Case Reports: Correlates of Response Following Adoptive Transfer of ADP-A2M4, Affinity-Enhanced T-Cells Targeting MAGE-A4 in Synovial Sarcoma

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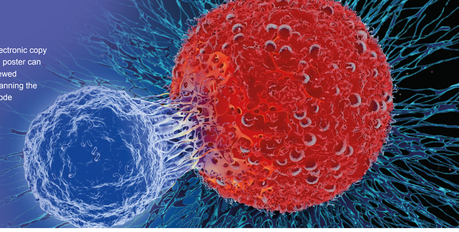
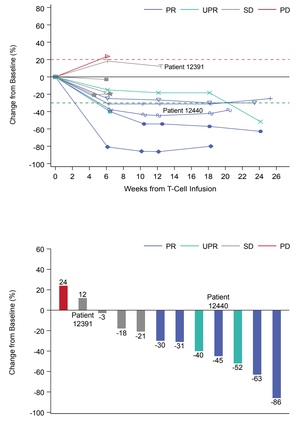


Introduction

- ADP-A2M4 is a genetically engineered autologous affinity-enhanced receptor immunotherapy (SPEAR T-cells) directed toward a MAGE-A4 peptide expressed in the context of HLA-A*02 on tumor cells
- ADP-A2M4 is currently being tested in a phase 1 dose escalation, multi-tumor clinical trial (NCT03132922; further study details can be accessed via the QR code below)
- Clinical responses with ADP-A2M4 have been reported in patients with advanced MAGE-A4$^+$ synovial sarcoma tumors[1]

Figure 1. Best overall response in 12 patients with post-baseline assessments



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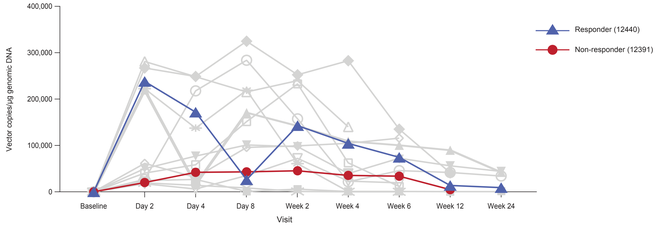
- Here, we describe intra-tumoral and peripheral correlates associated with clinical response and resistance in 2 patients with synovial sarcoma, 1 responder and 1 non-responder

Results

- In the first patient (12440) the BOR following ADP-A2M4 treatment was PR; in the second patient (12391) the BOR was SD

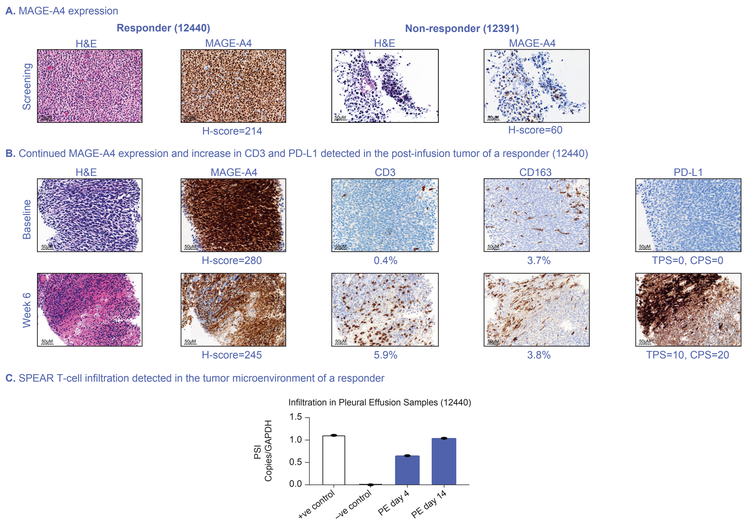
Patient ID	RECIST BOR	Transduced T-cell Dose	Lymphodepletion Regimen	CRS	CRS Max Grade
12440	PR	9.9498 billion	Flu 30 mg/m^2 × 4 days, Cy 600 mg/m^2 × 3 days	Yes	2
12391	SD	5.996 billion	Flu 30 mg/m^2 × 4 days, Cy 600 mg/m^2 × 3 days	No	N/A

Figure 2. High persistence of transduced ADP-A2M4 T-cells in a responder



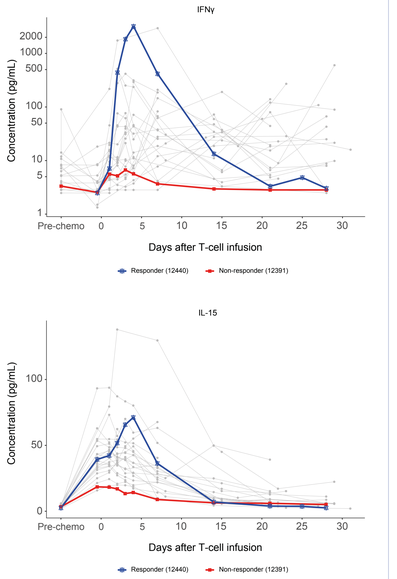
High persistence (by vector copies/µg DNA) in a responder (12440); lower levels in a non-responder (12391)
Persistence of transduced ADP-A2M4 T-cells was measured by qPCR of the lentiviral vector PSI sequence in genomic DNA extracted from PBMCs collected at the indicated visits
Vector (PSI) copy numbers are normalized on 1 µg genomic DNA. Grey lines and symbols represent the values obtained in other synovial sarcoma patients treated with ADP-A2M4

Figure 3. Intra-tumoral infiltration of SPEAR T-cells post-infusion without loss of antigen expression in a responder



A. IHC for MAGE-A4 was performed on enrollment (archival) pre-infusion FFPE biopsies taken from example responder and non-responder patients **B.** IHC for MAGE-A4 and immune markers was performed on FFPE tumor biopsies collected from the responder patient at the pre-infusion baseline visit and at early on-treatment following infusion. H-score = (1 × % tumor stained at 1+ intensity) + (2 × % tumor stained at 2+ intensity) + (3 × % tumor stained at 3+ intensity). CPS and TPS scoring for PD-L1 expression was performed as recommended by the manufacturer of the PD-L1 IHC 22C3 pharmDx assay in an RUO setting **C.** A digital PCR-based assay was performed on DNA extracted from frozen cells isolated from the patient's PE fluid to detect the lentiviral vector PSI sequence and GAPDH

Figure 4. Good induction of IFNγ and IL-15 observed in a responder

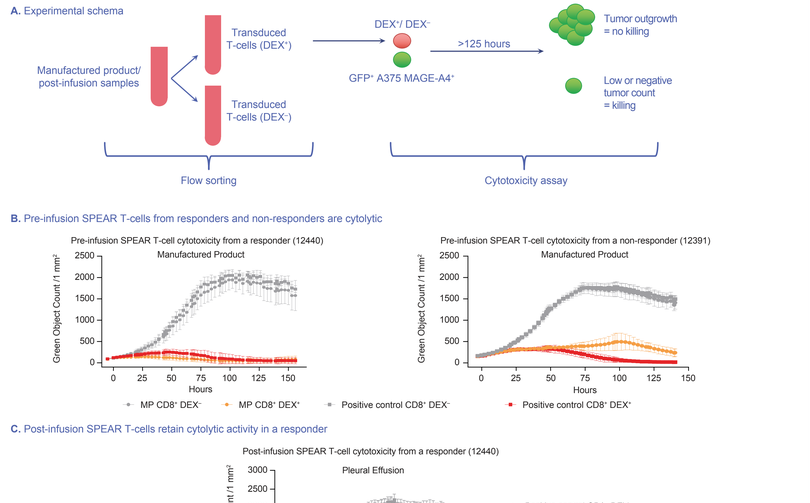


Serum cytokines were measured via a multiplexed electrochemiluminescence-based immunoassay (Meso Scale Diagnostics) at the indicated days pre- and post-infusion. Red lines represent cytokine values from the non-responding patient (12391) who did not have a CRS event, blue lines represent cytokine values from the responding patient (12440) who had a Grade 2 CRS event, and grey lines represent the values obtained in all other synovial sarcoma patients treated with ADP-A2M4

Conclusions

- High antigen expression levels, IL-15 and IFNγ cytokine induction, good engraftment, tumor site trafficking, and cytolytic function of SPEAR T-cells may be associated with favorable responses in synovial sarcoma patients treated with ADP-A2M4
- PD-L1 upregulation in response to SPEAR T-cell tumor infiltration and activity may represent a mechanism of resistance
- We continue to analyze biomarkers in the 10 additional synovial sarcoma patients who have been treated

Figure 5. Pre-infusion SPEAR T-cells and post-infusion SPEAR T-cells isolated from the tumor-adjacent fluid from a responder are cytolytic



A. Experimental schema for the cytotoxicity assay **B.** Patient MP **C.** Post-infusion samples along with a donor WAVE product sample (positive control) were defrosted and stained with live/dead stain, dextramer and antibody cocktail before FACS of SPEAR T-cells (CD8$^+$DEX$^+$). 3000 T-cells were added to 384 well flat bottom plates seeded with 375-750 GFP-expressing A375 tumor targets in 4 replicate wells. Growth of tumor targets was imaged at 3-hour intervals to assess T-cell cytotoxicity

Abbreviations

BOR, best overall response; CPS, combined positive score; CRS, cytokine release syndrome; Cy, cyclophosphamide; FACS, fluorescence-activated cell sorting; FFPE, formalin-fixed paraffin-embedded; Flu, fludarabine; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFP, green fluorescent protein; H&E, hematoxylin & eosin; HLA, human leukocyte antigen; IFN, interferon; IHC, immunohistochemistry; IL, interleukin; MAGE-A4, melanoma-associated antigen-A4; MP, manufactured product; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PD-L1, programmed cell death ligand-1; PE, pleural effusion; PR, partial response; PSI, packaging signal; qPCR, quantitative polymerase chain reaction; RECIST, response evaluation criteria in solid tumors; RUO, research use only; SD, stable disease; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor; TPS, tumor proportion score; UPR, unconfirmed partial response

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Reference

1. Van Tine BA, et al. ADP-A2M4 (MAGE-A4) in patients with synovial sarcoma. Abstract 5471. Presented at European Society for Medical Oncology (ESMO) 2019 Congress, 27 September to 1 October 2019, Barcelona, Spain.

SPEAR T-cell mechanism of action video can be viewed by scanning the QR code

Full trial details from ClinicalTrials.gov can be viewed by scanning the QR code