Multicenter phase I/IIa study using T-cell receptor gene therapy in metastatic melanoma

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To study the safety of the adoptive transfer of autologous T cells modified with a Mart-1 specific TCR in advanced stage (uveal) melanoma patients with disease progression upon standard cancer therapy. In addition, the toxicity according to CTC...

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

Summary

ID

NL-OMON47165

Source
ToetsingOnline

Brief title
T-cell receptor gene therapy in melanoma

Condition

- Ocular neoplasms
- Skin neoplasms malignant and unspecified

Synonym
maligne melanoma, skin cancer, uveal melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Via een grant van het NKI-AVL via Ton

Schumacher.

Intervention

Keyword: immunotherapy, melanoma, TCR gene therapy

Outcome measures

Primary outcome

Safety (CTCAE 4.0) of the TCR treatment

Objective response rate according to RECIST 1.1.

Secondary outcome

1-year progression free survival (PFS) and median overall survival.

Efficacy of induction of tumor specific T cell responses (as measured by the

persistence of MART1 specific T cells in peripheral blood samples at several

time points following adoptive transfer and in tumor biopsies when possible).

Study description

Background summary

Prior preclinical and clinical studies have provided proof for a beneficial effect of T lymphocytes in melanoma and other tumor types. Preclinical mouse models have shown that tumor reactivity can be endowed on non-reactive T cells by the transfer of T cell receptor (TCR) genes. Three phase I studies, using TCRs specific for melanoma antigens, have shown persistence of gene modified cells and a moderate clinical effect.
In this phase I/IIa study we will investigate the safety and efficacy of TCR gene therapy in patients with advanced (uveal) melanoma.

Study objective

To study the safety of the adoptive transfer of autologous T cells modified with a Mart-1 specific TCR in advanced stage (uveal) melanoma patients with disease progression upon standard cancer therapy. In addition, the toxicity according to CTC version 4.0 and response rate according to RECIST 1.1 will be documented.

To study the efficacy of this treatment strategy in inducing tumor-specific T cell immunity as measured by the presence of Mart-1 specific T cells in peripheral blood samples on several time points following adoptive transfer.
To study the objective response rate in this patient population.
To study whether the infusion of MART-1 specific TCR (1D3 HMCys) transduced T cells will lead to systemic release of inflammatory cytokines.
To study the progression-free survival and overall survival.

Study design

HLA-A2 positive patients will undergo leukapheresis to obtain T cells for transduction with a Mart-1 specific TCR (1D3 HM Cys). Patients will receive a non-myeloablative lymphocyte-depleting preparative regimen consisting of cyclophosphamide (30 mg/kg/day x 2 days i.v.) and fludarabine (25 mg/m2/day IV x 5 days). Following this regimen, patients will receive an intravenous adoptive transfer of a maximum of 2.5 x 10^10 transduced T cells.
Supportive care consisting of blood or platelet transfusions is given until spontaneous hematopoietic recovery occurs. A complete assessment of evaluable lesions will be conducted 4 weeks after cell infusion and periodically after that to obtain best objective response by RECIST.
At the first time point of documented response and/or at time of (proven) progression after treatment additional tumor biopsies will be taken for HLA expression and melanoma antigens expression.
Besides safety and efficacy, special focus will be on logistics and timing: planning of leukapheresis, admission to the hospital for start of chemotherapy, timing of transduced T cell infusion, and release from hospital.

Intervention

Eligible patients will undergo leukapheresis to isolate autologous T cells. These T cells will be transduced with a retroviral vector encoding the 1D3 HM Cys TCR, and subsequently expanded during short-term ex vivo culture. Upon pre-treatment with nonmyeloablative chemotherapy, patients will receive the adoptive transfer of autologous, TCR transduced T cells.

Study burden and risks

Patients with metastatic (stage IIIc-IV) melanoma have an extremely poor prognosis with a median survival of 9 months. In the past 30 years little if any improvement in survival has been reached despite the development of many new drugs and/or treatment options. Recently, however, two new drugs have been approved by the FDA for the treatment of metastatic melanoma based on survival benefit. Vemurafenib, an oral mutated BRAF inhibitor induces a response rate in about 50% of patients. Unfortunately, the median duration of this response is between 5-6 months. Eventually, all tumors will become resistant to vemurafenib. Ipilimumab, a fully human monoclonal antibody is directed against

CTLA4 on activated T-lymphocytes, has shown to augment melanoma-specific immunity. Ipilimumab induces objective responses in 10% of patients. However, at two years and beyond about 20% of patients are still alive. Despite these important new developments, there is still lots of room for improvement of the treatment of stage IIIc-IV melanoma patients.
Adoptive transfer of TCR gene modified cells is a promising new treatment modality and an effective strategy to create a large pool of tumor reactive T cells and has shown clinical responses in three recent trials (13-45%).
Although this treatment and toxicity has been demonstrated to be well manageable, common toxicities from non-myeloablative chemotherapy (transient bone marrow suppression requiring red cell and platelet support, increased chance of bacterial, viral and fungal infections, requiring antibiotics) may or will occur. Due to the infusion of Mart-1 specific T cells, patients may develop signs of melanoma associated autoimmune diseases such as vitiligo, hearing loss and uveitis. The latter two, which are the more serious side effects, have been shown to respond promptly to local corticosteroid treatment. However, the fact that these patients may have a substantial chance of durable objective responses, which otherwise would not occur, justifies for the burden and possible toxicities.

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

Patients must be >= 18 years of age.
Patients must have inoperable stage IIIc or stage IV cutaneous melanoma (AJCC), including ocular or mucosal melanoma, progressing after standard of care therapy
Patients must be HLA-A2 positive.
The primary tumor and/or metastasis have to be positive for MART-1
Patients must have a clinical performance status of ECOG 0 or 1.
Patients of both genders must be willing to practice a highly effective method of birth control during treatment and for four months after receiving the preparative regimen.
Patients must be able to understand and sign the Informed Consent document.

Exclusion criteria

Life expectancy of less than three months.
Requirement for systemic steroid therapy.
Patients who have a history of CNS metastases.
Patients with pleural effusion or ascites.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2012
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	22-03-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-09-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	26-02-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-05-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-04-2018
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	EUCTR2011-002941-36-NL
CCMO	NL37327.000.11