A randomized, open-label phase II/III study with dendritic cells loaded with allogeneic tumour cell lysate (PheraLys) in subjects with mesothelioma as maintenance treatment (MesoPher) after chemotherapy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON55474

Source
ToetsingOnline

Brief title
DENIM (DENdritic cell Immunotherapy for Mesothelioma)

Condition

- Mesotheliomas

Synonym
asbestos cancer, malignant pleural mesothelioma

Research involving

Human

Sponsors and support

Primary sponsor: Amphera B.V.
Source(s) of monetary or material Support: European Committee

Intervention

Keyword: allogeneic tumour cell lysate, dendritic cell immunotherapy, maintenance therapy, mesothelioma

Outcome measures

Primary outcome

The primary endpoint of the study is the overall survival. Overall survival

will be determined as the time from randomization until death. For subjects

who are alive at the end of the study or lost to follow-up, OS will be censored

on the last date when subjects are known to be alive.

Secondary outcome

• the estimated survival rate at 12 and 18 months after randomization will be

determined with the Kaplan Meier analysis.

• Progression-free survival (PFS), including symptomatic progression-free

survival. The time of the first CT scan showing progression will define the end

of the PFS.

• Overall response rate and duration of response.

Overall response rate is defined as the proportion of subjects with confirmed

CR or PR on CT scans, if possible measured following modified RECIST criteria.

• Change in quality of life: the European Organization for Research and

Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and its

lung cancer (LC)-specific module EORTC QLQ - LC13 will be used to evaluate

quality of life. Measures of QoL will be compared to baseline and changes over time and compared to each other.

• safety and tolerability of MesoPher: adverse events and serious adverse events, including local and systemic injection site reactions, laboratory assessments, electrocardiogram, vital signs, physical examination, and ECOG performance status.

Study description

Background summary

Malignant mesothelioma is a fatal disease with median survival time from first signs of illness to death around 12 months. A chemotherapy regimen consisting of a combination of pemetrexed and cisplatin or carboplatin is considered standard of care. The survival benefit of treatment with pemetrexed/cisplatin is around 3 months compared to cisplatin alone. Thus there is an unmet need for treatment.

The immune system plays a major role in all malignant diseases. Especially in mesothelioma, immune suppression induced by the tumor is high.

Dendritic cells can be loaded a lysate of tumor material of the patient itself (autologous dendritic cell-therapy), with synthetic peptides coding for parts of tumor-associated antigens, or with other sources of tumor-specific antigens (allogeneic dendritic cell-therapy).

MesoPher:
Amphera has developed 5 well-characterized clinical grade human malignant mesothelioma cell lines as an allogeneic source for the preparation of a tumor cell-lysate. These 5 cell lines were selected based on distinctive tumor- and immune-profiles in patients and represent cell lines generated from tumor material with opposing immune properties. Thus a wide variety of tumor associated antigens is present.

This lysate *PheraLys* is used to load dendritic cells of a subject with malignant mesothelioma ex vivo. In this way a dendritic cell immunotherapeutic product is prepared with the patient*s own dendritic cells exposed to an allogeneic source of tumor associated antigens, outside of the immunosuppressive environment in the patient. The lysate of these 5 cell lines

PheraLys is considered a key intermediate. The mature dendritic cells loaded with PheraLys is the drug substance *MesoPher*.

The advantages of PheraLys over loading dendritics cells with autologous tumor source are:
-unlimited access to tumor associated antigens
-no distressful, painful and risky tumor material resection from the patient
-immediate availability, superior quality and reliable comparative analysis of clinical outcome facilitated

Previous studies have shown that PheraLys is well tolerated. This study aims to evaluate its effects on overall survival.

Study objective

The primary objective of this study is to evaluate the overall survival (OS) rate (determined from the time of randomization in the study) of subjects who receive dendritic cell immunotherapy with MesoPher plus best supportive care (BSC) compared to BSC alone.
Secondary objectives:
• to evaluate the overall survival rate at 12, and 18 months after randomization, in subjects who receive dendritic cell immunotherapy with MesoPher plus BSC compared to BSC alone.
• to evaluate progression free survival in subjects who receive dendritic cell immunotherapy with MesoPher plus BSC compared to BSC alone.
• to evaluate the overall response rate and duration of response in subjects who receive dendritic cell immunotherapy with MesoPher plus BSC compared to BSC alone.
• to evaluate quality of life in subjects who receive dendritic cell immunotherapy with MesoPher plus BSC compared to BSC alone.
• to evaluate the safety and tolerability of dendritic cell immunotherapy with MesoPher.

Exploratory objectives:
• to evaluate the immunogenic effect of dendritic cell immunotherapy with MesoPher.
• to evaluate the effect of dendritic cell immunotherapy with MesoPher on immune-related cytokines in serum.
• to determine the T-cell response towards prespecified tumor antigens in subjects who receive dendritic cell immunotherapy with MesoPher.
• to determine the T-cell response towards the tumor cells included in the cell lines in subjects who receive dendritic cell immunotherapy with MesoPher.
• to determine the T-cell response towards Keyhole Limpet Hemocyanin (KLH) in subjects who receive dendritic cell immunotherapy with MesoPher.
• to evaluate the estimated overall survival rate at 6 and 24 months after randomization, in subjects who receive dendritic cell immunotherapy with

MesoPher plus BSC compared to BSC alone.

Study design

This is an open-label, randomized Phase II/III study in adult subjects with mesothelioma. The study includes a screening phase, a 7-month open-label treatment phase and follow-up evaluations.

Screening:
The signed ICF must be obtained before any study-specific procedures are performed. During the screening phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Schedule of Assessments.

Open-label treatment phase:
After screening subjects will be randomized in a 1:1 ratio to dendritic cell immunotherapy maintenance treatment with MesoPher plus BSC or BSC alone (115 subjects per group). Randomization will be stratified by histology (epithelioid vs other) and study center. Please see 'intervention' for study procedures relating to the treatment.

Computer tomography (CT) scans of the thorax and upper abdomen to assess response to treatment will begin at Week 6 (± 2 days) after start of MesoPher treatment (for subjects in Arm A). This means that the first CT scan will be made approximately 17 weeks after the last dose of chemo therapie. Therefore, for the subjects in group B, the first CT scan will also be made approximately 17 weeks after the last dose of first-line chemo therapie. For both groups CT scans will be repeated every 12 weeks. Blood samples for immuno-monitoring and biomarker studies will be collected from all subjects. Subjects will be monitored for adverse events by physical examinations and laboratory assessments. Organ functioning will closely be monitored. Special attention will be given to immune-related toxicity. One week after the 3rd MesoPher injection subject in Arm A will have a DTH for MesoPher.

Follow-up:
Follow-up evaluations will be performed every 6 weeks after the last dose of study drug in Week 30, with blood collection for safety labs every 6 weeks, and a CT scan of the thorax and upper abdomen to be performed every 12 weeks until the end of the study or disease progression. The last visit will be done at week 102, when a blood sample will be taken for immuno-monitoring and biomarkers. Thereafter, subjects will be followed up at regular intervals according to standard-of-care to collect information on the subjects* survival status. These contacts not part of this study protocol.

Intervention

Subjects in Arm A receive maintenance therapy.
After randomization subjects in Arm A will undergo leukapheresis to obtain monocytes from which dendritic cells will be generated. These dendritic cells will be loaded in vitro with an allogeneic tumor cell lysate (PheraLys). Treatment for subjects randomized to Arm A will start approximately 5 weeks after leukapheresis and within 9 to 13 weeks after the last dose of chemotherapy. They will receive 3 bi-weekly injections with MesoPher in addition to BSC. If not progressive and if the subject is in good clinical condition, another 2 injections will be given 3 and 6 months. Progression will be in comparison to the start of the injections and if the subject is in good clinical condition. Subjects will receive a maximum of 5 doses of MesoPher (Day 1, Day 15, Day 29, Week 18, and Week 30).

Subjects in Arm B will be treated according to the discretion of the local investigator, however maintenance treatment is not allowed.

Study burden and risks

The study is divided in 3 phases: screening, treatment and follow-up.

The screening visit may take up to 4 hours to assess eligibility, demographic and other baseline characteristics. The potential subjects will have a physical examination, review of their medical history, smoking- and ECOG performance status. They will complete Quality of Life questionnaires. Blood will be taken for serology, hematology and chemistry. Urinalyses and if applicable a pregnancy test will be done. Vital signs (blood pressure, pulse rate, respiratory rate, body temperature and pulse oximetry) will be measured, ECG and CT scan performed.

For patients in arm A the treatment phase consists of 14 visits. It starts with leukapheresis, which may take up to one day. Treatment starts 5 weeks later. The patient will come for 5 visits where they receive MesoPher, each followed by one visit where no treatment is given. Extra visits are planned at week 6, 12 and 26. During 6 visits 30 ml blood is taken for either immunomonitoring and biomarkers and 8 times 20 ml for evaluation of the safety of MesoPher. The blood draws will be combined as much as possible to keep the burden for the patient as low as possible. 3 CT scans and 6 ECG's will be made. At almost every visit physical examination will be done.

Patients in arm B do not have leukapheresis and will not receive MesoPher treatment but do attend the last 5 visits of the treatment phase. In this phase they will have 3 CT scans and 3 ECG's.

The follow-up phase consists of 12 visits. During each visit physical exam will be done and every other visit 20 ml blood will be taken for evaluation of the safety of MesoPher. During the last visit 38,5 ml will be taken for immuno-monitoring and biomarkers. In this phase a CT scan will be made every

other visit, 6 in total.

Throughout treatment and follow-up the subjects ECOG performance statuses and Quality of Life questionnaires will be completed.

All patients will receive Best Supportive Care throughout the whole study.

The greatest burden of the study for subjects will be the leukapheresis and the MesoPher injections. Subjects from the AvL-NKI will have to travel to the Erasmus MC, which usually will cost more travel time.
Subjects in arm B will not benefit from study participation, but they also will not have to undergo these procedures.

In the standard care these patients also have regular CT scans. Therefore making CT scans is not mentioned here as an extra burden related to the study.

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

- Signed informed consent within 8 weeks of their last chemo and the date of the informed consent must be such that it is possible to schedule the first study treatment 9 to 13 weeks after their last chemo therapy.
- Histologically confirmed diagnosis of pleural malignant mesothelioma, non-progressive after 4 to 6 cycles with first line chemotherapy with antifolate/cisplatin (as determined by CT scanning)
- Measurable disease on CT scanning, by modified RECIST criteria or RECIST 1.1. In absence of measurable disease a CT scan is needed to evaluate the disease.
- At least 18 years old
- WHO-ECOG performance status of 0 or 1

Exclusion criteria

- any concurrent medical, psychological or psychiatric disease or condition that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study
- serious intercurrent chronic or acute illness such as cardiac or hepatic disease considered by the investigator to constitute an unwarranted high risk for investigational dendritic cell treatment
- known active acute or chronic infection, including human immunodeficiency virus (HIV) and hepatitis B or C
-history of autoimmune disease
-subjects with an organ allograft

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-06-2018
Enrollment:	118
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	21-08-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-04-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2021
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2017-001774-41-NL
CCMO	NL62105.000.17