**SPEARHEAD-2 Trial Design: A Phase 2 Pilot Trial of ADP-A2M4 in Combination with Pembrolizumab in Patients with Recurrent or Metastatic Head and Neck Cancer**

### Introduction

- Genetically engineered autologous SPEAR T-cells targeting MAGE-A4 (ADP-A2M4) have shown promise in the clinic with responses in multiple solid tumor indications, including a confirmed partial response in a patient with head and neck cancer.
- MAGE-A4 is expressed in some recurrent/metastatic HNSCC.
- Non-clinical with pembrolizumab, in vivo PD-1 blockade of TILs is appraised as first-of-its-kind treatment of recurrent/metastatic HNSCC expressing PD-L1.
- Immunomodulatory pathways such as PD-L1/PD-1 can restrict the full potential of adoptive T-cell therapy.
- PD-1 upregulation in cancer cell lines observed after SPEAR T-cell infusion, possibly as a result of local interferon-gamma release.
- Upregulation of PD-1 on infused T-cells after exposure to antigens can limit the adoptive immune response and promote resistance.
- Therefore, a combination of ADP-A2M4 SPEAR T-cells plus pembrolizumab could neutralize the inhibitory effect of PD-L1 on ADP-A2M4 and other immune effector cells sparing PD-1.
- Pembrolizumab could potentially enhance ADP-A2M4 expansion and cytolytic function leading to a higher overall response rate, as well as deeper and more durable responses.

### Key Eligibility Criteria

- **Inclusion criteria**
  - Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression defined as a positive staining by IHC testing.
  - Tumors express PD-L1 (combined positive score ≥1) as determined by an FDA-approved test.
- **Exclusion criteria**
  - History of autoimmune disease.
  - History of stroke or CNS bleeding, transient ischemic attack or reversible ischemic neurologic deficit within last 6 months.
  - History of CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; OR, oxaliplatin; ORR, overall response rate; PD, progressive disease; RECIST, response evaluation criteria in solid tumors; SD, stable disease; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

### Trial Sites (Anticipated)

- Anticipated trial sites (as of publication date)
  - Mayo Clinic Arizona, Phoenix, AZ, USA; 6 Mayo Clinic Arizona, Phoenix, AZ, USA; 7 Adaptimmune, Abingdon, Oxfordshire, UK, and Philadelphia, PA, USA

### Key Endpoints

- **Primary**
  - Overall response rate, per RECIST v1.1
- **Secondary**
  - Progression-free survival
  - Safety monitoring
  - Toxicity
  - Safety monitoring
- **Exploratory**
  - T-cell expansion: T-cell manufacturing apheresis in cryomedia and cryopreservation in automated device
  - T-cell selection: lentiviral gene transfer of affinity enhanced TCR
  - T-cell expansion: T-cell expansion using automated device
  - T-cell persistence: T-cell persistence
  - T-cell function: T-cell function

### Trial Design

- This single-arm trial will enroll up to 10 patients to evaluate efficacy, safety, and tolerability of ADP-A2M4 with pembrolizumab.
- Checkpoint inhibition naive patients with recurrent/metastatic HNSCC who are HLA-A1, MAGE-A4, and PD-1 positive (+1%) will be eligible.
- Part A: a non-randomized phase with pembrolizumab as standard-of-care monotherapy.
- Followed by Part B: an intermittent phase, during which pembrolizumab will be administered after ADP-A2M4 infusion in patients without response or following PD in Part A.

### Objectives

- **Primary**
  - Evaluate the efficacy of ADP-A2M4 in combination with pembrolizumab in patients with recurrent/metastatic HNSCC.
- **Secondary**
  - Evaluate the safety, tolerability, and activity of ADP-A2M4 in combination with pembrolizumab.
- **Exploratory**
  - Characterize PD-1 and PD-L1 expression leading to a higher overall response rate, as well as deeper and more durable responses.

### References

1. Nivolumab and Ipilimumab.
2. KEYTRUDA (pembrolizumab) label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125267s046lbl.pdf
3. pembrolizumab clinicaltrials.gov identifier NCT02993032

### Disclosures

- All authors have indicated support from grants or contracts and/or consulting, or paid royalties for commercial activities which may have influenced the content of this educational activity.
- The speaker(s) and/or the speaker(s)’ employer(s) may or may not have financial interest in products or procedures discussed in this educational activity or in the material provided as part of this educational activity.

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**Speaker Disclosure**

- Panos Savvides, Michael K. Gibson, Ezra E.W. Cohen, and Natalie Hyland are employees of Adaptimmune, Abingdon, Oxfordshire, UK, and Philadelphia, PA, USA.
- Mark Dudley, Eric Zelenetz, Mark Dudley, and Mark Dudley are employees of Memorial Sloan Kettering Cancer Center, New York, NY, USA.
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**Anticipated trial sites (as of publication date):**

- Mayo Clinic Arizona, Phoenix, AZ, USA
- Memorial Sloan Kettering Cancer Center, New York, NY, USA
- Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
- University of Kansas Medical Center, KS, USA
- Memorial Sloan Kettering Cancer Center, New York, NY, USA
- Mayo Clinic Arizona, Phoenix, AZ, USA
- Vanderbilt-Ingram Cancer Center, Nashville, TN, USA