The Synovial Sarcoma Subset Analysis of the Multi-Histology Phase I Trial of ADP-A2M4 (MAGE-A4)

Brian A. Van Tine¹, David S. Hong², Dejka M. Araujo², Melissa Johnson³, Jeffrey Clarke⁴, David Liebner⁵, Kunle Odunsi⁶, Anthony J. Olszanski⁷, Paula M. Fracasso⁸, Samik Basu⁸, Erica Elefant⁸, Dennis Williams⁸, Trupti Trivedi,⁸ Marcus Butler⁹

¹Washington University in St. Louis, ²MDACC, ³Sarah Cannon, ⁴Duke, ⁵OSU, ⁶Roswell Park, ⁷Fox Chase Cancer Center, ⁸Adaptimmune, ⁹Princess Margaret Cancer Centre
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Background

ADP-A2M4 SPEAR (Specific Peptide Enhanced Affinity Receptor) T-cells

For most approaches, access to extracellular proteins only

- CAR-NK-cells
- Bispecific Ab
- ADC

For T-cells:

- Cancer cell
- T-cell

**TCR-based recognition**

- More options for targeting cancers by enhancing the natural immune system:
  - T-cells scan HLA-peptides with TCRs
  - Access to broader spectrum of extra- and intra-cellular proteins
- TCR is T-cell’s scan natural receptor construct
- Ability to target solid tumors, as opposed to normal tissues

**MOA video:**

https://youtu.be/zdI8IGXoQd0
Objectives

• Phase 1 Dose Escalation, Multi-Tumor Study to Assess the Safety, Tolerability and Antitumor Activity of ADP-A2M4 in HLA-A2⁺ Subjects with MAGE-A4⁺ Tumors (NCT03132922)
• This presentation focuses on data from patients with synovial sarcoma

Primary
• Evaluate safety and tolerability of ADP-A2M4 T-cell therapy

Secondary
• Evaluate the antitumor activity of ADP-A2M4 T-cells
• Evaluate potential therapy-related delayed AEs for 15 years post-infusion

Exploratory
• Evaluate the persistence, phenotype and functionality of transduced and non-transduced T-cells
• Characterize the tumor and serum factors that may influence response or resistance to ADP-A2M4 therapy
Methods: Study Design

- **HLA and MAGE-A4**
  - HLA screening followed by MAGE-A4 IHC Testing

- **Eligibility Assessment & Leukapheresis & Manufacturing of SPEAR T-cells**

- **Trial Assessments**
  - Safety Monitoring
  - Translational Studies
  - Efficacy Evaluation by RECIST

- **Long-term Follow Up**

- **Screening Study Enrollment**

- **Main Study Enrollment**
  - Baseline Tumor Measurements
  - Days -7 to -4
  - Days 1 to 3
  - Days 1-180 or until PD

- **SPEAR T-cell Infusion and Hospitalization**

**Additional Information**

- 11 patients treated with Flu 30 mg/m² x 4d, Cy 600 mg/m² x 3d
- 4 patients treated with high dose regimen of Flu 30 mg/m² x 4d, Cy 1800mg/m² x 2d
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>49 (31, 76)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>1</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td><strong>Prior lines of systemic therapy, median (range)</strong></td>
<td>2.5 (1, 6)</td>
</tr>
<tr>
<td><strong>Most common prior systemic therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Ifosfamide/ Anthracycline (concurrent)</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Ifosfamide/ Anthracycline or Anthracycline/ Ifosfamide (sequential)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Ifosfamide only</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td><strong>MAGE-A4 expression % of tumor cells 2+/3+ by IHC, median (range)</strong></td>
<td>94.3 (8.3, 100)</td>
</tr>
<tr>
<td><strong>Cell dose x 10^9, median (range)</strong></td>
<td>8.9 (3.41, 9.98)</td>
</tr>
</tbody>
</table>
## Safety: Adverse Events Occurring in >25% of Patients

<table>
<thead>
<tr>
<th>Term</th>
<th>Any grade, n (%)</th>
<th>Grade ≥ 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>14 (93.3)</td>
<td>14 (93.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>14 (93.3)</td>
<td>14 (93.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (87.7)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>CRS</td>
<td>12 (80.0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (73.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (66.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (60.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (60.0)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (53.3)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (53.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Sinus tachycardia/Tachycardia</td>
<td>7 (46.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>6 (40.0)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (40.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (33.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (33.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (33.3)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5 (33.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (33.3)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (26.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Tumor pain</td>
<td>4 (26.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data cut off 23-Oct 2019
Adverse Event of Interest

Aplastic Anemia (AA)

- AA has been reported in other cell therapies using a high-dose lymphodepletion regimen\(^1\)
- Three cases of fatal aplastic anemia reported in trials with three different TCRs using a lymphodepletion regimen of Flu 30 mg/m\(^2\) x 4d, Cy 1800 mg/m\(^2\) x 2d
  - 76-year-old patient with synovial sarcoma treated with ADP-A2M4 (MAGE-A4)
  - 73-year-old patient with synovial sarcoma treated with NY-ESO-1 TCR\(^1\)
  - 66-year-old patient with NSCLC treated with ADP-A2M10 (MAGE-A10, NCT02989064)
  (AA cases reported at ESMO 2019\(^2\))
- All cases were reported to regulatory agencies
- RT-PCR did not detect MAGE antigens in the bone marrow

Patients who were affected received a higher lymphodepleting regimen and were elderly; protocols have been amended
- Lower lymphodepletion regimen: Flu 30 mg/m\(^2\) x 4d, Cy 600 mg/m\(^2\) x 3d
- Patients must be $\leq$ 75 years old

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\(^1\) Mackall et al, *J Clin Oncol* 2016
\(^2\) Van Tine et al, *ESMO* 2019
ADP-A2M4 SPEAR T-Cells Induce Clinical Responses

Best overall response in 14 patients with post-baseline assessments

*2 patients had single scans †Patient with aplastic anemia

Data cut off 23-Oct 2019
ADP-A2M4 SPEAR T-Cells Induce Clinical Responses

Best overall response in 14 patients with post-baseline assessments

Data cut off 23-Oct 2019

*2 patients had single scans †Patient with aplastic anemia
Significant Tumor Reduction

46% reduction by RECIST 1.1.

- 67-year-old male
- 4-yr history of disease
  - Treated with surgery and radiotherapy
  - Recurrence in the pericardium treated with debulking and ifosfamide
- High MAGE-A4 expression
- SLD* was 155 mm
- 9.95 x 10^9 SPEAR T-cells

Baseline

Week 12

(*)SLD = Sum of the Longest Diameter of the target lesions

Washington University Physicians • Barnes-Jewish Hospital
Significant Tumor Reduction

Lung

Pleura

86% decrease in RECIST 1.1 and significant symptom improvement

- 53-year-old male
- Longstanding history of synovial sarcoma
  - Treated with surgery, radiotherapy, and multiple chemotherapy regimens
- High MAGE-A4 expression in tumor
  - Baseline SLD* 24 cm
  - $9.87 \times 10^9$ SPEAR T-cells
- Baseline scans
  - Extensive disease in the lung and pleura-based tumor masses
- Post-infusion
  - Grade 1 CRS and cytopenias
- Week 6 scans
  - One large pleura-based lesion disappeared and others reduced via RECIST 1.1 criteria

(*SLD = Sum of the Longest Diameter of the target lesions)
Reduction in Bulky Tumor

Lung

44% decrease by RECIST 1.1 and shortness of breath resolved

- 42-year-old male
- Diagnosed age 25 years
- Recently developed metastatic disease
- Moderate MAGE-A4 expression
- Baseline SLD* 20 cm
- 9.95 x 10⁹ SPEAR T-cells
- Baseline symptoms and scans
- Shortness of breath due to accumulation of fluid in pleural space
- Tumor (left lung) displacing major blood vessels and compressing right lung
- Post-infusion
- Grade 2 CRS and cytopenias
- Week 12 scans
- Tumor decreased and non-target lesion disappeared
- Patient lung expanded and shortness of breath resolved

(*SLD = Sum of the Longest Diameter of the target lesions)
Transduced T-Cells Peak Expansion

Higher peak expansion associated with decrease in tumor size from baseline

Data cut off 23-Oct 2019
Conclusions

- ADP-A2M4 SPEAR T-cells induced clinical responses by RECIST 1.1 in 7/14 and disease control in 13/14 assessed patients with synovial sarcoma
  - Additional follow up needed to determine durability of responses

- Most adverse events consistent with those typically experienced by cancer patients undergoing cytotoxic chemotherapy and/or cancer immunotherapy
  - CRS was common in the treated patient population

- Higher peak expansion is associated with decreases in tumor size from baseline

- The ADP-A2M4 Phase 2 SPEARHEAD-1 Trial in synovial sarcoma and myxoid/round cell liposarcoma is now enrolling in North America, and soon in Europe (NCT04044768)
Acknowledgments

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