Personalizing enzalutamide (Xtandi®) therapy by understanding the relation between the decrease in the expression profile of a panel of preselected microRNAs, tumor related mRNAs and treatment response in patients with mCRPC (ILUMINATE)

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Primary Objectives:To explore whether the decrease in a panel of early easily assessable biomarkers (PSA-mRNA, PCA3-mRNA and TMPRSS2:ERG gene fusion-mRNA, (currently under development) ARv7 mRNA, ARwt mRNA, miR-21, miR-141, miR-200a, miRrumc95,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON44900

Source
ToetsingOnline

Brief title
ILUMINATE

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC

Synonym
metastatic castration resistant prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Astellas Pharma Europe BV,bedrijven

Intervention

Keyword: drug exposure, drug response, Enzalutamide, mCRPC

Outcome measures

Primary outcome

To describe the relation between (early)biomarker response (%) and

therapeutical response (OR, SD, de novo resistent) after 3 and 6 months pf

therapy

Secondary outcome

- To explore the relation between Enzalutamide&N-desmethylenzalutamide exposure

(AUC) and decrease in biomarkers(%) from baseline

- To describe the relation between biomarker response en rPFS

- To describe the relation between (early) drug exposure and therapeutical

response

Study description

Background summary

Androgen deprivation therapy has been the standard of care for patients with advanced prostate cancer. Androgen deprivation results in tumor re-gression, relief of symptoms and a decrease in the concentration of pros-tate-specific antigen (PSA) in most patients. Unfortunately, the response to androgen deprivation therapy is not durable yet and disease progression occurs despite effective suppression of serum testosterone. This disease state is called

castration-resistant prostate cancer (CRPC) and is almost always associated with increased levels of prostate-specific antigen that suggests the involvement of androgen-receptor signalling. Especially intra-tumoral androgen levels are often increased in patients with progressive prostate cancer. CRPC therefore remains sensitive to further manipulations of the androgen receptor (AR) as demonstrated by the treatment efficacy of enzalutamide and abiraterone acetate in this group of patients.

Enzalutamide is an androgen-receptor-signalling inhibitor. It is distinct from the currently available anti-androgen agents in that it inhibits nuclear trans-location of the androgen receptor. In a phase I-II trial enzalutamide had significant antitumor activity regardless of previous chemotherapy status. The phase III AFFIRM study confirmed the activity of enzalutamide in a fixed dose of 160 mg once daily in men with metastatic CRPC (mCRPC) after che-motherapy with a significantly longer median overall survival in the enzalu-tamide treated group compared to the placebo treated group (18.4 months vs 13.6 months). More recently the phase III PREVAIL study confirmed the activity of enzalutamide in mCRPC prior to chemotherapy. The benefit was shown for both radiographic progression-free survival (HR 0.19; P<0.001) and overall survival (HR 0.71; P<0.001) compared to the placebo treated group. Unfortunately a small subset of patients is de novo resistant to en-zalutamide after three months (approximately 5-10%). Another 10-15% of the patients are potentially sub-optimally treated since they show progres-sion only shortly (within 6 months) after treatment. The biomarker PSA nowadays most frequently used may not reflect the status of disease accurately. Up to 20% of men with CRPC have an initial PSA increase before decline. Moreover the decline may occur up until 12 weeks after start of treatment or not at all. It is therefore urgent to find early and more reliable indicators for treatment response assessment. Recently, potentially promising prostate cancer specific biomarkers have been identified that can be used to selected those patients at risk of harbouring prostate cancer and to a priori select those patients who will respond to chemotherapy.

In this study we would like to explore whether early easily assessable and potentially more predictive biomarkers can be used to discriminate between patient who will develop 1. objective response; 2. stable disease or who are 3. de novo resistant to enzalutamide therapy.
Additionally we would like to explore the relation between enzalutamide & N-desmethylenzalutamide plasma concentrations and the decrease in these potentially more predictive biomarkers.

Study objective

Primary Objectives:
To explore whether the decrease in a panel of early easily assessable biomarkers (PSA-mRNA, PCA3-mRNA and TMPRSS2:ERG gene fusion-mRNA, (currently under development) ARv7 mRNA, ARwt mRNA, miR-21, miR-141, miR-200a, miRrumc95, miRrumc87 and miRrumc4417) can discriminate between patients who are 1.

Optimally treated (response after 3 and 6 months of therapy) 2. Suboptimally treated (progressive after 6 month of therapy) and 3 de novo resistant (progressive after 3 months of therapy).
Secondary Objectives:
- To explore the relation between enzalutamide & N-desmethylenzalutamide plasma exposure and the decrease in the se-lected biomarkers (the panel of mRNAs and microRNAs)
- To explore the relation between selected biomarker response under enzalutamide therapy and radiographic progression free survival
- To explore the relation between enzalutamide & N-desmethylenzalutamide exposure and radiographic progression free survival

Study design

The study is a open label phase IV pharmacokinetics/ pharmacodynamics study in chemotherapy naive patients with metastatic CRPC
A total of 40 patients will be enrolled into the study.

Study burden and risks

Patients participating in this study will have pharmacokinetic assessments at 1 month, 3 months and 6 months. On all
three days in the first ten patients a total of 10 blood samples will be collected over 24 hours after enzalutamide
ingestion. Additionally, pre-dose blood samples will be collected for the traditional and novel pharmacodynamic
biomarkers. All blood samples will be drawn from a once placed intravenous cannula (absolute volume approximately
45ml). For the next 30 patients an adjusted less intensive PK collection schedule will be derived based on the initial 10
patients. Participating in this study contributes to the knowledge on the most adequate use of enzalutamide in
patients with metastatic castration resis-tant prostate cancer.

The risk-classification is assessed as negligible to the patient population participating in this study.
Enzalutamide is registered in the Netherlands for mCRPC prechemotherapy at the same dose as used in this study.
The intervention embraces the measurement of pharmacokinetic and pharmacodynamic biomarkers and response.
Besides the venapunction there is no additional risk for the patients who participate in this study protocol.

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

- Male patients with metastatic castration resistant prostate cancer who are chemotherapy naive OR have been treated upfront with 6 cycles of docetaxel: conform the Chaarted or Stampede trials
-Age at least 18 years
-Patients from who it is possible to collect blood samples
-Patient who are able and willing to give written informed consent prior to screening and enrollment
-Life expectancy of > 6 months
-Measurable disease
*definition of CRPC according to EAU guidelines 2014

Exclusion criteria

Patients will be treated with enzalutamide in agreement with the drug label. Therefore the contra-indications of the drug label will be respected and no addi-tional strict exclusion criteria will be used in this study.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-07-2015
Enrollment:	48
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	21-04-2015
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-01-2017
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-000860-32-NL
CCMO	NL52714.091.15