



Clinical trial results:

PSCT16 Study: Vaccination with minor histocompatibility antigenloaded donor DC vaccines to boost graft-versus-tumor immunity after allogeneic stem cell transplantation

PSCT19 Study: Vaccination with PD-L1/L2-silenced minor histocompatibility antigen-loaded donor DC vaccines to boost graft-versus-tumor immunity after allogeneic stem cell transplantation (a phase I/II study)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-002879-34 |
| Trial protocol | NL |
| Global end of trial date | 06 October 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 13 December 2021 |
| First version publication date | 13 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | PSCT16 & PSCT19 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Radboud University Medical Center Nijmegen |
| Sponsor organisation address | Geert Grooteplein Zuid 8, Nijmegen, Netherlands, 6500 HB |
| Public contact | Trialbureau Hematologie-Oncologie, Radboud University Nijmegen Medical Centre, 31 243614794, studies.hemat@radboudumc.nl |
| Scientific contact | Trialbureau Hematologie-Oncologie, Radboud University Nijmegen Medical Centre, 31 243614794, studies.hemat@radboudumc.nl |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 October 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 October 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary Objective PSCT16:

- to evaluate the safety and toxicity of pre-emptive administration of donor DCs electroporated with mRNA encoding hematopoietic-restricted MiHA.
- to evaluate the capability and strength (i.e. % MiHA-specific T cells within total CD8+ T population) of MiHA mRNA-loaded donor DC to induce in vivo expansion of CD8+ memory T cells against hematopoietic-restricted MiHA.
- to evaluate the immune response to KLH

Primary Objective PSCT19:

The study is designed as a phase I/II study in 10 patients who had undergone HLA-matched allogeneic SCT:

- to evaluate the toxicity of pre-emptive administration of PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiHA.
- to evaluate the capability and strength (i.e. % MiHA-specific T cells within total CD8+ T population) of MiHA mRNA-loaded donor DC to induce in vivo expansion of CD8+ memory T cells against hematopoietic-restricted MiHA.
- to evaluate the immune response to KLH

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments), or the laws and regulations of the country whichever provides the greatest protection of the patient. The design of this study follows current views of the European Medicine Agency (EMA) for Advanced Medicinal Therapy Products (AMTP) in general and for Cellular Advanced Therapeutics (CAT) in particular.

The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice and Good Manufacturing Practice issued by the European Union.

The protocol has been approved by the Central Committee on Research Involving Human Subjects

Background therapy:

No background therapy was given

Evidence for comparator:

Not applicable

| | |
|---|--------------|
| Actual start date of recruitment | 03 June 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 16 |
|--------------------------------------|-----------------|

| | |
|------------------------------------|----|
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 13 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Prior to allogeneic stem cell transplantation HLA-A2+ and HLA-B7+ recipient donor pairs were asked permission for genotyping for MiHA mismatches for HA-1, LRH-1 and ARHGDIB. Patients with MiHA mismatches in the graft-versus-tumor direction, who met the inclusion criteria were asked informed consent for this dendritic cell vaccination study

Pre-assignment

Screening details:

For the pilot study (PSCT16), 17 patients were screened, of whom 4 included. One patient was withdrawn because he did not fulfill the criteria. For the PSCT19 study, 48 patients were screened, of whom 12 included. The screening criteria can be found in the protocols.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Overall trial |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pilot PSCT16 study |

Arm description: -

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MiHA mRNA-electroporated mature DCs |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20x10⁶ MiHA mRNA-electroporated mature DCs were infused on day 0, 14 and 28

| | |
|------------------|--------------|
| Arm title | PSCT19 study |
|------------------|--------------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH, 2,5x10⁵/kg, intravenous on day 0, 14, and 28

| Number of subjects in period 1 | Pilot PSCT16 study | PSCT19 study |
|--------------------------------|--------------------|--------------|
| Started | 4 | 12 |
| Completed | 4 | 12 |

Period 2

| | |
|------------------------------|------------------|
| Period 2 title | During treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pilot PSCT16 study |

Arm description: -

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MiHA mRNA-electroporated mature DCs |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20x10⁶ MiHA mRNA-electroporated mature DCs were infused on day 0, 14 and 28

| | |
|------------------|--------------|
| Arm title | PSCT19 study |
|------------------|--------------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH, 2,5x10⁵/kg, intravenous on day 0, 14, and 28

| Number of subjects in period 2 ^[1] | Pilot PSCT16 study | PSCT19 study |
|---|--------------------|--------------|
| | | |
| Started | 3 | 10 |
| Completed | 3 | 10 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 16 subjects were included in the study, 3 patients did not start the study

*In the PSCT16 study one patient did not meet inclusion criteria so this patient was not treated

*In the PSCT19 study one patient did not start treatment because the donor did not give consent for monocyte apheresis,

*In the PSCT19 study one patient did not have the right HLA type

Period 3

| | |
|------------------------------|--|
| Period 3 title | After the end of treatment (Follow-up) |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------------|
| Arm title | Pilot PSCT16 study |
|------------------|--------------------|

Arm description: -

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MiHA mRNA-electroporated mature DCs |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20x10⁶ MiHA mRNA-electroporated mature DCs were infused on day 0, 14 and 28

| | |
|------------------|--------------|
| Arm title | PSCT19 study |
|------------------|--------------|

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Monocyte-derived, PD-L1/L2-silenced donor DCs electroporated with mRNA encoding hematopoietic-restricted MiH, 2,5x10⁵/kg, intravenous on day 0, 14, and 28

| Number of subjects in period 3 | Pilot PSCT16 study | PSCT19 study |
|---------------------------------------|--------------------|--------------|
| Started | 3 | 10 |
| Completed | 3 | 10 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 14 | 14 | |
| From 65-84 years | 2 | 2 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 5 | 5 | |
| Male | 11 | 11 | |
| Disease | | | |
| Primary diagnosis of patients included in the study | | | |
| Units: Subjects | | | |
| Non Hodgkin lymphoma | 5 | 5 | |
| Acute myeloid leukemia | 4 | 4 | |
| Chronic myelomonocytic leukemia | 2 | 2 | |
| Hodgkin lymphoma | 1 | 1 | |
| Chronic myeloid leukemia | 1 | 1 | |
| Acute lymphoblastic leukemia | 1 | 1 | |
| Myelodysplastic syndrome | 1 | 1 | |
| Multiple myeloma | 1 | 1 | |

End points

End points reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Pilot PSCT16 study |
| Reporting group description: - | |
| Reporting group title | PSCT19 study |
| Reporting group description: - | |
| Reporting group title | Pilot PSCT16 study |
| Reporting group description: - | |
| Reporting group title | PSCT19 study |
| Reporting group description: - | |
| Reporting group title | Pilot PSCT16 study |
| Reporting group description: - | |
| Reporting group title | PSCT19 study |
| Reporting group description: - | |

Primary: Toxicity - Adverse events

| | |
|------------------------|---|
| End point title | Toxicity - Adverse events ^[1] |
| End point description: | Adverse events > grade 2 according to CTCAE in PSCT16 trial and adverse events > grade 1 to CTCAE in PSCT 19 trial Serious adverse events |
| End point type | Primary |
| End point timeframe: | Patiënts were screened for adverse events during study visits. The study visits were: prestudy, day 0, day 7, day 14, day 21, day 28, day 42, day 63 and day 84. |
| Notes: | [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This is a phase 1 trial, so adverse events are described and not compared between the two groups. |

| End point values | Pilot PSCT16 study | PSCT19 study | | |
|-------------------------------|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 ^[2] | 10 ^[3] | | |
| Units: Adverse events | | | | |
| Fever | 0 | 6 | | |
| Flu like symptoms | 0 | 5 | | |
| Fatigue | 0 | 2 | | |
| Musculoskeletal pain | 0 | 2 | | |
| Viral infections | 0 | 3 | | |
| Cough | 0 | 1 | | |
| Hypotension | 0 | 1 | | |
| Incomplete spinal cord injury | 0 | 1 | | |
| Malaise | 0 | 2 | | |
| Graft-versus-host disease | 0 | 0 | | |

Notes:

[2] - Adverse events > CTCEA grade 2 (according to study protocol)

Statistical analyses

No statistical analyses for this end point

Primary: GVHD

| | |
|-----------------|---------------------|
| End point title | GVHD ^[4] |
|-----------------|---------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Patiënts were screened for adverse events during study visits.

The study visits were: prestudy, day 0, day 7, day 14, day 21, day 28, day 42, day 63 and day 84.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis is not applicable for this endpoint. Graft-versus-host disease did not occur in any of the reporting groups.

| End point values | Pilot PSCT16 study | PSCT19 study | | |
|----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 10 | | |
| Units: Graft-versus-host disease | | | | |
| Graft-versus-host disease | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Immunological response of MiHA CD8+ T cells

| | |
|-----------------|--|
| End point title | Immunological response of MiHA CD8+ T cells ^[5] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The amount of MiHA specific CD8+ cells was counted prestudy and on day 0, 7, 14, 21, 28, 35, 63 and 84

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This analysis is still ongoing

| End point values | Pilot PSCT16 study | PSCT19 study | | |
|---|--------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: Increase in MiHA specific CD8+ T cells | | | | |

Notes:

[6] - This analysis is still ongoing

[7] - This analysis is still ongoing

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events reported spontaneously by the subject or observed by the investigator or his staff occurring until 84 days after the first DC vaccination will be recorded in the eCRF.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | NCI-CTCAE |
|-----------------|-----------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Pilot PSCT16 study |
|-----------------------|--------------------|

Reporting group description:

All patients included in the study who received at least one dose of treatment.

AE's of CTCAE grade 1 and 2 are not considered AE's in this protocol.

| | |
|-----------------------|--------------|
| Reporting group title | PSCT19 study |
|-----------------------|--------------|

Reporting group description:

AEs of CTCAE grade 1 are not considered adverse events in this study

| Serious adverse events | Pilot PSCT16 study | PSCT19 study | |
|---|--------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 10 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Pilot PSCT16 study | PSCT19 study | |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 10 / 10 (100.00%) | |
| Vascular disorders | | | |
| Hypotension | Additional description: Hypotension grade 3 on study day 23 after third vaccination during one day. | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Incomplete spinal cord injury | Additional description: Due to progression of multiple myeloma | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|-----------------|--|
| Fever subjects affected / exposed occurrences (all) | Additional description: > grade 1 fever | | |
| | 0 / 3 (0.00%) | 6 / 10 (60.00%) | |
| | 0 | 6 | |
| | | | |
| Flu like symptoms subjects affected / exposed occurrences (all) | Additional description: Flu like symptoms > grade 1 | | |
| | 0 / 3 (0.00%) | 5 / 10 (50.00%) | |
| | 0 | 5 | |
| | | | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 2 / 10 (20.00%) | |
| | 0 | 2 | |
| | | | |
| | | | |
| Malaise subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 2 / 10 (20.00%) | |
| | 0 | 2 | |
| | | | |
| | | | |
| Gastrointestinal disorders Viral gastro-enteritis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| | 0 | 1 | |
| | | | |
| | | | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| | 0 | 1 | |
| | | | |
| | | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | Additional description: Cough > grade 1 | | |
| | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| | 0 | 1 | |
| | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 1 / 10 (10.00%) | |
| | 0 | 2 | |
| | | | |
| | | | |
| Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) | 2 / 10 (20.00%) | |
| | 0 | 2 | |
| | | | |
| | | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 31 January 2018 | Amendement concerning PSCT19 trial -Hodgkin lymphoma has been added to inclusion criteria -Patiënts can be included after tapering of immune suppression instead of after tapering of ciclosporin A -Adverse events of grade 2 or higher will be described in the CRF -Donors will have a 12 liter apheresis instead of a 9 liter apheresis -Follow up will be performed on day 35 instead of day 42 |
| 04 July 2019 | Patients with myeloproliferative neoplasms can be included in the study |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported