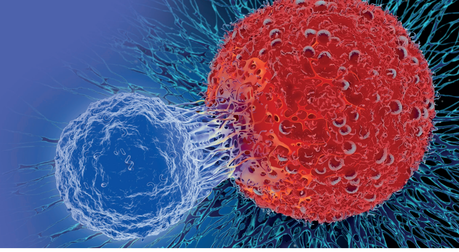
SPEARHEAD-1: Preliminary Translational Insights from a Phase 2 Trial of Afamitresgene Autoleucel (Formerly ADP-A2M4) in Patients with Advanced Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

Sandra P. D'Angelo[1], Steven Attia[2], Jean-Yves Blay[3], Kristen Ganjoo[4], Axel Le Cesne[5], Claudia Maria Valverde Morales[6], Albiruni Ryan Abdul Razak[7], Sandra J. Strauss[8], Brian Andrew Van Tine[9], Michael J. Wagner[10], Natalie Bath[11], Gareth Betts[11], Robyn Broad[11], Ian Donaldson[11], Chris Evans[12], Alasdair Gunn[11], Ashley Liddle[11], Cheryl McAlpine[11], Karen Miller[11], Jean-Marc Navenot[12], Paul Noto[12], Stavros Rafail[12], William Spinner[11], Alex Tipping[11], Erin Van Winkle[12], Ruoxi Wang[11], Swethajit Biswas[11], Elliot Norry[12], Dennis Williams[12], Dejka M. Araujo[13]

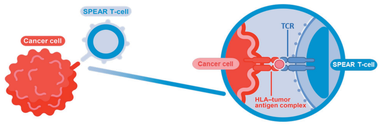
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Mayo Clinic, Jacksonville, FL; [3]Centre Léon Bérard, Lyon, France; [4]Stanford Cancer Center, Palo Alto, CA; [5]Institut Gustave Roussy-Gustave Roussy Cancer Center -DITEP, Villejuif Cedex, France; [6]Vall D'Hebron University Hospital, Barcelona, Spain;[7]Princess Margaret Cancer Centre, Toronto, ON; [8]University College London Hospitals, London, United Kingdom;[9]Washington University School of Medicine, St. Louis, MO; [10]University of Washington/Fred Hutch/Seattle Cancer Care Alliance, Seattle, WA; [11]Adaptimmune, Oxfordshire, United Kingdom; [12]Adaptimmune, Philadelphia, PA; [13]The University of Texas MD Anderson Cancer Center, Houston, TX



Introduction

- Patients with advanced synovial sarcoma or myxoid/round cell liposarcoma (MRCLS) have a high unmet medical need for more effective therapies
- MAGE-A4 is expressed in synovial sarcoma and MRCLS
- Afamitresgene autoleucel (afami-cel; formerly ADP-A2M4) is an autologous specific peptide enhanced affinity receptor (SPEAR) T-cell therapy that targets MAGE-A4 in the context of human leukocyte antigen (HLA)-A*02 expression
- In the Phase 2, open-label SPEARHEAD-1 (NCT04044768) trial in advanced synovial sarcoma and MRCLS, afami-cel has demonstrated an overall response rate of 34% in evaluable patients (**oral presentation; Van Tine, November 12th, 10–11 AM**)
- To support the continued investigation of potential mechanisms of response and acquired resistance in patients with synovial sarcoma and MRCLS, ongoing translational analyses are being performed
- An understanding of the mechanisms underpinning afami-cel therapeutic activity may enable future strategies to enhance responses

SPEAR T-Cells



T-cell receptor (TCR)-based recognition

- T-cells scan HLA peptides presented on diseased cells, including tumor cells
- TCRs targeting peptide antigens bind and activate the T-cell
- Natural TCRs can target both intra- and extracellular antigens
- Using TCRs engineered to recognize and bind to specific cancer peptides, SPEAR T-cells can target solid tumors

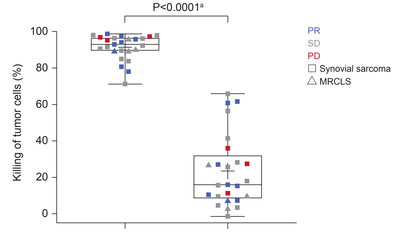
Methods

- Trial design is detailed in **oral presentation (Van Tine, November 12th, 10–11 AM)**
- Profiling of peripheral blood-derived samples taken pre- and post-afami-cel infusion included SPEAR T-cell peripheral persistence (qPCR), and multiplex serum immune marker measurements (Meso Scale Discovery, Rockville, MD), in addition to *in vitro* cytotoxicity of manufactured product (Incucyte, Sartorius, Goettingen, Germany)
- Analyses of pre- and post-afami-cel infusion tumor biopsy samples included MAGE-A4 expression immunohistochemistry, duplex CD3/RNAscope (immunohistochemistry/in situ hybridization), anti-CD3 immunohistochemistry analyses, and multiplex immunofluorescence (Ultivue, Cambridge, MA) for spatial analyses of T-cell infiltration in context with tumor microenvironment

Cytotoxicity

- *In vitro* killing of MAGE-A4+ tumour cells by manufactured product CD8+ SPEAR T-cells was significantly greater compared to CD4+ SPEAR-T cells (**Figure 1**), and consistent with the Phase 1 (NCT03132922) profile, highlighting consistency in afami-cel functionality *in vitro*
- Tumor killing capacity was similar in synovial sarcoma and MRCLS samples, and no significant association with clinical response was observed

Figure 1. Afami-cel cytotoxic activity is largely driven by CD8+ SPEAR T-cells, evident in all patients profiled to date



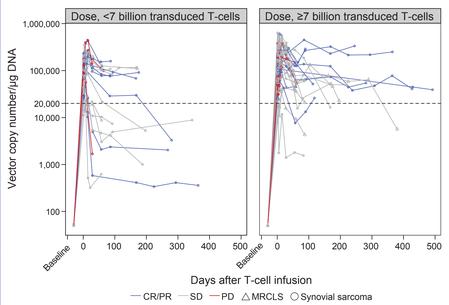
[a]Wilcoxon matched pairs signed rank test; 25 patients (PR, n=10; PD, n=3; SD, n=12; synovial sarcoma, n=21, MRCLS, n=4). Cytotoxicity measured at 72 hours. MRCLS, myxoid/round cell liposarcoma

Persistence

- Afami-cel was quantifiable in all sampling time points of patients evaluated (**Figure 2**)
- For 20 patients with ≥ 24 weeks post-infusion samples available, 70% had persistence >20,000 vector copies/µg DNA

Figure 2. Peripheral detection of afami-cel persists throughout the interventional phase

Peripheral detection of afami-cel, quantified as vector copy number per µg PBMC DNA, comparing patients with total transduced doses of <7 billion cells (n=20) versus ≥ 7 billion cells (n=30)



PBMC, peripheral blood mononuclear cell

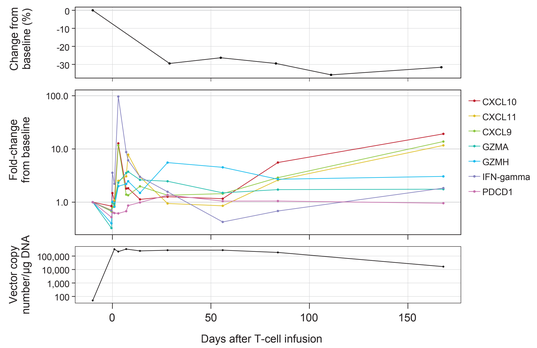
Induction of Immune Response

- Pre- and post-infusion patient serum samples were analysed for levels of 92 immuno-oncology related serum proteins
- Afami-cel administration led to upregulation of a subset of peripheral markers consistent with IFNγ and IFNγ-inducible/related markers (**Figure 3A**)
  - Identification of this subset of peripheral markers is consistent with that shown in the Phase 1 profile,[1] highlighting consistency in afami-cel functionality *in vivo*. Analyses in relation to clinical response is ongoing
- Longitudinal data collected over 6 months demonstrate sustained tumor response concomitant with enduring peripheral persistence of afami-cel and its induced biological signal, as informed by peripheral cytokine response (**Figure 3B**)
- Enduring coincident profile, as described above, was also evident in Phase 1 patients

Figure 3. Afami-cel-induced serum response profile corroborates IFNγ-driven mechanism of action, as observed in the Phase 1 profile. Responses can be sustained and may be associated with durable anti-tumor responses

A. Heatmap of maximal fold-change relative to pre-infusion levels in subset of markers that showed the greatest afami-cel-induced increase relative to pre-infusion serum levels. Left, n=16 synovial sarcoma treated in the Phase 1 trial; Right, n=17 synovial sarcoma treated in SPEARHEAD-1. Patients are ordered by unsupervised hierarchical clustering. Longitudinal profile for the patient indicated with an asterisk is shown **Figure 3B**

B. Longitudinal profile of an example patient (indicated by asterisk in **Figure 3A**). Afami-cel-induced sustained reduction in sum of longest diameter of target lesions, concurrent with enduring serum immune response and sustained peripheral persistence

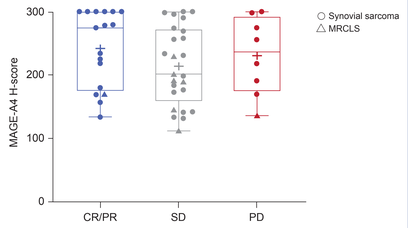


Tumor Biopsies

- Clinical responses have been seen across the range of eligible screening MAGE-A4 expression (**Figure 4**)
- CD3+ cells were detected in all evaluable post-infusion biopsies, with SPEAR T-cells present in >80% (**Figure 5**)

Figure 4. Clinical response evident at screening MAGE-A4 expression levels (H-score 134–300)

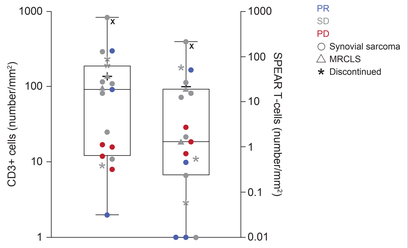
MAGE-A4 H-score at screening in 50 patients



CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. + indicates mean value in each subgroup

Figure 5. CD3+ cells were detected in all evaluable post-infusion biopsies, with SPEAR T-cells present in >80%

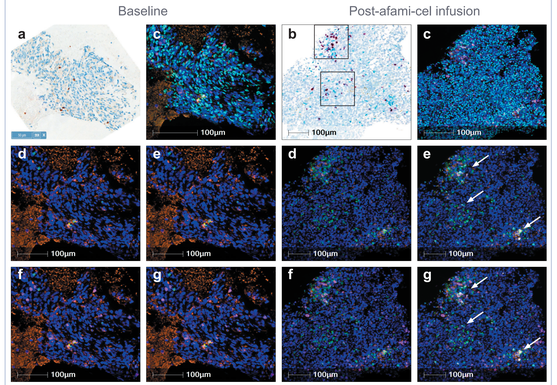
Quantification of CD3+ T-cell and afami-cel infiltration in 19 evaluable post-infusion tumour biopsies from 12 patients (10 synovial sarcoma, 2 MRCLS, 3 PR, 6 SD, 3 PD). Afami-cel was detected in 16 of the 19 (84.2%) biopsies from 11 of the 12 patients including those with PR, SD, and PD. For patient indicated with an "X", tumour biopsy images and analyses are shown in **Figure 6**



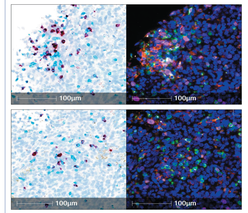
PR, partial response; SD, stable disease; PD, progressive disease; MRCLS, myxoid/round cell liposarcoma

Figure 6. SPEAR T-cells infiltrate tumors, are activated, and proliferate

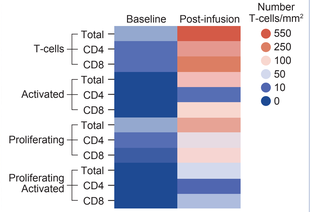
A. Spatial detection of intra-tumoral infiltration of T-cells/ afami-cel and co-localisation with tumour cell and phenotypic markers in baseline and post-infusion biopsies (lung) from the patient indicated with an "X" in **Figure 5**. CD3 expression at baseline (a: CD3+ [DAB]) and CD3 detection with afami-cel 21 days post-infusion (b: CD3+ IHC [teal] and TCR+ ISH [purple]). mIF detection for the following markers: c: tumor marker TLE-1 (cyan), CD3 (yellow),CD4 (orange), CD8 (green), granzyme B (white), Ki67 (pink), PD-L1 (red) and FoxP3 (gold). mIF images (d–g) represent the following phenotypes at baseline and post-infusion: T-cells, d: total (CD3+), CD4 (CD4+CD3+), CD8 (CD8+CD3+); Activated T-cells, e: total (CD3+GrzB+), CD4 (CD4+CD3+GrzB+), CD8 (CD8+CD3+GrzB+); Proliferating T-cells, f: total (CD3+Ki67+), CD4 (CD4+CD3+Ki67+), CD8 (CD8+CD3+Ki67+); Proliferating Activated T-cells, g: total (CD3+GrzB+Ki67+), CD4 (CD4+CD3+GrzB+Ki67+), CD8 (CD8+CD3+GrzB+Ki67+). Arrows highlight areas of T-cell activation that correspond with areas of afami-cel infiltration (b). Boxed areas (b) are shown in detail in **Figure 6B**.



B. Magnified boxed areas in post-infusion sample shown in **Figure 6A**. PD-L1 expression (shown in red) indicating adaptive immune response



C. Digital pathology image quantification of co-staining of T-cell markers in baseline and post-infusion tumor sample shown in **Figure 6A**



IHC, immunohistochemistry; ISH, in situ hybridization; mIF, multiplex immunofluorescence

Conclusions

- Afami-cel SPEAR T-cells successfully engrafted in all patients and maintained high levels of persistence in the majority of patients followed for at least 6 months post-infusion
- Consistency of afami-cel drug product functional profile *in vitro* and *in vivo* across the Phase 1 and Phase 2 clinical studies
- CD8+ SPEAR T-cells in drug products administered killed >70% tumour cells *in vitro*
- Serum cytokine response profile indicating IFNγ-driven mechanism of action, provides enduring peripheral signal of afami-cel induced immune response
- Clinical benefit seen across broad range of MAGE-A4 expression within samples evaluated
- Infiltrating afami-cel SPEAR T-cells co-localize with tumour and immune cells, with evidence of activated and proliferative state and adaptive-immune response

E-poster P146: Connective Tissue Oncology Society (CTOS), Virtual Congress 2021, 10−13 November
Presenter contact information: Sandra P. D'Angelo, dangelos@mskcc.org

Acknowledgements and Disclosures: We thank the patients and their caregivers for taking part in this trial, and we thank the investigators and their teams who participated in this work. This trial (NCT04044768) is sponsored by Adaptimmune. Editorial support and formatting assistance were provided by Gabrielle Knafler, MSc, PhD, of Excel Scientific Solutions, which was contracted and compensated by Adaptimmune for these services. **SP D'Angelo (previous 36 months):** Consulting or Advisory Role: Adaptimmune, Amgen, EMD Serono, GlaxoSmithKline, Incyte, Immune Design, Immunocore, Merck, Nektar; Research Funding: Amgen, Bristol-Myers Squibb, Deciphera, EMD Serono, Incyte, Merck, Nektar; Travel, Accommodations, Expenses: Adaptimmune, EMD Serono, Nektar **References:** 1. Van Tine BA, et al. CTOS; November 18-21, 2020; Virtual **Abbreviations:** SPEAR, specific peptide enhance affinity receptor; TCR, T-cell receptor, HLA, human leukocyte antigen; MRCLS, myxoid/round cell liposarcoma; IFN, interferon; qPCR, quantitative polymerase chain reaction