



Clinical trial results:

Prophylactic infusion of CD4 positive donor lymphocytes early after T-cell depleted stem cell transplantation

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-001447-19 |
| Trial protocol | NL |
| Global end of trial date | 01 May 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 30 November 2021 |
| First version publication date | 30 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | LUMCCD4PROTOCOL |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN51398568 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Leids Universitair Medisch Centrum, department of hematology |
| Sponsor organisation address | Albinusdreef 2, Leiden, Netherlands, 2333ZA |
| Public contact | Dr. P van Balen, LUMC, department of hematology, 0031 715262267, P.van_Balen@lumc.nl |
| Scientific contact | Dr. P van Balen, LUMC, department of hematology, 0031 715262267, P.van_Balen@lumc.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 | 10 November 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether CD4+ lymphocytes infusion given three months after T-cell depleted allogeneic SCT improves immunological recovery (number of circulating CD4+ lymphocytes) with an incidence of GvHD requiring systemic treatment not exceeding 30% of the patients.

Protection of trial subjects:

Patients are closely monitored in our outpatient clinic on a regular basis. A structured anamnesis was performed, as well as physical anamnesis and laboratory results. Furthermore bone marrow examination was performed (morphology, flow cytometry, bone marrow chimerism) at regular intervals (after transplantation: 3 months, 4.5 months, 6 months, 9 months, 12 months). (local lab, physical exam and structured anamnesis).

Background therapy:

All patients after alloSCT are monitored and treated according to local guidelines with regards to immunosuppressive treatment, antibiotic treatment.

Evidence for comparator:

At the time of initiation of this study all patients were eligible for prophylactic DLI 6 months after alloSCT. To assess whether prophylactic CD4 DLI 3 months after alloSCT would be beneficial in addition to unmodified DLI at 6 months, we compared patients in the control group (treated according to standard protocol and eligible for prophylactic unmodified DLI 6 months after alloSCT) to the experimental arm with prophylactic CD4 DLI at 3 months (the experimental arm was also eligible to receive unmodified prophylactic DLI at 6 months).

| | |
|---|-----------------|
| Actual start date of recruitment | 04 January 2008 |
| 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: 66 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 66 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 56 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

All adult patients treated with 10/10 HLA matched alemtuzumab based T-cell depleted stem cell transplantation from a related donor in the Leiden University medical center are eligible for inclusion. Patients were recruited between and 4 January 2008 and 1 May 2020 in the department of hematology.

Pre-assignment

Screening details:

Inclusion criteria: concomitant disease, WHO performance status of 0-2, Life expectancy longer than 3 months and providing informed consent.

Exclusion criteria: progressive disease, severe GVHD, systemic immunosuppressive treatment, pregnancy, positive HIV test

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Patients were randomized to receive either CD4 DLI or no treatment at 3 months after alloSCT. All patients were eligible to receive unmodified DLI at 6 months.

Both patient and doctor were aware of randomization arm.

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | CD4+ donor lymphocytes infusion |

Arm description:

Infusion of 1×10^6 CD4+ T-cells/kg 3 months after alloSCT

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | CD4 positive lymphocytes |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

1×10^6 CD4+ T cells/kg infused once at 3 months after alloSCT

| | |
|------------------|---------|
| Arm title | Control |
|------------------|---------|

Arm description:

No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | CD4+ donor lymfocyten infusion | Control |
|---------------------------------------|-----------------------------------|---------|
| Started | 33 | 33 |
| Completed | 29 | 31 |
| Not completed | 4 | 2 |
| Adverse event, serious fatal | 4 | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------------------------------|
| Reporting group title | CD4+ donor lymphocyten infusion |
| Reporting group description: | |
| Infusion of 1×10^6 CD4+ T-cells/kg 3 months after alloSCT | |
| Reporting group title | Control |
| Reporting group description: | |
| No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol | |

| Reporting group values | CD4+ donor lymphocyten infusion | Control | Total |
|---|---------------------------------|--------------|-------|
| Number of subjects | 33 | 33 | 66 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 60.5 | 59.1 | |
| inter-quartile range (Q1-Q3) | 57.4 to 64.4 | 50.2 to 61.7 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 14 | 24 |
| Male | 23 | 19 | 42 |
| Conditioning | | | |
| Conditioning regime for transplantation. Myeloablative conditioning consists of cyclophosphamide and TBI, while non-myeloablative conditioning consists of Fludarabine and Busulfan | | | |
| Units: Subjects | | | |
| Myeloablative | 8 | 6 | 14 |
| Non-myeloablative | 25 | 27 | 52 |
| HCT comorbidity score | | | |
| HCT comorbidity score before transplantation | | | |
| Units: Subjects | | | |
| 0-2 | 28 | 28 | 56 |
| 3-7 | 5 | 5 | 10 |
| Hematologic disease | | | |
| Hematologic disease for which a allogeneic stem cell transplantation was performed | | | |
| Units: Subjects | | | |
| CML | 1 | 2 | 3 |
| MPN | 1 | 2 | 3 |

| | | | |
|---|-----------|-----------|----|
| MDS/MPN overlap | 3 | 1 | 4 |
| MDS | 3 | 0 | 3 |
| AML | 14 | 15 | 29 |
| Multiple myeloma | 5 | 6 | 11 |
| Mature B-cell lymphoma | 3 | 5 | 8 |
| ALL/LBL | 2 | 2 | 4 |
| Leukemia with mixed phenotype | 1 | 0 | 1 |
| CD4+ T-cell count at randomization | | | |
| CD4+ T-cell count measured with flow cytometry at randomization. In patients who did receive CD4+ DLI, T-cell counts were measured before infusion. | | | |
| Units: cells/microlitre | | | |
| median | 113 | 112 | |
| inter-quartile range (Q1-Q3) | 69 to 233 | 64 to 198 | - |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | CD4+ donor lymphocytin infusion |
| Reporting group description: Infusion of 1×10^6 CD4+ T-cells/kg 3 months after alloSCT | |
| Reporting group title | Control |
| Reporting group description: No intervention 3 months. Patients are eligible to receive unmodified DLI 6 months after alloSCT according to standard LUMc protocol | |

Primary: CD4+ T-cell counts 6 months after alloSCT

| | |
|--|---|
| End point title | CD4+ T-cell counts 6 months after alloSCT |
| End point description: | |
| End point type | Primary |
| End point timeframe: The primary endpoint (CD4+ T-cell counts) is measured 3 months after randomization (6 months after alloSCT). | |

| End point values | CD4+ donor lymphocytin infusion | Control | | |
|---------------------------------------|---------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 ^[1] | 32 | | |
| Units: cells/microlitre | | | | |
| median (inter-quartile range (Q1-Q3)) | 155 (102 to 211) | 178 (132.5 to 223.2) | | |

Notes:

[1] - 4 patients did not survive until 3 months after alloSCT

Statistical analyses

| | |
|--|---|
| Statistical analysis title | CD4+ T-cell counts at 3 months |
| Statistical analysis description: Mann Whitney U test between CD4+ T-cell counts the two treatment arms at 3 months after inclusion | |
| Comparison groups | Control v CD4+ donor lymphocytin infusion |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.2917 |
| Method | Wilcoxon (Mann-Whitney) |

Primary: severe GvHD

| | |
|------------------------|---|
| End point title | severe GvHD |
| End point description: | Cumulative incidence of GvHD requiring immunosuppressive treatment. We used a competing risk analysis with relapse, unmodified DLI and death as competing events. |
| End point type | Primary |
| End point timeframe: | 3 months after randomization |

| | | | | |
|-----------------------------|---------------------------------|-----------------|--|--|
| End point values | CD4+ donor lymphocyten infusion | Control | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 33 | | |
| Units: Cumulative incidence | 9 | 9 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | competing events at 3 months.png GvHD.png |
|-----------------------------------|--|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cumulative incidence |
| Statistical analysis description: | Comparing cumulative incidence of developing GvHD requiring immunosuppressive treatment with log-rank test. |
| Comparison groups | CD4+ donor lymphocyten infusion v Control |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.8 |
| Method | Logrank |

Secondary: Overall survival

| | |
|------------------------|--|
| End point title | Overall survival |
| End point description: | Probability of overall survival after randomization in intention to treat analysis |
| End point type | Secondary |
| End point timeframe: | up to 5 years after randomization |

| End point values | CD4+ donor lymphocyten infusion | Control | | |
|-----------------------------|---------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 33 | | |
| Units: Overall survival | 44 | 52 | | |

| | |
|-----------------------------------|----------------------|
| Attachments (see zip file) | Overall survival.png |
|-----------------------------------|----------------------|

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Overall Survival |
| Statistical analysis description: Overall survival between two treatment arms | |
| Comparison groups | CD4+ donor lymphocyten infusion v Control |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5 |
| Method | Logrank |

Secondary: Relapse

| | |
|--|-----------|
| End point title | Relapse |
| End point description: Relapse requiring systemic treatment during follow-up. Competing risk analysis with death as a competing event | |
| End point type | Secondary |
| End point timeframe: up to 5 years after randomization | |

| End point values | CD4+ donor lymphocyten infusion | Control | | |
|-----------------------------|---------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 33 | | |
| Units: Cumulative incidence | 39 | 36 | | |

| | |
|-----------------------------------|-------------|
| Attachments (see zip file) | relapse.png |
|-----------------------------------|-------------|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Relapse |
| Statistical analysis description: Comparing relapse between two treatment arms | |
| Comparison groups | CD4+ donor lymphocyten infusion v Control |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5 |
| Method | Logrank |

Secondary: Any sign of GvHD

| | |
|--|------------------|
| End point title | Any sign of GvHD |
| End point description: Cumulative incidence of any signs of GvHD. Patients did not need to receive immunosuppressive. We used a competing risk analysis with relapse, unmodified DLI and death as competing events. | |
| End point type | Secondary |
| End point timeframe: 3 months after randomization | |

| End point values | CD4+ donor lymphocyten infusion | Control | | |
|-----------------------------|---------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 33 | | |
| Units: Cumulative incidence | 24 | 27 | | |

| | |
|-----------------------------------|-------------|
| Attachments (see zip file) | anyGvHD.png |
|-----------------------------------|-------------|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cumulative incidence |
| Comparison groups | CD4+ donor lymphocyten infusion v Control |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.6 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between randomization and 6 months after alloSCT

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | CD4+ donor lymphocytin infusion |
|-----------------------|---------------------------------|

Reporting group description:

All adverse events from randomization until 6 months after alloSCT

Serious adverse events: severe GvHD, relapse, death, infections requiring hospitalization

| | |
|-----------------------|----------|
| Reporting group title | Controle |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | CD4+ donor lymphocytin infusion | Controle | |
|---|--|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 33 (30.30%) | 9 / 33 (27.27%) | |
| number of deaths (all causes) | 4 | 1 | |
| number of deaths resulting from adverse events | 4 | 1 | |
| Blood and lymphatic system disorders | | | |
| GVHD | Additional description: Graft versus host disease between randomization and 6 months. | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 3 / 33 (9.09%) | |
| occurrences causally related to treatment / all | 4 / 4 | 3 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Relapse | Additional description: Relapse between 3 and 6 months. Fatality numbers reported until 6 months after alloSCT | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 6 / 33 (18.18%) | |
| occurrences causally related to treatment / all | 5 / 5 | 6 / 6 | |
| deaths causally related to treatment / all | 2 / 2 | 1 / 1 | |
| Immune system disorders | | | |
| Autoimmunity | Additional description: Autoimmunity between randomization and 6 months after alloSCT requiring IST | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 33 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|--|-----------------|--|
| Infection | Additional description: Any infection requiring hospitalization between randomization and 6 months after alloSCT | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 33 (12.12%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | CD4+ donor lymphocytin infusion | Controle | |
|---|--|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 2 / 33 (6.06%) | |
| Blood and lymphatic system disorders | | | |
| GvHD without IST | Additional description: Patients that did develop signs of GvHD, but did not need systemic immunosuppressive treatment for it. | | |
| subjects affected / exposed | 5 / 33 (15.15%) | 1 / 33 (3.03%) | |
| occurrences (all) | 5 | 1 | |
| Immune system disorders | | | |
| autoimmunity without immune suppression | Additional description: Any sign of autoimmunity, not requiring immunosuppressive treatment | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 33 (3.03%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| Since all patients were eligible to receive unmodified DLI at 6 months, the reported outcomes and all AE/SAE are reported until 6 months; afterwards the adverse events are probably related to the unmodified DLI. These results are not reported here. |
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Notes: