Radiation Sub-study to Characterize Safety and Tolerability of Low-dose Radiation in Combination with Afami-cel in Patients with Advanced Cancers (NCT03132922)

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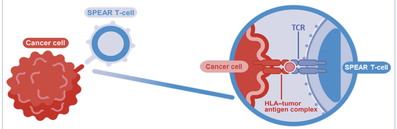
Introduction

- Afamitresgene autoleucel (afami-cel; formerly ADP-A2M4) is an autologous specific peptide enhanced affinity receptor (SPEAR) T-cell therapy that targets melanoma-associated antigen 4 (MAGE-A4) in human leukocyte antigen (HLA)-A*02 restricted fashion
  - Afami-cel monotherapy has demonstrated an acceptable safety profile and preliminary anti-tumor activity in patients with synovial sarcoma and advanced solid tumors[1-3]
- Low-dose radiation modulates stroma of solid tumors, potentially facilitating T-cell infiltration into tumors and antitumor activity[4]
- Here, we report on a Phase 1 sub-study evaluating safety and efficacy of low-dose radiation in combination with afami-cel in 4 patients

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

Trial Design

- Patients received afami-cel by infusion following low-dose radiation and lymphodepleting chemotherapy
- We applied 4.2–7 Gy per lesion or isocenter (maximum of 5)
- The lymphodepleting regimen included intravenous fludarabine 30 mg/m^2/day for 4 days (−7 to −4) and cyclophosphamide 600 mg/m^2/day for 3 days (−7 to −5)
- Afami-cel doses ranged from 1.2 x 10^9 to 10 x 10^9 transduced cells
- Afami-cel was administered as a single dose infusion on Day 1
- Peripheral blood mononuclear cell samples were profiled to determine the persistence of transduced T cells (quantitative PCR of vector-specific sequence Psi)
- Multiplex immune marker measurements (Meso Scale Discovery, Rockville, MD) were determined in pre-and post-treatment serum samples
- Analysis of tumor biopsy samples included MAGE-A4 and CD3 expression (immunohistochemistry), duplex CD3/RNAscope (immunohistochemistry/in situ hybridization), and multiplex immunofluorescence (Ultivue, Cambridge, MA) for spatial analyses of T-cell infiltration in context with the tumor microenvironment

Key Eligibility Criteria and Patient Characteristics

- Tumor types: Advanced urothelial cancer, melanoma, head and neck squamous cell carcinoma (HNSCC), ovarian cancer, non-small cell lung cancer, esophageal cancer, gastric cancer, synovial sarcoma, myxoid/round cell liposarcoma, and esophagogastric junction cancer
- HLA-A*02 and MAGE-A4 positive
- Aged between 18 and 75 years
- Measurable disease per RECIST v1.1
- Adequate organ function
- No symptomatic central nervous system metastases or active infection
- Must have at least one target lesion amenable to radiation
- No metastatic disease impinging on the spinal cord or threatening spinal cord compression

Table 1. As of December 27, 2020 (data cut-off), a total of 4 patients received low-dose radiation and afami-cel

Characteristic	N = 4
Sex, female, n (%)	3 (75)
Age, years, median (range)	60 (48, 71)
MAGE-A4 H-score, median (range)	252.5 (200, 300)
Melanoma, n (%)	2 (50)
HNSCC, n (%)	1 (25)
Ovarian cancer, n (%)	1 (25)

HNSCC, head and neck squamous cell carcinoma

Safety

- The most commonly (>1 patient) reported AEs considered related to T-cell infusion were cytokine release syndrome (3/4 patients), fatigue (2/4 patients), and pyrexia (2/4 patients)
- The only SAE considered to be related to T-cell infusion was neurotoxicity (Grade 3)

Table 2. Adverse events (AEs) related to T-cell infusion

Preferred term, N=4	Any grade, n (%)	Grade ≥ 3, n (%)
Patients with any AE	3 (75.0)	2 (50.0)
Cytokine release syndrome	3 (75.0)	0 (0.0)
Fatigue	2 (50.0)	0 (0.0)
Pyrexia	2 (50.0)	0 (0.0)
Cytomegalovirus viremia	1 (25.0)	0 (0.0)
Dyspnea	1 (25.0)	0 (0.0)
Headache	1 (25.0)	0 (0.0)
Hypotension	1 (25.0)	0 (0.0)
Neurotoxicity	1 (25.0)	1 (25.0)
Neutropenia/neutrophil count decreased	1 (25.0)	1 (25.0)
Rash mobilliform	1 (25.0)	0 (0.0)
Sinus tachycardia/tachycardia	1 (25.0)	0 (0.0)
Swelling face	1 (25.0)	0 (0.0)
Troponin T increased	1 (25.0)	1 (25.0)

Table 3. Serious adverse events (SAEs) and SAEs related to T-cell infusion

Preferred term, N=4	SAE, n (%)	Related SAE, n (%)
Patients with any SAE	3 (75.0)	1 (25.0)
Adrenal insufficiency	1 (25.0)	0 (0.0)
Hyperglycemia	1 (25.0)	0 (0.0)
Myocarditis	1 (25.0)	0 (0.0)
Neurotoxicity	1 (25.0)	1 (25.0)
Pneumonia aspiration	1 (25.0)	0 (0.0)
Pneumothorax	1 (25.0)	0 (0.0)

Efficacy

- Overall response rate was 33%: 1 PR (melanoma) out of 3 evaluable patients
- Disease control rate was 100%: 1 PR, 2 SD (1 ovarian and 1 HNSCC) out of 3 evaluable patients

Table 4. Best overall response amongst 3 evaluable patients[a]

Best overall response	Overall, N = 3
Complete Response	0
Partial Response	1
Stable Disease	2
Progressive Disease	0

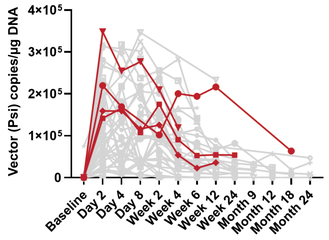
[a]Of 4 patients who received low-dose radiation and afami-cel, 1 patient (melanoma) was not evaluable at the time of data cut-off because no post-baseline scan had been completed

Translational analyses

- The persistence of afami-cel in the subgroup of patients who received low-dose radiation **(hereafter referred to as 'radiation sub-study' [RSS])** was consistent with that in the patients who did not receive low-dose radiation **(hereafter referred to as 'non-irradiated Phase 1')**, both in terms of amplitude (data not shown) and duration (**Figure 1**)

Figure 1. Prior low-dose radiation had no apparent affect on peripheral persistence of afami-cel

Longitudinal persistence of afami-cel in peripheral blood of non-irradiated Phase 1 patients (grey) and RSS patients (n=4; red)

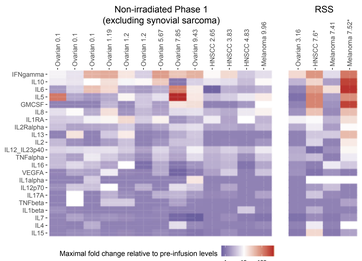


RSS, radiation sub-study

- Afami-cel-induced serum cytokine responses were compared with those in a subset of non-irradiated Phase 1 patients with the same indications (**Figure 2**)
- Overall serum cytokine response profile in non-irradiated Phase 1 patients was similar to that in RSS patients and was relatively greater with cytokine release syndrome (**Figure 2**)

Figure 2. Prior low-dose radiation has no apparent affect on afami-cel-induced serum response profile

Maximal fold-change in serum cytokines relative to pre-afami-cel infusion in non-irradiated Phase 1 patients (n=13; 9 ovarian, 3 HNSCC, 1 melanoma) vs. RSS patients (n=4; 1 ovarian, 2 melanoma, 1 HNSCC[+]). Asterisks indicate patients with Grade 2 cytokine release syndrome. Numbers next to indication are afami-cel doses (billions)

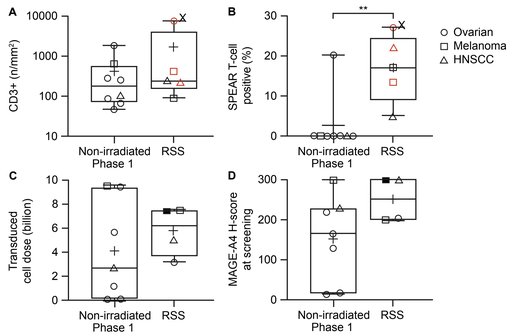


RSS, radiation sub-study; HNSCC, head and neck squamous cell carcinoma. + fold change relative to baseline shown as Day 0 sample not collected

- Evaluable post-infusion tumor biopsies from non-irradiated Phase 1 patients with the same indications (n=7) vs. RSS patients (n=3) show significantly greater detection of afami-cel. Non-significant trend for relatively greater afami-cel dose and screening H-score in RSS patients compared with non-irradiated Phase 1 patients (**Figure 3**)

Figure 3. Greater detection of SPEAR T-cells in tumor biopsies when infusion followed low-dose radiation

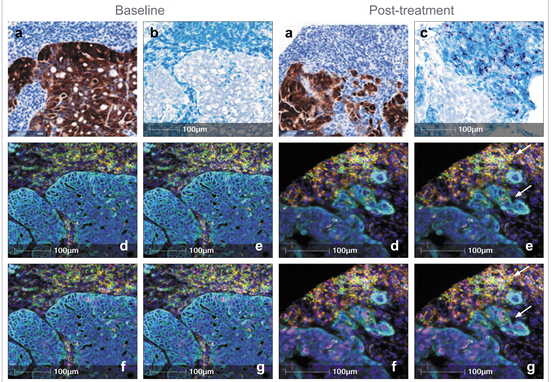
A. CD3+ T-cell enumeration. **B.** Percentage detection of afami-cel (**p=0.0093; Mann Whitney). "X" indicates patient shown in Figures 4A and B. Within RSS, biopsies are irradiated (red) or non-irradiated (black) **C.** Afami-cel dose. **D.** Screening H-score. Black filled square represents patient (PR; melanoma) with CD3+/afami-cel detected in post-treatment irradiated and non-irradiated biopsies but is excluded from A,B due to lack of tumor in hematoxylin and eosin staining



RSS, radiation sub-study

Figure 4. SPEAR T-cells infiltrate tumors, are activated, and proliferate

Spatial detection of intra-tumoral infiltration of SPEAR T-cells and co-localization with tumor cell and phenotypic markers in paired baseline and 30 day post-infusion biopsies derived from the irradiated tumor (retroperitoneal lymph node). MAGE-A4 expression (a: MAGE-A4+ [DAB, brown]). CD3 expression (b: CD3+ ([teal]) and detection with SPEAR T-cells (c: duplex CD3+ IHC [teal] and TCR+ ISH [purple]; "X" in Figure 3 A,B). mIF detection for the following markers: tumor marker PanCK (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, which correspond with areas of SPEAR-T cell infiltration (c)



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

Conclusions

- Low-dose radiation plus afami-cel has shown an acceptable safety profile
- Most AEs were consistent with those typically experienced by cancer patients undergoing lymphodepletion cytotoxic chemotherapy and adoptive cellular therapy
- Serum cytokine profile was consistent with afami-cel monotherapy, confirming no apparent impact of prior low-dose radiation on persistence and peripheral immune response
- SPEAR T-cells were evident in all post-infusion biopsies examined in patients who received low-dose radiation at increased levels compared to non-irradiated Phase 1 dose cohorts
- Results of this study need to be interpreted in the context of small sample size
- This radiation sub-study was terminated in July 2021 due to challenging enrollment
- Other trials are ongoing to deliver cell therapies for people living with cancer

References

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Abbreviations

AE, adverse event; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell liposarcoma; IFN, interferon; MAGE-A4, melanoma-associated antigen 4; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RSS, radiation sub-study, SAE, serious adverse event; SD, stable disease; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor

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