Safety and Efficacy From the Phase 1 SURPASS Trial of ADP-A2M4CD8, a Next-Generation T-Cell Receptor T-Cell Therapy, in Patients With Advanced Esophageal, Esophagogastric Junction, or Gastric Cancer

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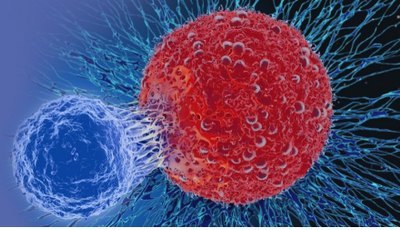
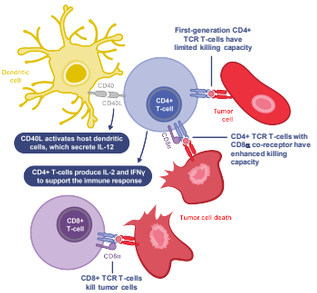


Introduction

- ADP-A2M4CD8 is a mixed CD4+ and CD8+ T-cell therapy with an affinity-enhanced T-cell receptor (TCR) targeting the melanoma-associated antigen A4 (MAGE-A4) and modified with addition of a CD8α co-receptor designed to provide additional functionality to CD4+ T-cells (**Figure 1**)
- ADP-A2M4CD8 has demonstrated an acceptable benefit to risk profile in the Phase 1 SURPASS trial (NCT04044859) in human leukocyte antigen A*02–eligible patients with unresectable or metastatic tumors positive for MAGE-A4[1]
- Here we report updated clinical outcomes in patients with esophageal, esophagogastric junction (EGJ), or gastric cancer

Figure 1. ADP-A2M4CD8 next-generation TCR T-cells



- Affinity-enhanced TCR 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 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+ T-cells can now both kill tumor cells as well as engage the broader immune system including dendritic cell activation

HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; MAGE-A4, melanoma-associated antigen A4; TCR, T-cell receptor

Methods

- SURPASS is a first-in-human trial consisting of a modified 3+3 dose-escalation design and an expansion cohort
  - A subset of patients receive combination therapy with nivolumab 480 mg administered intravenously every 4 weeks starting approximately 4 weeks after infusion of ADP-A2M4CD8 T-cells
- SURPASS is enrolling patients with advanced cancers: endometrial, esophageal, EGJ, gastric, head and neck, melanoma, non-small cell lung, ovarian, and urothelial
- Autologous T-cells are obtained by leukapheresis, transduced with a self-inactivating lentiviral vector expressing the MAGE-A4-specific TCR and the CD8α co-receptor, and infused back to the patients as ADP-A2M4CD8 following lymphodepleting chemotherapy
- Primary and secondary objectives are safety and anti-tumor activity, respectively
- Multiplex immunofluorescence (mIF) and chromogenic images were generated from Ultivue mIF 8plex assay kit, custom mIF 4plex, and in situ RNA hybridization (RNAscope)/immunohistochemistry (IHC) duplex assay
  - These kits stain tissue biopsy sections from baseline and post-infusion samples from patients with esophageal, EGJ, or gastric cancer taking part in SURPASS

Demographics and baseline characteristics

- As of November 23, 2022, 46 patients with MAGE-A4–positive cancer were treated with ADP-A2M4CD8, including 15 patients with esophageal (n=3), EGJ (n=10), and gastric cancer (n=2) (**Table 1**); of these, three (EGJ n=2, gastric n=1) were in combination with nivolumab
- Prior therapies included chemotherapy (n=15, 100%), PD-(L)1 inhibitors (n=9, 60%), anti-VEGFR (n=9, 60%), and anti-HER2 (n=4, 27%)
- All but one patient had liver, peritoneal, and/or retroperitoneal metastases

Table 1. Baseline characteristics of patients with esophageal, EGJ, or gastric cancer taking part in SURPASS

Characteristic	Nivolumab combination n=3	Monotherapy n=12
Sex, n (%)		
Male	3 (100.0)	10 (83.3)
Female	0	2 (16.7)
Age, years, median (min, max)	59.0 (53, 73)	55.5 (31, 71)
H-score,[a] median (min, max)	265 (145, 295)	227.5 (160, 300)
ECOG at baseline, n (%)		
0	1 (33.3)	1 (8.3)
1	2 (66.7)	11 (91.7)
Bridging therapy, yes, n (%)	3 (100.0)	9 (75.0)
Transduced cells, 10^9 cells, min, max	4.07, 7.95	1.02, 9.90
Prior lines of systemic therapy, median (min, max)	2.0 (1, 2)	3.0 (1, 5)
SLD ≥50 mm, n (%)	0	10 (83.3)

[a]H-score: 1×(% of 1+ cells)+2×(% of 2+ cells)+3×(% of 3+ cells). ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; SLD, sum of longest diameters of target lesions

Safety

- Safety data are presented for all patients participating in SURPASS who have received ADP-A2M4CD8 monotherapy (n=43; **Tables 2, 3**)
  - Safety in the esophageal, EGJ, and gastric subgroup is consistent with the overall study population
  - The nivolumab combination group had a similar safety profile as the monotherapy group but is based on a small sample size with limited follow-up at this data cut-off
    - All three patients in the nivolumab combination group experienced one or more adverse event (AE) related to T-cell therapy, including cytokine release syndrome (CRS), fatigue, pyrexia, rash, and febrile neutropenia (Grades 1–3)
- There were two related Grade 5 (fatal) serious AEs
  - 71-year-old male with adenocarcinoma of esophagus and history of chronic anemia, developed pancytopenia and died of bone marrow failure
  - 60-year-old female with ovarian cancer, with large tumor burden in lungs, developed pneumonia and Grade 5 CRS

Table 2. AEs related to T-cell therapy in ≥10% of patients who have received ADP-A2M4CD8 monotherapy

Preferred term	Monotherapy n=43; n (%)
Participants with any AEs	40 (93.0)
CRS	32 (74.4)
Neutropenia	13 (30.2)
Anemia	9 (20.9)
Fatigue	9 (20.9)
Pyrexia	8 (18.6)
Rash	7 (16.3)
Thrombocytopenia	7 (16.3)
Dyspnea	6 (14.0)
Hypoxia	6 (14.0)
ICANS	6 (14.0)
Leukopenia	6 (14.0)
Pleural effusion	6 (14.0)
Febrile neutropenia	5 (11.6)
Lymphopenia	5 (11.6)

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

Table 3. Grade 3 and 4 AEs related to T-cell therapy in two or more patients who have received ADP-A2M4CD8 monotherapy

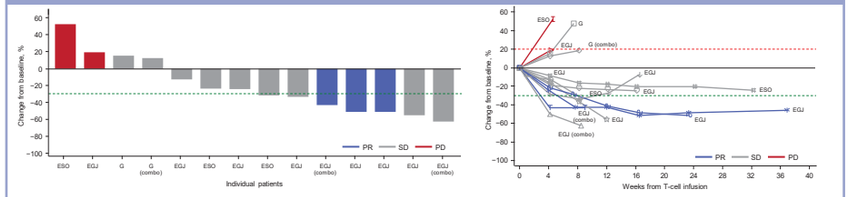
Preferred term	Monotherapy n=43; n (%)	
	Grade 3	Grade 4
Participants with any AEs	22 (51.2)	11 (25.6)
Anemia	6 (14.0)	0
Febrile neutropenia	5 (11.6)	0
CRS	4 (9.3)	1 (2.3)
Neutropenia	3 (7.0)	7 (16.3)
Hypoxia	3 (7.0)	1 (2.3)
Lymphopenia	2 (4.7)	2 (4.7)
Fatigue	2 (4.7)	0
Rash	2 (4.7)	0
ICANS	2 (4.7)	0
Thrombocytopenia	1 (2.3)	2 (4.7)
Leukopenia	0	5 (11.6)

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

Efficacy

- Overall response rate per Response Evaluation Criteria in Solid Tumors v1.1 by investigator review was 20.0% (three partial response [PR]/15 patients with esophageal, EGJ, or gastric cancer; **Figure 2**)
- Disease control rate was 80.0% (three PR + nine stable disease/15 patients), and duration of response ranged from 5.0–29.3 weeks

Figure 2. Change from baseline in target lesion SLD colored by investigator-assessed best overall response per RECIST v1.1

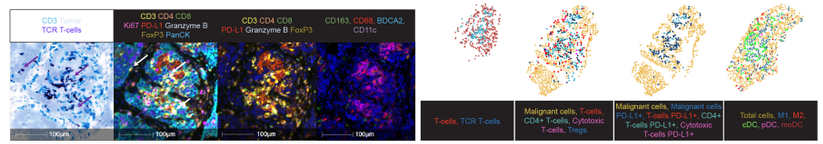


n=14, one non-evaluable patient not shown. Data show change from baseline in SLD through progression or prior to surgical resection. Combo refers to patients in the nivolumab combination group. EGJ, esophagogastric junction; ESO, esophageal; G, gastric; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SLD, sum of longest diameters of target lesions

Translational

- IHC, mIF, and RNAscope images of tumor biopsy sections reveal details about antigen expression and infiltrating cell types present, and their functional state (**Figure 3**)
  - IHC/RNAscope image and corresponding spatial plot show infiltrating endogenous T-cells and ADP-A2M4CD8 T-cells into tumor tissue
  - mIF and spatial plots can reveal the expression and spatial distribution of activated, proliferating, or PD-L1 status of CD4+ T-cells, cytotoxic T-cells, regulatory T-cells, and malignant tumor cells
  - The macrophage and dendritic cell panel (first from the right) illustrates M1 (pro-immune) and M2 (pro-tumor) macrophages in the tumor

Figure 3. Spatial plots enable further understanding of immune cell phenotypes and highlight interesting mechanistic questions regarding response in a post-treatment biopsy from a patient with esophageal cancer treated with ADP-A2M4CD8 monotherapy



The whole slides were scanned and image-registered together. The stacked images were analyzed using HALO image analysis software to generate mIF multi-color images and spatial plots. cDC, classical dendritic cells; FOXP3, forkhead box P3; M, macrophage; mIF, multiplex immunofluorescence; moDC, monocyte-derived dendritic cells; PanCK, pancytokeratin; pDC, plasmacytoid dendritic cells; PD-L1, programmed death-ligand 1; TCR, T-cell receptor

Conclusions

- Results indicate an acceptable benefit to risk profile and encouraging anti-tumor activity of ADP-A2M4CD8 in patients with esophageal, EGJ, and gastric cancers
- Translational investigation of on-study tumor biopsy samples reveals ADP-A2M4CD8 T-cell infiltration into the tumor area, becoming activated, and eliciting a cytotoxic phenotype (granzyme B) within the tumor. Assessment of PD-L1+ expression and spatial distribution provide context to the potential immunosuppressive environment that the T-cells need to overcome. The spatial proximity of T-cells and other infiltrating subtypes relevant to clinical responses, to each other and to the tumor cells, is being assessed

349: American Society of Clinical Oncology (ASCO), Gastrointestinal Cancer Symposium
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References
1. Hong DS, et al. E-poster 540P: ESMO 2021; Virtual

Footnotes and Abbreviations Used in Text
AE, adverse event; CRS, cytokine release syndrome; EGJ, esophagogastric junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MAGE-A4, melanoma-associated antigen A4; mIF, multiplex immunofluorescence; PD-(L)1, programmed death (ligand) 1; PR, partial response; TCR, T-cell receptor; VEGFR, vascular endothelial growth factor receptor

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Data cut-off
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