Clinical Trial Protocol

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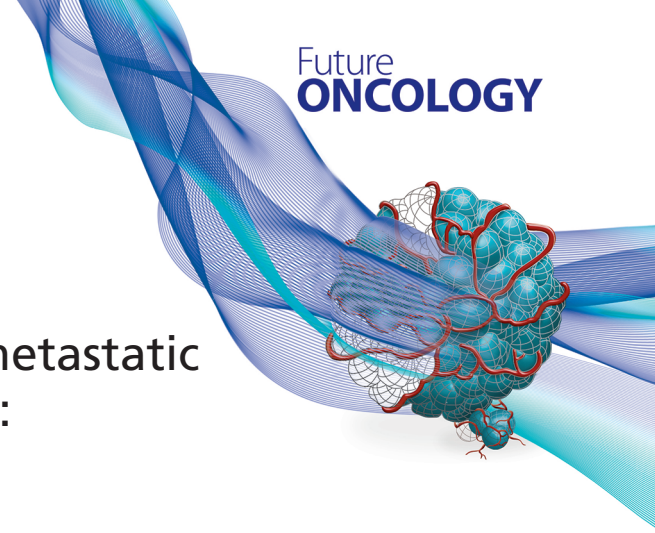

Talazoparib plus enzalutamide in metastatic castration-resistant prostate cancer: TALAPRO-2 phase III study design

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PARP inhibitors in combination with androgen receptor-targeted therapy have demonstrated potential in the treatment of metastatic castration-resistant prostate cancer (mCRPC). Here, we describe the design and rationale of the multinational, phase III, two-part TALAPRO-2 study comparing talazoparib plus enzalutamide versus placebo plus enzalutamide as a first-line treatment for patients with mCRPC with or without DNA damage response (DDR) alterations. This study has two co-primary end points: radiographic progression-free survival (rPFS) by blinded independent clinical review in all-comers (cohort 1) and in patients with DDR alterations (cohort 2). TALAPRO-2 will demonstrate whether talazoparib plus enzalutamide can significantly improve the efficacy of enzalutamide in terms of rPFS in both molecularly unselected and DDR-deficient patients with mCRPC (NCT03395197).

Clinical Trial Registration: NCT03395197 (ClinicalTrials.gov).

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Prostate cancer represents the second most common cancer diagnosis in men, and the fifth leading global cause of death with almost 1.3 million new cases and 360,000 fatalities (3.8% of all cancer deaths in men) reported in 2018 [1]. Despite significant advances in the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) in recent years, currently available therapies are not curative and subsequent progression of disease usually reflects reactivation of the androgen receptor (AR) signaling pathway [2]. Therefore, new therapeutic approaches, including novel therapies and treatment combinations, are required for patients with mCRPC [3].

Approximately 23–27% of men with advanced/metastatic prostate cancer, including mCRPC, harbor somatic and/or germline DNA damage response (DDR) alterations in a number of genes, including *BRCA1/2*, *ATM*, *FANCA* and *CHEK2* [4–7]. The relatively high prevalence of DDR alterations in patients with mCRPC provides an opportunity for treatment with PARP inhibitors in this setting [5,6].

PARP inhibitors have demonstrated efficacy in patients with mCRPC harboring DDR alterations, including *BRCA1/2*, *PALB2* and other gene alterations within the DDR pathway [8–11]. Based on pivotal phase II and III trials, two PARP inhibitors have recently been approved in multiple countries for patients with mCRPC carrying DDR

alterations. In 2020, olaparib was approved in the USA for patients with a deleterious or suspected deleterious DDR mutation who have progressed following treatment with enzalutamide or abiraterone, and in the EU for patients with germline and/or somatic *BRCA1/2* mutations who have progressed following prior therapy that included a new hormonal agent [12,13]. Similarly, the US FDA accelerated approval for rucaparib indicated for the treatment of patients with a deleterious *BRCA* mutation who have progressed following treatment with AR-directed therapy and a taxane-based chemotherapy [14]. Several ongoing and completed studies continue to investigate the potential of PARP inhibitors to treat patients with mCRPC with DDR alterations [15], including the TALAPRO-1 study of talazoparib in patients harboring DDR alterations, which has shown efficacy in prespecified interim analyses [16,17].

Talazoparib is a potent PARP inhibitor that also traps PARP on single-strand DNA breaks, thereby preventing DNA repair and selectively killing tumor cells with DDR alterations such as *BRCA1/2* (Figure 1A) [18–20]. Talazoparib has been approved in both the USA and the EU as a monotherapy for the treatment of patients with germline *BRCA1/2*-mutated, ERBB2-negative, locally advanced or metastatic breast cancer [21,22].

In addition to demonstrated efficacy as a monotherapy against tumor cells with DDR alterations, multiple preclinical studies and clinical evidence suggest the potential for PARP inhibitors to target tumors regardless of DDR alteration status when combined with an AR signaling inhibitor (Figure 1B) [23,24]. AR blockade downregulates DDR gene expression, which has been shown to induce '*BRCA*ness' and activate PARP [25,26]. In addition, studies have indicated that PARP activity supports AR function; therefore, PARP inhibition is expected to reduce AR signaling and complement the effect of androgen signaling inhibitors [23,27,28]. Clinical resistance to AR blockade has also been linked to DNA repair gene alterations and is also associated with co-deletion of *Rb* gene and *BRCA2*, which is in turn associated with PARP inhibitor sensitivity [29,30]. Finally, a phase II proof-of-concept study demonstrated that olaparib in combination with abiraterone significantly prolonged radiographic progression-free survival (rPFS) compared with abiraterone monotherapy in patients with mCRPC with and without DDR alterations [31].

Enzalutamide is an AR inhibitor that competitively inhibits androgen binding to androgen receptors, thus preventing AR nuclear translocation and interaction with DNA, resulting in decreased proliferation and induced cell death of prostate cancer cells [32]. Enzalutamide is approved for the treatment of CRPC and metastatic castration-

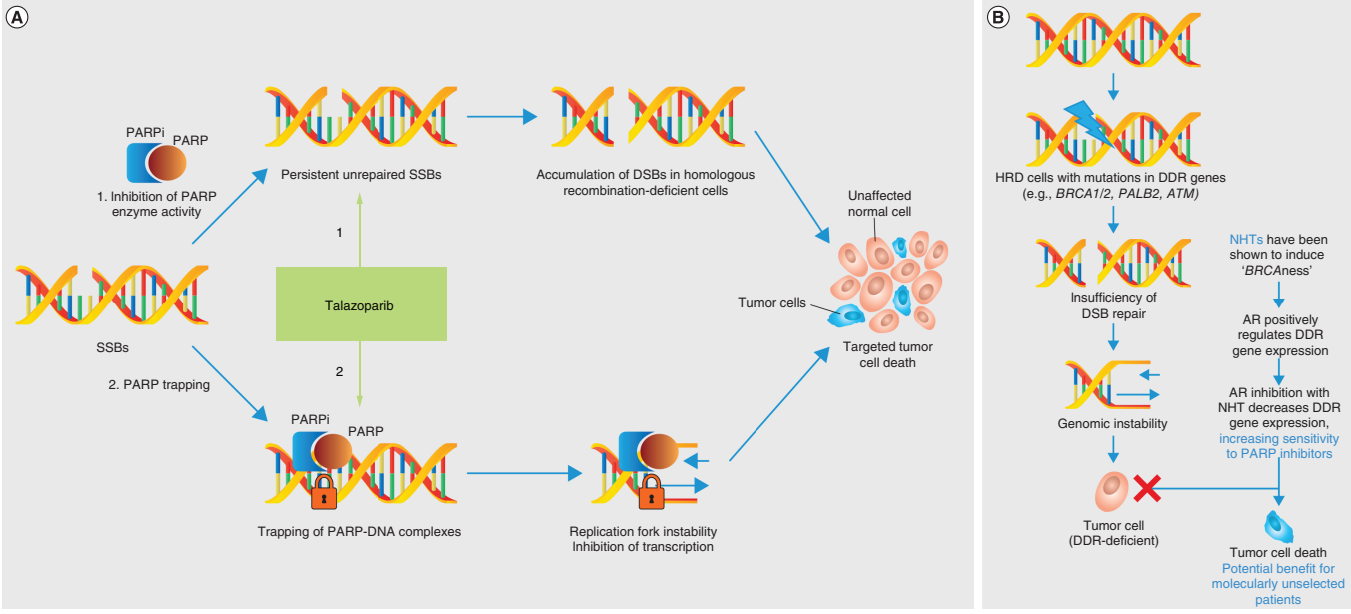

Figure 1. Mechanistic overview of PARP inhibition. (A) Dual cytotoxic mechanisms of PARPi; **(B)** PARPi in combination with NHT may benefit molecularly unselected patients.
Adapted with permission from [18].
AR: Androgen receptor; DDR: DNA damage response; DSB: Double-strand break; HRD: Homologous recombination deficiency; NHT: Novel hormonal therapy; PARPi: PARP inhibitor; SSB: Single-strand break.

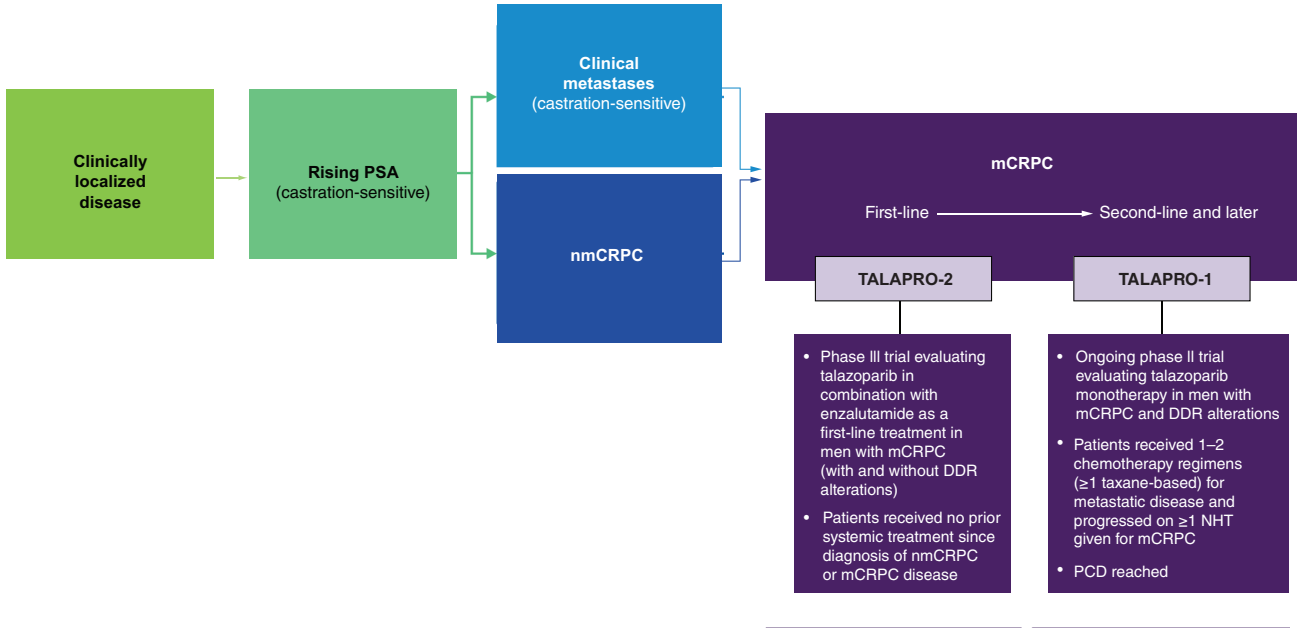

Figure 2. An overview of the treatment landscape of talazoparib in prostate cancer.
DDR: DNA damage response; mCRPC: Metastatic castration-resistant prostate cancer; NHT: Novel hormonal therapy; nmCRPC: Nonmetastatic castration-resistant prostate cancer; PCD: Primary completion date; PSA: Prostate-specific antigen.

sensitive prostate cancer (CSPC), and is currently being investigated in the neoadjuvant setting for CSPC and in high-risk nonmetastatic, hormone-sensitive prostate cancer patients who recur after primary therapy [33–35].

Overall, these studies suggest that talazoparib in combination with an AR inhibitor, such as enzalutamide, may be efficacious in the treatment of patients with mCRPC with or without DDR alterations, and provide a rationale for further assessment in a randomized controlled trial in this setting.

TALAPRO-2 trial

Study design

TALAPRO-2 is a multinational, phase III, two-part clinical trial that aims to evaluate the efficacy, safety, pharmacokinetics (PK) and patient-reported outcomes (PROs) of talazoparib in combination with enzalutamide as a first-line treatment for patients with mCRPC (with or without DDR alterations; Figures 2 & 3). Part 1 of the TALAPRO-2 study was the open-label, non-randomized portion to confirm the starting dose of talazoparib to be given in combination with enzalutamide, due to potential drug–drug interaction between enzalutamide, an *in vitro* modulator of P-glycoprotein drug transporters, and talazoparib [36]. Part 2 is a 1:1 randomized, double-blind, placebo-controlled study comparing oral talazoparib 0.5 mg/day plus oral enzalutamide 160 mg/day versus placebo plus enzalutamide 160 mg/day in patients with mCRPC with and without DDR alterations, and no prior systemic treatment since the diagnosis of nonmetastatic CRPC or mCRPC disease, with the exception of androgen deprivation therapy (ADT) and first-generation antiandrogens.

In part 1, patients with mCRPC (with unknown DDR alterations) initially received a talazoparib starting dose of 1 mg/day plus enzalutamide 160 mg/day (n = 13). Based on a review of prespecified target safety events and PK data, patients still receiving treatment in the study and started talazoparib dosing at 1 mg/day had their dose reduced to talazoparib 0.5 mg/day plus enzalutamide 160 mg/day. An additional six patients had an initial talazoparib starting dose of 0.5 mg/day plus enzalutamide 160 mg/day. Evaluation of data in part 1 of the TALAPRO-2 study demonstrated that talazoparib 0.5 mg/day plus enzalutamide 160 mg/day maintained similar steady-state talazoparib exposure as seen with talazoparib 1.0 mg/day monotherapy [36]. In addition, treatment with talazoparib 0.5 or 1.0 mg/day in combination with enzalutamide 160 mg/day showed promising signs of efficacy reflected by a reduction in prostate-specific antigen (PSA) levels from baseline; 92 and 100% of patients had a 50% decline from baseline in PSA in the 1 mg/day and 0.5 mg/day cohorts, respectively [36]. Due to a manageable safety profile in

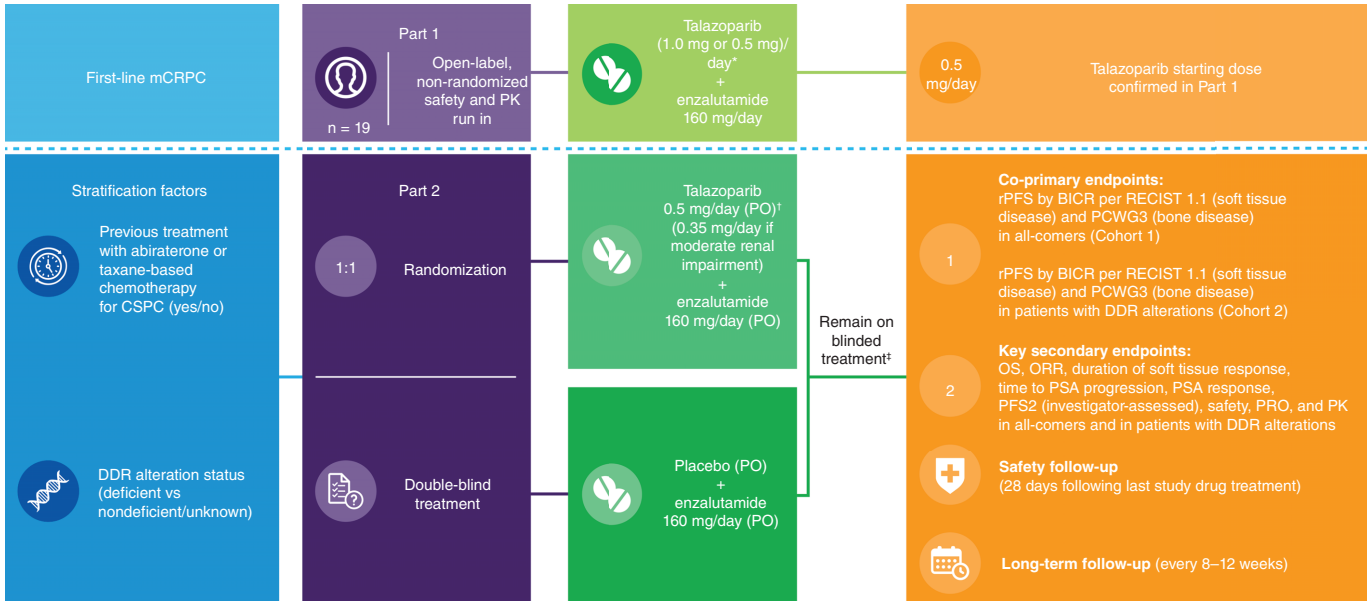

Figure 3. TALAPRO-2 trial design.
*Patients initially received a talazoparib starting dose of 1.0 mg/day orally prior to dose reduction to 0.5 mg/day based on safety and PK data.
†Dose of talazoparib 0.5 mg/day plus enzalutamide 160 mg/day was determined in part 1 as providing the same talazoparib exposure as talazoparib 1.0 mg/day monotherapy.
‡Remain on blinded treatment until radiographic progression and no longer clinically benefiting as per investigator opinion, the occurrence of an AE leading to permanent discontinuation, patient decision to discontinue treatment, or death.
AE: Adverse event; BICR: Blinded independent central review; CSPC: Castration-sensitive prostate cancer; DDR: DNA damage response; mCRPC: Metastatic castration-resistant prostate cancer; ORR: Objective response rate; OS: Overall survival; PCWG3: Prostate Cancer Working Group 3; PFS2: Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy, or death from any cause, whichever occurs first; PK: Pharmacokinetics; PO: By mouth; PRO: Patient-reported outcome; PSA: Prostate-specific antigen; RECIST: Response evaluation criteria in solid tumor; rPFS: Radiographic progression-free survival.

patients with mCRPC, a starting dose of talazoparib 0.5 mg/day in combination with enzalutamide 160 mg/day was confirmed for part 2 of the TALAPRO-2 study.

In part 2, for patients with moderate renal impairment (estimated glomerular filtration rate 30–59 ml/min/1.73 m^2), the starting dose of talazoparib is 0.35 mg/day to account for lower clearance in this subpopulation. Patients are stratified according to prior novel hormonal therapy or taxane-based chemotherapy for CSPC (yes/no), and DDR alteration status (positive or negative/unknown).

Enrollment

Enrollment for the TALAPRO-2 study began in December 2017. The enrollment goal was 1037 patients (19 patients in part 1, completed; 1018 patients in part 2, completed), with enrollment in the second part of the study conducted at 223 sites in 26 countries, including 32 states across the USA (Figure 4 & Supplementary Table 1) [37]. In part 2, two cohorts have been enrolled: an all-comers cohort (cohort 1) where patients are not required to have DDR alterations, and a second cohort including patients harboring DDR alterations (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A* and *CDK12*). Although all-comers (cohort 1) were unselected for DDR alterations, assessment of DDR alterations from a blood sample or the most recent tumor tissue sample completed prior to randomization was required for stratification (Supplemental Methods).

Key eligibility criteria

To be eligible to take part in TALAPRO-2, patients must be male and aged ≥18 years (≥20 years in Japan) with histologically/cytologically confirmed adenocarcinoma of the prostate, and have asymptomatic or mildly symptomatic mCRPC. Patients must have undergone bilateral orchiectomy or be receiving ongoing ADT with a gonadotropin-releasing hormone agonist/antagonist, and serum testosterone ≤50 ng/dl (≤1.73 nmol/l) at screening. Progressive disease at study entry is defined by ≥1 of the following three criteria: PSA progression,

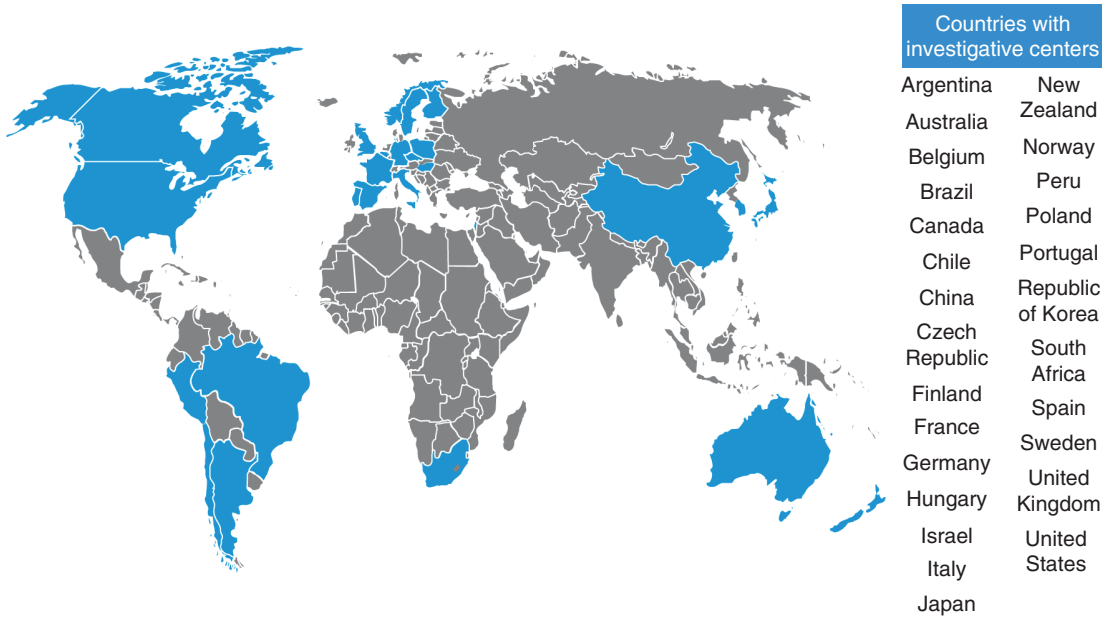

Figure 4. TALAPRO-2 enrollment (part 2).

defined as ≥2 rising PSA values from three consecutive assessments with ≥7 days between assessments; soft tissue disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; and bone disease progression per Prostate Cancer Working Group 3 (PCWG3) guidelines, with ≥2 new metastatic bone lesions on whole body radionuclide bone scan. Other key inclusion criteria are listed in Table 1.

Patients are not eligible to take part in the study if they have received any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state, with the exception of prior treatment with ADT and first-generation antiandrogens. Other exclusionary agents are listed in Table 1. Docetaxel and abiraterone received for CSPC are not exclusionary. Patients are also excluded from the study if they have known or suspected brain metastases, or active leptomeningeal disease; any history of myelodysplastic syndrome, acute myeloid leukemia, or prior malignancy (except for carcinoma *in situ* or nonmelanoma skin cancer, any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence or progression regardless of the stage, or American Joint Committee on Cancer Stage 0/1 cancer <3 years before randomization that has a remote probability of recurrence or progression as per investigator opinion); clinically significant cardiovascular disease; or significant renal, hepatic or bone marrow organ dysfunction (Table 1).

Study end points & evaluations

The TALAPRO-2 study has two co-primary end points: rPFS in all-comers, unselected for DDR alterations (cohort 1), and rPFS in patients with DDR alterations (cohort 2; Table 2). Efficacy analysis will include patients with DDR-deficient mCRPC from both cohorts 1 and 2. This approach allows testing of hypotheses in both populations. The study will be considered positive if at least one of the primary end points is statistically significant. To maintain the overall type I error, alpha will be split between the two primary end points. rPFS is defined as time from randomization to the evidence of radiographic progression per RECIST 1.1 (soft tissue disease) or PCWG3 (bone disease) by blinded independent central review (BICR) or death, whichever occurs first, and will be compared between the two treatment arms by a one-sided stratified log-rank test. Efficacy will be assessed by radiography every 8 weeks up to week 25 and every 12 weeks thereafter.

Secondary end points will be analyzed in all-comers (cohort 1) and in patients with DDR alterations (cohort 2), separately and include: overall survival defined as the time from randomization to death from any cause; objective response rate defined as the proportion of patients with measurable soft tissue disease at baseline with objective response per RECIST 1.1; duration of soft tissue response defined as the time from first objective evidence of complete response or partial response to first objective evidence of disease progression (assessed in soft tissue per RECIST 1.1) or death, whichever occurs first; confirmed PSA response ≥50%; and time to confirmed PSA

Table 1. Key inclusion and exclusion criteria.

Key inclusion criteria[†]	
Demographic	• Male, aged ≥18 years[‡]
Additional criteria	• ECOG performance status ≤1 • Life expectancy ≥12 months per investigator assessment • Prospective assessment of DDR mutation status by a gene mutation biomarker panel using blood or tumor tissue • Written informed consent
Prostate cancer status	• Histologically/cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features • Bilateral orchiectomy or ongoing ADT with a GnRH agonist/antagonist, with serum testosterone ≤50 ng/dl (≤1.73 nmol/l) at screening; ADT must continue throughout the study for patients who have not undergone bilateral orchiectomy • Asymptomatic or mildly symptomatic mCRPC • Progressive disease at study entry, defined by ≥1 of the following three criteria: ◦ PSA progression (≥2 rising PSA values from three consecutive assessments with ≥7 days between assessments) ◦ Soft tissue disease progression per RECIST 1.1 (CT or MRI) ◦ Bone disease progression per PCWG3, with ≥2 new metastatic bone lesions on whole body radionuclide bone scan
Key exclusion criteria	
Prior treatment	• Systemic life-prolonging treatment initiated in the nonmetastatic CRPC or mCRPC disease state[§] • Prior treatment with second-generation AR inhibitors (enzalutamide, apalutamide and darolutamide), a PARP inhibitor, cyclophosphamide or mitoxantrone for prostate cancer • The following agents are NOT exclusionary if received for CSPC: docetaxel, biologic therapy (e.g., sipuleucel-T), or radionuclide therapy, if discontinued 28 days prior to day 1 (part 1) or randomization (part 2); hormonal therapy (e.g., bicalutamide, nilutamide, flutamide, estrogens) or abiraterone, if discontinued prior to randomization • Prior treatment with platinum-based therapy ≤6 months (from the last dose) or any history of disease progression on platinum-based therapy ≤6 months (from the last dose) • Any investigational agent ≤4 weeks before day 1 or randomization • Prior treatment with opioids for pain related to either primary prostate cancer or metastasis ≤28 days before day 1 or randomization • Major surgery, defined by the investigator, ≤2 weeks before day 1 or randomization, or palliative localized radiation therapy ≤3 weeks before randomization • Use of potent P-gp inhibitors ≤7 days before day 1 or randomization
Clinically significant disease	• Clinically significant cardiovascular disease • Renal: eGFR <30 mL/min/1.73 m^2 by the MDRD equation • Hepatic: total serum bilirubin >1.5 × ULN or >3 × ULN in patients with Gilbert syndrome or with suspected extrahepatic source of elevation; AST or ALT >2.5 × ULN (>5 × ULN if liver function abnormalities are due to hepatic metastasis); or ALB <2.8 g/dl (at screening) • Neurologic: known or suspected brain metastasis or active leptomeningeal disease; symptomatic or impending spinal cord compression or cauda equina syndrome; seizure risk; history of loss of consciousness or TIA ≤12 months before randomization • Hematologic: ANC <1500/μl, platelets <100,000/μl, or hemoglobin <9 g/dl; no growth factors or blood transfusions ≤14 days before screening hematology values • Gastrointestinal: disorders affecting absorption • Prior cancers: including MDS and AML, with the exception of carcinoma *in situ* or nonmelanoma skin cancers, any prior malignancies ≥3 years before randomization with no subsequent evidence of recurrence/progression regardless of stage, or AJCC Stage 0/1 cancer <3 years before randomization that has a remote possibility of recurrence/progression in the opinion of the investigator

[†]Country-specific protocols may differ.
[‡]≥20 years in Japan.
[§]ADT and first-generation antiandrogens received for CRPC are not exclusionary; prior docetaxel and abiraterone in CSPC setting are allowed.
ADT: Androgen deprivation therapy; AJCC: American Joint Committee on Cancer; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count; AR: Androgen receptor; CRPC: Castration-resistant prostate cancer; CSPC: Castration-sensitive prostate cancer; CT: Computed tomography; DDR: DNA damage response; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; GnRH: Gonadotropin-releasing hormone; mCRPC: Metastatic castration-resistant prostate cancer; MDRD: Modification of Diet in Renal Disease (available at www.mdrd.com); MDS: Myelodysplastic syndrome; MRI: Magnetic resonance imaging; PARP: Poly(ADP-ribose) polymerase; P-gp: P-glycoprotein; PCWG3: Prostate Cancer Working Group 3; PSA: Prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumor; TIA: Transient ischemic attack; ULN: Upper limit of normal.

progression. Further secondary end points include time to initiation of cytotoxic chemotherapy or antineoplastic therapy; time to first symptomatic skeletal event; PFS on second-line therapy, defined as time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first; time to opiate use; safety; PK; and PROs (Table 2).

Time-to-event distributions will be estimated using Kaplan–Meier curves, and hazard ratios and associated 95% CIs estimated using a Cox proportional hazards model. The incidence of adverse events are characterized by type, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03), seriousness and relationship to study treatment. PK is characterized by pre-dose trough and post-dose plasma concentrations of talazoparib, enzalutamide and its N-desmethyl metabolite. PROs are assessed to evaluate the following changes from baseline: time to deterioration in pain using the Brief Pain Inventory Short Form; global health status/quality of life, functions and symptoms using the EORTC QLQ-C30 and QLQ-PR25 questionnaires; and general health status using the EQ-5D-5L health questionnaire. A full list of the PROs evaluated in the study can be found in Table 2.

Table 2. Study end points.

	Part 1
Primary end point	• Occurrence of target safety events
Secondary end point	• Multiple-dose PK parameters of talazoparib and enzalutamide and its N-desmethyl metabolite
	Part 2
Co-primary end points	• rPFS by BICR per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients unselected for DDR status (all-comers population; cohort 1) • rPFS by BICR per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients with DDR alterations (cohort 2)

Secondary end points analyzed for cohort 1 and cohort 2, separately	• OS
	• Proportion of patients with measurable soft tissue disease at baseline with OR per RECIST 1.1
	• Duration of soft tissue response per RECIST 1.1
	• Proportion of patients with PSA response ≥50%
	• Time to PSA progression
	• Time to initiation of cytotoxic chemotherapy
	• Time to initiation of antineoplastic therapy
	• Time to first symptomatic skeletal event (fracture, spinal cord compression, surgery, radiation to the bone)
	• PFS2 based on investigator assessment (time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first)
	• Time to opiate use for prostate cancer pain
	• Incidence of AEs and SAEs by type and severity (NCI CTCAE version 4.03)
	• PK characterized by pre-dose trough and post-dose plasma concentrations of talazoparib, enzalutamide and its N-desmethyl metabolite
	• PROs:
	  • Change from baseline and time to deterioration in pain symptoms per BPI-SF
	  • Change from baseline in general health status per EQ-5D-5L
	  • Change from baseline and time to definitive deterioration in cancer-specific global health status/QoL, functioning and symptoms per EORTC QLQ-C30
	• Time to definitive deterioration in disease-specific urinary symptoms per EORTC QLQ-PR25

AE: Adverse event; BICR: Blinded independent clinical review; BPI-SF: Brief Pain Inventory Short Form; DDR: DNA damage response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer cancer-specific global health questionnaire; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer disease-specific urinary symptoms questionnaire; EQ-5D-5L: European Quality of Life 5-dimension, 5-level scale; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Event; OR: Objective response; OS: Overall survival; PCWG3: Prostate Cancer Working Group 3; PFS2: Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy, or death from any cause, whichever occurs first (investigator-assessed); PK: Pharmacokinetics; PRO: Patient-reported outcome; PSA: Prostate-specific antigen; QoL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumor; rPFS: Radiographic progression-free survival; SAE: Serious adverse event.

Discussion & future perspective

PARP inhibitors are becoming increasingly recognized for their potential therapeutic role in men with mCRPC, particularly in the setting of DDR alterations [38,39]. Importantly, preclinical studies suggest that PARP inhibitors combined with androgen signaling inhibitors (such as enzalutamide or abiraterone) show enhanced activity relative to the respective single agents [23,24,27], thus providing a rationale for clinical studies co-targeting AR and PARP. Several phase II and III clinical trials of different PARP inhibitors have demonstrated the antitumor activity of single-agent PARP inhibition in men with mCRPC in different metastatic settings, including progression after AR-targeted therapy with or without taxane-based chemotherapy [9–11,16,40]. However, results from other studies suggest dose-limiting toxicities (NCT02924766) and novel emergent toxicities associated with drug–drug interactions when combining PARP inhibitors and androgen signaling inhibitors [36]. Further proof-of-concept data from a phase II study involving patients with mCRPC regardless of DDR alteration status showed that olaparib plus abiraterone resulted in a significant rPFS benefit compared with patients treated only with abiraterone [31]. However, several patients in this study had a partially characterized homologous recombination repair (HRR) status that may have in fact constituted an HRR gene mutation, thereby explaining the observed treatment effect in this setting [31]. Bringing PARP inhibitors forward in the treatment paradigm for mCRPC may lead to even greater benefits, and thus the TALAPRO-2 study explores the efficacy of talazoparib plus enzalutamide as a first-line treatment for men with mCRPC in all-comers as well as with DDR alterations.

A number of ongoing phase III trials are evaluating different PARP inhibitors given together with a novel androgen signaling inhibitor, irrespective of DDR alteration status, in patients with previously untreated mCRPC. Two of the trials are combining a PARP inhibitor with abiraterone (olaparib, NCT03732820; niraparib, NCT03748641) [41,42], while two other trials are combining enzalutamide with either talazoparib (TALAPRO-2, NCT03395197) or rucaparib (NCT04455750). Another phase III trial is combining niraparib and abiraterone in patients with deleterious HRR mutations and metastatic castration-sensitive prostate cancer (NCT04497844).

The results of these trials may improve our understanding of the observed preclinical interactions between AR signaling and DNA repair in the mCRPC setting.

There are also ongoing trials evaluating PARP inhibitors in metastatic hormone-sensitive prostate cancer, including studies of rucaparib monotherapy in patients harboring germline DNA repair gene mutations (NCT03413995) and enzalutamide plus talazoparib in hormone-sensitive prostate cancer (NCT04332744).

Patient enrollment for TALAPRO-2, which began in December 2017, was conducted in multiple regions, including the USA, Europe, Israel, South America, South Africa and the Asia-Pacific region (Figure 4) [37].

Conclusion

Overall, results from the phase III TALAPRO-2 trial will demonstrate whether talazoparib plus enzalutamide can significantly improve the efficacy of enzalutamide in terms of rPFS in both molecularly unselected and DDR-deficient patients with mCRPC receiving first-line treatment.

Executive summary

Background

- Despite significant advances in the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) in recent years, currently available therapies are not curative and subsequent progression of disease usually reflects reactivation of the androgen receptor signaling pathway.
- New therapeutic approaches are required for patients with mCRPC, including novel therapies and novel treatment combinations.
- PARP inhibitors have demonstrated efficacy in patients with mCRPC harboring DNA damage response (DDR) alterations, resulting in the approval of olaparib and rucaparib for patients with suspected or determined DDR alterations.
- Preliminary studies suggest the potential for PARP inhibitors to target tumors regardless of DDR alteration status when combined with an androgen receptor signaling inhibitor.

TALAPRO-2 study design & eligibility criteria

- TALAPRO-2 is a multinational, phase III, two-part clinical trial that aims to evaluate talazoparib in combination with the androgen receptor signaling inhibitor enzalutamide as a first-line treatment for patients 18 years or older (≥20 years in Japan) with mCRPC (with or without DDR alterations).
- The open-label, non-randomized portion (part 1) of the TALAPRO-2 study confirmed the starting dose of talazoparib to be given in combination with enzalutamide.
- The randomized, double-blind, placebo-controlled (part 2) portion compares oral talazoparib 0.5 mg/day plus oral enzalutamide 160 mg/day versus placebo plus enzalutamide 160 mg/day in patients with mCRPC, with no prior systemic treatment since the diagnosis of nonmetastatic CRPC or mCRPC disease.
- Patients are stratified by prior novel hormonal therapy or taxane for castration-sensitive prostate cancer and DDR alteration status (deficient vs nondeficient/unknown).
- The enrollment goal was 1037 patients (19 patients in part 1, completed; 1018 patients in part 2, completed).

Outcome measures/end points

- This study has two co-primary end points: radiographic progression-free survival (rPFS) by blinded independent clinical review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Working Group 3 (bone disease) in all-comers (cohort 1) and in patients with DDR alterations (cohort 2).
- Secondary end points include overall survival and objective response rate in all-comers (cohort 1) and in patients with DDR alterations (cohort 2).

Conclusion

- The TALAPRO-2 study will demonstrate whether talazoparib plus enzalutamide can significantly improve the efficacy of enzalutamide in terms of rPFS in both molecularly unselected and DDR-deficient patients with mCRPC receiving first-line treatment.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0811

Author contributions

Contributions to the study conception or design: N Agarwal, A Czibere, N Di Santo, M Elmeliegy, X Lin, ML Paccagnella and K Fizazi. Contribution to the 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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Ethical conduct of research

The study is being conducted in accordance with the protocol, 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.

Data-sharing statement

Pfizer will provide access to individual de-identified participant data and related study documents (e.g. protocol, statistical analysis plan [SAP], clinical study report [CSR]) upon request from qualified researchers, and subject to certain criteria, condition and exceptions.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68(6), 394–424 (2018).
2. Nuhn P, De Bono JS, Fizazi K *et al.* Update on systemic prostate cancer therapies: management of metastatic castration-resistant prostate cancer in the era of precision oncology. *Eur. Urol.* 75(1), 88–99 (2019).
3. Parker C, Castro E, Fizazi K *et al.* Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 31(9), 1119–1134 (2020).
4. Robinson D, Van Allen EM, Wu YM *et al.* Integrative clinical genomics of advanced prostate cancer. *Cell* 161(5), 1215–1228 (2015).
5. Armenia J, Wankowicz SAM, Liu D *et al.* The long tail of oncogenic drivers in prostate cancer. *Nat. Genet.* 50(5), 645–651 (2018).
6. Chung JH, Dewal N, Sokol E *et al.* Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis. Oncol.* 3 doi:10.1200/PO.18.00283 (2019).
7. Abida W, Armenia J, Gopalan A *et al.* Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. *JCO Precis. Oncol.* 2017 doi:10.1200/PO.17.00029 (2017).
8. De Bono J, Mateo J, Fizazi K *et al.* Olaparib for metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* 382(22), 2091–2102 (2020).
9. Abida W, Patnaik A, Campbell D *et al.* Rucaparib in men with metastatic castration-resistant prostate cancer harboring a *BRCA1* or *BRCA2* gene alteration. *J. Clin. Oncol.* 38(32), 2345–2357 (2020).
10. Smith MR, Sandhu SK, Kelly WK *et al.* Pre-specified interim analysis of GALAHAD: a phase II study of niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD). *Ann. Oncol.* 30, v884–v885 (2019).
11. Hussain M, Mateo J, Fizazi K *et al.* Survival with olaparib in metastatic castration-resistant prostate cancer. *N. Engl. J. Med.* 383(24), 2345–2357 (2020).
12. U.S. Food and Drug Administration. LYNPARZA® (olaparib) prescribing information. (2020). www.azpicentral.com/lynparza_tb/lynparza_tb.pdf#page=1
13. ESMO. EMA Recommends Extension of Indications for Olaparib. (2020). www.esmo.org/oncology-news/ema-recommends-extension-of-indications-for-olaparib2
14. U.S. Food and Drug Administration. RUBRACA® (rucaparib) prescribing information. (2020). www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf
15. Antonarakis ES, Gomella LG, Petrylak DP. When and how to use parp inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. *Eur. Urol. Oncol.* 3(5), 594–611 (2020).

• **A comprehensive systematic review of the use of PARP inhibitors in prostate cancer with a focus on ongoing phase II/III trials evaluating PARP inhibitors as a monotherapy or in combination in the treatment of metastatic castration-resistant prostate cancer (mCRPC).**

16. De Bono J, Mehra N, Higano CS *et al.* TALAPRO-1: a phase II study of talazoparib (TALA) in men with DNA damage repair mutations (DDRmut) and metastatic castration-resistant prostate cancer (mCRPC) – First Interim Analysis (IA). *Presented at: Genitourinary Cancers Symposium (ASCO-GU).* San Francisco, CA, USA (February 13–15 2020).
17. Mehra N, Fizazi K, Laird AD *et al.* 138P TALAPRO-1: talazoparib (TALA) monotherapy in men with DNA damage response alterations (DDRalt) and metastatic castration-resistant prostate cancer (mCRPC): exploration of DDRalt germline/somatic origin. *Ann. Oncol.* 31, S294–S295 (2020).

• **Results from the interim analysis of the phase II TALAPRO-1 (NCT03148795) study in patients with progressive CRPC and DNA damage response alterations.**

18. Murai J, Huang SY, Das BB *et al.* Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res.* 72(21), 5588–5599 (2012).
19. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. *Science* 355(6330), 1152–1158 (2017).

20. Murai J, Huang SY, Renaud A *et al.* Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol. Cancer Ther.* 13(2), 433–443 (2014).

21. U.S. Food and Drug Administration. TALZENNA® (talazoparib) prescribing information. (2020). http://labeling.pfizer.com/ShowLabeling.aspx?id=11046

22. European Medicines Agency. TALZENNA® (talazoparib) Summary of Product Characteristics. (2019). www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf

23. Asim M, Tarish F, Zecchini HI *et al.* Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat Commun* 8(1), 374–374 (2017).

- **This preclinical study demonstrates that combining androgen deprivation therapy (ADT) with PARP inhibitors improves response to ADT, and suggets that ADT and PARP inhibitor treatment combinations are likely to be more effective in the early stages of CRPC.**

24. Gui B, Gui F, Takai T *et al.* Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *Proc. Natl Acad. Sci. USA* 116(29), 14573–14582 (2019).

25. Polkinghorn WR, Parker JS, Lee MX *et al.* Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov.* 3(11), 1245–1253 (2013).

26. Li L, Karanika S, Yang G *et al.* Androgen receptor inhibitor–induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci. Signal.* 10(480), eaam7479 (2017).

- **This preclinical study in xenografts demonstrates the mechanistic rationale for the combination of enzalutamide and the PARP inhibitor olaparib in the treatment of patients with CRPC, and suggests that pharmaceutically induced '*BRCA*ness' may expand the clinical use of PARP inhibitors.**

27. Schiewer MJ, Goodwin JF, Han S *et al.* Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov.* 2(12), 1134–1149 (2012).

28. Kounatidou E, Nakjang S, Mccracken SRC *et al.* A novel CRISPR-engineered prostate cancer cell line defines the AR-V transcriptome and identifies PARP inhibitor sensitivities. *Nucleic Acids Res.* 47(11), 5634–5647 (2019).

29. Chakraborty G, Armenia J, Mazzu YZ *et al.* Significance of *BRCA2* and *RB1* co-loss in aggressive prostate cancer progression. *Clin. Cancer Res.* 26(8), 2047–2064 (2020).

30. Wyatt AW, Azad AA, Volik SV *et al.* Genomic alterations in cell-free DNA and enzalutamide resistance in castration-resistant prostate cancer. *JAMA Oncol.* 2(12), 1598–1606 (2016).

31. Clarke N, Wiechno P, Alekseev B *et al.* Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase II trial. *Lancet Oncol.* 19(7), 975–986 (2018).

- **A randomized, double-blind phase II trial combining olaparib and abiraterone in patients with metastatic castration-resistant prostate cancer. Olaparib plus abiraterone was associated with significantly improved radiographic PFS compared with abiraterone alone, regardless of homologous recombination repair mutation.**

32. U.S. Food and Drug Administration. XTANDI® (enzalutamide) prescribing information. (2020). www.accessdata.fda.gov/drugsatfda_docs/label/2020/213674s000lbl.pdf

33. ClinicalTrials.gov.. Neoadjuvant Androgen Deprivation Therapy Combined With Enzalutamide and Abiraterone Using Multiparametric MRI and 18FDCFPyL PET/CT in Newly Diagnosed Prostate Cancer. (2021). https://clinicaltrials.gov/ct2/show/NCT03860987

34. Montgomery B, Tretiakova MS, Joshua AM *et al.* Neoadjuvant enzalutamide prior to prostatectomy. *Clin. Cancer Res.* 23(9), 2169–2176 (2017).

35. ClinicalTrials.gov.. Safety and efficacy study of enzalutamide plus leuprolide in patients with nonmetastatic prostate cancer (EMBARK). (2021). https://clinicaltrials.gov/ct2/show/NCT02319837

36. Agarwal N, Shore ND, Dunshee C *et al.* Clinical and safety outcomes of TALAPRO-2: a two-part phase III study of talazoparib (TALA) in combination with enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC). *J. Clin. Oncol.* 37(Suppl. 15), 5076–5076 (2019).

- **Results from Part 1 of the phase III TALAPRO-2 study suggest the starting dose of talazoparib plus enzalutamide for the randomized portion (part 2) of the TALAPRO-2 study.**

37. ClinicalTrials.gov.. Talazoparib + enzalutamide vs. enzalutamide monotherapy in mCRPC (TALAPRO-2). (2021). https://clinicaltrials.gov/ct2/show/NCT03395197

38. Tripathi A, Balakrishna P, Agarwal N. PARP inhibitors in castration-resistant prostate cancer. *Cancer Treat. Res. Commun.* 24, 100199 (2020).

39. Stellato M, Guadalupi V, Sepe P *et al.* The emerging role of PARP inhibitors in prostate cancer. *Expert. Rev. Anticancer Ther.* 20(8), 715–726 (2020).

40. De Bono JS, Mehra N, Higano CS *et al.* TALAPRO-1: phase II study of talazoparib (TALA) in patients (pts) with DNA damage repair alterations (DDRm) and metastatic castration-resistant prostate cancer (mCRPC) – updated interim analysis (IA). *J. Clin. Oncol.* 38(Suppl. 15), 5566 (2020).

41. Clarke NW, Armstrong AJ, Thiery-Vuillemin A *et al.* PROPEL: a randomized, phase III trial evaluating the efficacy and safety of olaparib combined with abiraterone as first-line therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). *J. Clin. Oncol.* 37(Suppl. 7), TPS340 (2019).

42. Chi KN, Rathkopf DE, Attard G *et al.* A phase III randomized, placebo-controlled, double-blind study of niraparib plus abiraterone acetate and prednisone versus abiraterone acetate and prednisone in patients with metastatic prostate cancer (NCT03748641). *J. Clin. Oncol.* 38(Suppl. 6), TPS257 (2020).

NCT03395197

Talazoparib plus enzalutamide in first-line metastatic castration-resistant prostate cancer:

TALAPRO-2 Phase III study design

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Objective and rationale

Primary objective

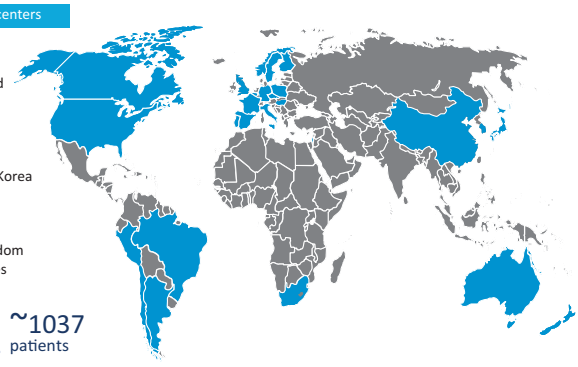
Demonstrate that talazoparib plus enzalutamide is superior to placebo plus enzalutamide in prolonging BICR-assessed rPFS in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR alterations

Rationale

Previous studies suggest that a PARP inhibitor in combination with an AR inhibitor may be efficacious in the treatment of mCRPC regardless of DDR alteration status [1-5]

Countries with investigative centers

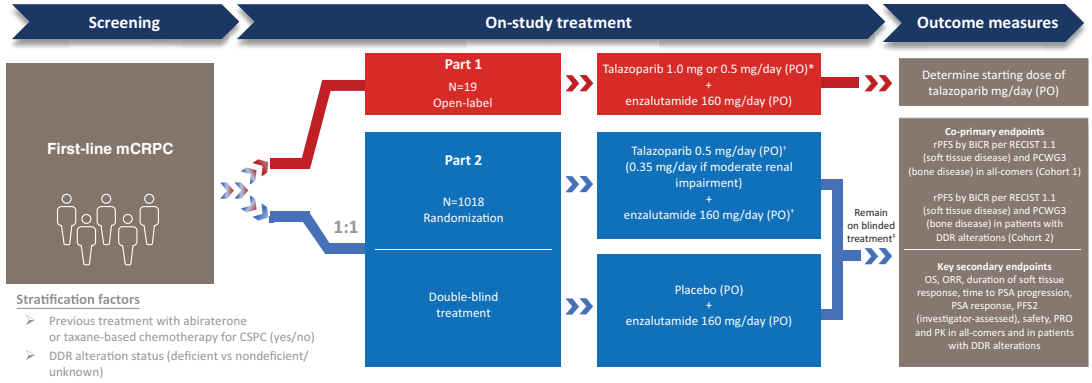
Argentina	Italy
Australia	Japan
Belgium	New Zealand
Brazil	Norway
Canada	Peru
Chile	Poland
China	Portugal
Czech Republic	Republic of Korea
Finland	South Africa
France	Spain
Germany	Sweden
Hungary	United Kingdom
Israel	United States



26 countries

~1037 patients

Study design



Key eligibility criteria

- Men aged ≥18 years§
- Histologically or cytologically confirmed adenocarcinoma of the prostate
- Asymptomatic or mildly symptomatic first-line mCRPC
- Prospective assessment of DDR alteration status by a gene alteration biomarker panel using blood or tumor tissue
- Bilateral orchiectomy or ongoing ADT with a GnRH agonist/antagonist, with serum testosterone ≤50 ng/dL (≤1.73 nmol/L) at screening¶
- ECOG performance status 0 or 1
- Progressive disease at study entry defined as at least one of the following:
  - PSA progression
  - Bone progression
  - Soft tissue progression

Glossary: *Patients initially received a talazoparib starting dose of 1.0 mg/day prior to dose reduction to 0.5 mg/day based on safety and PK data. †Dose of talazoparib 0.5 mg/day plus enzalutamide 160 mg/day was determined in Part 1 as providing the same talazoparib exposure as talazoparib 1.0 mg/day monotherapy. ‡Remain on blinded treatment until radiographic progression and no longer clinically benefiting as per investigator opinion, the occurrence of an AE leading to permanent discontinuation, patient decision to discontinue treatment, or death. §≥20 years in Japan. ¶ADT must continue throughout the study for patients who have not undergone bilateral orchiectomy. ADT: Androgen deprivation; AE: Adverse event; therapy; AR: Androgen receptor; BICR: Blinded independent central review; CSPC: Castration-sensitive prostate cancer; DDR: DNA damage response; ECOG: Eastern Cooperative Oncology Group; GnRH: Gonadotropin-releasing hormone; mCRPC: Metastatic castration-resistant prostate cancer; ORR: Objective response rate; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase; PCWG3: Prostate Cancer Working Group 3; PFS2: Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy, or death from any cause, whichever occurs first (investigator-assessed); PK: Pharmacokinetics; PO: By mouth; PRO: Patient-reported outcomes; PSA: Prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumors; rPFS: Radiographic progression-free survival.

References

1. Asim M, Tarish F, Zecchini HI *et al.* Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat. Comms.* 8(1), 374 (2017). 2. Gui B, Gui F, Takai T *et al.* Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *PNAS.* 116(29), 14573–14582 (2019). 3. Schiewer MJ, Goodwin JF, Han S *et al.* Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov.* 2(12), 1134–1149 (2012). 4. Kounatidou E, Nakjang S, McCracken SRC *et al.* A novel CRISPR-engineered prostate cancer cell line defines the AR-V transcriptome and identifies PARP inhibitor sensitivities. *Nucleic Acids Res.* 47(11), 5634–5647 (2019). 5. Clarke N, Wiechno P, Alekseev B *et al.* Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* 19(7), 975–986 (2018).

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