

Immunophenotype and Persistence of CD4⁺ and CD8⁺ T Cells in the Phase I Trial of a TCR-T Cell Therapy Targeting MAGE-A4

Hong DS. *et al.* Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. *Nature Medicine* 2023. <https://www.nature.com/articles/s41591-022-02128-z>

BACKGROUND

The intracellular melanoma-associated antigen A4 (MAGE-A4) is expressed in multiple solid cancers. Peptides of MAGE-A4 co-presented with human leukocyte antigens (HLA) are weakly recognized by natural T-cell receptors (TCR). This phase I trial examines the safety and dose range of afamitresgene autoleucel (afami-cel), an autologous T cell therapy created by Adaptimmune that expresses a high-affinity TCR targeting MAGE-A4 on HLA-A*02.

STUDY DESCRIPTION

Patients (38) diagnosed with 9 different solid tumor types received afami-cel infusion in 1 of 4 dose ranges. They were followed post-infusion to evaluate adverse events (AEs), dose-limiting toxicity (DLTs), persistence of the manufactured product, and clinical endpoints like partial response (PR), stable disease (SD), and progressive disease (PD). GMP-grade MHC Dextramer[®] reagents and flow cytometry were used to identify transduced CD8⁺ and CD4⁺ cells, assess transduction, determine phenotype composition of the manufactured product, and investigate the kinetics and long-term persistence of the therapy including population composition in post-infusion PBMC samples.

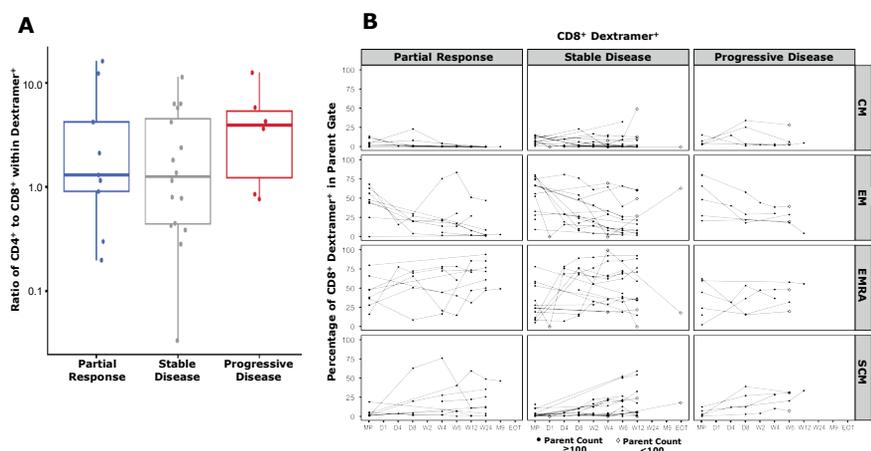
RESULTS

- The ratio of transduced CD4⁺ to CD8⁺ T cells in the infused product varied from 16.16 to 0.03, mostly biasing CD4⁺ cells. Median ratio was similar across clinical response (**Figure 1A**).
- afami-cel persistence peaked 7 days after infusion in most patients. Infused transduced cells were predominantly effector memory cells (EM) and terminally differentiated effector memory cells (EMRA).
- EMRA cells showed sustained presence over time, while the stem cell memory phenotype gradually increased (**Figure 1B**). Phenotype composition of the infused product was not associated with clinical response.

Fig.1. Composition of afami-cel before and after infusion.

GMP-grade MHC Dextramer[®] reagents were used to assess A) CD4-to-CD8 ratio of the manufactured product, and B) cell type subsets before and after infusion.

CM = central memory
EM = effector memory
EMRA = effector memory RA+
SCM = Stem cell memory



CONCLUSIONS

- afami-cel achieved clinically significant results for patients with multiple solid tumor types and showed a 94% disease control rate in patients with synovial sarcoma.
- CD4⁺ and CD8⁺ composition and phenotype profile of the manufactured product before and after infusion did not play a significant role in patient response to treatment.
- MHC Dextramer[®] (GMP) reagents offer high sensitivity, specific detection of engineered TCR-T cells, and enable the detailed characterization and longitudinal evaluation of a manufactured T cell therapy product.