New Phase 1 SURPASS Trial Cohort: Early-Line ADP-A2M4CD8 T-Cell Receptor T-Cell Therapy Plus Pembrolizumab in Urothelial Carcinoma

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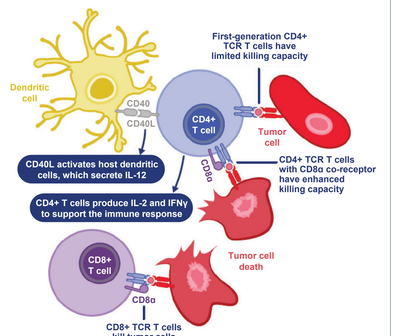
Introduction

- 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 cells



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:
  - Urothelial cancer (UC)
  - Esophageal or esophagogastric cancer
  - Gastric cancer
  - Non-small cell lung carcinoma
  - Head and neck carcinoma
  - Ovarian carcinoma
  - Melanoma
  - Endometrial carcinoma
- Enrollment in the monotherapy and nivolumab combination cohorts is ongoing but is now limited to patients with UC and head and neck carcinoma
- The primary endpoint is safety and tolerability; the secondary endpoint is anti-tumor activity
- 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 had ovarian (18/56 [32%]) or esophageal/esophagogastric junction/gastric (18/56 [32%]) cancers; 7/56 (13%) had UC (**Table 1**; all were men)
  - 86% of those with UC had previously received checkpoint inhibitors (anti–programmed death (ligand) 1 [PD(L)-1]), and 29% had previously received enfortumab vedotin
- 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 the esophagus with a history of chronic anemia who developed new lesions in the 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

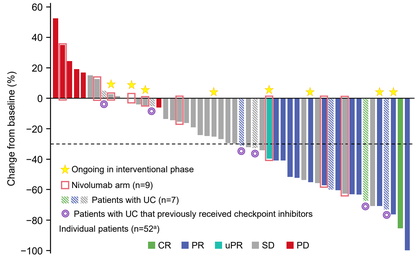
Table 1. Baseline characteristics and RECIST v1.1 responses of patients with UC in the SURPASS monotherapy cohort

MAGE-A4 expression at baseline, H score	Age	Patient characteristics	Prior lines of systemic therapy	Engineered T-cell dose (billion cells)	Best overall response	Duration of response, weeks
280	68	MSI/dMMR neg ALK pos Rest: Not done PD-L1: 5%	First line: Cisplatin + gemcitabine Second line: **Tislelizumab** + BGM-A33 Third line: Carboplatin Fourth line: Vinflunine	4.95	PR	11.00
300	67	PD-L1: 1% Molecular test: Neg	First line: Carboplatin + gemcitabine Second line: **Pembrolizumab** Third line: Docetaxel	7.89	SD	–
205	64	PD-L1: Unknown Molecular: Unknown	First line: Cisplatin + gemcitabine Second line: **Pembrolizumab** Third line: Cisplatin + doxorubicin + methotrexate + vinorelbine Fourth line: ABBV151 + **ABBV181** (anti-TGFB + anti–PD-1)	1.02	SD	–
145	64	MSI/dMMR pos Rest: Negative PD-L1: Unknown	First line: Cisplatin + doxorubicin + methotrexate + vinblastine	5.31	PR	42.43
200	60	PD-L1: Unknown Molecular: Unknown	First line: Carboplatin + gemcitabine Second line: **Avelumab** Third line: ABBV151 + **ABBV181** (anti-TGFB + anti–PD-1)	9.87	PR	19.00
130	72	PD-L1: 12% ALK pos BRCA1 pos Rest: Neg	First line: Carboplatin + gemcitabine + carboplatin Second line: **Pembrolizumab** Third line: **Enfortumab vedotin** Fourth line: Sacituzumab govitecan	6.57	SD	–
260	67	CPS: 2% Rest: Unknown	First line: Cisplatin + gemcitabine Second line: **Pembrolizumab** Third line: **Enfortumab vedotin**	1.41	CR	20.43

[a]H score: 1 x (% of 1+ cells) + 2 x (% of 2+ cells) + 3 x (% of 3+ cells). Data cut-off: August 14, 2023. ALK, anaplastic lymphoma kinase mutation; BRCA, breast cancer gene; CPS, combined positive score; CR, complete response; dMMR, mismatch repair deficiency; MAGE-A4, melanoma-associated antigen A4; MSI, microsatellite instability; neg, negative; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pos, positive; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TGFB, transforming growth factor beta; UC, urothelial cancer.

- At the August 2023 data 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

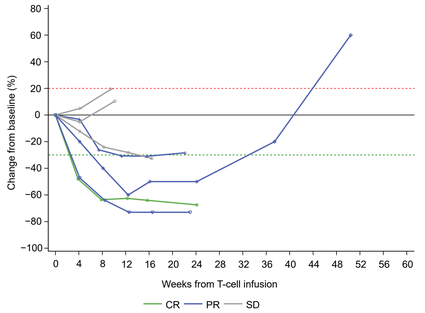
Figure 2. Change from baseline SLD, colored by best overall response per RECIST v1.1



[a]Patients who are not evaluable are not shown in this plot; therefore, it does not equal 56. Data cut-off: August 14, 2023. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the lesion diameters; UC, urothelial carcinoma; uPR, unconfirmed partial response.

- Similarly encouraging results were found in the subgroup of patients with UC, who all received ADP-A2M4CD8 monotherapy; the overall response rate was 57.1% (95% CI: 18.4–90.1) and the disease control rate was 100% (**Figure 3**)
- Median duration of response in these patients was 31 weeks (95% CI: 11–42)

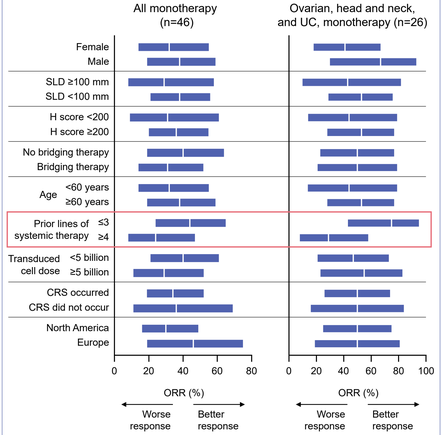
Figure 3. Change from baseline SLD, colored by best overall response per RECIST v1.1, in patients with UC



Data cut-off: August 14, 2023.
CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of the lesion diameters; UC, urothelial carcinoma.

- There was a trend of higher overall response rates in the subgroup of patients receiving fewer lines of prior systemic therapy, both across 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. ORRs 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. CRS, cytokine release syndrome; 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 in SURPASS to date, prompted design of two new cohorts
- One of these cohorts is recruiting patients with UC, who will receive ADP-A2M4CD8 in combination with pembrolizumab, as described in this poster

Methods: Dedicated early-line UC cohort

- The dedicated UC cohort will comprise up to 15 patients with unresectable locally advanced or metastatic UC. Inclusion criteria are shown in **Table 2**, and the study design is shown 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)

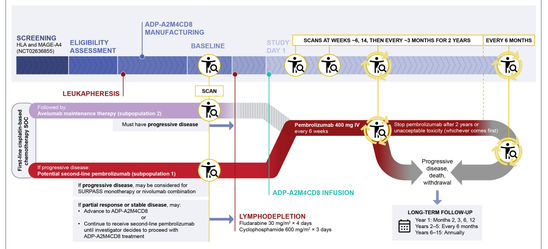
- The primary endpoint will be safety evaluation
- Anti-tumor activity is the secondary endpoint primarily measured with overall response rate per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator review, with time to response, duration of response, durable response, progression-free survival, and overall survival also being assessed

Table 2. Inclusion criteria for the SURPASS dedicated UC cohort

Age 18–75 years, inclusive
Histologically or cytologically confirmed UC with metastatic or unresectable locally advanced disease
≥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 cisplatin-based chemotherapy plus avelumab maintenance, with evidence of progressive disease prior to lymphodepletion, and no second-line therapy; *OR* Receipt of first-line cisplatin-based chemotherapy, and may be receiving second-line pembrolizumab monotherapy standard of care at baseline, with no evidence of progressive disease

ECOG PS, Eastern Cooperative Oncology Group performance status; HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen A4; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial cancer.

Figure 5. Study design for the SURPASS dedicated UC cohort



HLA, human leukocyte antigen; IV, intravenous; MAGE-A4, melanoma-associated antigen A4; SOC, standard of care; UC, urothelial cancer.

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 UC cohort has begun enrolling, with initial patients identified at Memorial Sloan Kettering Cancer Center (New York, NY, USA) and Vall d'Hebron Institute of Oncology (Barcelona, Spain); other centers will also participate
- Results from this cohort will further elucidate the potential benefits of ADP-A2M4CD8 in combination with pembrolizumab in this patient population

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Abstract ID: TPS708

References
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.
3. Gray K, et al. *Clin Cancer Res*. 2020;26:6003–16.

Abbreviations
ALK, anaplastic lymphoma kinase mutation; BRCA, breast cancer gene; CPS, combined positive score; CR, complete response; CRS, cytokine release syndrome; dMMR, mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group performance status; HLA, human leukocyte antigen; ICANS, immune effector cell–associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; IV, intravenous; MAGE-A4, melanoma-associated antigen A4; MSI, microsatellite instability; neg, negative; ORR, overall response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pos, positive; 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; TGFB, transforming growth factor beta; UC, urothelial cancer; uPR, unconfirmed partial response.

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Data cut-off
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