A PHASE Ib/II STUDY OF IPATASERTIB (GDC-0068) OR APITILISIB (GDC-0980) WITH ABIRATERONE ACETATE VERSUS ABIRATERONE ACETATE IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER PREVIOUSLY TREATED WITH DOCETAXEL-BASED CHEMOTHERAPY

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PHASE IIPrimary ObjectiveThe primary objective of the Phase II portion of the study is to estimate the efficacy as measured by radiographic progression-free survival of IPATASERTIB (GDC-0068) (dosed at either 400 mg or 200 mg daily) + abiraterone...

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

Summary

ID

NL-OMON45198

Source
ToetsingOnline

Brief title
Genentech GO27983

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy

Research involving
Human

Sponsors and support

Primary sponsor: GABA International
Source(s) of monetary or material Support: Farmaceutical Industry

Intervention

Keyword: abiraterone acetate, castration-resistant prostate cancer, GDC-0068, IPATASERTIB

Outcome measures

Primary outcome

Primary Efficacy Outcome Measure for PHASE II

The primary efficacy outcome measure in all patients and in patients with PTEN loss is as follows:

* Radiographic progression-free survival as the time from randomization to the first observation of disease progression, as assessed by the investigator, or death (* 30 days after the last dose of study treatment) from any cause on study.

Secondary outcome

Secondary Efficacy Outcome Measures for PHASE II

The secondary efficacy outcome measures in all patients and in patients with PTEN loss are the following:

* Overall survival, defined as the time from randomization until death from any cause

* PSA response, defined as a > 50% decrease in PSA from baseline, which is confirmed after * 4 weeks by a confirmatory PSA measurement

* Confirmed objective tumor response in patients with measurable soft tissue

disease at baseline, as assessed by the investigator per modified RECIST v1.1

* Duration of confirmed objective response in patients with measurable soft tissue disease at baseline, defined as the time from first observation of an objective confirmed tumor response until first observation of disease progression, as assessed by the investigator per modified RECIST v1.1

* Decrease in circulating tumor cells (CTCs), defined as < 5 CTC per 7.5 mL on treatment for patients with * 5 CTC per 7.5 mL at baseline

* Change in pain symptoms score, as assessed by the modified Brief Pain Inventory short form (mBPI-sf)

Pharmacokinetic and Pharmacodynamic Outcome Measures for PHASE Ib and II

For GDC-0068 and its metabolite (G-037720), APITILISIB (GDC-0980), and abiraterone, the following pharmacokinetic parameters will be reported as applicable:

* Total exposure (AUC) from Time 0 to the last measurable concentration (AUC0* last)

* Time to maximum observed plasma concentration (tmax) and maximum observed plasma concentration (Cmax)

* Minimum observed plasma concentration (Cmin; trough concentration)

* Clearance relative to bioavailability (CL/F), volume of distribution relative to bioavailability (V/F), and half-life, if data allow

Safety Outcome Measures for PHASE II

The safety and tolerability of IPATASERTIB (GDC-0068) (400 mg vs. 200 mg vs.

placebo) when combined with abiraterone will be assessed using the following

outcome measures.

* Incidence, nature, and severity of AEs, graded according to the NCI CTCAE v4.0

* Clinically significant changes in vital signs, physical findings, and

clinical laboratory results

Study description

Background summary

Prostate adenocarcinoma is the most common malignancy affecting men in the Western world.
The activity of anti-androgen therapies, including bicalutamide, GnRH agonist, and abiraterone, has resulted in improved survival for patients with prostate cancer. However, nearly all patients who present with hormone-sensitive advanced prostate cancer progress to CRPC and require other forms of therapy. When given as single agents, both IPATASERTIB (GDC 0068) and APITILISIB (GDC-0980) have demonstrated activity in nonclinical models, including but not limited to in vitro and in vivo models of PTEN-deficient prostate cancer. Additionally, both agents enhanced the anti tumor effects of anti-hormone therapy in nonclinical studies. Given the strong implication of PI3K/Akt activity in prostate cancer cell survival and therapeutic resistance, IPATASERTIB (GDC-0068) and/or APITILISIB (GDC-0980) could be particularly effective given in combination with abiraterone in PTEN loss CRPC dependent of the PI3K/Akt pathway for growth and survival.
Despite the success of the abiraterone studies, CRPC remains an incurable disease with limited progression-free and overall survival. Hence the purpose of this study is to evaluate whether combined inhibition of androgen signaling (with abiraterone) and PIK3/Akt signaling (with IPATASERTIB (GDC-0068) or APITILISIB (GDC-0980) is safe and will improve the efficacy of single-agent abiraterone in patients with CRPC.

Study objective

PHASE II
Primary Objective
The primary objective of the Phase II portion of the study is to estimate the efficacy as measured by radiographic progression-free survival of IPATASERTIB (GDC-0068) (dosed at either 400 mg or 200 mg daily) + abiraterone and prednisone/prednisolone versus placebo + abiraterone and

prednisone/prednisolone.
Efficacy will be measured in all patients and in patients with PTEN loss.

Study design

A Phase II, double-blind, randomized comparison of IPATASERTIB (GDC-0068) GDC (dosed 400 mg or 200 mg daily) with abiraterone and prednisone/prednisolone versus placebo with abiraterone and prednisone/prednisolone
Patients with histologically or cytologically confirmed prostate cancer who have been previously treated with docetaxel will be enrolled in this study. Disease progression will be based on changes in PSA, radiographic bone metastasis, and measurable disease. The safety of IPATASERTIB (GDC-0068) in combination with abiraterone will be monitored by a scientific oversight committee (SOC) and an internal monitoring committee (IMC).

Intervention

During this study, all patients will receive treatment with abiraterone, which is 1000 mg daily dosing with 5 mg of prednisone/prednisolone twice daily.

In PHASE II portion of the study, patients will receive IPATASERTIB (GDC-0068) (dosed 400 mg or 200 mg daily) or placebo with abiratoron and prednisone/prednisolone. IPATASERTIB (GDC-0068) or placebo needs to taken once daily by mouth on each day of the 28 day treatment cycles.

Study burden and risks

DURING 3 TREATMENT CYCLES WITH TREATMENT COMPLETION VISIT AS INDICATED IN APPENDIX A -FLOWCHART
7 x vital signs
1 x oxygen saturation
2 x weight
1 x complete physical examination
4 x limited physical examination
1 x MUGA or ECHO for LVEF (left ventricular ejection fraction)
4 x ECOG status
4 x ECG
1 x tumor assessment and after cycles 3, 5, 7, 9 and every 3 cycles thereafter (CT-scan of MRI)
1 x bone scan and after cycles 3, 5, 7, 9 and every 3 cycles thereafter
7 x blood sample
1 x urine analysis
1 x DL assessment
1 x tumor sample
1 x biopsy (or current available sample)
4 x short pain questionnaire

- pain diary; daily during the first 12 weeks
- daily medication diary
- daily IPATASERTIB (GDC-0068) or APITILISIB (GDC-0980)- (or placebo- for phase Ib), abirateron- and prednison- tablets intake

De side effects and risks are mentioned below as indicated in the the addenda of the patient information.

Side effects in increased glucose and insulin metabolism:
* Changes in glucose and insulin metabolism: In patients treated with IPATASERTIB (GDC 0068) increases in blood glucose levels and insulin levels have been reported. These changes were reversible mostly within 24 hours, prior to the next treatment with IPATASERTIB (GDC-0068), and also when treatment with IPATASERTIB (GDC 0068) was stopped.
* Your glucose and insulin levels will be monitored closely during the study by your doctor. Insulin is a hormone in your blood that enables the cells in your body to absorb and use the glucose from your blood. Increases in blood glucose and insulin can be indicative of diabetes.
* You should report any new signs of increased thirst or other symptoms of dehydration, increased frequency and volume of urination, sweet smell of urine, weight loss, blurry vision, or fatigue to your doctor immediately. These symptoms may indicate high blood glucose.
* If you have changes in your blood glucose, the study doctor may start you on an oral anti diabetic drug to control or prevent these symptoms. Your study doctor will provide you with more information on this and possible use of anti diabetic drugs, as well as potentially side effects of the oral anti-diabetic agent.
* Home glucose monitoring may be instituted and more frequent clinic visits and fingerstick glucose monitoring may be required. A fingerstick blood glucose test is performed by piercing the skin (typically, on the finger tip) to draw blood, then placing the blood on a chemically active disposable strip which indicates the result either by changing color, or changing an electrical characteristic, the latter being measured by an electronic meter.

* Abiraterone Side Effects in Clinical Studies
Abiraterone may result in abnormal amounts of corticosteroids that your body normally makes. This can result in increased amounts of a certain type of corticosteroid called a mineralocorticoid, which can cause high blood pressure and decreased levels of potassium in your blood. Hypertension should be controlled and potassium levels normalized before starting abiraterone, and these should be monitored regularly while receiving treatment. Abiraterone should be used with caution in patients with a history of heart disease.

Abiraterone may result in insufficient amounts of another type of corticosteroid called a glucocorticoid. This may lead to a condition called adrenal insufficiency, and you will be monitored for signs or symptoms of this while receiving abiraterone. You may receive treatment with

prednisone/prednisolone, which are other types of corticosteroids, in order to help offset the effects of abiraterone on the corticosteroid metabolism of your body. Some of the potential side effects associated with prednisone/prednisolone are further described below. The amount of prednisone/prednisolone needed may vary.

Abiraterone may produce injury to the liver, which can be detected by increases in enzymes released by damaged liver cells. These effects on the liver may lead to interruption, dose reduction, or discontinuation of abiraterone. Your liver function will be monitored throughout the study.

Taking abiraterone with food may significantly increase the amount that is absorbed by your body. Abiraterone must be taken on an empty stomach to avoid such large increases in absorption. Abiraterone may also interfere with the metabolism of IPATASERTIB (GDC-0068), causing increases in IPATASERTIB (GDC-0068) levels. Your drug levels will be monitored while you are on the study.
Please refer to the abiraterone (Zytiga) prescribing information for further details on the abiraterone safety profile which your study doctor can provide you.

* Safety Monitoring for Prednisone/prednisolone
Prednisone and prednisolone are in a class of medications called corticosteroids. They work to treat patients with low levels of corticosteroids by replacing corticosteroids that are normally produced naturally by the body. The work to treat other conditions by reducing swelling and redness and by changing the way the immune system works.

Corticosteroids may cause side effects such as mood changes, increased blood pressure or increased blood sugar levels, and reduced resistance to infection. Your study doctor can provide more information about corticosteroids. Most of these risks are associated with corticosteroids occur following prolonged use and/or high doses.

* Risks related to the procedures
Blood Drawing Risks
During this study, small amounts of blood will be drawn from a vein to perform tests that allow your doctors to see how you are doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising and/or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.

Risks of Exposure to Radiation and Contrast Material
CT and MRI scans are special tests used to study the internal organs of your body and are necessary to measure your response to this treatment. You will be exposed to radiation from the CT scans every 8*12 weeks. Your exposure to X-rays is limited, and poses minimal risk to your health. In addition, you

would likely undergo these scans even if you did not participate in this study because your physician would need to monitor your cancer.

As part of CT, MUGA and MRI scans, contrast material may need to be taken by mouth and/or injected into your vein to make certain organs and tumor sites visible on the scan. Oral contrast may cause side effects such as nausea, constipation, diarrhea, and abdominal bloating. Pain, bruising, redness, swelling, and/or infection may occur at the site where a needle is inserted to administer the contrast material into your vein. You may have an allergic reaction to the contrast material that could cause rash, hives, shortness of breath, wheezing, and itching, and rarely may cause your heart to stop beating (*cardiac arrest*). The use of contrast material during these tests would be a normal part of measuring response of your cancer to therapy even if you were treated outside of a clinical trial. Lastly, you may feel uncomfortable during the tests since you are not allowed to move during the procedure, and may experience claustrophobia (fear of being in small places).

Contacts

Public
Genentech, Inc

Genentech Inc. 1 DNA Way,
South San Francisco CA 94080-4990
US
Scientific
Genentech, Inc

Genentech Inc. 1 DNA Way,
South San Francisco CA 94080-4990
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all the following criteria to be eligible for study entry: Histologically confirmed metastatic or advanced prostate adenocarcinoma that has been previously treated with docetaxel-based therapy and has progressed during treatment of at least one hormonal therapy (luteinizing hormone-releasing hormone, bicalutamide, etc.) * Availability at the site of a representative formalin-fixed, paraffinembedded tumor specimen that enabled the definitive diagnosis of prostate cancer, accompanied by an associated pathology report (required prior to randomization) The specimen must contain adequate viable tumor cells (e.g., a minimum of 50 viable tumor cells or tumor tissue derived from prostatectomy or * 50% tumor content if sample is a core biopsy).
Specimen may consist of a tissue block (preferred) or 15-20 unstained, serial slides. Cytologic or fine-needle aspiration samples are not acceptable. If archival tissue is either insufficient or unavailable, the patient may still be eligible, upon discussion with the Medical Monitor, assuming the patient Can provide * 5 unstained, serial slides or Is willing to consent to and undergo a pretreatment core or excisional biopsy of the tumor (if fresh biopsy is permitted by local regulatory
authorities and ethics committees).. Cytologic or fine-needle aspiration samples are not acceptable. * Two rising PSA levels * 2 ng/mL measured * 1 week apart during or following the most recent prior therapy for prostate cancer that meet the Prostate Cancer Working Group 2 (PCWG2) criteria for progression before initiation of study treatment or radiographic evidence of disease progression in soft tissue or bone, with or without disease progression on the basis of the PSA value.

Exclusion criteria

* Small cell or neuroendocrine prostate carcinoma
* History of Type I or Type II diabetes mellitus requiring insulin
Patients who are on a stable dose of oral diabetes medication * 4 weeks
prior to initiation of study treatment may be eligible for enrollment.
* Malabsorption syndrome or other condition that would interfere with
enteral absorption
* Congenital long QT syndrome or QTc > 480 msec

Study design

Design

Study phase:	2
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):	04-02-2014
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	abiraterone acetate
Generic name:	Zytiga
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	IPATASERTIB
Generic name:	NA
Product type:	Medicine
Brand name:	prednisone/prednisolone
Generic name:	Decortin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	30-05-2012
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-11-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-02-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2016
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2018
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	EUCTR2011-004126-10-NL
ClinicalTrials.gov	NCT01485861
CCMO	NL40182.091.12