Official Title: A Phase I/II Trial of MB-dNPM1-TCR.1 in HLA-A*02:01-positive Patients with Relapsed or Refractory NPM1-mutated AML to Determine Safety and Obtain First Data on Efficacy

Short title: MB-dNPM1-TCR.1 in Relapsed/refractory AML

Objective

The goal of this Phase I/II, single arm, prospective, open label, dose escalation trial is to assess safety, feasibility and efficacy of ex vivo expanded autologous T cells genetically modified to express a T cell receptor (TCR) specific for dNPM1 peptides restricted to human leukocyte antigen (HLA) A*02:01 in patients with relapsed or refractory AML.

Study overview

The investigational medicinal product (IMP) MB-dNPM1-TCR.1 is designed to effectively target malignant myeloid cells in patients suffering from relapsed or refractory AML with mutated NPM1. Autologous T cells will be genetically engineered using a lentiviral vector to express a T cell receptor (TCR) specific for certain dNPM1 peptides restricted to human leukocyte antigen (HLA) A*02:01. The dNPM1-TCR transduced T cells specifically target the HLA/dNPM1 peptide complex on the cell surface of leukemic myeloid cells and eliminate these. During the treatment, the patients will undergo a leukapheresis, a lymphodepleting chemotherapy and an administration of the expanded dNPM1-TCR transduced T cells.

Since this is a first in human trial, the primary goal in phase I is to establish the recommended dose of MB-dNPM1-TCR.1 for phase II. We assess the maximum tolerated dose (MTD) with toxicity defined as patients experiencing dose limiting toxicity (DLT) until day 28 after infusion of MB-dNPM1-TCR.1. Therefore a BOIN trial design will be used to guide dose escalation and de-escalation decisions in phase I.

Study population

HLA-A*02:01 positive patients with relapsed, refractory or MRD+ acute myeloid leukemia with NPM1 mutation without standard treatment options, defined as:

- No morphological CR after at least two courses of intensive chemotherapy, decitabine or other standard therapy or
- MRD positive after at least two courses of intensive chemotherapy and not eligible for allogeneic stem cell transplantation or
- Relapsed bone marrow or blood disease after CR after first line treatment and not eligible to undergo allogeneic stem cell transplantation or
- Bone marrow or blood relapse, non-response or MRD positivity after allogeneic stem cell transplantation and not eligible to receive Donor Lymphocyte Infusion (DLI) according to local standards, relapse after DLI.

Intervention

This is an open label, single arm, intervention study. The following is applicable to all study subjects:

- Leukapheresis
- Optional: Bridging therapy
- Lymphodepletion (day -5 to -3), consisting of fludarabine i.v. 30 mg/m^2 and cyclophosphamide i.v. 300 mg/m^2
- Infusion of IMP (day 0)

Outcome measures

Primary endpoint

- Maximum tolerated dose (MTD), as identified by a BOIN design at a target toxicity rate of 30%, with toxicity defined as patients experiencing dose limiting toxicity (DLT) until day 28 (week 4) after infusion of MB-dNPM1-TCR.1.

Secondary endpoints

- TCR T cell persistence: percentage and total number of MB-dNPM1-TCR+ cells in peripheral blood and/or bone marrow over time.
- Best objective response (BOR) during 12 weeks after infusion of MB-dNPM1-TCR.1. BOR is defined in relation to disease activity before thawing the leukapheresis for manufacturing (day -18 and -15).
- Overall survival (OS): the time between the date of infusion of MB-dNPM1-TCR.1 and the date of death from any cause.
- Progression-free survival (PFS): the time between the date of infusion of MB-dNPM1-TCR.1 and the date of objective disease progression or death from any cause whichever occurs first.
- Duration of response (DOR): the time between the date of the first objective response (CRMRD- CR, CRi, MLFS, PR, SD) and the date of assessment of relapse or the date of death due to AML, whichever occurs first.
- Safety and toxicity assessment of MB-dNPM1-TCR.1 per (serious) adverse events ((S)AE) reporting.
- Feasibility to manufacture: proportion of thawed apheresis products, from which MB-dNPM1-TCR.1 drug products are produced.