

Memorial Sloan Kettering Cancer Center  
IRB Number: 06-138 A(12)  
Approval date: 21-Oct-2020

***MSK PROTOCOL COVER SHEET***

***A Phase I/IIa Trial For The Treatment of Relapsed or Chemotherapy Refractory  
Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous  
T Cells Genetically Targeted to the B Cell Specific Antigen CD19***

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## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

**Title:** A Phase I/IIa Trial for the Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma using Autologous T cells Genetically Targeted to the B cell Specific Antigen CD19

### **Objectives:**

**Phase I:** The primary objective is to assess the safety of autologous T cells genetically modified to express chimeric antigen receptor (CAR) targeting CD19 antigen (19-28z) with or without conditioning chemotherapy.

**Phase IIa:** The primary objective is to compare the relative engraftment and persistence of the two CAR modified CD19-targeted T cells expressing different co-stimulatory signaling domain CD28 (19-28z) and 4-1BB (CART-19:CD3z-4-1BB) in the CAR construct.

**Rationale:** Most patients with B cell leukemia and lymphoma remain incurable with current treatment modalities. We have developed a novel immunotherapy based on the genetic modification of patient T cells to recognize the B cell-specific cellular marker CD19. T cells can be genetically modified with a replication defective retroviral vector or lentivirus vector containing a gene encoding a CAR specific for the CD19 antigen attached to the costimulatory signaling domain of CD28 (19-28z) or 4-1BB (CART-19:CD3z-4-1BB), respectively. *In vitro*, both retrovirally transduced 19-28z<sup>+</sup> T cells and lentivirally transduced CART-19:CD3z-4-1BB<sup>+</sup> T cells lyse CD19<sup>+</sup> tumor cell lines. *In vivo*, 19-28z<sup>+</sup> T cells eradicate established systemic Burkitt lymphoma in a SCID-Beige model of disease, and CART-19:CD3z-4-1BB<sup>+</sup> T cells eradicate established acute lymphoblastic leukemia (ALL) in NOD/SCID/ $\gamma$ c<sup>-/-</sup> mice. In order to compare the performance of co-stimulatory signaling domains (CD28 vs. 4-1BB) and viral vector system (retrovirus vs. lentivirus) *in vivo*, some patients on the trial will receive the 19-28z<sup>+</sup> and CART-19:CD3z-4-1BB<sup>+</sup> T cells mixed at 1:1 ratio. In addition, based on the preclinical evidence that conditioning chemotherapy prior to the T cell infusion enhances engraftment, expansion and long-term survival of these adoptively transferred modified T cells, some patients on this trial will receive infusions of modified T cells following conditioning chemotherapy.

**Patient Population:** Patients with CD19<sup>+</sup> chronic lymphocytic leukemia (CLL) or CD19<sup>+</sup> indolent B-cell lymphoma who have relapsed or chemotherapy refractory disease, or who have evidence of residual disease following therapy will be eligible.

**Study Design:** This is a two-stage protocol, consisting of a single-institution phase I safety study and multi-institution phase IIa extension study. The first stage is a standard 3-step phase I dose escalation trial to assess the safety of 19-28z CAR expressing autologous T cells with or without prior conditioning chemotherapy. In Step 1, a cohort of patients will receive the lowest planned dose of 19-28z<sup>+</sup> modified T cells. In Step 2, a cohort of patients will receive cyclophosphamide conditioning chemotherapy followed by the lowest planned dose of 19-28z<sup>+</sup> modified T cells. If less than 33% of patients in the cohort experience unanticipated dose-limiting toxicity, in Step 3, a cohort of patients will be treated with the investigator's choice conditioning chemotherapy followed by the higher dose of 19-28z<sup>+</sup> modified T cells. If less than 33% of patients in the initial cohort (Step 3) experience unanticipated dose-limiting toxicity, the cohort in Step 3 may be expanded to include up to 15 patients. In Step 3, an additional cohort of Waldenstrom's

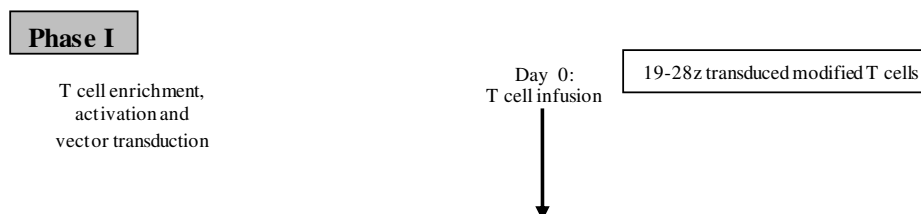
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Macroglobulinemia (WM) patients will be treated with the investigator's choice conditioning chemotherapy followed by 19-28z<sup>+</sup> T cells. However, to maximize safety for WM patients, they will be treated at the lower dose of modified T cells ( $1 \times 10^6$  19-28z<sup>+</sup> T cells/kg). If no toxicity is observed in the initial cohort, the dose may be increased in a standard 3-step dose-escalation scheme as described above.

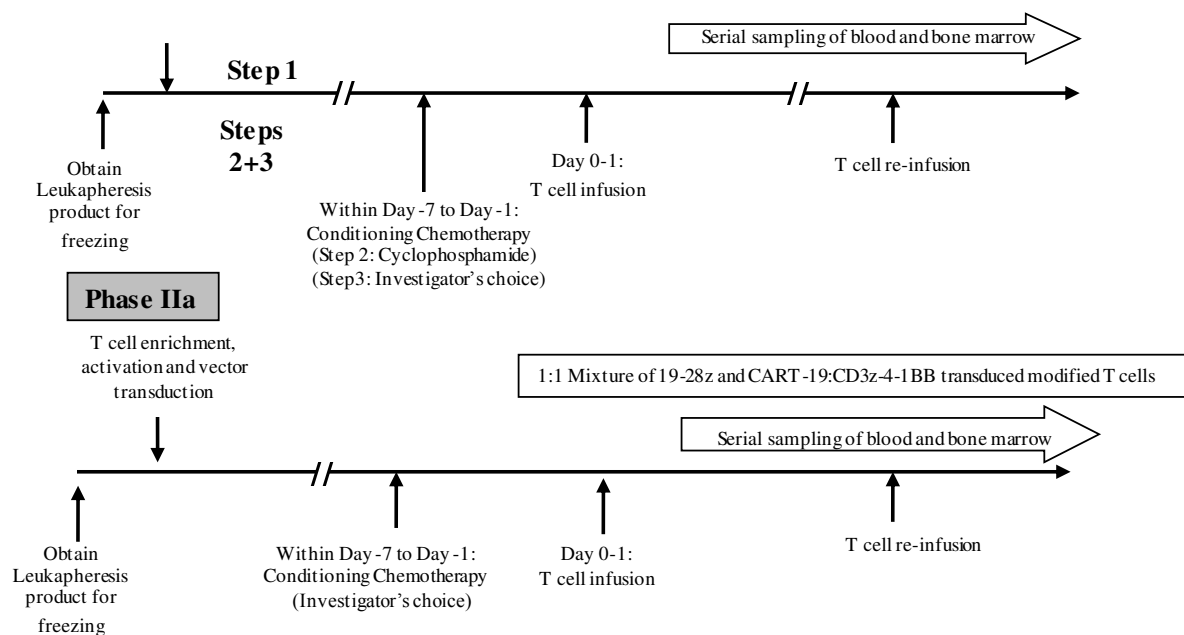
In the phase IIa extension part of the study, 12 patients from MSKCC will be enrolled, and be treated with co-infusion of 19-28z and CART-19:CD3z-4-1BB<sup>+</sup> modified T cells mixed at 1:1 ratio at the MTD of T cells determined from the phase I trial. The phase IIa is a multi-institution study where a total 24 patients will be enrolled; 12 patients from MSKCC, 6 patients from the University of Pennsylvania (protocol #805613), and six patients from the Children's Hospital of Pennsylvania. Data collected from this portion of the study will be analyzed as a pooled meta-analysis.

**Treatment Plan:** Following enrollment, patients will have a leukapheresis product obtained from peripheral blood in the blood donor room at MSKCC. Collected leukapheresis product will be transported to the Gene Transfer and Somatic Cell Engineering Facility (GTF) and stored in liquid nitrogen. On a suitable day, the cryopreserved cells will be thawed, and T cells will be transduced with either a retroviral vector for the 19-28z CAR or a lentiviral vector for the CART-19:CD3z-4-1BB chimeric receptor. These T cells will be expanded and after the appropriate number of cells is generated, the modified T cells may be infused fresh or be frozen according to standard operation procedures. Modified T cell infusions will be administered either as a single infusion (Step 1), or in a fractionated manner with approximately 1/3 of the T cell dose infused on the first day and the remaining 2/3 of the dose the next day (Steps 2/3 and Phase IIa). In Steps 2-3 (Phase I) and in the Phase II portion of the protocol, the modified T cell infusion will occur 2-7 days following the completion of 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 physician's discretion.

The overall treatment schema of the protocol is shown below.



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**Time to Completion:** A minimum of four patients and a maximum of 22 patients will be needed to complete the phase I portion of the study. The Phase IIa extension study is a multi-institution study where 12 patients will be enrolled from MSKCC for this trial. 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 4-30 patients. Therefore, this trial will take 3 years to complete.

## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

### Primary objective:

- **Phase 1:** The primary objective is to assess the safety of autologous T cells genetically modified to express chimeric antigen receptor (CAR) targeting CD19 antigen (19-28z) with or without conditioning chemotherapy.
- **Phase IIa:** The primary objective is to compare the relative engraftment and persistence of the two CAR modified CD19-targeted T cells expressing different co-stimulatory signaling domain CD28 (19-28z) and 4-1BB (CART-19:CD3z-4-1BB) in the CAR construct.

### Secondary objectives:

- To compare the *in vivo* survival of genetically modified 19-28z CAR+ T cells after T cell infusion alone or in combination with conditioning chemotherapy.
- To compare the gene transfer/expression efficiency of the two viral vectors (retrovirus vs. lentivirus).
- To assess the anti-leukemic activity of adoptively transferred CD19-targeted modified T cells linked to the CD28 (19-28z) and 4-1BB signaling domains (CART-19:CD3z-4-1BB).