

Memorial Sloan Kettering Cancer Center
IRB Number: 16-1570 A(12)
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MSK PROTOCOL COVER SHEET

A Phase I Trial of CD19-Targeted EGFRt/19-28z/4-1BBL "Armored" Chimeric Antigen Receptor (CAR) Modified T Cells in Patients with Relapsed or Refractory CD19+ Hematologic Malignancies

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Phase I Trial of CD19-Targeted EGFRt/19-28z/4-1BBL “Armored” Chimeric Antigen Receptor (CAR) Modified T Cells in Patients with Relapsed or Refractory CD19+ Hematologic Malignancies

Objectives: The primary objective is to assess the safety of intravenously administered EGFRt/19-28z/4-1BBL CAR T cells in patients with relapsed or refractory CD19+ hematologic malignancies.

Patient Population: Patients with CD19+ hematologic malignancies who have relapsed or refractory disease will be eligible for the study. Eligible disease subtypes include the following:

- Chronic lymphocytic leukemia (CLL)
- Indolent non-Hodgkin lymphoma (iNHL): FL, marginal zone lymphoma (MZL), Waldenstrom Macroglobulinemia (WM)
- Diffuse large B cell lymphoma (DLBCL), Transformed B cell lymphoma, High grade B cell lymphoma Acute lymphoblastic leukemia (ALL) including chronic myeloid leukemia (CML) in lymphoid blast crisis and Burkitt's lymphoma

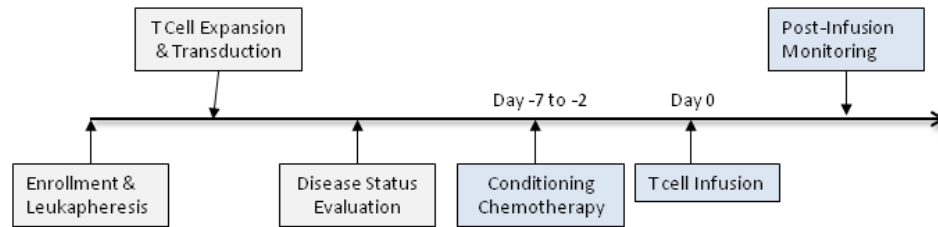
Study Design: This is a standard phase I dose escalation trial. Cohorts of 3-6 patients will be infused with escalating doses of EGFRt/19-28z/4-1BBL CAR T cells to establish the maximum tolerated dose (MTD). There are 4 planned dose levels: 1×10^5 , 3×10^5 , 1×10^6 , and 3×10^6 CAR T cells/kg (Table 1). 3-6 patients will be treated in each cohort and dose escalation will proceed to the next cohort if less than 33% of patients in a cohort experience unanticipated dose-limiting toxicity (DLT). If unacceptable toxicity is seen in 1 of 3 patients in any given cohort, up to 6 patients will be treated in that cohort using a conventional dose escalation scheme. If 2 of 6 patients in any given cohort experience unacceptable toxicity, the MTD of T cells will have been exceeded, and established at the previous cohort dose level. If the first dose level exceeds the MTD, a subsequent cohort of 3-6 patients will be treated at the -1 dose level of 3×10^4 EGFRt/19-28z/4-1BBL CAR T cells/kg.

Treatment Plan: Following enrollment, patients will undergo leukapheresis of peripheral blood for further T cell enrichment, activation and genetic modification using a retroviral vector encoding a CD19 targeted CAR, the co-stimulatory ligand 4-1BBL and the EGFRt safety system (EGFRt/19-28z/4-1BBL). These T cells will be expanded and after the appropriate number of cells is generated, the modified T cells may be infused fresh or frozen for later use according to standard operation procedures. Modified T cell infusions will be administered 2-7 days following completion of the conditioning chemotherapy. Serial sampling of blood and bone marrow will be performed following treatment to assess toxicity, therapeutic effects, and survival of the genetically modified T cells. For patients who have obtained clinical benefit from the initial T cell therapy and did not experience any non hematologic grade 4 toxicities, additional modified T cells may be re infused later at the treating physicians's discretion. If patients receive the second infusion during the DLT time, that DLT time will extend for an additional 4 weeks following the second infusion. For patients who were treated, had progression of disease and were removed from study, duplicate enrollment is permitted if it is determined the patients could receive a benefit. If the patients meet all eligibility criteria, they can be enrolled onto study a second time as a new accrual, and receive treatment in a higher dose level cohort.



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Time to Completion: At least 4 patients will be needed to complete this study. The amount of time required to complete this trial will depend on the number of dose levels studied and the number of patients accrued to each cohort. We anticipate enrolling on average 1-2 patients per month for a total accrual of 37 patients. Therefore, this trial will take 18-24 months to complete.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To determine the toxicity and maximum tolerated dose (MTD) of EGFRt/19-28z/4-1BBL CAR T cells in patients with relapsed or treatment-refractory CD19+ hematologic malignancies

Secondary Objective:

- To assess the anti-tumor efficacy of EGFRt/19-28z/4-1BBL CAR T cells.
- To assess the in vivo persistence of EGFRt/19-28z/4-1BBL CAR T cells.

Exploratory Objective:

- To assess the change in cellular and cytokine tumor microenvironment following CAR T cell infusions.
- To assess the impact of infused CAR T cells on the endogenous anti-tumor immune response.
- To assess development of B cell aplasia.
- To assess the level of minimal residual disease (MRD) following modified T cell infusions.



Indolent non-Hodgkin Lymphoma (iNHL)

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