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Newcastle University

Health Technology Briefing
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Radium-223 dichloride with enzalutamide for treating hormone-relapsed metastatic prostate cancer

Company/Developer	Bayer AG

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 39013	NICE ID: N/A	UKPS ID: 673282

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Radium-223 dichloride in combination with enzalutamide are in clinical development for the treatment of hormone-relapsed metastatic prostate cancer. Hormone-relapsed metastatic prostate cancer occurs when prostate cancer, which has spread to other parts of the body, stops responding to hormonal treatment. Initially, treatments can control the cancer for months or years, but eventually, the cancer grows despite low testosterone levels. Symptoms may include frequent urination, urgency, difficulty urinating, tiredness, bone pain, and weight loss. Current treatment focuses on easing symptoms and helping people live longer, with approximately 53% of patients surviving five years.

Radium-223 mimics calcium and targets bone metastases, delivering powerful radiation that breaks the DNA in cancer cells, causing them to die. Enzalutamide blocks signals from male hormones that prostate cancer cells need to grow which slows their growth and causes cancer cell death. These two drugs are being tested together because they attack cancer in different ways, which might help prevent resistance to treatment and improve patient outcomes. Radium-223 is given as an injection into a vein once every 6 months and enzalutamide is taken orally as capsules. If licenced radium-223 dichloride in combination with enzalutamide would offer an additional treatment option to patients living with hormone-relapsed metastatic prostate cancer.

Proposed Indication

Treatment of asymptomatic or mildly symptomatic castration resistant[a] prostate cancer patients metastatic to bone.[1]

Technology

Description

Radium-223 dichloride (Xofigo) mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/µ m) leads to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a potent cytotoxic effect. Additional effects on the tumour microenvironment including osteoblasts and osteoclasts also contribute to the in vivo efficacy. The alpha particle range from radium-223 is less than 100 µ m (less than 10 cell diameters) which minimises damage to the surrounding normal tissue.[2] 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.[3]

The combination of radium-223 dichloride and enzalutamide is currently in clinical development for the treatment of asymptomatic or mildly symptomatic patients with metastatic hormone-relapsed (also known as castration-resistant) prostate cancer.[1,4] In the PEACE III trial (NCT02194842) radium-223 dichloride will be administered 55kBq/kg standard dose monthly for 6 months and given in combination with enzalutamide at a dose of 160 mg daily.[1] Radium-223 is given as an injection into a vein and enzalutamide is taken orally as capsules.[5]

Key Innovation

Androgen deprivation therapy, such as enzalutamide, is the mainstay of treatment for prostate cancer; however, resistance inevitably develops, leading to hormone-relapsed prostate cancer that most commonly metastasises to bone.[6] Radium-223 is already used to treat cancers that have spread to the bones.[5] Combining therapeutic agents with differing modes of action is an approach that has been explored successfully in many solid tumour types, with the aim of delaying the development of resistance and improving outcomes for patients.[6] The phase II trial, NCT02225704, confirmed the combination of radium-223 and enzalutamide to be well tolerated, with most patients completing all planned cycles. Adverse events were in keeping with previously reported data for these therapies as single agents. The promising efficacy results reported here demonstrate significant anti-tumour activity with this combination.[6]

If licensed, radium-223 dichloride and enzalutamide will offer an additional treatment option for patients with of asymptomatic or mildly symptomatic patients with metastatic hormone-relapsed prostate cancer.

Regulatory & Development Status

Radium-223 dichloride is currently marketed in the EU/UK technologies for the following indication:[2]

- The treatment of adult patients with metastatic castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of

[a] Also known as hormone-relapsed.

systemic therapy for metastatic castration-resistant prostate cancer (other than luteinising hormone-releasing hormone analogues), or ineligible for any available systemic metastatic castration-resistant prostate cancer treatment.

Radium-223 dichloride is also in phase II and/or III clinical development in combination with other technologies for:[7]

- Metastatic breast cancer

Enzalutamide is currently marketed in the EU/UK in combination with other technologies for the following indications:[8]

- The treatment of adult men with metastatic hormone-sensitive prostate cancer
- The treatment of adult men with high-risk biochemical recurrent non-metastatic hormone-sensitive prostate cancer who are unsuitable for salvage-radiotherapy.

Enzalutamide is also currently marketed in the EU/UK as a monotherapy for the following indications:[8]

- The treatment of adult men with high-risk biochemical recurrent non-metastatic hormone-sensitive prostate cancer who are unsuitable for salvage-radiotherapy.
- The treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer
- The treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- The treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Enzalutamide is also in phase II and/or III clinical development as a monotherapy or in combination for, but not limited to: [9]

- Hepatic impairment
- COVID-19
- Hepatocellular carcinoma

Enzalutamide and Radium-223 dichloride in combination are not in clinical development for any other indication.

Patient Group

Disease Area and Clinical Need

The prostate is a gland that functions to help make semen. Prostate cancer can develop when cells in the prostate start to grow in an uncontrolled way and mainly affects men over 50.[10] Prostate cancer does not usually cause any symptoms until the cancer has grown large enough to put pressure on the tube that carries urine from the bladder out of the penis (urethra). Symptoms of prostate cancer can include, needing to urinate more frequently, as well as difficulty in starting to urinate (hesitancy).[11] Metastatic prostate cancer occurs when the cancer that began in the prostate has spread to other parts of the body. This usually means it can no longer be cured but treatment can help to reduce symptoms and help the patient live longer. In metastatic hormone-relapsed prostate cancer, the cancer starts to grow again after the initial treatment, as the androgen depletion therapy no longer works leading to continuous rise in serum prostate-specific antigen levels, the progression of pre-existing disease, and/or the appearance of new metastases.[4,12,13] If the cancer has spread, symptoms can include tiredness, bone pain and unexplained weight loss.[14]

Prostate cancer is the most common cancer in men with around 490,000 men living with and after prostate cancer in the UK and one in eight men will be diagnosed in their lifetime. One and five year survival rates for stage 4 prostate cancer are 89.8% and 53.2%, respectively.[15] Prostate cancer is the most common cancer in males in the UK, accounting for 28% of all new cancer cases in males (2017-19). Incidence rates for prostate cancer in the UK are highest in males aged 75 to 79 (2017-2019).[16]In England (2022-23) there were 86,381 finished consultant episodes (FCEs) and 81,717 admissions for malignant neoplasm of prostate (ICD-10 code C61), which resulted in 61,419 day cases and 78,764 FCE bed days.[17]

Recommended Treatment Options

NICE currently recommends the following therapies for the treatment of hormone-relapsed metastatic prostate cancer:

- Abiraterone[18]
- Enzalutamide[19,20]
- Olaparib[21]
- Docetaxel[22]
- Radium-233 dichloride[23]
- Cabazitaxel[24]

Clinical Trial Information

Trial	PEACE III; NCT02194842, 2014-001787-36 ; A Randomized Multicentre Phase III Trial Comparing Enzalutamide vs. a Combination of Ra223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Castration Resistant Prostate Cancer Patients Metastatic to Bone. **Phase III** – Active, Not recruiting **Locations:** 6 EU countries, UK, Canada, and other countries **Actual primary completion date:** February 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=446 (actual); Asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer without visceral metastasis; aged 18 years and older.
Intervention(s)	Radium-223 dichloride 55k Bq/kg injection every 6 months + 160 mg oral Enzalutamide daily.
Comparator(s)	Enzalutamide given at a dose of 160 mg daily.
Outcome(s)	Radiological progression-free survival 46 months after first patient entry. See trial record for full list of all outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Enzalutamide is already marketed in the UK. The cost (list price) of enzalutamide is £2,734.67 for a 112-capsule pack of 40 mg enzalutamide (excluding VAT; BNF online, price correct of May 2020). The daily dose of enzalutamide is 160 mg and costs £97.67 per day.[25]

Radium-223 dichloride is already marketed in the UK. The company's submission states that radium-223 is available at a radioactivity of 6 MBq in a 6-ml vial at a net price of £4,040 (excluding VAT).[26]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Abemaciclib with abiraterone acetate and prednisone for treating hormone-relapsed metastatic prostate cancer (TA11252). Suspended March 2024.
- NICE technology appraisal in development. Ipatasertib with abiraterone and prednisone for hormone-relapsed metastatic prostate cancer (TA10779). Suspended November 2023.
- NICE technology appraisal in development. Atezolizumab with cabozantinib for treating hormone relapsed metastatic prostate cancer after 1 therapy (TA11163). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer (ID4004). Expected publication date: 15 January 2025.
- NICE technology appraisal. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer (TA951). February 2024.
- NICE technology appraisal. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer (TA887). May 2023.
- NICE technology appraisal. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA259). July 2016.
- NICE technology appraisal. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). July 2016.
- NICE technology appraisal. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
  NICE technology appraisal. Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE technology appraisal. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). May 2016.
- NICE technology appraisal. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). June 2006.
- NICE clinical guideline. Prostate cancer: diagnosis and management (NG131). May 2019. Last updated: December 2021.
- NICE quality standard. Prostate cancer (QS91). June 2015. Last updated: December 2021.

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.
- 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
- 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

- European Association of Urology (UAU). Guidelines on prostate cancer. 2024.[27]
- European Society for Medical Oncology. Clinical Practice Guidelines – Prostate Cancer. 2020.[28]
- European Urology. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II—2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. 2021.[29]

Additional Information

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