A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for the Treatment of Participants with Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Published: 08-09-2020
Last updated: 14-12-2024

This study has been transitioned to CTIS with ID 2023-506365-64-00 check the CTIS register for the current data. The purpose of this study is to investigate if niraparib added to a standard treatment (consisting of abiraterone acetate plus...

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

Summary

ID

NL-OMON56019

Source
ToetsingOnline

Brief title
Amplitude

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
Metastatic prostate cancer with specific genetic changes; Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: Abiraterone Acetate, Castration-Sensitive Prostate Cancer, Gene-Mutated Metastatic, Niraparib

Outcome measures

Primary outcome

• To determine if niraparib, AA plus prednisone compared with AA plus

prednisone in participants with deleterious germline or somatic HRR

gene-mutated mCSPC provides superior radiographic progression-free survival

(rPFS).

Secondary outcome

• To assess the clinical benefit of niraparib and AA plus prednisone compared

with AAP in participants with deleterious germline or somatic HRR gene-mutated

mCSPC.

• To characterize the safety profile of niraparib and AA plus prednisone

compared with AAP in participants with deleterious germline or somatic HRR

gene-mutated mCSPC.

Study description

Background summary

There are several options to treat patients with metastatic prostate cancer. One of the options is treatment with medicines that work in a very specific way. It must therefore first be investigated how (with which type of potential medication) your prostate cancer could be treated best. Niraparib is a type of anticancer medicine called a PARP inhibitor. PARP helps cells repair damaged DNA. By inhibiting PARP, the damaged DNA in cancer cells cannot be repaired, especially in cells with other known DNA repair gene defects (DRD). This leads to death of cancer cells and thus helps to control the cancer.
In this study, in patients with castration sensitive prostate cancer with a known DNA repair gene defect, the combination of niraparib and abiraterone acetate plus prednisone (AA-P) will be compared to AA-P alone. The combination therapy may be more effective for patients with DNA repair defects than AA-P alone, as they generally have worse response to standard of care therapies than other patients.
Recent studies have demonstrated the efficacy of combining a PARP inhibitor with existing therapy (with abiraterone acetate) plus prednisone in men with metastatic castration resistant prostate cancer. Incidentally, niraparib is already registered in the Netherlands (called Zejula®) and it is used for treatment of certain other kinds of cancers and abiraterone acetate is also registered in The Netherlands (called ZYTIGA®) and it is used with prednisone for the treatment of metastatic prostate cancer.

Study objective

This study has been transitioned to CTIS with ID 2023-506365-64-00 check the CTIS register for the current data.

The purpose of this study is to investigate if niraparib added to a standard treatment (consisting of abiraterone acetate plus prednisone) will work better than abiraterone acetate and prednisone alone in treating men with metastatic prostate cancer with specific genetic changes.

Study design

This is a randomized, placebo-controlled, double-blind, multinational Phase 3 study to evaluate the safety and efficacy of niraparib, and AAP, and prednisone compared with AAP in men over the age of 18 years with deleterious germline or somatic HRR gene-mutated mCSPC.

Approximately 788 participants will be randomly assigned on a 1:1 basis to either niraparib 200 mg, AA 1000 mg plus prednisone 5 mg daily or AA 1000 mg plus prednisone 5 mg daily. All participants must be receiving background androgen deprivation therapy (ADT; ie, gonadotropin-releasing hormone analogue or surgical castration).
The study will consist of 4 phases; a Prescreening Phase for biomarker evaluation for eligibility only, a Screening Phase, a Treatment Phase, and a Follow-up Phase.
Efficacy, safety, pharmacokinetics (PK), and biomarkers will be assessed according to the Schedule of Activities (SoA).
Administration of the study medicines is continuous; however, a cycle is defined as 28 days. Study medication should continue until disease progression, unacceptable toxicity, death, withdrawal of consent, or termination of the study by the sponsor.
Participants will be followed until death or termination of the study. In addition to survival follow-up, data will continue to be collected to evaluate all of the secondary and other endpoints. The Euro-Quality of Life Questionnaire will also be administered for up to 1 year after study medication discontinuation.
Participants will be monitored for safety during the Prescreening, Screening, and Treatment Phases and up to 30 days after the last dose of study medication during the follow-up phase. Adverse events (AEs) including clinically significant laboratory abnormalities reported as AEs, will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.
An Independent Data Monitoring Committee will be commissioned for this study and will perform regular review of study data.

Intervention

Participants will be randomized on a 1:1 basis to 1 of 2 treatments groups:
• niraparib 200 mg and AA 1000 mg plus prednisone 5 mg daily
• AA 1000 mg plus prednisone 5 mg daily
All study medications will be administered orally once daily. Matching placebos will also be administered.
All participants will receive ADT (ie, gonadotropin-releasing hormone analogue or surgical castration).

There are two groups in this study. You will randomly, or by chance, be put into one of the groups. You will have a 50% chance of being put into 1 of 2 groups:
Group 1:
• 200mg Niraparib*
• 1000mg Abiraterone Acetate*
• 4 placebo tablets for Abiraterone Acetate
• 5mg Prednisone
*Niraparib and Abiraterone Acetate may be combined into 1 tablet (you will

receive two tablets)

Group 2:
• 2 placebo tablets
• 1000mg Abiraterone Acetate
• 5mg Prednisone

Study burden and risks

NIRAPARIB
At present, the most frequent (over 10% of the patients) possible observed side effects are:
Decrease in red blood cells that carry oxygen; this may make you feel tired or short of breath. Decrease in a type of blood cell called platelets that help stop bleeding; this may increase your risk of bleeding, Decrease in a type of white blood cell called neutrophils that fight infection; and may lead to a potentially life-threatening condition caused by the body*s response to an infection with or without fever, triggering changes that can damage multiple organ systems (neutropenia, neutropenic infection, neutropenic sepsis and febrile neutropenia), difficulty with emptying the bowels, often because of hard stools (constipation), nausea, vomiting, decreased appetite, abdominal pain, diarrhea, indigestion, sleeplessness, trouble sleeping, headache, feeling tired, lack of energy / fatigue), urinary tract infection, inflammation of the lining of the airways (bronchitis), back pain, joint pain, breathlessness or difficulty breathing, common cold, increased blood pressure, feeling lightheaded or like you are about to faint (dizziness), cough, noticeably rapid, strong, or irregular heartbeat and altered sense of taste; this means that foods might taste differently than you are used to.

ABIRATERONE ACETATE
At present, the most frequent (over 20% of the patients) possible observed side effects are:
Hypokalaemia (low blood potassium, a mineral that helps regulate heart rate/function, fluid balance in the body and is needed for adequate body function) and hypertension (high blood pressure).

For prednisone and ADT
Please consult your study doctor and the package insert for information on the risks associated with use.
You can find more information about all possible side effects and risks in Appendix C of the informed consent.

Drawing blood may be painful You may get a bruise or irritation at the place where the needle goes into your skin. Some patients may faint and, in rare cases, can get an infection.

CT and bone scans involve using X-rays and radioactive markers. The amount of

radiation you will be exposed to in this study is about 20 mSv for each CT-scan and about 2,5 mSv for each bone scan. To compare: the background radiation in the Netherlands is ~2.5 mSv per year.
If you participate in scientific research involving exposure to radiation more often, you should discuss with the study doctor whether participation at this moment would be safe.
The radiation used during the study may lead to damage to your health. However, this risk is small. We nevertheless advise you not to participate in another scientific study involving exposure to radiation in the near future.
Examinations or procedures involving radiation for medical reasons are not a problem.

Contacts

Public
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL
Scientific
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. 18 years of age or older
2. Pathological diagnosis of prostate adenocarcinoma.
3. Willing to provide an archival tumor tissue sample or a fresh tumor tissue sample. If germline positive for deleterious germline or somatic HRR gene mutations, an archived or fresh tumor tissue sample is not required.
4. Metastatic disease documented by conventional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) (for soft tissue leasions) or 99mTc bone scan (for bone leasions). Participants with a single bone lesion on Technetium-99m (99mTc) bone scan with no other non-nodal metastatic disease must have confirmation of bone metastatis by CT or MRI. Participants with lymph node-only disease are not elegible.
5 Must have at least one of the deleterious germline or somatic HRR gene mutations listed in Table 4.
6. Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade <2.
7. Androgen deprivation therapy (either medical or surgical castration) must have been started >14 days prior to randomization and participants be willing to continue androgen deprivation therapy (ADT) through the treatment phase. Participants who start a GnRH agonist <28 days prior to randomization will be required to take a first-generation anti-androgen for >14 days prior to randomization. The anti-androgen must be discontinued prior to randomization.
8. Participants who have received prior docetaxel treatment must meet the following criteria:
a. Received a maximum of 6 cycles of docetaxel therapy for mCSPC
b. Received the last dose of docetaxel <2 months prior to randomization
c. Maintained a response to docetaxel of stable disease or better, by investigator
assessment of imaging and PSA, prior to randomization.
9. Other allowed prior therapy for mCSPC:
a. Maximum of 1 course of radiation and 1 surgical intervention for symptomatic control of prostate cancer (example, uncontrolled pain, impending spinal cord compression or obstructive symptoms). Participants with radiation or surgical interventions to all known sites of metastatic disease will be excluded from trial participation). Radiation must be completed prior to randomization.
b. Up to a maximum of <6 months of ADT prior to randomization.
c. Up to a maximum of 45 days of abiraterone acetate + prednisone (AA-P) prior to randomization.
d. Up to a maximum of 2 weeks of ketoconazole for prostate cancer prior to randomization.
10. Allowed prior treatments for localized prostate cancer (all treatments must have been
completed >=1 year prior to randomization):
a. <=3 years total of ADT
b. All other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies.

11. Clinical laboratory values at Screening:
a. Absolute neutrophil count >=1.5 x 109/L
b. Hemoglobin >=9.0 g/dL, independent of transfusions for at least 28 days
c. Platelet count >=100 x 109/µL
d. Serum albumin >=3.0 g/dL
e. Creatinine <2 x upper limit of normal (ULN)
f. Serum potassium >=3.5 mmol/L
g. Serum total bilirubin <=1.5× ULN or direct bilirubin <=1 x ULN (Note: In participants with Gilbert*s syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin, and if direct bilirubin is <=1.5 × ULN, participant may be eligible as determined by the medical monitor)
h. AST or ALT <=3 × ULN
12. Able to swallow the study medication tablets whole.
13. Must provide informed consent (written or remote/virtual) indicating that he understands the purpose of, and procedures required for, the study and is willing to participate in the study including providing a DNA sample.
14. While on study medication and for 3 months following the last dose of study medication, a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak. The investigator should advise of the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study medication. Highly effective methods of contraception include:
a. established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system;
b. barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
15. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 3 months after receiving the last dose of study medication.

Exclusion criteria

1. Pathological finding consistent with small cell ductal or neuroendocrine carcinoma of the prostate.
2. Prior treatment with a PARP inhibitor.
3.Prior AR-targeted therapy (eg, ketoconazole for prostate cancer, apalutamide, enzalutamide, darolutamide), immunotherapy, or radiopharmaceutical agents with the exception of only 30 days of AA-P allowed prior to randomization.
4. Initiation of treatment with a bisphosphonate or denosumab for the management of bone metastasis <28 days prior to randomization.
5. History of adrenal dysfunction

6. Long-term use of systemically administered corticosteroids >5 mg of prednisone or the equivalent) during the study is not allowed. Short-term use (<=4 weeks, including taper) and locally administered steroids (eg, inhaled, topical, ophthalmic, and intra-articular) are allowed, if clinically indicated.
7. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:
a. non-muscle invasive bladder cancer;
b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured;
c. breast cancer - adequately treated lobular carcinoma in situ or ductal carcinoma in situ;
d. malignancy that is considered cured with minimal risk of recurrence.
8. History or current diagnosis of MDS/AML.
9. Current evidence within 6 months prior to randomization of any of the following: severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, clinically significant arterial or venous thromboembolic events (eg, pulmonary embolism), or clinically significant ventricular arrhythmias.
10. Presence of sustained uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg). Participants with a history of hypertension are allowed, provided that blood pressure is controlled to within these limits by an antihypertensive
treatment.
11. Known allergies, hypersensitivity, or intolerance to the excipients of niraparib, AA, or niraparib/AA FDC (refer to the IBs for niraparib and AA).
12. Current evidence of any medical condition that would make prednisone use contraindicated.
13. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study medication.
14. Participants who have had the following <=28 days prior to randomization:
a. A transfusion (platelets or red blood cells);
b. Hematopoietic growth factors;
c. Major surgery (sponsor should be consulted regarding what constitutes major surgery).
15. Known active hepatitis B virus (eg, hepatitis B surface antigen reactive) or active hepatitis C virus (HCV; eg, HCV ribonucleic acid [RNA] [qualitative] is detected).
16. Human immunodeficiency virus positive participants with 1 or more of the following:
a. Not receiving highly active antiretroviral therapy or on antiretroviral therapy for less than 4 weeks.
b. Receiving antiretroviral therapy that may interfere with the study medication (consult the sponsor for review of medication prior to enrollment).
c. A change in antiretroviral therapy within 6 months of the start of screening (except if, after consultation with the sponsor on exclusion criterion 16.b, a

change is made to avoid a potential drug-drug interaction with the study medication).
d. CD4 count<350 at screening.
e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening.
f. Human immunodeficiency virus load >400 copies/mL.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-12-2020
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niraparib/abiraterone acetate
Generic name:	niraparib/abiraterone acetate
Product type:	Medicine
Brand name:	Zejula
Generic name:	niraparib
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Zytiga
Generic name:	abiraterone acetate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	11-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2023
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
EU-CTR	CTIS2023-506365-64-00
EudraCT	EUCTR2020-002209-25-NL
ClinicalTrials.gov	NCT04497844
CCMO	NL69021.056.20