A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs. Prednisone in Metastatic Castration-resistant Prostate Cancer Patients who have Received Prior Docetaxel and Prior Abiraterone or MDV3100

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

Summary

ID

NL-OMON37289

Source
ToetsingOnline

Brief title
COMET-1 XL184-307

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
bone metastases, Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: PPD
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Bone metastasis, Prostate cancer

Outcome measures

Primary outcome

Primary efficacy endpoint:

Overall survival

Secondary outcome

Secondary efficacy endpoint:

Bone scan response at the end of Week 12 by independent radiology facility (IRF)

Exploratory endpoints:

- Bone scan response at any time point by IRF

- Duration of bone scan response

- Progression free survival per investigator

- Levels of serum bone markers, e.g. NTx [N-terminal cross-linked telopeptides of type I collagen], CTx [C-terminal cross-linked telopeptides of type I collagen], and bone-specific alkaline phosphatase [ALP]) compared with baseline.

- Number of detectable circulating tumor cells (CTCs) compared with baseline

- Proportion of subjects with post-randomization investigator-assessed skeletal related events (SREs).

- Pharmacokinetics

- Changes in hemoglobin compared with baseline

- Number of post-randomization red blood cell transfusions

- Changes in PSA compared with baseline

- Pain response

- Changes in narcotic analgesic use in subjects requiring narcotics at baseline

at each time point

- Quality of life

- Health care resource utilization

Study description

Background summary

Prostate cancer is the most common non-cutaneous cancer diagnosed in men and the second-highest cause of death for men in the United States (Jemal et al. 2010). Ninety percent of prostate cancer patients with recurrent disease develop bone metastases which are the primary source of morbidity and the major contributor to mortality (Petrylak 2004; Tannock 2004). Debilitating pain as a complication of the bone metastases is one of the most common morbidities in subjects with Castration-resistant Prostate Cancer (CRPC).
In ongoing study XL184-203, cabozantinib treatment in patients with advanced prostate cancer has resulted in high rates of pain relief and reductions or discontinuations in narcotic use, along with evidence of substantial anti-tumor activity including high rates of bone scan resolution, soft-tissue lesion reduction, and 12-week disease control. These effects are expected to translate into an improvement in overall survival and symptom alleviation and as such, cabozantinib could provide a valuable new treatment option for subjects with CRPC who experienced disease progression on or after prior specified therapies.

Study objective

The objective of this study is to evaluate the effect of cabozantinib compared to prednisone on overall survival in men with previously treated metastatic castration-resistant prostate cancer with bone-dominant disease who have experienced disease progression on docetaxel-containing chemotherapy and

abiraterone or MDV3100.

Study design

A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib (XL184) vs. Prednisone.

Intervention

Based on treatment assignment, subjects will receive one of the following regimens:
- Cabozantinib arm: Oral cabozantinib (60 mg) once daily (qd) plus oral prednisone/prednisolone-matched placebo twice-daily (bid).
- Prednisone arm: Oral prednisone/prednisolone (5 mg) twice daily (bid) plus oral cabozantinib-matched placebo once daily (qd).

Subjects who are being maintained on daily doses of prednisone or prednisolone prior to enrollment will be allowed to continue to take these medications. In such cases, prednisone or prednisolone will be regarded as a concomitant medication after randomization. Subjects will receive study treatment as long as they continue to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, the need for subsequent systemic anti-cancer treatment, or until any of the other reasons for treatment discontinuation listed in the protocol. Treatment may continue after protocol-defined prostate cancer progression as long as the investigator believes that the subject is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs the risk of delaying treatment with alternative anti-cancer therapies which have been shown to prolong overall survival. Crossover between treatment arms will not be allowed.

Study burden and risks

Please refer to Appendix A for an overview of all study visits and procedures.
A summary of procedures:
- signature informed consent, demografics, medical and cancer history (screening), physical examination, vital signs, ECOG status, ECG, blood sampling (chemistry, hematology, pharmakinetics and -genetics, CTC and bone markers), quality of life and pain experience assessments. Tumor and skeleton assessments, determination of tumor markers.

The most common side effects that occur in more than 20% of cancer patients treated with Cabozantinib are Fatigue, Diarrhea, Loss of appetite, Nausea and Blisters, rash, or pain in hands or feet.
Prednisone (or prednisolone) can weaken the immune system, making it easier to get an infection or worsening an infection which the patient already have or

have recently had.

In ongoing study, Cabozantinib treatment in patients with advanced prostate cancer has resulted in high rates of pain relief and reductions or discontinuations in narcotic use, along with evidence of substantial anti-tumor activity including high rates of bone scan resolution, soft-tissue lesion reduction, and 12-week disease control. These effects are expected to translate into an improvement in overall survival and symptom alleviation and as such, Cabozantinib could provide a valuable new treatment option for subjects with castration resistance prostate cancer who experienced disease progression on or after prior specified therapies.

Contacts

Public
PPD

Bornweg 12C
6721 AH Bennekom 6721 AH
NL
Scientific
PPD

Bornweg 12C
6721 AH Bennekom 6721 AH
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Documented histological or cytological diagnosis of prostate cancer.
2. Serum testosterone levels less than 50 ng/dL within 28 days before randomization.
3. Evidence of bone metastasis related to prostate cancer on bone scans from a protocol-credentialed scanner using technetium-99m labeled methylene diphosphonate (Tc99-MDP) radiotracer within 28 days before randomization. ;Note: Tc99-MDP is the preferred tracer. In situations where this tracer is unavailable, other tracers such as Tc99 dicarboxypropane diphosphonate (Tc99-DPD), Tc99 hydroxymethylene diphosphonate (Tc99-HDP), or Tc99-hidroximetilenodifosfonato (Tc99-HMDP) may be used. At the discretion of the Sponsor other Tc99 bone-seeking radiopharmaceuticals not designated above may be allowed.
4. The subject must have received prior docetaxel (minimum cumulative dose of 225 mg/m2) and either abiraterone or MDV3100 treatment and have evidence of investigator-assessed prostate cancer progression on each agent independently.
For docetaxel: subjects must have progressed during or after docetaxel-containing therapy.
For abiraterone or MDV3100: subjects must have discontinued abiraterone or MDV3100 due to disease progression.
Prostate cancer progression is defined as:
a. PSA progression according to PCWG2 (Prostate Cancer Working Group 2) criteria: PSA level of at least 2 ng/mL which has subsequently risen on at least 2 successive occasions, at least 2 weeks apart. If the second risen value is lower than the first risen value, then an additional test for rising PSA will be required to document progression. The value of the additional test must be higher than the first risen value (Scher et al. 2008). or
b. Radiographic progression in soft tissue or bone lesions.
Note: There is no limit on other prior anti-cancer treatments, including prior cabazitaxel (except Exclusion Criterion #1).
5. Subjects without prior orchiectomy must be currently taking and willing to continue luteinizing hormone-releasing hormone (LHRH) analogue (agonist or antagonist) therapy until permanent discontinuation of study treatment.
6. Subject must have recovered to baseline or CTCAE v.4.0 (Common Terminology Criteria for Adverse Events, version 4.0) <= Grade 1 from toxicities related to any prior treatments, unless AE(s) are clinically non significant and/or stable on supportive therapy.
7. >= 18 years old on the day of consent.
8. ECOG performance status: 0-2
9. Adequate organ and marrow function, defined as follows, based upon laboratory tests performed within 7 days before randomization:
a. Absolute neutrophil count (ANC) >= 1500/mm3
b. Platelets >= 100,000/mm3
c. Hemoglobin >= 9 g/dL
d. Total bilirubin <= 1.5 x the upper limit of normal (for subjects with Gilbert*s disease, <= 3 mg/dL)
e. Serum albumin >= 3 g/dL
f. Serum creatinine <= 1.5 x the upper limit of normal or calculated creatinine clearance >= 50 mL/min or GFR > 30 mL/min.
Note: For GFR estimation, the Cockcroft and Gault equation should be used [GFR = CrCl (mL/min) = (140 - age) x wt (kg)/(serum creatinine x 72)]

g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 x the upper limit of normal
h. Lipase < 1.5 times the upper limit of normal
i. Serum phosphorus >= lower limit of normal
j. Urine protein/creatinine ratio (UPCR) <= 1
10. The subject must be capable of understanding and complying with the protocol requirements and must have signed the informed consent document.
11. Sexually active fertile subjects and their partners must agree to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months after the last dose of study treatment.

Exclusion criteria

1. The subject has received prior cabozantinib.
2. The subject has received docetaxel, abiraterone, or MDV3100 within 2 weeks before randomization.
3. The subject has received any other type of anti-cancer agent (except agents to maintain castrate status) within 2 weeks before randomization.
4. The subject has received radiation therapy within 4 weeks (includes radiation targeting bone metastases) or radionuclide treatment within 6 weeks of randomization. Subject is excluded if there is any prior history of radiation therapy to the mediastinum (unless radiation targeted bone metastases).
5. Radiographic evidence of metastasis to the liver.
6. The subject has known brain metastases or cranial epidural disease
7. The subject requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or FXa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (<= 81 mg/day), low-dose warfarin (<= 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
8. The subject requires chronic concomitant treatment of strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John*s Wort).
9. Uncontrolled, significant intercurrent illness including, but not limited to, the following conditions:
a. Cardiovascular disorders such as symptomatic congestive heart failure (CHF), uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 100 mm Hg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening), unstable angina pectoris, clinically-significant cardiac arrhythmias, history of stroke (including TIA, or other ischemic event) within 6 months before randomization, myocardial infarction within 6 months before randomization, history of thromboembolic event within 6 months before randomization
b. Gastrointestinal disorders such as malabsorption syndrome or gastric outlet obstruction.
c. Risks for GI perforation or fistula formation which include intra-abdominal tumor/metastases invading GI tract; active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis or appendicitis;

history of abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess, or prior GI surgery (particularly when associated with delayed or incomplete healing) within 6 months before first dose of study treatment. Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.
d. Risk for non-GI fistula formation which includes previous surgical intervention (such as PEG tube placement) and evidence of intraluminal disease involving the trachea or esophagus.
e. Other disorders such as active infection requiring systemic treatment; serious non-healing wound/ulcer/bone fracture; organ transplant; uncompensated hypothyroidism, uncontrolled diabetes mellitus
f. History of surgery within 6 months before randomization:
• With wound healing complications - major surgery within 6 months, minor surgery within 3 months;
• Without wound healing complications - major surgery within 3 months, minor surgery within 1 month
• Note: Complete wound healing from prior surgery is required at least 30 days before randomization.
10. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon of red blood, or other signs indicative of pulmonary hemorrhage within 3 months, or history of other significant bleeding within 6 months before randomization.
11. Cavitating pulmonary lesion(s) or a pulmonary lesion invading or encasing a major blood vessel.
12. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 msec within 7 days before randomization (see Section 5.5.4 for Fridericia formula).
Three ECGs separated by at least 3 minutes must be performed. If the average of these three consecutive results for QTcF is <= 500 msec, the subject meets eligibility in this regard.
13. Unable to swallow tablets or capsules.
14. A previously-identified allergy or hypersensitivity to components of the study treatment formulations.
15. Another diagnosis of malignancy requiring systemic treatment within 5 years before randomization.

Study design

Design

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

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-03-2013
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabozantinib
Generic name:	Cabozantinib
Product type:	Medicine
Brand name:	Prednison/ prednisolon
Generic name:	Prednison/ prednisolon
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-06-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2013

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-08-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2014
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	EUCTR2012-001834-33-NL
ClinicalTrials.gov	NCT01605227
CCMO	NL41100.091.12