A randomized phase II trial of docetaxel or cabazitaxel with or without darolutamide in men with metastatic castration-resistant prostate cancer.

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This study has been transitioned to CTIS with ID 2024-516939-28-00 check the CTIS register for the current data. To compare progression free survival (PFS) between treatment with docetaxel or cabazitaxel and darolutamide versus treatment with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53373

Source
ToetsingOnline

Brief title
Docetaxel or cabazitaxel with or without darolutamide in mCRPC

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Metastatic castration-resistant prostate cancer, metastatic prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Bayer

Intervention

Keyword: Cabazitaxel, Darolutamide, Docetaxel, Prostate Cancer

Outcome measures

Primary outcome

The main study endpoint is progression free survival, which is defined as time from randomization to radiologic, biochemical or pain progression or death from any cause, whichever occurs first, according to PCWG3

Secondary outcome

1. Overall survival, defined as time from randomization to death from any cause.

2. Time to progression, defined as time from randomization to radiologic, biochemical or pain progression, whichever occurs first.

3. The time to PSA progression, defined as time from randomization to biochemical progression.

4. The time to pain progression, defined as time from randomization to pain progression.

5. The number and severity of adverse events

6. Cell-free DNA aneuploidy scores and somatic aberrations in circulating tumor DNA

7. CTC-count.

8. Differential expression of relevant genes.

Study description

Background summary

Taxane efficacy in metastatic prostate cancer is limited due to resistance development. Several clinical phase III studies in metastatic castration-naïve prostate cancer (mCNPC) patients have shown that adding an androgen receptor signalling inhibitor (ARSi) to patients receiving a taxane and androgen deprivation therapy (ADT) improves survival endpoints. Adding ARSi darolutamide to docetaxel+ADT in mCNPC patients resulted in a robust OS benefit (HR 0.68). Importantly, the combination of a taxane and darolutamide is not prone to a drug-drug interaction, while there is a detrimental CYP3A4 inducing effect in the case of enzalutamide, resulting in a significant and clinically relevant reduction of cabazitaxel plasma concentrations. We have previously reported preclinical data showing that addition of an androgen receptor signaling inhibitor (ARSi) improves cabazitaxel efficacy, even in metastatic castration-resistant prostate cancer (mCRPC). As treatment options for mCRPC patients are scarce and patients often develop drug resistance relatively early, a new treatment regimen for this population to delay drug resistance is highly desired. We propose a randomized phase II trial to investigate the efficacy of docetaxel or cabazitaxel plus darolutamide compared to docetaxel or cabazitaxel monotherapy in men with metastatic CRPC, who have progressed on an ARSI.

Study objective

This study has been transitioned to CTIS with ID 2024-516939-28-00 check the CTIS register for the current data.

To compare progression free survival (PFS) between treatment with docetaxel or cabazitaxel and darolutamide versus treatment with docetaxel or cabazitaxel in mCRPC patients.

Study design

This is a randomized phase II trial.

Intervention

Before starting their taxane regimen, patients will be randomized 1 : 1 to receive darolutamide (600 mg b.i.d.) or not, until the end of their final taxane treatment cycle. Radiological follow-up will be according to standard of care. In addition, patients will undergo extra blood drawings at a maximum of 4 timepoints (baseline, after 3 and 6 cycles and at progression) for ctDNA and circulating tumour cell (CTC) analysis. Furthermore, a small subset of patients (n=25) will undergo a tissue biopsy twice and 40 patients will undergo diagnostic leukapheresis (DLA) for enrichment of CTCs for further molecular

analysis.

Study burden and risks

Patients in the darolutamide group, will receive darolutamide 600 mg b.i.d. during taxane treatment, in addition to current standard of care treatment. Major risks to be expected are side effects of darolutamide treatment. All patients will undergo extra blood drawings at a maximum of 4 timepoints and a subset will undergo DLA twice. Tissue biopsies will be performed in a small subset of patients. Standard complications of tissue biopsies are the relevant risk for these patients.

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. Age >= 18 years;
2. A confirmed diagnosis of progressive mCRPC (progression according to Prostate cancer Working Group (PCWG) 3 criteria), with an indication for docetaxel or cabazitaxel. Progression defined as >= 1 of the following 3 criteria:
a. Radiographic disease progression in soft tissue per RECIST v1.1
b. Radiographic disease progression in bone defined by the appearance of >= 2 new bone lesions on bone scan.
c. PSA progression defined as >= 2 sequential rises in PSA obtained >= 1 week apart with a minimal starting value of >= 1 ng/mL. A PSA value >= 2 ng/mL is required at study entry.
3. Patients should have had disease progression previously on at least one ARSi (abiraterone, apalutamide, darolutamide or enzalutamide). ARSi administration is allowed both in the mCNPC and in the mCRPC setting. Co-administration of docetaxel in mCNPC (triplet-therapy) is allowed.
4. WHO performance <= 2 (see appendix A)
5. Able and willing to sign the Informed Consent Form prior to screening evaluations
6. Adequate haematological, renal and liver function and chemistry, defined as:
a. Hemoglobin >= 6.0 mmol/L
b. Platelets >= 100 x 109/L
c. ALT/AST <= 3x ULN and <= 5x ULN in case of liver metastases
d. Creatinine clearance >= 50 ml/min
e. Serum testosterone <= 1.7 nmol/L

Exclusion criteria

1. Impossibility or unwillingness to take oral drugs
2. Hypersensitivity to taxanes
3. Known serious illness or medical unstable conditions that could interfere with this study requiring treatment (e.g. HIV, hepatitis, Varicella zoster or herpes zoster, organ transplants, kidney failure, serious liver disease (e.g. severe cirrhosis), cardiac and respiratory diseases)
4. Symptomatic peripheral neuropathy CTCAE grade >=2
5. Docetaxel-rechallenge.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-11-2023
Enrollment:	245
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nubeqa
Generic name:	Darolutamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-01-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	26-05-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	05-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-516939-28-00
EudraCT	EUCTR2022-003792-41-NL
CCMO	NL83539.078.23