A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)

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1) To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to overall survival (OS)2) To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to radiographic progression-free...

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

Summary

ID

NL-OMON54503

Source
ToetsingOnline

Brief title
MK7339-010

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
Metastatic Castration resistant Prostate Cancer (mCRPC)

Research involving
Human

Sponsors and support

Primary sponsor: Farmaceutische Industrie
Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Castration resistant, Olaparib, Pembrolizumab, Prostate Cancer

Outcome measures

Primary outcome

- OS: the time from randomization to death due to any cause

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

Secondary outcome

- TFST: the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first

- Objective response (OR): complete response (CR) or partial response (PR)

- DOR: the time from the earliest date of first documented evidence of confirmed CR or PR until the earliest date of disease progression or death from any cause, whichever comes first

- Time to PSA progression: the time from randomization to PSA progression

- Time to first SSRE: the time from randomization to the first symptomatic

skeletal-related event

- Time to radiographic soft tissue progression

- TTPP: the time from randomization to pain progression

- Adverse events

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 and disease progression following treatment with a next-generation hormonal therapy and/or docetaxel-based chemotherapy.

Study objective

1) To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to overall survival (OS)
2) To compare pembrolizumab plus olaparib to abiraterone acetate or enzalutamide with respect to radiographic progression-free survival (rPFS)

Study design

This is a randomized, active-controlled, parallel-group, multisite, open-label study of pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide in participants with mCRPC.

After a screening phase of up to 42 days, approximately 780 eligible participants will be randomly assigned in a 2:1 ratio to 1 of the following 2 study intervention arms:

Arm 1: pembrolizumab 200 mg IV Q3W plus olaparib (as tablets) 300 mg twice daily (BID)
Arm 2: abiraterone acetate 1000 mg once daily (QD) plus prednisone or prednisolone 5 mg BID (in participants previously treated with enzalutamide) OR enzalutamide 160 mg QD (in participants previously treated with abiraterone acetate)

There will be no crossover between treatment arms.

Intervention

Arm 1: pembrolizumab 200 mg IV Q3W plus olaparib (as tablets) 300 mg twice daily (BID)
Arm 2: abiraterone acetate 1000 mg once daily (QD) plus prednisone or prednisolone 5 mg BID (in participants previously treated with enzalutamide) OR enzalutamide 160 mg QD (in participants previously treated with abiraterone acetate)

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.

Participants randomized to pembrolizumab (200 mg IV Q3W) + olaparib (300 mg PO BID) will receive pembrolizumab on Day 1 of each 3-week dosing cycle. Dosing with olaparib will begin on pembrolizumab Cycle 1 Day 1 and continue on a daily dosing schedule. Treatment with pembrolizumab will continue for up to 35 cycles (approximately 2 years) unless a discontinuation criterion is met.

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. Have histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology. The diagnosis must be stated in a pathology report and confirmed by the investigator. 2. Have prostate cancer progression while receiving androgen deprivation therapy (or post bilateral orchiectomy) within 6 months before screening, as determined by the investigator 3. Have disease progression under the following conditions if the participant received anti-androgen therapy before screening: •*Evidence of progression >4 weeks since the last flutamide treatment. •*Evidence of progression >6 weeks since the last bicalutamide or nilutamide treatment. 4. Have current evidence of metastatic disease documented by bone lesions on bone scan and/or soft tissue disease shown by CT/MRI. 5. Have received prior treatment with abiraterone acetate OR enzalutamide, but not both. 6. Have received docetaxel chemotherapy regimen for mCRPC and have had PD during or after treatment with docetaxel. If docetaxel chemotherapy has been used more than once it will be considered as 1 therapy. Prior docetaxel for mCRPC is allowed if >=4 weeks have elapsed from the last dose of docetaxel before Day 1 of Cycle 1. 7. Have ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM). If the participant is currently being treated with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists (in participants who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks before the date of randomization, and treatment must be continued throughout the study. 8. If receiving bone resorptive therapy, including but not limited to bisphosphonates or denosumab, have been receiving stable doses for >=4 weeks before the date of randomization. 9. Have adequate organ function per central laboratory; as defined in the protocol 10. Be male. 11. Be >=18 years of age on the day of signing the informed consent. 12. Agree

to the use contraception during the intervention period and for the following days after last dose of study intervention: - olaparib: 95 days - abiraterone acetate: 7 days - enzalutamide: 30 days 13. Also agree to use a male condom when engaging in any activity that allows passage of ejaculate to another person of any sex. 14. 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. 15. Have provided tumor tissue from a fresh core or excisional biopsy (obtained within 12 months of screening) from soft tissue not previously irradiated. Samples from tumors progressing at a prior site of radiation are allowed; other exceptions may be considered after Sponsor consultation. 16. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, assessed within 7 days of randomization.

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 who have undergone potentially curative therapy are not excluded. 2. Has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or has features suggestive of MDS/AML. 3. Has persistent toxicities (CTCAE Grade >2) caused by previous cancer therapy, excluding alopecia and neuropathy. 4. Has received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 28 days prior to the date of randomization. 5. Is considered a poor medical risk due to a serious uncontrolled medical disorder, nonmalignant systemic disease, or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution computed tomography scan, or any psychiatric disorder that prohibits obtaining informed consent. 6. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study. 7. Has an active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy is not considered a form of systemic treatment. 8. Has a gastrointestinal disorder affecting absorption. 9. Is unable to swallow capsules/tablets. 10. Has a history of (noninfectious) pneumonitis requiring steroids, or has current pneumonitis. 11. Has an active infection, including tuberculosis, requiring systemic therapy. 12. 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 indicate that participation in the study is not

in the best interest of the participant, in the opinion of the treating investigator. 13. Has known active human immunodeficiency virus (HIV), hepatitis B virus (eg, hepatitis B surface antigen reactive) or hepatitis C virus (HCV) infection (eg, HCV RNA [qualitative] is detected). 14. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable 15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (at doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the date of randomization. 16. Has (Grade >=3) hypersensitivity to pembrolizumab and/or any of its excipients. 17. Has known hypersensitivity to the components or excipients in olaparib, abiraterone acetate, prednisone or prednisolone, or enzalutamide. 18. Has CTCAE Grade >=2 peripheral neuropathy, except when due to trauma. 19. Has ascites or clinically significant pleural effusion. 20. Has had a seizure or seizures within 6 months of signing the informed consent or has any condition that may predispose to seizures. 21. Has a history of loss of consciousness within 12 months of the screening visit. 22. Has symptomatic congestive heart failure. 23. Has had a myocardial infarction or uncontrolled angina within 6 months prior to the date of randomization. 24. Has a history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or torsade de pointes). 25. Has a history of Mobitz II second-degree or third-degree heart block without a pacemaker in place. 26. Has hypotension as indicated by systolic blood pressure (BP) <86 mmHg at the screening visit. 27. Has bradycardia as indicated by heart rate <50 beats/minute on the screening electrocardiogram (ECG). 28. Has uncontrolled hypertension as indicated by systolic BP >170 mmHg or diastolic BP >105 mmHg at the screening visit. 29. Has received an anticancer monoclonal antibody (mAb) before randomization. 30. Has received prior treatment with olaparib or any other PARP inhibitor. 31. Has received prior treatment with apalutamide or darolutamide. 32. Has received prior treatment with abiraterone acetate for metastatic hormone-sensitive prostate cancer. 33. Has undergone major surgery, including local prostate intervention (except prostate biopsy), within 28 days prior to the date of randomization, and has not recovered from the toxicities and/or complications. 34. Has used herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA (eg, saw palmetto) before the date of randomization. 35. Has received prior treatment with radium or other therapeutic radiopharmaceuticals for prostate cancer. 36. Has received prior radiotherapy within 2 weeks of the date of randomization. Participants must have recovered from all radiation-related toxicities, must not require corticosteroids, and must not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<=2 weeks of radiotherapy) for non-CNS disease. 37. Has received prior treatment 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. 38. Has received prior targeted small molecule therapy within 4 weeks prior to the date of randomization or has not recovered from AEs due to a previously administered agent 39. Is currently receiving either strong or moderate

inhibitors of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 2 weeks. 40. Is currently receiving either strong or moderate inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents. 41. Is currently being treated with CYP450-inducing antiepileptic drugs for seizures. Use of antiepileptic drugs for pain control is allowed in participants without seizures, unless these drugs are excluded due to CYP450 induction. 42. Has received 5α reductase inhibitors (eg, finasteride or dutasteride), estrogens, or cyproterone within 4 weeks prior to the date of randomization. 43. Has received a previous allogenic bone marrow transplant or double umbilical cord transplantation (dUCBT). 44. Has received a whole blood transfusion in the last 120 days prior to the date of randomization. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days of the date of randomization. 45. Has received a live vaccine within 30 days before the date of randomization. 46. Is currently participating in or has participated in a study of an investigational agent, or has used an investigational device, before the date of randomization. 47. Has a resting ECG indicating uncontrolled, potentially reversible cardiac conditions as judged by the investigator 48. Has a bone *superscan,* 49. Is expecting to father children within the projected duration of the study, starting with the screening visit through the duration after the last dose of study intervention listed in inclusion criterion #12

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-07-2019

Enrollment:	56
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:	Lynparza
Generic name:	Olaparib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xtandi
Generic name:	Enzalutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zytiga
Generic name:	Abitraterone Acetate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-03-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-06-2019

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2021
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:	22-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2022
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:	20-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	29-01-2024
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	EUCTR2018-004118-16-NL
ClinicalTrials.gov	NCT03834519
CCMO	NL68656.056.19