A Multinational, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

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Primary • To determine the efficacy of enzalutamide compared with placebo as assessed by metastasis-free survival (MFS). Secondary: • To evaluate the benefit of enzalutamide compared with placebo as measured by the following:- Time to PSA...

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

Summary

ID

NL-OMON50210

Source
ToetsingOnline

Brief title
MDV3100-14 Prosper

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Medivation Inc., a wholly owned subsidiary of Pfizer Inc.
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Double Blind, Enzalutamide, Phase III, Prostate Cancer

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

The primary efficacy endpoint of MFS is defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone and soft tissue disease will be as described in the Methods section. Assessment of images for determination of progression will be made by an independent, central, blinded radiology reviewer.

The primary endpoint analysis will be performed when at least 574 MFS events and at least 480 deaths are observed. A stratified log-rank test will be used to compare the treatment groups using a 2-sided test at the 0.05 level of significance.

Secondary outcome

Key Secondary Endpoints:

- Time to PSA Progression

- Time to First Use of New Antineoplastic Therapy

- Overall Survival

Additional secondary endpoints are as follows:

- Time to Pain Progression

- Time to First Use of Cytotoxic Chemotherapy

- Chemotherapy-Free Disease-Specific Survival

- Chemotherapy-Free Survival

- PSA Response

- Quality of Life as Assessed by the FACT-P questionnaire, EQ-5D-5L

Health Questionnaire, and QLQ-PR25 Module

The single MFS analysis will be performed after approximately 440 MFS

events occur. All secondary endpoints will be evaluated for efficacy at

this time.

Study description

Background summary

Prostate cancer progresses through a series of characteristic clinical states that reflect both the natural history of the disease and response to treatment. Following the initial evaluation and diagnosis of prostate cancer, approximately 90% of men undergo primary localized treatment with curative intent. After initiation of androgen deprivation therapy in men with rising prostate-specific antigen (PSA) after primary therapy, the next clinical state in the current model of prostate cancer progression is that of castration-resistant prostate cancer (CRPC), defined as progression despite castrate hormone levels (testosterone <= 50 ng/dL). CRPC is present in 10% to 20% of all men with prostate cancer, and is associated with a high risk of bone metastases, bone pain, pathologic fractures, spinal cord compression, decreased quality of life, and death from prostate cancer.

PSA doubling time and baseline PSA are useful for identifying the subset of men who are at high risk for morbidity and mortality from CRPC. For example, an analysis of 201 patients with nonmetastatic CRPC randomized to the placebo arm in an aborted randomized controlled trial of zoledronic acid showed that PSA doubling time and baseline PSA independently predicted risk of time to first bone metastases, overall survival, and metastasis-free survival (MFS). The relative risk of a shorter time to first bone metastases for patients with a PSA greater than 10 ng/mL was 3.18 (95% confidence interval [CI]: 1.74, 5.8) and the relative risk for a 0.01 increase in PSA velocity was 4.34 (95% CI: 2.30, 8.21).

Currently, although continued use of androgen deprivation therapy is part of clinical practice, no medicine is approved for treatment of patients with nonmetastatic CRPC or for prevention of metastasis, and the results of several studies designed to address these needs have been disappointing. Therefore, no standard of care is defined for nonmetastatic CRPC and accordingly, patients are encouraged to participate in clinical trials.

The androgen receptor remains the main driver of prostate cancer progression in CRPC. Enzalutamide is a potent androgen receptor inhibitor that significantly prolonged overall survival in men with metastatic CRPC previously treated with docetaxel. Patients with nonmetastatic CRPC at high risk for metastatic disease may therefore also derive significant benefit from treatment with enzalutamide. The Phase 3 study described herein is designed to address this unmet medical need.

Study objective

Primary
• To determine the efficacy of enzalutamide compared with placebo as assessed by metastasis-free survival (MFS).

Secondary:
• To evaluate the benefit of enzalutamide compared with placebo as measured by the following:
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- Overall survival
- Time to pain progression
- Time to first use of cytotoxic chemotherapy
- Chemotherapy-free disease-specific survival
- Chemotherapy-free survival
- PSA response rates
- Quality of life as assessed by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) health questionnaire, and Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module

• To evaluate safety

Study design

This multinational, Phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study will assess the efficacy and safety of enzalutamide versus placebo in approximately 1560 men with nonmetastatic CRPC. All patients will be required to maintain androgen deprivation during the study, either using a gonadotropin-releasing hormone (GnRH) agonist/antagonist or having a history of bilateral orchiectomy.

Central randomization to enzalutamide or placebo treatments (2:1) will be stratified by the following factors:
• PSA doubling time (< 6 months vs >= 6 months);
• Baseline use of a bone-targeting agent (yes vs no).

The primary efficacy endpoint is MFS, defined as the time from randomization to radiographic progression or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurs first. Assessment of bone disease will be done by whole-body radionuclide bone scan. A bone scan will consist of 5 regions including skull, thorax, spine, pelvis, and extremities. Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesion on bone scan. Confirmation with a second imaging modality (plain film, computed tomography [CT], or magnetic resonance imaging [MRI]) will be required when bone lesions are found in a single region on the bone scan. Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan will not require confirmation with a second imaging modality. Assessment of soft tissue disease will be done by CT or MRI. Radiographic progression for soft tissue disease is defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)

All study films should be read locally at the study site and submitted to the central imaging unit for independent central radiology review. Each study site should designate a radiologist or investigator as the primary imaging reviewer to ensure that all images are read consistently as specified in Section 9.1. of the protocol. Radiographic assessments will be approximately every 16 weeks, but images may be obtained sooner if progression is clinically suspected. Radiographic imaging will not be required after radiographic progression is confirmed by independent central radiology review according to protocol specifications

In addition to imaging, the following assessments of prostate cancer status will be made during the course of the study: survival status, pain intensity and interference using the Brief Pain Inventory Short Form (BPI-SF),opiate use for prostate cancer pain, PSA values, functional status deterioration as assessed by the FACT-P questionnaire, and quality of life as assessed by the EQ-5D-5L and QLQ-PR25 questionnaires. Assessments of safety will include

adverse events, clinical laboratory tests, physical examinations, and vital signs. An independent Data Monitoring Committee will periodically monitor the safety data.

Patients will have safety follow-up approximately 30 days after the last dose of study drug. If a new antineoplastic treatment is initiated before 30 days after the last dose of study drug, then safety follow-up will occur immediately before starting the new treatment. Long-term follow-up assessments will include monitoring for survival status, new antineoplastic therapies for prostate cancer, opiate medications, skeletal-related events, and interventions due to locoregional progression (eg, radiation, transurethral resection of the prostate, nephrostomy tube placement).

Intervention

Enzalutamide (160 mg/day) will be administered as four 40-mg soft gelatin capsules by mouth once daily with or without food. Placebo capsules, identical in appearance to enzalutamide capsules, will be administered to patients in the control arm in the same manner.

Study drug administration should continue until radiographic progression. Investigators are discouraged from obtaining PSA assessments at their local laboratories during the study and from discontinuing a patient*s study drug treatment due to PSA rise alone. Initiation of new therapy for prostate cancer (with the exception of cytotoxic chemotherapy, androgen receptor inhibitors, and investigational agents) at the time of radiographic progression will not mandate discontinuation of study drug if the investigator considers continuing study drug to be beneficial. Prostate cancer is a multiclonal disease, and a patient with confirmed disease progression may have other clones/foci that may benefit from continued treatment with study drug. In the ongoing, blinded, phase 3 PREVAIL study, approximately 34 of 1715 treated patients (2%) received study drug and antiandrogen or abiraterone after radiographic disease progression.

Initiation of bisphosphonates or other bone-targeting agents for bone health, such as denosumab, is not allowed during the study prior to development of bone metastasis; however, treatment with these agents should continue if initiated at least 4 weeks before enrollment. Standard of care supplementation with calcium and vitamin D is encouraged.

Study burden and risks

In the Phase 3 study CRPC2 (AFFIRM), the prespecified interim analysis at the time of 520 events demonstrated a statistically significant improvement in overall survival in patients with metastatic CRPC treated with enzalutamide versus placebo (hazard ratio [HR] = 0.631; 95% CI: 0.529, 0.752, $p < 0.0001$).9

The median survival was 18.4 months in the enzalutamide arm and 13.6 months in the placebo arm (Δ = 4.8 months). The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region, and type of disease progression at entry. Enzalutamide treatment was superior to placebo for all secondary endpoints including the proportion of patients with a reduction in PSA level by 50% or more (54% vs 2%, $p < 0.001$), soft tissue response rate (29% vs 4%, $p < 0.001$), quality of life response rate (43% vs 18%, $p < 0.001$), time to PSA progression (8.3 vs 3.0 months; HR 0.25, $p < 0.001$), rPFS (8.3 vs 2.9 months; HR 0.40, $p < 0.001$), and time to first skeletal related event (16.7 vs 13.3 months; HR 0.69, $p < 0.001$). Based on the AFFIRM data, the US FDA approved enzalutamide in August 2012 for men with metastatic CRPC who previously received docetaxel therapy.
The most common adverse reactions (>= 5%) in patients treated with enzalutamide (N = 800) in the Phase 3 study CRPC2 (AFFIRM) (N = 1199) were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 1 4 neutropenia occurred in 15% of enzalutamide treated patients (1% grade 3 4) and in 6% of placebo treated patients (no grade 3 4). Other treatment emergent adverse events reported in fewer than 5% of patients, but that may have been associated with enzalutamide treatment, included falls, nonpathologic fracture, dry skin, and pruritus. A possible cognitive effect of enzalutamide was reported in a greater proportion of patients in the enzalutamide group for the following adverse event terms: memory impairment, cognitive disorder, amnesia, and disturbance of attention. In addition, event terms related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide group. Discontinuations due to adverse events were reported for 16% of enzalutamide treated patients and 18% of placebo treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide treated patients and none (0%) of the placebo treated patients.
The safety and tolerability of enzalutamide were evaluated in an integrated safety analysis including patients from AFFIRM and 3 open label studies, and continues to be evaluated on an ongoing basis for all enzalutamide program studies. No study has been terminated early for safety reasons.
The totality of the efficacy and safety data suggests a positive benefit risk assessment for the use of enzalutamide in men with metastatic CRPC who have previously received docetaxel, and for the continued investigation of enzalutamide in men with earlier stage prostate cancer.

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 eligible to participate in this study must meet all of the following criteria: (the full list of inclusion criteria can be found on page 21 of the protocol)
1. Age 18 years or older and willing and able to provide informed consent;
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet cell, or small cell features;
3. Ongoing androgen deprivation therapy with a GnRH agonist/antagonist or prior bilateral orchiectomy (medical or surgical castration);
4. Testosterone <= 50 ng/dL (<= 1.73 nmol/L) at screening;
5. For patients receiving bisphosphonates or denosumab, dose must be stable for at least 4 weeks before randomization;
6. Progressive disease on androgen deprivation therapy at enrollment defined as a minimum of 3 rising PSA values (PSA1 < PSA2 < PSA3) assessed by a local laboratory (local PSA) with an interval of >= 1 week between each determination;

Exclusion criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria: (the full list of exclusion criteria can be found on page 22 of the protocol)
1. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo);
2. Treatment with hormonal therapy (eg, androgen receptor inhibitors, estrogens, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within 4 weeks of randomization;
3. Use of an investigational agent within 4 weeks of randomization;
4. Known or suspected brain metastasis or active leptomeningeal disease;
5. History of another invasive cancer within 3 years of randomization, with the exception of fully treated cancers with a remote probability of recurrence in the opinion of both the medical monitor and investigator;

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):	28-05-2014
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xtandi
Generic name:	Enzalutamide

Ethics review

Approved WMO Date:	31-07-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-11-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2015
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	02-02-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-01-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-04-2021

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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-11-2021
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2022
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	EUCTR2012-005665-12-NL
CCMO	NL44906.060.13