Clinical Trial Protocol

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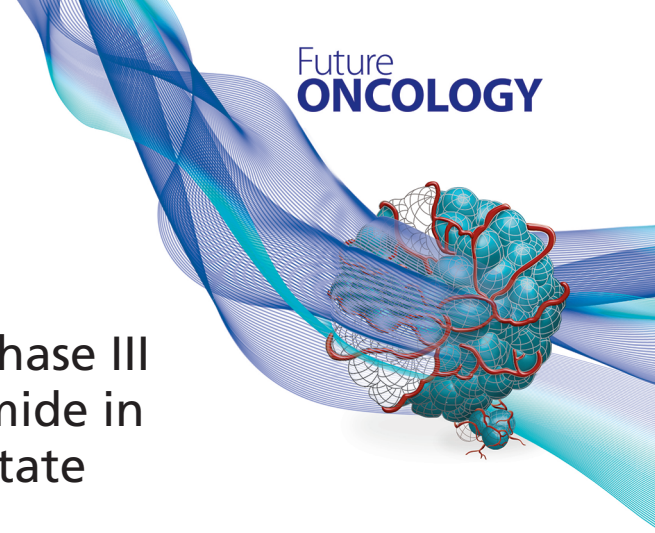

TALAPRO-3 clinical trial protocol: phase III study of talazoparib plus enzalutamide in metastatic castration-sensitive prostate cancer

Neeraj Agarwal*[,1], Fred Saad[2], Arun A Azad[3], Joaquin Mateo[4], Nobuaki Matsubara[5], Neal D Shore[6], Jayeta Chakrabarti[7], Hsiang-Chun Chen[8], Silvana Lanzalone[9], Alexander Niyazov[10] & Karim Fizazi[11]

[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
[2]University of Montréal Hospital Center, Montréal, Québec, H2L 4M1, Canada
[3]Peter MacCallum Cancer Centre, Melbourne, Victoria, 3000, Australia
[4]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, 08035, Barcelona, Spain
[5]National Cancer Center Hospital East, Chiba, 277-8577, Japan
[6]Carolina Urologic Research Center, Myrtle Beach, SC 29572, USA
[7]Pfizer Ltd., Tadworth, Surrey, KT20 7NS, UK
[8]Pfizer Inc., La Jolla, CA 92121, USA
[9]Pfizer Oncology, Milan, 20152, Italy
[10]Pfizer Inc., New York, NY, 10012, USA
[11]Institut Gustave Roussy, University of Paris Sud, Villejuif, 94800, France
*Author for correspondence: Tel.: +1 801 213 5658; Neeraj.Agarwal@hci.utah.edu

Poly(ADP-ribose) polymerase inhibitors in combination with androgen-receptor signaling inhibitors are a promising therapeutic option for patients with metastatic castration-sensitive prostate cancer (mCSPC) and homologous recombination repair (HRR) gene alterations. Here, we describe the design and rationale of the multinational, phase III, TALAPRO-3 study comparing talazoparib plus enzalutamide versus placebo plus enzalutamide in patients with mCSPC and HRR gene alterations. The primary end point is investigator-assessed radiographic progression-free survival (rPFS) per RECIST 1.1 in soft tissue, or per PCWG3 criteria in bone. The TALAPRO-3 study will demonstrate whether the addition of talazoparib can improve the efficacy of enzalutamide as assessed by rPFS in patients with mCSPC and HRR gene alterations undergoing androgen deprivation therapy.

Clinical Trial Registration:NCT04821622 (ClinicalTrials.gov)
Registry Name: Study of Talazoparib With Enzalutamide in Men With DDR Gene Mutated mCSPC.
Date of Registration: 29 March 2021.

Tweetable abstract: TALAPRO-3 is a phase III, randomized study that aims to evaluate the efficacy and safety of talazoparib plus enzalutamide versus placebo plus enzalutamide in men with metastatic castration-sensitive prostate cancer (mCSPC) and homologous recombination repair gene alterations.

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Prostate cancer is the second leading cause of cancer-related death in men in the USA [1]. Worldwide, an estimated 1,414,259 men were diagnosed with prostate cancer, and 375,304 men died from the disease in 2020 [2]. Approximately 5–15% of patients are diagnosed with metastatic disease at the time of initial diagnosis of prostate cancer, and this can be up to 40% in some Asian countries. In the USA, the incidence of metastatic disease at diagnosis has been increasing in recent years. In addition, many patients who are initially diagnosed with localized disease will eventually progress to metastatic disease [3–7]. While men with localized disease have a high 5-year survival rate

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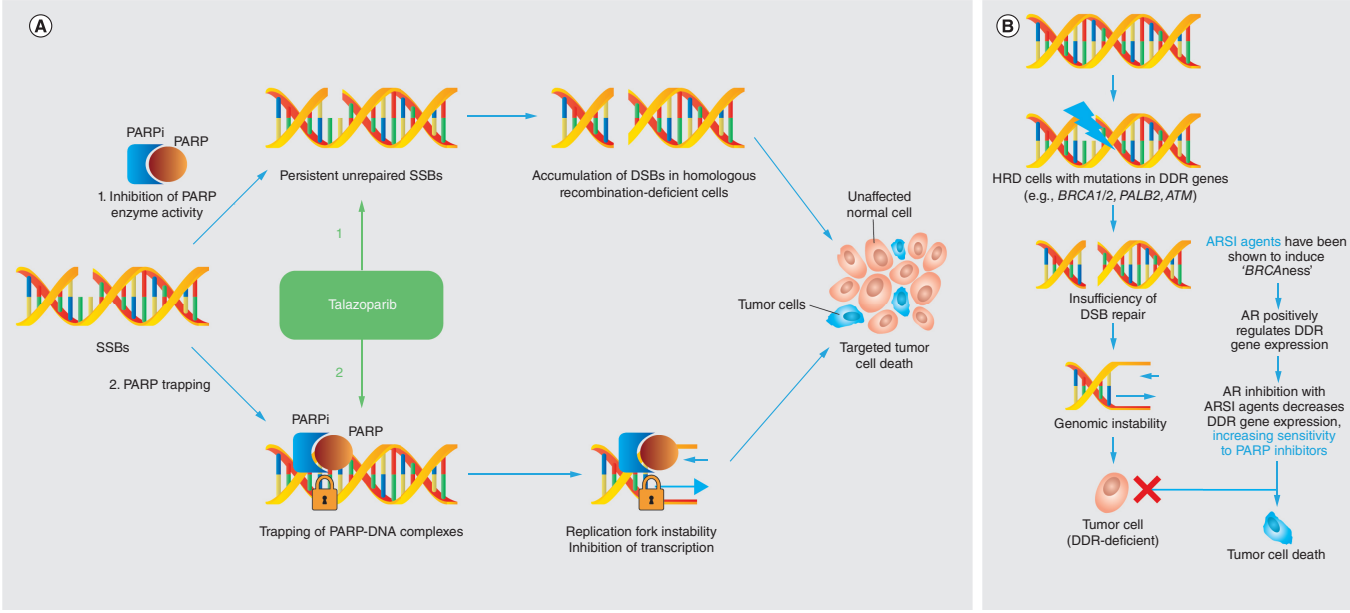


Figure 1. Mechanistic overview of PARP inhibition. (A) Dual cytotoxic mechanisms of PARP inhibitors; **(B)** PARP inhibitor in combination with an ARSI.
Adapted with permission from *Future Oncology* [29]. Reprinted (or adapted) from *Cancer Research* [30].
AR: Androgen receptor; ARSI: Androgen-receptor signaling inhibitor; DDR: DNA damage response; DSB: Double-strand break; HRD: Homologous recombination deficiency; PARP: Poly(ADP-ribose) polymerase; PARPi: Poly(ADP-ribose) polymerase inhibitor; SSB: Single-strand break.

of 99% if diagnosed at an early stage, men with metastatic disease have a poor survival of 30% at 5 years in the USA [8].

Historically, metastatic castration-sensitive prostate cancer (mCSPC) was treated with androgen deprivation therapy (ADT) with either medical castration through administration of a gonadotropin-releasing hormone (GnRH) agonist or antagonist or surgical castration [9,10]. However, despite initial response, the vast majority of men receiving ADT therapy alone will progress to metastatic castration-resistant prostate cancer (mCRPC), within a median of 1–2 years [11–14]. ADT in combination with docetaxel or an androgen-receptor signaling inhibitor (ARSI), such as enzalutamide, abiraterone acetate plus prednisone, and apalutamide, has become standard-of-care for men with mCSPC based on improvements in time-to-progression and overall survival (OS) compared with ADT alone [12,13,15–18]. Combination therapy with ADT and an ARSI is not curative in nature and thus, many men with mCSPC will still experience disease progression to mCRPC in approximately 3 years [13,16], highlighting the necessity of developing novel therapeutic strategies that prolong the time-to-progression and improve OS.

Alterations in DNA damage response (DDR) genes (e.g., *BRCA1/2, ATM, PALB2, CHEK2*) of germline or somatic origin involved directly or indirectly in homologous recombination repair (hereafter referred to as HRR genes) have been found in 23–27% of metastatic prostate cancers [19,20], with some alterations (e.g., in *BRCA2*) associated with poor prognosis and rapid progression to mCRPC [21–23]. Poly(ADP-ribose) polymerase 1 and 2 (PARP1/2) play essential roles in DNA repair by binding to single-strand breaks (SSB). When PARP1/2 are inhibited, SSBs can persist, resulting in stalled replication forks and conversion of SSBs into double-strand breaks (DSB), which in turn rely on the homologous recombination pathway for repair. Hence, alterations in HRR genes plus inhibition of PARP catalytic activity prevent DSBs from being repaired, causing cell death via synthetic lethality [24,25]. In preclinical models, HRR gene alterations, such as in *BRCA1/2*, have been shown to sensitize tumors to PARP inhibitors, such as talazoparib [24,26,27].

Talazoparib is a potent PARP inhibitor that both inhibits PARP activity and traps PARP on SSBs, preventing DNA repair and leading to synthetic lethality in cancer cells (Figure 1) [24,28–30]. Talazoparib is currently approved for the treatment of adult patients with germline *BRCA1/2*-altered HER2-negative locally advanced or metastatic breast cancer [31]. Talazoparib is also approved in the USA, in combination with enzalutamide, for the treatment of adult patients with HRR gene-mutated mCRPC following positive results from the phase III TALAPRO-2 study

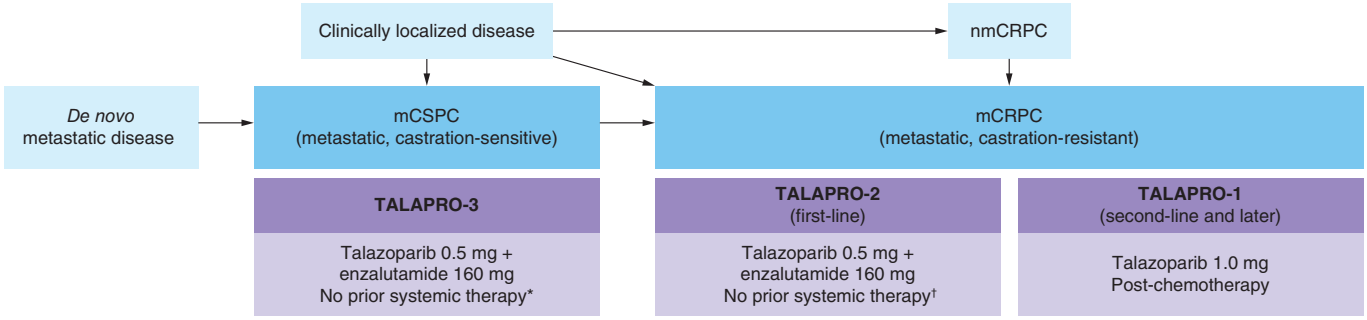


Figure 2. An overview of the talazoparib prostate cancer program.
*No prior life-prolonging systemic therapy for castration-sensitive prostate cancer, excluding ≤3 months androgen deprivation therapy with or without an approved androgen-receptor signaling inhibitor; treatment with estrogens, cyproterone acetate, or first-generation anti-androgens is allowed until randomization.
†No prior life-prolonging systemic therapy for castration-resistant prostate cancer, excluding androgen deprivation therapy and first-generation antiandrogens.
mCRPC: Metastatic castration-resistant prostate cancer; mCSPC: Metastatic castration-sensitive prostate cancer; nmCRPC: Non-metastatic castration-resistant prostate cancer.

which evaluated the combination as first-line therapy in patients with mCRPC with and without alterations in HRR genes [31,32]. In addition, TALAPRO-1, a phase II study of talazoparib monotherapy, demonstrated robust antitumor activity in heavily pretreated men with mCRPC and HRR gene alterations [33].

Despite prior ADT treatment, androgen receptor (AR) signaling continues to be active, and so further inhibition of AR signaling pathway has also been used [34]. Indeed, agents that target the AR signaling pathway, such as the ARSI enzalutamide, apalutamide, and darolutamide, and the androgen biosynthesis inhibitor abiraterone acetate, have significantly improved clinical outcomes for patients with mCSPC by slowing progression to mCRPC [16,35–38]. Interestingly, non-clinical models show that PARP1 activity is required for AR function; therefore, PARP inhibition may sensitize prostate cancer cells to AR-directed therapies [39]. In addition, AR blockade downregulates HRR gene expression, which may induce a '*BRCA*ness' phenotype and increase sensitivity to PARP inhibitors [40–42]. A non-clinical study has also showed that clinical resistance to AR blockade is sometimes associated with the deletion of *BRCA2*, which also confers sensitivity to PARP inhibitors [43]. Therefore, there is potential for co-operative interactions between PARP inhibitors, such as talazoparib, and the AR inhibitor enzalutamide, which is an approved treatment in mCSPC [44].

TALAPRO-3 study

Study design

TALAPRO-3 (NCT04821622) is a phase III, multinational, double-blind, randomized study that aims to evaluate the efficacy and safety of talazoparib plus enzalutamide versus placebo plus enzalutamide in men with mCSPC and HRR gene alterations (Figures 2 & 3). The protocol and any protocol amendments will be reviewed and approved by the institutional review board (IRB)/ethics committee (EC) before the study or amend is initiated. Written summaries of the study status will be provided by the investigator to the IRB/EC annually.

Genomic screening will be performed during the prescreening period using a peripheral blood sample and/or tumor tissue if available (only tumor tissue in China) to identify alterations in HRR genes. The FoundationOne Liquid CDx test that includes a HRR12 gene panel (*ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) will be used to determine the presence of HRR gene alterations. Upon sponsor pre-approval, historical FoundationOne Liquid CDx results may be considered as an alternative to a blood sample, or prior testing results of tumor tissue using FoundationOne CDx may be used for eligibility in case FoundationOne Liquid fails or is negative.

Eligible patients will be randomized (1:1) to talazoparib (0.5 mg/day) in combination with enzalutamide (160 mg/day) or placebo in combination with enzalutamide (160 mg/day). Patients will be stratified according to *de novo* mCSPC versus relapsed mCSPC; high-volume disease, defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies or pelvis, versus low-volume disease and *BRCA* versus non-*BRCA* mutational status. Talazoparib and placebo will be blinded, while enzalutamide will be open label. For patients with

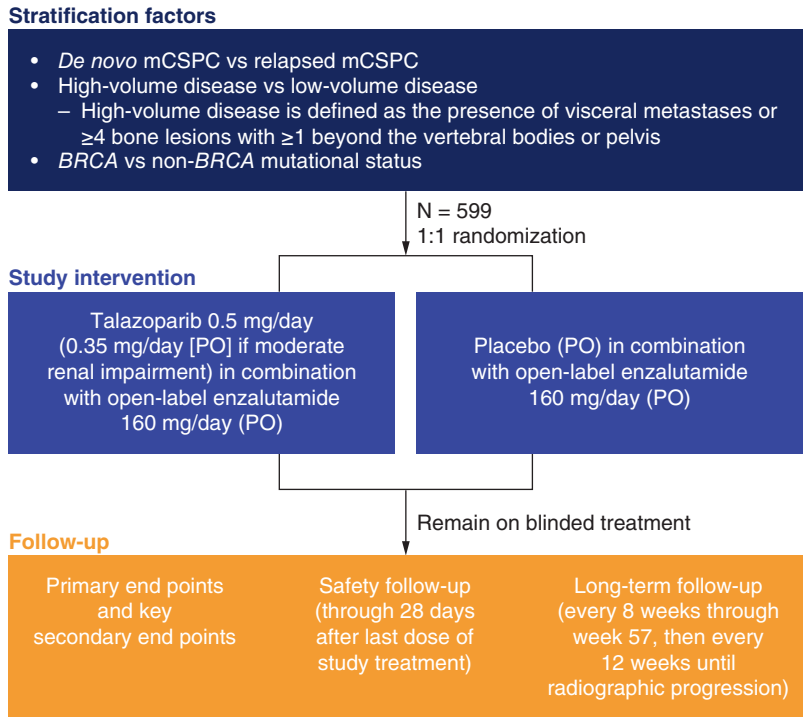


Figure 3. Study design.
mCSPC: Metastatic castration-sensitive prostate cancer; PO: Per oral.

moderate renal impairment (estimated glomerular filtration rate 30–59 ml/min/1.73 m^2), the dose of talazoparib will be 0.35 mg/day to account for lower clearance in this subpopulation. All patients will receive treatment until radiographic progression determined by the investigator, unacceptable toxicity, or an adverse event (AE) leading to permanent discontinuation, withdrawal of consent, patient decision to discontinue, or death.

The safety follow-up visit will occur approximately 28 days after permanent study intervention, discontinuation or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. Long-term follow-up will begin after safety follow-up.

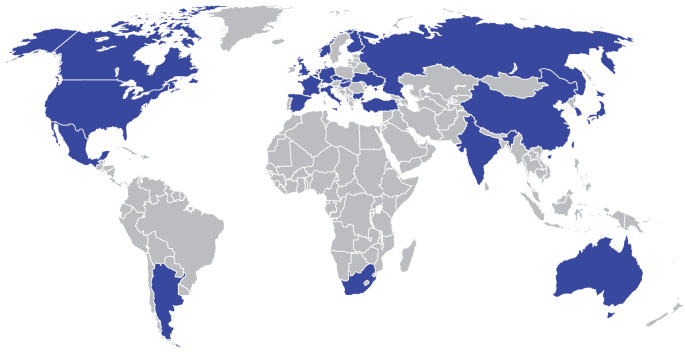
Enrollment

Enrollment for TALAPRO-3 began in May 2021 and the last patient was dosed in May 2023. The final number of randomized patients is 599. All patients with mCSPC harboring HRR gene alterations were enrolled and randomized 1:1 to each treatment arm. Patients were recruited across 27 countries, including the USA, Canada, South Africa and Australia, and in European, South American and Asia-Pacific countries (Figure 4).

Key eligibility criteria

To be eligible to participate in the TALAPRO-3 study, patients must be male and aged ≥18 years (≥20 years in Japan; ≥19 years in the Republic of Korea) with a histologically/cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, small cell, or signet cell features and with alterations in one or more HRR genes (as per HRR12 gene panel).

Eligible patients may have received ≤3 months of ADT (chemical or surgical) with or without an approved ARSI in the mCSPC setting. However, prior treatment of mCSPC with docetaxel is exclusionary due to the lack of consensus or guidelines that outlined the sequence of therapy for mCSPC at the time of the study design and the potential safety concerns due to the overlapping toxicities of talazoparib and docetaxel. In addition, patients who have not undergone bilateral orchiectomy must be receiving ongoing ADT with a GnRH agonist or antagonist, which should continue throughout the study. Patients must have metastatic disease documented by a positive bone scan for bone disease or on a CT or MRI scan for soft tissue disease. Other key inclusion criteria are listed in Table 1.



Countries with investigative centers	
Argentina	Mexico
Australia	The Netherlands
Belgium	Norway
Bulgaria	Republic of Korea
Canada	Russian Federation
China	Slovakia
Czech Republic	South Africa
Finland	Spain
France	Taiwan
Germany	Turkey
Hungary	Ukraine
India	UK
Italy	USA
Japan	

Figure 4. TALAPRO-3 enrollment.

Patients are not eligible to take part in the study if they have a history of seizures or any conditions that may predispose to a seizure, including any history of loss of consciousness or transient ischemic attack within 12 months of randomization, or known or suspected brain metastases, or active leptomeningeal disease.

Patients are also excluded if they have any history of myelodysplastic syndrome, acute myeloid leukemia, or prior malignancy except for the following: carcinoma *in situ* or non-melanoma skin cancer; a cancer diagnosed and treated ≥3 years before randomization with no subsequent evidence of recurrence; or a Stage 0 or Stage 1 (by American Joint Committee on Cancer) cancer <3 years before randomization that has a remote probability of recurrence in the opinion of the investigator and the sponsor. Patients with prior treatment in any setting with any ARSI, except as described in the inclusion criteria above and patients with active COVID-19 infection detected by approved tests or by clinical diagnosis are not eligible. Other key exclusion criteria are listed in Table 1.

Study end points & evaluations

In the TALAPRO-3 study, the primary end point is investigator-assessed radiographic progression-free survival (rPFS), defined as the time from the date of randomization to radiographic progression in soft tissue per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or in bone per Prostate Cancer Working Group 3 (PCWG3) criteria by the investigator, or death, whichever occurs first.

The key secondary end point is OS, defined as the time from randomization to the date of death due to any cause. Other secondary end points include objective response rate (ORR), defined as the proportion of patients with measurable soft-tissue disease at baseline who have confirmed objective response of complete response (CR) or partial response (PR) per RECIST 1.1; duration of soft tissue response, defined as the time from first objective evidence of a CR or PR to the first objective evidence of disease progression in soft tissue per RECIST 1.1 or in bone per PCWG3, or death, whichever occurs first; the proportion of patients with confirmed prostate-specific antigen (PSA) response ≥50%, and time to confirmed PSA progression, defined as a ≥25% increase in PSA with an absolute increase of ≥2 ng/ml above the nadir (or baseline for patients with no PSA decline), confirmed by a second consecutive PSA value at ≥21 days later.

Additional secondary and exploratory end points include time to initiation of antineoplastic therapy and time to progression on subsequent antineoplastic therapy, defined as the time from randomization to the start of second subsequent antineoplastic therapy after disease progression, or death from any cause, whichever occurs first; time to first symptomatic skeletal event; time to opioid use for prostate cancer pain; circulating tumor DNA burden (fraction) at baseline and on study per FoundationOne Liquid or another suitable validated assay; safety; pharmacokinetics (PK); biomarkers and patient-reported outcomes (PRO). Study end points are listed in Table 2.

Efficacy analyses will be performed every 8 weeks through week 57, and every 12 weeks thereafter in all randomized patients using the tumor assessments by the investigator as the primary data source. A sample-based

Table 1. Key inclusion and exclusion criteria of the TALAPRO-3 study.

Key inclusion criteria	
Demographics	• Male, aged ≥18 years at screening[†]
Additional criteria	• ECOG performance status ≤1 • Willing to provide tumor tissue when available (*de novo* or archived) for retrospective molecular profiling analysis and consent to provide saliva for retrospective sequencing of the same HRR genes tested on tumor tissue and blood and to serve as a germline control in identifying tumor mutations • Adequate organ function within 28 days before the first study treatment on day 1, defined by the following: ◦ ANC ≥1500/μl, platelets ≥100,000/μl, or hemoglobin ≥9 g/dl (may not have received growth factors or blood transfusions within 14 days before obtaining the hematology laboratory tests at screening) ◦ Total serum bilirubin <1.5 × ULN (<3 × ULN for patients with documented Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation) ◦ AST or ALT <2.5 × ULN (<5 × ULN if liver function abnormalities are due to hepatic metastasis) ◦ Albumin >2.8 g/dl ◦ eGFR ≥30 ml/min/1.73 m^2 by the MDRD equation • Signed informed consent
Prostate cancer status	• Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, small-cell or signet cell features • Ongoing ADT with a GnRH agonist/antagonist for patients who have not undergone bilateral orchiectomy; ADT must be initiated before randomization and must continue throughout the study • Metastatic prostate cancer documented by positive bone scan (for bone disease) or by CT or MRI scan (for soft tissue disease) • Confirmation of HRR gene mutation status (per HRR12 panel) by prospective or historical analysis of blood (FoundationOne Liquid CDx) and/or *de novo* or archival tumor tissue (FoundationOne CDx) • Palliative radiation or surgery for symptomatic control secondary to prostate cancer should be completed ≥2 weeks prior to randomization
Concomitant medication	• Treatment with estrogens, cyproterone acetate, or first-generation anti-androgens is allowed until randomization • Other prior therapy allowed for mCSPC: ≤3 months of ADT (chemical or surgical) with or without an approved ARSI[‡] in mCSPC (i.e., abiraterone plus prednisone, apalutamide, or enzalutamide), if required prior to randomization, with no radiographic evidence of disease progression or rising PSA levels prior to day 1
Key exclusion criteria	
Medical conditions	• History of seizure or any condition (as assessed by investigator) that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma), including any history of loss of consciousness or transient ischemic attack within 12 months of randomization • Major surgery within 4 weeks before randomization • Any history of MDS, AML, or prior malignancy except for the following: ◦ Carcinoma *in situ* or non-melanoma skin cancer ◦ A cancer diagnosed and treated ≥3 years before randomization with no subsequent evidence of recurrence • AJCC Stage 0 or Stage 1 cancer <3 years before randomization that has a remote probability of recurrence in the opinion of the investigator and the sponsor • Clinically significant cardiovascular disease, including any of the following: ◦ Myocardial infarction or symptomatic cardiac ischemia within 6 months before randomization ◦ Congestive heart failure New York Heart Association class III or IV ◦ History of clinically significant ventricular arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes) within 1 year before screening ◦ History of Mobitz II second-degree or third-degree heart block unless a permanent pacemaker is in place ◦ Hypotension as indicated by systolic blood pressure <86 mm Hg at screening ◦ Bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram • Uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening
Prior/concomitant therapy	• Prior ADT in the adjuvant/neoadjuvant setting, where the completion of ADT was ≤12 months prior to randomization and the total duration of ADT >36 months • Treatment with systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone within 4 weeks prior to randomization, intended for the treatment of prostate cancer • Any previous treatment with DNA-damaging cytotoxic chemotherapy (i.e., platinum-based therapy) within 5 years prior to randomization, except for indications other than prostate cancer • Prior treatment with a PARPi or known or possible hypersensitivity to enzalutamide, any of enzalutamide capsule excipients or any talazoparib/placebo capsule excipients • Prior treatment in any setting with any ARSI, except as described in the inclusion criteria • Prior or concurrent docetaxel • Current use of potent P-gp inhibitors within 7 days prior to randomization • Treatment with any investigational study intervention within 4 weeks before randomization; COVID-19 vaccines are an exception and can be administered without a washout period

[†]≥20 years in Japan; ≥19 years in the Republic of Korea.
[‡]Darolutamide is not included as it was not an approved androgen-receptor signaling inhibitor at the study entry.
ADT: Androgen deprivation therapy; ARSI: Androgen-receptor signaling inhibitor; AJCC: American Joint Committee on Cancer; ALT: Alanine aminotransferase; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count; AST: Aspartate transferase; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; GnRH: Gonadotropin-releasing hormone; HRR: Homologous recombination repair; mCSPC: Metastatic castration-sensitive prostate cancer; MDRD: Modification of diet in renal disease; MDS: Myelodysplastic syndrome; PARPi: Poly(ADP-ribose) polymerase inhibitor; P-gp: P-glycoprotein; PSA: Prostate-specific antigen; ULN: Upper limit of normal.

Table 2. TALAPRO-3 study end points.

Primary end point	Secondary end points
• rPFS based on investigator assessment per RECIST 1.1 (soft-tissue disease) and PCWG3 (bone disease) ◦ rPFS is defined as time from randomization to first evidence of radiographic progression by investigator, or death, whichever occurs first ◦ Efficacy will be assessed by radiography every 8 weeks through week 57, and every 12 weeks thereafter ◦ rPFS will be compared between the two arms by a two-sided stratified log-rank test	• OS, defined as the duration from the date of randomization until the date of death from any cause • Objective response (in participants with measurable soft-tissue disease)† • Duration of soft-tissue response† • Time to first symptomatic skeletal event (spinal cord compression, symptomatic pathologic bone fracture, or radiation or surgery to bone) • Proportion of patients with PSA response ≥50% • Time to PSA progression • Time to initiation of antineoplastic therapy • Time to opioid use for prostate cancer pain • Incidence and severity of AEs (graded by NCI CTCAE version 4.03) • PK of talazoparib, enzalutamide, and its N-desmethyl metabolite • ctDNA burden at baseline and on study Patient-reported outcomes: • Change from baseline in PGI-S, participant-reported pain symptoms (BPI-SF), general health status (EQ-5D-5L), cancer-specific global health status/QoL, functioning, and symptoms (EORTC QLQ-C30) • Time to deterioration in BPI-SF, global health status/QoL (EORTC QLQ-C30), and disease-specific urinary symptoms (EORTC QLQ-PR25)

†Per RECIST 1.1.

AE: Adverse event; BPI-SF: Brief Pain Inventory Short Form; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: Circulating tumor DNA; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: European quality of life 5D, 5-level scale; NCI: National Cancer Institute; OS: Overall survival; PCWG3: Prostate Cancer Working Group 3; PGI-S: Patient Global Impression of Severity; PK: Pharmacokinetics; PSA: Prostate-specific antigen; QLQ-C30: Quality of Life Questionnaire C30; QLQ-PR25: Quality of Life Questionnaire Prostate Cancer Module PR25; QoL: Quality of life; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; rPFS: Radiographic progression-free survival.

blinded independent central review approach will be implemented as an auditing tool for rPFS. Soft-tissue responses must be confirmed by a follow-up radiographic assessment ≥4 weeks later with no evidence of concurrent confirmed bone disease progression on repeated bone scans ≥6 weeks apart per PCWG3 criteria. The primary evaluation of ORR will be based on investigator assessment using derived response per RECIST 1.1.

Compliance with the study intervention will be assessed and documented by counting the number of returned capsules during each site visit. Patients will be considered non-compliant if ≥20% of monthly doses are missed.

Safety will be evaluated in all randomized patients who receive ≥1 dose of study intervention using AE, laboratory, and vital signs data. Treatment-emergent safety data will be defined as events from the first dose of study intervention through approximately 28 days after the last dose, or upon initiation of a new antineoplastic therapy, whichever occurs first. Incidence of AEs will be presented by type with and without regard to causality per investigator judgment and by frequency of overall toxicity graded by National Cancer Institute Common Terminology Criteria AE version 4.03.

PK data analyses will be conducted in patients who receive ≥1 dose of talazoparib or enzalutamide with an evaluable PK sample. Analyses will include descriptive summary statistics of the predose plasma concentrations of talazoparib, enzalutamide, and its N-desmethyl metabolite by study visit and treatment arm.

PROs will be evaluated as between-arm change from baseline and time to deterioration analyses. PROs will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (Core 30; EORTC QLQ C30) and its QLQ-PR25 prostate cancer module, Brief Pain Inventory-Short Form (BPI-SF), European Quality of Life 5 Dimension, 5 Level Scale (EQ-5D-5L) and patient global impression of severity (PGI-S) at day 1 (baseline), every 4 weeks through week 25, every 8 weeks until week 57 and then every 12 weeks until treatment is discontinued.

The EORTC QLQ-C30 comprises five multi-item functional subscales, three multi-item symptom scales, a global health score/quality-of-life subscale, and six single-item symptom scales assessing other disease and/or treatment-related symptoms. The EORTC QLQ-PR25 comprises two multi-item functional scales (sexual activity and sexual functioning) and four single-item symptom scales (urinary symptoms, bowel symptoms, hormonal treatment-related symptoms and incontinence aid).

Pain will be assessed using the BPI-SF questionnaire, a validated nine-item instrument that uses a self-reported scale to assess level of pain, its effect on activities of daily living and analgesic medication use.

The EQ-5D-5L is a validated and standardized instrument that measures the general health status of participants. Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort and anxiety/depression by choosing one of five possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire

also includes a visual analog scale to self-rate general health state on a scale from 'the worst health you can imagine' to 'the best health you can imagine'.

The PGI-S scale is a validated, generic, one-item questionnaire using balanced Likert scales that asks patients to rate the severity of their illness. The PGI-S can be used as an anchoring method to determine the minimal clinically significant difference for other PROs. Patients will rate the severity of their illness over the past 4 weeks on a five-point scale where 1 is 'None' and 5 is 'Very severe'.

Biomarkers will be assessed separately for blood, circulating tumor cells, tumor tissue, and saliva collected during the study.

Statistical analysis

Time-to-event distributions will be estimated using Kaplan–Meier curves, and hazard ratios and associated 95% CI will be estimated using a Cox proportional hazard model. To control the overall type I error rate for the study, a hierarchical testing approach will be used, whereby rPFS will be formally tested first. If it is significant, then OS will be tested at an overall two-sided 5% level of significance.

For all PROs, longitudinal mixed-effects analysis will be used to estimate the overall between arm differences in change from baseline scores. Time to deterioration analyses will be evaluated via the Kaplan–Meier method.

Stratified analysis of key efficacy end points including rPFS and OS will be conducted, in addition to *post hoc* subgroup analyses of the *BRCA* and non-*BRCA* groups.

Discussion & future perspective

The clinical benefit of PARP inhibitors in patients with metastatic prostate cancer and HRR gene alterations has been established. Olaparib improved OS and was approved in the USA for the treatment of patients with mCRPC and HRR gene alterations following treatment with enzalutamide or abiraterone [45,46], and in Europe as a monotherapy for the treatment of adult patients with mCRPC and *BRCA1/2* mutations who have progressed following prior therapy that included a new hormonal agent [47]. Rucaparib also demonstrated antitumor efficacy and received accelerated approval from the US FDA for men with *BRCA*-mutated mCRPC [48,49]. Non-clinical studies showed enhanced activity of PARP inhibitors in combination with an ARSI, such as enzalutamide or abiraterone, relative to the respective single agents, thus providing a rationale for clinical studies focusing on combination therapy as first-line treatment options for patients with mCRPC [39,50,51]. In addition, a phase III trial (NCT03748641) assessing niraparib in combination with abiraterone acetate and prednisone showed improved clinical outcomes in patients with HRR gene alterations [52]; another phase III trial (NCT03732820) also demonstrated the benefit of olaparib in combination with abiraterone in patients with newly diagnosed mCRPC, regardless of HRR status [53]. The TALAPRO-2 (NCT03395197) study is ongoing and OS data from patients with and without HRR gene alterations is awaited [54].

PARP inhibitors are also entering the arena, alone or in combination with an ARSI, in the mCSPC setting. In addition to the TALAPRO-3 study described in this paper, another ongoing phase III trial is evaluating niraparib in combination with abiraterone acetate and prednisone in mCSPC in patients with HRR-mutated disease (NCT04497844). Other PARP inhibitors, including olaparib (NCT05167175) and rucaparib (NCT03413995), are also under investigation in single-arm phase II studies, in combination with abiraterone acetate and prednisone, or alone, in patients with mCSPC and DDR alterations. These trials, inclusive of TALAPRO-3, collectively may lead to a transformation in clinical practice with incorporation of PARP inhibitors in the treatment paradigm for mCSPC patients harboring HRR gene alterations.

Conclusion

The TALAPRO-3 study will be conducted to demonstrate whether talazoparib in combination with enzalutamide can improve efficacy in terms of rPFS versus placebo plus enzalutamide in men with mCSPC and HRR gene alterations undergoing ADT.

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Executive summary

Background

- Despite the combination of androgen deprivation therapy (ADT) with an androgen-receptor signaling inhibitor (ARSI) becoming standard-of-care for patients with metastatic castration-sensitive prostate cancer (mCSPC), many patients will still progress to metastatic castration-resistant prostate cancer (mCRPC) in ~3 years, highlighting the need for novel therapeutic strategies.
- Poly(ADP-ribose) polymerase (PARP) inhibitors in combination with an ARSI have shown clinical benefits in the treatment of mCRPC.
- Talazoparib in combination with enzalutamide has recently been approved in the USA for the treatment of adult patients with HRR gene-mutated mCRPC.
- Homologous recombination repair (HRR) alterations in mCSPC are associated with shorter progression to mCRPC and have also been shown to sensitize tumors to PARP inhibitors, suggesting the potential use of PARP inhibitors in patients with mCSPC and HRR alterations.
- Talazoparib is a potent PARP inhibitor that has demonstrated robust antitumor activity in men with mCRPC with HRR gene alterations who received prior life-prolonging therapy for castration resistant disease.

TALAPRO-3 study design & key eligibility criteria

- TALAPRO-3 is a phase III, multinational, double-blind, randomized study that aims to evaluate the efficacy and safety of talazoparib plus enzalutamide versus placebo plus enzalutamide in men with mCSPC and HRR gene alterations.
- The study will compare the efficacy and safety of talazoparib (0.5 mg/day) plus enzalutamide (160 mg/day) to placebo plus enzalutamide (160 mg/day).
- Patients are stratified by the following factors: *de novo* mCSPC versus relapsed mCSPC; high-volume disease versus low-volume disease and *BRCA* versus non-*BRCA* mutational status.
- 599 patients were enrolled in 27 countries, including the USA, Canada, South Africa and Australia, and in European, South American and Asia-Pacific countries.

End points & evaluations

- The primary end point is investigator-assessed radiographic progression-free survival, defined as the time from the date of randomization to radiographic progression in soft tissue per RECIST 1.1, or in bone per PCWG3 criteria, or death, whichever occurs first.
- Key secondary end points include overall survival, objective response rate, duration of soft-tissue response, proportion of patients with prostate-specific antigen response ≥50%, circulating tumor DNA burden, safety and patient-reported outcomes.

Conclusion

- The TALAPRO-3 study will demonstrate whether talazoparib in combination with enzalutamide can improve the efficacy of enzalutamide in terms of radiographic progression-free survival in men with mCSPC and HRR gene alterations undergoing ADT.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0526

Author contributions

Contributed to study conception or design: N Agarwal, F Saad, A Azad, J Chakrabarti, H-C Chen, S Lanzalone, A Niyazov and K Fizazi. Contribution to acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript or revising it critically for important intellectual content: all authors. Final approval of the version to be published: all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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Ethical conduct of research

The study is being conducted in accordance with the protocol (Final Protocol Amendment 1), legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki. Additionally, informed consent has been obtained from the participants involved.

Data sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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