A randomized, open label, Phase IIB trial of Optimal Sequencing of Treatment Options for Poor Risk Metastasized Castration Resistant Prostate Cancer Previously Treated with Docetaxel (OSTRICh trial)

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Primary: * To assess Clinical Benefit Rate (CBR) in patients with mCRPC and poor prognostic factors treated with cabazitaxel or novel hormonal agents (abiraterone OR enzalutamide) as second-line therapy.Secondary: * To formally compare CBR in both...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON55594

Source
ToetsingOnline

Brief title
OSTRICh trial

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
metastasized castration resistant, Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Farnaceutich bedrijf Sanofi,Sanofi-aventis

Intervention

Keyword: metastasized castration resistant prostate cancer, Optimal Sequencing, Poor Risk

Outcome measures

Primary outcome

Primary endpoint:

To establish the Clinical Benefit Rate (CBR) in both study arms:

Percentage of patients that fulfill the criteria of clinical benefit. Patients are considered to have had a clinical benefit if they have a radiological response of any duration or stable disease for * 12 weeks, in the absence of symptomatic progression, or objective disease progression.

Radiological Response

Subjects that have measurable disease at screening will be evaluated for response on the basis of RECIST criteria v1.1, Tumor measurements using physical examination, chest, abdomen, pelvic CT scan, and/or MRI or other appropriate techniques deemed suitable by the investigator will be performed at screening within 28 days of subject registration and repeated at week 6, 12, 18 and 24 followed by every 12 weeks.

Symptomatic or objective disease Progression

Disease Progression is defined as the development of symptomatic or radiological progression at any time. Progression will be classified as any of the following:

1. Symptomatic progression: worsening of cancer-related symptoms mandating a stop of all treatments, a change in anti-cancer therapy (radiation, chemotherapy or antihormonal therapy), or * 2 level decrease in WHO PS or death of any cause. Radiotherapy does not account for symptomatic progression when administered in the first 4 weeks of this study.

2. Radiological progression: RECIST criteria v1.1 for measurable disease and/or appearance of * 2 new bone lesions on whole body bone scan confirmed on a subsequent scan. All radiological images will be assessed by an independent radiologist for central review of the RECIST criteria.

Secondary outcome

Secondary endpoints:

1. Formal comparison of the CBR in both study arms.

2. Rate of PSA >50% decrease from baseline

3. Duration of treatment; time from randomization to last day of treatment.

All time to event endpoints are met at death and censored at last follow-up;

4. Time To Symptomatic Progression TTSP;time from randomization to day of worsening of cancer-related symptoms mandating a stop of all treatments, a change in anti-cancer therapy (radiation, chemotherapy or antihormonal therapy) or * 2 level decrease in WHO PS. Radiotherapy does not account for symptomatic

progression when administered in the first 4 weeks of this study.

5. Time To Radiological Progression (TTRP); time from randomization to day of radiological progression: RECIST criteria v1.1 for measurable disease or appearance of * 2 new bone lesions on whole body bone scan confirmed on a subsequent scan.

6. Time To PSA Progression (TTPP); time from randomization to PSA progression (PCWG3 criteria: at least 2 rises at a minimum of 1-week intervals. The first PSA value must be * 2 ng/ml).

7. Progression Free Survival (PFS); time from randomization to the first date of progression on study medication as measured by PSA progrression (PCWG3 criteria), tumor progression (RECIST 1.1 criteria and PCWG3 criteria), symptomatic progression; stop of all treatments, a change in anti-cancer therapy (radiotherapy, chemotherapy or antihomonal therapy), >2 level decrease in WHO PS or death of any cause. Radiotherapy does not account for symptomatic progression when administered in the first 4 weeks of this study. PFS isassessed in patients who are treated with either arms as second line treatment and in patients who crossed over to the other treatment arm.

8. Overall Survival; time from randomization to date of death. Follow up will be maximum 3 years.

9. To evaluate safety and toxicity profile of cabazitaxel and novel hormone agents (abiraterone OR enzalutamide) all Adverse Events (AEs; assessed by CTCAE 4.03 grading) and Serious Adverse Events (SAEs) will be recorded during second line cabazitaxel/abiraterone OR enzalutamide treatment.

10. Quality of Life (QoL) as assessed by FACT-P questionnaire and Pain response

as assessed by BPI-S questionnaire and opiate use will be recorded during

second line cabazitaxel/abiraterone OR enzalutamide treatment

Study description

Background summary

There are multiple treatment options for mCRPC patients previously treated with docetaxel. Treatment options include chemotherapy e.g. cabazitaxel, bone-seeking radionuclides e.g. radium-223, and the new hormonal agents abiraterone and enzalutamide. Currently, there are no prospective data to support an optimal choice for second line treatment in the post-docetaxel space. Retrospective cohorts suggest a relation between patient characteristics, choice of second line treatment and patient benefit and survival. Patients with poor prognosis mCRPC might benefit more from cabazitaxel as a second line treatment then from novel hormonal treatment (abiraterone OR enzalutamide). Hallmarks of poor prognosis might be, among others, liver metastases, short duration of responsiveness to androgen deprivation therapy, short duration of response on docetaxel or progression during docetaxel treatment, elevated LDH and ALP and low serum albumin. In this prospective randomized trial, poor prognosis mCRPC patients, previously treated with docetaxel, will be randomized between cabazitaxel and abiraterone OR enzalutamide. Cabazitaxel, abiraterone and enzalutamide will be used according to the registered doses and schedules. Abiraterone, enzalutamide and radium-223 treatment prior to docetaxel is allowed, but not within the imposed docetaxel-cabazitaxel or novel hormonal treatment sequence. Cross-over to the other treatment arm is allowed at the time the patient meets the criteria for progressive disease, however, is no part of the randomization.
The aim of this study is to identify the optimal second line treatment option for patients with a poor prognosis mCRPC with respect to clinical benefit rate and quality of life.

Study objective

Primary:
* To assess Clinical Benefit Rate (CBR) in patients with mCRPC and poor prognostic factors treated with cabazitaxel or novel hormonal agents (abiraterone OR enzalutamide) as second-line therapy.

Secondary:
* To formally compare CBR in both study arms.
* Rate of PSA>50% decrease from baseline
* To determine duration of treatment

All time to event endpoints are met at death and censored at last follow-up;
* Time To Symptomatic Progression (TTSP), Time To PSA Progression (TTPP), and Time To Radiologic Progression (TTRP) in mCRPC patients treated with cabazitaxel or novel hormone agents (abiraterone OR enzalutamide) as second-line therapy and for those who cross over to the other study arm as a third-line therapy.
* To determine the Progression Free Survival (PFS) of mCRPC patients treated with cabazitaxel or novel hormone agents (abiraterone OR enzalutamide) as second-line therapy and for those who cross over to the other study arm as a third-line therapy.
* To determine the Overall Survival (OS) of mCRPC patients treated with cabazitaxel or novel hormone agents (abiraterone OR enzalutamide) as second-line therapy.
* To evaluate safety and toxicity profile of cabazitaxel and novel hormone agents (abiraterone OR enzalutamide) as a second line treatment.
* Quality of Life (QoL) as assessed by FACT-P questionnaire and Pain response as assessed by BPI-S questionnaire and opiate use of metastatic CRPC patients treated with cabazitaxel or novel hormone agents (abiraterone OR enzalutamide) as second-line therapy.

Exploratory Objectives
Three biomarker studies are included in this randomized trial. The value of the neutrophil to lymphocyte ratio, mutations in cfDNA and epigenetic modifications of cfDNA as predictive biomarkers will be explored.
(See page 28-31 of the study protocol)

Study design

This trial is a prospective, multicenter, national, randomized, open label phase IIB study, with optional cross over to the other study arm after primary endpoint has met.
In this study the efficacy in terms of CBR of cabazitaxel after docetaxel will be compared to enzalutamide OR abiraterone acetate after docetaxel treatment.

Patients with a progressive poor prognosis mCRPC and fulfilling all in- and exclusion criteria can be enrolled in the trial.

Study burden and risks

There will be no benefit for the patients who are willing to participate in the study.
They will receive a treatment with cabazitaxel, enzalutamide of abiraterone; a treatment they would have received if they did not participate in the study.
The risks of participation are low (as high as usual, since there is no difference from the standard of care).

Extra blood will be drawn during the usual blood drawings (38.5 ml, 3 times), and the patient will get extra scans during the study.
Patients are also asked to fill in questionnaires about pain, pain medication use and quality of life.
This will all cost extra time (approximately 9 hours per patient).

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

1. Histological diagnosis of prostate adenocarcinoma., 2. Able and willing to provide informed consent and to comply with the study procedures, 3. Age *18, 4. Evidence of bone, visceral and/or lymph node metastases on bone scan, CT-scan or MRI., 5. Must have received at least one prior regimen of docetaxel treatment for at least 12 weeks (four courses) and no other prostate cancer

treatments between docetaxel and randomization, other than prednisone., 6. Continued androgen deprivation therapy either by LHRH agonist/ antagonist or orchiectomy., 7. Treatment with curative intent is not an option and patient has an indication for systemic treatment as judged by the medical care provider, 8. Evidence of progressive metastatic disease by PSA progression (Prostate Cancer Working Group 3 (PCWG3) criteria: at least 2 rises at a minimum of 1-week intervals. The first PSA value must be * 2 ng/ml) and/or radiological progression as evaluated by chest, abdominal, or pelvic CT/MRI scan and/or bone scan within 28 days of registration (see Appendix III), 9. Poor prognosis disease as defined by any of the following:, a) The presence of liver metastases AND/OR, b) Development of castration-resistance within 12 months of orchiectomy or commencement of LHRH antagonist/agonist for metastatic disease AND/OR, c) Progressive disease during docetaxel treatment or <6 months after completion of docetaxel treatment, 10. WHO PS 0-2., 11. Serum testosterone < 50 ng/dL (< 1.7 nmol/L) within 28 days before treatment group allocation, 12. At least 21 days have passed since completing radiotherapy (exception for a single fraction of * 800 cGy to a restricted field or limited-field radiotherapy to non-marrow bearing area such as an extremity or orbit: at least 7 days prior to randomization)., 13. At least 21 days have passed since major surgery. , 14. Neuropathy * grade 1 at the time of registration. , 15. Has recovered from all therapy-related toxicity to * grade 2 (except alopecia, anemia and any signs or symptoms of androgen deprivation therapy) at the time of registration., 16. Eligible for cabazitaxel, abiraterone acetate or enzalutamide as per standard of care practices., 17. Men treated with cabazitaxel should use effective contraception throughout treatment and are recommended to continue this for up to 6 months after the last dose of cabazitaxel. Due to potential exposure via seminal liquid, men treated with cabazitaxel should prevent contact with the ejaculate by another person throughout treatment. Men being treated with cabazitaxel are advised to seek advice on conservation of sperm prior to treatment.

Exclusion criteria

1. Histologic evidence of small cell/neuroendocrine prostate cancer, 2. Any treatment other than prednisone between docetaxel and cabazitaxel/abiraterone OR enzalutamide sequence , 3. Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus). , 4. History of severe hypersensitivity reaction (* grade 3) to docetaxel, abiraterone or enzalutamide (whichever applies)., 5. History of severe hypersensitivity reaction (* grade 3) to polysorbate 80 containing drugs., 6. Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments)., 7. Patients who have a concurrent yellow fever vaccination (several weeks before start of treatment) must be excluded., 8. Dementia, altered mental status, or any psychiatric condition, if this is in conflict

with the study., 9. Unable to swallow a whole tablet or capsule, 10. Contraindications to the use of corticosteroid treatment, 11. Symptomatic peripheral neuropathy Grade *2 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v.4.0). , 12. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured and needing no subsequent therapy., 13. Inadequate organ and bone marrow function as evidenced by:, a. Hemoglobin <10.0 g/dL, b. Absolute neutrophil count <1.5 x 109/L, c. Platelet count < 100 x 109/L, d. AST/ SGOT and/ or ALT/ SGPT > 1.5 x ULN, Total bilirubin >1 x ULN (except for patients with documented Gilbert*s disease).

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2017
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jevtana
Generic name:	Cabazitaxel
Registration:	Yes - NL 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:	09-01-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-05-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2017
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-07-2021
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	EUCTR2016-004963-38-NL
CCMO	NL60114.031.16