls, broken bones, feeling anxious, dry skin, itching, memory problems, breast enlargement in men (gynaecomastia), symptom of restless legs syndrome (an uncontrollable urge to move a part of the body, usually the leg), reduced concentration and forgetfulness.<sup>4</sup>

Enzalutamide is currently in phase II trials in the EU for hepatocellular carcinoma and in phase III trials in the EU for hormone refractory, castration-resistance, androgen dependant prostate cancer and hormone sensitive prostate cancer.<sup>5</sup>

## INNOVATION and/or ADVANTAGES

If licensed, enzalutamide will offer an additional treatment option for patients with non-metastatic castration resistant prostate cancer. It is approved by the U.S. Food and Drug Administration and in Europe for the treatment of patients with metastatic castrate-resistant prostate cancer (CRPC), based on clinical studies showing statistically significant overall survival benefit versus placebo.<sup>6</sup>

## DEVELOPER

Pfizer, and Astellas Pharma Inc

## 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 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 very rare in Asian men. More than half of those diagnosed are aged 70 years and over.<sup>7</sup> There are three stages of prostate cancer; non-

metastatic or localised (confined to the prostate gland), locally-advanced (spread outside the capsule of the gland) and advanced prostate cancer (spread to other body organs).<sup>8</sup>

Non-metastatic prostate cancer is defined as cancer with no evidence of metastasis and at least one of the following three criteria: A Gleason score no higher than 6, prostate-specific antigen (PSA) level less than 10ng/ml or a local clinical stage between T1 and T2a.<sup>9</sup> A Gleason score is a system of grading prostate cancer tissue based on its microscopic appearance. The scores range from 2 to 10 with a higher score indicating that it is more likely to spread. A PSA test measures the amount of PSA in the blood and a raised level can be a sign of a problem with the prostate.<sup>10</sup> PSA doubling time is an important measure for disease activity and can be used to find patients who are at higher risk for adverse outcome. The clinical stage describes the size of the tumour (T) ranging from T1 (cancer is too small to be seen on a scan, or felt during examination of the prostate) to T4 (cancer has spread into other body organs).<sup>11</sup>

Because the cancer develops slowly, people often have no signs in the early stages and symptoms only become apparent when the prostate is large enough to affect the urethra. General symptoms of prostate cancer include: urinary tract infection, urinary frequency, sensation of incomplete emptying, haematuria (presence of blood in urine), dysuria (painful urination), haemospermia (blood in sperm), symptoms of acute kidney injury or chronic kidney disease and impotence.<sup>8</sup> Various risk factors for prostate cancer have been identified, including ageing, black ethnic origin and a family history.<sup>12</sup> Other factors include diet, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure.<sup>8</sup>

## CLINICAL NEED and BURDEN OF DISEASE

For the UK, the age-standardised incidence of prostate cancer was 175 per 100,000 in 2014 and the lifetime risk of being diagnosed with prostate cancer was estimated to be 1 in 8.<sup>13</sup>

For men (aged 15-99) in England and Wales diagnosed with prostate cancer, 85% will survive five years or more after diagnosis.<sup>14</sup>

In 2015, there were 63,964 admissions for prostate cancer (ICD-10 C61) in England, resulting in 102,107 bed days and 68,578 finished consultant episodes.<sup>15</sup> In the UK, prostate cancer is the second most common cause of cancer death, with around 11,300 deaths reported in 2014.<sup>16</sup>

In 2017, the population likely to be eligible to receive enzalutamide is estimated to be around 1.19% of men aged 40 and above.

## 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 January 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, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *European urology*. 2017 Apr 30;71(4):618-29.
- Gnanapragasam VJ, Payne H, Syndikus I, Kynaston H, Johnstone T. Primary radical therapy selection in high-risk non-metastatic prostate cancer. *Clinical Oncology*. 2015 Mar 31;27(3):136-44.
- Parker C, Gillissen S, Heidenreich A, Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015 Jul 22;26 (suppl\_5):v69-77

## CURRENT TREATMENT OPTIONS

There are several treatment options available to those with non-metastatic castration resistant prostate cancer. Many men with localised prostate cancer will not benefit from definitive treatment, and 45% of men with PSA-detected prostate cancer are candidates for deferred management (watchful waiting). In men with comorbidity and limited life expectancy, treatment of localised prostate cancer may be deferred to avoid loss of quality of life.<sup>8</sup> Treatment recommendations are dependent on the disease and patient characteristics. Guidelines recommend the use of:<sup>13</sup>

- Watchful waiting or observation

- Radical prostatectomy (surgical removal of the entire prostate gland between the urethra and bladder)
- External beam radiotherapy
- Brachytherapy (trans-perineal implantation of radioactive seeds into the prostate)
- Cryotherapy (local or general use of low temperatures in medical therapy)
- Hormone therapy (androgen deprivation or anti-androgens)

## EFFICACY and SAFETY

<b>Trial</b>	PROSPER, NCT02003924, MDV3100-14; adult male; enzalutamide vs placebo; phase III
<b>Sponsor</b>	Pfizer
<b>Status</b>	Recruitment has stopped
<b>Source of Information</b>	Trial registry <sup>17</sup>
<b>Location</b>	EU (incl UK), USA, South America, Asia, Australia and Oceania
<b>Design</b>	Randomized, double blind, placebo controlled study
<b>Participants</b>	N=1440 (planned); 18 years and older; males; prostate cancer; non-metastatic castration-resistant; progressing after definitive therapy; second line
<b>Schedule</b>	Randomised to placebo or enzalutamide 160 mg by mouth once daily up to 16 weeks
<b>Follow-up</b>	Not reported
<b>Primary Outcomes</b>	Metastasis free survival (MFS): $\geq 16$ weeks
<b>Secondary Outcomes</b>	Overall survival: $\geq 16$ weeks; Time to pain progression: $\geq 16$ weeks; Time to opiate use for prostate: $\geq 16$ weeks; Time to first use of cytotoxic: $\geq 16$ weeks; Time to first use of new antineoplastic therapy: $\geq 16$ weeks; Time to prostate-specific antigen (PSA) progression: $\geq 16$ weeks; FACT-P global score: $\geq 16$ weeks; Quality of life as assessed by EQ-5D-5L and QLQ-PR25: $\geq 16$ weeks
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	-

## ESTIMATED COST and IMPACT

### COST

Enzalutamide is already marketed individually in the UK for use before chemotherapy for men with advanced prostate cancer which is no longer responding to hormone treatment; a pack of 112 x 40mg capsules costs £2,735 and the unit cost per capsule costs £24.<sup>18</sup>

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability: <i>a potential improvement in quality of life</i> |
| <input type="checkbox"/> Other   | <input type="checkbox"/> No impact identified   |

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- |   |   |
|---|---|
| <input type="checkbox"/> Increased use of existing services   | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services              |
| <input type="checkbox"/> Other                                | <input checked="" type="checkbox"/> None identified         |

### IMPACT ON COSTS and OTHER RESOURCE USE

- |  |   |
|--|---|
| <input type="checkbox"/> Increased drug treatment costs          | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs                 | <input type="checkbox"/> Other reduction in costs     |
| <input checked="" type="checkbox"/> Other: <i>uncertain cost</i> | <input type="checkbox"/> None identified              |

### OTHER ISSUES

- |   |   |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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<sup>2</sup> ClinicalTrials.gov. *Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer (EMBARK)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02319837> [Accessed 11 July 2017]

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