Health Technology Briefing
April 2024

Darolutamide with androgen deprivation therapy for metastatic hormone sensitive prostate cancer

Company/Developer	Bayer AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31253	NICE ID: Not available	UKPS ID: 673281

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Darolutamide with androgen deprivation therapy (ADT) is in clinical development to treat prostate cancer that is metastatic (has spread to another part of the body) and hormone-sensitive, where the cancer is controlled by lowering levels of the hormone testosterone. Prostate cancer affects the prostate (a small gland only found in men), but symptoms generally do not appear until it is large enough to affect the urethra (the tube connecting the bladder to outside the body). Only 50% of patients diagnosed with metastatic hormone sensitive prostate cancer (mHSPC) survive five years or more after diagnosis. Therefore, treatment is focused on controlling further spread and managing symptoms. Treatments for mHSPC include chemotherapy, hormone therapy and radiotherapy, but these can be associated with significant adverse side effects.

Androgens are hormones that promote prostate cancer growth and are often targeted as part of prostate cancer therapy using ADTs and/or androgen receptor inhibitors. Darolutamide is an androgen receptor inhibitor. This means that it binds to androgen receptors and blocks them from stimulating the growth of prostate cancer cells. ADT refers to any therapy that reduces testosterone production or inhibits androgen receptors. Darolutamide is potentially associated with fewer significant side effects than other androgen receptor inhibitors, due to its lower blood-brain barrier penetration, which reduces the risk of seizures. Darolutamide is taken as an oral tablet. If licenced, darolutamide with ADT may offer an additional treatment option to patients with mHSPC and may improve survival.

Proposed Indication

For the treatment of metastatic hormone sensitive prostate cancer (mHSPC).[1]

Technology

Description

Darolutamide (NUBEQA;, BAY1841788) is a novel nonsteroidal androgen receptor (AR) inhibitor.[1,2] Androgen receptor signalling promotes prostate cancer growth.[2] Competitive inhibition of androgen receptors prevents nuclear translocation and androgen receptor-mediated transcription, therefore decreasing prostate cancer cell proliferation and tumour size.[4] Darolutamide can inhibit tumour growth by binding to the androgen receptor and its mutants (e.g. W742L and F877L) with high affinity and specificity.[3]

Darolutamide with ADT is in phase III clinical development for the treatment of adult males (18 years or older) with mHSPC.[1] In the phase III trial ARANOTE (NCT04736199), participants received 600mg of darolutamide (2 tablets of 300mg) capsules twice daily in addition to the investigator's choice of ADT.[1]

Key Innovation

The addition of darolutamide into the treatment regime with ADT may prolong survival of patients with mHSPC and delay the need for further treatments.[5,6] Darolutamide has demonstrated good tolerability, with many reported adverse events thought to be disease-related rather than drug-related.[6,7] This is because darolutamide has negligible blood-brain barrier penetration, which reduces the risk of seizures associated with other androgen receptor inhibitors.[7] This is predicted to result in a lower incidence of adverse events compared to other similar treatments as observed in a number of indirect treatment comparison studies.[8,9] If licensed, darolutamide will provide an additional treatment option for patients with mHSPC.

Regulatory & Development Status

Darolutamide has marketing authorisation in the UK/EU for the treatment of:[4]

- non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease
- mHSPC in combination with docetaxel

Darolutamide with ADT is also in phase III development for hormone-sensitive prostate cancer with high-risk biochemical recurrence (ARASTEP NCT05794906).[10]

Patient Group

Disease Area and Clinical Need

Prostate cancer affects the prostate, which is a small gland in the pelvis only found in men.[11] Prostate cancer occurs when abnormal cells start to divide and grow in an uncontrolled manner.[12] The symptoms of prostate cancer generally do not appear until the prostate is large enough to affect the urethra, causing an increased need to urinate (especially at night), difficulty in starting to urinate, straining when urinating, weak urine flow, the feeling that the bladder has not fully emptied, and blood in the urine or semen.[13] Metastatic prostate cancer is when the cancer spreads from the prostate gland to another part of the body. Some common symptoms include bone pain, fatigue, feeling generally unwell and weight loss.[14] Prostate

cancer can be 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).[15] When the cancer has spread to other parts of the body but still responds to ADT, it is defined as mHSPC.[16]

Between 2016-2018, prostate cancer was the most common cancer in men, accounting for 27% of new cancer cases in men in the UK.[17] In England in 2020, there were 36,016 newly diagnosed registered cases of malignant neoplasms of the prostate (ICD10 code: C61) and the directly age-standardised incidence rate in males was 143.8 per 100,000.[18] 20-30% of cases of prostate cancer are metastatic, meaning 7,203-10,805 cases of prostate cancer are metastatic .[19] In England (2022-23), there were 86,381 finished consult episodes (FCEs) and 81,717 admissions for neoplasms of the prostate, resulting in 61,419 day cases and 78,764 FCE bed days.[20] In England (2017-2019), there were 12,039 deaths from prostate cancer.[17] For patients diagnosed between 2013-2017 in England, prostate cancer survival for 10 or more years was 78%.[17]

Recommended Treatment Options

Treatment options recommended by NICE for mHSPC patients include:[21-24]

- Docetaxel chemotherapy plus ADT
- Anti-androgen monotherapy with bicalutamide
- Androgen deprivation therapy
- Enzalutamide plus ADT
- Apalutamide plus ADT
- Darolutamide plus ADT and docetaxel

Clinical Trial Information

Trial	**ARANOTE,** NCT04736199; **EudraCT** 2020-003093-48**,** A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Darolutamide in Addition to Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Men With Metastatic Hormone-sensitive Prostate Cancer (mHSPC) **Phase III** – Active, not recruiting **Locations:** Three EU countries, Canada and 11 other countries. **Primary Completion Date:** 15 March 2024
Trial Design	Randomised; parallel assignment; quadruple blinded
Population	N=662 (actual); subjects aged 18 and over with histologically confirmed adenocarcinoma of the prostate.
Intervention(s)	300mg darolutamide administered orally, twice daily with food, and ADT of the investigator's choice
Comparator(s)	Matched placebo.
Outcome(s)	Radiological progression-free survival. [Time Frame: time from the date of randomisation to the date of first documentation of radiological progressive disease or death due to any cause (estimated 36 months)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of 112 x 300mg tablets of darolutamide is £4,040.00.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Relugolix for treating hormone sensitive prostate cancer (TA11141). Expected date of issue to be confirmed.
- Technology appraisal guidance. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. (TA903). June 2023.
- Technology appraisal guidance. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer. (TA741). October 2021.
- Technology appraisal guidance. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. (TA721). August 2021.
- Technology appraisal guidance. Enzalutamide for treating hormone-sensitive metastatic prostate cancer. (TA712). July 2021.
- NICE clinical guideline. Prostate cancer: diagnosis and management. (NG131). May 2019
- NICE quality standard. Prostate cancer. (QS91). June 2015.

NHS England (Policy/Commissioning) Guidance

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- NHS England. Clinical Commissioning Policy: Proton Beam Therapy for Cancer of the Prostate. 16020/P. July 2016.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult), B15/S/a.
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Other Guidance

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Additional Information

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