Safety Data from a First-in-Human Phase 1 Trial of NKGD2 Chimeric Antigen Receptor T Cells in AML/MDS and Multiple Myeloma

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**Abstract/Summary:** This study employed a novel CAR fusing full-length human NKG2D with CD3ζ, that is capable of recognizing the multiple NKG2D ligands upregulated in multiple solid and hematologic malignancies.

**Trial Design:** A Phase 1 dose-escalation study was conducted to establish safety and feasibility of infusing NKG2D-CAR expressing T cells without lymphodepleting conditioning in subjects with AML/MDS-RARE or relapsed/refractory progressive multiple myeloma.

**Results:** From April 2015 through November 2016, 12 patients were infused in 4 cohorts from 1x10^6 to 3x10^6 NKGD2 CAR T cells. 7 subjects had AML/MDS.

**Feasibility:** CM-51 cells met release criteria in all cases. A median of 75.4% CD3+ T cells and 66.3% CD8+ T cells expressed the CAR construct.

**Safety:** No DLTs were seen.

**Activity:** At all these initial cell doses, there were no objective treatment responses at 28 days, although cases of unexpected survival without further therapy or in response to subsequent treatments were noted.

**Post-infection monitoring:** As anticipated from animal models, no CAR-T cell engraftment was detected, with one exception.

**Preliminary immune cell phenotyping and cytokine assays revealed no characteristic profiles except perhaps a transient spike in Rantes levels at 24 hours, specifically in patients with AML.

**In vitro correlatives:** All NKGD2 CAR-T products tested expressed IFNs in response to NKGD2 ligand-positive cell lines, and in 2 exploratory cases, against autologous CD34-containing PBMCs, and with NKG2D blocking antibodies.

**Next steps:** Correlative studies continue to elucidate in vivo function. Future studies of multiple infusions and higher doses of NKGD2 CAR-T cells in both hematologic malignancies and solid tumors is in planning to build upon these experiences.

**NLKG2D (Natural Killer Group 2D)-expressing cells play a role in immune surveillance.**

**NKGD2 is an activating receptor on natural and CAR Redirected T cells that can be recruited and expanded to completely replace wild-type lymphodepleting therapy and durable CD8+ T cell memory capable of protecting against tumor rechallenge, despite relatively short-term circulation in studies of CAR-T cells themselves.”

**NKG2D ligands consist of MHC Class I-related proteins MICA, MICB and ULBP binding proteins (ULBP1-6) and are found on multiple hematologic and solid malignancies but are largely absent on healthy tissue.”

**In syngeneic murine models of leukemia, myeloma, pancreatic cancer, melanoma, and ovarian cancer, adaptive therapy with NKGD2 CAR-T cells led to complete remissions without need for lymphodepleting therapy and durable CD8+ and CD4+ T cell memory.”

**Objectives:** Primary – Safety and feasibility

- Secondary – Progression-free survival and clinical anti-tumor effect

- ≥ 3 G3 non-hematologic toxicity or ≥ 2 Gr 4 CAR T cell-related autoimmunity

**Response Criteria:**

- **Safety Data from a First-in-Human Phase 1 Trial of NKGD2 Chimeric Antigen Receptor T Cells in AML/MDS and Multiple Myeloma**

**Background**

- NKGD2 (Natural Killer Group 2D)-expressing cells play a role in immune surveillance,

- NKGD2 is an activating receptor on natural and CAR Redirected T cells that can be recruited and expanded to completely replace wild-type lymphodepleting therapy and durable CD8+ T cell memory capable of protecting against tumor rechallenge, despite relatively short-term circulation in studies of CAR-T cells themselves.

- NKG2D ligands consist of MHC Class I-related proteins MICA, MICB and ULBP binding proteins (ULBP1-6) and are found on multiple hematologic and solid malignancies but are largely absent on healthy tissue.

- In syngeneic murine models of leukemia, myeloma, pancreatic cancer, melanoma, and ovarian cancer, adaptive therapy with NKGD2 CAR-T cells led to complete remissions without need for lymphodepleting therapy and durable CD8+ and CD4+ T cell memory capable of protecting against tumor rechallenge, despite relatively short-term circulation in studies of CAR-T cells themselves.

- All AML and MM patients had progressive disease or treatment failure.

- As of Dec, 2016, 7 of 12 subjects had died of their disease. Overall survival is 4.8 mos.

- 5 patients had “stable disease” in at least 1 parameter, and 4 each had “progressive disease” in at least 1 parameter.

- 1 patient (T7, AML, dose 1x10^6) demonstrated “stable disease” at 3 mos. He has improvement in all hematological parameters.

- Patient 7 (AML, dose 1x10^6), despite 50% blasts and p53 mutation at infusion, demonstrated relative peripheral blood hematologic stability for 3 months. Marrow results were not available.

- Patient 5 maintained stable disease (borderline on PR) for 8 mos. In an exploratory case of a patient with acute myeloid leukemia who had stable disease on multiple cycles of chemotherapy, patient had stable disease through the first 3 mos. of treatment.

- Patient 3 (MM, dose 1x10^6) demonstrated tumor progression (bordered on PR) in the marrow风筝 and spleen, but disease remained stable in the peripheral blood.

- No patients had disease progression subsequent to infusion reactions.

- Among AML/MDS and MM patients, a single dose of NKGD2 CAR-T cells without lymphodepleting therapy was feasible and well tolerated without DLTs over 28 days post infusion.

- Objective clinical responses were not seen. However, cases of unexpected survival and/or improvement in hematologic parameters were noted in both AML and MM patients, some with and without subsequent therapy.

- **Conclusion:**

Among AML/MDS and MM patients, a single dose of NKGD2 CAR-T cells without lymphodepleting therapy was feasible and well tolerated without DLTs over 28 days post infusion.

- Objective clinical responses were not seen. However, cases of unexpected survival and/or improvement in hematologic parameters were noted in both AML and MM patients, some with and without subsequent therapy.

**NKGD2 CAR-T-specific activity against autologous tumor models was demonstrated in an in vitro study of 2 patients tested.**

**This paves the way for studies of multiple infusions and higher doses of NKGD2-expressing CAR-T cells in numerous malignancies.”**