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Clinical and Translational Data From the Phase 1 SURPASS Trial of ADP-A2M4CD8 T-Cell Receptor (TCR) T-Cell Therapy Alone or Combined With Nivolumab in Solid Tumors

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Declaration of interests

Victor Moreno

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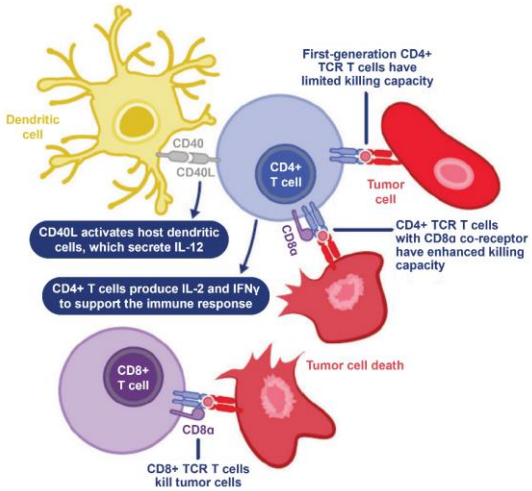
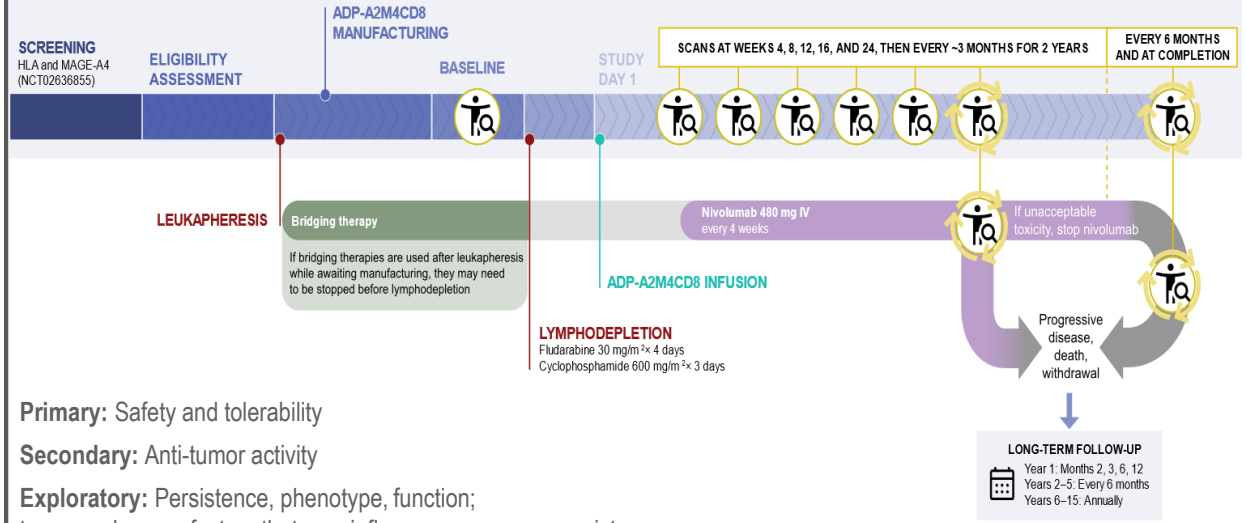
Phase 1 SURPASS (NCT04044859) trial of ADP-A2M4CD8 next-generation T-cell receptor T-cell therapy in solid tumors

Engineered for increased potency by expressing a CD8α co-receptor



SURPASS monotherapy and nivolumab combination therapy



Primary: Safety and tolerability

Secondary: Anti-tumor activity

Exploratory: Persistence, phenotype, function; tumor and serum factors that may influence response or resistance

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

Patient characteristics

Heavily pre-treated patients in multiple solid tumor indications

Characteristic	Monotherapy (n=46)	Combination (n=10)	Overall (N=56)
Male, n (%)	24 (52.2)	7 (70.0)	31 (55.4)
Female, n (%)	22 (47.8)	3 (30.0)	25 (44.6)
Age, y, median (range)	60 (31–75)	59 (46–73)	60 (31–75)
MAGE-A4 H score,[a] median (range)	248 (90–300)	243 (115–300)	248 (90–300)
Transduced T cells, range	1.02–9.95x10^9	1.60–9.88x10^9	1.02–9.95x10^9
ECOG, n (%) 0 1	 14 (30.4) 32 (69.6)	 5 (50.0) 5 (50.0)	 19 (33.9) 37 (66.1)
Prior systemic therapies, median (range)	3.0 (1–8)	3.5 (1–5)	3.0 (1–8)
Bridging therapy, n (%)	26 (56.5)	9 (90.0)	35 (62.5)

Tumor type, n (%)	Monotherapy (n=46)	Combination (n=10)	Overall (N=56)
Ovarian	15 (32.6)	3 (30.0)	18 (32.1)
Esophagogastric junction, esophageal, gastric	14 (30.4)	4 (40.0)	18 (32.1)
Urothelial	7 (15.2)	–	7 (12.5)
Head and neck	4 (8.7)	–	4 (7.1)
Non-small cell lung cancer	2 (4.3)	1 (10.0)	3 (5.4)
Melanoma	2 (4.3)	2 (20.0)	4 (7.1)
Synovial sarcoma	1 (2.2)	–	1 (1.8)
Myxoid/round cell liposarcoma	1 (2.2)	–	1 (1.8)

[a]H score: 1 x (% of 1+ cells) + 2 x (% of 2+ cells) + 3 x (% of 3+ cells).
Data cut-off August 14, 2023.
ECOG, Eastern Cooperative Oncology Group; MAGE-A4, melanoma-associated antigen A4.

Safety

AEs of any causality in ≥30% of participants, and of those, numbers of Grade ≥3

Preferred term, n (%)	AE, overall (N=56)	Grade ≥3, overall (N=56)
Participants with any AE	55 (98.2)	50 (89.3)
Neutropenia/neutrophil count decreased	45 (80.4)	43 (76.8)
CRS	42 (75.0)	8 (14.3)
Anemia/RBC decreased	38 (67.9)	26 (46.4)
Lymphopenia/lymphocyte count decreased	35 (62.5)	35 (62.5)
Nausea	30 (53.6)	1 (1.8)
Leukopenia/WBC decreased	29 (51.8)	29 (51.8)
Fatigue	26 (46.4)	6 (10.7)
Thrombocytopenia/platelet count decreased	24 (42.9)	16 (28.6)
Rash	23 (41.1)	6 (10.7)
Constipation	20 (35.7)	0
Diarrhea	20 (35.7)	1 (1.8)
Decreased appetite	19 (33.9)	4 (7.1)
Pyrexia	18 (32.1)	0
Vomiting	18 (32.1)	2 (3.6)

Incidence and **severity** of events in the **nivolumab combination** group (n=10) were **comparable** to those in the **monotherapy** group (n=46)

Data cut-off August 14, 2023.
AE, adverse event; CRS, cytokine release syndrome; RBC, red blood cell; WBC, white blood cell.

Safety

Summary of AEs of special interest

All CRS	Overall (N=56)
CRS, n (%)	42 (75.0)
Grade 1	19 (33.9)
Grade 2	15 (26.8)
Grade 3	5 (8.9)
Grade 4	2 (3.6)
Grade 5	1 (1.8)
Time to first CRS, d, median (range)	2.5 (1–9)
Time to resolution, d, median (range)	5.0 (1–19)
Tocilizumab use, n (%)	34 (60.7)
Corticosteroid use, n (%)	9 (16.1)

- Nine of the 56 (16%) patients experienced AEs of immune effector cell–associated neurotoxicity syndrome; two (4%) were Grade 3
- 15 (27%) patients experienced prolonged cytopenia at Week 4

Data cut-off August 14, 2023.
AE, adverse event; CRS, cytokine release syndrome.

There were three related Grade 5 (fatal) events:

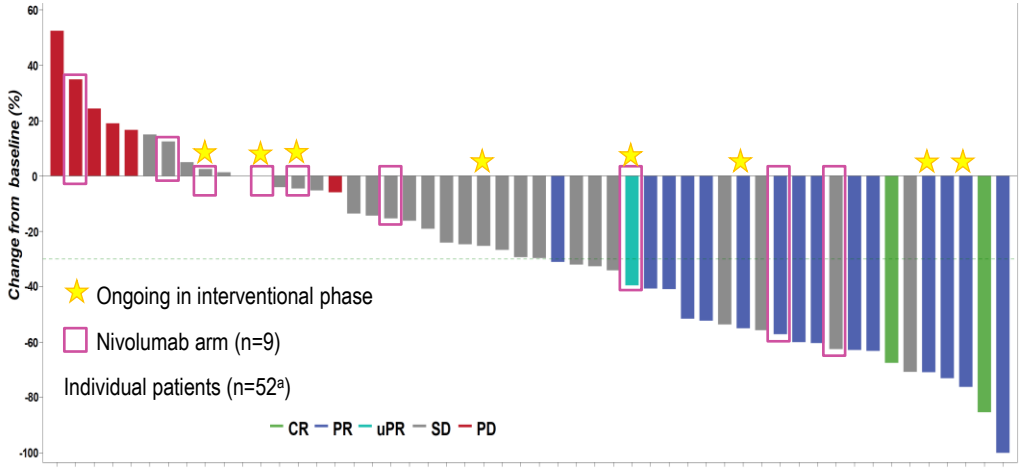
CRS
- 60-year-old with ovarian cancer
- Large tumor burden in lungs and previous lung radiotherapy
- Cause of death: pneumonia and CRS

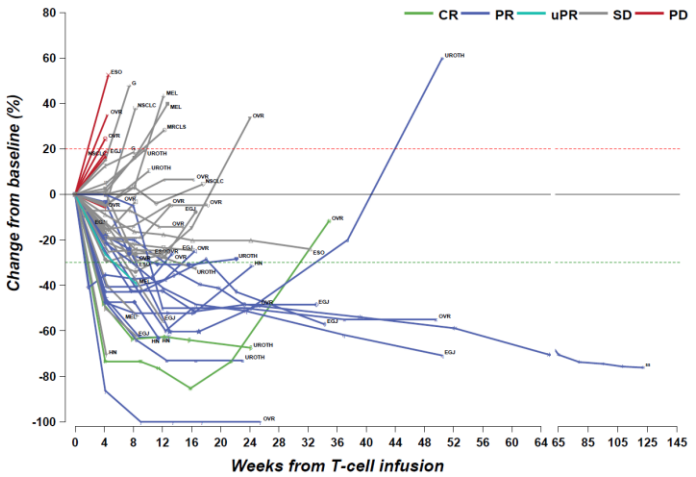
Pancytopenia
- 71-year-old man with adenocarcinoma of esophagus
- History of chronic anemia
- Cause of death: bone marrow failure

Myositis
- 69-year-old with ovarian cancer
- Developed myositis >8 months post T-cell infusion following major dental procedure and concurrent with influenza infection
- History of myositis with prior cancer immunotherapy

Efficacy (all tumor types)

Change in baseline SLD colored by best overall response per RECIST v1.1 by investigator review



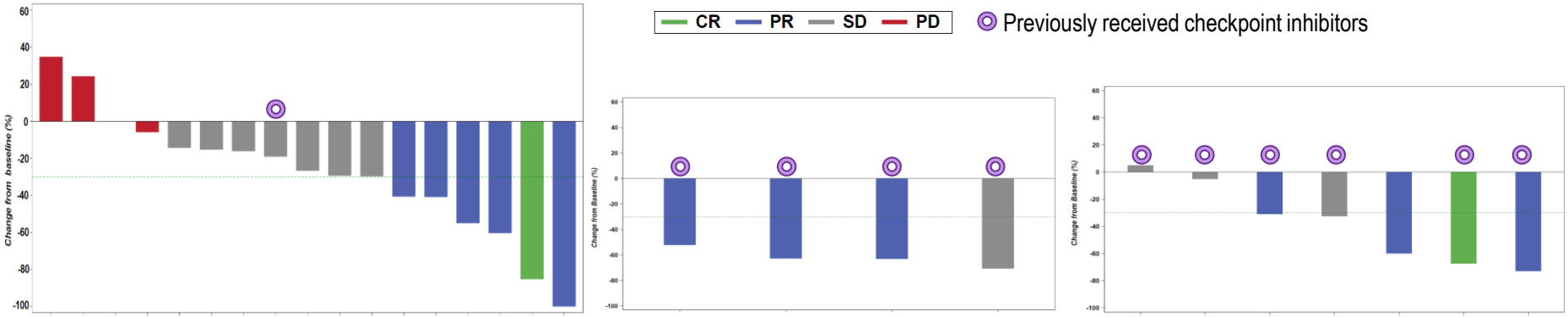


Group	Overall response rate, n (%); 95% CI	Duration of response, weeks
Monotherapy (n=46)	16 (34.8); 21.4–50.3	Median: 21 (95% CI: 12–38)
Nivolumab arm (n=10)	1 (10.0); 0.3–44.5	30

[a]Patients who are not evaluable are not shown in this plot; hence, 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; uPR, unconfirmed partial response.

Efficacy (ovarian, head and neck, urothelial cancers)

Change in baseline SLD colored by best overall response per RECIST v1.1 by investigator review; encouraging efficacy and duration of response in indications of focus



Patients with ovarian cancer | Patients with head and neck cancer | Patients with urothelial cancer

Patients with:	Ovarian cancer (monotherapy)	Head and neck cancer	Urothelial cancer	Ovarian, head and neck, urothelial
Overall response rate, n (%); 95% CI	6 (40.0); 16.3–67.7	3 (75.0); 19.4–99.4	4 (57.1); 18.4–90.1	13 (50.0); 29.9–70.1
Duration of response, wk, median (95% CI)	17 (12–38)	9 (7–20)	31 (11–42)	19 (11–31)

Responses were also observed in patients with esophagogastric junction cancer and synovial sarcoma.

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.

ORR by baseline characteristics

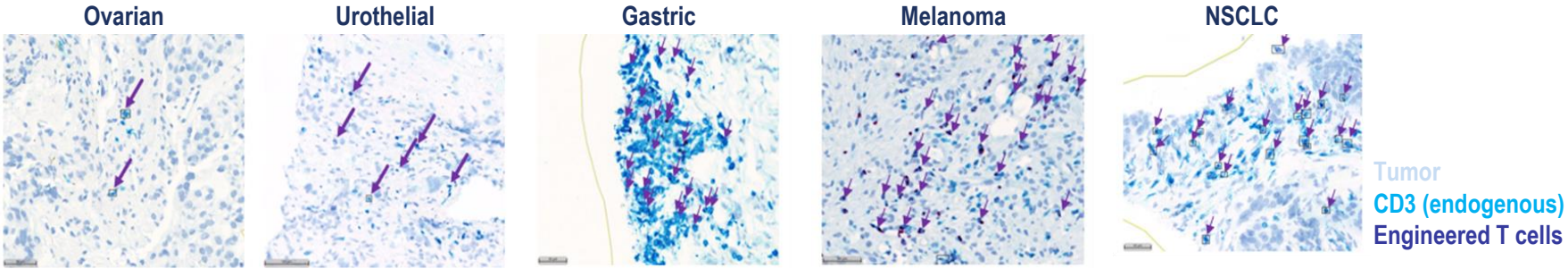
Better responses with fewer lines of previous therapy

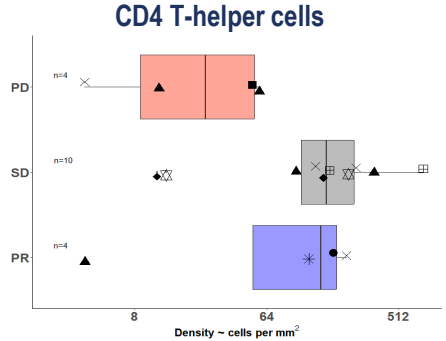
Characteristic	Subgroup	All tumor types, monotherapy, n/N (%); 95% CI	Ovarian, H&N, urothelial, monotherapy, n/N (%); 95% CI
Baseline SLD	<100 mm	12/32 (38); (21–56)	10/19 (53); (29–76)
	≥100 mm	4/14 (29); (8–58)	3/7 (43); (10–82)
Prior lines of systemic therapy	≤3	11/25 (44); (24–65)	9/12 (75); (43–95)
	≥4	5/21 (24); (8–47)	4/14 (29); (8–58)
H score	<200	4/13 (31); (9–61)	4/9 (44); (14–79)
	≥200	12/33 (36); (20–55)	9/17 (53); (28–77)
Bridging therapy	Yes	8/26 (31); (14–52)	6/12 (50); (21–79)
	No	8/20 (40) (19–64)	7/14 (50); (23–77)
Transduced cell dose	<5x10^9	10/25 (40); (21–61)	7/15 (47); (21–73)
	≥5x10^9	6/21 (29); (11–52)	6/11 (55); (23–83)
Any-grade CRS	Yes	12/35 (34); (19–52)	9/18 (50); (26–74)
	No	4/11 (36); (11–69)	4/8 (50); (16–84)
Age	<60 y	7/22 (32); (14–55)	4/9 (44); (14–79)
	≥60 y	9/24 (38) (19–59)	9/17 (53); (28–77)
Sex	Male	9/24 (38); (19–59)	6/9 (67); (30–93)
	Female	7/22 (32); (14–55)	7/17 (41); (18–67)
Geographical region	North America	10/33 (30); (16–49)	8/16 (50); (25–75)
	Europe	6/13 (46); (19–75)	5/10 (50); (19–81)

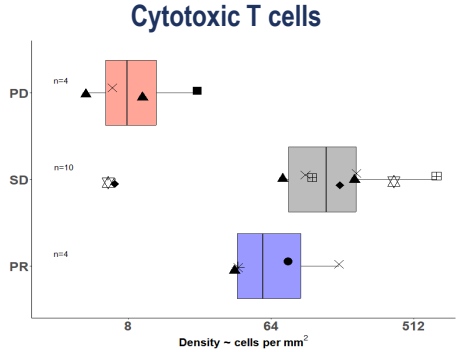
Data cut-off August 14, 2023.
CRS, cytokine release syndrome; H&N, head and neck; ORR, overall response rate; SLD, sum of the lesion diameters.

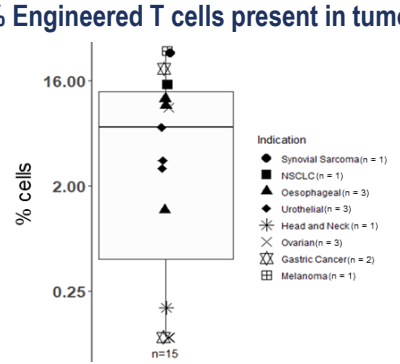
Translational analyses

Engineered and endogenous T cells infiltrate solid tumors across indications in SURPASS









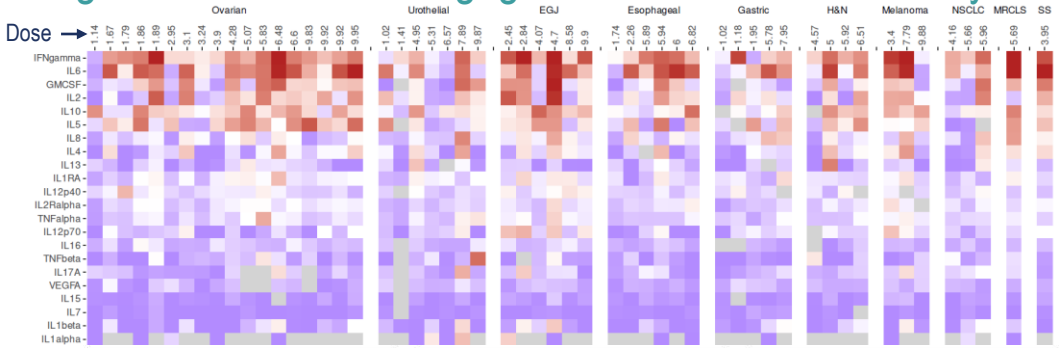
Data cut-off August 29, 2023.

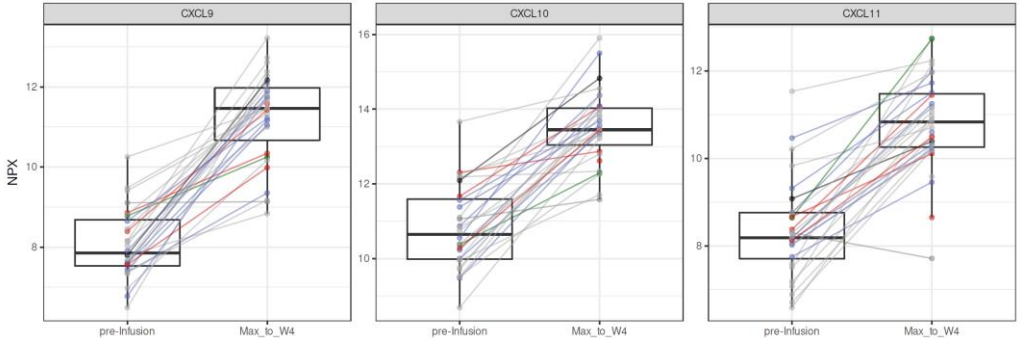
NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

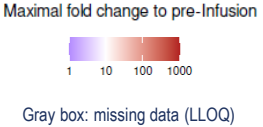
Translational analyses

Pharmacodynamic signals demonstrate engagement of broad immune system

Induction of serum responses across solid tumor indications, and at relatively low doses







Examples of induction of non–T-cell serum proteins

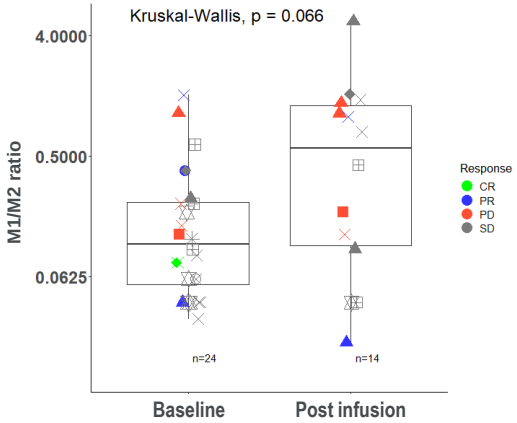
Data cut-off August 29, 2023.

CR, complete response; EGJ, esophagogastric junction; GMCSF, granulocyte-macrophage colony-stimulating factor; H&N, head and neck; IFN, interferon; IL, interleukin; LLOQ, lower limit of quantification; max, maximum; MRCLS, myxoid/round cell liposarcoma; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; SS, synovial sarcoma; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; W, Week.

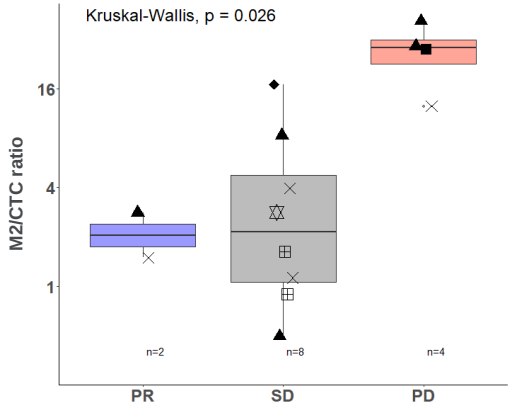
Translational analyses

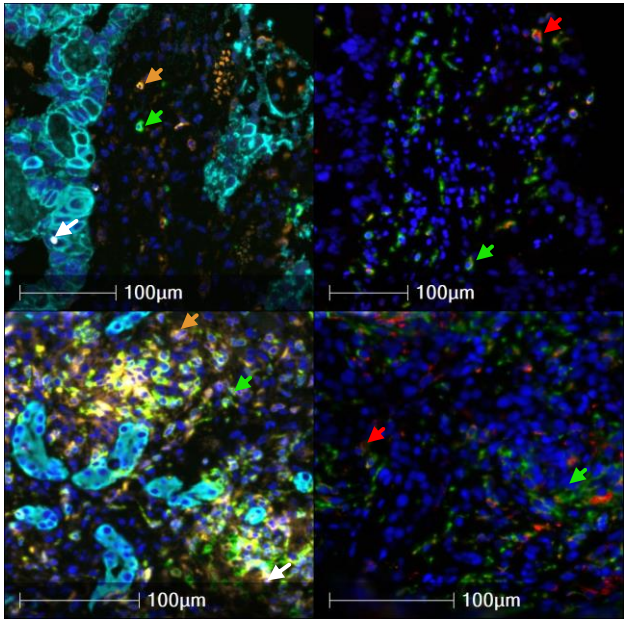
ADP-A2M4CD8 initiates a broad intra-tumoral adaptive and innate immune response

Higher M1/M2 ratio post infusion indicates a strong innate anti-tumor response[a]



Lower M2/cytotoxic T-cell ratio associated with response rate indicative of innate and adaptive response





Adaptive (Ultivue panel): CD3 CD4 CD8 GrzB PanCK/Sox10

Innate (macrophage panel): M1 M2

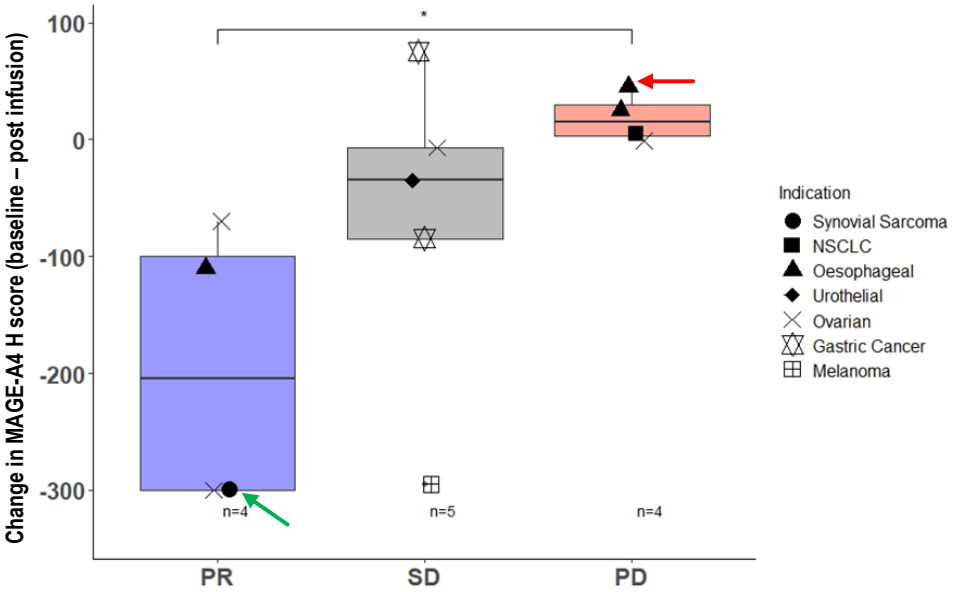
[a]M2 macrophages are generally considered pro-tumorigenic, whereas M1 macrophages are considered pro-immunogenic.

Data cut-off August 29, 2023; Ultivue panel data: July 20, 2023; macrophage panel data: July 28, 2023.
CR, complete response; CTC, cytotoxic T cell; PD, progressive disease; PR, partial response; M1, CD68; M2, CD163; SD, stable disease.

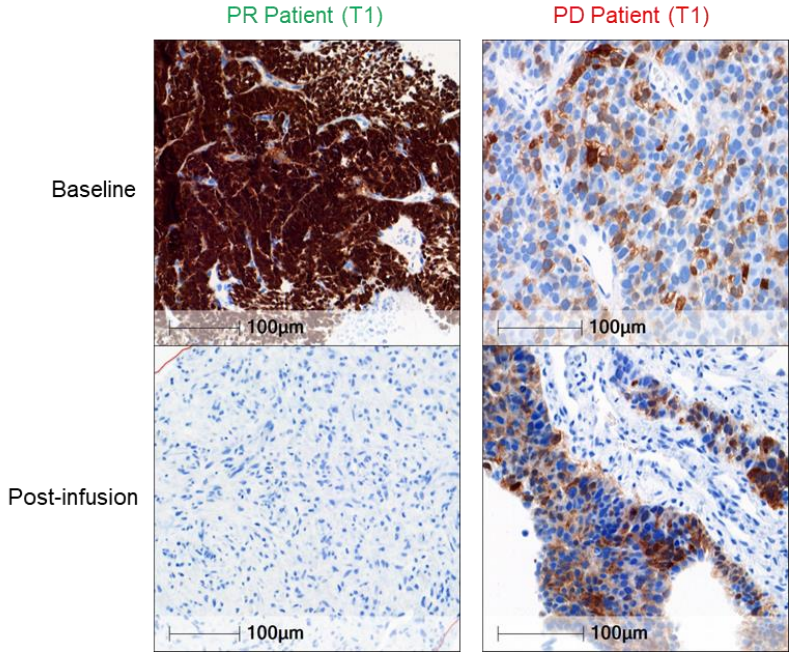
Translational analyses

ADP-A2M4CD8 reduces antigen positive tumor cells; greatest reduction with response

Change in MAGE-A4 H score following ADP-A2M4CD8 infusion



MAGE-A4 tumoral expression changes



Data cut-off, MAGE-A4 data: August 11, 2023.

MAGE-A4, melanoma-associated antigen A4; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- ADP-A2M4CD8 continues to show an acceptable benefit-to-risk profile in multiple MAGE-A4+ unresectable or metastatic tumors, including in patients receiving nivolumab combination therapy
- CRS was frequent, tolerable, and manageable by tocilizumab and corticosteroids when indicated
- Clinical responses appear to be higher for participants with certain tumor types and fewer prior lines of systemic therapy
  - Results suggest targeting participants with ovarian, head and neck, or urothelial cancers for ADP-A2M4CD8 TCR T-cell therapy, and a potential benefit to earlier screening and apheresis of trial participants
- Clinical responses are associated with strong evidence of ADP-A2M4CD8 tumor infiltration, broad immune engagement, and anti–MAGE-A4+ tumor activity

CRS, cytokine release syndrome; MAGE-A4, melanoma-associated antigen A4; TCR, T-cell receptor.

Co-authors and acknowledgments

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