Adoptive therapy with TCR gene-engineered T cells to treat patients with MAGE-C2-positive melanoma and head and neck cancer.

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This study has been transitioned to CTIS with ID 2024-516922-70-00 check the CTIS register for the current data. Phase I• Primary objectives:o To study the safety and feasibility of AT with autologous MC2 TCR T cells, combined with epigenetic drug…

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

Summary

ID

NL-OMON52657

Source
ToetsingOnline

Brief title
MAGE-C2 TCR T cell therapy

Condition

- Ocular neoplasms
- Miscellaneous and site unspecified neoplasms benign
- Skin neoplasms malignant and unspecified

Synonym
head and neck squamous cell carcinoma, maligne melanoma, skin cancer, uveal melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,KWF

Intervention

Keyword: head and neck cancer, Immunotherapy, melanoma, TCR gene therapy

Outcome measures

Primary outcome

Primary endpoints:

Phase I

• AEs according to CTCAE 5.0

• Recommended Phase II dose

• Feasibility to deliver this sequence of treatment

Phase II

• Objective response rate according to RECIST v1.1

• PFS

• OS

Secondary outcome

Secondary and exploratory endpoints

Phase I & II

• Persistence and function of MC2-specific T cells in peripheral blood.

• Systemic release of inflammatory cytokines after administration of autologous

MC2 TCR T cells

• Immune parameters, in particular T cell parameters, in blood and tumor

tissues (when available) prior to and during treatment.

• Global DNA hypomethylation and histone acetylation in PBMCs after epigenetic

treatment and administration of autologous MC2 TCR T cells

Study description

Background summary

• In patients with advanced melanoma and other tumor types, prior clinical studies have shown efficacy of T lymphocytes directed towards tumor antigens. To this end, tumor reactivity can be imposed by the transfer of T cell receptor (TCR) genes into previously non-reactive T cells.
• MAGE-C2 (MC2) is a Cancer Germline Antigen (CGA) that is highly expressed in melanoma and head and neck squamous cell carcinoma (HNSCC), but not in normal mature tissues. MC2 can evoke clinically effective T cell responses, as demonstrated in previous vaccination studies.
• In this phase I/IIa study, we will investigate the safety of adoptive T cell therapy (AT) with T cells gene-engineered to express MC2-specific TCRs in patients with advanced melanoma or HNSCC.

Study objective

This study has been transitioned to CTIS with ID 2024-516922-70-00 check the CTIS register for the current data.

Phase I
• Primary objectives:
o To study the safety and feasibility of AT with autologous MC2 TCR T cells, combined with epigenetic drug treatment, in patients with advanced melanoma or HNSCC. Adverse events (AEs) will be documented according to CTCAE v5.0.
o To define the maximum tolerated dose (MTD) of MC2 TCR T cells in the combination treatment.
• Secondary and exploratory objectives:
o To study presence and function of MC2 TCR T cells in peripheral blood samples after treatment.
o To study the systemic release of inflammatory cytokines after administration of autologous MC2 TCR T cells.
o To study immune parameters, in particular T cell parameters, in blood and tumor tissues (when available) prior to and during treatment.
o To document the induction of global DNA hypomethylation and histone acetylation in peripheral blood mononuclear cells (PBMC) by epigenetic drug treatment.

Phase II
• Primary objectives:
o To assess the efficacy of AT with autologous MC2 TCR T cells at MTD, combined with epigenetic drug treatment, in patients with advanced melanoma or HNSCC. Tumor response will be evaluated using RECIST v1.1.
• Secondary objectives:
o To determine the following outcomes in patients treated with MC2 TCR T cells at MTD:
- Progression free survival
- Duration of response
- Overall survival
• Exploratory objectives:
o To study presence and function of MC2 TCR T cells in peripheral blood samples after treatment.
o To study the systemic release of inflammatory cytokines after administration of autologous MC2 TCR T cells.
o To study immune parameters, in particular T cell parameters, in blood and tumor tissues (when available) prior to and during treatment.
o To document the induction of global DNA hypomethylation and histone acetylation in PBMCs by epigenetic drug treatment.

Study design

Study design
• This is a single institution phase I/IIa trial consisting of an accelerated titration phase I design and a subsequent single arm (2-stage) phase IIa study. In the phase I part, the recommended T cell number for phase IIa will be determined.
• Eighteen patients with advanced melanoma or HNSCC, a HLA-A2 genotype and MC2-positive tumors will be included in the study.
• Screening will consist of genotyping for HLA-A2 and MC2 immunohistochemistry on tumor tissue.
• Prior to T cell transfer (day 0), patients will be treated with the epigenetic drugs valproic acid (VP, dose 50 mg/kg/d, 7d; days -9 to day -2) and 5-azacitidine (AZA, dose 75mg/m2/d, 7d; days -9 to day -2).
• Phase I: patients will be treated with one single intravenous administration of TCR T cells at 5 different escalated doses of 5x10e7, 5x10e8, 5x10e9, 1x10e10, and the total number of cultured TCR T cells (i.e. usually 1 - 5 x10e10 TCR T cells).
• In case of any grade 3 AE in the accelerated titration phase, the phase I part will continue in a classical 3x3 phase I design with semi-logaritmic dose escalation.
• In case 1 (or 3) patient(s) has(ve) been treated in a particular dose level, but not before 3 weeks after treatment of the (3rd) patient, AEs will be evaluated and the project team (PI, co-investigator, project leaders) together IDMC will decide whether the trial will continue to the next dose level.
• If dose limiting toxicities (DLT) are observed in 2 out of 6 patients (3x3

extended cohort), the previous dose level will be the maximum tolerated dose (MTD) (see section 4.4).
• Phase IIa: Simon 2-stage design starts with 6 patients at MTD and at 1 clinical response will be extended with 6 additional patients.
• Clinical response evaluation according RECIST v1.1 will be performed at 8 and 12 weeks after T cell infusion and every 3 months thereafter.
• In both bhase I and IIa, peripheral persistence, differentiation state and tumor recognition of peripheral and intra-tumoral TCR T cells will be evaluated, as well as additional immune and T cell parameters in blood and tumor tissue.

Intervention

Autologous T cells, obtained by leukapheresis, will be transduced with a retroviral vector encoding the MC2 TCR. Subsequently, these TCR T cells will be expanded ex vivo in the presence of defined cytokines. Following pre-treatment with epigenetic drugs, TCR T cells will administered intravenously. For safety measures, AEs will be documented according to CTCAE 5.0. Tumor response will be evaluated using RECIST v1.1. Tumor biopsies will be taken before treatment (to assess MC2 expression) at 4 weeks after MC2 TCR T cell infusion and at progressive disease to evaluate therapy induced changes of the tumor microenvironment. An optional tumor biopsy may be taken after epigenetic pre-treatment and prior to MC2 TCR T cell infusion to document the in vivo upregulation of the MC2 expression.

Study burden and risks

For patients included in this phase I/IIa trial, no standard therapies are available in the Netherlands.
Previous trials have shown efficacy of AT in several patient populations. In patients with metastatic melanoma or synovial carcinoma, AT with a CGA NY-ESO TCR T cells has shown very limited AEs and significant objective clinical responses of 55 and 61%, respectively.[1, 2] In patients with multiple myeloma, infusion of NY-ESO TCR T cells 2 days after an autologous stem cell transplant (preceded by Melphalan) resulted in a clinical response of 80%, thereby inducing various serious AEs (SAEs), which were reversible. In patients with melanoma, AT using autologous TCR T cells with affinity enhanced TCRs for MAGE-A3 has shown clinical responses, but also fatal on- and off target toxicities as a result of either targeting a common epitope of the MAGE-A antigen superfamily or a TCR with a non-restricted binding motif. In the current study, these (S)AEs are not expected as the MC2-specific TCR has a restricted binding motif without enhanced affinity.
Here we have chosen to target MAGE-C2 treat is expessed in melanoma and HNSCC, but not in healthy tissues, therfore the risk of 'on target' toxicity is expected to be low. The MAGE-C2-specific TCR (TCR16) has a stringent bindings motief, and is noy affinity enhanced, therefor the risk of off target toxicity

is expected to be low. Nevertheless, in case patients may experience a cytokine release syndrome (CRS) with severe symptoms in the current study, patients will be treated with high dose corticosteroids, the anti-IL6R antibody tocilizumab [6], and the anti-CD52 antibody alemtuzumab, depending on the severity of the symptoms.
In addition, the doses of the administered epigenetic drugs are well tolerated and are only associated with mild transient leucopenia and neutropenic fever.
In this patient population, the potential burden and AEs are justified by the substantial chance of (durable) tumor responses as a result of the proposed treatment.

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, including ocular or mucosal melanoma, progressing after standard of care therapy, or recurrent/metastatic HNSCC
Patients must be HLA-A2 positive.
The primary tumor and/or metastasis have to be positive for MAGE-C2
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 active/symptomatic CNS metastases.
Patients with pleural effusion or ascites.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-10-2020
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	29-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-09-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-06-2024
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
EU-CTR	CTIS2024-516922-70-00
EudraCT	EUCTR2019-000657-31-NL
ClinicalTrials.gov	NCT04729543
CCMO	NL69911.000.19