A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641)

Published: 29-05-2019
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This study has been transitioned to CTIS with ID 2022-500785-10-00 check the CTIS register for the current data. 1) To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to overall survival (OS)2) To compare...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON52743

Source
ToetsingOnline

Brief title
MK3475-641

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
Castration-Resistant metastatic Prostate Cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Castration resistant, enzalutamide, pembrolizumab, Prostate cancer

Outcome measures

Primary outcome

- overall survival (OS): the time from randomization to death due to any cause

- radiographic progression-free survival (rPFS): the time from randomization to radiographic progression, or death due to any cause, whichever occurs first

Secondary outcome

- Time to initiation of the first subsequent anti-cancer therapy or death (TFST)

- Prostate-specific antigen (PSA) response rate

- Objective response rate (ORR)

- Duration of response (DOR)

- Time to PSA progression

- Time to radiographic soft tissue progression

- Time to pain progression (TTPP)

- Time to Symptomatic Skeletal-Related Event (SSRE)

- Safety and toleability (Adverse events (AEs)

Study description

Background summary

Prostate cancer represents one of the most commonly diagnosed cancer malignancies and the second leading cause of cancer-related deaths in men worldwide. There remains an unmet medical need for patients with mCRPC with disease progression following treatment with a NHA and/or docetaxel-based chemotherapy.

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (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 intravenous (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, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in mCRPC.

Study objective

This study has been transitioned to CTIS with ID 2022-500785-10-00 check the CTIS register for the current data.

1) To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to overall survival (OS)

2) To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to radiographic progression-free survival (rPFS)

Study design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind/mask study of pembrolizumab plus enzalutamide versus placebo plus enzalutamide in participants with mCRPC.

Approximately 1200 participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms following a screening period of up to 42 days. There will be no crossover between treatment arms.

Arm 1: pembrolizumab 200 mg every 3 weeks (Q3W) plus enzalutamide 160 mg once daily (QD)

Arm 2: placebo Q3W plus enzalutamide 160 mg QD

Intervention

Arm 1: pembrolizumab 200 mg every 3 weeks (Q3W) plus enzalutamide 160 mg once daily (QD)
Arm 2: placebo Q3W plus enzalutamide 160 mg 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 through an IV line, during three-week cycles, up to a maximum 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 medicine. Pembrolizumab has been administered in a large number of cancer participants 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)

Inclusion criteria

1. Histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology.
2. Have prostate cancer progression while on ADT (or post bilateral orchiectomy) within 6 months prior to randomization, as determined by the investigator.
3. Have progression under the following conditions if the participant received anti-androgen therapy prior to enrollment:
a. Evidence of progression >4 weeks since last flutamide treatment.
b. Evidence of progression >6 weeks since last bicalutamide or nilutamide treatment.
4. Have current evidence of metastatic disease documented by either bone lesions on bone scan and/or soft tissue disease by CT/MRI. Participants whose disease spread is limited to regional pelvic lymph nodes are not eligible.
5. Have met one of the following criteria with regards to abiraterone acetate exposure:
a. not received prior abiraterone acetate (ie, abiraterone naïve)
b. received prior abiraterone acetate for the treatment of mHSPC, for a minimum of 4 weeks and must not have progressed while on treatment.
c. received prior abiraterone acetate for the treatment of mCRPC and either progressed on treatment after a minimum of 8 weeks treatment (minimum 14 weeks for those with bone progression) or become intolerant of the drug after a minimum of 4 weeks treatment.
6. Have ongoing androgen deprivation with serum testosterone <50 ng/mL (<2.0 nM). If the participant is currently being treated with luteinizing hormone-releasing hormone agonists or antagonists (participants who have not undergone an orchiectomy) this therapy must have been initiated at least 4 weeks prior to randomization and treatment must be continued throughout the

study.
7. Participants receiving bone resorptive therapy must have been on stable doses for >=4 weeks prior to randomization.
8. Demonstrate adequate organ function as defined in the protocol
9. Participant is male.
10. Participant is >=18 years of age on day of signing the informed consent.
11. Participants are eligible to participate if they agree to the following during the intervention period and for at least 45 days after the last dose of enzalutamide:
Either:
-Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
OR
-Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
*Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
*Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
13. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.
14. Have provided newly obtained core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated (samples from tumors progressing in a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation). Participants with bone only or bone predominant disease may provide a bone biopsy sample. However, if obtaining a fresh biopsy is not feasible, then participants may provide an archival tumor tissue sample after Sponsor consultation (SCF). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archive tissue.
15. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 7 days of randomization.

Digital proficiency is recommendable (in order to complete digital questionnaires).

Inclusion criteria for 2nd course retreatment:

Either:
- Stopped initial study intervention after CR, and
- Treated with at least 8 cycles of study intervention before discontinuing treatment, and
- Received at least 2 treatments with pembrolizumab beyond the date initial CR was declared

OR:
- Had SD, PR, or CR and stopped study intervention after completion of 35 cycles of study intervention for reasons other than disease progression or intolerability

AND:
- Experienced radiographic disease progression after stopping initial treatment, and
- Upon unblinding at the time of centrally verified disease progression, were found to have received pembrolizumab, and
- No new anticancer treatment was administered after the last dose of study intervention (exception: enzalutamide study treatment), en
- Meet all safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- the study is ongoing

Exclusion criteria

1. Has a known additional malignancy that is progressing or has required active treatment in the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ that have undergone potentially curative therapy are not excluded.
2. Has an active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy is not considered a form of systemic treatment.
3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone or equivalent) 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 (eg, gastrectomy,

active peptic ulcer disease within last 3 months).
7. Is unable to swallow tablets/capsules.
8. Has an active infection (including tuberculosis) requiring systemic therapy.
9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
10. Has known active HIV, active hepatitis B virus (HBsAg positive and/or detectable HBV DNA) or known active hepatitis C virus (HCV) (defined as anti HCV Ab positive and detectable HCV RNA infection). Testing is not required unless mandated by local regulation.
11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to randomization and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to randomization. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
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 (including, but not limited to prior cerebrovascular accident, transient ischemic attack, or brain arteriovenous malformation; or intracranial masses such as a schwannoma or meningioma that is causing edema or mass effect).
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 clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, torsades de pointes).
17. Has a history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
18. Has hypotension as indicated by systolic blood pressure <86 millimeters of mercury (mmHg) at the Screening Visit.
19. Has bradycardia as indicated by a heart rate of <50 beats per minute on the Screening electrocardiogram (ECG).
20. Has uncontrolled hypertension as indicated by systolic blood pressure >170 mmHg or diastolic blood pressure >105 mmHg at the Screening visit.
21. Has severe hypersensitivity (Grade >=3) to pembrolizumab end/or enzalutamide and/or any of its excipients.
22. Has history of prostate cancer progression on ketoconazole.
23. Has had prior treatment with any second-generation androgen receptor inhibitor (eg, enzalutamide, apalutamide, darolutamide).
24. 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 (eg, CTLA-4, OX- 40, CD137).
25. Has received prior treatment with radium or other therapeutic radiopharmaceuticals for prostate cancer.

26. Has had prior chemotherapy for mCRPC. Prior docetaxel for mHSPC is allowed if more than 4 weeks have elapsed from the last dose of docetaxel.
27. Has received prior targeted small molecule therapy or abiraterone treatment within 4 weeks prior to randomization or who has not recovered (ie, Grade <=1 or at baseline), with the exception of Grade <=2 neuropathy or Grade <=2 alopecia from AEs due to a previously administered agent.
28. Has received an anticancer mAb within 4 weeks prior to randomization or has not recovered (ie, Grade <=1 or at baseline) from AEs due to mAbs administered more than 4 weeks prior to randomization.
29. Has used herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto) within 4 weeks prior to randomization.
30. Has received treatment with 5-α reductase inhibitors (eg, finasteride, dutasteride), estrogens, and/or cyproterone within 4 weeks prior to randomization.
31. Has received a live vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
32. Has received prior radiotherapy within 2 weeks of randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<=2 weeks of radiotherapy) to non- CNS disease.
33. 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.
34. Has a *superscan* bone scan. This is defined as an intense symmetric activity in the bones and diminished renal parenchymal activity on baseline bone scan such that the presence of additional metastases in the future could not be evaluated.
35. Is to father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study intervention.
36. 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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-10-2019
Enrollment:	58
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:	29-05-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	05-07-2019
Application type:	First submission
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:	11-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2021
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:	24-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2022
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	CTIS2022-500785-10-00
EudraCT	EUCTR2018-004117-40-NL
ClinicalTrials.gov	NCT03834493
CCMO	NL68665.056.19