NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Talazoparib in addition to enzalutamide for metastatic castration-resistant prostate cancer

NIHRIO ID	24066	**NICE ID**	10429
Developer/Company	Pfizer Limited	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Talazoparib in addition to enzalutamide is in clinical development for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the most common type of cancer in men in the UK. The cancer is called advanced (metastatic) prostate cancer when the cancer cells have spread to other parts of the body like bones, lymph nodes outside the pelvis or rarely to the liver or lungs. It is not possible to cure metastatic prostate cancer but is possible to keep it under control. Prostate cancers that continue to grow despite hormonal therapies are called "castration-resistant" (also "hormone-refractory" or "hormone-relapsed") prostate cancer.

Talazoparib is administered orally in capsule form and can lead to cancer cell death by blocking DNA repair by an enzyme called PARP. By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and the cells die. Enzalutamide is an androgen receptor inhibitor that is already approved for the treatment of mCRPC. The addition of talazoparib is thought to increase the sensitivity of enzalutamide to the cancer cells, thereby improving treatment outcomes. If licensed, this combination would provide an additional first-line treatment for men with mCRPC.

PROPOSED INDICATION

Treatment metastatic castration-resistant prostate cancer (mCRPC).[1]

TECHNOLOGY

DESCRIPTION

Talazoparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as gene transcription, DNA repair, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by 2 mechanisms, PARP trapping and inhibition of PARP catalytic activity, 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.[2]

Enzalutamide is a potent androgen receptor (AR) signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; 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 and also inhibits nuclear translocation of activated receptors. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.[3]

Talazoparib in addition to enzalutamide is currently in clinical development for patients with mCRPC. In the phase III clinical trial (TALAPRO-2, NCT03395197), participants will receive talazoparib 0.5 mg orally once daily plus enzalutamide 160 mg orally once daily.[1] As PARP activity has been shown to support AR function, inhibition of PARP is expected to increase sensitivity to AR-directed therapies. Therefore, 0.5 mg of talazoparib exposes patients to the correct concentration due to the interaction with enzalutamide.[4]

INNOVATION AND/OR ADVANTAGES

There is an unmet need to develop and advance innovative therapies beyond currently used androgen receptor signaling inhibitors for first line mCRPC. Recent studies have shown potential for synergistic effects in treating prostate cancer by combining androgen receptor and PARPi signaling inhibitors, such as talazoparib and enzalutamide. Currently there no approved combination treatments utilising these two classes of therapy.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Talazoparib in combination with enzalutamide does not have currently have Marketing Authorisation in the EU/UK for any indication.

In 2019, talazoparib as a monotherapy was approved by the EMA for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer.

PATIENT GROUP

DISEASE BACKGROUND

The most common cancer in men in the UK is prostate cancer.[6] A small gland in the pelvis found only in men which is located between the penis and the bladder and surrounds the urethra is affected. The main purpose of the prostate is to help in semen production.[7] Advanced prostate cancer means the cancer has spread from the prostate to other parts of the body (metastatic prostate cancer). It most commonly spreads to lymph nodes in other parts of the body or to the bones. It can also spread to other organs.[8]

Prostate cancer cells usually need testosterone to grow.[9] Prostate cancer which has spread to other parts of the body and which keeps growing even when the amount of testosterone in the body is reduced to very low levels (via testosterone suppression therapy) is known as metastatic castration-resistant prostate cancer (mCRPC). Prostate-specific membrane antigen (PSMA), a transmembrane protein, is expressed by virtually all prostate cancers, and its expression is further increased in metastatic, poorly differentiated, and hormone-refractory carcinomas.[10]

Advanced prostate cancer can cause symptoms, such as fatigue (extreme tiredness), bone pain, and problems urinating. The symptoms depend on where the cancer has spread to.[5] Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts on their daily lives, particularly physical and emotional health, relationships and social life.[6]

CLINICAL NEED AND BURDEN OF DISEASE

Prostate cancer is the most common cancer amongst males in the UK, accounting for 26% of all new cancer cases in this population (2017 data).[7] Prostate cancer is more common in black Caribbean and black African men than in white men and is less common in Asian men. Around 35% of the men diagnosed with prostate cancer in the UK each year are aged 75 years and over.[6] Additional factors which increase the risk of developing prostate cancer include having a family history of the condition, and lifestyle factors (e.g. consuming a lot or red meat and foods that are high in fat).[8,9]

In 2018 in England, there were 49,810 newly identified malignant neoplasms of the prostate (ICD10: C61).[10] 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).[11] When standardised by age in England (2018), there was a rate of 204 incidences per 100,000 person-years.[12] 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).[13]

In England and Wales (2019), there were 10,872 recorded deaths due to malignant neoplasm of the prostate (ICD10: C61).[14] 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.[20] 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).[13]

According to Hospital Episode Statistics (HES) data, in 2019-20 there were 80,002 admissions with a primary diagnosis of neoplasm of the prostate (ICD-10 code C61), resulting in 85,244 finished consultant episodes (FCE), 85,828 FCE bed days and 57,769 day cases.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The decision about the best approach to treat and care for cancer should be discussed among a multidisciplinary team and the choice of treatment depends on several factors such as where the cancer is, how far it has grown or spread (the stage), type of cancer, how abnormal the cells look under a microscope (the grade), and general health and level of fitness of the patient. The aim of treatment for advanced prostate cancer is to control it, relieve symptoms and maintain quality of life. The main treatments are chemotherapy, hormone therapy, radiotherapy, steroids and symptom control.[16]

CURRENT TREATMENT OPTIONS

For men with mCRPC NICE recommends:[17]

Corticosteroids
Corticosteriods, such as dexamethasone (0.5mg daily), as a third-line hormonal therapy after ADT and anti-ADT are recommended.

Abiraterone
Abiraterone in combination with prednisone or prednisolone is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- only when the company provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

Enzalutamide
Enzalutamide is recommended, within its marketing authorisation, as an option for treating metastatic hormone-relapsed prostate cancer:

- in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated
- when the company provides it with the discount agreed in the patient access scheme

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

PLACE OF TECHNOLOGY

If licensed, talazoparib in combination with enzalutamide will provide an additional first-line treatment option for adult men with mCRPC.

CLINICAL TRIAL INFORMATION

Trial	**TALAPRO-2**; NCT03395197; 2017-003295-31; A phase 3, randomized, double-blind, placebo-controlled study of

	talazoparib with enzalutamide in metastatic castration-resistant prostate cancer **Phase III-** Active, recruiting **Primary completion date:** January 2022
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N = 1150 (planned); 18-99 years old men; histologically or cytologically confirmed adenocarcinoma of the prostate withoutsmall cell or signet cell features; asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer (mCRPC) (score on BPI-SF Question #3 must be < 4); For enrollment into Part 2 only (optional in Part 1): assessment of DDR mutation status; Consent to a saliva sample collection for a germline comparator unless prohibited by local regulations or ethics committee decision; surgically or medically castrated, with serum testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening; metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan; Progressive disease at study entry in the setting of medical or surgical castration; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1; Life expectancy ≥ 12 months as assessed by the investigator; Able to swallow the study drug and have no known intolerance to study drugs or excipients.
Intervention(s)	Talazoparib; orally; 0.5 mg once daily plus enzalutamide; orally; 160 mg once daily
Comparator(s)	Placebo plus enzalutamide; orally; 160 mg once daily
Outcome(s)	- Confirm the dose of talazoparib (part 1) [Time Frame: Day 1 up to 28 days] determined based on the safety profile - Radiographic PFS (part 2) in unselected patients and in patients harboring DDR deficiencies [Time Frame: randomization up to 25 months] time from the date of randomization to first objective evidence of radiographic progression by blinded independent review, or death (occurring within 168 days of treatment discontinuation), whichever occurs first See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Talazoparib capsule:[18]

- 30 capsules of 0.25 mg - £1655.00
- 30 capsules of 1 mg - £4965.00

Enzalutamide tablet:[19]

- 112 tablets of 40 mg - £2734.67

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Radium–223 dichloride for treating hormone relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE technology appraisal guidance. Abiraterone for treating metastatic hormone relapsed prostate cancer before chemotherapy (TA387). April 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (NG131). May 2019.
- 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.
- 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. Prostate Cancer Guidelines. 2021[20]
- Parker c, Castro E, Fizazi K. et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[21]
- Cassinello J, Arranz J.A., Piulats J.M. et al. SEOM clinical guidelines for the treatment of metastatic prostate cancer. 2017.[22]
- Mottet N, Cornford P, van den Bergh R.C.N. et al. SIOG Guidelines on Prostate cancer.[23]
- Canadian Urologic Oncology Group (CUOG) and the Canadian Urological Association (CUA). Guidelines for the management of castrate-resistant prostate cancer. 2010.[30]

ADDITIONAL INFORMATION

REFERENCES

1 Clinical Trials.gov. *Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC (TALAPRO-2). Trial ID*. 2018. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT03395197 [Accessed 31 August 2021].

2 eMC. *Talzenna 0.25 mg hard capsules*. Available from: https://www.medicines.org.uk/emc/product/10734/smpc [Accessed 31 August 2021].

3 eMC. *Xtandi 40 mg film coated tablets*. Available from: https://www.medicines.org.uk/emc/product/10318/smpc [Accessed 31 August 2021].

4 Adashek, J. J., Jain R. K., Zhang J. *Clinical development of PARP inhibitors in treating metastatic castration-resistant prostate cancer*. Cells. 2019;8(8):860. Available from: https://pubmed.ncbi.nlm.nih.gov/31404966/ 31 August 2021

5 Prostate Cancer UK. *Advanced prostate cancer*. Available from: https://prostatecanceruk.org/prostate-information/just-diagnosed/advanced-prostate-cancer [Accessed 1 September 2021].

6 Appleton, L., Wyatt D., Perkins E., Parker C., Crane J., Jones A., et al. *The impact of prostate cancer on men's everyday life*. European journal of cancer care. 2015;24(1):71-84. Available from: https://doi.org/10.1111/ecc.12233 1 September 2021

7 Cancer Research UK. *Prostate cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero [Accessed 1 September 2021].

8 Cancer Research UK. *What is prostate cancer?* Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 31 August 2021].

9 American Cancer Society. *Prostate Cancer Risk Factors*. Available from: https://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html [Accessed 1 September 2021].

10 Public Health England. *Incidence: Base Numbers*. 2019. Available from: https://www.cancerdata.nhs.uk/incidence/base_numbers [Accessed

11 Public Health England. *Staging Data in England*. 2020. Available from: https://www.cancerdata.nhs.uk/stage_at_diagnosis [Accessed

12 Public Health England. *Incidence: Age Standardised*. 2019. Available from: https://www.cancerdata.nhs.uk/incidence/age_standardised_rates [Accessed

13 Cancer Research UK. *Selected Cancers, Number of Projected and Observed Cases and European Age-Standardised Incidence Rates per 100,000 people by Cancer Type and Sex*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed

14 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality*. 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset [Accessed 8 Sept 2021].

15 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20*. 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 1 September 2021].

16 cancer Research UK. *Making decisions about treatment for advanced cancer*. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/advanced-treatment/making-decisions-about-treatment [Accessed 1 September 2021].

17 National Insitute for Health and Care Excellence (NICE). *Treatment options before chemotherapy is indicated*. . Available from: https://pathways.nice.org.uk/pathways/prostate-cancer#path=view%3A/pathways/prostate-cancer/treating-hormone-relapsed-metastatic-prostate-cancer.xml&content=view-node%3Anodes-treatment-options-before-chemotherapy-is-indicated [Accessed 1 September 2021].

18 British National Formulary (BNF). *TALAZOPARIB*. Available from: https://bnf.nice.org.uk/medicinal-forms/talazoparib.html [Accessed 1 September 2021].

19 BNF. *ENZALUTAMIDE*. Available from: https://bnf.nice.org.uk/medicinal-forms/enzalutamide.html [Accessed 1 September 2021].

20 European Association of Urology. *Prostate Cancer*. 2021. Available from: https://uroweb.org/guideline/prostate-cancer/ [Accessed

21 Parker, C., Castro E., Fizazi K., Heidenreich A., Ost P., Procopio G., et al. *Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Annals of Oncology. 2020;31(9):1119-34. Available from: https://doi.org/10.1016/j.annonc.2020.06.011 1 September 2021

22 Cassinello, J., Arranz J., Piulats J., Sánchez A., Pérez-Valderrama B., Mellado B., et al. *SEOM clinical guidelines for the treatment of metastatic prostate cancer (2017)*. Clinical and Translational Oncology. 2018;20(1):57-68. Available from: https://link.springer.com/article/10.1007/s12094-017-1783-2 1 September 2021

23 Urology, E. A. o. *SIOG Guidelines on Prostate cancer*. Available from: https://uroweb.org/wp-content/uploads/EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-large-text-V2.pdf [Accessed 1 September 2021].

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.