A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Published: 05-10-2010
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To determine if orteronel plus prednisone improves radiographic progression-freesurvival (rPFS)To determine if orteronel plus prednisone improves overall survival (OS)

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male benign
Study type	Interventional

Summary

ID

NL-OMON39549

Source
ToetsingOnline

Brief title
C21004

Condition

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

Synonym
castration-resistant prostate cancer (mCRPC), chemotherapy-naïve, metastatic, progressive, prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Chemotherapy-Naive, Orteronel, prednisone, Prostate Cancer

Outcome measures

Primary outcome

Primary Objectives:

To determine if orteronel plus prednisone improves radiographic progression-free

survival (rPFS)

To determine if orteronel plus prednisone improves overall survival (OS)

Secondary outcome

Key Secondary Objectives:

To determine if orteronel plus prednisone improves 50% prostate-specific

antigen (PSA)

response at 12 weeks

To evaluate changes in circulating tumor cell (CTC) counts

To evaluate whether orteronel improves time to pain progression

Other Secondary Objectives:

To assess the safety of orteronel plus prednisone

To determine if orteronel plus prednisone increases the time to radiographic

disease

progression or skeletal-related event (SRE)

To determine if orteronel plus prednisone decreases frequency of SREs

To determine if orteronel plus prednisone increases 90% PSA response and best

PSA

response

To determine if orteronel plus prednisone increases time to PSA progression

To evaluate if orteronel plus prednisone improves time to docetaxel chemotherapy

To measure the time to subsequent antineoplastic therapy

To determine tumor response rate and duration of response in patients with tumor

lesions that are measurable by the Response Evaluation Criteria in Solid Tumors

(RECIST 1.1)

To assess global health status as measured by the European Organization for

Research

and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30), a

patientreported

outcome (PRO) instrument

To collect blood orteronel concentration data for use in a future integrated

pharmacokinetic (PK) analysis

Study description

Background summary

Orteronel is an orally bioavailable, reversible nonsteroidal inhibitor of 17,20-lyase, a key enzyme in androgen synthesis. This study is designed to investigate whether the androgen synthesis inhibitor orteronel improves radiographic progression-free survival (rPFS) and overall survival (OS) in men with progressive metastatic castration-resistant prostate cancer (mCRPC) that has not previously been treated with chemotherapy for metastatic disease (chemotherapy naïve).

Study objective

To determine if orteronel plus prednisone improves radiographic progression-free survival (rPFS)
To determine if orteronel plus prednisone improves overall survival (OS)

Study design

This is a randomized, double-blind, multicenter, phase 3 study evaluating orteronel plus prednisone compared with placebo plus prednisone in the treatment of men with progressive, chemotherapy-naïve, metastatic, castration-resistant prostate cancer (mCRPC). Patients in the 2 treatment groups will receive blinded orteronel (or placebo) in addition to open-label prednisone and gonadotropin-releasing hormone (GnRH) analogue therapy. Patients who have undergone orchiectomy and have a testosterone concentration of < 50 ng/dL may participate in the study without prior or ongoing concomitant GnRH analogue treatment. Two formal interim analyses are planned for this study.
Patients will return for regularly scheduled study visits (treatment/short-term follow-up) for as long as they: 1) continue to take orteronel, or 2) discontinue orteronel but have not yet experienced disease progression. Patients will discontinue scheduled study visits if they experience disease progression and decide to discontinue orteronel. Patients may remain on orteronel after disease progression and return for scheduled visits (short-term follow-up) until they receive subsequent antineoplastic therapy.
All patients will be followed for survival (long-term follow-up) after discontinuing the treatment/short-term follow-up portion of the study. Long-term follow-up will continue until death or discontinuation of the study by the sponsor.

Intervention

Twice a day 400 mg Orteronel or placebo (oral)
Twice a day 5 mg Predison (oral)

Study burden and risks

Extra procedures: MUGA/ECHO (Screening, Cyclus (C) 4, C7, C13, Q6C, EOT); ECG (Scr, C2, C7, C13, Q12C, EOT); CT/MRI and botscan (Scr, C3, C5, C7, C10, C13, Q3C).
The subjects have to take studymedication plus prednison twice a day on determined times.
The subjects have to register in their diaries the time they take the studymedication and prednison. It is expected that they complete the diaries and bring it with them during each visit.
The subjects have to complete 3 different questionnaires regarding pain, quality of life and health status.

Patients who received orteronel, experienced the following adverse events: fatigue, headache, elevated aminotransferases, a decrease in LVEF, itching and rash, decreased preformance, worsened but controlled hypertension, episodic nausea, vomiting, diarrhea and dehydration (see IB for detailed information on safety).

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Male patients 18 years or older.
2. Voluntary written consent, given before performance of any study related procedure not part of standard medical care, and with the understanding that consent may be withdrawn at any time without prejudice to future medical care.
3. Adenocarcinoma of the prostate either histologically or cytologically confirmed.
4. Metastatic disease radiographically documented by CT/MRI or bone scan.
5. Progressive disease based on PSA and/or radiographic criteria, defined as 1 or more of the following:
• Radiographic disease progression based on RECIST 1.1 (refer to Section 15.1 of protocol) in patients with measurable soft tissue lesions. For patients with bone disease, progression will be assessed following recommendations by the Prostate Cancer Working Group (PCWG2; refer to Section 15.1); appearance of 2 or more new lesions on bone scan, confirmed, if necessary, by other imaging modalities (such as CT scan or MRI), if results of the bone scans are ambiguous.
• PSA progression is defined as an increase in PSA, as determined by 2 separate measurements taken at least 1 week apart and confirmed by a third. If the third measurement is not greater than the second measurement, then a fourth measurement must be taken and must be greater than the second measurement for the patient to be eligible for randomization in the study. Furthermore, the confirmatory PSA measurement (ie, the third or, if applicable, fourth PSA measurement) must be >= 2 ng/mL. Notes: Determination of PSA progression can be based on results from a local laboratory. The PSA value obtained from the central laboratory during the screening process does not have to be used in the determination of PSA progression, but that value should be at least greater than the first PSA used for determination of PSA progression. If a patient has received prior antiandrogen therapy (eg, bicalutamide, MDV-3100), PSA progression must be evident and documented after discontinuation of antiandrogen therapy.
6. Prior surgical castration or concurrent use of an agent for medical castration (eg, GnRH analogue) with testosterone at screening < 50 ng/dL.
7. Either absence of pain or pain, regardless of cause, not requiring use of any opioid or narcotic analgesia in the 2 weeks prior to randomization.
8. Screening PSA >= 2 ng/mL. (Screening PSA value must be obtained from the central laboratory.)
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Section 15.2.2).
10. Screening clinical laboratory values as specified below:
• Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be <=2.5 X the upper limit of normal (ULN).
• Total bilirubin <= 1.5 X ULN.
• Estimated creatinine clearance using the Cockcroft-Gault formula must be > 40 mL/minute

(see Section 15.4).
• Absolute neutrophil count (ANC) >=1500/µL and platelet count >= 100,000/µL.
11. Patients, even if surgically sterilized (ie, status postvasectomy), who:
• Agree to practice effective barrier contraception during the entire study treatment period and for 4 Months after the last dose of study drug, or
• Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
12. Screening calculated ejection fraction of >= 50% by multiple gated acquisition (MUGA) scan, or by echocardiogram (ECHO). (The same modality should be used for a patient throughout the study.)
13. Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to randomization, and otherwise noted in other inclusion/exclusion criteria.
14. Life expectancy of 12 months or more based on general health and prostate cancer disease status as judged by the investigator.

Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:
1. Prior therapy with orteronel, ketoconazole, aminoglutethimide, or abiraterone.
2. Known hypersensitivity to compounds related to orteronel, orteronel excipients, prednisone, or GnRH analogue.
3. All antiandrogen therapy (including bicalutamide) is excluded within 4 weeks prior to first dose of study drug. Any other therapies for prostate cancer, other than GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride), must be discontinued 2 weeks before the first dose of study drug.
4. Continuous daily use of oral prednisone, oral dexamethasone, or other systemic corticosteroids for more than 14 days within 3 months prior to screening (inhaled, nasal, and local steroids are allowed [eg, joint injection]).
5. Prior chemotherapy for PC, with the exception of neoadjuvant/adjuvant therapy as part of initial primary treatment for local disease that was completed 2 or more years prior to screening.
6. Exposure to radioisotope therapy within 4 weeks of receiving the first dose of study drug; exposure to external beam radiation within 4 weeks of receiving the first dose of study drug.
7. Documented central nervous system metastases.
8. Treatment with any investigational compound within 30 days prior to the first dose of study drug or ongoing active participation in another experimental trial related to the treatment of PC. (Patients who are in long-term follow-up following active treatment in other trials are eligible.)
9. Current spinal cord compression, current bilateral hydronephrosis, or current bladder neck outlet obstruction. Note: Patients with definitive local therapy for urinary tract obstruction, eg with stents, may be eligible after a review by the study project clinician.

10. Diagnosis of or treatment for another systemic malignancy within 2 years before the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
11. History of myocardial infarction, unstable symptomatic ischemic heart disease, ongoing arrhythmias of Grade > 2 (NCI CTCAE, version 4.02)(77), thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion restrictive cardiomyopathy) within 6 months prior to first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.
12. New York Heart Association Class III or IV heart failure (see Section 15.5 of protocol).
13. ECG abnormalities of:
• Q-wave infarction, unless identified 6 or more months prior to screening
• QTc interval > 460 msec
14. Uncontrolled hypertension despite appropriate medical therapy (blood pressure [BP] of greater than 160 mmHg systolic and 90 mmHg diastolic at 2 separate measurements no more than 60 minutes apart during the Screening visit). Note: Patients may be rescreened after adjustments of antihypertensive medications.
15. Known human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator*s opinion, potentially interfere with participation in this study. Patients will be tested for hepatitis B or C or HIV infection during screening if they are considered by the investigator to be at higher risk for these infections and have not been previously tested, or if testing is required by the independent ethics committee or institutional review board.
16. Uncontrolled nausea, vomiting, or diarrhea despite appropriate medical therapy.
17. Known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption or tolerance of orteronel, including difficulty swallowing tablets.
18. Likely inability to comply with the protocol or cooperate fully with the investigator and site personnel.
19. Those patients whose prostate cancer is confined to just the prostate bed or immediate adjacent tissue.

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):	26-04-2011
Enrollment:	55
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	05-10-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-02-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	31-03-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-04-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-04-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-05-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-05-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-05-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-06-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2011
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-08-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-08-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	12-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	29-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2010-018661-35-NL
ClinicalTrials.gov	NCT01193244
CCMO	NL33419.060.10