Kompetenznetz "Akute und chronische Leukämien"

KURZPROTOKOLL

CAR.CD19 for lymphoid disease

Öffentlicher Titel	Phase I/II-Studie zur Behandlung mit durch viral transduzierte T-Lymphozyten bei Patienten mit CD19 positiver lymphoider Erkrankung
Wissenschaftl. Titel	Treatment of patients with relapsed or refractory CD19+ lymphoid disease with T lymphocytes transduced by RV-SFG.CD19.CD28.4-1BBzeta retroviral vector – a unicenter phase I/II clinical trial
Kurztitel	CAR.CD19 for lymphoid disease
Studiennummer KN/ELN	LN_NN_2018_650
Studiengruppe	NN
Studienart	mehrarmig, prospektiv, offen, monozentrisch
Studienphase	Phase I/II
Erkrankung	Akute lymphatische Leukämie (ALL) - Alle Subtypen
Leukämiestadium	rezidiviert/refraktär MRD positiv
Einschlusskriterien	- Stratum 1-2 (Adults): - - Confirmed CD19+ ALL, CLL, DLBCL, FL or MCL in patients >= 18 years - - ALL: - -> Confirmed CD19+ ALL (Philadelphia (Ph) + and Ph-) by cytology and flow cytometry (FACS) AND Relapsed or refractory disease (including “molecular relapse” with minimal residual disease (MRD) levels > 10-3 at two occasions > 2 weeks apart) with confirmed CD19-expression on malignant cells - -> Any relapse after allogeneic stem cell transplantation (alloSCT) (>= 6 months from alloSCT at time of CAR TC infusion) OR - -> Any relapse failing to achieve an MRD level of < 10-3 after >= 2 lines of treatment OR - -> Primary refractory as defined by not achieving a CR after >= 2 lines of treatment - - CLL/NHL: Confirmed CD19+ CLL/NHL (including CLL, DLBCL, FL or MCL): - -> CLL in need of treatment with: - (1) Early relapse (within 2 years) after end of chemoimmunotherapy or chemoimmunotherapy refractoriness plus failure or intolerance of both BTK and BCL2 inhibitors OR - (2) Relapse after alloSCT, ineligible for or refractory to standard interventions (donor lymphocyte infusions (DLI), CD20 antibodies, chemoimmunotherapy) - -> DLBCL with: - (1) Refractoriness to a 2nd or later line of chemoimmunotherapy OR - (2) Relapse after autoSCT plus ineligibility for alloSCT (including refractoriness to one line of salvage chemoimmunotherapy) OR - (3) Relapse after alloSCT - -> FL in need of treatment with: - (1) Relapse <2 years after chemoimmunotherapy AND ineligibility for or failure of autoSCT AND ineligibility for or failure of idelalisib OR - (2) Relapse after alloSCT, ineligible for or refractory to standard interventions (donor lymphocyte infusions, CD20 antibodies, chemoimmunotherapy) - -> MCL with: - (1) Relapse after standard first-line therapy AND ineligibility for or failure to BTKi salvage therapy OR - (2) Relapse after alloSCT AND ineligibility for or failure to BTKi salvage therapy - -> Measurable disease/MRD at time of enrollment

- -> Life expectancy >= 12 weeks
- -> ECOG performance status <= 2 at the time of screening
- -> Adequate organ function: Renal function defined as: serum creatinine of <= 2 x ULN or eGFR >= 30 mL/min/1.73 m2
- -> Liver function defined as:
- (1) ALT <= 5 times the ULN for the respective age
- (2) Bilirubin <= 2.0 mg/dl with the exception of patients with hyperbilirubinemia explained by Gilbert–Meulengracht syndrome (may be included if total bilirubin is <= 3.0 x ULN and direct bilirubin <= 1.5 x ULN) or extrahepatic disease (e.g. chronic hemolytic anemia)
- -> minimum level of pulmonary reserve defined as <= grade 1 dyspnea and pulse oxygenation > 90% on room air
- -> Hemodynamic stability and LVEF >= 40% as confirmed by echocardiogram
- -> Absolute neutrophil count (ANC) >= 500/mm3
- -> Absolute lymphocyte count (ALC) >= 100/mm3
- -> Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants must agree to use highly effective methods of contraception for one year following CD19.CAR TC therapy
- -> Ability to understand the nature of the trial and the trial related procedures
- -> Written informed consent must be obtained prior to any screening procedures
- Stratum 3 (Children and Adolescents with ALL):
- -> Age of > 3 years until < 18 years at the time of screening
- -> CD19+ ALL (Ph+ and Ph-) confirmed by cytology and flow cytometry (FACS) AND Relapsed or refractory disease (including “molecular relapse” with PCR-MRD > 10-3 at two occasions > 2 weeks apart) with confirmed CD19-expression on malignant cells
- -> Any relapse after alloSCT (>= 6 months from alloSCT at time of CAR TC infusion) OR
- -> Any relapse failing to achieve an MRD level of < 10-3 after >= 2 lines of treatment OR
- -> Primary refractory as defined by not achieving a CR after >= 2 lines of treatment
- -> Measurable disease/MRD at time of enrollment
- -> Life expectancy >= 12 weeks
- -> ECOG performance status <= 2 (age >= 16 years) or Lansky performance status >= 50 (age < 16 years) at the time of screening
- -> Adequate organ function:
- (1) Renal function defined as serum creatinine-clearance >= 30 mL/min/1.73 m2
- (2) Liver function defined as:
- a) ALT <= 5 times the ULN for the respective age
- b) Bilirubin <= 2.0 mg/dl with the exception of patients with hyperbilirubinemia explained by Gilbert–Meulengracht syndrome or extrahepatic disease (e.g. chronic hemolytic anemia)
- -> minimum level of pulmonary reserve defined as <= grade 1 dyspnea and pulse oxygenation > 90% on room air
- -> Hemodynamic stability and LVEF >= 40% or shortening fraction > 29% as confirmed by echocardiogram
- -> Absolute neutrophil count (ANC) >= 500/mm3

- -> Absolute lymphocyte count (ALC) >= 100/mm3
- -> Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and postpubertal male participants must agree to use highly effective methods of contraception for one year following CD19.CAR TC therapy
- -> Written informed consent of the study patient and/or the legal representative must be obtained prior to any screening procedures

Ausschlusskriterien

- Stratum 1-2:
- -> The following medications are excluded:
- (1) Immunosuppressive medication with the exception of <= 30 mg prednisolone/d or equivalent at the time of CAR TC transfusion
- (2) Bridging/maintenance therapy including chemo- and immunotherapy must be stopped >= 2 weeks prior to leukapheresis, but can be continued between leukapheresis and lymphodepletion
- (3) Intrathecal chemotherapy is possible at any time, but not during lymphodepletion until 14 days after CD19.CAR TC transfusion
- (4) Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CD19.CAR TC infusion
- (5) Florid/acute or chronic Graft-versus-Host disease (GvHD)
- (6) Uncontrolled active hepatitis B or C
- (7) HIV-positivity
- (8) Uncontrolled acute life-threatening bacterial, viral or fungal infection
- (9) Severe concomitant disease (e.g. uncontrolled arterial hypertension, heart failure NYHA III-IV, uncontrolled diabetes mellitus, uncontrolled hyperlipidemia)
- (10) Unstable angina and/or myocardial infarction within 3 months prior to screening
- (11) Any previous or concurrent malignancy
- -> The following exceptions do not constitute exclusion criteria:
- (1) Adequately treated basal cell or squamous cell carcinoma (adequate wound healing is required prior to study entry)
- (2) In situ carcinoma of the cervix or breast, treated curatively without evidence of recurrence >= 3 years prior to the study
- (3) CLL or FL transformed into an aggressive B cell lymphoma
- (4) A primary malignancy which is in complete remission for >= 5 years
- (5) Pregnant or nursing (lactating) women
- (6) Intolerance to the excipients of the cell product
- (7) Active CNS involvement in ALL patient at the time of screening is not an exclusion criterion, but patients with CNS 3 status at clinical screening (d-14) are not eligible for CD19.CAR TC transfusion
- (8) Participation in another clinical trial at the time of screening
- Stratum 3 (Children and Adolescents with ALL):
- -> The following medications are excluded:
- (1) immunosuppressive medication with the exception of < 0.5 mg/d*kg BW prednisolone-equivalent at the time of CD19.CAR TC transfusion
- (2) Bridging/Maintenance therapy including chemo- and immunotherapy must be stopped >= 2 weeks prior to leukapheresis, but can be continued between leukapheresis and lymphodepletion
- (3) Intrathecal chemotherapy is possible at any time, but not during lymphodepletion until 14 days after CD19.CAR TC transfusion

- (4) Any donor lymphocyte infusions (DLI) must be completed > 6 weeks prior to CD19.CAR TC infusion
- (5) Florid/acute or chronic Graft-versus-Host disease (GvHD)
- (6) Uncontrolled active hepatitis B or C
- (7) HIV-positivity
- (8) Uncontrolled acute life-threatening bacterial, viral or fungal infection
- (9) Severe concomitant disease (e.g. any life-limiting genetic disorder). Patients with Down Syndrome will not be excluded.
- (10) Any previous or concurrent malignancy
- -> The following exceptions do not constitute exclusion criteria:
- (1) Lymphoblastic lymphoma transformed into a CD19+ acute lymphoblastic leukemia
- (2) A primary malignancy which is in complete remission for >= 5 years
- (3) Pregnant or nursing (lactating) women
- (4) Intolerance to the excipients of the cell product
- (5) Active CNS involvement at the time of screening is not an exclusion criterion, but patients with CNS 3 status at clinical screening (d-14) are not eligible for CD19.CAR TC transfusion
- (6) Participation in another clinical trial at the time of screening

Alter	Alle Altersgruppen>3J
Status	Aktiv
Beginn der Rekrutierung	07.09.2018
Studienleiter/in	Schmitt, Prof. Dr. med., Michael Universitätsklinikum Heidelberg E-Mail: Michael.Schmitt@med.uni-heidelberg.de
Sponsoren	Universität Heidelberg
Registrierung in anderen Studienregistern	ClinicalTrials.govNCT03676504 European Clinical Trials Database - EUDRACT2016-4808-60