ADP-A2M4 (MAGE-A4) IN PATIENTS WITH SYNOVIAL SARCOMA

Brian A. Van Tine¹, David S. Hong², Dejka M. Araujo², Melissa Johnson³, Jeffrey Clarke⁴, David Liebner⁵, Kunle Odunsi⁶, Anthony J. Olszanski⁷, Samik Basu⁸, Erin Van Winkle⁸, Tom Holdich⁸, Trupti Trivedi⁸, Rafael Amado⁸, Marcus Butler⁹

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

Van Tine, Brian

**Personal financial interests**
- Advisory Role/Consultant: Epizyme; CytRx; Janssen; Plexxicon
- Consultant, Advisory Role/Speaker, Research/Trial Support, Travel Support: Lilly
- Speaker Bureau: Caris
- Research Grant/Consulting/Ad Board: Pfizer
- Consultant: Bayer
- Research Grant: Merck; Tracon
- Advisory Board: Immune Design; Daiichi Sankyo
- Speaker: Adaptimmune

**Institutional financial interests**
- Research Grant: Lilly; Merck
- Trial Support: Oncothyreon; Glioknik; Celidex Therapeutics; ImClone Systems; Peregrine Pharmaceuticals; BIND Therapeutics; Regeneron Pharmaceuticals; MabVax Therapeutics; Millenium; AbbVie; Janssen Research Foundation; Jounce Therapeutics; EMD Serono; Puma Biotechnology; VentiRx Pharmaceuticals; Taiho Pharmaceuticals; Gilead Sciences; Incyte; Daiichi Pharmaceutical; Novartis; Pfizer; Acerta; Inventiv Health; Celgene; Sanofi; AstraZeneca; Merrimack Pharmaceuticals; Biothera Pharmaceuticals; Medimmune; Blueprint Medicines; Bristol-Myers Squibb; Enzymchem Lifesciences Corporation; Eisai; Genentech; Corvus; Johnson & Johnson; Threshold Pharmaceuticals; Bayer; BeiGene; GlaxoSmithKline; Molecular Insight Pharmaceuticals; Gem Pharmaceuticals; Deciphera Pharmaceuticals; Forma Therapeutics, Bavarian Nordic; Hoffman-LaRoche; Caris Life Sciences; Morphotek; Soligenix; Eleison Pharmaceuticals; AADI; Immune Design; TRACON Pharmaceuticals; NanoCarrier; Advenchen Laboratories; Karyopharm Therapeutics; Hutchison MediPharma

This study (NCT03132922) is sponsored by Adaptimmune LLC
BACKGROUND

Synovial Sarcoma and MAGE-A4 Expression

- Synovial sarcoma represents ~10% of all soft tissue sarcomas
- Metastatic disease has poor prognosis
- MAGE-A4 is highly expressed in synovial sarcoma patients
  - 2017 study\(^1\) showed that 82% of synovial sarcoma tumor samples expressed MAGE-A4 by immunohistochemistry
- ADP-A2M4 SPEAR T-cells are autologous CD4\(^+\) and CD8\(^+\) T-cells genetically engineered to express an affinity-enhanced T-cell receptor (TCR) that recognizes the HLA-A2-restricted peptide MAGE-A4\(^{230-239}\) (GVYDGREHTV)

\(^1\) Iura et al, *Human Pathology* 2017
For most approaches, access to extracellular proteins only

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 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
- This presentation focuses on data from patients with synovial sarcoma

Primary

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

Secondary

- Evaluate the anti-tumor 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

**Screening Study Enrollment**
- HLA and MAGE-A4 screening followed by MAGE-A4 IHC Testing

**Main Study Enrollment**
- Eligibility Assessment & Leukapheresis & Manufacturing of SPEAR T-cells

**Baseline Tumor Measurements**
- Days -7 to -4

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

**SPEAR T-cell Infusion and Hospitalization**
- Day 1

**Long-term Follow Up**
- Years 1-15

- 9 patients treated with Cy 600 mg/m² x 3d, Flu 30 mg/m² x 4d
- 4 patients treated with high dose regimen of Cy 1800mg/m² x 2d, Flu 30 mg/m² x 4d
# PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>N=13*</th>
<th>Male: 8</th>
<th>Female: 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Median: 53</td>
<td>Range: 31 - 76</td>
</tr>
<tr>
<td>ECOG status</td>
<td>ECOG 0 = 7</td>
<td>ECOG 1 = 6</td>
</tr>
<tr>
<td>Race</td>
<td>White: 11</td>
<td>Asian: 2</td>
</tr>
<tr>
<td>Prior lines of systemic therapies</td>
<td>Median: 2</td>
<td>Range: 1 - 5</td>
</tr>
<tr>
<td>Cell dose x 10^9</td>
<td>Median: 9.7</td>
<td>Range: 3.41 - 9.98</td>
</tr>
</tbody>
</table>

*13th treated patient did not have post-baseline assessment at time of data cut off.

Data cut off 3-Sep-19
### SAFETY: ADVERSE EVENTS ≥ GRADE 3

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade ≥3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (76.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>CRS</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Acute left ventricular failur</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Anal abscess</td>
<td>1 (7.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade ≥3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Endocarditis staphylococcal</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Sciatica</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Troponin increased</td>
<td>1 (7.7%)</td>
</tr>
</tbody>
</table>

Most AEs were typical for this treatment and patient population.

Any Grade CRS is common in synovial sarcoma patients treated with ADP-A2M4.

Data cut off 3-Sep-19
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)
- All cases were reported to regulatory agencies
- RT-PCR did not detect MAGE antigens in the bone marrow

Caution should be used with high-dose lymphodepletion in heavily pretreated older patients; protocols have been amended
- Moderate lymphodepletion regimen: Flu 30 mg/m\(^2\) x 4d, Cy 600 mg/m\(^2\) x 3d
- Patients must be ≤75 years old

\(^1\) Mackall et al, *J Clin Oncol* 2016
ADP-A2M4 SPEAR T-CELLS INDUCE CLINICAL RESPONSES

Best overall response in 12 patients* with post-baseline assessments

*13th treated patient did not have post-baseline assessment at time of data cut off

Data cut off 3-Sep-19
SIGNIFICANT TUMOR REDUCTION

Baseline scans:
- Extensive disease in the lung and pleura-based tumor masses

Week 6 scans:
- One large pleura-based lesion disappeared and others reduced via RECIST 1.1 criteria

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 x 10⁹ SPEAR T-cells
- Did well post-infusion
  - Grade 1 CRS and cytopenias
- Baseline scans:
  - Extensive disease in the lung and pleura-based tumor masses
- Week 6 scans:
  - One large pleura-based lesion disappeared and others reduced via RECIST 1.1 criteria

*Sum of the Longest Diameter of the target lesions
REDUCTION IN BULKY TUMOR

44% decrease by RECIST 1.1 and shortness of breath resolved

- 42-year-old male
- Diagnosed age 25
  - Recently developed metastatic disease
  - Moderate MAGE-A4 expression
    - Baseline SLD 20 cm
  - 9.95 x 10^9 SPEAR T-cells
  - Did well post-infusion
    - Grade 2 CRS and cytopenias
  - At baseline
    - Shortness of breath due to accumulation of fluid in pleural space
    - Tumor (left lung) displacing major blood vessels and compressing right lung
  - Week 12 scans:
    - Tumor decreased and non-target lesion disappeared
    - Patient lung expanded; shortness of breath resolved
TRANSDUCED T-CELLS PEAK EXPANSION

Higher peak expansion associated with decrease in tumor size from baseline

Data cut off 3-Sep-19
CONCLUSIONS

- ADP-A2M4 SPEAR T-cells induced clinical responses by RECIST 1.1 in 7/12 and clinical benefit rate in 11/12 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

We thank the patients and their caregivers for taking part in this trial.

We thank the investigators and their teams who participated in this work.