A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High-Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy.

Published: 15-04-2015
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This study has been transitioned to CTIS with ID 2024-513521-23-00 check the CTIS register for the current data. All efficacy and safety objectives will compare enzalutamide plus leuprolide and enzalutamide monotherapyversus placebo plus leuprolide…

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

Summary

ID

NL-OMON55847

Source
ToetsingOnline

Brief title
EMBARK (MDV3100-13)

Condition

- Reproductive neoplasms male malignant and unspecified
- Genitourinary tract disorders NEC

Synonym

prostate carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Nonmetastatic, progressing, Prostate Cancer

Outcome measures

Primary outcome

To evaluate efficacy, as measured by metastasis-free survival (MFS) between

enzalutamide monotherapy versus placebo plus leuprolide.

Secondary outcome

To evaluate efficacy, as measured by the following:

* MFS between enzalutamide monotherapy versus placebo plus leuprolide.

* Time to prostate-specific antigen (PSA) progression;

* Time to first use of new antineoplastic therapy;

* Overall survival

Other secondary endpoints:

* Time to distant metastasis

* Proportion of patients per group who remain treatment-free 2 years after

suspension of study drug treatment at week 37 due to undetectable

* Proportion of patients per group with undetectable PSA 2 years after

suspension of study drug treatment at week 37 due to undetectable PSA

* Proportion of patients per group with undetectable PSA at 36 weeks on study

drug

* Time to resumption of any hormonal therapy following suspension at week 37

due to undetectable PSA

* Time to castration resistance

* Time to symptomatic progression

* Time to first symptomatic skeletal event

* Time to clinically relevant pain

* Quality of life

* Safety

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 in the United States undergo
primary localized treatment with curative intent. Of those, approximately one-third
experience rising prostate-specific antigen (PSA) or biochemical recurrence after primary
therapy. This rise in PSA uniformly represents recurrence of prostate cancer, the likely
presence of micrometastatic disease, and an increased risk of morbidity and mortality from
prostate cancer.
Despite the recurrence of prostate cancer, most men with biochemical recurrence after
primary therapy do not develop metastases or die from prostate cancer. However, a subset of men with rising PSA following primary therapy will develop clinically apparent
metastases and will die as a result of the disease. Despite available prognostic factors, no

therapies are approved for hormone-sensitive high-risk nonmetastatic prostate cancer with
evidence of disease recurrence by PSA but without overt metastases.
To benefit men with early-stage disease and features indicating a high risk of morbidity and
mortality from prostate cancer progression, a desirable therapy must demonstrate a favorable
safety profile and good efficacy in terms of delaying metastasis and death from prostate
cancer, that is, in prolonging metastasis-free survival (MFS). Ideally, short-term treatment
with such a therapy may eradicate or suppress the disease manifestations for a prolonged
period, thereby decreasing the need for exposure to the harmful effects of long-term surgical
or medical castration.
This phase 3 randomized study is designed to address this unmet medical need in a defined
patient population of men with hormone-sensitive high-risk nonmetastatic prostate cancer
progressing after definitive therapy, and will determine whether enzalutamide plus leuprolide
or enzalutamide monotherapy is more effective than placebo plus leuprolide.
High-risk
prostate cancer is defined in this study as biochemical recurrence with a PSA doubling time
* 9 months and screening PSA threshold of >= 2.0 ng/mL for patients who had prior radical
prostatectomy or >= 5.0 ng/mL and greater than or equal to the nadir + 2 ng/mL for patients
who had prior radiotherapy.

Study objective

This study has been transitioned to CTIS with ID 2024-513521-23-00 check the CTIS register for the current data.

All efficacy and safety objectives will compare enzalutamide plus leuprolide and enzalutamide monotherapy
versus placebo plus leuprolide.

Study design

an international, phase 3, randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide

Intervention

Study drug treatment will continue uninterrupted in the absence of disease progression until the central laboratory PSA evaluation at week 36. Based on PSA values at week 36, study drug treatment will either continue or be suspended at week 37. Following week 37, PSA and testosterone will be measured every 3 months by the central laboratory. Study drug treatment will be reinitiated if subsequent central laboratory PSA values increase to >= 2.0 ng/mL for patients with prior prostatectomy or >= 5.0 ng/mL for patients without prostatectomy. Study drug treatment may be suspended only once during this study (at week 37) due to undetectable PSA. Patients with detectable PSA values at week 36 will continue treatment without suspension until permanent treatment discontinuation criteria are met.

Study burden and risks

As of August 2019, over 9000 patients with prostate cancer, over 400 female patients with breast cancer, 100 patients with hepatocellular carcinoma (HCC) and over 300 patients with no known cancer (including healthy male patients and patients with liver impairment) have received at least 1 dose of enzalutamide in completed and ongoing clinical studies. Available data for enzalutamide in men with metastatic prostate cancer that has progressed despite therapy with a luteinizing hormone-releasing hormone (LHRH) analogue or bilateral orchiectomy support a positive benefit-risk profile for the use of enzalutamide as an investigational agent for treatment in earlier-stage prostate cancer, including patients with high-risk nonmetastatic prostate cancer progressing after definitive therapy.

Contacts

Public
Medivation, Inc., a wholly owned subisdairy of Pfizer Inc.

235 East 42nd Street 0000
New York NY 10017
US

Scientific
Medivation, Inc., a wholly owned subisdairy of Pfizer Inc.

235 East 42nd Street 0000
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age 18 years or older and willing and able to provide informed consent.
2. Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signetcell, or small cell features.
3. Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. Prostate cryoablation is not considerd definitive therapy for this study, but its prior to use is not exlusionary
4. PSA doubling time <= 9 months as calculated by the sponsor.
5. Screening PSA by the central laboratory >= 1 ng/mL for patients who had radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer and at least 2 ng/mL above the nadir for patients who had radiotherapy only as primary treatment for prostate cancer.
6. Serum testosterone >= 150 ng/dL (5.2 nmol/L) at screening.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.
8. Estimated life expectancy of >= 12 months.
9. Able to swallow the study drug and comply with study requirements.
10. Throughout study, the patient and his female partner who is of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception)

from screening through 3 months after the last dose of study drug or per local guidelines where these require additional description of contraceptive methods. Two acceptable methods of birth control thus include the following:
* Condom (barrier method is required)
AND
* One of the following is required:
- Established and ongoing use of oral, injected, or implanted hormonal method of contraception by the female partner
- Placement of an intrauterine device or intrauterine system by the female partner
- Additional barrier method including contraceptive sponge and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner
- Tubal ligation in the female partner performed at least 6 months before screening
- Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy), performed at least 6 months before screening
11. Throughout the study, the patient must use a condom if having sex with a pregnant woman.
12. Must agree not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.

Exclusion criteria

1. Prior or present evidence of distant metastatic disease as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) or chest x-ray for soft tissue disease and whole-body radionuclide bone scan for bone disease. Patients with soft tissue pelvic disease may be eligible if the short axis of the largest lymph node is < 20 mm for lymph nodes below aortic bifurcation. If the screening bone scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT, or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis by central radiology review, the patient is not eligible for enrollment unless otherwise approved by the sponsor. Positron-emission tomography (PET) is not an evaluable imaging modality for this study.
2. Prior hormonal therapy. Neoadjuvant/adjuvant therapy to treat prostate cancer <= 36 months in duration and >= 9 months before randomization, or a single dose or a short course (<= 6 months) of
hormonal therapy given for rising PSA >= 9 months before randomization is allowed.
3. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for prostate cancer.
4. Prior systemic biologic therapy, including immunotherapy, for prostate

cancer.
5. Major surgery within 4 weeks before randomization date.
6. Treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks of randomization.
7. For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator in consideration of appropriate guidelines (eg, American Society for Radiation Oncology / American Urological Association [ASTRO/AUA]; European Association of
Urology [EAU]).
8. Participation in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis (eg, TAK-700, ARN-509, ODM-201); patients who received placebo are allowed.
9. Use of any other investigational agent within 4 weeks before randomization date.
10. Known or suspected brain metastasis or active leptomeningeal disease.
11. History of another invasive cancer within 3 years before screening, with the exception of fully treated cancers with a remote probability of recurrence. The medical monitor and investigator must agree that the possibility of recurrence is remote.
12. Absolute neutrophil count < 1500/µL, platelet count < 100,000/µL, or hemoglobin < 10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors or blood transfusions within 7 days before the hematology values obtained at screening.
13. Total bilirubin (TBili) >= 1.5-times the upper limit of normal (except patients
with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >= 2.5-times the upper limit of normal at screening.
14. Creatinine > 2 mg/dL (177 µmol/L) at screening.
15. Albumin < 3.0 g/dL (30 g/L) at screening.
16. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke or significant brain trauma). History of loss of consciousness (unless of cardiac origin) or transient ischemic attack within 12 months before randomization
17. Clinically significant cardiovascular disease including the following:
- Myocardial infarction within 6 months before screening
- Unstable angina within 3 months before screening
- New York Heart Association class III or IV congestive heart failure or a history of New York Heart Association class III or IV congestive heart failure unless a screening echocardiogram or multigated acquisition scan performed within 3 months before the randomization date demonstrates a left ventricular ejection fraction >= 45%
- History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
- History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
- Hypotension as indicated by systolic blood pressure < 86 mm Hg at

screening
- Bradycardia as indicated by a heart rate of <= 45 beats per minute on the screening electrocardiogram (ECG)
- Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening
18. Gastrointestinal disorder affecting absorption.
19. Hypersensitivity reaction to enzalutamide or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
20. Contraindication to the use of leuprolide, such as a previous hypersensitivity reaction to an LHRH analogue or any of the excipients in the leuprolide injection.
21. Ongoing drug or alcohol abuse as per investigator judgment.
22. Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the study, which places the patient at undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor.

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):	05-10-2015
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eligard
Generic name:	Leuprolide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MDV3100, XTANDI
Generic name:	Enzalutamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-04-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-08-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2024-513521-23-00
EudraCT	EUCTR2014-001634-28-NL
ClinicalTrials.gov	NCT02319837
CCMO	NL52476.056.15