TALAPRO 1: A Phase 2, Open-Label, Response Rate Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)

Published: 12-10-2016
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PrimaryTo evaluate the efficacy of single agent talazoparib in DNA damage repair (DDR) + metastatic CRPC, as measured by best objective responserate (ORR).Secondary:To evaluate efficacy with respect to the following parameters:• Time to objective...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53009

Source
ToetsingOnline

Brief title
MDV3800-06 - TACTIC

Condition

- Other condition

Synonym
Metatastic Castration Resistant Prostate Cancer and advanced Prostate Cancer

Health condition

Metastatic Castration Resistant Prostate Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: DNA repair defects, Parp inhibitor, Prostate Cancer, Talazoparib

Outcome measures

Primary outcome

The primary efficacy endpoint is best objective response rate (ORR). The

proportion of patients with a best overall soft tissue response of CR or PR per

RECIST 1.1

Secondary outcome

The secondary efficacy endpoints:

• Time to objective response

• Duration of response

- Proportion of patients with conversion of CTC count

- Time to PSA progressionand response, PSA, survival status monitoring, pain

and quality of life questionnaires, and CTC enumeration.

Study description

Background summary

PARP inhibition has been shown to produce clinical responses in metastatic CRPC, particularly in patients with genomic defects in DNA repair genes. PARP inhibitors are thought to induce cell toxicity not only by inhibiting PARP catalytic activity but also by trapping PARP-DNA complexes, which prevent DNA repair, replication, and transcription. Nonclinical studies have shown that talazoparib has potent cytotoxic effects via both mechanisms, with greater cell toxicity from PARP trapping.

Study objective

Primary
To evaluate the efficacy of single agent talazoparib in DNA damage repair (DDR) + metastatic CRPC, as measured by best objective response rate (ORR).

Secondary:
To evaluate efficacy with respect to the following parameters:
• Time to objective response
• Duration of response
• Proportion of patients with PSA response >= 50%
• Proportion of patients with conversion of CTC count
• Time to PSA progression
• Radiographic PFS
• Overall survival
* To evaluate the safety of talazoparib in this patient population.
* To evaluate the following patient-reported outcomes:
-Time to deterioration in pain as assessed by the Brief Pain Inventory Short Form (BPI-SF);
-Change from baseline in pain per BPI-SF;
-Change from baseline in general health status as assessed by the European Quality of Life 5-Domain 5-Level Scale (EQ-5D-5L).
To evaluate the pharmacokinetics (PK) of talazoparib

Study design

This is an international, phase 2, open-label, response rate study of talazoparib (also known as MDV3800, BMN 673), a poly(ADP-ribose) polymerase (PARP) inhibitor in development for treatment of men with metastatic castration-resistant prostate cancer (CRPC). Eligible patients must have histologically confirmed adenocarcinoma of prostate previously treated with 1 to 2 chemotherapy regimens including at least 1 taxane-based regimen for

treatment of metastatic prostate cancer, and progressed on at least 1 line of novel hormonal therapy (enzalutamide and/or abiraterone acetate/prednisone) for treatment of metastatic CRPC. Patients must consent to a fresh tumor biopsy prior to enrollment in the study, unless they have sufficient archival tissue for molecular analyses. A genomic defect in a DNA repair gene that is likely to or that may sensitize to PARP inhibition as assessed by a gene mutation biomarker panel is required for participating in the study. Patients must have an ECOG performance status of 0-2 and measurable soft tissue metastatic disease by CT or MRI per RECIST 1.1. Progressive disease at study entry is required, as documented by either PSA progression, soft tissue disease progression per RECIST 1.1 or bone disease progression per PCWG3 criteria. Ongoing androgen deprivation therapy (medical or surgical castration) is required during the study. Prior treatment with a PARP inhibitor, platinum, cyclophosphamide, or mitoxantrone chemotherapy is not allowed.
Approximately 150 patients will be enrolled and assigned to 2 overlapping cohorts of patients with a genomic defect in a DNA repair gene likely to sensitize to PARP inhibition (16 gene subset of the gene mutation biomarker panel of 177 genes) or with a genomic defect likely to or that may sensitize to PARP inhibition (genomic defect in genes included in the mutation biomarker panel of 177 genes). All patients will receive monotherapy with talazoparib 1 mg/day (0.75 mg/day for patients with moderate renal impairment). Talazoparib treatment will continue until radiographic progression is determined by independent central review, unacceptable toxicity, withdrawal of consent, or death.

Intervention

Talazoparib capsules 1 mg/day orally will be administered until radiographic progression

Study burden and risks

The doses of talazoparib in this protocol are supported by nonclinical studies and phase 1 studies in patients with advanced malignancies. Antitumor activity has been observed and warrants further exploration in a larger patient population. The expected adverse events 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. The benefit-risk profile of talazoparib is not yet well characterized.

Contacts

Public

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Scientific
Pfizer Inc.

Science Center Drive 10555
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.For patients who are at least 18 years of age, there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
2.Histologically or cytologically confirmed adenocarcinoma of the prostate without signet cell, or small cell features. Histologic confirmation may be based on a de novo tumor biopsy obtained for
purposes of screening. Biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.
3.Patients must have measurable soft tissue disease per RECIST1.1.
4.DNA damage repair gene alterations likely to sensitize to PARP inhibition (DDR positive) as determined by:
•Prospective testing of de novo or archival tumor tissue (via central laboratory) or prior historical (with Sponsor preapproval) testing of tumor tissue using the Foundation Medicine, FoundationOne® NGS gene panel test; Archival or de novo tumor tissue also should be submitted prior to Day 1 if

possible to support concordance analyses and additional molecular profiling.
5.Unless prohibited by local regulations or ethics committee (EC) decision, consent to a saliva sample collection for retrospective sequencing of DDR genes used to assess patient eligibility based on tumor tissue, and to serve as a germline control in identifying tumor mutations.
6.Serum testosterone <= 1.73 nmol/L (50 ng/dL) at screening.
7.Bilateral orchiectomy or ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) agonist/antagonist (surgical or medical castration).
8.Progressive disease at study entry defined as 1 or more of the following 3 criteria:
•A minimum of 3 rising PSA values with an interval of at least 1 week between determinations. The screening central laboratory PSA value must be >= 2 µg/L (2 ng/mL) if qualifying solely by PSA progression.
•Soft tissue disease progression as defined by RECIST 1.1.
•Bone disease progression defined by PCWG3 with 2 or more new metastatic lesions on bone scan.
9.Metastatic disease. Patients whose only evidence of metastasis is measurable soft tissue disease below the aortic bifurcation will be acceptable. Neither bone metastases on bone scan nor non- measurable soft tissue disease alone will qualify a patient.
10.Previous treatment with 1 or 2 chemotherapy regimens including at least 1 taxane based regimen for metastatic (non castrate or castrate) prostate cancer. Patients may have received radium 223 and/or cabazitaxel, or were deemed unsuitable, declined, or did not have access
to these therapies.
11.Documented disease progression (either radiographic or biochemical) on at least 1 novel hormonal therapy (enzalutamide and/or abiraterone acetate/prednisone) for the treatment of metastatic CRPC, irrespective of prior NHT treatment for non castrate prostate cancer or nonmetastatic (M0) CRPC.
12.Bisphosphonate or denosumab dosage must have been stable for at least 4 weeks before day 1 for patients receiving these therapies.
13.ECOG performance status of 0 to 2.
14.Estimated life expectancy of >= 6 months as assessed by the investigator.
15.Able to swallow the study drug, have no known intolerance to study drugs or excipients, and comply with study requirements.
16.Must use a condom when having sex with a pregnant woman from the time of the first dose of study drug through 105 days after last dose of study drug. An additional highly effective form of contraception (Section 4.3.1) must be used from the time of the first dose of study drug through
105 days after last dose of study drug when having sex with a non pregnant female partner of childbearing potential.
17.Must agree not to donate sperm from the first dose of study drug to 105 days after the last dose of study drug.
18.Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

Exclusion criteria

1.Use of systemic chemotherapeutic (including but not limited to taxanes), hormonal, biologic, or radionuclide therapy for treatment of metastatic prostate cancer (other than approved bone targeting agents and GnRH agonist/antagonist) or any other investigational agent within
4 weeks before day 1.
2.Prior treatment with a PARP inhibitor, cyclophosphamide, or mitoxantrone chemotherapy. Patients who discontinued prior platinum based chemotherapy 6 months prior to screening or whose disease previously progressed on platinum based therapy at any time in the past
are also excluded.
3.Treatment with any concurrent cytotoxic chemotherapy or investigational drug(s) within 4 weeks or 5 half lives of the drug (whichever is longer) before Day 1 and/or during study participation.
4.Radiation therapy within 3 weeks (within 2 weeks, if single fraction of radiotherapy) before day 1.
5.Major surgery within 2 weeks before day 1.
6.Clinically significant cardiovascular disease, including any of the following:
•Myocardial infarction or symptomatic cardiac ischemia within 6 months before screening.
•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.
7.Significant organ dysfunction as defined by any one of the following laboratory abnormalities:
•Renal: eGFR < 30 mL/min /1.73 m2 by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com]).
•Hepatic:
•Total serum bilirubin > 1.5 times the upper limit of normal (ULN) (> 3 × ULN for patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation);
•Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >= 2.5 times ULN (if liver test abnormalities are due to hepatic metastasis, then AST or ALT >= 5 × ULN);
•Albumin < 2.8 g/dL.
•Bone marrow reserve: absolute neutrophil count < 1500/µL, platelets < 100,000/µL, or hemoglobin < 9 g/dL (NOTE: may not have received growth factors

or blood transfusions within 14 days before obtaining the hematology values at screening).
8.Known or suspected brain metastasis or active leptomeningeal disease.
9.Symptomatic or impending spinal cord compression or cauda equina syndrome.
10.Diagnosis of myelodysplastic syndrome.
11.History of another cancer within 3 years before enrollment with the exception of nonmelanoma skin cancers, or American Joint Committee on Cancer stage 0 or stage 1 cancer that has a remote probability of recurrence in the opinion of the investigator and the sponsor.
12.Gastrointestinal disorder affecting absorption.
13.Current or anticipated use of the following P gp inhibitors (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, verapamil, and valspodar), P gp inducers (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's
wort), or BCRP inhibitors (curcumin, cyclosporine, elacridar [GF120918] and eltrombopag).
14.Any other acute or chronic medical or psychiatric condition (concurrent disease, infection, or comorbidity) that interferes with ability to participate in the study, causes undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
15.Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the
study.
16.Fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 105 days after the last dose of investigational product.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MDV3800
Generic name:	Talazoparib

Ethics review

Approved WMO Date:	12-10-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-06-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	30-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-09-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-03-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	23-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2016-002036-32-NL
CCMO	NL59035.091.16