Optimizing abiraterone (zytiga®)therapy by exploring the relation between an early biomarker-drug exposure-as a predictor for drug response in patients with mCRPC (OPTIMUM study)

Published: 15-01-2015
Last updated: 21-04-2024

Primary Objectives:*To explore whether early abiraterone exposure (AUC) is corre*lated to treatment response after 3 months and 6 months of therapy (primarily based on radiographic response (RECIST re*sponse: SD, PR, CR) and secondary on...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44680

Source
ToetsingOnline

Brief title
OPTIMUM

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
metastatic castration resistant prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Jansen Cilag BV,Janssen Cilag BV

Intervention

Keyword: Abiraterone, drug exposure, drug response, mCRPC

Outcome measures

Primary outcome

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

response

Secondary outcome

- Delta changes (%) of the biomarkers from baseline measurement

- To describe the relation between biomarker and therapeutical response

- To describe the relation between biomarker and drug exposure

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 and relief of symptoms and a decrease in the concentration of prostate*specific antigen (PSA) in most patients. Unfortunately, the response to treatment is not durable and virtually all patients develop castration*resistant prostate cancer (CRPC). However, as demonstrated by the efficacy of abiraterone acetate, CRPC remains sensitive to further manipulations of the androgen receptor (AR). Abiraterone acetate, a prodrug of abiraterone, is a selective and irreversible blocker of cytochrome P450 C17 (CYP17), a crucial enzyme in testosterone and estrogen synthesis, resulting in virtually undetectable serum and intratumoral androgen levels. Unfortunately, also the response to abiraterone acetate is not durable yet. Moreover, a substantial group of the patients treated with abiraterone is initially not responsive to the therapy with abiraterone in the pre* and post chemotherapy setting.
Since the currently used fixed dose results in a substantial interpatient vari*

ability (40.5 * 140.6%) in drug exposure the unresponsive patients might be those that are underexposed to abiraterone. Additionally, in the PK * PSA * survival modeling a relation between drug exposure, PSA decrease and sur*vival was present. Therefore, in this study we would like to explore the rela*tion between abiraterone plasma concentrations (as an early pharmacoki*netic biomarker) and drug response (primarily based on radiology and sec*ondary on biochemistry).
Additionally, we would like to investigate whether other exploratory early easily assessable pharmacodynamic (=PD) biomarkers in combination with the more traditional PD biomarkers could give earlier insight in treatment response.
The traditional biomarkers measured are PSA, dehydroepiandrosterone (DHEA), lactic acid dehydrogenase (LDH) and alkaline phosphatase (AP).
The exploratory biomarkers measured are circulating tumor mRNA, as de*tected by PSA mRNA, PCA3 mRNA, TMPRSS2:ERP gene fusion mRNA and the currently under development ARv7 (splice variant 7) mRNA and ARwt (full length) mRNA in peripheral blood mononuclear cells (PBMC).

Study objective

Primary Objectives:
*To explore whether early abiraterone exposure (AUC) is corre*lated to treatment response after 3 months and 6 months of therapy (primarily based on radiographic response (RECIST re*sponse: SD, PR, CR) and secondary on biochemistry (*25% de*crease in PSA). In case of only bone lesions: SD is defined as no new lesions; PD is defined as * 2 new lesions (PCWG2 criteria)

Secondary Objectives:
*To explore the relation between novel early and easily assessa*ble biomarkers (PSA*mRNA, PCA3*mRNA, TMPRSS2:ERP gene fusion*mRNA, (currently under development)ARv7 mRNA and ARwt mRNA) and treatment response after 3 months and 6 months of therapy*
To explore whether the degree of reductions in these novel bi*omarkers are related to abiraterone exposure (AUC) after 3 and 6 months of therapy
*To explore the relation between traditional PD biomarkers (se*rum PSA, DHEA, LDH, AP) and treatment response after 3 and 6 months of therapy
*To explore whether the degree of reductions in PSA, DHEA, LDH, AP are related to abiraterone exposure (AUC) after 3 and 6 months of therapy

Study design

The study is an open label phase II intervention pharmacokinetics/ pharma* codynamics study in patients with metastatic CRPC.
A total of 50 patients with metastatic CRPC will be enrolled into the study.

Intervention

no therapeutical intervention. Exclusively determine pharmacokinetics and pharmacodynamics of abiraterone for the indication according to the drug label (CRPC)

Study burden and risks

Patients participating in this study will have pharmacokinetic assessments at 1 month, 3 months and 6 months (one pre-dose sample per PKday). 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 40ml). Participating in this study contributes to the knowledge on the most ade*quate use of abiraterone acetate in patients with metastatic castration resis*tant prostate cancer. The risk*classification is assessed as negligible to the patient population participating in this study. Abiraterone acetate is registered in the Netherlands for mCRPC pre*chemotherapy 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

* patients with metastatic castration resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated * OR * who have been treated upfront with 6 cycles of docetaxel: conform the Chaarted or Stampede trials
*Age *18 years
*Feasible to collect blood samples from
*Life expectancy of > 6 months
*Measurable disease
- Able and willing to give written informed consent prior to screening and enrollment

Exclusion criteria

Patients will be treated with abiraterone acetate 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:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	10-07-2015
Enrollment:	34
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-03-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-04-2015
Application type:	Amendment
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:	28-01-2016
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-05-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2020
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	EUCTR2014-004513-90-NL
CCMO	NL51702.091.14