

**NIHR Innovation Observatory
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Darolutamide 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: localised, locally-advanced and advanced (or metastatic) prostate cancer. The symptoms may vary depending on the stage of cancer but can include pain, tiredness, 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. becoming metastatic). Prostate cancer growth and spread depends on the hormone, testosterone. Cancer that do not respond to hormonal treatment to reduce the level of testosterone are known as castration-resistant prostate cancer.

Darolutamide is a hormonal drug under development for castration-resistant prostate cancer that has not spread (non-metastatic). It acts by blocking testosterone receptors from getting activated on the cancer cells and consequently reducing the size of the cancer. Darolutamide is taken orally twice a day. If licenced, darolutamide will provide an additional treatment option for men with non-metastatic castration-resistant prostate cancer that are at high risk of their cancer spreading to other parts of the body.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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

Non-metastatic, castration-resistant prostate cancer (nmCRPC); high risk as defined by a prostate specific antigen (PSA) doubling time of ≤ 10 months – first line

TECHNOLOGY

DESCRIPTION

Darolutamide (ODM-201, BAY-1841788) is a novel nonsteroidal androgen receptor (AR) inhibitor with potential antineoplastic activity. AR antagonist darolutamide binds to ARs in target tissues; subsequently, inhibiting androgen-induced receptor activation and facilitating the formation of inactive complexes that cannot translocate to the nucleus. This prevents binding to, and transcription of, AR-responsive genes that regulate prostate cancer cell proliferation. This ultimately leads to an inhibition of growth in AR-expressing prostate cancer cells.¹

Darolutamide is under development for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC).¹ The medicinal product is administered orally and the proposed place in treatment is as an add-on to standard therapy.

In the currently ongoing phase III trial, darolutamide is administered twice a day in 300 mg tablets (x2) until unacceptable toxicity, confirmed metastasis or death.¹⁹

This product is not currently licenced in the EU for any indication.

Darolutamide is also at phase III in clinical trials for metastatic hormone sensitive prostate cancer.²

INNOVATION and/or ADVANTAGES

If licensed, darolutamide will offer an additional treatment option for high risk non-metastatic castration-resistant prostate cancer patients; darolutamide has the potential to increase the metastasis-free survival time.

DEVELOPER

Bayer plc.

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.³ 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), haematospermia (blood in sperm), symptoms of acute kidney injury or chronic kidney disease and impotence.⁶ Various risk factors for prostate cancer have been identified, including ageing, black ethnic origin and a family history.⁴ Other factors include diet, pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure.⁶

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).⁵ At an advanced stage the cancer most commonly spreads to lymph nodes in other parts of the body or to the bones. It can also spread to other organs.⁶ About 50% of men diagnosed with localised prostate cancer will get metastatic cancer during their lifetime. Finding cancer early and treating it can lower that risk.⁷

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). Usually, the earliest sign of resistance to ADT is a rising serum PSA level before metastases are detectable. A raised level of PSA in the blood can be a sign of a problem with the prostate.⁸

Men at high-risk of developing metastases can be identified by a short PSA doubling time (PSADT). For patients with a PSADT \leq 10 months, treatment is recommended, with the goal of delaying time to development of metastases.⁹

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 the Prostate-specific Antigen (PSA) tests and the population is getting older. In adults, prostate cancer is the second most common cancer in the UK. In men, it is the most common cancer in the UK.¹⁰ In 2016, 40,484 men were newly diagnosed with prostate cancer¹¹ and 10,178 deaths from prostate cancer were recorded.¹² About nine in 10 (85%) men diagnosed with prostate cancer in England and Wales survived their disease for five years or more (2010-11).¹³

Using ONS population projections, the company estimated that in 2016 in England and Wales there would have been 41,768 cases of prostate cancer. For the UK, it is estimated that 11.2% of patients progress to non-metastatic CRPC (nmCRPC) this gives an estimate of 4,590 patients in England and Wales and a total of 5,141 including the population of Scotland and Northern Ireland.¹⁴ The proportion of nmCRPC patients classified as high risk (PSA doubling time \leq 10 months) is 16% (Bayer data on file). The eligible UK patient population to receive darolutamide would equate to 16%*5,141=823 patients.^a

The Hospital Episodes Statistics for 2016/2017 recorded 75,276 finished consultant episodes (FCE), 70,295 admissions and 97,382 FCE bed days for malignant neoplasm of the prostate (ICD-10 code C61). 48,567 of these admissions were day cases.¹⁵

^a Information provided by company in UK PharmaScan record

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.

OTHER GUIDANCE

- Mottet N et al. TB. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. 2017¹⁶
- Gnanapragasam VJ et al. Primary radical therapy selection in high-risk non-metastatic prostate cancer. 2015¹⁷
- Parker C et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015¹⁸

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.⁸ Guidelines recommend the use of:¹⁶

- 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)

Treatment recommendations are dependent on the disease and patient characteristics, currently there is no standard treatment for castrated patients with rising PSA and no evidence of metastases.

EFFICACY and SAFETY

Trial	ARAMIS, NCT02200614; darolutamide vs placebo; phase III
Sponsor	Bayer plc
Status	Ongoing, recruiting
Source of Information	Trial registry ¹⁹
Location	EU countries (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled
Participants	n=1500 (planned); aged 18 years or older; male; prostate cancer; castration-resistant with castrate level of serum testosterone; prostate-specific antigen doubling time of ≤ 10 months and PSA > 2ng/ml
Schedule	Randomised to: <ul style="list-style-type: none"> • Arm 1: Darolutamide (BAY1841788; ODM-201) tablets 2 x 300mg twice a day, orally • Arm 2: Matching placebo tablets x 2 twice a day, orally
Follow-up	Until unacceptable toxicity, confirmed metastasis or death
Primary Outcomes	Metastasis-Free Survival (up to 72 months)
Secondary Outcomes	<ul style="list-style-type: none"> • Overall Survival (up to 72 months) • Time to first symptomatic skeletal event (up to 72 months) • Time to initiation of first cytotoxic chemotherapy for prostate cancer (up to 72 months) • Time to pain progression (up to 72 months) • Safety and tolerability (up to 72 months) • Changes in health-related QoL are assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P), European Organization for Research and Treatment of Cancer Quality of life Questionnaire – Prostate Cancer Module (EORTC-QLQ-PR25) and European QoL 5-domain scale (EQ-5D-3L) questionnaire.^b
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date 16 th April 2018, study estimated completion date 30 th June 2020.

^b Information provided by company

ESTIMATED COST and IMPACT

COST

The cost of darolutamide is not yet known.

The following anti-androgens are currently marketed and used in the prostate cancer broader population in the UK.^{20,21,22}

Drug	Dose	Unit cost
Xtandi (enzalutamide) 40 mg capsules	160 mg once daily	£24.40
Casodex (bicalutamide) 150mg tablets	150 mg once daily	15p

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: *improved quality of life for patients*
- 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: *trial results not yet published* None identified

REFERENCES

- ¹ GlobalData. *Darolutamide*. Available from <https://pharma.globaldata.com/> [Accessed 19 January 2018, log in required]
- ² ClinicalTrials.gov. *ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer (ARASENS)*. Available from <https://clinicaltrials.gov/ct2/show/NCT02799602> [Accessed 19 January 2018]
- ³ Cancer Research UK. *About Prostate Cancer*. Available from: <http://www.cancerresearchuk.org/about-cancer/prostate-cancer/about> [Accessed 19 January 2018]
- ⁴ Wilt TJ, Ahmed HU. Prostate cancer screening and the management of clinically localized disease. *BMJ*. 2013 Jan 29;346:f325.
- ⁵ European Association of Urology. *Prostate Cancer: Epidemiology and Aetiology*. Available from: <http://uroweb.org/guideline/prostate-cancer/#3> [Accessed 19 January 2018]
- ⁶ Cancer Research UK. *About advanced prostate cancer*. <http://www.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/about-advanced-cancer> [Accessed 19 January 2018]
- ⁷ WebMD. *What is metastatic prostate cancer?* Available from <http://www.webmd.com/prostate-cancer/advanced-prostate-cancer-16/metastatic-prostate-cancer> [Accessed 19 January 2018]
- ⁸ Pullar B, Shah N. Prostate Cancer. *Surgery (Oxford)*. 2016 Oct; 34(10): 505-511. Available from doi.org/10.1016/j.mpsur.2016.07.007 [Accessed 15 February 2018]
- ⁹ Anantharaman A, Small EJ. Tackling non-metastatic castration-resistant prostate cancer: special considerations in treatment. *Expert review of anticancer therapy*. 2017 Jul 3;17(7):625-33. Available from DOI: 10.1080/14737140.2017.1333903 [Accessed 15 February 2018]
- ¹⁰ Cancer Research UK. *Prostate cancer*. Available from <http://www.cancerresearchuk.org/about-cancer/prostate-cancer> [Accessed 19 January 2018]
- ¹¹ Office for National Statistics. *Cancer Registration Statistics, England, 2016*. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland> [Accessed 15 February 2018]
- ¹² Office for National Statistics. *Death Registrations Summary Statistics, England and Wales, 2016*. Available from <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables> [Accessed 15 February 2018]
- ¹³ Cancer Research UK. *Prostate Cancer Survival*. Available from <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Two> [Accessed 19 January 2018]
- ¹⁴ Morgan C, McEwan P, Chamberlain G, Cabrera C, Parry D. Castration –resistant prostate cancer (CRPC): A UK epidemiology study. *Value in health*, S1098-3015(10)72108-2 Available from [http://www.valueinhealthjournal.com/article/S1098-3015\(10\)72108-2/pdf](http://www.valueinhealthjournal.com/article/S1098-3015(10)72108-2/pdf) [Accessed 19 January 2018]
- ¹⁵ NHS Digital. *Hospital Admitted Patient Care Activity, 2016-17*. Available from: <https://digital.nhs.uk/catalogue/PUB30098> [Accessed 19 January 2018].
- ¹⁶ 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. Available from doi.org/10.1016/j.eururo.2016.08.003 [Accessed 15 February 2018]

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- ¹⁷ 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. Available from DOI: 10.1177/2051415816651362 [Accessed 15 February 2018]
- ¹⁸ Parker C, Gillessen 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
- ¹⁹ ClinicalTrials.gov. *Efficacy and Safety Study of BAY1841788 (ODM-201) in Men with High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS)*. Available from <https://clinicaltrials.gov/show/NCT02200614> [Accessed 19 January 2018]
- ²⁰ Prostate Cancer UK. *Tablets to block the effects of testosterone (anti-androgens)*. Available from <https://prostatecanceruk.org/prostate-information/treatments/hormone-therapy> [Accessed 19 January 2018]
- ²¹ National Institute for Health and Care Excellence. *Enzalutamide*. Available from <https://bnf.nice.org.uk/drug/enzalutamide.html> [Accessed 6 February 2018]
- ²² National Institute for Health and Care Excellence. *Bicalutamide*. Available from <https://bnf.nice.org.uk/drug/bicalutamide.html#hepaticimpairment> [Accessed 6 February 2018]