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Newcastle University

Health Technology Briefing
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Talazoparib with enzalutamide for previously untreated homologous recombination repair-mutated metastatic hormonal-sensitive prostate cancer

Company/Developer	Pfizer Limited

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31420	NICE ID: Not available	UKPS ID: 664033

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Talazoparib in combination with enzalutamide is in clinical development for the treatment of homologous recombination repair (HRR)-mutated metastatic hormonal-sensitive prostate cancer (mHSPC). Prostate cancer is a cancer of the prostate gland and is the most common type of cancer in men in the UK. The cancer is called metastatic when it has spread to other parts of the body. mHSPC means the cancer is being controlled by keeping the testosterone level as low as would be expected if the testicles were removed. Alterations to the HRR pathway (a mechanism by which DNA damage is repaired) are common in metastatic prostate cancer and may be associated with poorer outcomes. There is therefore a need to develop new treatment options for this population.

Talazoparib blocks the action of enzymes called human poly-ADP ribose polymerase (PARP), which are proteins that help to repair damaged DNA in cells (both in normal and in cancer cells) during cell division. Therefore, where PARP proteins are blocked, the damaged DNA in cancer cells cannot be repaired, and as a result the cancer cells die. Enzalutamide blocks the action of testosterone. Because prostate cancer needs testosterone, enzalutamide thus slows down the growth of the cancer. Talazoparib and enzalutamide are administered orally. If licensed, talazoparib in combination with enzalutamide will provide an additional treatment option for patients with HRR gene-mutated mHSPC.

Proposed Indication

For the treatment of adult patients with homologous recombination repair (HRR)-mutated metastatic hormonal-sensitive prostate cancer (mHSPC).[1,2]

Technology

Description

Talazoparib (Talzenna, BMN-673) is an inhibitor of human poly-ADP ribose polymerase (PARP) enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signaling pathways such as DNA repair, gene transcription, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by two mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription, thereby resulting in apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased apoptosis.[3]

Talazoparib in combination with enzalutamide is in clinical development for the treatment of patients with HRR-mutated mHSPC. In the phase III clinical trial (TALAPRO-3, NCT04821622), talazoparib (0.5 mg) is administered orally once daily in combination with orally administered enzalutamide (160 mg/day).[1]

Key Innovation

Despite improvements in the treatment of advanced prostate cancer, metastatic prostate cancer remains incurable, and is also associated with therapy resistance.[4,5] Additional therapeutic options are needed for patients with HRR gene alterations, which are associated with worse outcomes in mHSPC.[6]

Enzalutamide is an androgen receptor (AR) inhibitor and established therapy for mHSPC. Since PARP activity has been shown to support AR function, PARP inhibition is expected to increase sensitivity to AR-directed therapies.[2] PARP inhibition can exploit a deficiency of cancer cells to repair DNA double-strand breaks through HRR.[7] Therefore, by combining enzalutamide with talazoparib, a PARP inhibitor, the underlying genetic mechanisms associated with HRR-mutated mHSPC may be targeted.[8] If licensed, talazoparib in combination with enzalutamide will offer an additional treatment option for HRR gene mutated mHSPC.

Regulatory & Development Status

Talazoparib also has Marketing Authorisation in the EU in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated.[9,10]

Talazoparib currently has Marketing Authorisation in the EU/UK as a monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer.[3]

Patient Group

Disease Area and Clinical Need

Prostate cancer is cancer of the prostate gland, characterised by abnormal cells starting to divide and grow in an uncontrolled way.[11] Prostate cancer usually does not 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 frequent need to urinate, straining while urinating, and blood in urine or in semen.[12] The exact cause of prostate cancer is unknown, however it is more common in men over 50, obese men, and men with a family history of prostate cancer or breast cancer.[13] Hormonal-sensitive prostate cancer (HSPC) means the cancer is being controlled by keeping the testosterone level as low as what would be expected if the testicles were removed by castration.[14] With mHSPC, the cancer has spread from the prostate to other parts of the body, such as lymph nodes in other parts of the body, the bones, or other organs such as the lungs.[15,16] The homologous recombination repair (HRR) pathway is a DNA damage repair (DDR) mechanism and is the most frequently mutated pathway in advanced prostate cancer.[6,16,17]

Prostate cancer is the most common cancer in males in the UK, accounting for 27% of all new cancer cases in males (2016-18). In females and males combined, prostate cancer is the 2nd most common cancer in the UK, accounting for 14% of all new cancer cases (2016-18). The age standardised incidence rate of prostate cancer in England is 186.4 per 100,000 amongst males.[18] 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.[19] In England (2017), there were 41,201 patients diagnosed with malignant neoplasm of prostate and 10,146 deaths registered where malignant neoplasm of prostate was the underlying cause.[20] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year age-standardised survival rates were 96.6% and 86.6% respectively.[21]

Recommended Treatment Options

NICE guidelines recommend the following treatment options for hormone-sensitive metastatic prostate cancer in adults:[22-24]

- Enzalutamide plus androgen deprivation therapy
- Darolutamide with androgen deprivation therapy and docetaxel
- Apalutamide with androgen deprivation therapy

Clinical Trial Information

Trial	**TALAPRO-3;** NCT04821622; EudraCT 2021-000248-23; A Phase 3, Randomized, Double-Blind, Study of Talazoparib with Enzalutamide Versus Placebo with Enzalutamide in Men with DDR Gene Mutated Metastatic Castration-Sensitive Prostate Cancer **Phase III** – Active, not recruiting **Location(s):** Ten EU countries, UK, USA, Canada and other counties **Primary completion date:** Sept 2025
Trial Design	Randomised, parallel assignment, quadruple-blind

Population	N (actual) = 599; males; aged 18 years and older; Subjects with confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, small cell or signet cell features and confirmation of DDR gene mutation status
Intervention(s)	Talazoparib (oral) 0.5mg once daily + enzalutamide (oral) 160 mg/day
Comparator(s)	Placebo + enzalutamide (oral) 160 mg/day
Outcome(s)	Primary outcome measure: Radiological progression-free survival [Time Frame: randomization up to 3 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Talazoparib is already licensed in the UK;[25]

- A pack of 30 x 0.25mg capsules costs £1655
- A pack of 30 x 1mg capsules costs £4965

Relevant Guidance

NICE Guidance

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

NHS England (Policy/Commissioning) Guidance

- 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. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.

Other Guidance

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- Public Health England. Prostate cancer risk management programme. 2016.[29]

Additional Information

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