A phase III, open label, randomized study to assess the efficacy and safety of Olaparib (Lynparza*)versus Enzalutamide or Abiraterone acetate in men with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations

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To determine the efficacy (as assessed by rPFS) and safety of olaparib versus investigator choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal...

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

Summary

ID

NL-OMON45674

Source
ToetsingOnline

Brief title
PROfound

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
Castration resistant prostate cancer, prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever / sponsor: AstraZeneca

Intervention

Keyword: homologous recombination repair gene mutations, metastatic castration-resistant prostate cancer, Olaparib (Lynparza)

Outcome measures

Primary outcome

To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with BRCA1, BRCA2 or ATM qualifying mutations (Cohort A)

Secondary outcome

-To determine the efficacy (as assessed by ORR) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (Cohort A)

- To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations (Cohort A+B).

- To determine the efficacy (as assessed by time to pain progression) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in

subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (Cohort A)

- To determine the efficacy (as assessed by overall survival) of olaparib

versus investigator choice of enzalutamide or abiraterone acetate

in subjects with BRCA1, BRCA2 or ATM qualifying gene mutations (Cohort A)

Study description

Background summary

Prostate cancer is a heterogeneous disease and there is no cure for the patients who reach the metastatic castration resistant stage of the disease. Prostate cancer is the most common cancer in men in the Netherlands.

Patients with metastatic castration-resistant prostate cancer will have a median overall survival around the 3 years when starting early with enzalutamide or abiraterone therapy. The median overall survival within the same healthy patient population is around the 15 years and therefore there is a need for an effective and well tolerated treatment for this patient population.

In a small percentage of all the prostate tumors, there is a mutation in the following genes: BRCA1, BRCA2, and ATM (<15%).
Mutations in these genes result in tumors that are deficient for homologous recombination, making them suitable for the treatment with a PARP inhibitor, wherein the synthetic lethality process can be utilized.

Olaparib inhibits the protein PARP. PARP is responsible for DNA repair. Cancer arises often from genetic abnormality and when that happens the PARP effectiveness can be increased. Olaparib can prevent the survival of cancer cells by preventing repair of damaged DNA is, causing the cancer cells to die.

This phase III study will compare the effectiveness (based on radiographic progression-free survival) of Olaparib compared with enzatulamide or abiraterone (choice of the investigator) in patients with metastatic castration-resistant prostate cancer with mutations in one of the HRR genes.

Study objective

To determine the efficacy (as assessed by rPFS) and safety of olaparib versus investigator choice of enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene

mutations.

Study design

Phase III, open-label, randomized study. Randomisation 2:1 to:
- Olaparib (300 mg orally twice daily)
- Enzalutamide (160 mg orally od) of Abiraterone (1000 mg orally met 5 mg prednison bid).

Approximately 340 subjects will receive treatment until progression. Adter discontinuation of olaparib patients will enter the follow up phase. Patients who are treated with Enzalutamide or Abiraterone can after progression switch to olaparib after discussion with the physcian (cross over arm)

Intervention

Treatment with Olaparib 300 mg bid or Enzalutamide 160 mg orally od or Abiraterone acetate 1000 mg od with 5 mg bid prednisone.

Study burden and risks

On several days during the study patients will undergo the following assessments:

Anamnesis (at the screening visit also the medical history), Physical Examination, WHO performance status, Vital signs (bloodpressure, pulse, temperature), weight, bonescan and CT or MRI scan, ECG, Blood and urine assessments , tumor biopsy(if necessary).

Related side effects are:
Very often (> 10%): anemia, neutropenia, lymphopenia, nausea, vomiting, dyspepsia, diarrhea, decreased appetite, headache, dizziness, dysgeusia, fatigue (among which asthenia). Increased bloodcreatinin, increase of average corpusculair volume.

Often (1-10%): trombocytopenia. stomatitis, stomach pain.

Further have been reported:

secondary myelodysplastic syndrome or secondary acute myeloïde leukemia (in most cases fatal); esp. in case of predisposing factors (history of cancer of dysplasia of bone marrow, simultaneous use of DNA damaging treatments and radiotherapy).
Pneumonotis, (in some cases fatal), esp in case of predisposing factors (lungmetastases, underlying lungdisease, history of smoking, former chemo- and

radiotherapy)

Contacts

Public
Astra Zeneca

Louis Pasteurlaan 5
Zoetermeer 2719 EE
NL
Scientific
Astra Zeneca

Louis Pasteurlaan 5
Zoetermeer 2719 EE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically confirmed diagnosis of prostate cancer
- Documented evidence of metastatic castration resistant prostate cancer (mCRPC).
- Subjects must have progressed on prior new hormonal agent (e.g. abiraterone acetate and/or enzalutamide) for the treatment of mCRPC.
- Ongoing therapy with LHRH analog or bilateral orchiectomy.
- Radiographic progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy).
- Qualifying HRR mutation in tumor tissue.

Exclusion criteria

- Any previous treatment with PARP inhibitor, including olaparib
- Subjects who have any previous treatment with DNA-damaging cytotoxic chemotherapy (prior taxane chemotherapy allowed)
- Other malignancy (including MDS and MGUS) within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumors curatively treated with no evidence of disease for >=5 years
- Subjects with known brain metastases

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-05-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lynparza
Generic name:	Olaparib
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Xtandi
Generic name:	Enzalutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zytiga
Generic name:	Abiraterone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-12-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-03-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-04-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	03-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Not approved Date:	23-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	26-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2016-000300-28-NL
CCMO	NL59750.031.16
Other	nog niet bekend