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

Ezra E.W. Cohen[1], Lara Dunn[2], Prakash Neupane[3], Michael K. Gibson[4], Rom Leidner[5], Panayiotis Savvides[6], Natalie Hyland[7], Trupti Trivedi[7], Mark Dudley[7], Swethajit Biswas[7], Dennis Williams[7], Elliot Norry[7]

[1]Moores Cancer Center at University of California San Diego, San Diego, CA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Kansas Medical Center, Kansas City, KS, USA; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [5]Providence Cancer Institute, Providence, OR, USA; [6]Mayo Clinic Arizona, Phoenix, AZ, USA; [7]Adaptimmune, Abingdon, Oxfordshire, UK, and Philadelphia, PA, USA

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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,[1] including a confirmed partial response in a patient with head and neck cancer
- MAGE-A4 is expressed in some recurrent/metastatic HNSCC
- Monotherapy with pembrolizumab, an anti-PD-1 checkpoint inhibitor, is approved as first-line treatment of recurrent/metastatic HNSCC expressing PD-L1[2,3]
- Immunosuppressive pathways such as PD-L1/PD-1 can restrict the full potential of adoptive T-cell therapies
- PD-L1 upregulation can be observed in tumor cells 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 antigen can limit the adaptive immune response and promote resistance
- Therefore, a combination of ADP-A2M4 SPEAR T-cells plus pembrolizumab could relieve the inhibitory effect of PD-L1 on ADP-A2M4 and other immune effector cells carrying 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

Figure 1. SPEAR T-cells

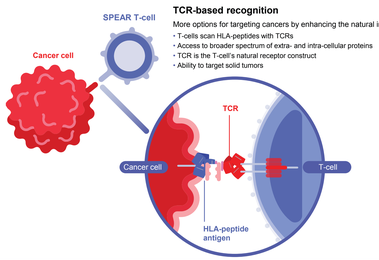
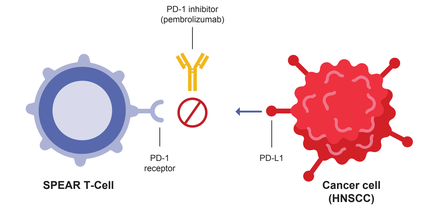


Figure 2. PD-1 inhibition



Objectives

Primary	• Evaluate the efficacy of ADP-A2M4 in combination with pembrolizumab in patients with recurrent HNSCC
Secondary	• Evaluate the safety and tolerability of ADP-A2M4 in combination with pembrolizumab
Exploratory	• Characterize the tumor and serum factors that may influence response or resistance to ADP-A2M4 in combination with pembrolizumab

Key Endpoints

Primary

- Overall response rate, per RECIST v1.1

Secondary

- Adverse event profile
- Best overall response
- Duration of response
- Progression-free survival
- Overall survival

Exploratory

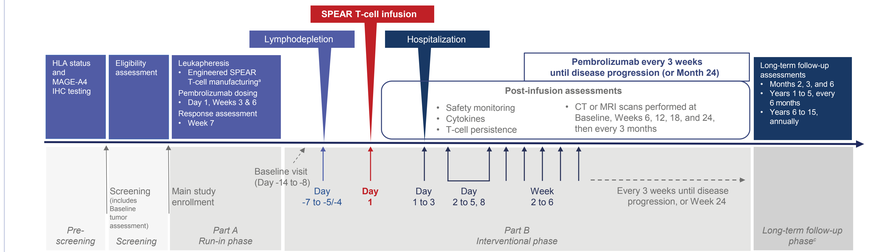
- To characterize:
  - Target antigen expression (including processing and presentation)
  - TILs and T-cells in peripheral blood pre- and post-infusion (ie, phenotype, persistence, and function)

Trial Design

- This single-arm trial will treat up to 10 patients to evaluate efficacy, safety, and tolerability of ADP-A2M4 with pembrolizumab
- Checkpoint inhibitor-naïve patients with recurrent/metastatic HNSCC who are HLA-A*02, MAGE-A4+, and PD-L1 positive (>1%) will be eligible
- Part A is a run-in-phase with pembrolizumab as standard-of-care monotherapy
- Followed by Part B, an interventional phase, during which pembrolizumab will be administered after ADP-A2M4 infusion in patients without response or following PD in Part A

- **Part A**
  - Patients will undergo leukapheresis. Collected T-cells will be transduced with a lentiviral vector expressing a high-affinity MAGE-A4 specific T-cell receptor, before being expanded
  - Patients will receive pembrolizumab monotherapy (200 mg intravenous) every 3 weeks for a minimum of 3 cycles
  - Disease status will be assessed at Week 7
  - Patients without a response by Week 7 will proceed to Part B
  - Patients who respond to pembrolizumab after 3 cycles will continue treatment in Part A until PD, when they will become eligible for ADP-A2M4 treatment in Part B
- **Part B**
  - Patients will undergo lymphodepleting chemotherapy with fludarabine 30 mg/m^2/day for 4 days (Day -7 through Day -4) and cyclophosphamide 600 mg/m^2/day for 3 days (Day -7 through Day -5)
  - One week after the start of lymphodepletion, patients will receive ADP-A2M4 at a dose range of 1–10 × 10^9 transduced T-cells
  - After ADP-A2M4 infusion, patients will restart pembrolizumab infusions and will receive pembrolizumab every 3 weeks until PD
- Safety Review Committee will review safety and benefit:risk during Part B
- Disease will be assessed by investigators per RECIST v1.1 using CT/MRI scans post T-cell infusion

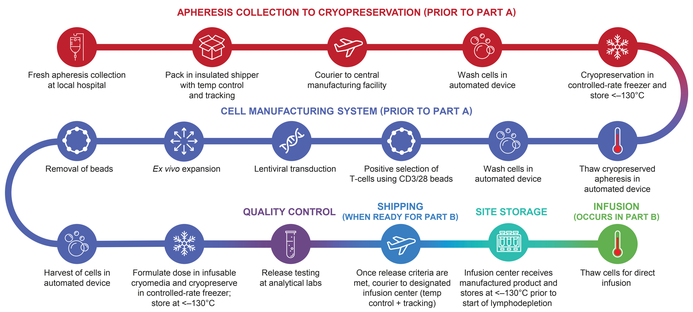
Figure 3. SPEARHEAD-2 trial design



[a]T-cell selection; lentiviral gene transfer of affinity enhanced TCR; T-cell expansion
[b]Transition to Part B is response-dependent; at Week 7 scans
- PD/SD → patient moves to Part B
- CR/PR → patient remains in Part A until PD
- SD with clinical benefit → patient remains in Part A until PD

[c]For 15 years following SPEAR T-cell infusion (ClinicalTrials.gov ID: NCT04408898)

Figure 4. The patient cell journey in SPEARHEAD-2



Key Eligibility Criteria

Inclusion criteria
Aged ≥18 and ≤75 years at the time the Pre-screening Informed Consent Form is signed
Histologically or cytologically confirmed diagnosis of HNSCC with metastatic or unresectable, recurrent disease
Checkpoint inhibitor-naïve at screening, and pembrolizumab is indicated per the approved label
Positive for HLA-A*02:01, HLA-A*02:03, or HLA-A*02:06 allele, via Adaptimmune-designated central laboratory testing
Tumors express PD-L1 (combined positive score ≥1) as determined by an FDA-approved test
Tumor (either an archival specimen or a fresh biopsy) shows MAGE-A4 expression defined as ≥30% of tumor cells that are ≥2+ by IHC, via Adaptimmune-designated central laboratory testing
ECOG of 0 or 1 with adequate organ function (defined in the protocol)

Exclusion criteria
Positive for HLA-A*02:05
Prior gene therapy using an integrating vector, anti-cancer therapies within protocol-defined time frames prior to leukapheresis and lymphodepletion
History of autoimmune disease
Clinically significant cardiovascular or pulmonary disease
History of stroke or CNS bleeding; transient ischemic attack or reversible ischemic neurologic deficit within last 6 months
Active infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or human T-cell leukemia virus
CNS metastases

Trial Sites (Anticipated)

Anticipated trial sites (as of publication date)	Investigator
Mayo Clinic Arizona, AZ, USA	Panos Savvides
Memorial Sloan Kettering Cancer Center, NY, USA	Lara Dunn
Moores Cancer Center at University of California San Diego, CA, USA	Ezra E.W. Cohen
Providence Cancer Institute, OR, USA	Rom Leidner
University of Kansas Medical Center, KS, USA	Prakash Neupane
Vanderbilt-Ingram Cancer Center, TN, USA	Michael K. Gibson

Abbreviations

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; MAGE-A4, melanoma-associated antigen-A4; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte

Disclosures

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Presenter contact information: Ezra E.W. Cohen, University of California San Diego, San Diego, CA, USA; ecohen@health.ucsd.edu

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Full trial details from ClinicalTrials.gov can be viewed by scanning the QR code here https://clinicaltrials.gov/ct2/show/NCT04408898

SPEAR T-cell mechanism of action video can be viewed by scanning the QR code here https://youtu.be/zdI8IGXoQd0