TALAPRO-3: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, STUDY OF TALAZOPARIB WITH ENZALUTAMIDE VERSUS PLACEBO WITH ENZALUTAMIDE IN MEN WITH DDR GENE MUTATED METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Published: 10-06-2021
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2024-510809-28-00 check the CTIS register for the current data. Primary objectiveTo demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54222

Source
ToetsingOnline

Brief title
C3441052 TALAPRO-3

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
castration sensitive, Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Industry

Intervention

Keyword: cancer, mCSPC, Prostate, Talazoparib

Outcome measures

Primary outcome

Investigator-assessed rPFS per Response Evaluation Criteria in Solid Tumors

(RECIST 1.1 [soft tissue disease]) and Prostate Cancer Working

Group (PCWG3 [bone disease]) in participants with mCSPC harboring DDR

deficiencies.

Secondary outcome

- OS in participants with mCSPC harboring DDR deficiencies (alpha-protected).

- Proportion of participants with measurable soft tissue disease at baseline

with an objective response per RECIST 1.1.

- Duration of soft tissue response per RECIST 1.1.

- Proportion of participants with PSA response 50% in participants with

detectable PSA values at baseline.

- Time to PSA progression.

- Time to initiation of antineoplastic therapy.

- Time to first symptomatic skeletal event.

- Time to opioid use for prostate cancer pain.

- Incidence of adverse event (AEs) characterized by type, severity (graded by

National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03), timing, seriousness and relationship to study intervention.

- Predose trough plasma concentrations of talazoparib, enzalutamide and its N-desmethyl metabolite

- Change from baseline in participant-reported pain symptoms per Brief Pain Inventory Short Form (BPI-SF);

- Change from baseline in participant-reported general health status per European Quality of Life 5 Dimension, 5 Level Scale EQ-5D-5L;

- Change from baseline in participant-reported cancer

- specific global health status/ quality of life (QoL), functioning, and symptoms per European Organisation for Research and Treatment of Cancer cancerspecific global health questionnaire (EORTC QLQ-C30);

- Time to deterioration in participant-reported pain symptoms per BPI-SF;

- Time to definitive deterioration in participant-reported global health status/QoL per EORTC QLQ-C30;

- Time to definitive deterioration in participant-reported disease specific urinary symptoms per European Organisation for Research and Treatment of Cancer disease-specific urinary symptoms questionnaire (EORTC QLQPR25).

- Change from baseline in patient global impression of severity (PGI-S).

- ctDNA burden at baseline and on study, as assessed using FoundationOne® liquid or another suitable validated assay.

Study description

Background summary

Talazoparib is a potent, small molecule PARPi in development for the treatment of a variety of human cancers. Talazoparib exerts cytotoxic effects via 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARPi does not readily dissociate from DNA, thereby preventing DNA repair, replication, and transcription

Single-agent treatment with talazoparib has demonstrated potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies that enrolled participants with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA-damaging chemotherapy, including temozolomide and irinotecan, in both in vitro and in vivo preclinical models.

Enzalutamide is an oral small-molecule inhibitor of the AR that has been shown to overcome acquired resistance to first-generation nonsteroidal antiandrogens, such as bicalutamide, nilutamide, and flutamide. The efficacy and safety of enzalutamide was initially demonstrated in CRPC and has been approved by FDA for patients with mCRPC and also for patients with non-metastatic CRPC

In clinical trials, the use of talazoparib and other compounds having a similar action have shown that these types of drugs can reduce tumor size and slow tumor growth in patients with defects in other genes important for DNA repair. Pre-clinical studies show that enzalutamide blocks the repair of certain errors that may happen in the DNA when cells divide. As a result of these findings there is a potential rationale of combining talazoparib and enzalutamide in patients with mCSPC with DNA damage repair defects.

Study objective

This study has been transitioned to CTIS with ID 2024-510809-28-00 check the CTIS register for the current data.

Primary objective
To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging investigator--assessed Radiographic Progression-free Survival (rPFS), in participants with mCSPC harboring DDR deficiencies.

Key Secondary Objective
•To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging overall survival (OS)

in participants with mCSPC harboring DDR deficiencies.

Other Secondary Objectives
•To evaluate antitumor activity in participants with mCSPC harboring DDR deficiencies with respect to the following:
•Objective response in measurable soft tissue disease;
•Duration of response in measurable soft tissue disease;
•Prostate specific antigen (PSA) response;
•Time to PSA progression;
•Time to initiation of antineoplastic therapy;
•Time to first symptomatic skeletal event;
•Opioid use for prostate cancer pain.
•To evaluate safety of talazoparib and enzalutamide administered in combination.
•To evaluate the pharmacokinetics (PK) of talazoparib and enzalutamide (and its N desmethyl metabolite) when dosed in combination.
• To evaluate the following participant reported outcomes in each treatment arm in participants with mCSPC harboring DDR deficiencies:
• Pain symptoms;
• Cancer specific global health status/QoL, functioning, and symptoms outcomes;
• General health status.
• To assess the relationship between ctDNA burden and outcome.

Study design

A phase 3, randomized, double-blind, placebo controlled interventional study

Intervention

Eligible participants will be randomly assigned to either of 2 treatment groups as follows:
* 0.5 gr once daily Talazoparib in combination with enzalutamide.
* Placebo capsules identical in appearance to talazoparib capsules in combination
with enzalutamide.

Study burden and risks

-Physical Examination: Screening, Day 1, then at each visit
-Blood pressure, pulse rate, and weight: Screening, Day 1, then at each visit
-12-lead ECG: Screening, then as needed
-Provide a saliva sample, Day 1
-Completion of 5 questionnaires (electronically): Day 1 and at each visit. (can also be done at home)
-completion of the pain log and analgesic log electronically: Day 1, then every

day for the last 7 days before each visit
-completion of the dosing diary electronically: Day 1, then daily until the patient stops study treatment
-blood draws with a max of 60 ml per occurrence: Every 4 weeks till week 25, then every 8 weeks and every 12 weeks after the first year
- Tumor biopsy may be performed during the study.
- CT scan of chest, CT or MRI of abdomen and pelvis, and bone scan: 8 times in the first year, 4-5 in subsequent years.
The radiation exposure is similar to what participant would have under SOC and should not create a significant risk to health.
-Due to the potential risk of the effect on the sperm appropriate method of contraception must be used starting at screening and continuing for at least 4 months following the last dose of study drug

The talazoparib doses used in combination with enzalutamide in this protocol are supported by nonclinical studies, safety and PK data from Part 1 of the TALAPRO-2 study, Phase 1-3 studies in participants with advanced malignancies, and studies in participants with DDR-deficient mCRPC. Enzalutamide is widely used for the treatment of various stages of prostate cancer with a well-established safety profile. Talazoparib is approved for the treatment of patients with metastatic HER2-negative breast cancer and gBRCA 1/2 mutations. In addition, it has shown antitumor activity in patients with solid tumors (ie, ovarian, peritoneal, pancreatic) harboring BRCA1/2 mutations. Antitumor responses have been demonstrated in DDR-deficient mCRPC in the TALAPRO-1 study. The expected AEs with talazoparib include myelosuppression, gastrointestinal toxicity, fatigue, and alopecia. The activity of talazoparib as monotherapy and in combination with other agents is being evaluated in multiple indications.
In conclusion, clinical experience with talazoparib in various cancers have demonstrated that talazoparib is generally well-tolerated. The AEs associated with talazoparib are detectable through routine laboratory and clinical monitoring and may be managed by dosing interruption, dose reduction, and standard supportive care.
Based on the cumulative safety data and the potential benefit afforded by the mechanism of action of talazoparib, clinical development of talazoparib in combination with enzalutamide for the treatment of DDR-deficient mCSPC is justified.

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply: Age and Sex: 1.Male participants at least 18 years of age at screening (Refer to Appendix 9 of the protocol for Japan and Republic of Korea) . Type of Participant and Disease Characteristics: 2.Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, small cell or signet cell features. If the participant does not have a prior histological diagnosis, a baseline de novo biopsy must be used to confirm the diagnosis and may also be used to support biomarker analysis. 3.Confirmation of DDR gene mutation status (as per the genes included in DDR12 panel described in Table 6) by prospective or historical analysis (with sponsor pre-approval) of blood (liquid biopsy) and/or de novo or archival tumor tissue using FoundationOne® CDx or FoundationOne CDx®. 4.Willing to provide tumor tissue when available (de novo or archived) for retrospective molecular profiling analysis, if not already provided as part of inclusion criterion 3. 5.Unless prohibited by local regulations or ethics committee decision, consent to a saliva sample collection for retrospective sequencing of the same DDR genes tested on tumor tissue and blood (liquid biopsy), or a subset thereof, and to serve as a germline control in identifying tumor mutations. 6. Ongoing ADT with a GnRH agonist or antagonist for participants who have not undergone bilateral orchiectomy must be initiated before randomization and must continue throughout the study. 7.Metastatic prostate cancer documented by positive bone

scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue). Participants whose disease spread is limited to regional pelvic lymph nodes are not eligible. Note: a finding of superscan at baseline is exclusionary. Allowed Prior Treatments: 8.Note: prior treatment of mCSPC with docetaxel is no longer permitted. 9.Treatment with estrogens, cyproterone acetate, or first-generation anti-androgens is allowed until randomization. 10.Other prior therapy allowed for mCSPC; <=3 months of ADT (chemical or surgical) with or without approved NHT in mCSPC (ie, abiraterone + prednisone, apalutamide, or enzalutamide), if required prior to randomization with no radiographic evidence of disease progression or rising PSA levels prior to Day 1. 11.Participant may have received palliative radiation or surgery for symptomatic control secondary to prostate cancer, which should have been completed at least 2 weeks prior to randomization. 12.ECOG performance status 0 or 1 (see Appendix 11 of the protocol). 13.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 participants 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 m2 by the MDRD equation, see Appendix 10 of the protocol). 14.Sexually active participants that in the opinion of the investigator are capable of ejaculating, must agree to use a condom when having sex with a partner (female or male) from the time of the first dose of study treatment through 4 months after last dose of study treatment (or, if talazoparib/placebo has been stopped more than a month earlier than enzalutamide, through 3 months after last dose of enzalutamide). Must also agree for female partner of childbearing potential to use an additional highly effective form of contraception (Section 5.3 of the protocol) from the time of the first dose of study treatment through 4 months after last dose of study treatment (or, if talazoparib/placebo has been stopped more than a month earlier than enzalutamide, through 3 months after last dose of enzalutamide)when having sex. 15.Must agree not to donate sperm from the first dose of study treatment to 4 months after the last dose of study treatment (or, if talazoparib/placebo has been stopped more than a month earlier than enzalutamide, through 3 months after last dose of enzalutamide). 16.Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures, including being able to manage electronic diaries. The PRO assessments are not required to be completed if a participant does not understand the language(s) available for a specific questionnaire and/or cannot complete the specific questionnaire independently. Further inclusion criteria are detailed in the protocol.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply: Medical Conditions: 1.Other acute or chronic medical [concurrent disease, infection, including chronic stable HIV, HBV, or HCV infection (refer to Appendix 13 of the protocol), or co-morbidity] or psychiatric condition including recent (within the past year) or active suicidal ideation/behaviour or laboratory abnormality that interferes with a participant's ability to participate in the study, may increase the risk of associated with study participation or study treatment administration, or may interfere with the interpretation of study results, and, in the investigator's judgment, make the participant inappropriate for entry into the study. HIV/HBV/HCV testing is not required unless mandated by local health authority. 2.History of seizure or any condition (as assessed by investigator) that may predispose to seizure (eg, prior cortical stroke, significant brain trauma), including any history of loss of consciousness or transient ischemic attack within 12 months of randomization. 3.Major surgery (as defined by the investigator) within 2 weeks before randomization. 4.Known or suspected brain metastasis or active leptomeningeal disease. 5.Symptomatic or impending spinal cord compression or cauda equina syndrome. 6.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. •American Joint Committee on Cancer 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. 7.In the opinion of the investigator, any clinically significant gastrointestinal disorder affecting absorption. 8.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 (eg, 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. However, participants can be rescreened after adequate control of blood pressure is achieved. 9.Active COVID-19 infection detected by viral test or based on clinical diagnosis (as assessed by investigator). Asymptomatic participants with no active COVID-19 infection detected but positive antibody tests, indicating past infection are allowed. Prior/Concomitant Therapy: 10.Prior ADT in the adjuvant/neoadjuvant setting, where the completion of ADT was less than 12 months prior to randomization and the total duration of ADT exceeded 36 months. 11.Participant received 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. 12.Any previous treatment with DNA-damaging cytotoxic chemotherapy (ie, platinum based therapy) within 5 years prior to randomization, except for indications other than prostate cancer. 13.Prior treatment with a PARPi or known or possible hypersensitivity to enzalutamide, any of enzalutamide capsule excipients or to any talazoparib/placebo capsule excipients. 14.Prior treatment in any setting with NHT, except as described in Inclusion Criterion #10. 15.Current use of potent P-gp inhibitors within 7 days prior to randomization. For a list of potent P-gp inhibitors refer to Section 6.5 of the protocol. Prior/Concurrent Clinical Study Experience: 16.Treatment with any investigational study intervention within 4 weeks before randomization. Exception: COVID-19 vaccines authorized under an emergency use authorization (or equivalent) can be administered without a washout period.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-07-2022
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Talzenna
Generic name:	Talazoparib

Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xtandi
Generic name:	ENZALUTAMIDE
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-01-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-11-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-04-2022
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-05-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-02-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	04-03-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510809-28-00
EudraCT	EUCTR2021-000248-23-NL
ClinicalTrials.gov	NCT04821622
CCMO	NL77466.100.21