Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-365)

Published: 01-07-2021
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-506987-15-00 check the CTIS register for the current data. 1) Objective: To evaluate the safety and tolerability of the pembrolizumab combination therapy.2) Objective: To estimate PSA response...

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

Summary

ID

NL-OMON52154

Source
ToetsingOnline

Brief title
MK3475-365

Condition

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

Synonym
prostaatkanker, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Farmaceutische Industrie
Source(s) of monetary or material Support: Merck;Sharp and Dohme

Intervention

Keyword: castration-resistant, combination therapies, metastatic, prostate cancer

Outcome measures

Primary outcome

Primary Objective(s) & Hypothesis(es) 1) Objective: To evaluate the safety and tolerability of the pembrolizumab combination therapy. 2) Objective: To estimate PSA response rate of the pembrolizumab combination therapy. PSA response is defined as a reduction in the PSA level of 50% or more from baseline measured twice at least 3 weeks apart. 3) Objective: To estimate the objective response rate (ORR) based on RECIST 1.1 assessed by BICR.

Secondary outcome

1) Time to PSA progression

2) Overall response rate (ORR)

3) Radiographic progression-free survival (rPFS)

4) Overall Survival (OS)

5) the duration of response (DOR) based on RECIST 1.1

6) disease control rate (DCR) based on RECIST 1.1

7) For cohort A only:

- response according to RECIST 1.1 by BICR

- PSA response rate

- conversion in the circulating tumor-cell (CTC) count.

8) 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 new hormonal agent 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 ligand PD-L1 and ligand 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 2023-506987-15-00 check the CTIS register for the current data.

1) Objective: To evaluate the safety and tolerability of the pembrolizumab combination therapy.
2) Objective: To estimate PSA response rate of the pembrolizumab combination therapy. PSA response is defined as a reduction in the PSA level of 50% or more from baseline measured twice at least 3 weeks apart.
3) Objective: To estimate the objective response rate (ORR) based on RECIST 1.1 assessed by BICR.

Study design

This is a nonrandomized (with the exception of Cohort I and J which are

randomized 1:1), multicenter, multicohort, open-label, Phase Ib/II trial of pembrolizumab (MK-3475) combination therapy in subjects with metastatic castration-resistant prostate cancer
(mCRPC).

Approximately 1200 participants will be assigned to one of the cohorts. Screening procedures are to be completed within 42 days prior to treatment allocation/randomization

Subjects will be assigned to one of the following cohorts based on prior treatment for mCRPC and other eligibility criteria for each cohort. The investigator*s choice of standard of care will also be used to allocate subjects due to some overlap in entrance criteria. Cohorts A, B, C, D, E, G, and J will enroll subjects with adenocarcinoma (AC); Cohorts F, H, and I will enroll subjects with treatment emergent neuroendocrine (t-NE) cancer.

Intervention

Cohort A (AC) (closed):
Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W) + olaparib 400 mg (capsules)/300 mg (tablets) by mouth (PO) twice a day (bid)

Cohort B (AC) (closed):
Pembrolizumab 200 mg IV q3w + docetaxel 75 mg/m2 IV Q3W + prednisone 5 mg PO bid

Cohort C (AC) (closed):
Pembrolizumab 200 mg IV q3w + enzalutamide 160 mg PO every day (QD)

Cohort D (AC) (closed):
Pembrolizumab 200 mg IV Q3W + abiraterone acetate 1000 mg PO qd + prednisone 5 mg PO bid

Cohort E (AC):
Pembrolizumab 200 mg IV Q3W + lenvatinib 20 mg PO QD

Cohort F (t-NE):
Pembrolizumab 200 mg IV q3w + lenvatinib 20 mg PO QD

Cohort G (AC):
Pembrolizumab 200 mg IV Q3W + MK-7684 (vibostolimab) 200 mg IV Q3W coformulation (MK-7684A)

Cohort H (t-NE):

Pembrolizumab 200 mg IV Q3W + MK-7684 (vibostolimab)
200 mg IV Q3W coformulation (MK-7684A)

Cohort I (t-NE):
Subjects will be randomly assigned on a 1:1 ratio to receive chemotherapy with (Arm 1) or without pembrolizumab (Arm 2); both arms are t-NE.
Arm 1: Pembrolizumab 200 mg IV Q3W + carboplatin titrated to an AUC of 5 IV Q3W on Day 1 + etoposide 100 mg/m2 IV Q3W on Days 1, 2, and 3.

Arm 2: Carboplatin titrated to an AUC of 5 IV Q3W on Day 1 + etoposide 100 mg/m2 IV Q3W on Days 1, 2, and 3.

Cohort J (AC):
Approximately 20 participants will be enrolled in the initial cohort to receive belzutifan monotherapy 120 mg
QD (Arm J1). If an efficacy signal is detected in the monotherapy arm based on a totality of evidence, Cohort
J may be expanded where subsequent 180 participants will be randomized 1:1 to receive either belzutifan 120 mg QD
(Arm J1) or belzutifan 120 mg QD and pembrolizumab 200 mg Q3W (Arm J2), about 90 per arm in the expansion
cohort. Arm J1 will explore the safety and efficacy of belzutifan monotherapy. Arm J2 will explore the safety
and efficacy of the combination of belzutifan and pembrolizumab. Exploratory analyses of between-group
comparisons for Cohort J without formal hypothesis testing may be conducted in this estimation study.
Arm J1: Belzutifan 120 mg QD
Arm J2: Pembrolizumab 200 mg IV Q3W + belzutifan 120 mg QD

Note: (Amendment 08), Cohorts A, B, C, and D are fully enrolled and closed to enrollment

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, Biopsy, 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 different combination threapies, 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)

Inclusion criteria

The below-mentioned inclusion criteria are the most important ones. A complete list of cohort specific inclusion criteria can be found in the protocol. - Be willing and able to provide documentad written informed consent/assent for the trial - Be >= 18 years of age on day of signing informed consent - Have histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology (cohorts A-E, G, J) - Have t-NE prostate cancer defined by >=1% neuroendocrine cells in a recent biopsy specimen from a metastasis - Have provided tumor tissue from a site not previously irradiated -

Have prostate cancer progression within 6 months prior to screening - Have progression if the subject received anti-androgen therapy prior to enrollment - Have ongoing androgen deprivation with serum testosterone <50 ng/dl - Subjects receiving bone resorptive therapy must have been on stable doses for >=4 weeks prior to first dose of trial treatment - Agree to use an adequate method of contraception, if the subject is of reproductive potential, starting with the first dose of study therapy through 120 days after the last dose of study therapy - Demonstrate adequate organ function

Exclusion criteria

The below-mentioned exclusion criteria are the most important ones. A complete list of cohort specific exclusion criteria can be found in the protocol.
- Has had prior anticancer mAb within 4 weeks prior to first dose of trial treatment of who has not recovered form AEs due to mAbs administered more than 4 weeks prior to first dose of trial treatment
- Is currently participating in and receiving study therapy or has participated in a study of an investigational device within 4 weeks of randomization
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days of randomization
- If a subject has undergone major surgery, they must have recovered adequately from the toxicities/complications prior to starting therapy
- Has had a prior radium treatment or treatment with other therapeutic radiopharmaceuticals for prostate cancer
- Has a known additional malignancy that has had progression or has required active treatment in the last 3 years
- Has an active autoimmune disease that has requires systemic treatment in past 2 years
- Has a history of (non-infectious) pneumonitis/interstitial lung disease that required
steroids or current pneumonitis/interstitial lung disease.
- Has an active infection requiring systemic therapy
- 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 investigator
- has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial
- Has previously participated in any other pembrolizumab trials, or received prior therapy with an anti-PD-1, anti-PD-L1 and anti-PD-L2
- Has known history of HIV
- Has known active hepatitis B, or C virus
- Has received a live vaccine within 30 days of the first dose of trial treatment
- 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
- Has known active central nervous system metastases and/or carcinomatous meningitis
- Has had prior chemotherapy, targeted small molecule therapy, abiraterone acetate treatment, enzalutamide treatment, or radiation therapy within 2 weeks prior to first dose of trial treatment or who has not recovered from AEs due to previously administered agent
- Has a "superscan" bone scan
- Has had prior solid, organ or bone marrow transplant

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-05-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

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

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

Ethics review

Approved WMO Date:	01-07-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-01-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	07-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-11-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	01-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-01-2024
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
EU-CTR	CTIS2023-506987-15-00
EudraCT	EUCTR2016-002312-41-NL
ClinicalTrials.gov	NCT02861573
CCMO	NL75767.028.21