Trial Description

Title

Treatment of chemo-refractory viral infections after allogeneic stem cell transplantation with multispecific T cells against CMV, EBV and AdV: A phase III, prospective, multicentre clinical trial

Trial Acronym

TRACE

URL of the trial

https://www.trace-study.de/trace

Brief Summary in Lay Language

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Brief Summary in Scientific Language

For a growing number of patients suffering from various conditions as, e.g., haematological malignancies or diverse genetic disorders, haematopoietic stem cell transplantation (HSCT) or bone marrow transplantation offer the only possible curative options. However, HSCT is associated with three major risks: graft rejection, graft-versus-host disease (GvHD) and opportunistic, mostly viral, infections or reactivations resulting from delayed immune reconstitution. Delayed immune reconstitution, however, often is the direct result of the severe pre-transplantation conditioning treatment and T-cell depletion of the transplant necessary to fight the risks of graft rejection and GvHD. Therefore, the risk for life-threatening opportunistic, mostly viral, infections is increased in post-transplantation patients. The most common infections after HSCT are Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Adenovirus (AdV).
The standard treatment approach for viral infections/reactivations is chemotherapy which shows limited efficacy and does not restore immunity. Therefore, effective new treatment options are required for this condition. Previous investigations have shown that sufficient T-cell immunity is essential for the control and prevention of viral reactivations and newly occurring infections after HSCT. The infusion of T-cells is therefore a promising new approach to treat immune-comprised patients. However, infusion with unselected T cells is associated with an increased risk for GvHD due to the high content of alloreactive T cells. A very promising approach to minimize this problem is to remove alloreactive T cells and enrich, isolate and purify virus-specific T cells.
This approach has been studied for nearly two decades and the data published up to date indicate that virus-specific T-cell responses after adoptive T-cell transfer protect against virus-related complications post HSCT and restore T-cell immunity, in particular for AdV-, CMV- and EBV-infections. Despite these promising results, virus-specific T-cell transfer is not yet translated into daily clinical practice due to the lack of prospective clinical trials confirming the efficacy of this treatment approach.
The overall goal of this phase III, double-blind placebo-controlled study is to

confirm efficacy of multivirus-specific T cells to bring this treatment method in clinical routine. Multivirus-specific T cells generated in this study will be directed against all three most common post-HSCT viral infections: AdV, CMV and EBV. Thus, T-cell immunity will be restored to fight and prevent new viral infections. After an initial screening visit, patients eligible to participate in the study will be treated within 28 days after screening. Patients will be randomized in a 2:1 (treatment: placebo) ratio and receive a single infusion with either multivirus-specific T cells or placebo. Patients will be followed up on the day of treatment, 1 day after and 1, 2, 4, 8 and 15 weeks after treatment. Treatment success will be measured by assessing different parameters including symptoms, quality of life, viral load and T-cell immunity in blood samples.
Patients eligible to participate in this study are adult and paediatric patients who have received allogeneic stem cell transplantation and suffer from new or reactivated EBV, AdV or CMV infection refractory to standard antiviral treatment for two weeks. Patients from the six European countries Germany, Belgium, Netherlands, UK, France and Italy will be enrolled. In total 130 patients plus 19 screening failures are expected to participate in the study.

Do you plan to share individual participant data with other researchers?

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Description IPD sharing plan

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Organizational Data

- DRKS-ID: **DRKS00018985**
- Date of Registration in DRKS: **2019/12/09**
- Date of Registration in Partner Registry or other Primary Registry: **2018/02/27**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **18-595 fed , Ethik-Kommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München**

Secondary IDs

- EudraCT-No.
(for studies acc. to Drug Law): **2018-000853-29**
- Other Secondary-ID: **NL67592.000.19 (central ethics portal Nehterlands CCMO)**
- Other Secondary-ID: **251752 (central ethics portal for UK: IRAS)**

Health condition or Problem studied

- MedDRA: **C02**
- Free text: **stem cell transplantation**

Interventions/Observational Groups

- Arm 1: **Multivirus (CMV, EBV, AdV-) specific T cells**
- Arm 2: **Placebo (NaCl)**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, investigator/therapist, caregiver, assessor, data analyst**
- Control: **Placebo**
- Purpose: **Treatment**
- Assignment: **Other**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

- Percentage of patients with viral clearance (defined as two consecutive negative PCRs)
- Percentage of patients with progression between Day 7 and Week 8 after T-cell transfer

Secondary Outcome

- Incidence and severity of newly occurring GvHD =/< grade II until Week 8 and Week 15.
- Incidence of newly occurring acute GvHD grade I from Day O to Week 8 and Week 15.
- Incidence of chronic GvHD from Day 7 to Week 8 and to Week 15 after T-cell Transfer
- Time to newly occurring acute and chronic GvHD.
- Acute toxicity: maximum toxicity on the day of T-cell transfer evaluated by measuring vital signs prior to and at different times after the T-cell transfer and monitoring of specific adverse events (chills, nausea, vomiting, diarrhoea, abdominal pain, allergic reactions, respiratory dysfunction or headache from 1 hour prior to T-cell transfer to 4 hours post infusion).
- Change in viral load of underlying viral infection as assessed by quantitative PCR analysis of peripheral blood; samples taken weekly from Day 7 to Week 8 after T-cell transfer as compared to samples taken at Day 0.

- Time to 1 log change in viral load.
- Percentage of patients with ≥1 log decrease in CMV, EBV or AdV viral load at Week 8.
- Number of reactivations of the underlying viral infection following initial viral clearance until end of follow-up.
- Number of patients with reduction or clearance of clinical symptoms of underlyingviral infection from Day 7 to Week 8 after T-cell transfer as compared to Day 0.
- Overall survival rate (OS): From Day 0 to end of follow-up.
- Number of days requiring antiviral chemotherapy after T-cell transfer from Day 7 to Week 8 after T-cell transfer.
- Time to last administration of defined antiviral medication or switch to prophylactic treatment from Day 0 to Week 8 after T-cell transfer.
- Number of new viral reactivations (CMV, AdV or EBV) other than the underlying viral infection per patient as assessed by PCR analysis and clinical symptoms throughout the study.
- Number of days hospitalized after T-cell transfer from Day 7 to Week 8.
- EQ-5D and FACT-BMT for adult patients (≥18 years), and PEDS-QL for paediatric patients (<18 years) at Screening and Week 8.
- T-cell phenotyping, samples taken at Screening, Day 0 and each visit from Day 7 to Week 15 after T-cell transfer.
Analysis of virus-specific T cells: number of in vivo expanded virus-specific T cells in peripheral blood samples taken at Screening, Day 0, Day 7 to Week 15 after T-cell transfer.
- Assessment of the number and viability of CD3+ cells and percentage of IFN-gamma+ cells and cellular composition in the IMP.
- Drop-out rate at Day 0 and reasons for drop-out.
- Number of days from Screening to Day 0 (day of T-cell transfer).
- Documentation of incidence, severity and type of adverse events from Day 0 to Week 8 and serious adverse events throughout the study.
- Physical examination and vital signs from Screening to Week 8; Karnofsky/Lansky index will be assessed at Screening and at Week 8.
- Laboratory values for clinical chemistry and haematology from Screening to Week 8.
- Documentation of all concomitant medication from Screening to Week 8.
- During follow-up Week 15, only antiviral therapy, immunosuppression and SAE-related concomitant medication as well as chemotherapy will be documented.
- Non-therapeutic DLI has to be documented as concomitant medication (definition see exclusion criteria).
- Treatment with multivirus-specific T cells after Week 8 will also be documented as concomitant medication.

Countries of recruitment

- DE **Germany**
- NL **Netherlands**
- IT **Italy**
- FR **France**
- BE **Belgium**
- UK **United Kingdom**

Locations of Recruitment

- University Medical Center **Dr. von Haunersches Kinderspital, Abteiltung Hämatologie und Onkologie, Munich**
- University Medical Center **Medizinische Klinik III (Onkologie), München**
- University Medical Center **Klinik und Poliklinik für Innere Medizin III, Technische Universität München (MRI-TUM), München**
- University Medical Center **Allgemeine Pädiatrie, Hämatologie/Onkologie, Tübingen**
- University Medical Center **Medizinische Klinik und Poliklinik II, Zentrum Innere Medizin, Würzburg**
- University Medical Center **Medizinische Hochschule Hannover - Zentrum für Kinderheilkunde und Jugendmedizin , Hannover**
- University Medical Center **Klinik für Kinder-Onkologie, -Hämatologie und klinische Immunologie, Düsseldorf**
- University Medical Center **Klinik für Kinderheilkunde III, Essen**
- University Medical Center **Charité Berlin - Klinik für Pädiatrie mit Schwerpunkt Onkologie/Hämatologie/SZT, Berlin**
- University Medical Center **Medizinische Klinik und Poliklinik I - Hämatologie und Zelltherapie, internistische Onkologie, Hämostaseologie, Leipzig**

Recruitment

- Planned/Actual: **Planned**
- (Anticipated or Actual) Date of First Enrollment: **2019/12/20**
- Target Sample Size: **149**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **2 Months**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

1. Adult or paediatric patients (>2 months of age) after HSCT suffering from new or reactivated CMV or EBV or AdV infection, refractory to standard antiviral treatment for two weeks (defined as ≤1 log decrease in viral load over two weeks) as confirmed by quantitative blood PCR analysis
2. Original HSCT-donor available with an immune response at least to the virus causing the therapy-refractory infection
3. Written informed consent given (patient or legal representative)

Exclusion criteria

1. Acute GvHD > grade II or extensive chronic GvHD at time of T-cell transfer
2. Treatment with steroids (>1 mg/kg Prednisone equivalent) at Screening
3. Therapeutic donor lymphocyte infusion (DLI) from 4 weeks prior to IMP infusion until 8 weeks post IMP infusion. In case of T-cell depleted HSCT, a prescheduled prophylactic DLI ≤3 x 105 T cells/kg BW is not considered an exclusion criteria.
4. Organ dysfunction or failure as determined by Karnofsky (age >16 years) or Lansky (age ≤16 years) score ≤30%
5. Concomitant enrolment in another clinical trial interfering with the endpoints of this study
6. Any medical condition which could compromise participation in the study according to the investigator's assessment
7. Progression of underlying disease (disease that has led to the indication of HSCT, e.g. leukaemia) that will limit the life expectance below the duration of the study
8. Second line or experimental antiviral treatment other than Ganciclovir/Valganciclovir, Foscarnet, Cidofovir and Rituximab from Screening until 8 weeks after IMP infusion
9. Known HIV infection. In case patients do not have a negative HIV test performed within 6 months before enrolment in the study, HIV negativity has to be confirmed by a negative laboratory test.
10. Female patient who is pregnant or breast-feeding, or adult of reproductive potential not willing to use an effective method of birth control from Screening until the last follow-up visit (FU6, Visit 8) Note: women of childbearing potential must have a negative serum pregnancy test at study entry
11. Known hypersensitivity to iron dextran
12. Patients unwilling or unable to comply with the protocol or unable to give informed consent.

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

European Commission

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting ongoing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

Deutsches Register Klinischer Studien
German Clinical Trials Register

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*