A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA) (KEYNOTE-921)

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To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to overall survival (OS)

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

Summary

ID

NL-OMON52582

Source
ToetsingOnline

Brief title
MK3475-921

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: Industrie

Intervention

Keyword: castration resistant, docetaxel, Pembrolizumab, Prostate Cancer

Outcome measures

Primary outcome

To evaluate;

- overall survival (OS)

- radiographic progression-free survival (rPFS)

Secondary outcome

To evaluate:

- the first subsequent anti-cancer therapy or death (TFST)

- Prostate-specific antigen (PSA) response rate

- Objective response rate (ORR) and the duration of response (DOR)

- Time to pain progression (TTPP)

- Time to first symptomatic skeletal- related event (SSRE)

- Time to PSA progression

- Time to radiographic soft tissue progression

- the safety and tolerability

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

To compare pembrolizumab plus docetaxel plus prednisone to placebo plus docetaxel plus prednisone with respect to overall survival (OS)

Study design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind/mask study of pembrolizumab/placebo plus docetaxel plus prednisone in participants with mCRPC.
After a screening phase of up to 42 days, approximately 1000 eligible participants will be randomly assigned in a 1:1 ratio to 1 of the following 2 study intervention arms:
• Arm 1: pembrolizumab plus docetaxel plus prednisone/prednisolone

• Arm 2: placebo plus docetaxel plus prednisone/prednisolone

Intervention

Group 1:

1x per 3 weeks 200 mg pembroluzimab and 75mg/m2 docetalex by IV Infusion and twice a day 5mg prednison taken orally

Groep 2:
1x per 3 weeks placebo and 75mg/m2 docetalex by IV Infusion and twice a day 5mg prednison taken orally

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.

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)
Elderly (65 years and older)

Inclusion criteria

1. Have histologically- or cytologically-confirmed (if acceptable according to local health authority regulations) adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the investigator
2. Have prostate cancer progression while on androgen deprivation therapy (or post bilateral orchiectomy) within 6 months prior to screening, as determined by the investigator, by means of one of the following:
a. PSA progression using local laboratory values as defined by a minimum of 2 consecutive rising PSA levels with an interval of >=1 week between each assessment where the PSA value at screening should be >=1 ng/mL
b. Radiographic disease progression in soft tissue based on RECIST 1.1 criteria with or without PSA progression
c. Radiographic disease progression in bone based on PCWG, defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression
3. Have progression under the following conditions if the participant received antiandrogen 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 received prior treatment with one (but not more than one) NHA (eg, abiraterone acetate, enzalutamide, apalutamide, or darolutamide) for mHSPC or CRPC and either
a) progressed through treatment after a minimum of 8 weeks treatment (minimum 14 weeks for those with bone progression)

OR
b) have become intolerant of the drug (minimum 4 weeks treatment)
6. 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 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 (including, but not limited to, bisphosphonate or denosumab) must have been on stable doses for >=4 weeks prior to randomization
8. Demonstrate adequate organ function; all screening labs should be performed in the central laboratory within 10 days of the first dose of study intervention
9. Participant is male
10. Participant is >=18 years of age on day of signing informed consent
11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of pembrolizumab or 180 days after the last dose of docetaxel, whichever is longer:
a) Refrain from donating sperm
PLUS either:
b) 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
a) Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause as detailed below:
Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant
12. Male participants must agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex
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

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 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 trial, interfere with the participant*s participation for the full duration of the trial, or is not in the best interest of the participant, 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 (including tuberculosis) requiring systemic therapy
9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis
10. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial
11. Has known active human immunodeficiency virus, hepatitis B virus or hepatitis C virus. Testing at screening is not required unless mandated by local regulations
12. Has known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable, have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to randomization.
13. Has severe hypersensitivity (>=Grade 3) to pembrolizumab and/or any of its excipients
14. Has CTCAE Grade >=2 peripheral neuropathy, except when due to trauma
15. Has ascites and/or clinically significant pleural effusion
16. Has symptomatic congestive heart failure (New York Heart Association Class III or IV heart disease)
17. Has received a whole blood transfusion in the last 120 days prior to entry into the study. Packed red blood cells and platelet transfusions are acceptable if not given within 28 days of the first dose of study intervention

18. Has received colony-stimulating factors within 28 days prior to the first dose of study intervention
19. Has had a prior anticancer mAb within 4 weeks prior to randomization or who has not recovered from AEs due to mAbs administered more than 4 weeks prior to randomization
20. 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 treatment randomization
21. Has received prior treatment with radium or other therapeutic radiopharmaceuticals for prostate cancer
22. 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
23. Has received prior treatment with docetaxel or another chemotherapy agent for mCRPC
24. Has hypersensitivity to docetaxel or polysorbate 80
25. Participant is currently receiving either strong or moderate inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study
26. Has received prior targeted small molecule therapy or abiraterone acetate or enzalutamide within 4 weeks prior to the first dose of study intervention, or has not recovered from AEs due to a previously administered agent
27. Has received prior radiotherapy within 2 weeks of start of study intervention. 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
28. Has received a live vaccine within 30 days prior to randomization
29. Has received treatment with 5alfa reductase inhibitors, estrogens, and/or cyproterone within 4 weeks prior to randomization.
30. Has received prior treatment with ketoconazole for prostate cancer.
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 the first dose of study intervention
32. Has a *superscan* bone scan
33. Is expecting to conceive or father children within the projected duration of the study,starting with the screening visit through 120 days after the last dose of study intervention
34. 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:	Recruitment stopped
Start date (anticipated):	18-09-2019
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Prednison
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-03-2019

Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-05-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-11-2019

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2020

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2022

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
Other	122753
EudraCT	EUCTR2018-004116-22-NL
CCMO	NL68667.028.19