# Adoptive TIL therapy plus anti-PD1 in metastatic melanoma

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To evaluate the safety and toxicity of ACT and low-dose IFN-alpha plus nivolumab according to CTCAE 4.0 criteria. Toxicity grade 3 or less and SAE related to treatment but that do not result in treatment termination are considered acceptable for...

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

## Summary

### ID

NL-OMON44437

**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:** anti-PD1, melanoma, TIL

## Outcome measures

### Primary outcome

The primary objective of this phase I/II clinical trial is to evaluate the safety and toxicity of TIL and IFN-alpha plus nivolumab according to CTCAE 4.0 criteria. Acceptable toxicity is defined as *20% of the patients experiencing serious adverse events as a result of study treatment.

### Secondary outcome

Secondary objectives include the evaluation of the clinical response according to RECIST 1.1 criteria and immune response criteria (irRC), progression-free survival (PFS), overall survival (OS), and quality of life. If more than six patients have a clinical response, there is evidence to proceed to phase III at the end of the study.

Furthermore,

* 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

# 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. In this study we will be treating patients who already progressed on the standard treatment lines.
In 2011 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. After this pilot study we treated 22 patients, who were more heavily pre-treated with immunomodulating therapies. In total 6/22 patients showed clinical benefit. From the treatment of 32 patients with interferon-alpha and T-cells we concluded that this combination is well tolerated by our study population.

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-reactiveT cells and that ipilimumab-refractory patients may benefit from subsequent ACT plus nivolumab treatment.

### Study objective

To evaluate the safety and toxicity of ACT and low-dose IFN-alpha plus nivolumab according to CTCAE 4.0 criteria. Toxicity grade 3 or less and SAE related to treatment but that do not result in treatment termination are considered acceptable for continuation of the study.

Secondary objectives include:

* To evaluate of the clinical response according to RECIST 1.1 criteria and immune related response criteria (irRC), overall survival (OS), progression-free survival (PFS) and quality of life. Clinical benefit is defined as Stable Disease (SD), Partial Response (PR), or Complete Response (CR).
* To study the potential working mechanisms of the different treatment compounds
* To establish a possible prognostic biomarker profile
* To perform immunomonitoring on the infusion product
* To analyse potential correlations between the clinical response and hypothesis related immune parameters

**Study design**

The ACTME study is an investigator initiated, single center phase I/II clinical trial for patients with progressive unresectable stage III or stage IV melanoma.

**Intervention**

Eligible patients will undergo surgery, to obtain material of a melanoma metastasis. This material will be used to culture tumor infiltrating lymphocytes (TIL) for the ACT. Before the start of nivolumab, imaging will be performed (CT and/or MRI), to define target lesions according to RECIST 1.1. Two weeks after surgery patients will start with an initial 2 cycles of nivolumab 2-weekly. In the meanwhile the TILs will be cultured.
After an initial 14 days of culturing the obtained TILs will be expanded to large numbers required for infusion using the so called rapid expansion protocol. Once enough TILs have been cultured the patients will start with low dose daily subcutaneous IFN-alpha injections (3 million IU/day) seven days before the first TIL infusion and continue with IFN-alpha injections for a total of eleven weeks. Three infusions of TILs will be administered intravenously with an interval of three weeks. At the day of the first TIL infusion the patients will also receive nivolumab, which will be continued every 2 weeks until progressive or intolerable toxicity for up to two years. At week 9 after the first cycle of three TIL infusions plus nivolumab, the tumor response will be evaluated by CT and/or MRI and will be described according to RECIST 1.1 and immune response criteria (irRC).
An additional cycle of TIL infusions in combination with IFN-alpha and nivolumab will be administered after the first cycle of TIL infusions unless disease progression or complete response is observed during the evaluation of CT/MRI scans at week 9. In patients with a complete regression of all metastases after one cycle of three TIL infusions, additional cycles of TIL infusions are not considered necessary to remain the state of complete clinical remission. After the first cycle of three TIL infusions, when possible, surgery or a biopsy of another metastasis will be performed to culture more TIL and to compare biological and immunological markers before and after treatment.

## Study burden and risks

Eligible patients will undergo surgery to obtain a melanoma metastasis. Prior to the start of nivolumab treatment imaging will be performed. The imaging performed before nivolumab treatment is started will be used to define the lesions at baseline. 75 ml of blood will be drawn before the start of nivolumab and before the start of low-dose IFN-alpha. Two weeks after surgery patients will start with nivolumab infusions and will receive 2 courses 2-weekly before cultured TILs are given, three infusions 3-weekly.
During every visit for TIL infusion physical examination, vital signs, CBC differential and blood chemistry will be performed and 50ml of blood will be drawn.
During one cycle patients will have approximately 12 visits in the hospital, of which only one requires hospitalisation for 24 hours. If the treatment results in an initial clinical response/disease stabilization without indications of SAE related to treatment, the purpose is to give one additional cycle of three TIL infusions similar to the first cycle to obtain further clinical benefit.
Quality of life is already measured in this group of patients by the Dutch Melanoma Treatment Registry as standard of care. We will analyse this data without further burdening the patients.
Side effects of nivolumab are largely known from clinical trials and clinical practice. Treatment-associated side effects of higher grade (grade 3 or 4) according to the common terminology criteria for adverse events (CTCAE) are relatively rare. However, new immune-mediated side effects can occur and affect the skin, liver (hepatitis), kidneys (nephritis), gastrointestinal tract (diarrhea and colitis), lungs (pneumonitis) and endocrine organs (hyperthyroidism, hypothyroidism and hypophysitis).
TIL infusions may induce melanoma associated autoimmune diseases such as vitiligo and uveitis. Uveitis can be managed adequately with topical corticosteroid treatment, vitiligo in most cases is permanent but is related to a better response to treatment.
Possible side effects of interferon-alpha include leucopenia, fever, chills, myalgia, headache, diarrhea and alopecia. But as described by Verdegaal and colleagues the treatment with the combination of tumor specific T cell and low-dose interferon-alpha, similar to the dose used in our current study, is well tolerated.
In our 32 patients treated with low-dose IFNa in combination with TIL, there were no TIL related adverse events and five patients had an IFN-alpha induced grade 3 leukopenia, which was transient and seemed to be related to a better response.
As we mentioned previously in a personal communication with other investigators combining ACT (with toxic lymphodepleting chemotherapy and IL-2) with anti-PD1, the PI stated that they did not observe any toxicity that was substantially different from either TIL therapy or PD1 antibody monotherapy.
We also contacted researchers in Pittsburgh, who investigated the combination of anti-PD1 treatment and high-dose Peginterferon alpha, and concluded that

this combination was well tolerated with no dose limiting toxicities.

Patients with unresectable stage III or stage IV melanoma have a poor prognosis with a median survival of 6-9 months without treatment. In our study we include patients who failed on all regular treatment options, meaning their median survival will be even less. The chance to obtain a further improvement in clinical benefit in these patients, partially justifies for the burden and possible toxicities.
Even though this study mainly focusses on safety and toxicity of a new combination of treatments, nivolumab is already registered for the treatment of metastatic melanoma and treatment with adoptive T-cell transfer and low-dose IFN-alpha has shown promising results in our 32 treated patients. In our study design we have tried to minimalize the extra burden for the patients, by combining treatment dates and moments at which blood will be drawn.

## 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. Progressive disease on prior treatment with f.e. BRAF-inhibitors, MEK-inhibitors or immunotherapy, including anti-PD1 treatment. Systemic therapy 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 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.
9. Subjects with a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment. Inhaled or topical steroids and adrenal replacement steroid doses >10mg daily prednisone equivalent are permitted in the absence of active autoimmune disease
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

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| 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 |

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|---|---|
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Roferon A |
| Generic name: | Interferon alpha-2a |
| Registration: | Yes - NL outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 12-10-2017 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Not approved Date: | 26-10-2017 |
| 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 | NL63381.000.17 |