A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

Published: 22-01-2020
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1. To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to radiographic progression free survival (rPFS)2. To compare pembrolizumab plus enzalutamide plus ADT versus placebp plus enzalutamide...

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

Summary

ID

NL-OMON49942

Source
ToetsingOnline

Brief title
MK3475-991

Condition

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

Synonym

hormone-sensitive prostate cancer, metastasized hormone-senstive prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: MSD/Merck Sharp & Dohme

Intervention

Keyword: enzalutamide, mHSPC, pembrolizumab, prostate cancer

Outcome measures

Primary outcome

1. To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to radiographic progression free survival (rPFS)

2. To compare pembrolizumab plus enzalutamide plus ADT versus placebp plus enzalutamide plus ADT with respect to overall survival (OS)

Secondary outcome

- time from randomisation to initiation of the first subsequent anti-cancer therapy or death, whichever comes first

- time from randomisation to the first skeletal symptoms

- time to PSA progression

- time to radiographic soft tissue progression

- time from randomisation to pain progression

- time from randomisation to disease progression as determined by investigator

- a PSA decline of >=50% from baseline

- PSA <0.2 mg/ml during study intervention

- duration of the respons

- safety and tolerability (adverse events)

Study description

Background summary

Prostate cancer represents the second most common malignancy diagnosed in men worldwide. While many men diagnosed with locally confined disease may be treated definitively with radiation or surgery, approximately one third of men have recurrent disease and go on oo develop metastatic prostate cancer. Once prostate cancer has become metastatic there are no longer any curative treatments and expected median survival is less than five years. Patients with metastases have traditionally been treated first with ADT, usually with LHRH agonist or antagonist that results in suppression of testosterone production in the testes. This alone often succeeds in controlling disease for some time, years in many cases. However, prostate cancer progresses invariably and requires additional systemic therapies to re-establish control of disease.

The current standard of care for patients with high-volume of high-risk mHSPC is a combination docetaxel or abiraterone owht ADT upfront. More recently, it was shown that a combination of ADT with second-generation androgen receptor inhibitors apalutamide and enzalutamide results in a significant prolongation of overall survival. While these therapies are inititally effective, patients invariably succumb to their disease and the effectiveness of subsequent therapies diminishes after progression on the prior therapy. Thus, there remains a significant unmet need for novel therapies or combination regimens for patients with metastatic prostate cancer.

Pembrolizumab is a potent humanized IgG4 monoclonal anitbody with high specifity of binding to the PD-1 receptor. thus inhibiting its interaction with PD-1L and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expessed on the cell surface of activated T-celld under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. As a

consequence, the PD-1/PD-1L pathway is an attractive target for therapeutic intervention in mHSPC.

Study objective

1. To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to radiographic progression free survival (rPFS)

2. To compare pembrolizumab plus enzalutamide plus ADT versus placebp plus enzalutamide plus ADT with respect to overall survival (OS)

Study design

This is a randomized, multicenter, dubble-blind, placebo-controlled, phase 3 trial in participants with mHSPC with either pembrolizumab in combination with enzalutamide and ADT versus placebo in combination with enzalutamide and ADT.

Around 1232 participants will be randomly assigned 1:1 to one of the two treatment arms aftyer a screening period of no longer than 42 days. Cross-over is not possible.

Arm 1: Pembrolizumab 200mg every three weeks (Q3W) in combination with enzalutamide 160 mg daily (QD)

Arm 2: Placebo Q3W in combination with enzalutamide 160mg QD

Intervention

Arm 1: Pembrolizumab 200mg every three weeks (Q3W) in combination with enzalutamide 160 mg daily (QD)

Arm 2: Placebo Q3W in combination with enzalutamide 160mg QD

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, IV line insertion, CT/MRI or bone scans, physical exams, possibly confrontational questionnaires and patients will be asked to visit the hospital regularly.

Patients will be administered with pembrolizumab or placebo thourgh IV line, during three-week cycles, up to a maxmimum of 35 treatments. Enzalutamide (160 mg PO QD) treatment will begin on the same day as day 1, cycle 1 of pembrolizumab/placebo and will be continued on a daily dosing cycle until criteria for discontinuation are met (eg. disease progression)

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational drug. Pembrolizumab has been administered in a large number of cancer patients with a well characterized safety profile and has received regulatory approval for multiple malignancies. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W). Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Has histologically- or cytologically-confirmed adenocarcinoma of the

prostate without small cell histology
2. Has metastatic disease as assessed by investigator and verified by BICR (prior to randomization) by either >=2 bone lesions on bone scan and/or visceral disease by CT/MRI
3. Once randomized, participant must be willing to maintain continuous ADT with a LHRH agonists or antagonists during study treatment or have a history of bilateral orchiectomy
4. Has an ECOG performance status of 0 or 1 assessed within 10 days of randomization.
5. Participants receiving bone resorptive therapy must have been on stable doses for >=4 weeks prior to randomization.
6. Demonstrates adequate organ function
7. Is male, >=18 years of age at the time of signing the informed consent
8. Agree to the following during the intervention period and for at least 120 days after the last dose of study intervention:
• Refrain from donating sperm
PLUS either:
• Be abstinent from heterosexual intercourse as their preferred and usual lifestyleand agree to remain abstinent
OR
• Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause)
9. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study.
10. Has provided newly obtained core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated. However, if obtaining a new biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation (SCF).

Exclusion criteria

1. Has a known additional malignancy that is progressing or has required active treatment in the last 3 years
2. Has an active autoimmune disease that has required systemic treatment in past 2 years
3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention
4. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant*s participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator
5. Has undergone major surgery including local prostate intervention (excluding prostate biopsy) within 28 days prior to randomization and not recovered

adequately from the toxicities and/or complications.
6. Has a gastrointestinal disorder affecting absorption.
7. Is unable to swallow tablets/capsules
8. Has an active infection requiring systemic therapy.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has known active HIV, hepatitis B virus
11. Has known or suspected CNS metastases and/or carcinomatous meningitis or HCV
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study
13. Has a history of seizure or any condition that may predispose to seizure.
14. Has a history of loss of consciousness within 12 months of the Screening Visit.
15. Has had myocardial infarction or uncontrolled angina within 6 months prior to randomization.
16. Has (a history of) New York Heart Association class III or IV congestive heart failure
17. Has a history of clinically significant ventricular arrhythmias
18. Has a history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
19. Has hypotension as indicated by systolic blood pressure <86 mm Hg at the Screening Visit.
20. Has bradycardia as indicated by a heart rate of <50 beats per minute on the Screening ECG
21. Has uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at the Screening visit
22. Has severe hypersensitivity (Grade >=3) to pembrolizumab and/or any of its excipients.
23. Has hypersensitivity reaction to enzalutamide or any of its capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
24. Has received any prior pharmacotherapy, radiation therapy or surgery for metastatic prostate cancer with the following exceptions:
a. Up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent first-generation antiandrogens prior to randomization, with no radiographic evidence of disease progression or rising PSA prior to randomization if participant was not treated with docetaxel for metastatic prostate cancer.
b. May have 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 4 weeks prior to randomization
c. For participants with low-volume metastatic disease (defined as <4 bone lesions), may have 1 course of definitive radiotherapy (ie, EBRT) to the prostate if it was administered at least 4 weeks prior to randomization.
d. Up to 6 cycles of docetaxel therapy with final treatment administration completed within 2 months of randomization and no evidence of disease

progression during or after completion of docetaxel therapy. In these participants, up to 6 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent first-generation antiandrogens is permitted.
25. Has received prior ADT as neoadjuvant/adjuvant therapy for non-metastatic prostate cancer for >39 months in duration or within 9 months prior to randomization or with evidence of disease progression while receiving ADT
26. Has had prior treatment with a next generation hormonal agent
27. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor
28. Has used herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels within 4 weeks prior to randomization
29. Has received treatment with 5-α reductase inhibitors, estrogens, cyproterone acetate and/or androgens within 4 weeks prior to randomization.
30. Has received a live vaccine within 30 days prior to randomization.
31. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.
32. Has a *superscan* bone scan
33. Has had an allogenic tissue/solid organ transplant.

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):	04-08-2020

Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xtandi
Generic name:	Enzalutamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	05-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	24-06-2023
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
EudraCT	EUCTR2019-003633-41-NL
CCMO	NL72054.056.20