Adoptive TIL therapy plus anti-PD1 in metastatic melanoma

Published: 02-03-2017
Last updated: 12-04-2024

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Ethical review	Not approved
Status	Will not start
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON45469

Source
ToetsingOnline

Brief title
ACTME

Condition

- Metastases

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Bristol-Myers Squibb

Intervention

Keyword: melanoma, TIL

Outcome measures

Primary outcome

The primary objective of this phase I/II clinical trial is to evaluate the

safety and toxicity of ACT plus nivolumab according to CTCAE 4.0 criteria.

Secondary outcome

Secondary objectives include the evaluation of the clinical response according

to RECIST 1.1 criteria and immune related response criteria (irRC) and overall

survival (OS). Clinical benefit is defined as Stable Disease (SD), Partial

Response (PR), or Complete response (CR).

An additional endpoint is to determine the induced immune response in the

patient's blood and serum and in the T cells used for infusion.

Study description

Background summary

Patients with unresectable stage III/IV melanoma have an extremely poor prognosis with a median survival of 6-9 months. Despite development of new drugs and treatment options, further improvement is still necessary. Recently, we published the results of our clinical study in metastatic melanoma patients that were treated by adoptive T-cell transfer (ACT) in combination with low dose interferon-alpha. The treatment was safe and five out of ten treated patients showed clinical benefit.
We previously showed that the majority of the T cells used for adoptive transfer were PD-1 positive. By blocking the interaction of PD-1 and PD-L1 or PD-L2 using the anti-PD-1 antibody nivolumab, the anti-tumor reactivity of T cells can be strongly enhanced. We propose to enhance the clinical benefit of ACT by combining it with nivolumab since this will enhance the tumor-reactivity of both naturally occurring tumor infiltrated as well as adoptively transferred T cells. Importantly, clinical efficacy of anti-PD1 in

ipilimumab-refractory stage IV melanoma patients has been reported, indicating that these checkpoint-blocking antibodies may unleash a different set of tumor-reactive T cells and that ipilimumab-refractory patients may benefit from subsequent ACT plus nivolumab treatment.

Study objective

1. The primary objective of this phase I/II clinical trial is to evaluate the safety and toxicity of ACT plus nivolumab according to CTCAE 4.0 criteria. Toxicity grade 3 or less and SAE related to treatment but that does not result in treatment termination are considered acceptable for continuation of the study.
2. Secondary objectives include the evaluation of the clinical response according to RECIST 1.1 criteria and immune related response criteria (irRC) and overall survival (OS). Clinical benefit is defined as Stable Disease (SD), Partial Response (PR), or Complete response (CR).

Furthermore, immune related parameters will be analyzed in patient*s tumor material, blood and serum and in the TILs used for infusion and correlations with clinical response will be evaluated.

Study design

This is a phase I/II clinical trial.

Intervention

A metastatic lesion will be removed and used to culture tumor-infiltrating T cells and if possible an autologous tumor cell line. Seven days before the first T cell infusion the patients will start with injections of IFN-alpha that will be continued for twelve weeks in total. T cells will be administered as three consecutive infusions with a three week interval. If the patient does nog have progressive disease upon evaluation after the first cycle of three T cell infusions a second cycle of T cell infusions plus interferon-alpha will be administered just like the first cycle.
Four weeks before the start of the first T cell infusion the patient will start with anti-PD1 (nivolumab) treatment every two weeks, this will be continued throughout and between the cycles. If the patient has clinical benefit, nivolumab treatment can be continued for up to two years.

Study burden and risks

The patients will be operated to obtain metastatic melanoma tissue that will be used to culture tumor infiltrating T cells. Before start of therapy 75ml of blood will be drawn for further analysis of immune parameters.
If enough tumor reactive T cells are obtained the actual treatment of the

patients wil consist of three infusions of T cells given with a three week interval. Daily IFN-alpha injections will be initiated one week before the first infusion and continued for a total of twelve weeks. Peripheral venous blood will be drawn at several time points before (75 ml) and after (50 ml each) T cell infusions to monitor the immunological response and to evaluate chemical an hematological parameters. For the first T cell infusion patients will be hospitalized for 24 hours in order to carefully monitor vital functions following T cell transfer. If the first infusion of T cells is well tolerated without any SAE, administration of the following T cells does not require hospitalization but day care will be sufficient.
T cell infusions may induce melanoma associated auto-immune disease such as vitiligo and uveitis, which can be managed adequately with topical corticosteroid treatment.
Side-effects of nivolumab are largely known from clinical trials and clinical practice. Treatment-associated side effects of higher grade according to the common terminology criteria for adverse events are relatively rare. However, new immune-mediated side effects can occur and can affect the skin, liver (hepatitis), kidneys (nephritis), gastrointestinal tract (diarrhea and colitis), lungs (pneumonitis) and endocrine organs (hyperthyroidism, hypothyroidism and hypophysitis).
Despite recent developments with respect to new treatment options including BRAF inhibitors (vemurafenib) and anti-CTLA4 or PD-1 antibodies (ipilimumab, nivolumab), patients with metastatic melanoma still have a poor prognosis and adoptive T cell therapy has been shown to be a good treatment option, resulting in response rates up to 50%. More importantly, the obtained responses after ACT are durable and side effects and treatment burden are limited. Experience with TIL infusion studies, performed in three independent centers abroad (NIH, Bethesda, USA, Sheba Hospital, Israel) and Herlev Hospital, Copenhagen, Denmark) and at the NKI, Amsterdam, shows that the risks related to treatment are very low. The majority of the reported adverse events are attributed to the extensive conditioning regimen and/or high dose IL-2 applied in these protocols. These conditioning or additional treatments are not applied in our protocol which further enhances the safety and low risk of the treatment.
Toxicities attributable to melanoma-reactive T cells may result from reactivity against target antigens present on non-malignant melanocytes and other non-malignant cells. Indeed, melanocyte destruction after ACT has been reported to result in vitiligo. The risk that additional antigens expressed on normal cells are targeted is very low, since we showed that generated melanoma-reactive T cells mainly recognized autologous tumor cells and not partially HLA-matched allogenic melanoma cell lines, indicating that the majority of T cells recognize private melanoma associated antigens. Furthermore, toxicities related to treatment with T cells that lyse off-target tissue has not been observed in our phase I/II trial and is also not reported thus far in patients treated in the US, Israel and Denmark.

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. 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 mol/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. Prior treatment is allowed, including anti-PD1 treatment, but systemic therapy must have been discontinued for at least four weeks before study entry. Radiotherapy and targeted therapy should be discontinued for at least two weeks before study entry.

Exclusion criteria

1. Patients with brain metastases who are neurologically unstable and/or on use of 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. 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.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

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:	Roferon A
Generic name:	Interferon alfa-2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-03-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	22-03-2017
Application type:	First submission
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	NL59778.000.17