A phase I study to investigate the safety and tolerability of TEG001 cell suspension for infusion in patients with relapsed/refractory Acute Myeloid Leukemia (AML)/high-risk Myelodysplastic Syndrome (MDS) (IPSS-R > 4.5) or relapsed/refractory Multiple Myeloma (MM)

Protocol Synopsis

Rationale

Recent clinical trials have shown great promise for genetically engineered T cells in the treatment of various cancer patients. Especially trials using CD19 Chimeric Antigen Receptors (CARs) revealed very encouraging clinical results, paving the way to expand T cell engineering with a broadened arsenal of receptors to target a larger variety of tumour types.

Defining αβT Cell Receptors (TCRs) or antibody-based CARs with a favourable efficacy safety balance remains a challenge for tumours which don't express a tumour specific antigen or express antigens also found on healthy indispensable tissue. To address this issue, we have found the γδTCR present on γδT cells to be an interesting alternative class of receptors. γδT cells are part of the endogenous immune system participating in daily cancer immune surveillance. γδT cells have a different mode of sensing malignant cells in comparison to the adaptive immune system. Tumour cells have an altered metabolic state, which causes specific surface molecules (i.e. the extracellular region of BTN3A1) to undergo a conformational change rendering it recognizable to γδTCRs. Therefore, we have screened γδT cell repertoires for potent anti-cancer reactive immune cells. We have selected the specific, highly reactive γ9δ2TCR (clone 5) from the natural immune repertoire of a healthy individual, which shows reactivity towards a broad range of solid and haematological tumour cells. We have developed a GMP manufacturing strategy to generate αβT cells engineered to express a defined γδTCR, so called TEGs. αβT cells engineered to express this defined γ9δ2TCR (clone 5) are called TEG001.

αβT cells proliferate upon recognition of a tumour cell mediated through an endogenous αβTCR or through an exogenous introduced receptor (TCR/CAR). T cells engineered to express a defined γδT cell receptor (TEGs) combine the antitumor reactivity of a specific and highly reactive γδTCR with the proliferative capacity of autologous αβT cells. Given the proposed broad tumour reactivity displayed by TEG001 cells and the dismal prognosis for patients with relapsed/refractory AML/high-risk MDS or relapsed/refractory MM, we propose these patients as candidates for this First In Man (FIM), safety study. This study is based on nonclinical data demonstrating tumour reactivity of TEG001 in in vitro and in vivo cancer models. TEG001 showed tumour reactivity towards malignant cell lines as well as towards primary material from patients with various haematological malignancies. Moreover, inhibition of tumour cell growth and prolonged survival after TEG001 treatment was shown in vivo in severely immunodeficient murine strains with various haematological malignancies.

Objective

The primary objective is to determine the Maximum Tolerated Dose (MTD). Secondary objectives are to assess the safety profile and tolerability of TEG001 cell suspension for infusion until Day 56, to assess feasibility of the generation of an autologous TEG001 cell product in the target population, to assess the clinical response to TEG001 at Day 56 and to investigate the kinetics and persistence of TEG001

product until Day 56. Exploratory objectives are to assess additional efficacy endpoints, cytokine levels (including cytokines reported to correlate with cytokine release syndrome (CRS)), baseline and extended immune monitoring, identification of biological correlations with clinical outcome and toxicity, and further monitoring of TEG001 responses.

Study design

This is a single centre open label Phase I safety dose escalation study with 3 dose levels. A standard 3+3 dose escalation study design will be followed. There is no stratification or randomization. A maximum of 18 eligible study subjects will be treated, until up to 6 subjects have either reached the MTD or completed the study at the maximum dose level.

Study population

Patients with relapsed/refractory AML/high-risk MDS (IPSS-R > 4.5) and relapsed/refractory MM, with only standard of care directed towards support and symptom relief, but no therapeutic treatment options.

Intervention

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

- *Bridging chemotherapy* (prior to Day 0) is dependent on disease status of high risk MDS and AML subjects and consists of classical re-induction chemotherapy (such as high dose cytarabine, hypomethylating agents or corticosteroids) and will be required for
  - Subjects with leukemic blasts > 30% blasts in bone marrow (for AML)
  - Subjects with circulating leukemic cells
  - Subjects with rapidly progressive disease at investigator discretion
- *Conditioning regimen* (Day -4 to -2) will consist of fludarabine i.v. 25 mg/m2 (Day -4, Day -3, Day -2) and cyclophosphamide i.v. 900 mg/m2 (Day -2)
- *Infusion of IMP* (Day 0) will consist of a single dose of TEG001 cell suspension for infusion and will be administered intravenously at the designed dose level
- *Concomitant medication* will consist of a dose of Pamidronate (PAM) 30 mg which will be administered on Day 0 and on Day 28

Main study parameters/endpoints

The primary endpoint is the number of subjects with one or more dose-limiting toxicities (DLTs) in order to determine the maximum tolerated dose (MTD).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

The risk of administering TEG001 cell suspension for infusion is acceptable in light of the potential benefit of tumour control in the target population. The elaborate schedule of study events which includes a 7-day hospital admission and among others multiple blood and bone marrow samples, is deemed necessary to safely treat study subjects.

Schematic study scheme