A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC).

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OBJECTIVE AND HYPOTHESISPrimary ObjectiveThe primary objective is to determine whether abiraterone acetate in combination with low-doseprednisone and androgen deprivation therapy (ADT) is superior to ADT alone in improving rPFS and OS insubjects...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON44898

Source
ToetsingOnline

Brief title
LATITUDE

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: ADT therapy, Metastatic Prostate cancer, Newly diagnosed high risk Abiraterone Acetate

Outcome measures

Primary outcome

EFFICACY EVALUATIONS: with protocol amendment INT-2 dd 18 April 2014 the

radiographic progression-free survival (rPFS) was added as a co-primary

endpoint with overall survival (OS)

Efficacy Endpoints

Co-primary endpoint: rPFS and OS

Overall survival (OS) is defined as the time from randomization to date of

death from any cause. Survival

data will be collected throughout the Double-blind Treatment Phase and during

the Follow-up Phase.

Once a subject has completed the Double-blind Treatment Phase, OS follow-up

will be performed every

4 months for up to 60 months (5 years) or until subject death, lost to

follow-up, withdrawal of consent, or

study termination.

rPFS is defined as the time from randomization to the occurence of radiographic

progression or death from any cause.

Secondary outcome

Secondary: time to next skeletal related event, time to prostate specific

antigen (PSA) progression, time to next subsequent therapy for prostate cancer,

time to initiation of chemotherapy and time to pain progression.

Exploratory: PSA response rate, PRO measures (EQ-5D-5L [Euro-QoL], Brief Pain

Inventory-Short

Form [BPI-SF], Functional Assessment Cancer Therapy-Prostate [FACT-P], Brief

Fatigue Inventory

[BFI]), pain measures (time to pain progression), time to symptomatic local

progression defined as

occurrence of urethral obstruction or bladder outlet obstruction, and prostate

cancer specific survival.

Study description

Background summary

ZYTIGA® (abiraterone acetate) is a prodrug of abiraterone, an irreversible inhibitor of
17* hydroxylase/C17, 20-lyase (cytochrome P450c17 [CYP17]), a key enzyme required for testosterone

synthesis. Marketing authorization for ZYTIGA and prednisone/prednisolone was granted in April 2011
in the United States and in September 2011 in the European Union. Treatment with ZYTIGA improves
survival in patients with metastatic castration-resistant prostate cancer. This study will test whether
ZYTIGA also improves radiographic progression free survival (rPFS) and overall survival (OS) in patients with newly diagnosed metastatic, hormone-naive prostate
cancer (mHNPC) who are at an increased risk for rapid disease progression.

Study objective

OBJECTIVE AND HYPOTHESIS

Primary Objective

The primary objective is to determine whether abiraterone acetate in combination with low-dose
prednisone and androgen deprivation therapy (ADT) is superior to ADT alone in improving rPFS and OS in
subjects with mHNPC with high-risk prognostic factors.

Secondary Objective

The secondary objectives are to evaluate the clinically relevant improvements as well as the safety of
abiraterone acetate plus low-dose prednisone and ADT compared with ADT alone and to identify
microRNA (miRNA) and mRNA profiles predictive of abiraterone acetate response or resistance in this
patient population.

Hypothesis

The hypothesis is that addition of abiraterone acetate to ADT as initial therapy (compared with ADT
alone) will improve rPFS and OS in men with newly-diagnosed, high-risk mHNPC.

Study design

OVERVIEW OF STUDY DESIGN

This is a multinational, multicenter, randomized, double-blind, active-controlled study designed to
determine if newly diagnosed subjects with mHNPC who have high-risk prognostic

factors will benefit
from the addition of abiraterone acetate and low-dose prednisone to ADT. In this study, ADT refers
specifically to luteinizing hormone releasing hormone (LHRH) agonists or orchiectomy. Approximately
1200 subjects will be enrolled. The study population includes newly diagnosed (within 3 months prior to
randomization) adult men with high-risk mHNPC (high-risk prognosis defined under Subject Selection).
Subjects will be stratified by presence of visceral disease and Eastern Cooperative Oncology Group
(ECOG) performance grade of 0, 1 vs. 2 prior to randomization. Subjects must have distant metastatic
disease as documented by positive bone scan or metastatic lesions on CT or MRI to be eligible. Eligible
subjects may have received ADT or had an orchiectomy within 3 months of randomization. Subjects may
also receive anti-androgens for up to 3 months prior to randomization but the continued use of antiandrogens
is to be terminated before randomization. Abiraterone acetate and low-dose prednisone will be
considered as study drugs.
The study will consist of a Screening Phase of up to 28 days before randomization to establish study
eligibility and document baseline measurements; a Double-blind Treatment Phase; and a Follow-up Phase
of up to 60 months to monitor survival status and subsequent prostate cancer therapy. Each cycle is
28 days. Treatment will continue until disease progression, withdrawal of consent, or the occurrence of
unacceptable toxicity. Subjects who meet all of the inclusion criteria and none of the exclusion criteria
will be centrally randomized in a 1:1 ratio to the active group (abiraterone acetate [1,000 mg once daily]
plus low-dose prednisone [5 mg once daily] plus ADT [LHRH agonist or orchiectomy]) or the control
group (abiraterone acetate and prednisone placebos plus ADT [LHRH agonist or orchiectomy]).

In the event of a positive study result (efficacy boundary is crossed) at either of the interim analyses or at
the time of the final analysis, all subjects will have the opportunity to enroll in an Open-label Extension
Phase. The Open-label Extension Phase will allow subjects to receive active drug (abiraterone acetate
plus prednisone) for up to 3 years. Two interim analyses for OS in addition to the final analysis are planned for

this study after observing 50% (421 events) and 65% (548 events) of the total number of required (842)
events for the final analysis. It is expected that the rPFS analysis will likely occur in conjunction with the first interim OS analysis.

Subjects will be monitored for safety throughout the study. Adverse events including laboratory adverse
events will be graded and summarized using National Cancer Institute Common Terminology Criteria for
Adverse Events (NCI-CTCAE), Version 4.0. Dose modification guidelines are provided. An Independent
Data Monitoring Committee (IDMC) will be commissioned for the study to perform regular safety review
and at the planned interim analyses.

Intervention

See study design

Study burden and risks

The risks of this trial are comparable witht the risks associated with standard of care. Side effects of abiraterone acetate and prednicon are commonly known and are described in the ICF form, protocl and IB. Addition of abiraterone acetate to the ADT therapy as initial treatment (compared to ADT alone) demonstrated an increased OS in patients with newly diagnosed men with high risk mHNPC.

For side effects of AA and prednisone and risks related to reseach procedures: see ICF (pg 6-7 and addendum E) and protocol pg 32-34.

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. Newly diagnosed metastatic prostate cancer within 3 months prior to randomization with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology;2. Distant metastatic disease documented by positive bone scan or metastatic lesions on computed tomography or magnetic resonance imaging scan;3. At least two of the following high-risk prognostic factors: Gleason score of *8; presence of 3 or more lesions on bone scan; presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI scan;4. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1 or 2;5. Adequate hematologic, hepatic, and renal function;6. Agrees to protocol-defined use of effective contraception

Exclusion criteria

1. Active infection or other medical condition that would make prednisone use contraindicated;2. Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day;3. Pathological finding consistent with small cell carcinoma of the prostate;4. Known brain metastasis;5. Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer; the following exceptions are permitted: up to 3 months of androgen deprivation therapy (ADT) with lutenizing hormone releasing hormone agonists or orchiectomy with or without concurrent anti-androgens prior to Cycle 1 Day 1; patients may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 28 days prior to Cycle 1 Day 1, all adverse events associated with these procedures must be resolved at least to Grade 1 by Cycle 1 Day 1.;6. Uncontrolled hypertension (systolic blood pressure >=160 mmHg or diastolic BP >=95 mmHg; patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment);7. Active or

symptomatic viral hepatitis or chronic liver disease, ascites or bleeding disorders secondary to hepatic dysfunction.;8. History of adrenal dysfunction;9. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease ;10. Atrial fibrillation, or other cardiac arrhythmia requiring pharmacotherapy;11. Other malignancy (within 5 years), except non-melanoma skin cancer;12. Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 28 days of Cycle 1 Day 1 or currently enrolled in an investigational study;13. Any condition or situation which, in the opinion of the investigator, would put the patient at risk, may confound study results, or interfere with the patient*s participation in this study

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:	Recruitment stopped
Start date (anticipated):	12-02-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

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

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

Ethics review

Approved WMO Date:	17-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-002940-26-NL
CCMO	NL43377.029.13