Afamitresgene Autoleucel (Afami-cel; Formerly ADP-A2M4) Demonstrates Durable Clinical Responses by Inducing Broad Immune Engagement With Anti-Tumor Activity

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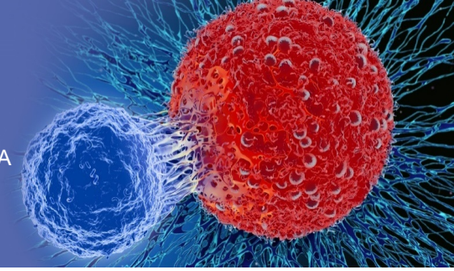


Introduction

- Afami-cel is a mixed CD4+ CD8+ autologous T-cell receptor (TCR) T-cell therapy engineered to target the cancer testis antigen melanoma-associated antigen A4 (MAGE-A4) in human leukocyte antigen (HLA) A*02-positive patients with advanced/metastatic synovial sarcoma (SyS) or myxoid/round cell liposarcoma (MRCLS)
- Pooled data from the Phase 1 (NCT03132922) and Phase 2 (SPEARHEAD-1, NCT04044768) trials of afami-cel showed an acceptable benefit-to-risk profile, with an overall response rate of 36.2% and a median duration of response of 52.0 weeks in SyS and MRCLS[1]
- To support the continued investigation of potential mechanisms of durable anti-tumor activity, we previously showed that afami-cel induces broad and enduring peripheral cytokine responses[2] and that afami-cel tumoral infiltration is associated with increased presence of activated and proliferative cytotoxic T-cells in the tumor microenvironment[3]
- Here, we report the results of translational analyses exploring immune system responses in SyS and MRCLS patient samples from the Phase 1 and 2 trials (data cutoff: Phase 1, September 1, 2020; Phase 2, August 29, 2022)

Methods

- Exploratory peripheral analyses measured 92 proteins simultaneously using Olink Target Immuno-Oncology panel (Olink, Boston, MA) in pre- and post-treatment serum samples from 68 patients
- Tumoral immune profiles were characterized in pre- and post-infusion biopsies from ≥15 patients:
  - Single-plex immunohistochemistry (IHC) staining for MAGE-A4, CD3, and HLA Class I identification
  - Duplex IHC/in situ hybridization using RNAscope technology (Advanced Cell Diagnostics, Newark, CA) for CD3 and engineered TCR T-cell identification
  - Multiplex immunofluorescence to analyze the immunophenotypes of cell types involved in innate and adaptive immunity (Ultivue, Cambridge, MA)
  - Gene set variation analysis of Reactome[4] immune system pathway categories and microenvironment cell populations (MCP) in RNA sequencing data (Q2 Solutions | EA Genomics, Morrisville, NC; Personalis, Menlo Park, CA)

Results

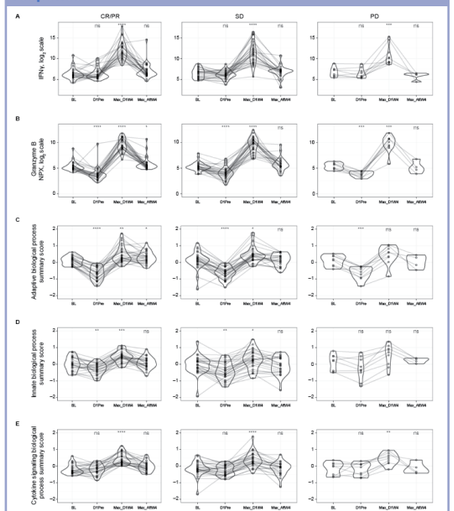
Afami-cel induces broad peripheral immune responses

- Serum analyses showed significant post-treatment responses in markers associated with multiple pathways, including cytokine signaling and gene expression, eg, interferon gamma (**Figure 1A**), programmed cell death and signal transduction, eg, granzyme B (**Figure 1B**)
- Serum from patients with disease control (complete or partial response, stable disease) showed a significant increase after afami-cel infusion in marker subsets categorized in the adaptive (**Figure 1C**) and innate (**Figure 1D**) immune systems, and a more significant increase in cytokine signaling markers (**Figure 1E**), compared with samples derived from patients with progressive disease

Afami-cel induces broad tumoral immune system engagement and immune cell infiltrate that associates with durable clinical tumor shrinkage

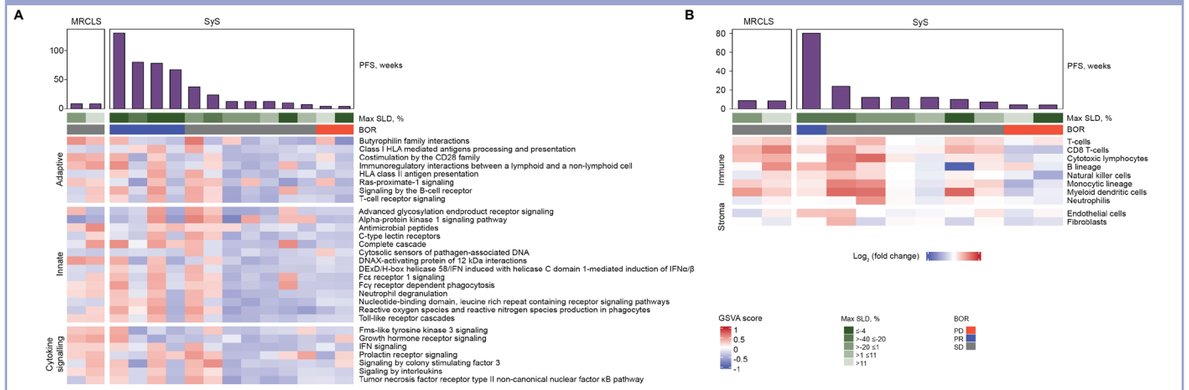
- Baseline tumor analyses showed relatively greater expression of genes associated with adaptive immune, innate immune, and cytokine signaling gene expression in patients with SyS who had relatively longer progression-free survival (PFS) (**Figure 2A**)
- Generally, SyS patients with longer PFS showed greater fold-change in MCP-defined immune cells after afami-cel infusion (**Figure 2B**), consistent with relatively greater spatial protein detection of pro-immune infiltrate (**Figure 3**)

Figure 1. Afami-cel induces broad peripheral immune responses



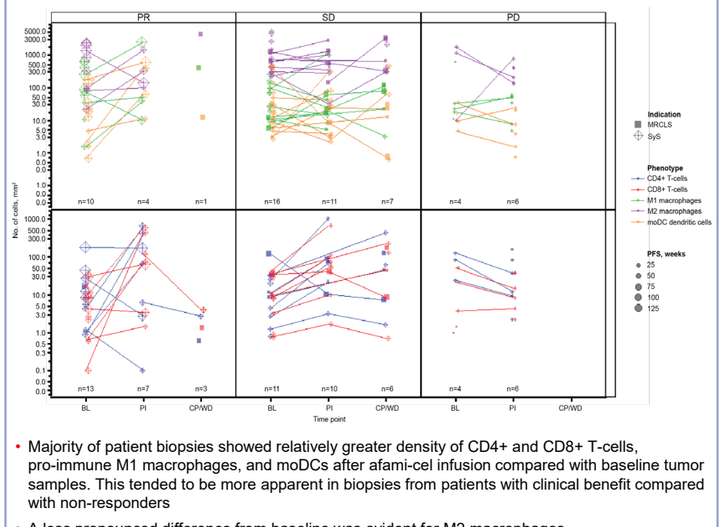
Serum levels (Log_2NPX) of (A) IFNγ and (B) granzyme B. Z-score for serum levels of markers (number) categorized in Reactome[4] immune system pathways: (C) adaptive (14), (D) innate (8), and cytokine signaling (39). Data points represent value per patient in samples taken at baseline, Day 1 pre-infusion, and the maximum value within 4 weeks (Max_D1W4) and beyond 4 weeks (Max_AftW4) post infusion. Total of 68 patients including 2 CR (SyS), 27 PR (25 SyS, 2 MRCLS), 30 SD (23 SyS, 7 MRCLS) and 9 PD (8 SyS, 1 MRCLS) by RECISTv1.1. BL, baseline; CR, complete response; IFN, interferon; MRCLS, myxoid/round cell liposarcoma; NPX, normalized protein expression; ns, not significant; PD, progressive disease; PR, partial response; SD, stable disease; SyS, synovial sarcoma. Wilcoxon test comparison of BL vs. other three time point/ranges: *P< 0.05; **P<0.01; ***P<0.001; ****P<0.0001

Figure 2. Differential tumor gene expression in relation to immune response and cell population



(A) RNAseq expression data from pre-infusion MRCLS and SyS tissue samples showing adaptive immune, innate immune, and cytokine signaling pathways. (B) Post infusion over baseline fold change in RNAseq expression for analysis of microenvironment cell populations in tissue samples. BOR, best overall response per RECIST v1.1; GSVA, gene set variation analysis; HLA, human leukocyte antigen; IFN, interferon; MRCLS, myxoid/round cell liposarcoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RNAseq, RNA sequencing; SD, stable disease; SLD, sum of longest diameters of target lesions; SyS synovial sarcoma

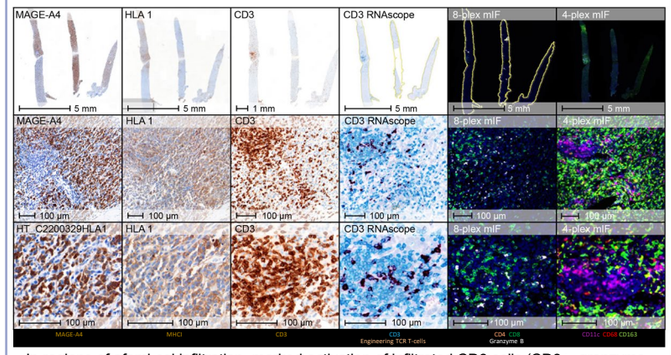
Figure 3. Trend for greater immune infiltrate in post-afami-cel tumor biopsies



- Majority of patient biopsies showed relatively greater density of CD4+ and CD8+ T-cells, pro-immune M1 macrophages, and moDCs after afami-cel infusion compared with baseline tumor samples. This tended to be more apparent in biopsies from patients with clinical benefit compared with non-responders
- A less pronounced difference from baseline was evident for M2 macrophages
- HLA Class I expression was generally greater after afami-cel infusion, consistent with a relatively higher immune infiltrate (data not shown)

Density (no. cells per mm^2 tumor) of immune cell phenotypes in baseline and post-treatment biopsies. Pixel size correlates with PFS (weeks). n indicates number of tumor biopsies per time point per clinical response group. Samples from the same patient are connected by the line. BL, baseline; CP/WD, completion/withdrawal; H-score, histoscore; HLA, human leukocyte antigen; moDC, monocyte-derived dendritic cells; MRCLS, myxoid/round cell liposarcoma; PI, post infusion; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SyS, synovial sarcoma

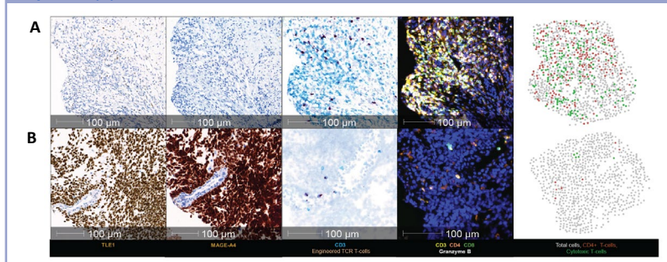
Figure 4. Afami-cel and immune infiltration into MAGE-A4– and HLA I–positive tumor regions



- In regions of afami-cel infiltration, marked activation of infiltrated CD8 cells (CD8+, granzyme B+) and high densities of monocyte-derived dendritic cells (CD11c+, CD163+), M1 (CD68+) and M2 (CD163+) macrophages is evident, indicating induction of innate and adaptive immunity

Consecutive sections of biopsy taken 240 days after afami-cel infusion, showing infiltration of CD3+ and engineered TCR T-cells into regions positive for both MAGE-A4 and HLA Class I. HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen A4; mIF, multiplex immunofluorescence; MRCLS, myxoid/round cell liposarcoma; SD, stable disease; TCR, T-cell receptor

Figure 5. Comparative post-afami-cel tumoral profiles from a responder (A) and non-responder (B)



- Images reveal relatively greater detection of activated cytotoxic T-cells (CD3+, CD4+, CD8+, granzyme B+) and afami-cel (CD3+TCR+) in post-treatment tumor biopsies from a patient with PR (A) compared with a patient with PD (B)
- Also noted was a reciprocal detection of tumor cells (TLE-1+ and MAGE-A4+) in these regions, which were relatively high in post-infusion biopsy samples from a patient with PD (B) compared with negligible detection in a patient with PR (A)

IHC and multiplex immunofluorescence images from a non-responding (PD) and a responding (PR) patient; stacked images were analyzed using HALO image analysis software (Indica Labs, Albuquerque, NM) to generate multi-color images and spatial plots of selected phenotypes. IHC, immunohistochemistry; MAGE-A4, melanoma-associated antigen A4; PD, progressive disease; PR, partial response; TCR, T-cell receptor; TLE-1, transducin-like enhancer of split 1

Conclusions

- Afami-cel induces peripheral and tumoral innate and adaptive immune responses, a hallmark of durable anti-tumor activity
- Following afami-cel infusion, a greater tumoral immune infiltrate was demonstrated at the gene and spatial protein levels compared with baseline
- RNA sequencing and serum analysis has elucidated some key insights into biological pathway activation, that encourages further investigation

892: American Association for Cancer Research (AACR), April 14–19, 2023; Orlando, FL, USA

References

1. D'Angelo SP, et al. J Clin Oncol. 2022;40(suppl 16):11562. 2. D'Angelo SP, et al. Poster 146 presented at: CTOS 2021; Virtual. 3. Van Tine, BA et al. Paper 61 presented at: CTOS 2022; Vancouver, BC, Canada. 4. Gillespie M, et al. Nucleic Acids Res. 2022; 50(D1):D687

Footnotes and Abbreviations Used in Text

IHC, immunohistochemistry; HLA, human leukocyte antigen MAGE-A4, melanoma-associated antigen A4; MCP, microenvironment cell populations; MRCLS, myxoid/round cell liposarcoma; PFS, progression-free survival; SyS, synovial sarcoma; TCR, T-cell receptor

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- Martin Isabelle (email – Martin.Isabelle@adaptimmune.com): Employee of Adaptimmune and holds stock/stock options in Adaptimmune.