A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer

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The purpose of this study is to understand if a new treatment for prostate cancer (niraparib) added to a standard treatment (abiraterone acetate plus prednisone) will work better than the standard treatment alone.Cohort 3: the purpose is to evaluate…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON54643

Source
ToetsingOnline

Brief title
Magnitude

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
metastatic prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag BV

Intervention

Keyword: cancer, DNA Repair Defects, metastatic prostate, Niraparib, PARP-inhibitor

Outcome measures

Primary outcome

Radiographic progression-free survival (rPFS)

Secondary outcome

-Overall Survival

-Time-to-symptomatic progression

-Time to initiation of cytotoxic chemotherapy

-Observed plasma concentrations of niraparib

and abiraterone and estimated population PK

and exposure parameters for niraparib

-Incidence and severity of AEs

-Clinical laboratory test results

Study description

Background summary

In patients with metastatic prostate cancer, DNA-repair anomalies are identified in approximately 15% to 20% of tumors. PARP inhibition leads to an accumulation of unrepaired single-strand breaks, which result in stalling and collapse of replication forks and, consequently, to double-strand breaks

(DSBs). Normally, DSBs are repaired through homologous recombination. If not repaired, DSBs result in cell death.
In addition to facilitating DNA-repair, dual roles for PARP in supporting AR activity have been observed in the preclinical setting.In the clinical setting, recent data have shown the efficacy of combining AR-targeted therapy and a PARP inhibitor in patients with metastatic prostate cancer.8 The patients treated with a combination of olaparib and AA-P had improved rPFS compared with those treated with AA-P alone. This benefit was seen in both patients with and without HRR.

Cohort 3: the fixed dose combination tablet would reduce the number of pills to 2 tablets per day plus prednisone. Reducing the pill burden for patients with cancer may improve compliance. In cohort 3 the sponsor will evaluate the safety and efficacy of the regular-strength FDC tablet formulation in the same patient population as cohort 1+2. The sponsor is also developing a low-strength FDC tablet formulation to allow dose modications to address the need for patients with toxicities.

Study objective

The purpose of this study is to understand if a new treatment for prostate cancer (niraparib) added to a standard treatment (abiraterone acetate plus prednisone) will work better than the standard treatment alone.
Cohort 3: the purpose is to evaluate the efficacy and safety of the FDC tablet formulation of Niraparib and AA, plus prednisone.

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the
efficacy and safety of niraparib 200 mg once daily in combination with AA 1,000 mg once daily
and prednisone 10 mg (2 x 5 mg), compared to AA-P plus placebo in subjects with metastatic
prostate cancer. Subjects in each cohort will be randomized in a 1:1 ratio to receive either
niraparib plus AA-P or placebo plus AA-P.

The study will consist of 4 phases:
• Prescreening Phase for biomarker evaluation only
• Screening Phase of up to 28 days to establish study eligibility
• Treatment Phase
• Follow-up Phase of up to 60 months to monitor survival status and other information
The biomarker status for all subjects will be assessed using the sponsor*s required assays during the Prescreening Phase. Subjects will be assigned to a

cohort based on their biomarker status. A treatment cycle is defined as 28 days. Imaging will be performed
very 8 weeks for the first 6 months and then every 12 weeks thereafter. Subjects must discontinue study medication in the event of documented unequivocal clinical progression. If the subject has radiographic progression, but not unequivocal clinical progression, and alternate treatment is not initiated, the subject may continue study treatment at the investigator*s discretion. After discontinuing study drug, subjects will be contacted every 3 months for survival follow-up. Selected patient-reported outcomes (PROs) questionnaires will also be administered every 3 months for up to 2 years after treatment discontinuation.
Cohort 1: Subjects with mCRPC and DNA Repair Defects (DRD)
Cohort 1 will evaluate the combination of niraparib and AA-P versus placebo and AA-P in subjects with mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AA-P) and DRD. The cohort will enroll approximately 400 subjects (per protocol amendment 3 50% of patients in cohort 1 need to have a BRCA mutation, stop enrollment of patient with an ATM mutation in cohort 1).
Cohort 2: Subjects with mCRPC and No DRD
Cohort 2 will evaluate the combination of niraparib and AA-P versus placebo and AA-P in subjects with mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AA-P) and who do not have DRD. The cohort will enroll approximately 600 subjects.
Groep 3: patients with mCRPC that will receive a FDC tablet formulation of niraparib and abiraterone
Cohort 3 will be an open label cohort that will start after cohort 1 and 2 are completed. If futility analysis of cohort 2 is not met, then approximately 100 patients will be enrolled in cohort 3; approximately 60 patients without HRR gene alterations and approximately 40 patients with HRR gene alterations (approximately 20 of whom should have BRCA mutation). If futility analysis of cohort 2 is met, then approximately 40 patients with HRR gene alterations (approximately 20 of whom should have BRCA mutation) will be enrolled.

Intervention

Cohort 1+2
Abiraterone acetate 1,000 mg (four 250 mg tablets) will be taken orally once daily continuously,
concomitantly with oral prednisone 5 mg twice a day.
Niraparib 200 mg (two 100 mg capsules) or placebo should be taken daily around the same time as AA-P.

Cohort 3
Regular strength FDC niraparib/AA (2 tablets of 100mg/500mg) will be taken orally once daily continuously,
concomitantly with oral prednisone 5 mg twice a day.

Low strength FDC niraparib/AA (2tablets of 50mg/500mg) will be taken orally once daily continuously,
concomitantly with oral prednisone 5 mg twice a day. This is to be able to lower the dose of niraparib in case of toxicities.

Study burden and risks

The procedures required in the trial are also done in the standard treatment setting, although certain procedures (eg.
blooddraws for pharmacokinetics, pharmacodynamics and biomarkers as well as the number of CT/MRI and bone scans)
are done more often than in the standard treatment. The trial medication can lead to side effects. The extra trial procedures
and possible side effects observed until now are considered to be acceptable, taken into account the expected therapeutic
benefit of the trial medication.
The procedures for cohort 3 are the same as for cohort 1+2 except for the dose modifications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed metastatic prostate cancer with no prior systemic therapy in the
mCRPC setting
2. Can provide blood sample for determination of HRR
3. Willing to provide a fresh or archival tumor tissue sample for determination of HRR
4. HRR status (as identified by the sponsor*s required assays or positive BRCA1 or BRCA2 germline testing results from certified laboratories as acceptable for screening.) as follows:
a. Cohort 1: positive for HRR (per protocol amendment 3: stop enrollment of subjects with ATM mutations into Cohort 1 and to ensure at least 50% of Cohort 1 are subjects with BRCA mutations)
b. Cohort 2: not positive for HRR (ie, no HRR)
c. Cohort 3: positive or not positive for HRR gene alterations
5. Must be able to continue GnRHa during the study if not surgically castrate
6. ECOG PS grade of 0 or 1
7. Adequate hematologic and metabolic values at screening

Exclusion criteria

1. Prior treatment with a PARP inhibitor
2.Systemic therapy in the mCRPC setting; or AA-P outside of the mCRPC setting.
3.For subjects who received 2 to 4 months of AA-P prior to randomization for the treatment of mCRPC, evidence of progression by PSA (per PCWG3) during screening.
4.. Severe or unstable angina, myocardial infarction, symptomatic congestive heart failure,
arterial or venous thromboembolic events (e.g, pulmonary embolism, cerebrovascular
accident including transient ischemic attacks), or clinically significant ventricular
arrhythmias within 6 months prior to randomization or New York Heart Association (NYHA) Class II to IV heart disease.
5.. Presence of uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg or
diastolic BP >100 mmHg). Subjects with a history of hypertension are allowed, provided

that BP is controlled to within these limits by anti-hypertensive treatment.
6. Active or symptomatic viral hepatitis or chronic liver disease (as evidenced by ascites or
bleeding disorders secondary to hepatic dysfunction)
7. Subjects who have had the following <=30 days prior to planned Cycle 1 Day 1:
a. a transfusion (platelets or red blood cells)
b. hematopoietic growth factors
c. an investigational agent for prostate cancer
d. major surgery
e. radiation therapy

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:	Recruitment stopped
Start date (anticipated):	26-08-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Prednisone acis®
Generic name:	Prednisone acis®
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Zejula
Generic name:	Niraparib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zejula+Zytiga
Generic name:	Niraparib+Abiraterone
Product type:	Medicine
Brand name:	Zytiga
Generic name:	Abiraterone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-05-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2019
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	16-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-003364-12-NL
ClinicalTrials.gov	NCT03748641
CCMO	NL67657.056.18

Study results

Date completed:	20-09-2023
Actual enrolment:	11