Abstract

Introduction: Conventional CAR T-cells in current clinical trials express a single-chain antibody variable fragment that restricts recognition to various UL16 binding proteins (ULBPs 1-6). We have developed a third-generation CAR T cell (CS1 T cell) with a single chain variable fragment that restricts recognition to NKG2D ligands, including MHC class I chain-related A (MICA) and B (MICB). In preclinical models, CS1 T cells without cytotoxicity related to CAR T cells when exposed to ULBPs and MICA/B.

Background

• Pre-clinical and clinical observations emphasize the role of NKG2D-expressing cells in immune surveillance and antitumor immunity
• NKG2D is an activating receptor expressed on natural killer cells and other hematopoietic cells as a homodimer in association with the natural adapter protein DAP10, which provides costimulation and is critical for cell survival and cytokine expression
• NKG2D ligands consist of MHC class I-related proteins HLA-E, -G, -F, and various UL16 binding proteins (ULBPs 1-6), also called RAET1 proteins
• NKG2D ligands, often multiple ligands, are found on lymphocytes, monocytes, macrophages, oversensitive cancer cells, melanoma, and ovarian cancer, as well as on other malignancies but protein expression is absent or minor in healthy tissues
• In syngeneic murine models of leukemia, myeloma, melanoma, ovarian cancer, and breast cancer, NKG2D may be upregulated in tumors and have a role in antitumor immunity

Methods:

• Objectives: To determine the safety, efficacy, and characteristics of autologous CS1 T cells in patients with myeloma without standard therapy options (NCT02203825).

• Tumor assessment with serial blood samples and bone marrow aspirates was conducted to evaluate CS1 T-cell proliferation and persistence.

• CS1 T cells were dosed on viable T cells, measuring CS1 T cells, and detecting CS1 T cells without cytotoxicity related to CAR T cells when exposed to ULBPs and MICA/B.

• All myeloma patients had undergone at least 1 pt from each disease group at each dose level.

Introduction:

At these initial cell doses, no patient to date has had an objective tumor response at the high cell doses tolerated, with no DLTs. CAR T cells generally have not persisted beyond 1 week, and there have been no cases of cytokine release syndrome, cell death, or tumor lysis syndrome.

At least 1 pt from each disease group at each dose level.

Phase I: Dose-Escalation Trial—Single Infusion

Safety Data from a First-in-Human Trial of NK2G01 Chimeric Antigen-Receptor T Cells in AML/MDS and Multiple Myeloma

Safety and feasibility of a single infusion of CM-CS1 T cells without lymphodepleting conditioning in 13 evaluable subjects with AML/MDS or refractory relapsing multiple myeloma (MM) without standard therapy options (NCT02203825). Dose-escalation spanned 4 cohorts [half-log increments from 1x10⁶ to 3x10⁸ CM-CS1 T cells] according to a 3+3 design.

Results:

From April 2015 through July 2016, 11 subjects were infused, and 10 completed the DLT period. Eight of 11 were male, and all had AML/HDS, and median age was 70 (range 44-79). Median percentage of blasts in bone marrow for AML/HDS patients was 50% (range 4-68%). All myeloma patients had undergone ≥1 therapies including ≥1 autologous SCT.

Dose-escalation proceeded from 1x10⁵ to 3x10⁸ CM-CS1 T cells, dosed on viable T cells. The first 3 subjects completed their 28 day evaluation period without DLTs. There have been no cases of cytokine release syndrome, cell death, or tumor lysis syndrome.

Conclusion:

Future clinical trials are planned.

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