A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel.

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PrimaryTo assess the safety and tolerability of olaparib when given in addition to abiraterone and torecommend, by assessment of dose-limiting toxicities and other safety and tolerability data, adose of olaparib for further study when given in...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON40368

Source
ToetsingOnline

Brief title
D081DC00008 - Part A, open-label safety run-in study

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Abiraterone, Olaparib, Phase I, Prostate cancer

Outcome measures

Primary outcome

Primary outcome variables:

• Safety and tolerability

* Assessment of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0, vital signs (including blood pressure, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology).

* Incidence of dose-limiting toxicities (DLTs)

Secondary outcome

Secondary outcome variables:

• Pharmacokinetics

* Olaparib and abiraterone PK parameters (where the data allow): maximum plasma concentration at steady state (Cmax ss), time to reach maximum plasma concentration at steady state (tmax ss), area under the plasma

concentration-time curve at steady state (AUCss), minimum plasma concentration

at steady state (Cmin ss)

Study description

Background summary

Prostate cancer is a heterogeneous disease and androgen deprivation therapy with luteinizing hormone releasing hormone (LHRH) analogs or orchidectomy is usually initially effective at controlling metastatic disease, but patients inevitably progress from an androgen-sensitive to a castration-resistant phenotype. Until recently, effective treatment at this stage has been largely limited to docetaxel chemotherapy after studies showed it could improve overall survival in this population. Cabazitaxel, enzalutamide, abiraterone acetate (hereafter referred to as abiraterone) and radium-223 have now been shown to give further improvements in time to progression and overall survival when used after docetaxel therapy.

The optimum strategy for managing patients after docetaxel has not been established, but in many countries all 4 of these agents are licensed for use in the post-docetaxel phase of metastatic CRPC, with enzalutamide and abiraterone, which both target the androgen receptor (AR) pathway, being preferred because of their good tolerability profiles and absence of chemotherapy-associated side effects. In Part A of this study, metastatic CRPC patients will be recruited irrespective of whether they have already had chemotherapy in order to facilitate recruitment to this part of the study.
Recent pre-clinical data demonstrate a role for PARP-1, distinct from its role in DNA repair, in AR-dependent transcriptional signalling. Specifically relevant to this study is the observation that PARP-1 inhibition co-operates with androgen depletion to suppress cell proliferation. Furthermore, chromosomal rearrangements placing coding region on erythroblast transformation-specific (ETS) genes (eg, ETS-related gene [ERG]) occur with high frequency in prostate cancer and result in AR-dependent expression of pro-tumourigenic ETS genes. ERG has been shown to physically interact with PARP-1, and PARP-1 inhibition preferentially sensitises ETS over-expressing xenografts to PARP inhibition. In addition, over-expression of ERG leads to accelerated
carcinogenesis in mouse prostates with phosphatase and tensin homolog (PTEN) deletion, and PTEN loss itself has been suggested to sensitise cells to PARP inhibitors
Hence, there is a rationale for combination of olaparib with abiraterone in prostate cancer and a possibility that this combination may be preferentially active based on measures of ETS fusions (eg, ERG expression), AR status and

PTEN. There may also be a small number of patients who may benefit due to the presence of a BRCA
mutation in their tumour. Although only a small number of patients have germline mutations,the number with somatic mutations may be significantly higher.
This study will evaluate the investigational drug olaparib when given on a background of the approved drug abiraterone in patients with metastatic CRPC.
Part A of this study will provide an initial assessment of safety/tolerability and potential for pharmacokinetic (PK) interaction between the drugs. For the randomised phase of this study, only post-chemotherapy CRPC patients will be studied (chemotherapy-naive CRPC patients will be recruited in another study). This therefore facilitates a robust assessment of the primary endpoint of radiologic progression-free survival (radiologic PFS, rPFS) within a reasonable timeframe for a Phase II study.

Study objective

Primary
To assess the safety and tolerability of olaparib when given in addition to abiraterone and to
recommend, by assessment of dose-limiting toxicities and other safety and tolerability data, a
dose of olaparib for further study when given in addition to abiraterone.

Secondary
To evaluate the presence of any drug interaction between olaparib and abiraterone by
determination of steady state exposure to olaparib in the presence and absence of abiraterone,
and determination of steady state exposure to abiraterone in the presence and absence of
olaparib.

Study design

This is a study in patients with metastatic CRPC. Part A is an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics (PK) of olaparib when given in addition to abiraterone 1000 mg once daily. Abiraterone is indicated in combination with prednisone or prednisolone for the treatment of patients with metastatic CRPC. Prednisone or prednisolone 5 mg twice daily (bid) will be administered with the abiraterone in this study, but throughout this protocol the treatment will
be referred to simply as abiraterone.
All patients will attend a screening visit within 28 days before starting study treatment.

Patients will attend the clinic on the first day of study treatment, then at 1, 2, 4, 8 and 12 weeks, and every 12 weeks thereafter.
Cohort 1 (up to 6 patients)
At least 3 and up to 6 evaluable patients will be enrolled in Cohort 1.
Patients will receive olaparib 200 mg bid and abiraterone 1000 mg once daily.
Dose-limiting toxicities (DLTs) will be assessed by a Safety Review Committee (SRC) after a minimum of 14 days* treatment.
Cohort 2 (12 patients)
If the combination of olaparib 200 mg bid and abiraterone 1000 mg once daily is tolerated, a cohort of 12 patients (split into 2 groups of 6 patients) will be treated with olaparib 300 mg bid given in addition to abiraterone 1000 mg once daily.
Dose-limiting toxicities will be assessed by the SRC after a minimum of 14 days* treatment with both olaparib and abiraterone.
Group 1:
Patients will receive olaparib alone (300 mg bid) for between 3 and 7 days. Blood samples will then be collected to determine the steady state PK profile for olaparib. Patients will then receive abiraterone (1000 mg once daily) starting from the day after the olaparib PK profile has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 5 days, then blood samples will be collected again to determine both olaparib and abiraterone PK profiles.
Group 2:
Patients will receive abiraterone alone (1000 mg once daily) for between 5 and 7 days. Blood samples will then be collected to determine the steady state PK profile for abiraterone.
Patients will receive olaparib (300 mg bid) starting immediately after the 24-hour abiraterone PK sample has been collected. Olaparib and abiraterone will continue to be dosed in combination for at least 3 days, then blood samples will be collected again to determine both
olaparib and abiraterone PK profiles.
Cohort 3 (12 patients)
If 4 or more DLTs occur in Cohort 2, a further 12-patient cohort may be recruited and treated with olaparib 200 mg bid given in addition to abiraterone 1000 mg once daily and evaluated for safety, tolerability and PK as above. If >=4 DLTs occur in this cohort, the study will be
stopped.

Optional blood samples for pharmacogenetic research will be obtained from consenting patients and stored for long-term exploratory purposes.

A follow-up visit will be conducted 30 days (±7 days) after the last dose of study treatment (olaparib/placebo or abiraterone).

Intervention

The investigational product (olaparib) and additional study drugs (abiraterone

and prednisone/prednisolone) should be taken orally with water. Patients should aim to take their doses at similar times each day, with the twice daily doses approximately 12 hours apart.
Patients must fast (except water) from at least 2 hours before until 1 hour after each dose (morning and evening).
Cohort 1:
200 mg olaparib (2 x 100 mg tablets) bid.
1000 mg abiraterone (4 x 250 mg tablets) once daily in the morning and prednisone or prednisolone 5 mg (1 x 5 mg tablet) bid.
Cohort 2, Group 1:
300 mg olaparib (2 x 150 mg tablets) bid, starting on Day 1.
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg bid, starting the day after completion of the olaparib PK profiling.
Cohort 2, Group 2:
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg bid, starting on Day 1.
300 mg olaparib (2 x 150 mg tablets) bid, starting after completion of the abiraterone PK profiling (after the 24-hour sample).
Cohort 3, Groups 1 and 2 (if required):
200 mg olaparib (2 x 100 mg tablets) bid, as described for Cohort 2, Groups 1 and 2.
1000 mg abiraterone (4 x 250 mg tablets) once daily, in the morning, and prednisone or prednisolone 5 mg bid, as described for Cohort 2, Groups 1 and 2.

Duration of treatment
Patients will continue to receive study treatment until disease progression, or until a time when the Investigator considers that they are no longer deriving clinical benefit, or they stop taking treatment for any other reason including having met any of the criteria for treatment discontinuation.

Study burden and risks

Once patients with prostate cancer have progressed from an androgen-sensitive to a castrationresistant phenotype, docetaxel is an accepted first-line treatment, with cabazitaxel, enzalutamide and abiraterone indicated in the post-docetaxel phase. There is a clear clinical need to enhance the care of patients who have suffered disease progression during orfollowing docetaxel therapy. Because of abiraterone*s effectiveness in this setting and thepromise of PARP inhibition enhancing its effects, a randomised trial comparing olaparib plusabiraterone to placebo plus abiraterone is appropriate.

In view of the potential for olaparib, given in addition to abiraterone, to have anti-tumour
activity in metastatic CRPC population, the current study is designed to allow for patients to continue on olaparib/abiraterone therapy until progression of disease. However, patients may stop treatment at any time if they choose to do

so or if the Investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing or stopping olaparib are provided. The assessment of HRQL will provide information on patients* experience of the treatment and will be part of the benefit-risk assessment.

The molecular targeting of olaparib to specific subsets of tumours may provide an opportunity for more effective and potentially less toxic cancer treatments in the advanced disease setting compared with currently available regimens. Based on the available data on efficacy and safety (see the olaparib IB), AstraZeneca believes that olaparib continues to demonstrate an overall positive benefit-risk balance to support its further clinical development. The benefitrisk assessment, therefore, strongly favours the current and proposed olaparib study in patients with advanced prostate cancer.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

For inclusion in the study, patients should fulfil the following criteria:
1. Provision of signed and dated written informed consent prior to any study specific procedures.
2. Male aged 18 years and older.
3. Histologically or cytologically proven diagnosis of prostate cancer.
4. Candidate for abiraterone therapy with documented evidence of metastatic castration-resistant prostate cancer. Metastatic status is defined as at least one documented metastatic lesion on either bone scan or CT/MRI scan. Castrationresistant prostate cancer is defined as rising PSA or other signs of disease progression despite treatment with androgen deprivation therapy and the presence of a castrate level of testosterone (<=50 ng/dL).
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 with no deterioration over the previous 2 weeks.
6. Patients must have a life expectancy >=12 weeks.
7. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations, and completing PRO instruments.
8. Patients must be on a stable concomitant medication regimen, defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing.;For the Pharmacogenetic optional study 1 extra criterion:
- provide informed consent for the pharmacogenetic sampling and analysis

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:
1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, its agents and/or staff at the study site).
2. Previous treatment in the present study.
3. Treatment with any of the following:
* Previous exposure to any 2nd generation anti-hormonal including abiraterone and enzalutamide
* More than 2 prior courses of chemotherapy for metastatic prostate cancer
* Previous use of immunotherapy or radium-223 for the treatment of metastatic prostate cancer
* Any investigational agents or study drugs from a previous clinical study within 30 days of the first dose of study treatment
* Any previous exposure to a CYP17 (17α-hydroxylase/C17,20-lyase) inhibitor
* Substrates of CYP2D6 with a narrow therapeutic index (eg, thioridazine)
* Potent inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of

study treatment (3 weeks for St John*s Wort)
* Any previous treatment with a PARP inhibitor, including olaparib.
4. With the exception of alopecia or toxicities related to the use of gonadotropinreleasing hormone agonists, any unresolved toxicities from prior therapy greater than CTCAE Grade 2 at the time of starting study treatment.
5. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment.
6. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
7. Any of the following cardiac criteria:
* Mean resting QTc >470 msec obtained from 3 ECGs
* Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block
* Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.
8. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for >=5 years.
9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
* Platelet count <100 x 109/L
* Haemoglobin (Hb) <100 g/L
* Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN) if no demonstrable liver metastases or >5 x ULN in the presence of liver metastases
* Total bilirubin >1.5 x ULN if no liver metastases or >3 x ULN in the presence of liver metastases (except in the case of Gilbert*s disease)
* Creatinine >1.5 x ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 x ULN
* If bone metastases are present and liver function is otherwise considered adequate by the Investigator then elevated alkaline phosphatase (ALP) will not exclude the patient.
10. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of olaparib or abiraterone.
11. History of hypersensitivity to active or inactive excipients of olaparib or abiraterone or drugs with a similar chemical structure or class to olaparib or abiraterone.
12. Patients with myelodysplastic syndrome/acute myeloid leukaemia.
13. Current disease or condition known to interfere with absorption, distribution, metabolism, or excretion of drugs, at the Investigator*s discretion.
14. Major surgery within 2 weeks of starting study treatment and patients must have

recovered from any effects of any major surgery.
15. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely;For the Pharmacogenetic optional study 2 extra criteria are set:
• Previous allogeneic bone marrow transplant.
• Non-leukocyte depleted whole blood transfusion within 120 days of the date of the pharmacogenetic sample collection.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib
Generic name:	AZD2281

Ethics review

Approved WMO Date:	06-03-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-06-2014

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-11-2020
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2013-003520-37-NL
ClinicalTrials.gov	NCT01972217
CCMO	NL46930.068.14