BOB1-TCR therapy for treatment of relapsed or refractory B cell malignancies - A Phase 1/2 clinical trial

Trial synopsis

Informed Consent and screening
Patients with relapsed or refractory B-cell malignancies who have undergone several lines of prior therapy and for whom no standard of care treatment options are available are eligible for the present trial. Patients may be screened after written informed consent has been obtained.

Leukapheresis
Autologous CD8 T cells for the manufacture of LUMC-BOB1-B7-TCR.1 are obtained by leukapheresis. Leukapheresis material for IMP manufacture may be derived either from fresh leukapheresis or, when a patient is not eligible for fresh leukapheresis, from cryopreserved leukapheresis material of an earlier date.

Bridging therapy (optional)
Patients may be treated with bridging therapy between screening and the initiation of lymphodepletion in order to achieve temporary disease control.

Lymphodepleting chemotherapy (day -5 to day -3)
Participants will receive preconditioning with lymphodepleting chemotherapy: Cyclophosphamide 300 mg/m2/d IV and Fludarabine 30 mg/m2/d IV on days -5 to -3 before IMP infusion.

IMP infusion (day 0)
LUMC-BOB1-B7-TCR.1 is administered as a single-dose, slow intravenous infusion via a large peripheral vein or central line over a period of approximately 5-60 minutes.

Follow up per patient
Follow-up after IMP infusion is organized in 4 periods of 24 months total. The first period lasts for 28 days and entails a hospital admission of at least 8 days during which study participants will be monitored closely for dose limiting toxicities and other AEs. Patients then enter the second period of follow-up during which patients will be monitored until week 12 after IMP infusion by visits to the outpatient clinic. During the third period of follow-up, which lasts until month 12 after IMP infusion, patients will visit the outpatient clinic every 3 months. Finally, the fourth period of follow-up consists of visits to the outpatient clinic every 6 months until month 24 after IMP infusion. Afterwards, patients will be invited for long-term follow-up (LTFU) with yearly visits to the outpatient clinic, which will last for another 13 years.

Objectives
The objective of this trial is to determine feasibility, safety and efficacy of LUMC-BOB1-B7-TCR.1 treatment in patients positive for Human Leukocyte Antigen (HLA)-B*07:02 with relapsed or refractory B-cell malignancies.

General inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Disease persistence or progression of B-cell Acute Lymphoblastic Leukemia (B-ALL), Multiple Myeloma (MM) or non-Hodgkin B-cell lymphoma without standard treatment options as judged by the treating clinician and by a board of at least two other hematologists of the LUMC
2. Disease entity specific inclusion criteria as specified below
3. Age ≥ 18 years
4. Patients must be able to understand and be willing to give signed informed consent
5. Positive for HLA-B*07:02 according to genotyping results
6. Reliable source of autologous CD8 T cells must be available:
    - At least 0.03 x 10^9 CD8+ T cells/L in PB or, alternatively,
    - Cryopreserved leukapheresis material available that meets all qualification prerequisites as defined by the investigational medicinal product dossier (IMPD)
7. No treatment with other investigational therapeutic product within 3 months prior to IMP infusion
8. No treatment with T-cell engaging bispecific antibodies (BsAbs) within 6 months prior to leukapheresis or, alternatively, no treatment with BsAbs within 2 months prior to the projected date of IMP infusion and availability of cryopreserved leukapheresis material for IMP manufacture harvested prior to start of BsAb treatment
9. In patients with prior Chimeric Antigen Receptor (CAR) therapy: no CAR therapy within 6 months prior to leukapheresis and CAR T cells in PB below limit of detection
   or, alternatively, availability of cryopreserved leukapheresis material harvested prior to CAR therapy and no CAR therapy within 3 months prior to IMP infusion
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-3
11. Negative pregnancy test in women of childbearing potential
12. For fertile men and women, agreement to use highly effective contraceptive methods for the period between screening and 12 months after IMP infusion

Additional inclusion criteria in B-ALL patients

Relapsed or refractory B-ALL defined as disease activity without standard treatment options as judged by the treating clinician after

- ≥2 lines of therapy, including two lines of chemotherapy, or
- ≥1 lines of therapy, including allogeneic hematopoietic stem cell transplantation (HSCT)
- Subjects who cannot tolerate HSCT are allowed

Additional inclusion criteria in MM patients

Relapsed or refractory MM defined as disease activity without standard treatment options as judged by the treating clinician after

- ≥3 lines of therapy, including an immunomodulatory drug, a proteasome inhibitor and anti-CD38 therapy in any order during the course of treatment
- Subjects who could not tolerate immunomodulatory drugs, proteasome inhibitors and/or anti-CD38 therapy are allowed

Additional inclusion criteria in non-Hodgkin B-cell lymphoma patients

1. Diagnosis of non-Hodgkin B-cell lymphoma, including: Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM)

2. Relapsed or refractory disease defined as disease activity without standard treatment options as judged by the treating clinician
    - DLBCL/transformed FL: ≥3 lines of therapy, these should include anti-CD19 CAR therapy and anti-CD20 therapy, bendamustine, lenalidomide, anthracycline chemotherapy and/or glucocorticoids in any order during the course of treatment
    - FL: ≥3 lines of therapy, these should include anti-CD20 therapy, bendamustine, lenalidomide, anthracycline chemotherapy and/or glucocorticoids in any order during the course of treatment
    - MCL: ≥3 lines of therapy, these should include anti CD20 therapy, bendamustine, a Bruton's tyrosinekinase (BTK) inhibitor, anthracycline chemotherapy and/or glucocorticoids in any order during the course of treatment o MZL: ≥3 lines of therapy, these should include anti CD20 therapy, a BTK inhibitor, anthracycline chemotherapy and/or glucocorticoids in any order during the course of treatment
    - WM: ≥3 lines of therapy, these should include anti CD20 therapy, a BTK inhibitor, proteasome inhibitor, anthracycline chemotherapy and/or glucocorticoids in any order during the course of treatment
    - Subjects who were not able to receive one of the aforementioned therapies (e.g. due to contra indications or due to production failure) may be included in the trial provided that they meet all other requirements regarding previous lines of treatment

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant or breast feeding women
2. Active infection with HIV, HBV, HCV or HTLV 1/2
3. Active cerebral localization of B-cell malignancy (cerebral involvement in the past is allowed)
4. Active Graft versus Host Disease requiring current immunosuppression
5. Any clinically significant, advanced or unstable disease or inadequate main organ function that may put the patient at increased risk for severe complications of trial participation at the discretion of the investigator
6. Use of systemic immune suppression including, but not limited to: immunosuppressive agents such as cyclosporine or corticosteroids (at an equivalent dose of 0.5 mg prednisone/kg body weight per day, or higher), inhaled corticosteroids and physiological replacement for adrenal insufficiency are allowed
7. Unwillingness or inability to comply with procedures required in this clinical trial protocol
8. Uncontrolled central nervous system disease
9. Uncontrolled life-threatening infections or uncontrolled disseminated intravascular coagulation; however, if these problems resolve, the start of IMP production and treatment can be initiated on a delayed schedule
10. Known hypersensitivity against any drug of the mandatory trial procedures
11. Has received vaccination with live vaccines 6 weeks prior to treatment