

# mHag UTA2-1 loaded PD-L silenced DC vaccination after allo SCT

No registrations found.

<b>Ethical review</b>	Positive opinion
<b>Status</b>	Pending
<b>Health condition type</b>	-
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON22602

### Source

Nationaal Trial Register

### Brief title

UTA2-1DC

### Health condition

Multipel Myeloma (MM), Chronic Lymphocytic Leukemia (CLL), Non Hodgkin Lymphoma (NHL); Acute Myeloide Leukemie (AML)

## Sponsors and support

**Primary sponsor:** VU University Medical Center

**Source(s) of monetary or material Support:** ZON-MW

## Intervention

## Outcome measures

### Primary outcome

- To evaluate the toxicity and feasibility of a preemptive minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination
- To evaluate the effect of minor H ag UTA2-1 peptide-loaded, PD-L1/2 silenced donor DC

vaccination on the immune status of the recipient in correlation with the induction of UTA2-1 specific T cell responses after vaccination.

## **Secondary outcome**

-to evaluate the efficacy of the minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination to induce a GvT effect.

# **Study description**

## **Background summary**

Background of the study:

Allogeneic stem cell transplantation (allo-SCT) is the only curative option for a number of hematological malignancies including acute and chronic leukemia, lymphoma and myeloma, due to a donor T cell-mediated Graft versus Tumor effect (GvT). Unfortunately sustained complete remissions are only achieved in 30-60% of patients depending on disease category and disease characteristics. Furthermore allo SCT can cause severe and sometimes fatal side effects mainly due to Graft versus Host Disease (GvHD). Therefore strategies are urgently needed to improve the efficacy and safety of allo SCT. An attractive strategy to improve the safety and efficacy of allo SCT is targeting donor T cells towards hematopoietic-system-specific minor histocompatibility antigens (minor Hags). We have recently discovered the UTA2-1, a novel HLA-A2 restricted hematopoietic minor Hag antigen with a ~60% population frequency and high expression in multiple myeloma (MM), B cell malignancies and in acute myeloid leukemia (AML). We have recently shown that after a failed low dose Donor lymphocyte infusion (DLI) a second low dose DLI combined with vaccination of patients with DCs loaded with the peptides of minor Hags, including UTA2-1, is clinically feasible, safe and induces peptide specific T cell responses, but in a minority of patients. Furthermore these responses were not sufficiently robust to induce meaningful clinical responses in these DLI non responder patients, indicating that the vaccination strategy needs to be improved toward achieving better immune responses. Recently it became clear that the DC antigen presentation capacity can be significantly improved by knocking out the two important inhibitory molecules, PD-L1 and PD-L2. We therefore now propose an improved strategy, in which UTA2-1 positive patients, who underwent an allo transplantation from an UTA2-1 negative donor will be vaccinated with UTA2-1 loaded, PD-L1/L2 knocked out donor DCs, in a pre-emptive fashion, just after stopping the GvHD preventive treatment, where the tumor load is very low or barely detectable.

Objective of the study:

- To evaluate the toxicity and feasibility of a preemptive minor H ag UTA2-1 peptide-loaded,

PD-L silenced donor DC  
vaccination.

- To evaluate the effect of a minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination on the immune status of the recipient in correlation with toxicity and response

Study design:

A single center phase I/II trial with the primary goal to evaluate the safety and efficacy of a preemptive vaccination strategy with UTA2-1 loaded, PDL1/L2 silenced DCs after donor stem cell transplantation.

Study endpoints are CTC toxicity grade 3 and 4 , b. Acute and chronic GvHD, c. Clinical response and duration of response , d. Immune effects including minor H ag UTA2-1-specific CD8+ T cell responses. For clinical efficacy response criteria related to the different hematological malignancies will be applied.

Study population:

The treatment will be applied in patients with MM, chronic lymphocytic leukemia (CLL) B-cell Non-Hodgkin Lymphomas

and patients with acute leukemia (AML) who were previously treated with an allogeneic, UTA2-1 mismatched donor SCT. Hence, patient and donor should be both positive for HLA-A2.1; but they should display an incompatibility in the UTA2-1 antigen in the GvT direction ( patient is positive and donor is negative for this antigen). Patients with  $\geq$  grade 2 GVHD, extensive chronic GVHD and patients being treated with corticosteroids, chemotherapy or other immunosuppressive medications will be excluded.

Intervention (if applicable):

Suitable patients will be vaccinated with ex vivo cultured, UTA2-1 peptide loaded donor DCs that are furthermore silenced for PD-L1/L2 molecules via siRNA transfection DCs will be administered at a total dose of minimal 45 and maximal  $90 \times 10^6$  DCs, in 3 servings with two weeks intervals. Patients will be examined for the occurrence of side-effects, anti-tumor effect, influence on the immune system and the development of specific immune responses against the UTA2-1 antigen. Upon positive results of the research this vaccination strategy can become a standard treatment for the treatment of appropriate patients with malignant hematologic diseases, with the ultimate aim to increase the chances of cure.

Primary study parameters/outcome of the study:

-To evaluate the toxicity and feasibility of a preemptive minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination  
- To evaluate the effect of minor H ag UTA2-1 peptide-loaded, PD-L1/2 silenced donor DC vaccination on the immune

status of the recipient in correlation with the induction of UTA2-1 specific T cell responses after vaccination.

Secondary study parameters/outcome of the study (if applicable):

-to evaluate the efficacy of the minor H ag UTA2-1 peptide-loaded, PD-L silenced donor DC vaccination to induce a GvT effect.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):

Burden associated with participation:

The procedures include a total of 3 DC vaccinations, 3 times repeated with an interval of 2 weeks between each vaccination: blood sampling for evaluation of the immune effects: 40 ml of blood will be obtained at week -2 and at weeks 0, 1, 2, 4, 6, 10, 14 and 20 after the first vaccination. In addition, routine investigations at the outpatient clinic weekly or two weekly are performed to monitor the general physical status and tumor load of the patients. This may include bone marrow investigations, immunophenotyping and imaging techniques like CT scans, MRI and/or PET scans.

Risks associated with the investigational product.

The major potential risk in therapeutic interventions after allo SCT is the induction of GvHD. In our two previous phase I/II trials we combined unloaded or peptide loaded host or donor DC vaccinations with DLI. No GvHD or other toxicity was recorded in these trials. Since in the current trial we will use only hematopoietic restricted minor H ag UTA2-1 loaded on donor DCs in a preemptive way, thus without combining the vaccination with DLI, we expect no GvHD associated with DC vaccinations. However, in this trial the donor DCs will be silenced for inhibitory molecules PD-L1 and PD-L2. Therefore (GvHD related) toxicity is still one of the major endpoints of the study since such a PD-L silenced, peptide loaded donor DC vaccination has never been applied before.

## **Study objective**

The goal of the proposed study is to test the null hypothesis that vaccination will not boost the cytotoxic T cell responses against UTA2-1 in >20% of the patients.

## **Study design**

every 2 weeks until day +94, thereafter every month until 12 months, at progression and follow-up every 2 months for 5 years after registration

## **Intervention**

Patients will be vaccinated with ex vivo cultured, UTA2-1 peptide loaded donor DCs that are

furthermore silenced for PD-L1/L2 molecules via siRNA transfection DCs will be administered at a total dose of minimal 45 and maximal  $90 \times 10^6$  DCs, in 3 servings with two weeks intervals.

## Contacts

### Public

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### Scientific

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## Eligibility criteria

### Inclusion criteria

1. Patients with Multiple Myeloma (MM) or Chronic Lymphocytic Leukemia (CLL) or non hodgkin lymphoma (any grade) or acute myeloid leukemia (AML)
2. Recipient and donor have a mismatch in UTA2-1 mHag in the Graft versus Tumor (GvT) direction (recipient UTA2-1 positive, donor UTA2-1 negative).
4. Recipient and donor are positive for HLA-A\*0201
5. Age 18-75 years
6. Absence of acute GvHD > grade 2 or extensive chronic GvHD
7. No treatment with immunosuppressive drugs such as prednisone, cyclosporine A and MMF at least 4 weeks prior to planned vaccination date.
8. WHO performance 0-2
9. Absence of severe cardiac hepatic, renal, or metabolic disease
10. Written informed consent

### Exclusion criteria

1. WHO performance 3-4
2. Presence of severe cardiac hepatic, renal, metabolic disease
3. Rapidly progressive disease,

4. Life expectancy < 3 months

## Study design

### Design

Study type:	Interventional
Intervention model:	Other
Allocation:	N/A: single arm study
Masking:	Open (masking not used)
Control:	N/A , unknown

### Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-08-2019
Enrollment:	17
Type:	Anticipated

### IPD sharing statement

**Plan to share IPD:** Undecided

## Ethics review

Positive opinion	
Date:	01-07-2019
Application type:	First submission

## 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
NTR-new	NL7846
Other	METC CCMO : (NL66760.000.18)

## Study results