Initial Safety, Efficacy, and Product Attributes from the SURPASS Trial with ADP-A2M4CD8, a SPEAR T-Cell Therapy Incorporating an Affinity Optimized TCR Targeting MAGE-A4 and a CD8α Co-Receptor

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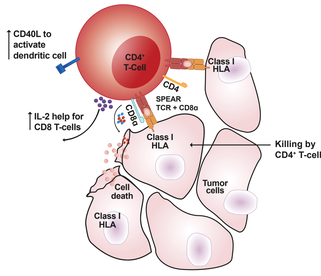
Background

- The ongoing SURPASS trial (NCT04044859) evaluates safety and efficacy of next-generation ADP-A2M4CD8 SPEAR T-cells co-expressing the CD8α co-receptor with the engineered MAGE-A4c1032 T-cell receptor (TCR)
- To increase the potency of CD4$^+$ T-cells, a CD8α co-receptor was genetically engineered alongside the TCR in ADP-A2M4CD8, to increase TCR binding avidity and enhance the polyfunctional response of engineered CD4$^+$ T-cells against MAGE-A4$^+$ tumors[1] (**Figure 1**) with the aim of achieving:
  - Greater cytotoxic function of CD4$^+$ cells
  - Improved cross-talk with antigen-presenting cells
  - Enhanced engagement of the wider immune system
- Increased potency and functionality aim to produce more effective and durable anti-tumor activity
- Given the anti-tumor activity observed (to date) with TCRs targeting MAGE-A4[2], this trial will focus on enrolling patients with gastroesophageal (gastric, esophageal, and EGJ), head and neck (HNSCC), lung, and bladder cancers; the trial remains open to patients with ovarian cancer, melanoma, MRCLS, or synovial sarcoma

Figure 1. ADP-A2M4CD8 Next-Generation SPEAR T-Cells Better Engage CD4$^+$ T-Cells to Provide a More Robust Anti-Tumor Immune Response[3]



- SPEAR T-cells consist of a mix of CD8$^+$ and CD4$^+$ T-cells that are modified with a TCR recognizing a tumor antigen
- The TCR binds with the tumor antigen (ie, HLA-A2/MAGE-A4), and this interaction is stabilized by CD8α
- CD4$^+$ T-cells engage the tumor antigen with the TCR alone
- ADP-A2M4CD8 next-generation CD4$^+$ T-cells engage the antigen with the TCR and the interaction is stabilized by CD8α
- The stabilized TCR interaction results in a more potent T-cell response because the CD4$^+$ T-cells can now kill tumor cells
- ADP-A2M4CD8 next-generation CD4$^+$ T-cells maintain helper cell capabilities

Objectives

Primary	Evaluate the safety and tolerability of ADP-A2M4CD8
Secondary	Evaluate the anti-tumor activity of ADP-A2M4CD8
Exploratory	Identify serum and tumor factors that influence response or resistance to ADP-A2M4CD8

Trial Design

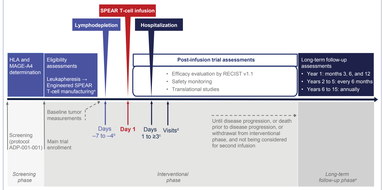
- The ongoing SURPASS trial evaluates the safety and tolerability of next-generation SPEAR T-cells, ADP-A2M4CD8, in patients with MAGE-A4$^+$ tumors in the context of HLA-A*02
- This is a first-in-human dose-escalation trial using a modified 3+3 design, with up to 2 dose cohorts plus an expansion cohort

Transduced Cell Dose Cohorts

Cohort	Number of patients	Transduced cell doses
1	3–6	1 × 10^9 (range 0.8–1.2 × 10^9)
2	3–6	5 × 10^9 (range 1.2–6 × 10^9)
Expansion	Up to 30 (includes dose escalation)	1.2–10 × 10^9

- DLTs are adjudicated by a Safety Review Committee, regardless of the investigator's attribution

SURPASS Trial Design



[a]T-cell selection; lentiviral gene transfer of affinity-enhanced TCR; T-cell expansion
[b]Lymphodepletion with fludarabine 30 mg/m^2/day for 4 days and cyclophosphamide 600 mg/m^2/day for 3 days
[c]Hospitalization for T-cell infusion for minimum of 3 days, and discharged at Investigator's discretion
[d]Days 2 to 5, 8; Weeks 2 to 6, 8, 10, 12, 18, and 24; then every 3 months until Year 2; then every 6 months
[e]Up to 15 years following SPEAR T-cell infusion (Day 1)

Key Eligibility Criteria

Inclusion criteria
Diagnosis of advanced gastroesophageal cancers, HNSCC, non-small cell lung cancer, ovarian cancer, urothelial carcinoma, synovial sarcoma, MRCLS, or melanoma
HLA-A*02 positive
MAGE-A4 ≥2+ immunohistochemistry staining in ≥30% of tumor cells
Age ≥18 and ≤75 years
Measurable disease according to RECIST v1.1
Must have received or refused standard anti-tumor regimens with no more than 3 lines of prior systematic therapy in the metastatic or unresectable locally advanced setting
ECOG performance status of 0 or 1
Adequate organ function
Exclusion criteria
Prior gene therapy using an integrating vector, anti-cancer therapies within protocol-defined time frames prior to leukapheresis, and lymphodepletion
Unresolved autoimmune or immune-mediated disease
Leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases
Active infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus, or human T-cell leukemia virus

Results

- As of October 1, 2020, 6 patients (MRCLS 1, EGJ cancer 2, ovarian cancer 1, HNSCC 1, esophageal cancer 1) were treated with ADP-A2M4CD8 (range ~1–5.7 billion transduced cells)

Table 1. Patient characteristics

Characteristic	N=6
Sex, n (%)	
Male	4 (67)
Female	2 (33)
Median age, years (range)	58.5 (31–71)
Race, n (%)	
White	6 (100)
Cancer type, n (%)	
EGJ	2 (33)
MRCLS	1 (17)
Ovarian	1 (17)
HNSCC	1 (17)
Esophageal	1 (17)
ECOG performance status, n (%)	
0	2 (33)
1	4 (67)
Prior lines systemic therapy, median (range)	3 (3–5)

Table 2a. Any Adverse Event Occurring in >1 Patient

Term	Any Grade N (%)	Grade ≥3 N (%)[a]
Patients with any AEs	6 (100)	6 (100)
Leukopenia	6 (100)	5 (83)
Lymphopenia/lymphocyte decreased	6 (100)	6 (100)
Neutropenia/neutrophil count decreased	6 (100)	6 (100)
Anemia/red blood cell decreased	4 (67)	3 (50)
Cytokine release syndrome	4 (67)	0
Fatigue	4 (67)	0
Headache	4 (67)	0
Nausea	4 (67)	0
Decreased appetite	3 (50)	0
Alopecia	2 (33)	0
Dyspnea	2 (33)	0
Hypocalcemia	2 (33)	0
Hypomagnesemia	2 (33)	0
Hyponatremia	2 (33)	2 (33)
Hypophosphatemia	2 (33)	1 (17)
Thrombocytopenia/platelet count decreased	2 (33)	2 (33)
Weight decreased	2 (33)	0

[a]There was one report each of Grade 3 hyperglycemia and hypokalemia
Data cut-off: October 1, 2020

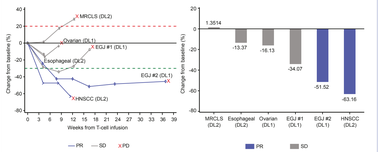
Table 2b. Adverse Events Related to T-Cell Infusion

Term	Any Grade N (%)	Grade ≥3 N (%)
Patients with any AEs	6 (100)	3 (50)
Lymphopenia	1 (17)	1 (17)
Neutropenia	2 (33)	2 (33)
Cytokine release syndrome	4 (67)	0
Fatigue	3 (50)	0
Decreased appetite	1 (17)	0
Hypocalcemia	1 (17)	0
Hypomagnesemia	1 (17)	0
Weight decreased	1 (17)	0
Acute kidney injury	1 (17)	0
Hypoxia	1 (17)	0
Neurotoxicity	1 (17)	0
Pleural effusion	1 (17)	0
Pruritus	1 (17)	0
Pustule	1 (17)	0
Pyrexia	1 (17)	0
Vomiting	1 (17)	0

There were no DLTs in Cohorts 1 and 2. One patient in Cohort 2 had an SAE of cytokine release syndrome considered to be related to T-cell infusion. No other SAEs were reported at the time of data cut-off
Data cut-off: October 1, 2020

Figure 2. Five of Six Patients Demonstrate Initial Tumor Shrinkage With Two Responses

- Initial tumor shrinkage in 5 of 6 patients following T-cell infusion
- Two patients had an objective PR (per RECIST) after treatment; all other patients have had best overall response of SD



Data cut-off: October 1, 2020

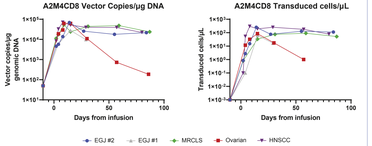
Table 3. Manufactured Product Characteristics

	EGJ #2	Ovarian	EGJ #1	HNSCC	MRCLS	Esophageal
Best overall response	PR	SD	SD	PR	SD	SD
Change from baseline (%)	-52	-16	-34	-63	1.4	-13.4
MAGE-A4 at baseline (H-score[a])	300	35	180	295	200	260
Dose (billion transduced cells)	1.2	1.1	1.0	4.6	5.7	5.9
Transduction (%)	62.5	45.8	39.3	29.1	49.7	52.2
Expansion *in vitro* (-fold change)	2.7	16.0	5.1	16.9	10.2	19.5
CD4$^+$ (% of CD3$^+$)	38.8	80.2	45.5	83.2	83.6	66.4
CD4$^+$CD8$^+$TCR$^+$ (billion)	0.5	1.0	0.5	3.9	4.6	4.1
CD8$^+$ (CD4$^-$) (% of CD3$^+$)	60.6	17.6	47.4	15.7	14.4	32.7
CD8$^+$TCR$^+$ (CD4$^-$) (billion)	0.7	0.2	0.6	0.7	0.8	1.8

[a]H-score is calculated based on the fraction of cells expressing antigen in the tumor and the intensity of expression. Range of the assay is 0–300 (arbitrary units)

- MP characteristics do not clearly predict clinical outcome
- All MP have a low number (0.2–1.8 × 10^9) of endogenous CD8$^+$ (non-CD4$^+$) T-cells
- CD4$^+$CD8$^+$ T-cells represent a substantial fraction (0.4–0.8) of SPEAR T-cells in all patients
- MP had a median 13.1-fold expansion during manufacturing (range 2.1- to 19.5-fold); median of 48% of T-cells in the MP expressed the TCR (range 30%–63%); absolute number of CD4$^+$ cells in the final MP varied (range 0.5–4.6 × 10^9)

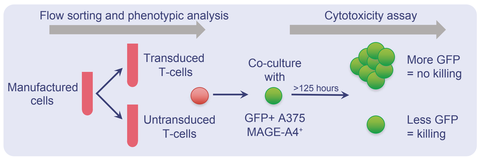
Figure 4. Transduced T-cells Were Detected in Peripheral Blood of All Patients[a]



- Vector DNA sequences in peripheral blood lymphocytes were quantified prior to T-cell infusion (baseline, plotted as limit of detection) and at multiple times after infusion[a]
- There was no correlation between transduced cell levels in peripheral blood and dose administered
- Persistence of SPEAR T-cells in peripheral blood does not correlate with response in this population
- The average vector copy number per cell in the MP, the vector copies per µg of genomic DNA, and the absolute lymphocyte count at the time of sampling were used to quantify the transduced cell number in the peripheral blood sample[a]

[a]All samples with available data are plotted. Samples for some timepoints were not collected

Figure 3. Conversion of Non-Cytolytic CD4$^+$ Cells to Cytolytic CD4$^+$CD8$^+$ Cells
Potent cell killing demonstrated *in vitro* for transduced CD4$^+$ and CD8$^+$ cells from infused cells



- Peripheral blood cells from patients were isolated, transduced, and expanded using standard cell manufacturing procedures with ADP-A2M4CD8. Manufactured products derived for 4 patients were flow sorted into transduced (TCR$^+$CD4$^+$CD8$^+$ and TCR$^+$CD8$^+$CD4$^-$) and non-transduced (TCR$^-$CD4$^+$CD8$^-$ and TCR$^-$CD8$^+$CD4$^-$) T-cell fractions, and evaluated for *in vitro* killing potency using target cells expressing GFP and the MAGE-A4 peptide in the context of HLA-A2 (A375). GFP signal over time was tracked, and increased with target cell growth, such that cytolytic potency is associated with a reduction in GFP signal
- In each case for which data are available (products manufactured for four patients), un-transduced cells (grey) did not kill target, and transduced CD4$^+$ cells also expressing CD8 (orange) killed target as well as transduced CD8$^+$ cells (blue). Mean values from four replicate wells are shown, error bars indicate SD

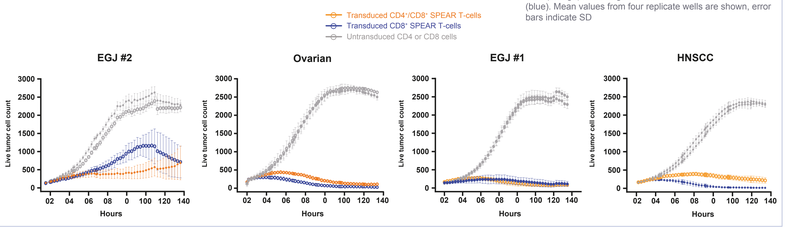
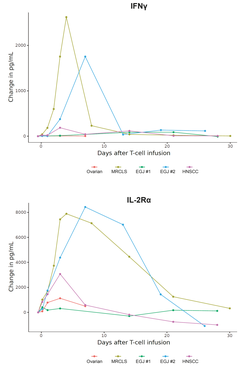


Figure 5. ADP-A2M4CD8 May Induce a Transient Increase in Peripheral Cytokines



- Preliminary analyses have profiled levels of 22 cytokines in initial patient serum samples
- Transient increases post-infusion were evident for several cytokines; example cytokine profiles are depicted for IFNγ and IL-2Rα
- The most pronounced SPEAR T-cell induced increase was evident for serum IFNγ concentration
- Broader peripheral immune marker profiling is underway

Conclusions

- ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile, and patients with gastroesophageal cancers and head and neck cancer have demonstrated clinical responses
- Five of six patients demonstrated initial tumor shrinkage
- Preclinical observations showed that CD8 co-expression could improve CD4$^+$ T-cell potency. Early clinical data presented here support a more potent product when CD8$^+$ is co-transduced with MAGE-A4 TCR
- This trial is ongoing in an expansion cohort of patients
- A phase 2 trial is being planned with the ADP-A2M4CD8 product in patients with gastroesophageal cancers

Abbreviations

AE, adverse event; DL, dose level; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; IFN, interferon; IL, interleukin; MAGE-A4, melanoma-associated antigen-A4; MP, manufactured product; MRCLS, myxoid/round cell liposarcoma; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SAE, serious adverse event; SD, stable disease; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor

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Full trial details from ClinicalTrials.gov can be viewed by scanning the QR code here https://clinicaltrials.gov/ct2/show/NCT04044859

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