Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-199)

Published: 09-05-2016
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To estimate the objective response rate (ORR) by RECIST 1.1 in subjects with measurable disease assessed by central imaging vendor in Cohorts 1 and 2 combined, Cohort 1, Cohort 2 and Cohort 4.

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

Summary

ID

NL-OMON55373

Source
ToetsingOnline

Brief title
MK3475-199

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)

Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Pembrolizumab, Prostate Cancer

Outcome measures

Primary outcome

Cohorts 1, 2, and 4 - Objective Response Rate (ORR) - per RECIST 1.1 assessed by central imaging vendor: Proportion of subjects int he analysis population who have complete response (CR) or partial response (PR) where responses are determined by RECIST 1.1 assessed by central imaging vendor.

Secondary outcome

1.Duration of Response (DOR) per PCWG3-modified RECIST 1.1 assessed by central imaging vendor.

For subjects who demonstrated CR or PR, DOR is defined as the time from first documented evidence of CR of PR until disease progression assessed by central imaging vendor where progressive disease (PD) in bone-only tumors will be determined by radionuclide bone scan using RECIST 1.1/PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1 or death due to any cause, whichever occurs first

2.Duration of Response (DOR) - per RECIST 1.1 assessed by central imaging vendor.

For subjects who demonstrated CR or PR, DOR is defined as the time from first documented evidence of CR of PR until progressive disease (PD) assessed by central imaging using RECIST 1.1 or death due to any cause, whichever occurs first.

3. Disease Control Rate (DCR) - assessed by central imaging vendor

Proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 6 months, by central imaging vendor where progressive disease (PD) in bone-only tumors will be determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1

4. PSA Response Rate

Proportion of subjects in the analysis population who have PSA response defined as more than 50% decline from baseline measured twice at least 3 weeks apart.

5. Time to PSA Progression, defined as the time from first day of study treatment to the date of PSA progression. Subjects without PSA progression will be censored at the last PSA assessment date. PSA progression is defined as the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented. For subjects who had an initial PSA decline during treatment, this must be confirmed by a second value 3 or more weeks later.

6. Radiographic progression-free survival (rPFS) - per PCWG3-modified RECIST 1.1 assessed by central imaging vendor. It is defined as the time from first day of study treatment to the documented disease progression by central imaging vendor where progressive disease (PD) in bone-only tumors will be determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1 or death due to any cause, whichever occurs first.

7. Overall Survival (OS)

Overall survival (OS) is defined as the time from first day of study treatment

to the time of death.

8. Duration of PSA response (Cohorts 4 and 5 only)

Duration of PSA response is defined as the time from PSA response, when the PSA value first declines by at least 50% of the baseline (must be confirmed y a second value), to the date of PSA progression at which there is an increase of 25% or more from the nadir PSA, provided the absolute increase from the nadir PDA is at least 2 ng/mL.

9. Time to initiation of cytotoxic chemotherapy (Cohorts 4 and 5 only)

Time to initiation of cytotoxic chemotherapy is defined as the time from first day of study treatment to the time of initiation of cytotoxic chemotherapy for prostate cancer.

10. Time to new-anticancer therapy (Cohorts 4 and 5 only)

Time to new-anticancer therapy is defined as the time from first day of study treatment to the time of new-anticancer therapy for prostate cancer

11. Time to first skeletal-related event (Cohorts 4 and 5 only)

Time to initiation of first skeletal-related event is defined as the time from first day of study treatment to the first skeletal-related event, which is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change or antineoplastic therapy to treat bone pain. See Section 8.6.1 for censoring rules.

12. Safety endpoints: Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs). Safety

will be assessed by reported adverse experiences using CTCAE, Version 4.0.

Study description

Background summary

Prostate cancer represents the second most common malignancy diagnosed in men worldwide where the annual incidence has been estimated to be over 1 million and over 300,000 deaths are expected annually. In the US, approximately one in every six men will be diagnosed with prostate cancer in his lifetime.

While many men are diagnosed with locally confined disease and may be treated definitively with radiation or surgery, men who go on to develop or are diagnosed with metastatic prostate cancer, an incurable entity, are typically treated first with androgen deprivation therapy (ADT), usually with a GnRH 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 reestablish control of disease. The point at which prostate cancer progresses in spite of ADT alone is referred to as castrate resistance, and the disease at this point is known as (metastatic) castrate-resistant prostate cancer (mCRPC).

A number of important systemic therapies have been developed to treat mCRPC and have received regulatory approval and now comprise the current therapeutic landscape. Docetaxel became the first systemic therapy to improve survival for men with mCRPC in a randomized study with docetaxel demonstrating superior survival of median 18.9 months versus 16.5 for mitoxantrone. Cabazitaxel, a second taxane was studied versus mitoxantrone in patients after docetaxel, and it too was found to be associated with superior survival * median 15.1 months versus 12.7 with mitoxantrone. Finally, the targeted endocrine therapies, enzalutamide and abiraterone, were examined in randomized clinical trials in patients with mCRPC before treatment with chemotherapy and found to have superior overall survival versus control therapy (placebo and prednisone, respectively).

Cabazitaxel can be a toxic therapy. Deaths occurred on study due to treatment-related neutropenia, and mortality has been reported due to treatment-related diarrhea. Its label contains a black box warning regarding risks from neutropenia, severe hypersensitivity, and other label warnings and precautions pertain to diarrhea, renal failure, prohibitive risk in elderly patients * 65, and hepatic impairment. Consequently, cabazitaxel is not well

utilized and consensus guidelines, such as NCCN, recommend that men with mCRPC after docetaxel should be encouraged to participate in clinical trials. Thus, an unmet medical need remains for patients after treatment in the mCRPC setting with targeted endocrine therapy and docetaxel.

Study objective

To estimate the objective response rate (ORR) by RECIST 1.1 in subjects with measurable disease assessed by central imaging vendor in Cohorts 1 and 2 combined, Cohort 1, Cohort 2 and Cohort 4.

Study design

This is a nonrandomized, multinational, open-label trial of pembrolizumab (MK-3475) in subjects with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel-based chemotherapy.

Intervention

Intervention with medicine, for a description of the concerned medicine, see C16.

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on day 1. At every visit, a physical examination will be performed, vital signs will be measured, ECGs made and blood samples will be collected.
The subjects will also be asked to complete questionnaires on their health and symptoms.
There will be a tumor biopsy at screening (this can be omitted in case there is adequeate tumor tissue available).
Trial subjects may experience physical and/or psychological discomfort with some of the study procedures, such as blood sampling, administration of the IV line ECGs, CT/MRI/bone scans, and tumor biopsy.
The main side effects reported with the trial medication include fatigue, itching, rash, frequent or irregular bowel movements, pain in joints, muscles, or bones, stomach ache and nausea.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be *18 years of age on day of signing informed consent.
3. Have histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the Investigator.
4. Have RECIST 1.1-measurable prostate cancer on computed tomography (CT) or magnetic resonance imaging (MRI) scans (Cohorts 1, 2 and 4) or detectable bone metastases by whole body bone scintigraphy and no RECIST 1.1-measurable tumors (Cohorts 3 and 5), as determined by central review. Disease must be either metastatic or locally confined inoperable disease that cannot be treated with definitive intent.
5. Have supplied tumor tissue from a newly obtained biopsy or provided a tumor tissue specimen *12 months prior to the screening date and an archival specimen, if available, from a site not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization; other exceptions may be considered after Sponsor

consultation). Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to enrollment. Subjects in Cohorts 1, 2 and 4 with visceral / measurable lesions must provide a newly obtained biopsy performed after the last line of systemic therapy where safely available or a specimen obtained *12 months prior to the screening date and an archival specimen, if available. Subjects in Cohort 3 and 5 must at least provide an archival specimen.
For Cohorts 1, 2, and 3 only:
6. Have been treated with:
a. At least one targeted endocrine therapy (defined as second generation antiandrogen therapies that include but are not limited to abiraterone acetate with prednisone, enzalutamide, and next generation targeted agents such as ARN-509).
b. At least one regimen / line of chemotherapy that contained docetaxel.
c. No more than two chemotherapy regimens.
d. No more than three regimens / lines of the aforementioned treatments (having failed / progressed on chemotherapy and targeted endocrine therapy).
For Cohorts 4 and 5 only:
7. For chemotherapy-naive subjects with mCRPC either having failed or showing early signs of failing on enzalutamide treatment as defined by PCWG3-guidelines (eg, signs of clinical progression, increased alkaline phosphatase, PSA increase, or positive imaging assessments). Subjects can have failed prior abiraterone treatment before current enzalutamide treatment. Subjects must have had a clinically meaningful response to enzalutamide treatment. Enzalutamide must have been initiated no less than 4 weeks prior to the first dose of trial treatment and be continued throughout the study.
All Cohorts:
8. Have documented prostate cancer progression within 6 months prior to screening, as determined by the Investigator, by means of one of the following:
a. PSA progression as defined by a minimum of 3 rising PSA levels with an interval of * 1 week between each assessment where the PSA value at screening should be * 2 ng/mL.
b. Radiographic disease progression in soft tissue or bone with or without PSA progression
9. Have ongoing androgen deprivation with total serum testosterone < 50 ng/dL (< 2.0 nM). If the subject is currently being treated with LHRH agonists (subjects who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to first dose of trial treatment. This treatment must be continued throughout the study.
10. Subjects receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have been on stable doses for * 4 weeks prior to first dose of trial treatment.
11. Have a performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
12. Subjects are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of

time required to continue contraception after the last dose of enzalutamide is 30 days.
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle and agree to remain abstinent.
OR
- Must agree to use contraception unless confirmed to be azoospermic, as detailed below:
- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOBCP who is not currently pregnant.
- Contraceptive use by men should be consistent with local regulation. If the contraception requirements in the local label for any of the study interventions is more stringent.
13. Demonstrate adequate organ function as defined in protocol

Exclusion criteria

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of trial treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (replacement therapy for adrenal insufficiency is permitted).
3. Has had a prior anti-cancer mAb within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., * Grade 1 or at baseline) from AEs due to mAbs administered more than 4 weeks earlier.
4. Has had prior chemotherapy, targeted small molecule therapy, or external beam radiation therapy within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., * Grade 1 or at baseline) from AEs due to a previously administered agent. Treatment with Radium-223 is allowed as long as the last dose has been administered no less than 4 weeks prior to the first dose.
5. Has a known additional malignancy that has had progression or has required active treatment in the last 3 years. Exceptions include basal cell carcinoma of the skin, and squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment 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 the first dose of trial treatment. This exception does not include

carcinomatous meningitis which is excluded regardless of clinical stability.
7. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
8. Has evidence of interstitial lung disease and / or a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
9. Has an active infection requiring systemic therapy.
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject*s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Has previously participated in any other pembrolizumab (MK-3475) trial, or received prior therapy with an anti-PD-1, anti-PD-L1, and anti-PD-L2 (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
15. Has received a live vaccine within 30 days of planned start of study therapy. Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
Additionally, the following apply to Cohorts 4 and 5 only:
16. Has received prior chemotherapy (e.g., docetaxel) for mCRPC.
17. Has any condition (cardiac, neurologic, absorption) other than clinically failing or showing early signs of failing on enzalutamide treatment that would require imminent discontinuation of enzalutamide treatment

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-09-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-05-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2016
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	18-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2018
Application type:	Amendment
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Approved WMO Date:	08-08-2018
Application type:	Amendment
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Approved WMO Date:	22-08-2018
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Approved WMO Date:	16-01-2019
Application type:	Amendment
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Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
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Approved WMO Date:	30-04-2020
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	(Assen)
Approved WMO Date:	28-10-2020
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Approved WMO Date:	24-03-2021
Application type:	Amendment
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Approved WMO Date:	06-06-2021
Application type:	Amendment
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Approved WMO Date:	13-09-2021
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Approved WMO Date:	30-09-2021
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Approved WMO Date:	15-12-2021
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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	EUCTR2015-003644-40-NL
CCMO	NL57447.056.16