PEMbrolizumab Plus Lenvatinib In Second Line And Third Line Malignant Pleural MEsotheLiomA Patients.

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Primary: 1. To determine the objective response rate (ORR), defined by Modified (i)RECIST criteria for pleural mesothelioma, of the combination of pembrolizumab - lenvatinib in pre-treated patients with MPM. Secondary:1. To describe the safety of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON52501

Source
ToetsingOnline

Brief title
PEMMELA

Condition

- Mesotheliomas

Synonym
Asbestos cancers, malignant mesothelioma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Eisai,Merck Sharp & Dohme (MSD),MSD B.V.;Eisai

Intervention

Keyword: lenvatinib, Malignant pleural mesothelioma, pembrolizumab, recurrent

Outcome measures

Primary outcome

Primary:

1. To determine the objective response rate (ORR), defined by Modified RECIST 1.1 criteria for pleural mesothelioma, of the combination of pembrolizumab-lenvatinib in pre-treated patients with MPM to be compared with historical controls.

Secondary outcome

Secondary:

1. Extent of exposure, AEs, SAEs, treatment related AEs (TRAEs/SAEs) , AE*s leading to discontinuation of study drug(s)/withdrawal, fatal TRAEs and deaths. Other AEs that the investigator deemed important to report and reasons for discontinuation of study drug(s). AE grading will be performed by NCIE Common Terminology Criteria for Adverse Events Version 5.0.

2. To describe the disease control rate (DCR) at 3 and 6 months, progression free survival (PFS), overall survival (OS), duration of response (DOR) and

3. To describe the DCR, ORR, DOR and PFS by independent radiological review

Exploratory:

1. Exhaled breath analyses as potential biomarker.

2. Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

3. The ORR, PFS and OS of pembrolizumab and lenvatinib in the second course

setting (see second course)

Study description

Background summary

There is no standard second line treatment in malignant pleural mesothelioma (MPM). Pembrolizumab has shown to be active in in small phase II studies in MPM. Its activity however, is limited, with a response rate up to 20%. So, there is a need for new treatment combinations with drugs that might exhibit a synergistic interaction with pembrolizumab. The mechanisms of actions of lenvatinib, which has a broad spectrum of activities, predicts many synergistic interactions with PD-1 blocking. Since the arrival of nivolumab plus ipilimumab as first line standard of care treatment in mesothelioma, no treatment options are investigated in this group of patients in the second line. The aim of this study is to characterize the potential clinical activity, toxicity and biomarkers of outcome of pembrolizumab - lenvatinib in patients with recurrent MPM.

Study objective

Primary:
1. To determine the objective response rate (ORR), defined by Modified (i)RECIST criteria for pleural mesothelioma, of the combination of pembrolizumab - lenvatinib in pre-treated patients with MPM.

Secondary:
1. To describe the safety of pembrolizumab- lenvatinib in patients with MPM.
2. To describe the disease control rate (DCR) at 3 and 6 months, clinical benefit, progression free survival (PFS), overall survival (OS), duration of response (DOR) and time to progression (TTP).
3. To describe ORR and PFS by independent radiological review.

Exploratory objectives
1. The immunological status in the tumors before study and after 6 weeks of treatment with pembrolizumab+ lenvatinib. This research will include PD-L1 status, mutational load and other potential biomarkers (e.g. micro vessel density count).
2. To explore the value of exhaled breath analyses.
3. The ORR, PFS and OS of pembrolizumab and lenvatinib in the second course setting (see second course)

Study design

PEMMELA is a Dutch prospective single center, single arm, open label, investigator-initiated phase II trial for patients with unresectable malignant pleural mesothelioma who have disease progression or recurrence after 1 or 2 lines of chemotherapy.
The primary endpoint is ORR defined by Modified RECIST 1.1 for pleural malignant mesothelioma. For details about the endpoints, see chapter 9, statistical considerations.

Intervention

All subjects will receive continious daily treatment with lenvatinib 20mg once daily and 200mg pembrolizumab iv tri-weekly intil disease progression of unacceptable toxicity for a maximum of 2 years.

Study burden and risks

Although single agent PD-1 blocking, with pembrolizumab or nivolumab resulted in an ORR around 20% in pre-treated MPM patients, the progression free survival was limited to 2.6 -6.1 months. New therapeutic strategies are needed to improve for patients with recurrent MPM.
The combination of angiogenesis blocking (by lenvatinib) and PD-1 blocking (pembrolizumab) seemed promising in both pre-clinical models and other solid tumours (see section 1.5). Up to 7 studies have been presented with safety data (see appendix F). Although patients are at risk of greater toxicity when they receive combination therapy (see section 1.6), all previous studies with lenvatinib-pembrolizumab concluded that the toxicity was manageable and it outweighs the large activity of the combination therapy.
We integrated both safety data of single agent lenvatinib and pembrolizumab and the data of the combination therapy in our treatment schedule. For example; telephonic contact after 24-48 hours after the first gift of study medication and visit at day 8 of cycle 1, an urine dipstick every 3 weeks and strict rules for controlled blood pressure as inclusion criteria. In general, it appears that the incidence of TRAEs increases with increasing doses. We have provided rules for dose interruption and dose reduction for both lenvatinib and pembrolizumab (section 5.2.). AEs of special interest are mention in section 5.2.3. We will perform continue safety monitoring (see section 9.5). The accrual can be halted if excessive numbers of dose reductions and/or stopping with trial medication because of toxicity is seen, that is, more than expected based on previous phase I/II data (see appendix F). A lung function test will be performed every six weeks, as surrogate for quality of live as recommended by a patient advocate.
Currently all MPM patients are treated with platinum-pemetrexed in the first line. Although MPM is known for inter-tumor heterogeneity, no personalized medicine is available yet. Small phase II studies with PD(L)-1 blocking could

not reveal a relationship between PD-L1 expression and response. The PEMMALA study will determine both the clinical activity and safety of lenvatinib-pembrolizumab and will search for mechanism of action in blood and biopsies. We will take a biopsy of the pleura before start of treatment, after signing of informed consent. A second, optional, biopsy will be taken of pleura after 6 weeks of treatment. These samples can provide import information about the nature of MPM, can give signs of activity on a pathologic level and hopefully provide information which can be used to develop biomarkers for MPM. Blood samples for research purposes will be taken at baseline and at day 1 of cycle 2, 3 and 6. *

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. Histologically or cytologically diagnosed malignant pleural mesothelioma, age at least 18 years
2. 2. Progressive disease after at least 1 and maximal 2 prior systemic treatment lines:
- Cohort 1: patients, in which one of the lines contains a platinum-based doublet (both cisplatin and carboplatin are allowed) for unresectable MPM
- Cohort 2: patients with only in which one of the lines contains nivolumab-ipilimumab immunotherapy as first line treatment for unresectable MPM. No prior chemotherapy.
3. Measurable disease. At least one measurable lesion according to Modified (i)RECIST for pleural mesothelioma. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions
4. WHO-ECOG performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to date of allocation
5. Adequate organ function
6. Ability to understand the study and give signed informed consent (or legally acceptable representative if applicable) prior to beginning of protocol specific procedures including the approval of the thoracoscopy or transthoracic pleural biopsy before the first treatment cycle and an optional biopsy before the third treatment cycle
7. No presence of clinically relevant treatment-related toxicity from previous chemotherapy, targeted therapy and/or radiotherapy. Note: Participates must have recovered from all AEs due to previous therapies to <=Grade 1 or baseline. Participants with <=2 neuropathy may be eligible8. No active uncontrolled infection, severe cardiac dysfunction (i.e. unstable angina, history of myocardial infarction within the past 12 months prior to screening, congestive heart failure > NYHA II, serious cardiac arrhythmia), unstable peptic ulcer, unstable diabetes mellitus or other seriously disabling condition
9. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP <=150/90 mmHg at screening ad no change in hypertensive medication within 1 week before the cycle 1/day1.
10. No prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with another agent agents direct to another stimulatory or co-inhibitory T-cell receptor (eg CTLA-4, OC-40, CD137) or TKI or antibody targeting angiogenesis in the first cohort. Patients who have been treated with autologous tumor cell vaccination (eg. Dendritic cell-based immunotherapy) will be eligible in the first cohort.
11. No major injuries and/or surgery within the past 4 weeks prior to first study dose with incomplete wound healing
12. No active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
13. A female is eligible if she is not pregnant and not breastfeeding. A male

participant who agrees to use contraception as detailed in age and reproductive status breastfeeding

Exclusion criteria

1. presence of clinically relevant treatment-related toxicity from previous chemotherapy, targeted therapy and/or radiotherapy. Note: Participates must have recovered from all AEs due to previous therapies to <=Grade 1 or baseline. Participants with <=2 neuropathy may be eligible
2. active uncontrolled infection, severe cardiac dysfunction (i.e. unstable angina, history of myocardial infarction within the past 12 months prior to screening, congestive heart failure > NYHA II, serious cardiac arrhythmia), unstable peptic ulcer, unstable diabetes mellitus or other seriously disabling condition
3. prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with another agent agents direct to another stimulatory or co-inhibitory T-cell receptor (eg CTLA-4, OC-40, CD137) or TKI or antibody targeting angiogenesis in the first cohort. Patients who have been treated with autologous tumor cell vaccination (eg. Dendritic cell-based immunotherapy) will be eligible in the first cohort.
4. concomitant administration to any other experimental drugs under investigation <= 4 weeks prior to first admission of pembrolizumab- lenvatinib

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):	05-03-2021
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:	LENVIMA, KISPLYX
Generic name:	Lenvatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-02-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-11-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	08-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2019-002560-28-NL
CCMO	NL71641.031.19