Safety and Efficacy From the SURPASS Trial With ADP-A2M4CD8, a SPEAR T-cell Therapy Incorporating a CD8α Co-receptor and an Affinity Optimized TCR Targeting MAGE-A4

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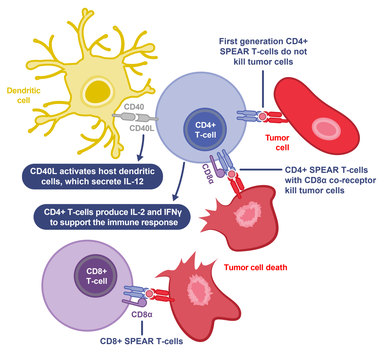
Introduction

- The ongoing Phase 1 SURPASS trial (NCT04044859) evaluates the 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. This is intended to increase TCR binding avidity and enhance the polyfunctional response of engineered CD4+ T-cells against MAGE-A4+ tumors[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 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 esophagogastric junction [EGJ] cancers), head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), urothelial cell carcinoma (UCC), and ovarian cancers

ADP-A2M4CD8 next-generation SPEAR T-cells



- SPEAR T-cells are a mix of CD4+ and CD8+ T-cells engineered with a TCR recognizing an intracellular tumor antigen in an HLA-restricted fashion
- ADP-A2M4CD8 are next-generation SPEAR T-cells targeting MAGE-A4 with a CD8α co-receptor introduced into T-cells alongside the TCR
- The co-expression of CD8α adds CD8+ killer cell capability to CD4+ helper cells, while also maintaining/enhancing their helper cell capabilities
- The enhanced TCR interaction results in a more potent response because the ADP-A2M4CD8 next-generation CD4+ SPEAR T-cells can now both kill tumor cells as well as engage the broader immune system, including dendritic cell activation

Trial Design

- The SURPASS trial evaluates the safety and efficacy of next-generation ADP-A2M4CD8 SPEAR T-cells 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
- The number of transduced cells ranged from 0.8×10^8 to 1.2×10^8 (Group 1), 1.2×10^8 to 6.0×10^8 (Group 2), and 1.2×10^9 to 10.0×10^9 (Expansion)
- Dose-limiting toxicities are adjudicated by a Safety Review Committee, regardless of the investigator's attribution

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

Key Eligibility Criteria and Patient Characteristics

- Advanced gastric, esophageal, EGJ, UCC, NSCLC, or HNSCC cancers
- HLA-A*02 and MAGE-A4 positive
- Aged between 18 and 75 years
- Measurable disease per RECIST v1.1
- ECOG performance status ≤1
- Adequate organ function
- No active autoimmune or immune-mediated disease
- No leptomeningeal disease, carcinomatous meningitis, or symptomatic CNS metastases
- No active infection

Table 1. Patients treated with ADP-A2M4CD8 as of the data cut-off (Aug 2, 2021)

Characteristic (N=25)	Overall
Male sex, n (%)	13 (52)
Median age, years (range)	58 (31–75)
Median H-score,[a] (range)	267.5 (130–300)
ECOG performance status at baseline 0, 1, n (%)	8 (32), 17 (68)
Range transduced cells, billion	1.0–9.9

[a]N=24

Safety

- Eighteen (72%) patients experienced cytokine release syndrome (CRS) related to T-cell infusion: Grade 1 or 2 (14); Grade 3 (4) (**Table 2**).
- The most common serious adverse event (SAE) of any grade (>30% of patients) was CRS (**Table 3**)
- Four (16%) patients experienced immune effector cell-associated neurotoxicity syndrome (ICANS) related to T-cell infusion: Grade 1 (1); Grade 2 (1); Grade 3 (2) (**Table 2**)
- Three (12%) patients experienced a T-cell–related SAE of ICANS (**Table 3**)
- Five (20%) patients experienced prolonged cytopenia at Week 4
- One patient experienced an SAE of Grade 5 pancytopenia

Table 2. AEs related to T-cell infusion in ≥10% of patients

Preferred term (N=25)	Any grade, n (%)	Grade ≥3, n (%)
Participants with any AE	22 (88)	13 (52)
CRS	18 (72)	4 (16)
Neutropenia/neutrophil count decreased	8 (32)	8 (32)
Fatigue	7 (28)	2 (8)
Pyrexia	7 (28)	0 (0)
Anemia/red blood cell count decreased	4 (16)	4 (16)
Hypoxia	4 (16)	3 (12)
Leukopenia/white blood cell count decreased	4 (16)	4 (16)
Rash	4 (16)	1 (4)
Sinus tachycardia/tachycardia	4 (16)	0 (0)
ICANS	4 (16)	2 (8)
Decreased appetite	3 (12)	1 (4)
Dyspnea	3 (12)	1 (4)
Headache	3 (12)	0 (0)
Pleural effusion	3 (12)	0 (0)
Thrombocytopenia/platelet count decreased	3 (12)	2 (8)

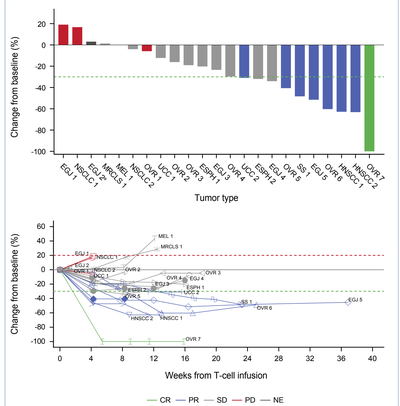
Table 3. SAEs and SAEs related to T-cell infusion in >1 patient

Preferred term (N=25)	SAE, n (%)	Related SAE, n (%)
Participants with any AE	12 (48)	11 (44)
CRS	8 (32)	8 (32)
ICANS	3 (12)	3 (12)
Drug reaction with eosinophilia and systemic symptoms	2 (8)	2 (8)
Hypoxia	2 (8)	2 (8)
Pyrexia	2 (8)	2 (8)

Efficacy

- The majority of patients experienced some anti-tumor activity with a disease control rate of 86% (1 complete response [CR], 7 partial response [PR], and 11 stable disease [SD]; out of 22 evaluable patients; **Table 4** and **Figure 1**)
- The overall response rate was 36% (1 CR and 7 PR; out of 22 evaluable patients; **Table 4** and **Figure 1**)
- The initial durability is promising, with some responses lasting ≥24 wk as of the data cut-off (**Table 4** and **Figure 1**, bottom)

Figure 1. Tumor shrinkage seen in 18 patients with 8 responses



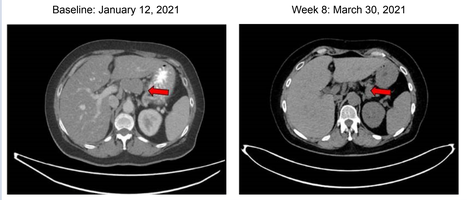
[a]Patient had a post-baseline scan that did not meet the ≥4 wk duration for stable disease

Table 4. Best overall response among 22 evaluable patients across treatment groups

Best overall response (N=22[a])	Overall, n (%)	Indication (n=1 unless otherwise indicated)
CR	1 (4.5)	Ovarian cancer
PR	7 (31.8)	Ovarian cancer (2), HNSCC (2), synovial sarcoma, EGJ cancer, UCC
SD	11 (50.0)	Ovarian cancer (3), EGJ cancer (2), esophageal cancer (2), NSCLC, MRCLS, melanoma, UCC
PD	3 (13.6)	EGJ cancer, NSCLC, ovarian cancer

[a]Of 25 patients dosed, 3 were not evaluable at the time of data cut-off: 2 patients (1 with ovarian cancer and 1 with esophageal cancer) did not have post-baseline scans; 1 patient (EGJ cancer) had a post-baseline scan that did not meet the ≥4 wk duration for stable disease

Figure 2. Confirmed CR in 1 patient with Grade 3 serous ovarian cancer (pT3bN1)



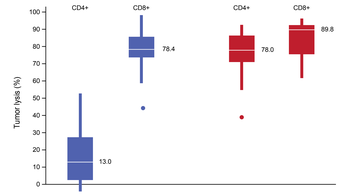
- Baseline: High MAGE-A4 expression with 95% tumor cells with 3+ staining; prior history of multiple surgeries and systemic therapies
- Patient was treated with 3.24 billion ADP-A2M4CD8 SPEAR T-cells in the Expansion group
- CR was noted at Week 4, with CR confirmed at Week 8 and ongoing at data cut-off
- AEs were consistent with the known safety profile of cytotoxic chemotherapy and adoptive cell therapy. One related SAE (Grade 1, pyrexia/fever) resolved within 1 week

Translational

- SPEAR T-cell persistence (data not shown) indicates that ADP-A2M4CD8 is detectable in the peripheral blood of patients up to 320 days post-infusion, with evidence of *in vivo* transduced T-cell expansion post-infusion

Figure 3. ADP-A2M4CD8 next-generation CD4+ SPEAR T-cells lyse tumor cells in vitro

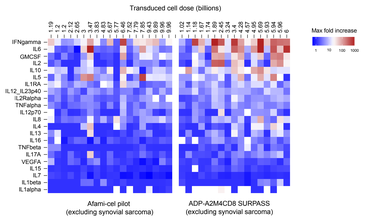
- Addition of the CD8α co-receptor to SPEAR T-cells expressing the MAGE-A4-targeted TCR results in greater cytotoxic function of CD4+ SPEAR T-cells



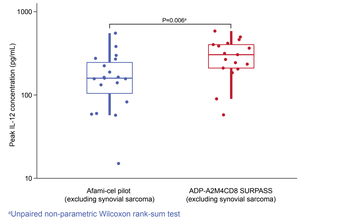
Lysis: 100−(% tumor cells remaining in presence of SPEAR T-cells) at 72 h, compared with no T-cells. Includes all samples with paired CD4+ and CD8+ data at the time of data cut-off. Medians are shown next to boxes (N=21, blue; N=18, red)

Figure 4. ADP-A2M4CD8 next-generation CD4+ SPEAR T-cells show activity *in vivo*, including induction of host immune response

- Post-infusion increases in a subset of the 22 measured serum cytokines were detected
- Maximum observed fold inductions from baseline indicate that SURPASS patients (right panel) show evidence of pharmacodynamic effects at lower SPEAR T-cell doses



- IL-12 is not known to be produced by T-cells. Increased serum IL-12 following ADP-A2M4CD8 infusion is consistent with engagement of the patient's antigen-presenting cells



[a]Unpaired non-parametric Wilcoxon rank-sum test

Conclusions

- ADP-A2M4CD8 SPEAR T-cells have shown an acceptable safety profile
- Emerging efficacy data are promising, with responses in multiple solid tumors (CR in ovarian cancer; PRs in ovarian cancer [2], HNSCC [2], synovial sarcoma, EGJ cancer, UCC) and encouraging early durability
- ADP-A2M4CD8 next-generation CD4+ SPEAR T-cells show improved tumor cell lysis and inflammatory cytokine activation in patient samples
- Safety and efficacy, including duration of response, will continue to be evaluated in the ongoing SURPASS trial, which is enrolling eligible patients with gastroesophageal cancers, HNSCC, NSCLC, UCC, and ovarian cancer
- A Phase 2 trial, SURPASS-2, with ADP-A2M4CD8 will start later this year for patients with esophageal and EGJ cancers

References

1. Hong DS, et al. Presented at Society for Immunotherapy of Cancer (SITC), Virtual Congress, November 9–14, 2020. #379.
2. Van Tine BA, et al. Presented at Connective Tissue Oncology Society (CTOS), Virtual Congress, November 18–21, 2020. #3463188.

Abbreviations

AE, adverse event; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome; ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IL, interleukin; MAGE-A4, melanoma-associated antigen-A4; MEL, melanoma; MRCLS, myxoid/round cell liposarcoma; NSCLC, non-small cell lung cancer; OVR, ovarian; 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; SS, synovial sarcoma; TCR, T-cell receptor; UCC, urothelial cell carcinoma

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