A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

Published: 23-05-2008
Last updated: 07-05-2024

Primary objective:To compare the clinical benifit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of...

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

Summary

ID

NL-OMON32133

Source
ToetsingOnline

Brief title
Phase 3 study of Abiraterone Acetate plus Prednisone in metastatic CRPC

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Metastatic prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Cougar Biotechnology, Inc
Source(s) of monetary or material Support: Cougar Biotechnology;Inc

Intervention

Keyword: Abiraterone Acetate, Metastatic Castration Resistent Prostate Cancer, Phase III study

Outcome measures

Primary outcome

The primary efficacy endpoint is:

Overall survival

Secondary outcome

Secundary efficacy endpoints:

Proportion of patients achieving a PSA decline >= 50% according to the PSA

Working Group criteria

Time-to-PSA progression based on PSA WG criteria

Progression-free survival (PFS) based on imaging studies

Other endpoints:

Proportion of patients with objective tumor response by modified RECIST

(baseline lymph nodes size must be >= 2 cm to be considered a target lesion)

Proportion of patients experiencing pain palliation using BPI-SF and analgesic

score

Time to pain progression

Time to first skeletal-related event

Modified PFS based on criteria for discontinuation of study treatment

Proportion of patients achieving a decline in circulation tumor cells

(CTCs)/7.5 ml to less than 5

Quality of life total score and each subscale score as assessed by FACT-P

Safety endpoints:

All patients who receive at least one dose of abiraterone acetate or placebo

will be analyzed for safety. Safety summary will include adverse events,

clinical laboratories parameters, and vital signs. Serious adverse events and

deaths will be listed.

Study description

Background summary

Despite the improved survival in CRPC patients treated with docetaxel-based regimens, the median survival of patients receiving docetaxel chemotherapy 17.5-18.9 months. Once the disease progresses after failing docetaxel-based therapy, there is no treatment that hase proven to improve survival. Thus, new therapies are urgently needed.
Recently, phase I and II studies have been carried out with Abiraterone Acetate in patients with CRPC. Antitumor effects were evident with PSA response and durable objective responses.

The mechanisms of actions of abiraterone acetate and docetaxel are not overlapping. In a recently conducted Phase 2 study where abiraterone acetate was administered to patients with advanced prostate cancer who had progressive disease after docetaxel-based chemotherapy, approximately half of the patients had a PSA reduction of > 50%. In patients with soft tissue metastatis on imaging studies, tumor shrinkage was observed as well. Therefore, it appears that resistance to docetaxel is independent of sensitivity to androgen-deprivation therapy.

A Phase 2 study was conducted to evaluate the safety and efficacy of abiraterone acetate in castration resistant prostate cancer (CRPC) after

failing docetaxel-based chemotherapy while receiving low dose prednisone. Preliminary data so far shows few adverse events. In particular, adverse events known to be associated with abiraterone acetate monotherapy, namely, hypokalemia, hypertension, and fluid retention appear to be less frequent when abiraterone acetate is used in combination with low-dose prednisone. In this Phase 3 study, prednisone 5 mg bid has been selected for use in both study treatment groups. The use of prednisone as a single agent, sometimes prescribed ot palliate symptoms in advanced CRPC also justifies the placebo-controlled design where the placebo group will receive low dose prednisone rather than no treatment.

The primary hypthesis of this randomized, double-blind, placebo-controlled study is that patients receiving abiraterone acetate and prednisone will achieve a 25% improvement in overall survival compared with patients receiving placebo and prednisone. It is also anticipated that abiraterone acetate will increase the proportion of patients gaining PSA responses as defined by PSA WG criteria, prolong the PSA and radiographic progression-free survival, possibly palliate pain, reduce skeletal-related events due to metastatic bone disease and improve QOL.

Study objective

Primary objective:
To compare the clinical benifit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of which contains docataxel.

Secondary objectives:
To further evaluate the safety profile of abiraterone acetate plus prednisone
To further characterize the PK of abiraterone acetate when administered concurrently with prednisone
To further explore the potential utility of CTC's as a surrogate for clinical benefit
To evaluate the impact of abiraterone acetate plus prednisone on health related quality of life (QOL)

Study design

Structure:
Phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled study with a randomization allocation of 2:1 (abiraterone acetate : placebo). Abiraterone acetate and placebo tablets will be referred to a study medication in a blinded fashion.

Randomization will be stratified according to the following:

ECOG performance status: 0-1 versus 2
Worst pain over the past 24 hours on BPI-SF: 0-3 (absent) versus 4-10 (present)
1 versus 2 prior chemotherapy regimens
Type of progression: PSA only versus radiographic progression

Intervention

Patients randomized to the abiraterone acetate group will receive a dose of 1000 mg daily (QD). Study medication will be administered as 4 x 250-mg abiraterone acetate tablets or 4 placebo tablets.
Prednisone will be administered as 5 mg orally twice a day (bid) for both groups.

Study burden and risks

Participating patients need to come to the site for regular visits: screening visit, day 1 cycle 1, day 15 cycle 1, day 1 every following cycle and end of study visit.
During these visits the following procedures will be performed: completion of QoL-questionnaire, analgesic usage questionnaire, completion of fatigue scale, physical examination, vital signs, ECG, MUGA-scan or cardiac echo, assessment of adverse events, bloodsamples, urinalysis, CT-/MRI-scan, bone scan (see protocol page 77).

In a recently conducted phase 2 study to evaluate the safety and efficacy of abiraterone acetate in CRPC after failing docetaxel-based chemotherapy while receiving low dose prednisone half of the patients had a PSA reduction of >= 50%. In patients with soft tissue metastasis tumor shrinkage was observed as well. This study showed few adverse events.

Therefore from the risk benefit assessment it seems that treatment effect will be greater than the risk for patients when participating in the study.

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

4. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
5. At least one but not more than 2 cytotoxic chemotherapy regimens for metastatic castration-resistant prostate cancer. At least one regimen must have contained docetaxel.
6. Documented prostate cancer progression by at least the following:
* PSA progression according to the PSA WG eligibility criteria (protocol appendix 3)
* Soft tissue disease progression by modified RECIST criteria (protocol appendix 4)
* Metastatic bone disease on bone scan with >= 2 new lesions and a concurrent PSA >= 5 ng/mL
7. Ongoing androgen deprivation with serum testosterone < 50 ng/dL
8. (ECOG) Performance Status of <= 2
9. Hemoglobin >= 9.0 g/dL independent of transfusion
10. Platelet count >= 100,000/µL
11. Serum albumin >= 3.0 g/dL
12. Serum creatinine < 1.5 x ULN or a calculated creatinine clearance of 60 mL/min
13. Serum potassium >= 3.5 mmol/L

Exclusion criteria

1. Serious or uncontrolled co-existing non-malignant disease, including active and uncontrolled infection
2. Abnormal liver functions consisting of any of the following:
* Serum bilirubin >= 1.5 x ULN

* AST or ALT >= 2.5 x ULN (for patients with known liver metastatis, AST or ALT <= 5 x ULN is allowed)
3. Uncontrolled hypertension (systolic BP >= 160 mmHg, or diastolic BP >= 95 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy.
4. Active or symptomatic viral hepatic or chronic liver disease
5. History of pituitary or adrenal dysfunction
6. Clinically significant heart disease
7. Other malignancy, except non-melanoma skin cancer, with a >= 30% probability of recurrence within 12 months.
8. Known brain metastatis
9. History of gastrointestinal disorders which may interfere with the absorption of the study drug.
11. Prior therapy with ketoconazole for prostate cancer
12. Surgery or local prostatic intervention within 30 days of first dose.
13. Radiotherapy, chemotherapy or immunotherapy within 30 days or single fraction of palliative radiotherapy within 14 days of administration of Cycle 1 day 1.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2008
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Abiraterone Acetate
Generic name:	Abiraterone Acetate
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	prednisolone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-05-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-03-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-08-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	08-09-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2011
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	EUCTR2007-005837-13-NL

Register	ID
CCMO	NL22011.091.08