First-Line ADP-A2M4CD8 T-Cell Receptor T-Cell Therapy Plus Pembrolizumab in Head and Neck Cancers: An Additional Cohort of the Phase 1 SURPASS Trial

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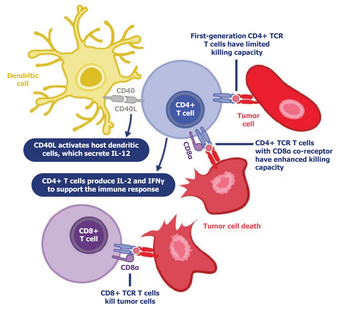
INTRODUCTION

- ADP-A2M4CD8 is a mixed CD4+ and CD8+ T-cell therapy (**Figure 1**). Autologous T cells are collected by leukapheresis and transduced with a lentiviral vector so that they express:
  - An affinity-enhanced T-cell receptor (TCR) that targets the melanoma-associated antigen A4 (MAGE-A4)
  - An additional CD8α co-receptor designed to provide additional functionality to CD4+ T cells
- MAGE-A4 is a cancer testis antigen expressed in a variety of solid tumors[1]

Figure 1. ADP-A2M4CD8 next-generation T cell



IFN, interferon; IL, interleukin; TCR, T-cell receptor.

- The safety and efficacy of ADP-A2M4CD8 are being investigated in the ongoing Phase 1 SURPASS trial (NCT04044859)
- Enrollment in the monotherapy and nivolumab combination cohorts of the SURPASS trial comprised eligible adult participants with advanced solid tumors expressing MAGE-A4, including:
  - Head/neck carcinoma
  - Urothelial cancer
  - Esophageal or esophagogastric cancer
  - Gastric cancer
  - Non-small cell lung carcinoma
  - Ovarian carcinoma
  - Melanoma
  - Endometrial carcinoma
- Ongoing enrollment in the monotherapy and nivolumab combination cohorts is limited to patients with urothelial and head and neck carcinoma
- The primary endpoint is safety and tolerability; the secondary endpoint is anti-tumor activity by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- As of August 14, 2023, a total of 56 patients had been enrolled and treated with ADP-A2M4CD8 in SURPASS, 46 as monotherapy and 10 in combination with nivolumab[2]
- Most patients (36/56 [64.3%]) had ovarian or esophageal/esophagogastric junction/gastric cancers; 4 (7.1%) had head and neck carcinoma (**Table 1**)
  - 100% of those with head and neck carcinoma had previously received checkpoint inhibitors (anti–programmed death (ligand) 1 [PD(L)-1])
- Incidence and severity of adverse events were comparable in the monotherapy and combination groups

Adverse events of special interest

- Overall, 42 patients (75%) experienced cytokine release syndrome (CRS)
  - Grade ≥3: 8 (14%), including 1 (2%) fatal case
- Nine patients (16%) experienced immune effector cell–associated neurotoxicity syndrome (ICANS)
  - Grade ≥3: 2 (4%)
- Fifteen patients (27%) had Grade ≥3 cytopenia at Week 4 post T-cell infusion (prolonged cytopenia)
- There were three related Grade 5 adverse events:
  - CRS in a 60-year-old with ovarian cancer who had large tumor burden in lungs and previous lung radiotherapy; cause of death: pneumonia and CRS
  - Pancytopenia in a 71-year-old man with adenocarcinoma of esophagus with a history of chronic anemia who developed new lesions in liver; cause of death: bone marrow failure
  - Myositis in a 69-year-old with ovarian cancer; she had a history of myositis with a prior cancer immunotherapy, and she developed myositis >8 months post T-cell infusion following a major dental procedure and concurrent with an influenza infection

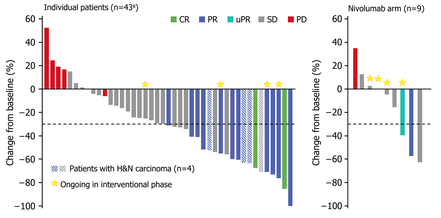
Table 1. Baseline characteristics and RECIST v1.1 responses of patients with head and neck carcinoma in the SURPASS monotherapy cohort

MAGE-A4 expression at baseline, H score[a]	Age	Sex	Prior lines of systemic therapy	Engineered T-cell dose (billion cells)	Best overall response	Duration of response, weeks
295	70	Female	1st line: Cisplatin 2nd line: Carboplatin + paclitaxel + **pembrolizumab** 3rd line: Cetuximab + panitumumab + **pembrolizumab**	4.57	PR	7.43
140	50	Male	1st line: Carboplatin + gemcitabine 2nd line: **Pembrolizumab** 3rd line: Docetaxel	5.92	PR	8.71
280	69	Male	1st line: Fluorouracil + carboplatin + cetuximab 2nd line: **Nivolumab** 3rd line: Taxane + cetuximab	5.00	PR	20.14
300	43	Female	1st line: Cisplatin + docetaxel + fluorouracil 2nd line: Cetuximab 3rd line: Fluorouracil + carboplatin 4th line: **Nivolumab**	6.51	SD	[b]

Data cut-off August 14, 2023.
[a]H score: 1 x (% of 1+ cells) + 2 x (% of 2+ cells) + 3 x (% of 3+ cells). [b]Interval until PD was 8 weeks.
H score, histochemical score; MAGE-A4, melanoma-associated antigen 4; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

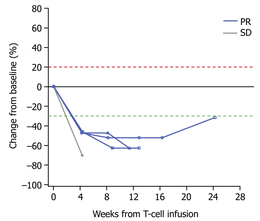
- At the August 14, 2023 cut-off point, the overall response rate was 16/46 patients (34.8%) (95% CI: 21.4–50.3) in the monotherapy arm, and 1/10 (10%) (95% CI: 0.3–44.5) in the combination arm
- **Figure 2** shows the change from baseline in the sum of the lesion diameters in all evaluable patients
- Similarly encouraging results were found in the subgroup of patients with head and neck cancer, who all received ADP-A2M4CD8 monotherapy; the overall response rate was 75.0% (95% CI: 19.4–99.4) and the disease control rate was 100% (**Figure 3**)
- Median duration of response in these patients was 9 weeks (95% CI: 7–20)

Figure 2. Change from baseline SLD colored by best overall response per RECIST v1.1



Data cut-off August 14, 2023. The patient with head and neck carcinoma with best overall response of SD had a uPR.
[a]Patients who are not evaluable are not shown in this plot; hence, it does not equal 56.
CR, complete response; H&N, head and neck; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the lesion diameters; uPR, unconfirmed partial response.

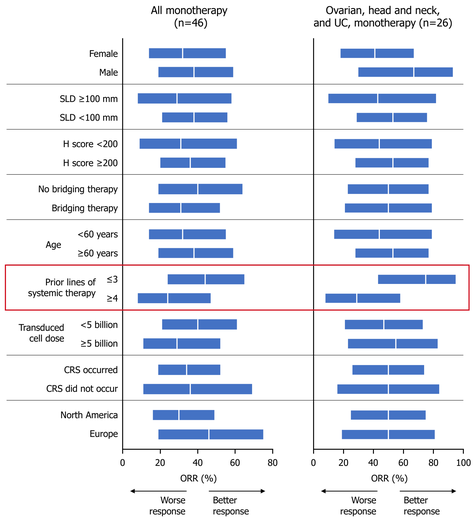
Figure 3. Change from baseline SLD colored by best overall response per RECIST v1.1 in patients with head and neck carcinoma



Data cut-off August 14, 2023. All four patients have now discontinued from the interventional phase of SURPASS due to disease progression.
PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the lesion diameters.

- There was a trend of higher overall response rates in the subgroup of patients receiving fewer lines of prior systemic therapy, both in all tumor types and in the subset of patients with ovarian, head and neck, and urothelial cancers (**Figure 4**), suggesting it could be beneficial to receive ADP-A2M4CD8 earlier

Figure 4. Overall response rates in various subgroups receiving monotherapy in SURPASS



Data cut-off: August 14, 2023. H score is a measure of MAGE-A4 expression. ORRs shown by white bars with blue 95% CIs.
This subset of tumor types was analyzed separately because they appear to be where ADP-A2M4CD8 is most effective and where development is focusing.
CRS, cytokine release syndrome; H score, histochemical score; MAGE-A4, melanoma-associated antigen A4; ORR, overall response rate; SLD, sum of the lesion diameters; UC, urothelial cancer.

- Knowledge of the mechanism of action, along with in vitro and pre-clinical results,[3] suggests that simultaneous inhibition of immunosuppressive pathways, such as with the immune checkpoint (PD-1/PD-L1) inhibitors, could enhance the anti-tumor activity of TCR T-cell therapy
- This, along with the encouraging results of SURPASS to date, prompted design of two new cohorts
- One of these cohorts is recruiting patients with head and neck carcinoma, who will receive ADP-A2M4CD8 in combination with pembrolizumab, as described in this poster
- Although 1/10 patients receiving ADP-A2M4CD8 in combination with nivolumab had partial response to date, we anticipate the new combination cohort will be more effective, because it will be used in immune checkpoint inhibitor–naïve patients, in an earlier line, and in a tumor type that seems susceptible

METHODS: DEDICATED HEAD AND NECK CANCER COHORT

- The dedicated head and neck cancer cohort will comprise up to 15 patients with unresectable locally advanced or metastatic head and neck carcinoma with a combined positive score (CPS) ≥1. Inclusion criteria are shown in **Table 2**, and the design in **Figure 5**
- Patients will receive the same lymphodepletion regimen as the overall cohort, followed by ADP-A2M4CD8 infusion, and pembrolizumab 400 mg (starting in Week 2 following T-cell infusion, then administered every 6 weeks for ≤2 years, until unacceptable toxicity or disease progression)
- The primary endpoint will be safety evaluation
- Anti-tumor activity is the secondary endpoint, primarily measured with overall response rate per RECIST v1.1 by investigator review, with time to response, duration of response, durable response, progression-free survival, and overall survival also being assessed

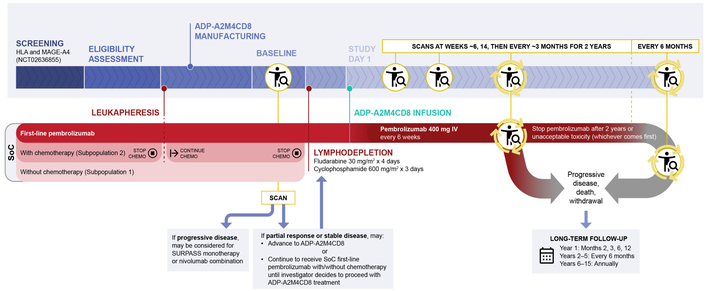
Table 2. Inclusion criteria for the SURPASS dedicated head and neck cohort

Age 18–75 years, inclusive
Histologically or cytologically confirmed head and neck carcinoma with metastatic or unresectable locally advanced disease with CPS ≥1
≥30% of tumor cells expressing MAGE-A4 (≥2+ by immunohistochemistry)
Measurable disease according to RECIST v1.1 prior to lymphodepletion
ECOG PS 0 or 1
Positivity for HLA-A*02:01, HLA-A*02:02, HLA-A*02:03, or HLA-A*02:06 allele
Receipt of first-line pembrolizumab SoC with (Subpopulation 2) or without (Subpopulation 1) chemotherapy, with no evidence of progressive disease prior to lymphodepletion

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen 4; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care.

STUDY DESIGN

Figure 5. Study design for the SURPASS dedicated head and neck cohort



HLA, human leukocyte antigen; IV, intravenous; MAGE-A4, melanoma-associated antigen 4; SoC, standard of care.

CONCLUSIONS

- Interim results of the Phase 1 SURPASS trial suggest an acceptable safety profile for ADP-A2M4CD8, coupled with promising anti-tumor activity in patients with various types of solid tumors
- The newly added dedicated head and neck cohort has begun enrolling, and patients with head and neck carcinoma can also enroll in the ongoing cohort receiving ADP-A2M4CD8 in combination with nivolumab
- Results from the new cohort will further elucidate the potential benefits of ADP-A2M4CD8 in combination with pembrolizumab in this patient population

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ABBREVIATIONS

CPS, combined positive score; CR, complete response; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; H&N, head and neck; H score, histochemical score; ICANS, immune effector cell–associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; IV, intravenous; MAGE-A4, melanoma-associated antigen A4; PD, progressive disease; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the lesion diameters; SoC, standard of care; TCR, T-cell receptor; uPR, unconfirmed partial response.

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1. Wang T, et al. Poster (LB001) presented at: AACR 2022; New Orleans, LA.
2. Moreno V, et al. Oral (1019O) presented at: ESMO 2023; Madrid, Spain.
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CONTACT INFORMATION

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