

Section 2. Scientific Abstract

This single-center, proof-of-concept human gene therapy trial (protocol IRB# Pending) evaluates the safety, feasibility, and persistence of adoptively transferred CD19-specific allogeneic T cells in research participants with advanced B-cell malignancies after receiving donor derived hematopoietic progenitor cells. The T cells, are rendered specific for CD19 by electrotransfer, using a Nucleofector device, of two *Sleeping Beauty* (SB) DNA plasmids expressing (i) SB11 hyperactive transposase and (ii) transposon coding for chimeric antigen receptor (CAR), designated CD19RCD137, that can activate T cells through chimeric CD137 and CD3-z endodomain upon binding cell surface CD19 via a scFv derived from an anti-human CD19 mouse monoclonal antibody. In compliance with current Good Manufacturing Practice (cGMP) for Phase I/II trials, the genetically modified T cells are recursively expanded to clinically-meaningful doses on gamma-irradiated artificial antigen presenting cells (aAPC, designated "clone 4") derived from a master cell bank (or a derived working cell bank) of K562 cells those were genetically modified by lentiviral transduction to co-express (i) CD19, (ii) 4-1BBL (CD137L), (iii) CD86, (iv) CD64 and (v) a membrane-bound IL-15 (mIL-15). The same SB DNA plasmids and aAPC are currently used for three investigator-initiated clinical trials NIH/OBA RAC# 0804-922, 0910-1003, 1001-1022 with respective FDA-approved IND# 14193, 14577, 14739 which infuse patient-derived and donor-derived CD19-specific T cells after autologous and allogeneic hematopoietic stem-cell transplantation. Two other trials (NIH/OBA RAC # 1201-1142 and 1210-1192) seek to infuse T cells in patients with CLL after lymphodepleting chemotherapy. We note that proposed trial is similar to our trial targeting CD19 on B-cell, (IRB # 2009-0525, RAC # 0910-1003, IND# 14577) infusing allogeneic CD19-specific T cells in patients with B-cell after infusion of donor derived hematopoietic progenitor cells. The major change in the current trial compared to RAC# 0910-1003 is that we now propose a CAR that activates T cells through CD137 signaling endodomain (CD19RCD137) instead of CD28 T-cell signaling domain (CD19RCD28). Based on the recent data from us and others, inclusion of CD137 signaling domain in CAR has shown to improve *in vivo* persistence of genetically modified T cells, which influences clinical outcomes in tumor-bearing mouse models as well as in humans. In the upcoming trial, research participants will be eligible to receive one planned intravenous infusion of donor-derived genetically modified ex vivo-propagated T cells after infusion of donor derived hematopoietic progenitor cells. Additional T-cell modifications may be undertaken pending institutional and federal regulatory approvals. It is estimated to take up to 50 days to manufacture and release the genetically modified T cells. The primary objective of this study are to assess the safety, feasibility, and persistence of the allogeneic donor-derived T-cell infusions. The secondary objectives are to assess the (i) host immune response against the CD19-specific chimeric antigen receptor, (ii) homing ability of the adoptively transferred T cells, and (iii) disease response. The first patient will be enrolled in the first cohort at Dose level A (not to exceed $10^6/m^2$) and after 3 T-cell infusions have been completed, the successive cohorts of patients at Dose level B,C,D will be enrolled. The T-cell infusion dosing for subsequent cohorts are as follows: Dose level B $>10^6/m^2$ but less than or equal to $10^7/m^2$, Dose level C $>10^7/m^2$ but less than or equal to $5 \times 10^7/m^2$, Dose level D $>5 \times 10^7/m^2$ but less than or equal to $10^8/m^2$. We will employ three parallel (3+3) designs to find the maximum tolerated dose (MTD) of DLI in each of the following four treatment arms: Arm 1: DLI will be administered intravenously between 6 weeks and 12 weeks following date of transplant as a planned DLI. Arm 2: DLI will be administered at any point after disease recurrence following transplant in pediatric and adult patients. Arm 3: DLI will be administered intravenously between 6 weeks and 12 weeks following date of transplant as a planned DLI in pediatric patients, aged 1-17 years-old. Arm 4: DLI will be administered as planned DLI or after recurrence in adult and pediatric patients undergoing transplant with a haplo-identical family donor. We will enroll a maximum of 24 patients in cohorts of size 3 in each treatment arm for a total maximum accrual of 96 patients. We will start at the lowest of 4 doses and search for the MTD in each arm. We anticipate that not all enrolled patients will receive an infusion.