Adoptive TIL therapy with low-dose PEG-IFNa plus nivolumab in metastatic melanoma

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The primary endpoint is the evaluation of the safety and toxicity of TIL with nivolumab and, thereafter, the safety and toxicity of the combination of PEG-IFNa, nivolumab plus TIL. Safety and toxicity will be evaluated according to CTCAE 4.0...

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

Summary

ID

NL-OMON56101

Source
ToetsingOnline

Brief title
ACTME

Condition

- Metastases

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Imaginab

Intervention

Keyword: immuno-PET, melanoma, nivolumab, PEG-IFNa, TIL

Outcome measures

Primary outcome

Evaluating the safety and toxicity of first TIL and nivolumab and later of the combination of TIL, PEG-IFNa and nivolumab based on the CTCAE 4.0 criteria.

Secondary outcome

Secondary objectives include the evaluation of the disease control rate according to RECIST 1.1 criteria and immune response criteria (irRC), progression-free survival (PFS), overall survival (OS), and quality of life.

- Potential working mechanisms of the different treatment compounds will be studied in PBMCs of the patients

- We will investigate a prognostic biomarker profile while investigating amongst others the blood counts and values, markers on the infused TIL*s, changes in the PBMCs and responses on previous treatments

- To find potential differences between the patients that have a clinical response and/or had a clinical response in the past on immunotherapy with immunomonitoring of the infusion T cell product

- To determine whether there is a potential correlations between the clinical response and hypothesis related immune parameters in the patient*s tumor material, blood, serum and the TILs used for infusion

- To study differences in immunological characteristics between CD8-rich and CD8-poor metastases within a patient detected using CD8-immunoPET/CT, including differences between TIL derived from both locations.

- To describe the clinical response to ACT in relation to [89Zr]Zr-crefmirlimab

berdoxam uptake on a lesion level.

- To study if [89Zr]Zr-crefmirlimab berdoxam uptake in non-affected tissues is

related to immune-related adverse events caused by ACT.

Study description

Background summary

The number of people diagnosed with melanoma has increased significantly in recent years. Many patients already have advanced stages of melanoma at the moment of diagnosis, which limits the survival. Despite the fact that a number of drugs have been approved for the treatment of advanced melanoma, there is still a need for new treatments for this disease. Patients with an irresectable stage III or metastatic stage IV melanoma have a very poor prognosis with a median survival of 6-9 months. The patients participating in this trial have already had progressive disease on the standard lines of treatment.

In 2011, we published the results of our clinical study in patients with metastatic skin melanoma treated with adoptive T-cell transfusion in combination with low-dose IFNa. This treatment was safe and five out of ten patients treated showed a clinical improvement. The T-cells used for these infusions were PBMC-derived. Afterwards we started to grow T-cells from the tumor, namely tumor infiltrating lymphocytes (TIL). In recent years, we have treated 24 patients with TIL and IFNa. In contrast to the previous 10 patients, 18/24 patients had already been pre-treated with, amongst others, immunotherapy.
Seven out of the 24 (5 of the 18 pre-treated) patients had clinical improvement after T-cell transfusion with IFN-alpha, namely stable disease.
Compared to the Rosenberg protocol used in many other centers/countries (T-cell transfusion in combination with high dose IL-2, chemotherapy and possibly radiation) our protocol is much less toxic. To improve clinical effectiveness, we want to add nivolumab to our schedule.
The majority of the T-cells administered is PD-1 positive. We believe that the clinical benefit of ACT can be increased by combining this with anti-PD1 (nivolumab), as this will increase both the tumor reactivity of the normally occurring tumor infiltrating lymphocytes and that of the adoptively infused T cells.

With this new protocol we aim to solve 4 of the most important aspects curtailing the efficacy of these immunotherapies:

1) the lack of sufficient numbers of activated tumor-reactive T cells in patients by providing ACT
2) the inhibition of T-cell effector function through PD-1 signalling by administration of nivolumab
3) the toxicity of high-dose IL-2
4) long term hospitalization of patients due to the conditioning-regimen used in most ACT protocols by replacing it with low-dose PEG-IFNa treatment.
Notably, PD-1 antibodies in combination with PEG-IFNa at higher and comparable doses has been tested and shown to have an acceptable safety profile. The combination of TIL and IFNa have also been shown to be safe. This suggests that the combination of these three compounds should be feasible.

Finally, in an expansion cohort of 12 patients, we will analyse if ACT derived from CD8-rich metastases show higher (in vitro) antitumor activity than from CD8-poor metastases as determined with CD8-immunoPET/CT imaging.

Study objective

The primary endpoint is the evaluation of the safety and toxicity of TIL with nivolumab and, thereafter, the safety and toxicity of the combination of PEG-IFNa, nivolumab plus TIL. Safety and toxicity will be evaluated according to CTCAE 4.0 criteria.

Secondary endpoints include the evaluation of the disease control rate assessed by physical examination and imaging studies (CT and/or MRI) and will be evaluated according to RECIST 1.1 and immune related response criteria (irRC). Furthermore, overall survival (OS) and progression-free survival (PFS) will be evaluated and immune related parameters will be analysed. The CD8-immunoPET/CT will be used to study the heterogeneity in CD8 T cell infiltration in the different metastases within a patient.

Study design

Is a prospective, single centre, investigator initiated, phase I/II clinical trial.

Intervention

Phase 1, Cohort 1 (n=9): Adding TIL therapy to anti-PD1 immunotherapy. The TIL will be added 4 weeks after the first nivolumab infusion (on the same day as the third nivolumab infusions). TIL will be given three times, three-weekly.

Phase 1, Cohort 2 (n=9): Adding PEG-IFNa to the treatment with TIL and nivolumab immunotherapy. PEG-IFNa will be added 3 weeks after the first nivolumab administration. Thereafter, PEG-IFNa will be continued for 11 weeks in total. If no trSAE occur during the first treatment cycle, within a month

after ending the first cycle a second cycle can be given.

Phase 2 (n=25, including the 9 patients that were already treated in phase 1 cohort 2): Patient will be treated with TIL, PEG-IFNa and nivolumab. In this phase of the trial we will use the international standard dosing of nivolumab: 480mg every four weeks. Whether the second treatment cycle will be given depends on the effectiveness of the treatment. If the tumor has progressed of a complete response occurs, the second treatment cycle will not be given. Finally, in an expansion cohort of 12 patients, we will analyse if ACT derived from CD8-rich metastases show higher (in vitro) antitumor activity than from CD8-poor metastases as determined with CD8-immunoPET/CT imaging.

Study burden and risks

The risk of participating in the trial is the toxicity of TIL and nivolumab, with or without the combination low dose PEG-IFNa. So far there are two publications showing that the combination of PEG-IFNa in the same or higher dose as we use is well tolerated in combination with nivolumab. Furthermore, our own research groups and recently another group has shown that the combination of IFN-alpha with TIL is also well tolerated. Therefore, we will first start with the combination TIL and anti-PD1 in 9 patients to investigate the safety of this combination.
In all patients participating in this trial tissue will be obtained by means of a (small) surgical procedure. If possible, tissue will be taken again after the cycle(s) have been completed. The surgical procedure can be painful and in rare cases there may be bleeding and/or infection. There are no known side-effects from the immuno-PET scan.

The appointments for TIL and anti-PD1 treatment are combined as much as possible. As the second TIL administration falls between two nivolumab infusions, patients will therefore have to come to the hospital extra for this. Two hospital visits will be omitted in the phase II part of the trial, by using the international standard nivolumab dose of 480mg every four weeks.
In addition, extra blood will be taken at fixed time-points. Each cycle includes 7 blood samples, 350ml blood will be taken in total.
The patients who undergo immuno-PET scan wil have an extra appointment for this scan.

Contacts

Public
Academisch Medisch Centrum

Albinusdreef 2 2

2333ZA Leiden 2333 ZA
NL
Scientific
Academisch Medisch Centrum

Albinusdreef 2 2
2333ZA Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >= 18 years.
2. Histologically or cytologically proven metastatic skin melanoma.
3. Melanoma must be at one of the following AJCC 2009 stages:
-Unresectable (or residual) regional metastatic melanoma, i.e. in terms of AJCC 2009 classification unresectable stage III melanoma, or
-Stage IV melanoma, i.e. distant metastatic disease (any T, any N, M1a, M1b or M1c), and normal LDH.
4. Patients with brain metastases have to be neurologically stable for at least 2 months and should not use dexamethasone.
5. Presence of measurable progressive disease according to RECIST version 1.1.
6. Expected survival of at least 3 months.
7. WHO performance status <=1.
8. Within the last 2 weeks prior to study day 1, vital laboratory parameters should be within normal range, except for the following laboratory parameters, which should be within the ranges specified :
Lab Parameter Range
Hemoglobin >= 6,0 mmol/l
Granulocytes >= 1,500/µl
Lymphocytes >= 700/µl

Platelets >= 100,000/µl
Creatinine clearance >= 60 min/ml
Serum bilirubin <= 40 µmol/l
ASAT and ALAT <= 5 x the normal upper limit
LDH <= 2 x the normal upper limit
9. Viral tests:
-Negative for HIV type 1/2, HTLV and TPHA
-No HBV (hepatitis B virus) antigen or antibodies against HBc in the serum
-No antibodies against HCV (hepatitis C virus) in the serum
10. Able and willing to give valid written informed consent.
11. Progressive disease on prior treatment with f.e. BRAF-inhibitors, MEK-inhibitors or immunotherapy, including anti-PD1 treatment. Systemic therapy with BRAF-/MEK-inhibitors must have been discontinued for at least two weeks before start of study treatment. Treatment with immunotherapy must have been discontinued for at least four weeks before start of study treatment.

Exclusion criteria

1. Patients with brain metastases who are neurologically unstable and/or use dexamethasone.
2. Clinically significant heart disease (NYHA Class III or IV).
3. Other serious acute or chronic illnesses, e.g. active infections requiring antibiotics, bleeding disorders, or other conditions requiring concurrent medications not allowed during this study.
4. Active immunodeficiency disease, or autoimmune disease requiring immune suppressive drugs or autoimmune adverse events following treatment with checkpoint inhibitors. Vitiligo is not an exclusion criterion
5. Other malignancy within 2 years prior to entry into the study, except for treated non-melanoma skin cancer and in situ cervical carcinoma.
6. Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study.
7. Lack of availability for follow-up assessments.
8. Pregnancy or breastfeeding.
9. Subjects with a condition requiring systemic chronic steroid therapy (>= 10mg/day prednisone or equivalent) or any immunosuppressive therapy within 14 days prior to planned date for first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids, and adrenal replacement therapy are allowed.
10. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the associated with the participation, study drug administration, or would impair the ability of the patient to receive protocol therapy
11. Known allergy to penicillin or streptomycin (used during the culturing of T cells)

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-07-2018
Enrollment:	58
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pegasys
Generic name:	peginterferon-alpha-2a
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-03-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2024
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	EUCTR2016-004426-41-NL
CCMO	NL64805.000.18