A First-in-Human Phase I Trial of NKG2D Chimeric Antigen Receptor-T Cells in AML/MDS and Multiple Myeloma

Sarah Nikiforov1,2, Joana Murad1, Heather Daley1, Helene Negre1, Jake Reder3, Charles L. Sentman4, Frédéric Lehmann5, Sarah Sninsky5, Rachel Allen6, Ilene Galinsky1, Nikhil Munshi7, Richard Stone1,2, Robert Soiffer1,2, Jerome Ritz1,2, Susanne Baumeister1,2,6

Abstract

Background: Canvarol CAR T cell constructs encode a single chain antibody variable fragment, complementarity determining domains, and signaling domain of CD3ζ. This construct recognizes T1 tumor antigen and a limited set of cancers. This study employs a novel CAR using full-length human Natural Killer Group 2D (NKG2D) gene with the human CD3ζ intracellular signaling domain. NKG2D CAR receives costimulation via naturally expressed DA10 and activates T cells directly to kill and secrete cytokines upon recognition of MICA, MICB, UL16, and UL18 binding proteins. These NKG2D ligands are up-regulated in many solid tumors and hematologic malignancies but absent or poorly expressed on healthy tissues. In multiple myeloma cancers, NKG2D CAR T cells induced complete remissions, T cell memory, and altered tumor microenvironment via cytokines. We demonstrated manufacture of autologous NKG2D CAR T-cells in a GMP environment from healthy adults and patients with AML and myeloma was feasible. Following isolation of mononuclear cells, T cells are activated with anti-CD3 and IL-2, undergo 2 transductions with SPG retroviral vector containing NKG2D CAR construct, and expand in media containing IL-2. Validation studies yielded consistent robust cell expansion, high vector-driven NKG2D expression on T cells, potent IFNγ production during tumor cell co-culture, viral copy number/cell < 5, and no replication-competent retrovirus in NKG2D CAR (CM)-T cells.

Methods: A phase I dose-escalation study to establish safety and feasibility of a single infusion of CM-CS1 T cells without lymphodepleting conditioning is currently enrolling subjects with AML/MDS-RB±E without standard therapy options or relapsed/refractory progressive multiple myeloma (ClinicalTrials.gov: NCT01751505). Dose-escalation will proceed in 8 cohorts (3×2 to 3×3 CM-CS1 T cells) according to a 3+3 design followed by expansion cohorts at the MTD in AML/MDS and myeloma.

As of May 2016, 6 subjects have been treated. Three cohorts have been completed without DLTs. Enrollment to Cohort 4 is proceeding as planned. Future studies may include lymphodepletion, multiple infusions, and cytokine chemotherapy in both hematologic and solid tumor malignancies.

Objectives: To assess the safety, immunologic characterization, and clinical activity of autologous NKG2D CAR-T cells.

Trial Design and Experience to Date

Phase 1 Dose-Escalation Trial—Single Infusion

 inclusion criteria
- Histologically confirmed AML, MDS-RB±E not in remission and without reasonable standard treatment options
- Relapsed/refractory progressive multiple myeloma with progressive disease

exclusion criteria
- Chemotherapy or radiotherapy within 3 weeks of infusion
- Active infections, autoimmune disease or CNS involvement
- Prior T cell, stem cell or gene-modified cellular therapy

Objectives
- Safety and feasibility
- Secondary—Progression-free survival and clinical anti-tumor effect
- Up to 15 years of gene therapy safety monitoring

Key Design Aspects
- Single dose IV administration of CM-CS1 T cells
- No prior lymphodepleting chemotherapy
- 3+3 escalation - clinical Fibonacci sequence
- At least 1 patient with each disease cohort
- Escalation design allows determination of separate MTDs for individual diseases
- Multiple safety evaluation periods

Correlative Immunobiology Objectives
- Persistence, trafficking and biactivity of CM-CS1 cells
- Impact on endogenous milieu and secondary anti-tumor responses
- Levels of soluble NKG2D ligands and antibodies against NKG2D ligand expression to assess antigen-escape

Experience to Date
- 9 patients treated in first 3 cohorts
- Feasibility and safety — no DLTs to date

Multiple Potential Mechanisms of Action

NKG2D CAR technology is R&D Manager at Celdara Medical, LLC; 4. Geisel School of Medicine at Dartmouth, 5. Children’s Hospital Boston, 6. Children’s Hospital of Philadelphia, 7. Children’s Hospital in Cleveland, OH. Affiliations/Disclosures

References
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