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HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Darolutamide in addition to docetaxel and androgen deprivation therapy for metastatic hormone-sensitive prostate cancer

NIHRIO ID	12807	**NICE ID**	10600
Developer/Company	Bayer AG plc	**UKPS ID**	643459

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Darolutamide in addition to docetaxel and androgen deprivation therapy (ADT) is in clinical development for the treatment of patients with metastatic hormone-sensitive prostate cancer. Prostate cancer affects the prostate (a small gland in the pelvis only found in men), but symptoms generally do not appear until the prostate is large enough to affect the urethra (the tube connecting the bladder to outside the body). Metastatic prostate cancer is when the cancer spreads to another part of the body. Common symptoms of metastatic prostate cancer include bone pain and fatigue.

Androgen receptors promote prostate cancer growth, darolutamide is a nonsteroidal androgen receptor inhibitor and can prevent cancer growth. Docetaxel in combination with ADT are commonly used in practice, the addition of darolutamide (taken orally) may improve survival and offer an additional treatment option for those patients with metastatic hormone-sensitive prostate cancer.

PROPOSED INDICATION

Darolutamide in addtion to docetaxel and androgen deprivation therapy (ADT) for the treatment of patients with metastatic, hormone-sensitive prostate cancer (mHSPC).[a]

TECHNOLOGY

DESCRIPTION

Darolutamide (NUBEQA; BAY1841788; ODM-201) is a novel nonsteroidal androgen receptor inhibitor.[1] Androgen receptors promote prostate cancer growth.[1] Darolutamide is an androgen receptor antagonist that possesses a unique chemical structure and negligible blood-brain barrier penetration that inhibits tumour growth. This is achieved by binding to the androgen receptor and its mutants (e.g. W742L and F877L) with high affinity and specificity.[2] Docetaxel is a taxane, a chemotherapeutic agent that produce antitumour activity by causing stabilisation of cellular microtubules and inhibits cell division.[3] Androgen deprivation therapy (ADT) reduces serum testosterone to castration levels, thereby depriving prostate cancer cells of the signals required for growth and survival.[1]

Darolutamide in addition to docetaxel and ADT is currently in phase III clinical development for treatment of adult males (≥18 years old) with mHSPC (NCT02799602; ARASENS). During the trial patients are provided with 600mg (2 tablets of 300mg) capsules twice per day (1200mg total) in addition to standard ADT (luteinizing hormone releasing hormone (LHRH) agonist/antagonist or orchiectomy) and 6 cycles of docetaxel.[4]

INNOVATION AND/OR ADVANTAGES

The addition of darolutamide to docetaxel and ADT therapy may allow for an additional treatment option for patients with mHSPC. The addition of darolutamide into the treatment regime may increase overall survival.[1] Additionally, including darolutamide with docetaxel and ADT therapy is not expected to further impact the quality of life of patients in any significant way. Darolutamide has demonstrated a placebo-like tolerability profile in the ARAMIS trial attributed to its unique molecular structure which facilitates a low blood-brain barrier penetration compared to similar androgen receptor inhibitors. 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.[5,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Darolutamide (NUBEQA) is currently licenced as a monotherapy for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease.[7]

Docetaxel is currently licenced as a monotherapy for:[8]

[a] Information provided by Bayer AG plc on UK PharmaScan

- Patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.
- Patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

Docetaxel is currently licenced in combination with:[8]

- Doxorubicin for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.
- Doxorubicin and cyclophosphamide as an adjuvant treatment for patients with operable node positive or negative breast cancer. For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.
- Trastuzumab of the treatment of patients with metastatic breast cancer whose tumours over express HER2 and who previously have not received chemotherapy for metastatic disease.
- Capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.
- Cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.
- Prednisone or prednisolone for the treatment of patients with metastatic castration-resistant prostate cancer.
- Cisplatin and 5 fluorouracil for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.
- Cisplatin and 5 fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

Very common adverse events (frequency ≥ 1/10) of darolutamide as a monotherapy include: fatigue/asthenic conditions, neutrophil count decreased, bilirubin increased, and AST increased.[7]

Very common adverse events (frequency ≥ 1/10) of docetaxel as a single agent for:[8]

- Breast cancer are infections (including sepsis and pneumonia), neutropenia, anaemia, febrile neutropenia, hypersensitivity, anorexia, peripheral sensory neuropathy, peripheral motor neuropathy, dysgeusia, dyspnoea, stomatitis, diarrhoea, nausea, vomiting, alopecia, skin reaction, nail disorders, myalgia, fluid retention, asthenia, and pain.
- Non-small cell lung cancer are infections, neutropenia, anaemia, thrombocytopenia, anorexia, peripheral sensory neuropathy, nausea, stomatitis, vomiting, diarrhoea, alopecia, skin reaction, asthenia, fluid retention, and pain.

Darolutamide is currently in phase III clinical development for men with high-risk nonmetastatic castration resistant prostate cancer, high-risk prostate cancer, and prostatic neoplasms. It is also currently in phase II clinical development for advanced prostate cancer

(detected by PSMA), prostate cancer (including metastatic), breast cancer in females, and for the management of oligoprogressive castration resistant prostate cancer.[9]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer affects the prostate, which is a small gland in the pelvis only found in men. It is located just below the bladder and in front of the rectum, surrounding the urethra, and produces fluid that makes up part of semen.[10] Prostate cancer occurs when abnormal cells start to divide and grow in an uncontrolled manner. This most commonly starts in the outer gland cells of the prostate, known as acinar adenocarcinomas.[11]

The symptoms of prostate cancer generally do not appear until the prostate is large enough to affect the urethra, causing an increased need to pee (especially at night), difficulty in starting to pee, straining when peeing, weak flow, the feeling that the bladder has not fully emptied,[12] and blood in the urine or semen. Metastatic advanced prostate cancer is when the cancer spreads from the prostate gland to another part of the body. Some common symptoms of metastatic advanced prostate cancer including bone pain, fatigue, feeling generally unwell, weight loss for no known reason.[13]

Prostate cancer can be classified into localised (confined to the prostate gland), locally advanced (spread outside the capsule of the prostate gland), and advanced cancer (spread to other parts of the body; also known as metastatic prostate cancer).[14] When the cancer has spread to other parts of the body (advanced) but still responds to ADT it is defined as mHSPC.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Prostate cancer is the most common cancer in men in the UK.[16] Approximately, in the UK, 1 in 8 men will be diagnosed with prostate cancer in their lifetime.[17] While the exact causes of prostate cancer are unknown, there are three main risk factors for getting prostate cancer; ageing (≥ 50 years old), family history of prostate cancer (e.g. father or brother), and being of African-Caribbean or African descent.[17]

In 2018 in England, there were 49,810 newly identified malignant neoplasms of the prostate (ICD10: C61).[18] Of these cancers, 11,889 (23.9%) were locally advanced prostate cancer (stage III), and 8,442 (17%) had spread from the prostate (stage IV).[19] When standardised by age in England (2018), there was a rate of 204 incidences per 100,000 person-years.[20] The European-age standardised incidence rate of prostate cancer is projected to increase by 2035 from 208 per 100,000 in 2014 to 232 per 100,000 (number of projected cases equivalent to 77,348).[21]

In England and Wales (2019), there were 10,872 recorded deaths due to malignant neoplasm of the prostate (ICD10: C61).[22] Survival statistics for patients diagnosed between 2013 and 2017 show a 1-year net survival rate of 88.3% and a 5-year net survival rate of 49% for men diagnosed with advanced (stage IV) prostate cancer.[23] The European-age standardised mortality rates for prostate cancer by 2035 is predicted to decrease from 57 per 100,000 to 47 per 100,000 (number of projected deaths equivalent to 18,336).[21]

According to the Hospital Episode Statistics (HES) data for England, in 2019-20 there were 80,002 admissions with a primary diagnosis of neoplasm of the prostate (ICD10: C61) and 85,244 finished consultant episodes.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of prostate cancer is dependent upon the stage of the cancer and the general health of the patient. Advanced stages of prostate cancer treatment aim to control the cancer and relieve symptoms. Treatment generally includes chemotherapy, hormone therapy, radiotherapy, steroids and symptom control (e.g. treatments to help with bone pain).[25] Hormone therapy, also known as androgen suppression therapy, aims to lower androgen levels and make prostate cancer shrink or grow more slowly.[26]

CURRENT TREATMENT OPTIONS

For people with metastatic prostate cancer NICE recommendations advise the following:[27]

- Offer docetaxel chemotherapy for newly diagnosed metastatic prostate cancer, if patient does not have significant comorbidities. Starting within 12-weeks of commencing ADT and use six 3-weekly cycles at a dose of 75mg/m^2 (with or without daily prednisolone).
- Offer bilateral orchidectomy to all people with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy.
- Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. For people who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide (150mg). Begin ADT and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function.
- Degarelix as an option for treating advanced hormone-dependent prostate cancer in people with spinal metastases, only if the commissioner can achieve at least the same discounted drug cost as that available to the NHS in June 2016.

For people with hormone-relapsed metastatic prostate cancer NICE recommendations advise the following options of treatment if bone metastasis is present:[28]

- Spinal MRI if patient has extensive metastases to the spine.
- Zoledronic acid to prevent or reduce skeletal-related events.
- Bisphophonates (oral or intravenous) for pain relief, when other treatments (incl. analgesics and palliative radiotherapy) have not given satisfactory pain relief.
- Radium-223 dichloride if they have already had docetaxel or docetaxel is contraindicated/not suitable for them. Only recommended if the company provides it with the discount agreed in the patient access scheme.

For people with hormone-relapsed metastatic prostate cancer NICE recommendations advise the following options of treatment before chemotherapy is indicated:[29]

- Corticosteriods, such as dexamethasone (0.5mg daily), as a third-line hormonal therapy after ADT and anti-ADT are recommended.
- Abiraterone in combination with prednisone or prednisolone is recommended, in people who have no or mild symptoms after ADT has failed, and before chemotherapy. Only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.
- Enzalutamide is recommended in people who have no or mild symptoms after ADT has failed and before chemotherapy is indicated. Only when the company provides it with the discount agreed in the patient access scheme.

Docetaxel is recommended for the treatment of hormone-refractory metastatic prostate cancer, only if their Karnofsky performance status score is 60% or more.[30]

PLACE OF TECHNOLOGY

If licenced, darolutamide in addition to docetaxel and ADT would offer an alternative treatment option for patients with mHSPC.

CLINICAL TRIAL INFORMATION

Trial	**ARASENS; NCT02799602; A randomized, double-blind, placebo controlled phase III study of Darolutamide (ODM-201) versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone sensitive prostate cancer.** **Phase III – Active, not recruiting** **Locations – Number of EU countries, UK, USA, Canada, and other countries** **Estimated Primary Completion Date – October 2021**
Trial design	Randomized, parallel assignment, quadruple blinding.
Population	*N* = 1303 (actual), men aged 18 years or older with histologically or cytologically confirmed adenocarcinoma of prostate that is metastatic. They are candidates for ADT and docetaxel, may have started ADT with or without first generation anti androgen, but no longer than 12-weeks before randomization. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and have adequate bone marrow, liver, and renal function.
Intervention(s)	Participants receive 600mg (2 oral tablets of 300mg) of darolutamide twice daily with food (1200mg daily dose), in addition to standard ADT (luteinizing hormone releasing hormone (LHRH) agonist/antagonist or orchiectomy) and 6 cycles of docetaxel.
Comparator(s)	Participants receive a placebo matching the darolutamide tablets in appearance (oral), in addition to standard ADT (LHRH agonist/antagonist or orchiectomy) and 6 cycles of docetaxel.

Outcome(s)	Overall survival (time frame: approximately 70 months)
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Darolutamide is already marketed in the UK. The NHS indicative price for a pack of 112 x 300mg tablets costs £4,040.[31] There is also a patient access scheme in place for darolutamide, which offers a discount on the list price to the NHS.[b]

Docetaxel is already marketed in the UK. The NHS indicative price varies between suppliers and according to the concentration. For example, the cost of docetaxel 160mg/16ml concentrate for solution for infusion vials (Pfizer Ltd) costs £1,069.50.[32]

There are multiple ADT LHRH treatments currently marketed in the UK. The NHS indicative price varies between the drugs, suppliers, administration, and concentration. Examples of agonist therapy include:

- Goserelin 3.6mg implant pre-filled syringes (AstraZeneca UK Ltd) cost £70.00 per vial.[33]
- Triptorelin 3mg powder and solvent for suspension for injection vials (Ipsen Ltd) cost £69.00 per vial.[34]

Antagonist ADT LHRH also varies, for example, degarelix 80mg powder and solvent for solution for injection vials (Ferring Pharmaceuticals Ltd) has an indicative NHS cost of £129.37 per vial.[35]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Cabazitaxel for hormone-relapsed 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. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). April 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 technology appraisal guidance. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006.
- NICE technology appraisal guidance. Radium–223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE guideline. Prostate cancer: diagnosis and management (NG131). May 2019.

[b] Information provided by Bayer AG plc

- NICE quality standard. Prostate cancer (QS91). June 2015. (Last updated: May 2019).

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.
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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.